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APPENDIX A

Summary of External Peer Review and Public Comments and Disposition

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APPENDIX A. SUMMARY OF EXTERNAL PEER REVIEW AND PUBLIC COMMENTS AND DISPOSITION

EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (Reanalysis) has undergone a formal, independent, expert panel review performed by U.S. Environmental Protection Agency's (EPA's) Science Advisory Board (SAB) in accordance with EPA guidance on peer review (2006c, 2000). The SAB Dioxin Review Panel held two public face-to-face meetings to deliberate on the charge questions on July 13−15, 2010 and October 27−29, 2010, as well as two public teleconferences on March 1 and 2, 2011. The SAB Dioxin Review Panel was asked to consider the accuracy, objectivity, and transparency of EPA's Reanalysis. Initially, the charge questions presented to the SAB Dioxin Review Panel were divided into six sections: *General Charge Questions, Transparency and Clarity in the Selection of Key Data Sets for Dose-Response Analysis, The Use of Toxicokinetics in the Dose-Response Modeling for Cancer and Noncancer Endpoints, Chronic Oral Reference Dose, Cancer Assessment,* and *Feasibility of Quantitative Uncertainty Analysis From NAS Evaluation of the 2003 Reassessment*. Because of EPA's decision to release the cancer assessment and quantitative uncertainty sections in a separate document, SAB and public comments related to those topics are not addressed in this appendix but will be addressed in the Reanalysis Volume 2. A summary of comments made by the SAB Dioxin Review Panel and EPA's responses to these comments, arranged by charge question, follow. In many cases, the comments have been synthesized and paraphrased in development of this appendix. In response to a Federal Register notice (75 FR 28610 [May 21, 2010]), EPA also received, comments from the public on the draft document. Each section provides EPA's charge question, followed by SAB comments and specific recommendations related to the charge question, and then EPA's responses to the recommendations. Major public comments that are relevant to specific sections, along with EPA responses to the comment, are provided at the end of each respective section. Section A.5 lists the references cited in this Appendix.

A.1. GENERAL CHARGE QUESTIONS

A.1.1. SAB Comments and Recommendations and EPA Responses

SAB Charge Question 1.1

Is the draft Response to Comments clear and logical? Has EPA objectively and clearly presented the three key NRC recommendations?

Comment: In general, the Report was clear, logical, and responsive to many but not all of National Academy of Sciences (NAS) recommendations; although there are opportunities for improvement. The Panel found that EPA was effective in developing a clear, transparent, and logical response to NAS recommendations, and that EPA has objectively and clearly presented the three key NAS recommendations. The Executive Summary was valuable in providing a concise and accurate summary. The Report was dense and repetitive in some places, and could benefit from greater clarity in writing. Although the Panel found that the Report was clear in its presentation of the key NAS recommendations, it was not complete in consideration of two critical elements: (1) nonlinear dose response for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) carcinogenicity and (2) uncertainty analysis.

> ***Response:*** EPA is moving forward to complete the draft Reanalysis and is planning to publish two reports (U.S. EPA's *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* Volumes 1 and 2 [Reanalysis Volumes 1 and 2]) that together will respond to the recommendations and comments on TCDD dose-response assessment included in the NAS 2006 review. The current report, Reanalysis Volume 1, includes the following information and corresponds to Sections 2 through 4 of the external review draft Reanalysis:
>
> 1. The study selection criteria used for the selection of studies for both noncancer and cancer TCDD dose-response analysis
> 2. The results of EPA's study selection process for both cancer and noncancer TCDD dose-response information
> 3. EPA's choice and use of a kinetic model to quantify appropriate dose metrics for both cancer and noncancer data sets
> 4. A noncancer oral RfD for TCDD, including justification of approaches used for dose-response modeling of noncancer endpoints
> 5. A qualitative discussion of uncertainties in the RfD and a quantitative sensitivity analysis of the choices made in the development of points of departure (PODs) for RfD derivation
>
> Reanalysis Volume 2 will address the SAB comments related to the nonlinear dose response for TCDD carcinogenicity and quantitative uncertainty analysis. In Volume 2, EPA will complete the evaluation of cancer mode of action, cancer

dose-response modeling, including justification of the approaches used for dose-response modeling of the cancer endpoints, and an associated quantitative uncertainty analysis. These issues correspond to Sections 5 and 6 of the external review draft Reanalysis.

In addition to editing the document for greater clarity in writing, EPA has restructured Section 2 of the Reanalysis, moving large portions of summary text to appendices to reduce density and enhance readability of the document.

Recommendation No. 1*:* Provide greater clarity and transparency in the discussion of studies that did not satisfy inclusion criteria. Given the enormity of this task, it can be done generally to indicate how the issue was considered.

Response: In Sections 2.3.1 and 2.3.2, EPA has clarified further the study considerations and inclusion criteria for both the human and animal studies, respectively. These clarifications included a statement that positive studies (i.e., studies reporting health outcomes) take precedence over null studies (i.e., studies not reporting health outcomes) for quantitative assessment. However, null studies are used by EPA when considering the biological significance of the critical endpoint(s) used as the basis for deriving an RfD and in qualitatively considering the overall database for hazard identification.

EPA also has added a new Figure 4-2 that provides an overview of the disposition of all noncancer animal studies. For the noncancer animal studies, additional details are provided in Section 2 and Appendix D; a new Table D-2 shows the excluded animal studies and identifies the study inclusion criteria that were not met. For the epidemiologic studies that were evaluated, EPA reviewed and clarified the reasons for study exclusion; details are provided in Section 2 and Appendix C (see Tables C-2 through C-57).

Recommendation No. 2*:* Carefully review the document using a qualified technical editor.

Response: EPA has had the document reviewed by a qualified technical editor.

Recommendation No. 3: Include a glossary.

Response: Section 1.5 now refers to the IRIS online glossary available at http://epa.gov/iris/help_gloss.htm noting that this glossary provides definitions of terms typically used in IRIS documents, such as the Reanalysis.

Recommendation No. 4*:* Find additional efficiencies (e.g., greater use of appendices and elimination of redundancies) to yield a more succinct and approachable document.

Response: To improve readability, EPA has eliminated redundancies among sections of the document and moved the detailed epidemiologic and animal study summaries from the main text in Section 2 to Appendices C and D, respectively.

SAB Charge Question 1.2

Are there other critical studies that would make a significant impact on the conclusions of the hazard characterization or dose-response assessment of the chronic noncancer and cancer health effects of TCDD?

***Comment**:* The Panel did not identify any other critical studies that would impact the hazard characterization or the dose-response assessment but feels that the Report should provide more clarity on the exclusion of null epidemiologic studies.

***Recommendation No. 5**:* Provide more discussion and clarity on exclusion of null epidemiologic studies.

Response: EPA has added as discussion of this issue in Section 2.3.1 with respect to epidemiologic study selection criteria.

A.2. TRANSPARENCY AND CLARITY IN THE SELECTION OF KEY DATA SETS FOR DOSE-RESPONSE ANALYSIS

In general, the Panel favorably viewed EPA's efforts in developing the section of the Report that presents how transparency and clarity was ensured (see Section 2) when selecting key data sets. The comments and recommendations provided below will help EPA further improve Section 2.

A.2.1. SAB Comments and Recommendations and EPA Responses

SAB Charge Question 2.1

Is this section responsive to the NAS concerns about transparency and clarity in data set selection for dose-response analysis?

***Comment**:* The Panel found that Section 2 was responsive to NAS concerns about transparency and clarity. The Panel commended EPA's use of flow diagrams and Appendix B to increase transparency and clarity. The Panel noted, however, that clarity could be improved by providing search words used for the MedLine searches. The Panel also noted that the Report was overly verbose, which was detrimental to its overall clarity.

Response: EPA has further employed the use of flow diagrams and tables to show the disposition of studies and study/endpoint combinations in the process used to derive the TCDD RfD (e.g., see Figures 2-4, 4-2, and Tables D-1 and D-2). EPA has added a new Appendix to the Reanalysis (see Appendix I) that lists the search terms used to conduct the literature search. EPA has improved the readability of the document by moving summary text to appendices and eliminating redundancies in the text where feasible.

***Recommendation No. 6**:* Carefully and extensively edit to revise and consolidate Section 2 and the Report as a whole. Restructure Section 2 to make it easier to follow a study from one section of the Report to another. Then, use Section 2 as the foundation to improve overall document integration.

Response: In response to these recommendations, EPA has conducted extensive editing and revisions to provide a clear, cohesive document. To improve readability, the detailed epidemiologic and animal study summaries have been moved from the main text in Section 2 to Appendices C and D, respectively). The rationale for study selection and

tabular presentation of results remain the main focus of Section 2. Further, EPA has edited or added figures and tables to document the disposition of studies throughout the study selection process (see Figure 2-4 and Tables D-1 and D-2) and for the development of candidate RfDs (see Figures 4-1, 4-2, and 4-3).

SAB Charge Question 2.2

Are the epidemiology and animal bioassay study criteria/considerations scientifically justified and clearly described?

***Comment**:* The Panel's discussion of Charge Question 2.2 is highly integrated with Charge Question 2.3. Therefore, comments and specific recommendations that stem from these two questions are presented together under Charge Question 2.3.

Response: See recommendations and responses under Question 2.3 below.

SAB Charge Question 2.3

Has EPA applied the epidemiology and animal bioassay study criteria/considerations in a scientifically sound manner? If not, please identify and provide a rationale for alternative approaches.

***Comment**:* The Panel found that study criteria and considerations were scientifically justified and clearly described, and that they were presented in a scientifically sound manner, but improvements could be made for clarity and on the rationale for decisions to include or exclude particular studies or groups of studies from the data sets. The panel also noted that the rationale for distinct criteria for epidemiological and animal studies should be made stronger, and data set selection for noncancer and cancer endpoints had room for further clarification and justification.

***Recommendation No. 7**:* Better justify the rationale (including both scientific and practical reasons) for using studies where exposure is primarily to TCDD (or for animal studies only to TCDD) to calculate the reference dose.

Response: EPA has added extensive text to Section 2.3 that discusses the rationale for focusing on TCDD studies, rather than studies on dioxin-like compounds (DLCs) or DLC mixtures. In identifying studies for quantitative TCDD dose-response analysis, EPA has focused on TCDD studies and has not included studies on DLCs or DLC mixtures. Because the TCDD database is quite robust, inclusion of the DLC literature would likely increase the uncertainty in TCDD dose response unnecessarily. In addition, using studies evaluating information primarily or exclusively on TCDD, as the index chemical, provides the most appropriate data for the risk assessment of dioxins and DLCs using the TEF approach. EPA has included additional information to clarify that background DLC exposures are evaluated in the context of the potential impact on TCDD-only quantification in certain cases as an uncertainty analysis (see new Section 4.5), particularly when TCDD exposures are relatively low.

Recommendation No. 8: Incorporate studies with dioxin-like chemicals into a qualitative discussion of the weight-of-evidence for cancer and noncancer endpoints.

Response: In the context of qualitative assessment of the critical effects, EPA has added a focused discussion of the Goodman et al. (2010) review of studies assessing DLC exposure and thyroid hormone levels in children (see response to Recommendation #34). The Goodman et al. (2010) review was evaluated with respect to elevated TSH levels in neonates, one of the co-critical endpoints forming the basis for the RfD. EPA found no DLC exposure studies that evaluated the other co-critical endpoint, decreased sperm concentrations in men exposed to TCDD as boys.

Recommendation No. 9: Further clarify the justifications for study inclusion and exclusion criteria/considerations more effectively and clearly. Specifically, remove criterion that studies must explicitly state TCDD purity because it is highly unlikely that a study would be conducted using impure TCDD.

Response: EPA has removed the criterion for stating TCDD purity from the animal study selection criteria.

Recommendation No. 10: Revise the explanation of the in vivo mammalian bioassay evaluation, indicating that the "study design is consistent with standard toxicological practices" because it is too vague. If possible, provide a reference in which these practices are described.

Response: EPA has revised the explanation of this criterion to be clear that it excludes only those studies that use genetically-altered species.

Recommendation No. 11: Consider eliminating the use of the phrase "outside the range of normal variability."

Response: EPA has removed this phrase from the criteria.

Recommendation No. 12: Provide a definition when the term "common practice" is used, and if possible, cite appropriate Agency documents.

Response: EPA has removed the phrase "common practice" from the Reanalysis report and referenced the relevant Agency guidance documents where appropriate. In addition, the Agency guidance used has been highlighted in a text box in Section 2.

Recommendation No. 13: Provide more discussion of data set limitations relevant to study inclusion/exclusion criteria.

Response: The epidemiology study summaries (Appendix C) have been edited with respect to study evaluation, meeting the study inclusion criteria and considerations, and suitability for dose-response modeling; Tables C-2 and C-3 summarize the cancer and noncancer studies, respectively, identifying which criteria and considerations were met.

Recommendation No. 14: Better justify and explain considerations relating to selection of epidemiology studies.

Response: The descriptions for study quality considerations and study inclusion criteria have been edited for clarity. Details of the implementation of these specific considerations and criteria in the study summaries and tables presented in Appendix C have also been edited.

Recommendation No. 15: Specifically, for Consideration #2 on Page 2-6 of the report, the Panel recommends the following revisions: Define and clarify the term "susceptible to important biases." It is nonspecific, and the biases should be explained.

Response: EPA has added clarifying language to Consideration #2 in Section 2 of the Reanalysis. The examination of biases included assessing the likelihood of selection bias, information bias, and confounding for the individual studies. EPA has also included text in the individual study summaries in Appendix C to specify possible sources of bias, and to determine the potential impact of these biases on individual study results.

Recommendation No. 16: Clarify what is meant by "control for potential confounding exposures." Does this refer to only dioxin-like exposures?

Response: EPA has added clarifying language to Consideration #2 to address this comment, which now reads "control for or account for confounding factors." EPA has also provided explanations of specific confounding factors that were identified in the individual study summaries and tables in Appendix C. Assessment of the potential for confounding, therefore, was not limited to dioxin-like chemicals and is specified for each study summary and summary tables as appropriate.

Recommendation No. 17: Clarify the phrase "bias arising from study design." Does it refer to selection bias, or is it used more broadly to describe how exposure and outcome are measured and covariate data collected?

Response: EPA has clarified Consideration #2 to address this comment; the current phrase "bias arising from limitations of study design" was referring to selection bias. EPA has also listed the main potential sources of bias (e.g., selection bias, information bias, and confounding) earlier in Consideration #2 to help clarify this.

Recommendation No. 18: Define "bias arising from statistical analyses." Might this refer to model misspecification?

Response: EPA has added clarifying language to Consideration #2 to address this comment; the phrase "bias arising from statistical analyses" has been reworded to read "bias (e.g., selection or information bias) arising from limitations of the study design, data collection, or statistical analysis." This would include model misspecification, such as adjustment for the incorrect functional form of certain confounders in multivariate regression modeling.

Recommendation No. 19: For Consideration #3 on Page 2-7 of the report, the Panel recommends the following revisions: Provide more discussion and clarity on the exclusion of null epidemiologic studies.

Response: EPA has added clarifying text under Consideration #3 to address this issue. This consideration addresses the use of null studies (i.e., studies reporting no association between TCDD and the health endpoint of interest) for the quantitative dose-response assessment used to derive an RfD; such studies are still used in qualitative assessments. Theoretically, a no-observed-adverse-effect level (NOAEL) can be identified from a null study and used to derive an RfD; that is, the highest available exposure dose from such a study could provide a NOAEL, which could serve as a basis for an RfD after appropriate uncertainty factors were applied. However, a NOAEL from a study in which no adverse effects have been observed is not usually chosen for RfD derivation when other available studies demonstrate lowest-observed-adverse-effect levels (LOAELs). The large and comprehensive database available to assess quantitative TCDD dose response provides many positive studies that are considered stronger candidates for derivation of an RfD than the studies for which only a NOAEL can be identified. However, null studies are used by EPA to discuss the biological significance of the critical endpoint(s) used as the basis for deriving an RfD.

Recommendation No. 20: In Exclusion Criterion #3 on Page 2-7, define "reported dose."

Response: EPA has deleted the sentence under Criterion #3 that contained this phrase as it did not enhance understanding of the criterion.

Recommendation No. 21: Clarify the discussion in Section 2 of the consideration of confounding and other potential sources of bias. Specifically, the Panel noted that the differences between males and females with regard to TCDD half-life are discussed, but the description of the number of males and females in each study population were often missing or very difficult to determine. Also, in the occupational cohort studies, the possibility of men and women performing different job tasks also increased the possibility that the men and women were exposed at different levels. However, when the job categories with assigned TCDD exposure levels were presented, there was often no discussion of the numbers by gender in the categories. For example, the Manz et al. study (1991) of the Hamburg cohort (1,583 men and 399 women) does not describe the TCDD categories by gender. In addition, the validity of the TCDD exposure levels assigned to the categories was examined "in a group of 48 workers who provided adipose tissue samples" (page 2-41, lines 18−19). How were these workers selected? How many were approached but refused to provide a sample? Assessment of selection bias in this and other similar circumstances was lacking in some of the studies. This is particularly notable in the lack of overall response rates reported for several of these studies. Inclusion of these factors in the study review would be very helpful.

Response: EPA has revised the summaries of the epidemiological studies in Appendix C to include clarifying text, response rates, and potential sources of bias where reported in the studies.

Recommendation No. 22: Clarify the discussion of the consideration that "statistical precision, power, and study follow-up are sufficient." These metrics can be difficult to determine with the smaller sample size populations, but there are studies that can be very useful even given the small samples.

Response: EPA has revised Consideration #5 and added clarifying text to address this issue. As stated in the consideration, EPA attempted to assess the possibility of not detecting an association that might be present due to limited statistical power of smaller studies. In addition, EPA examined all reported effect estimates in each study irrespective of statistical significance.

A.2.2. Summary of Public Comments and EPA Responses

Comment: Three commenters were concerned that the study inclusion criteria favored studies showing positive associations between TCDD and health endpoints and that this would preclude a weight-of-evidence analysis. The commenters were further concerned that the study inclusion criteria in the draft Reanalysis were inconsistent with EPA's Information Quality Guidelines (2002), Assessment Factors Handbook (2003), Risk Assessment Principles and Practices documentation (2004), and the recommendations of the NAS committee that reviewed the 2003 Reassessment (NAS, 2006).

Response: The study inclusion criteria apply only to the selection of data sets for dose-response modeling for the purpose of defining potential PODs and not to the elimination of studies from any further consideration. The focus of this process is on first identifying exposure levels associated with adverse effects, then determining an exposure level at which those effects do not occur. The process does not eliminate "negative" studies for other purposes, such as supporting the cancer weight-of-evidence determination or assessing confidence in the endpoint(s) chosen for the POD for derivation of the RfD. EPA considered all studies, negative and positive, in the qualitative assessment of the RfD in Section 4 of the Reanalysis. The study inclusion criteria are consistent with EPA RfD and cancer assessment guidelines. The study selection process in this context is also consistent with the NAS committee recommendation that EPA justify the selection of studies for dose-response modeling.

Comment: One commenter asked EPA to consider recent publications addressing dioxin toxicology in their selection of an overall data set. They provided the following list of seven publications:

Budinsky, R.A., J.C. Rowlands, S. Casteel et al. (2008). A pilot study of oral bioavailability of dioxins and furans from contaminated soils: Impact of differential hepatic enzyme activity and species differences. Chemosphere 70:1774–86.

Budinsky, R.A., C.R. Kirman, L.J. Yost, B.F. Baker, L.L. Aylward, J.M. Zabik, J.C. Rowlands, T.F. Long, and T. Simon. (2009). Derivation of Soil Cleanup Levels for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Toxic Equivalence (TEQD/F) in Soil Through Deterministic and Probabilistic Risk Assessment of Exposure and Toxicity. Presentation at Society of Toxicology Annual Meeting. March.

Charnley, G. and R.D. Kimbrough. (2006). Overview of exposure, toxicity and risks to children from current levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds in the USA. 2005. Food and Chemical Toxicology 44:601–615.

Garabrant D.H., A. Franzblau, J. Lepkowski, B.W. Gillespie, P. Adriaens, A. Demond, E. Hedgeman, K. Knutson, L. Zwica, K. Olson, T. Towey, Q. Chen, B. Hong, C-W. Chang, S-Y. Lee, B. Ward, K. LaDronka, W. Luksemburg, and M. Maier. (2009). The University of Michigan Dioxin Exposure Study: Predictors of human serum dioxin concentrations in Midland and Saginaw, Michigan.

Hays, S.M. and L.L. Aylward. (2003). Dioxin risks in perspective: past, present, and future. Regulatory Toxicology and Pharmacology 37:202–217.

Kimbrough R.D., C.A. Krouskas, M. Leigh Carson, T.F. Long, C. Bevan, and R.G. Tardiff. (2009). Human uptake of persistent chemicals from contaminated soil: PCDD/Fs and PCBs. Regulatory Toxicology and Pharmacology 2009 Dec 24; [Epub ahead of print], Center for Health Risk Evaluation P.O. Box 15452 Washington, DC 20003, United States.

LaKind, J.S., S.M. Hays, L.L. Aylward, and D.Q. Naiman. (2009). Perspective on serum dioxin levels in the United States: an evaluation of the NHANES data. Journal of Exposure Science and Environmental Epidemiology 19:435-441.

Response: EPA has reviewed these studies and considered their applicability in informing the hazard identification dose response following TCDD exposure. None of these studies provide in vivo mammalian dose-response study results that would be useful in quantitative dose-response analysis for derivation of an RfD or oral slope factor for TCDD, nor do they inform the hazard identification. Therefore, none of these studies qualifies as an appropriate study type in EPA's study selection process for quantitative TCDD dose-response assessment.

Comment: One commenter felt that the development of the proposed RfD was not transparent because it did not rely on toxicological assessment work completed since the 2003 Reassessment. Additionally, the commenter requested additional clarity and transparency in the rationale for the Agency's selection of key data and more explanation of why EPA did not pursue benchmark dose modeling for the two human data sets used to derive the RfD.

Response: EPA collected and evaluated studies through October 2009, including studies from the 2003 Reassessment and newer studies found via literature searches and through public submissions. EPA notes that the RfD is based on two studies published in 2008. In addition, EPA has included evaluations of several relevant studies published in 2010 and 2011; EPA identified these studies as it continues to monitor the dioxin health effects literature.

Regarding the comment requesting additional transparency in the study selection process, EPA has provided additional clarity on the study inclusion criteria with revisions to the Reanalysis based on SAB and public comments.

EPA relied on the study authors' modeling of the epidemiologic study data, which included the important covariates affecting the relationship between health outcome and TCDD exposure. The current version of EPA's benchmark dose modeling software does not allow for modeling of covariates reported in epidemiologic studies.

A.3. THE USE OF TOXICOKINETICS IN DOSE-RESPONSE MODELING FOR CANCER AND NONCANCER ENDPOINTS

A.3.1. SAB Comments and EPA Responses

SAB Charge Question 3.1

The 2003 Reassessment utilized first-order body burden as the dose metric. In the draft Response to Comments document, EPA used a physiologically based pharmacokinetic (PBPK) model (Emond et al., 2006; 2005; 2004) with whole blood concentration as the dose metric rather than first-order body burden. This PBPK model was chosen, in part, because it includes a biological description of the dose-dependent elimination rate of TCDD. EPA made specific modifications to the published model based on more recent data. Although lipid-adjusted serum concentrations (LASC) for TCDD are commonly used as a dose metric in the literature, EPA chose whole blood TCDD concentrations as the relevant dose metric because serum and serum lipid are not true compartments in the Emond PBPK models (LASC is a side calculation proportional to blood concentration). Reviewers were asked to comment on Questions 3.1.a–d.

SAB Charge Question 3.1.a

The justification of applying a PBPK model with whole blood TCDD concentration as a surrogate for tissue TCDD exposure in lieu of using first-order body burden for the dose-response assessment of TCDD.

Comment: The use of whole blood concentration is a better choice than body burden, as was used in the 2003 Reassessment, because it is more closely related to the biologically relevant dose metric. However, the rationale for the use of blood concentration rather than lipid adjusted serum concentration (LASC) should not be based on the Emond model structure. The question that should be addressed is only whether blood concentrations or LASCs provide better surrogates for cross-species and cross-study comparisons of free dioxin concentration in the target tissues. LASC is the preferred measure for reporting dioxin biomonitoring data and is the measurement reported in most of the human epidemiological studies. A metric that considers blood lipid content is also more likely to reflect free dioxin concentration in the plasma and, hence, free concentration in the target tissue. The EPA pointed out that the LASC was related to the blood concentration by a scalar; however, EPA incorrectly concluded that the metrics are equivalent and later discussed the fact that the relationship between them was subject to inter-individual and inter-species variation. If the LASC were used to drive the distribution of TCDD to tissues, the pharmacokinetic outcome would be different from using blood as the driver because the tissue:blood ratio would differ. If the blood fat:blood and tissue:blood values were accounted for in the model, the use of blood and LASC would be similar. It is not clear at this point how this issue was addressed in the dose metric calculations. Consideration of this issue is unlikely to drastically affect the outcome of the risk calculations, but it would be important for a quantitative uncertainty analysis.

> ***Recommendation No. 23:*** The use of the blood metric is acceptable for the PBPK model. Clarify how the model deals with studies that report the concentration of dioxin in plasma, serum, blood, or blood fat:blood measurements.

Response: The issue of whether LASC or whole-blood concentration is the more relevant metric (for interspecies extrapolation) hinges on how the Emond rat PBPK model was calibrated. The rat model was calibrated to whole tissue concentrations (liver, fat, whole blood) and not LASC or other tissue lipid concentrations. Relative whole-tissue concentrations reflect the relative tissue fat content, so the difference in LASC:whole-blood ratios between rats and humans is handled implicitly in the model. The rat model intake predictions are a function of whole-blood concentrations rather than LASC. The human model is structured the same way. Therefore, human whole-blood concentrations should be equated with rat whole-blood concentrations for obtaining the equivalent human intakes. EPA has clarified that the TCDD LASC values reported in the epidemiology studies were used directly to estimate equivalent human intakes from the Emond PBPK model.

EPA also clarified that, for interspecies extrapolation, whole-blood concentrations were used because distribution of TCDD to the liver and subsequent processing for dose-dependent elimination in the liver in this model is dependent on whole-blood concentrations, not LASC. In both the Emond rodent and human models, LASC values are calculated post-processing by application of scalars representing the proportion of plasma and fat in the whole-blood compartment. That is, translating results from the rodent model to the human model requires an estimate of the TCDD concentration in the whole-blood compartment whether starting from whole-blood concentrations or LASC. This approach assumes that differences in serum and serum lipid fractions between rodents and humans do not result in large differences among the species in the transfer of TCDD from blood to liver.

SAB Charge Question 3.1.b

The scientific justification for using the Emond et al. model as opposed to other available TCDD kinetic models.

Comment*:* The Emond model provided the best available basis for the dose metric calculations in the assessment; however, additional discussion of other published models and quantitative evaluation of the impact of model selection on dose metric predictions should also be provided.

> ***Recommendation No. 24:*** Discuss how the model was intended to be used in the assessment, which would then dictate why a particular model was selected. That is, for the intended purposes, was the Emond model more robust and/or simpler than other models, and did it contain sufficient details for biological determinants deemed important by the Agency?
>
> > ***Response:*** EPA has clarified that the Emond PBPK model was used to (1) estimate oral intakes corresponding to measured LASC TCDD concentrations in human subjects and (2) estimate animal blood concentrations based on measured doses in bioassays as the appropriate dose metric for modeling equivalent human intakes. EPA has also clarified that the Emond model was selected because of its technical sophistication for simulating physiological processes associated with TCDD and because the model covered all of the relevant life stages (particularly gestational and childhood exposures), which the alternative model (CADM) did not. Other models were not presented because they did not account for dose-dependent elimination processes, which EPA established as an *a priori* criterion for PBPK model selection, based on the current scientific understanding of TCDD kinetics.

SAB Charge Question 3.1.c

The modifications implemented by EPA to the published Emond et al. model.

Comment: The model changes are minor, scientifically appropriate, and well supported.

Response: No response necessary.

SAB Charge Question 3.1.d

Whether EPA adequately characterized the uncertainty in the kinetic models.

Comment: The Report presents a reasonably thorough qualitative characterization of the uncertainty in the kinetic models that is sufficient to support their use in the assessment; however, a more quantitative uncertainty analysis is needed. It is critical to demonstrate the dependence of human equivalent dose (HED) and risk predictions on uncertainty and variability in the model parameters. Dose metric uncertainty needs to be determined under the same exposure conditions that dose metrics are calculated—both for the various studies that serve as the basis for the dose-response assessments and for human exposures at the corresponding HEDs and risk-specific doses.

The Hill coefficients for CYP1a1 and CYP1a2 induction used in the Emond model were 1.0 and 0.6, respectively, based on fitting of kinetic data from single doses of dioxin (Santostefano et al., 1998; Wang et al., 1997). However, Walker et al. (1999) subsequently estimated a Hill coefficient of 0.94 for both CYP1a1 and CYP1a2 induction using chronic exposures, which were more relevant to the use of the Emond model in the dioxin risk assessment. The value of 0.6 used in the Emond model was well outside the confidence interval of 0.78 to 1.14 reported by Walker et al. (1999). The use of a Hill coefficient value well below unity would lead to a nonlinear model behavior that is biologically implausible (hypersensitivity to induction at doses near zero). As a result, when the human model was used for extrapolation to lower doses (as in the calculation of risk-specific doses), the model would tend to estimate a lower exposure level for a given blood concentration. This effect could be seen in Table ES-1 of the Report, where a 5 order-of-magnitude change in risk was associated with a 6 order-of-magnitude change in risk-specific dose. That is, the model-estimated risk-specific doses in the vicinity of 10^{-6} risk were about a factor of 10 lower (more conservative) than linear extrapolation. The evidence for this parameter needs to be carefully reviewed and the reasonable range of values determined. At the least, the Emond human model calculations will need to be repeated with multiple values to characterize the resulting uncertainty in the estimates.

When this is done, the Agency should also consider increasing the fat:blood partition in the human model from 100 to 200 to be more consistent with the human data (Maruyama et al., 2002; Iida et al., 1999; Patterson et al., 1989; Schecter and Ryan, 1989; Schecter et al., 1989). The Hill coefficient is not likely to have as significant an effect on calculations with the animal models, because low-dose extrapolation was not performed in the animals, but this should also be verified by sensitivity/uncertainty analysis of the animal models. Public comments were submitted to the Panel, recommending consideration of a Hill coefficient value of 1.0 and pointing out why lower values are inappropriate (comments from Drs. Thomas Starr, July 7, 2010 and October 26, 2010 and Melvin E. Andersen, November 4, 2010).

Recommendation No. 25: Undertake additional efforts to fully characterize the uncertainty in the model, with special consideration of the Hill coefficient value.

Response: In response to this comment, EPA has conducted a sensitivity analysis by varying each parameter in the PBPK models individually to determine the effect on the average whole-blood concentrations (as the dose metric used for species extrapolations and reference dose calculations). In addition, the effect of varying the Hill parameter on the model fits to literature data was explored. In response to this comment, two sections were added to Section 3. Section 3.3.4.3.2.5 describes the results of the sensitivity analysis preformed on the PBPK models as suggested by the SAB reviewers, and Section 3.3.4.3.2.6 documents the impact of changing the Hill coefficient on PBPK model simulations of dioxin blood levels in humans. Included in this section is a sensitivity analysis using alternative CYP1A2 induction parameters determined from data presented in Budinsky et al. (2010). The Walker et al. (1999) CYP1A1 and CYP1A2 induction analysis, in which a value of 0.94 was found for the Hill coefficient, uses a different model structure formulation than the one in the Emond model, in which the parameters have different interpretations, such that the Hill coefficient values represent different processes and are not strictly comparable.

Further, in an additional sensitivity analysis reported in Section 4.5.1.1.1, EPA also evaluated the impact on the RfD of changing the Hill coefficient to a value of 1, noting that the Hill coefficient was the most influential variable in the Emond PBPK model (see Section 3.3.4.3.2.5) and that the value of 0.6 results in a supralinear relationship between intake and blood concentrations at very low doses. The value of 1 was chosen for the sensitivity analysis of the Hill coefficient because that is the lowest value where the model is no longer supralinear; otherwise the value of 1 has no biological or empirical basis. When the Hill coefficient is set to a value of 1, and applying an uncertainty of 30 (see Section 4.3.5), the resulting candidate RfD would be 2×10^{-4} ng/kg-day (2×10^{-11} mg/kg-day).

EPA's sensitivity analysis for the Emond PBPK model parameters also addresses the fat:blood partition coefficient (PC_{FB}) issue (i.e., SAB's suggestion to increase the value to 200). To clarify the nature of the parameter, the PC_{FB} of 100 in the Emond model is a fitted value in the original rat model (Wang et al., 1997), in which other parameters (including the value of 0.6 for the Hill coefficient, the most influential parameter in the model) were also fitted simultaneously against animal and human data. EPA has evaluated the literature cited by the SAB and has concluded that a PC_{FB} of 160 is more representative of the data presented in those papers. A value of 158 is estimated by Patterson et al. (1988) based on 50 individuals from Times Beach, MO. Iida et al. (1999) measured levels of 2,3,7,8-TCDD in blood and adipose tissue from eight human subjects, who varied in age (19 to 82 years) and gender (four females and four males). Using the individual measurements presented in Iida et al. (1999) and assuming relative lipid contents of 0.85 and 0.0057 in adipose tissue and blood, respectively, EPA estimated a mean and median PC_{FB} of 166 and 161, respectively. A value of 247 reported by Maruyama et al. (2002) was based on the data from Iida et al. (1999), however, EPA was unable to reproduce the value of 247 reported by these authors. Schecter and Ryan (1989) present data on a single individual who was also exposed to high levels of DLCs and PCBs in an acute event (transformer explosion). Several serum and fat measurements were taken over the next 5 years, during which time the

patient lost 30 pounds and took medication to reduce serum lipids. The combination of all of these factors suggest that the internal concentrations may not have equilibrated in this time frame and introduces too much uncertainty for use of these data in estimating a PC_{FB} for TCDD. Schecter et al. (1989) report fat TCDD concentrations but not blood or serum concentrations. In the sensitivity analysis that EPA conducted on the Emond PBPK model, the elasticity of a 50% increase in the fat:blood partition coefficient at exposures equal to the RfD POD (0.02 ng/kg-day) was -0.064 (see Table 2-12), which means that increasing the parameter value from 100 to 150 would result in a 6.4% decrease in the TCDD blood concentration at this exposure level; a further increase to 160 would result in about a 7% decrease. EPA estimates that, using the 160 value for the fat:blood partition coefficient, the LOAEL corresponding to the Baccarelli et al. (2008) scenario would increase by 10% to 0.022 ng/kg-day, with no change in the RfD. The LOAEL corresponding to the Mocarelli et al. (2008) scenario would increase by 40% to 0.028 ng/kg-day.

SAB Charge Question 3.2

Several of the critical studies for both noncancer and cancer dose-response assessment were conducted in mice. A mouse PBPK model was developed from an existing rat model in order to estimate TCDD concentrations in mouse tissues, including whole blood. Reviewers were asked to comment on Questions A.3.2.a–c.

SAB Charge Question 3.2.a

The scientific rationale for the development of EPA's mouse model based on the published rat model (Emond et al., 2006; 2005; 2004).

***Comment**:* The Panel agrees that an appropriate approach was used to develop the mouse model on the basis of the published rat model and the available mouse kinetic data. It should be noted that the NAS recommendation to use human data for dose metric could be accomplished because dose-dependent elimination of TCDD has been described in humans, albeit in just a few cases. Dose-dependent elimination has been reported repeatedly in animals, and the PBPK model reflected this dose-dependence. Using CYP1A2 data from humans (caffeine metabolism) and mice would offer an opportunity to validate and/or adjust the mouse model.

Recommendation No. 26: Conduct an external peer review of the mouse model because it has not been published in the peer-reviewed literature.

Response: EPA has recommended that the authors submit their work for publication in the peer-reviewed literature. Although EPA used revised estimates for some of the published parameters, no modifications were made to the structure of the Emond model. Using these revised parameters, EPA has described the evaluation of the PBPK model in Section 3. An important point is that the mouse data were not used directly in estimation of reference values.

SAB Charge Question 3.2.b

The performance of the mouse model in reference to the available data.

***Comment**:* The Panel found that the mouse model performed reasonably well, apart from under-prediction of urinary excretion data. The urinary excretion data can be improved by taking into account the fact that urine contains metabolites only, which partition differently from the parent compound. The model appeared to be adequate for use in estimating dose metrics for the assessment, but with greater uncertainty than the rat and human models. This was considered a reasonable approach to solve a deficiency in published PBPK models to meet the needs of this assessment.

The Panel noted, however, that the EPA's suggestion in the RfD chapter that the clustering of mouse points of departure (PODs) at the lowest doses was due to mouse model failure, was inappropriate, and should be rewritten.

> ***Recommendation No. 27:*** Use the mouse model and try to get the model published in the peer-reviewed literature to enhance scientific credibility.
>
> > ***Response:*** EPA has revised the text describing the mouse PODs to eliminate the impression that the result was due to failure of the mouse PBPK model, which was not intended. See the response above (Recommendation 26) regarding the comment on the publication of the mouse model.

SAB Charge Question 3.2.c

Whether EPA adequately characterized the uncertainty in the mouse and rat kinetic models. Please comment specifically on the scientific justification of the kinetic extrapolation factor from rodents to humans.

***Comment**:* EPA provided an adequate characterization of the qualitative uncertainty in the mouse and rat kinetic models sufficient to justify their use, together with the human model, to estimate rodent-to-human extrapolation factors. On the other hand, formal recalibration of the PBPK model parameters using a Hierarchical Bayesian approach such as Markov chain Monte Carlo analysis was not considered necessary or particularly useful. However, a more quantitative uncertainty analysis is needed.

> ***Recommendation No. 28:*** Perform a more quantitative uncertainty analysis using methods suggested in response to Charge Question 6.2.[1]
>
> > ***Response:*** In response to this recommendation and other comments, EPA has conducted a sensitivity analysis and added it to Section 3 (see Sections 3.3.4.3.2.5 and 3.3.4.3.2.6; also see response to Recommendation 25). EPA has undertaken additional quantitative sensitivity analyses for the kinetic modeling and some exposure assumptions relevant to the development of the RfD (see Section 4.5; see also responses to Recommendations 29 and 32).

[1] SAB comments on Sections 5 and 6 are not addressed in Volume 1 of the Reanalysis, but can be viewed at the following URL: http://yosemite.epa.gov/sab/sabproduct.nsf/WebReportsLastMonthBOARD/2A45B492EBAA8553852578F9003ECBC5/$File/EPA-SAB-11-014-unsigned.pdf.

SAB Charge Question 3.3

Please comment on the use of the Emond et al. PBPK model to estimate human intakes based on internal exposure measures.

***Comment**:* The modified Emond model is the best available approach for estimating exposures on the basis of internal exposure measurements. Nevertheless, there is considerable uncertainty associated with attempting to reconstruct prior exposures in a human population (e.g., Seveso).

> ***Recommendation No. 29:*** Describe the modeling of the Cheng et al. (2006), Mocarelli et al. (2008), and Baccarelli et al. (2008) studies in more detail, and quantitatively evaluate the impact of model parameter uncertainty and exposure uncertainty in these studies.
>
> > ***Response:*** EPA has revised the document to describe the modeling of Mocarelli et al. (2008) and Baccarelli et al. (2008) in more detail. Sensitivity analyses pertaining to the choice of model inputs have been performed for Mocarelli et al. (2008) and Baccarelli et al. (2008) and are described in Section 4.5 of the document. Cheng et al. (2006) is a cancer-modeling study and will be addressed in Volume 2 of this report.

SAB Charge Question 3.4

Please comment on the sensitivity analysis of the kinetic modeling (see Section 3.3.5).

***Comment**:* The Report only presented the sensitivity analysis published by Emond et al. (2006), which was not entirely adequate for the purposes of this assessment. The analysis left out the Hill coefficient, which was one of the most important parameters in the model for low-dose extrapolation (Evans and Andersen, 2000). Moreover, model sensitivities were species, dose, and dose-scenario dependent, so they need to be determined under the same exposure conditions as those for which dose metrics were calculated: both for the various studies that serve as the basis for the dose-response assessments and for human exposures at the corresponding HEDs and risk-specific doses. This represents the most pragmatic path forward for an evaluation of model sensitivity as it relates to potential environmental regulation.

> ***Recommendation No. 30:*** Provide a sensitivity analysis of the model to authenticate the model for its intended purpose.
>
> > ***Response:*** EPA has conducted a sensitivity analysis (see response to Recommendations 25 and 28).

SAB Charge Question 3.5

Both EPA's noncancer and cancer dose-response assessments are based on a lifetime average daily dose. Did EPA appropriately estimate lifetime average daily dose? If not, please suggest alternative approaches that could be readily developed based on existing data.

***Comment**:* The Panel agrees with the average daily dose calculation approaches, but it was not clear to some Panel members how the computational estimates of internal dose for newborns were carried out because a lactation model was not used. This is important because of the use of TSH (thyroid stimulating hormone) in newborns as a critical effect.

Recommendation No. 31: Explain how the early life-stage internal doses are calculated.

> ***Response:*** Internal TCDD doses for newborns were not estimated in the Reanalysis. The increased TSH levels at 72 hours after birth are modeled as a function of maternal exposure, with the assumption that the actual critical exposures occurred in utero and were not due to breast feeding. EPA has clarified that the Emond PBPK model accounts for physiological changes including body weight and tissue volumes over different life stages, including during gestation. The only life stage that is not accounted for in the Emond model is infants exposed to TCDD through breast milk. The details of how the model estimates tissue and blood levels of TCDD during the other life stages following TCDD exposures are described in Section 3 and by Emond et al. (2006; 2005; 2004).

A.3.2. Summary of Public Comments and EPA Responses

Comment: One commenter noted that CADM (i.e., Concentration- and Age-Dependent Elimination Model) should be given more consideration as a credible alternative to the Emond et al. model. When CADM and the Emond et al. model have been evaluated on the same human data sets, CADM appears to provide substantially better results, and the Emond et al. model appears to markedly overpredict the early serum concentration levels. Another commenter noted that CADM allows estimation of the relevant risk-specific doses using the PBPK model but is applied in the exposure range relevant to real-world exposures, reproduces the elimination behavior of TCDD relevant to risk assessment and risk management, and takes into account background body burdens of TCDD and non-TCDD contributors to TEQ and their impact on TCDD elimination behavior.

> ***Response:*** EPA used the Emond model for human toxicokinetics because the model covered all of the relevant life stages (particularly gestational and childhood exposures), which CADM does not, and also because of its technical sophistication for simulating physiological processes associated with TCDD toxicokinetics. The Emond model also is able to account for background TCDD and DLC body burdens and their impact on TCDD elimination behavior; pertinent simulations and discussions on these aspects have been added in the new Section 4.5.
>
> For animal bioassays, EPA undertook, and reported in the document, modeling analyses that compared the predicted values from both the Emond PBPK model and CADM for all administered doses. Throughout the document, separate simulations for both the PBPK model and CADM were conducted for comparison to experimental or literature data for animals. In Section 3, EPA presents extensive comparisons of the Emond model and CADM. In Appendix E, EPA also presents whole blood, fat, and liver TCDD concentrations and body burdens that were predicted by both the Emond model and CADM for each key animal bioassay.

Comment: One commenter noted that the Hill function dependence of CYP1A2 induction on AhR-bound TCDD has a nonphysical, nonsensically infinite slope at zero dose, due to the fact that its exponent parameter has a numerical value smaller than 1, namely 0.6. This phenomenon has no predictive value at low doses. According to the commenter, the values that are predicted at low doses are simply artifactually constrained by the supralinear shape of the Hill function, which is imposed by the data at far higher doses. Because no data occur in the low-dose region that is well below the EC50, no counterbalancing force exists that would keep the Hill exponent

value at or greater than 1. This leads to artifactual and arbitrarily large increases in the oral slope as the TCDD intake approaches zero.

> ***Response:*** EPA has conducted a sensitivity analysis for the Hill coefficient (see response to Recommendation 25) and has evaluated the impact of eliminating the supralinear behavior on relative human intakes. Changing the Hill coefficient to 1, which results in linear low-dose behavior, and optimizing to a limited number of human data sets results in somewhat lower oral intake rate estimates associated with the TCDD serum concentrations in the range of interest (i.e., near the RfD and LOAEL POD). This result is well within the range of other uncertainties evaluated by EPA (see Section 4.5). EPA has concluded that, given the uncertainties in the value of this parameter and interdependent parameters in the model, and the lack of a substantial impact on predicted intakes in the range of the POD for the RfD, there is no mechanistic or empirical basis on which to change the value of the Hill coefficient or related parameters. In response to this comment, two sections were added to Section 3. Section 3.3.4.3.2.5 describes the results of the sensitivity analysis performed on the PBPK models as suggested by this reviewer and the SAB reviewers, and Section 3.3.4.3.2.6 illustrates the impact of changing the Hill coefficient on PBPK model simulations of dioxin blood levels using available human data.

Comment: Two commenters noted that EPA incorrectly assumed a partition factor of 100 for TCDD in human fat compared to blood. The commenters state that available human data demonstrate that the actual partition factor is between 150 and 200 (Iida et al., 1999; Patterson et al., 1989).

> ***Response:*** While EPA has not changed the value in the model, a sensitivity analysis was conducted that indicated this is not a sensitive parameter in the model (see response to Recommendation 25).

Comment: Some commenters felt that use of modeled concentrations is not acceptable for deriving toxicity values when measured data are available. The commenters noted that EPA's use of modeled whole-blood concentration results in underestimation of PODs, HEDs at the BMDLs, and calculated reference dose.

> ***Response:*** EPA modeled the blood concentrations for the rat exposures in NTP (2006), when actual liver and fat TCDD concentrations were reported in the study. This was done primarily for consistency across all rat bioassays. The whole liver concentrations are not likely to be relevant because they include TCDD bound to CYP1A2, which is not part of the biologically-active TCDD fraction. However, in response to this comment, EPA has added a sensitivity analysis (See Section 4.5.1.2.) that evaluates the effect of using the measured fat TCDD concentrations on modeled human intakes based on (NTP, 2006).

Comment: Several commenters noted that the Emond et al. (2005) PBPK model did not account for the enhanced elimination rate of TCDD observed in infants and children, which would substantially underestimate the daily dose rates associated with identified target body burdens, and, thus, underestimate the derived RfD estimated in modeling for the Mocarelli et al. (2008)

data set. Commenters provided references of Clewell et al. (2004), Ott et al. (1987), Hochstein et al. (2001), Kerger et al. (2006), Leung et al. (2006), and Milbrath et al. (2009) and suggested that EPA address the role of differential elimination rates in children in their quantitative analysis of a reference dose.

> ***Response:*** The changes in elimination rate with age reported in Kerger et al. (2006) are thought to reflect growth processes as a child ages. The Emond PBPK model accounts for this phenomenon implicitly by modeling growth and age-related changes in fat content and physiology explicitly. Including an explicit variable-elimination term in the model would then "double count" for this effect. The TCDD half-life calculations in Kerger et al. (2006) are based on blood level rather than whole-body measurements. Blood levels of the chemical are influenced by the dynamic processes of storage in fat deposits and elimination rates (including binding to proteins in the liver). The inclusion of these physiological process and the dynamic interplay among them provide the biological basis for an observed increase in elimination rate in children. At early life stages, less fat volume in the body results in more TCDD available for deposit in liver. More TCDD in the liver results in a higher elimination rate. Leung et al. (2006) indicated that the more rapid clearance in children was due to their lower fat content, which is accounted for in the model.

Comment: A commenter noted that non-TCDD TEQ contributes to the induction of CYP1A2, which will influence the elimination rate for TCDD. Given the current background body concentrations of TCDD and other TEQ contributors, the commenter felt that the appropriate application of the PBPK model would be to start from current background concentrations (including some accounting for non-TCDD TEQ).

> ***Response:*** Induced levels of CYP1A2 due to dioxin are calculated using a Hill function. The relative difference between induced levels of CYP1A2 and basal levels of the enzyme are then used to describe the dose–dependent elimination rate for TCDD in the liver. Application of the PBPK model to estimate the elimination of TCDD is based on an assumption that background effects of dioxin-like chemicals and any others that may influence CYP1A2 levels in the liver are implicitly included in the basal-level estimates. EPA also added a simulation of total TEQ background exposure as a sensitivity analysis in Section 4.5 to investigate this phenomenon. Issues pertaining tomodeling non-TCDD TEQ are discussed in Section 4.5 and, also in this Section, EPA has presented several alternative approaches for incorporating background DLC exposure into the derivation of the RfD. In the sensitivity analysis, EPA estimates that average total-TEQ PODs based on background non-TCDD TEQ exposures could range from no change to the POD to 2.5-fold higher than the TCDD-only POD of 0.02 ng/kg-day used in the derivation of the RfD.

Comment: Several commenters noted deficiencies and limitations with the PBPK model, and some stated that EPA failed to adhere to its own guidance on selection and application of PBPK models (i.e., U.S. EPA (2006a), *Guidelines on PBPK Model Selection in Risk Assessments* report). Specifically, the PBPK model was not peer reviewed and was not validated. Two commenters noted a need for an uncertainty analysis of key parameters in the model, such as the Hill coefficient.

Response: Although EPA used revised estimates for some of the published parameters, no modifications were made to the structure of the Emond model. Using these revised parameters, EPA describes the evaluation of the PBPK model in Section 3. Also, see the response to Recommendation 25 concerning the sensitivity analysis.

A.4. REFERENCE DOSE

A.4.1. SAB Comments and EPA Responses

SAB Charge Question 4.1

The Mocarelli et al. (2008) and Baccarelli et al. (2008) studies were selected as co-critical studies for the derivation of the RfD. Is the rationale for this selection scientifically justified and clearly described? Please identify and provide the rationale for any other studies that should be selected, including the rationale for why the study would be considered a superior candidate for the derivation of the RfD. In addition, male reproductive effects and changes in neonatal thyroid hormone levels, respectively, were selected as the co-critical effects for the RfD. Please comment on whether the selection of these critical effects is scientifically justified and clearly described. Please identify and provide the rationale for any other endpoints that should be selected as the critical effect.

Comment: The use of the Mocarelli et al. (2008) and Baccarelli et al. (2008) studies was appropriate for identifying "cocritical" effects for the RfD calculation, and the rationale for selecting these two studies over others was clearly described. However, the weaknesses of the two studies were not always clearly delineated. For example, in the Baccarelli (2008) study, there was limited discussion of how the presence of polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and coplanar polychlorinated biphenyls (PCBs) that were also found in the blood might confound the interpretation of TCDD association with elevated TSH levels. In addition, there was no discussion of the potential impact of residential histories (e.g., individuals who may have moved in and out of Zone A after the accident). The Panel believes that more discussion of the strengths and weaknesses of these two studies is needed.

The Panel found that in isolation from each other, and lacking a description of supportive animal and epidemiological studies, the studies were less useful for setting the RfD, and emphasizes the need to consider supportive animal and epidemiological studies for dioxin and dioxin-like compounds in order to demonstrate a consistent and integrative signal of toxicity across species and endpoints for TCDD. While Figures 4.3 and 4.4 show quantitative comparisons across RfDs and benchmark dose lower bounds (BMDLs) from animal and epidemiological studies, the figures do not indicate which endpoints are being measured, and consistency in signal is not readily apparent.

The Panel noted that although it has been addressed in the Report, the discussion of the known human age-specific variability in endpoints such as sperm counts should be expanded, though the data from Mocarelli et al. (2008) do show ranges and variance (in Figure 3 and Table 2), and neonatal TSH levels.

Recommendation No. 32: Provide a discussion of the strengths and weaknesses of the Mocarelli et al. (2008) and Baccarelli et al. (2008) studies with an indication of whether the weaknesses affect determination of the RfD.

Response: In Appendix C, EPA presents an assessment of both the Baccarelli et al. (2008) and Mocarelli et al. (2008) studies, delineating their strengths and weaknesses. Section 4.4 identifies and describes qualitatively a number of uncertainties associated with the derivation of the RfD from the Baccarelli et al. (2008) and Mocarelli et al. (2008) studies. Additionally, in Section 4.5.1, EPA presents a quantitative sensitivity analysis that highlights the uncertainty associated with deriving an RfD from the Baccarelli et al. (2008) and Mocarelli et al. (2008) studies. In this analysis, EPA focused on several important assumptions that were made in defining variables for modeling the exposure history of the cohorts and in estimating a chronic intake leading to the observed effect; the analysis presents the quantitative impact of making alternative assumptions for those variables on the POD estimates. EPA also modeled the potential impact of background DLC exposure on the PODs derived from both of the principal studies. EPA did not discuss the potential impact of residential histories because the PODs from both studies were based entirely on measured serum TCDD concentrations, irrespective of zone of residence. Zonal averages were not used in any way in the derivation of the RfD.

With respect to age-specific variability in sperm concentrations as relates to the interpretation of Mocarelli et al. (2008), EPA notes that all the men evaluated in the study were between the ages of 22 and 31 at the time of semen collection and would not expect any substantial age-related differences. EPA does present group sperm concentrations at one standard deviation below the mean as reported by Mocarelli et al. (2008).

Recommendation No. 33: Label the endpoints for studies included in Figures 4.3 and 4.4.

Response: EPA agrees with the SAB Panel's recommendation and has modified Figure 4-4 by adding the last name of the first author of each study and the year of publication and Figure 4-5 by adding the health endpoint or health outcome as suggested. Table 4-5 lists the study endpoints described in Figure 4.3 along with other study information.

Recommendation No. 34: Discuss the comprehensive database of both animal studies and human epidemiological studies, including studies with dioxin-like compounds (e.g., studies cited in Goodman et al. (2010), together to demonstrate a consistent and integrative signal of toxicity across species and endpoints for TCDD.

Response: EPA methodology does not require that a consistent and integrative signal of toxicity across species and endpoints be demonstrated for derivation of an RfD. However, concordance of effects, both qualitatively and quantitatively, across endpoints and species is considered, primarily in the assessment of confidence in the RfD. In response to this recommendation and consistent with EPA methodology, EPA has modified the Reanalysis as follows.

Section 4.3.6 has been revised to provide additional supporting information for the critical effects noted in the two co-principal studies: neonatal thyroid effects from Baccarelli et al. (2008) and sperm effects from Mocarelli et al. (2008).

In Section 4.3.6.1, EPA has evaluated the Goodman et al. (2010) review and added a discussion of the findings. EPA concluded that, because of relatively low DLC exposures in the studied populations and different timings of measurements in the cited studies, it would be unlikely that any consistent patterns would be detected. EPA

confirmed that there were no additional studies identified in this review that meet the selection criteria outlined in Section 2.

EPA has added an analysis of the qualitative and quantitative concordance of key effects across species and studies in Appendix D and referenced in Section 4.4 as part of the discussion of qualitative uncertainty in the RfD. The analysis includes effects from all of the animal and human studies listed in Table 4-5 in six categories: male reproductive effects, female reproductive effects, developmental effects, immunotoxicity, neurotoxicity, and thyroid toxicity. Coverage of effects was expanded beyond those in Table 4-5 to include effects at doses higher than the LOAEL in each study.

SAB Charge Question 4.2

In the Seveso cohort, the pattern of exposure to TCDD is different from the average daily exposure experienced by the general population. The explosion in Seveso created a high-dose pulse of TCDD followed by low-level background dietary exposure in the exposed population. In the population, this high-dose pulse of TCDD was slowly eliminated from body tissues over time. There is uncertainty regarding the influence of the high-dose pulse exposure on the effects observed later in life.

SAB Charge Question 4.2.a

Mocarelli et al.(2008) reported male reproductive effects observed later in life for boys exposed to the high dose pulse of TCDD between the ages of 1 and 10. EPA identified a 10 year critical exposure window. In the development of the candidate RfD, EPA used an exposure averaging approach that differs from the typical approach utilized for animal bioassays. EPA determined that the relevant exposure should be calculated as the mean of the pulse exposure and the 10-year critical exposure window average. Please comment on the following:

SAB Charge Question 4.2.a.i

EPA's approach for identifying the exposure window and calculating average exposure for this study.

***Comment**:* The Panel discussed extensively extrapolation issues posed by the pattern of exposure from Seveso. Issues raised included the question of whether the same endpoints and/or dose response would be expected from such exposure scenarios with high-dose acute exposures when extrapolating to low-dose chronic exposures.

Recommendation No. 35: Provide a discussion of published examples in which dioxin studies were conducted using both high-dose acute and low-dose chronic exposures in animals for the same endpoint and how the outcomes compare both qualitatively and quantitatively. Determine whether similar results were observed for similar endpoints. Several chronic dioxin animal studies may be useful in this regard (Sand et al., 2010; Yoshizawa et al., 2010; 2009).

Response: EPA is aware of only one rodent toxicology study—Kim et al. (2003)—directly comparing health outcomes following the administration of either a high acute TCDD dose or a low longer-term continuous TCDD dose in animals where the

long-term average tissue TCDD concentrations in both dose groups were comparable; the effects were more severe for the acute exposure regimen.

Another animal study, Sand et al. (2010), used an initial-loading dose, weekly-maintenance-dose protocol in which the loading dose is 10 times higher than the weekly maintenance dose but did not evaluate the equivalent continuous exposure, and so does not inform the issue. Both of the Yoshizawa et al (2010; 2009) studies were analyses of the NTP (2006) study that is already presented in the Reanalysis, and has no acute vs. continuous component. One other study, Bell et al. (2007), mentioned in Recommendation 37 following, allows for acute/continuous comparison for in utero and lactational exposures, addressing a very different developmental period than the one in question for the Seveso cohort children (average age >6 years). This study found that acute exposure had a significantly lower impact on preputial separation in male rat pups than did the equivalent continuous exposure (similar terminal TCDD body burdens), the opposite of the finding of Kim et al. (2003). EPA does not consider this finding very informative for the specific exposure scenario and critical exposure period relevant to the RfD.

Recommendation No. 36: Discuss the life-stage-specific approach to hazard and dose-response characterization for children's health risk assessment found in EPA's *Framework for Assessing Health Risks of Environmental Exposures to Children* (U.S. EPA, 2006b).

Response: The approach outlined in EPA's *Framework for Assessing Health Risks of Environmental Exposures to Children* (U.S. EPA, 2006b) encourages evaluation of the potential for toxicity during all developmental lifestages, based on knowledge of external exposure, critical windows of development for different organ systems, MOAs, anatomy, physiology, and behavior that can affect external exposure and internal dose metrics. EPA has followed the framework in evaluating the available data for TCDD and in developing the Reanalysis. The concepts explored in this framework are those that apply to all risk assessments—namely problem formulation, analysis, and risk characterization. The Reanalysis is not a risk assessment but rather a hazard identification and dose-response assessment for noncancer outcomes. It does not contain information on problem formulation or risk characterization; however, it does follow standard EPA procedures.

Recommendation No. 37: Consider adding to the discussion, Bell et al. (2010), which summarized and presented data on some differences between chronic versus acute exposure in maternal transfer.

Response: EPA considered this recommendation as discussed in the response to Recommendation 35. An analysis of the data has led EPA to consider the findings of Bell et al. (2010) not to be informative in the context of the Seveso exposures on which the RfD is based.

SAB Charge Question 4.2.a.ii

Please comment on EPA's designation of a 20% decrease in sperm count (and an 11% decrease in sperm motility) as a LOAEL for Mocarelli et al. (2008).

***Comment**:* The Panel found that changes from normal sperm counts and sperm motility are of public health relevance and, therefore, of interest for determining an RfD. There is general support for EPA's approach of using the WHO reference value for determining relevant TSH levels, but the Panel feels that further discussion of WHO reference values for male reproductive parameters should be included in the Report. Additionally, the Report should indicate that life stage differences clearly exist in sperm counts in humans; cite and discuss the EPA life stage document (U.S. EPA, 2006b).

Recommendation No. 38: Include discussion of background information regarding WHO reference values for male reproductive parameters (e.g., Skakkebaek, 2010).

Response: EPA has added additional discussion of WHO reference values for male reproductive parameters and a discussion of the Skakkebaek (2010) study in Section 4.3.4.2.

Recommendation No. 39: Discuss standard deviations or range of changes from the Mocarelli (2008) study to provide a better understanding of the potential magnitude of effect.

Response: In Section 4.3.4.2, EPA discusses the magnitudes and standard deviations of the effects reported in Mocarelli et al. (2011).

SAB Charge Question 4.2.b

For Baccarelli et al. (2008), the critical exposure window occurs long after the high-dose pulse exposure. Therefore, the variability in the exposure over the critical exposure window is likely to be less than the variability in the Mocarelli et al. (2008) subjects. EPA concluded that the reported maternal exposures from the regression model developed by Baccarelli et al. (2008) provide an appropriate estimate of the relevant effective dose as opposed to extrapolating from the measured infant TCDD concentrations to maternal exposure. Additionally, EPA selected a LOAEL of 5 μ-units TSH per ml blood in neonates; as this was established by World Health Organization (WHO) as a level above which there was concern about abnormal thyroid development later in life. Please comment on the following:

SAB Charge Question 4.2.b.i

EPA's decision to use the reported maternal levels and the appropriateness of this exposure estimate for the Baccarelli et al. (2008) study.

Comment: The Panel supports EPA's decision to use the Baccarelli et al. (2008) estimates of the relevant effective doses. Because the bulk of the calculations were based on zonal averages, clarify how these measurements relate to ranges and variations in exposure in utero.

Response: The Baccarelli et al. (2008) calculations presented in the Reanalysis are derived from the individual exposure measures by the study authors and are not based on zonal averages. EPA has clarified this for the RfD derivation in Section 4.3.

SAB Charge Question 4.2.b.ii

EPA's designation of 5 μ-units TSH per ml blood as a LOAEL for Baccarelli et al. (2008).

***Comment**:* The change in TSH levels reported by Baccarelli et al. (2008) was of public health relevance and, therefore, of interest for determining an RfD. Any follow-up data on thyroid hormone levels in the population studied should be discussed in the Report, if available.

> ***Recommendation No. 40:*** Better describe the potential adverse health outcomes related to altered neonatal TSH levels (e.g., effects on both cognitive and motor deficits). For example, in addition to effects on growth, both cognitive and motor deficits have been found in young adults with congenital hypothyroidism (Oerbeck, 2007, 2003). The Report could better describe the consequences of transient hypothyroidism on reproductive outcomes (e.g., Anbalagan et al., 2010). Other references that relate to this question include Chevrier et al. (2007), Dimitropoulos et al. (2009), and Ye (2008).
>
> > ***Response:*** EPA has added a discussion of the potential adverse health outcomes associated with altered neonatal TSH levels in Section 4.3.4.1. The discussion includes information about thyroid hormone disruption during pregnancy and the neonatal period, potentially leading to neurological deficiencies, particularly in the attention and memory domains(Oerbeck et al., 2005). It also addresses some of the uncertainties in the relationship between human neonatal TSH levels and measures of neurological function such as IQ. EPA also identified animal bioassays, reporting that perturbations in thyroid status can lead to altered brain development (e.g., Sharlin et al., 2010; Royland et al., 2008; 2008; Ausó et al., 2004; Lavado-Autric et al., 2003). Discussion of these findings has been added to Section 4.3.4.1.

SAB Charge Question 4.3

Please comment on the rationale for the selection of the uncertainty factors (UFs) for the RfD. If changes to the selected UFs are proposed, please identify and provide a rationale.

***Comment**:* The Panel agrees that the appropriate UFs were included. The exclusion or inclusion of the UFs in the Report is obvious, clearly discussed, and adequately rationalized. The Report would be more transparent if EPA included a short discussion for the basis of the decision not to include a UF for data quality.

> > ***Response:*** EPA has clarified its choice of UFs for the candidate RfDs in Section 4.3.5 and Table 4-7.

SAB Charge Question 4.4

EPA did not consider biochemical endpoints (such as CYP induction, oxidative stress, etc.) as potential critical effects for derivation of the RfD for TCDD due to the uncertainties in the qualitative determination of adversity associated with such endpoints and quantitative determination of appropriate response levels for these types of endpoints in relation to TCDD exposure. Please comment on whether the decision not to consider biochemical endpoints is scientifically justified and clearly described.

***Comment**:* Biochemical endpoints such as P450 activation, increased oxidative stress, etc. may be acceptable endpoints to establish PODs, particularly when the quantitative relationship between the biochemical endpoint and an adverse health outcome is clearly evident. However, with respect to TCDD, the Panel agrees that more traditional endpoints (e.g., immune, endocrine, reproductive) are more appropriate because associations of these endpoints with health outcomes are well studied and provide a stronger association to an adverse outcome than biochemical endpoints. However, because of the wealth of data on P450s and their importance in disease development, normal development, and chemical response to exogenous agents, EPA should discuss biochemical endpoints, particularly P450s, relevant to establishing and strengthening the proposed reference dose.

> ***Response:*** In general, there is a lack of information linking these particular endpoints to downstream adverse effects for the noncancer effects observed in the available studies. Some of these endpoints, such as CYP (P450) induction and oxidative stress are discussed in Section 5 of the 2010 External Review Draft of the Reanalysis in the context of the mode or action for carcinogenesis or are evaluated quantitatively as potential cancer precursor effects. EPA intends to consider these endpoints further in Volume 2 of the Reanalysis. In the context of noncancer effects, however, an expansive coverage of these endpoints will not necessarily provide a better understanding of the RfD, given the lack of information on the relevant modes of action. For these reasons, further analysis of these data with respect to their relevance to strengthening the reference dose was not conducted.

SAB Charge Question 4.5

In using the animal bioassays, EPA averaged internal blood TCDD concentrations over the entire dosing period, including 24 hours following the last exposure. Please comment on EPA's approach for averaging exposures including intermittent and one day gestation exposure protocols.

***Comment**:* For animal studies, it has been shown that for some effects, acute exposure could give different results than chronic exposure. For TCDD, however, its persistence might suggest that such differences would be partly negated. In Baccarelli et al. (2008), there was extensive discussion regarding the use of the exposure average time for the TCDD concentrations. This is of biological significance as several papers have indicated the unique aspects of high peak exposure of TCDD as occurred in Seveso and in several of the animal studies. The endpoints affected as a result of these peaks do not always translate to impacts from lower chronic exposures. It would be helpful to discuss any available animal studies comparing high-dose acute versus low-dose chronic effects on similar endpoints for dioxin or dioxin-like compounds (as stated earlier in this section).

> ***Response:*** See EPA's response to Recommendation 35. For the Baccarelli et al. (2008) study, the exposures over the critical exposure window (gestation) were relatively constant compared to the exposures experienced by the subjects studied in Mocarelli et al. (2008) and other Seveso cohort studies.

SAB Charge Question 4.6

Please comment on the benchmark dose (BMD) modeling conducted by EPA to analyze the animal bioassay data and EPA's choice of points of departure (PODs) from these studies.

***Comment**:* The Panel agrees with the BMD modeling approaches used in this section. However, the justification for EPA's conclusions that the animal data had sufficient limitations that precluded their use to establish an RfD is quite diverse and poorly linked to specific studies.

> ***Recommendation No. 41:*** Discuss several of the best animal studies in some detail so that their limitations are more apparent.
>
> > ***Response:*** Summaries of all of the studies are presented in Appendix D, with some discussion of their limitations. Strengths and limitations of all of the animal bioassays at the lower end of the candidate RfD range are presented in Table 4-6. Two studies of note (Bell et al., 2007; NTP, 2006) are discussed in more detail in Section 4.4. Table 4-4 and Appendix G, which summarizes the BMD modeling, highlight some of the limitations of the BMD modeling for each modeled data set.
>
> ***Recommendation No. 42:*** Better cite the endpoint guidance that is present within EPA documents for defending approaches used and application of BMD models for the critical effects: this is especially necessary given public comments that EPA was not following its own guidelines.
>
> > ***Response:*** In response to this comment, EPA has added Text Box 2-1. In this text box, EPA identifies the risk assessment guidelines and guidance documents that it relied upon during development of the dose-response assessment.

SAB Charge Question 4.7

For the animal bioassay modeling, EPA applied the kinetic extrapolation at the level of the POD prior to applying the uncertainty factors because EPA has less confidence in the kinetic model output at lower doses reflective of the RfD. Please comment on whether the kinetic extrapolation at the level of the POD prior to applying the uncertainty factors was scientifically justified and clearly described.

***Comment**:* The EPA approach of applying the kinetics on the actual data present at the POD is preferred in this assessment (see additional discussion in the response to Charge Question 3).

> ***Response:*** No response necessary.

SAB Charge Question 4.8

Please comment as to whether EPA's qualitative discussion of uncertainty in the RfD is justified and clearly described.

***Comment**:* The Panel agreed that EPA provided a clear and justified discussion of the uncertainties in deriving the RfD using the Seveso cohort. The Panel agrees with EPA that the major limitation of the Seveso cohort is the uncertainty arising from how well the effects

resulting from high-dose acute exposure translate to low-dose daily exposures. It may be useful to re-review the animal studies to identify if there are any studies where dioxin or DLCs were administered by acute as well as chronic (or even subchronic), and comparable endpoints were examined. If so, the information can be used to help confirm or refute the accuracy of the "average daily dose" adjustment. This is of particular concern in the Mocarelli study as "time periods of susceptibility" appear in male reproductive development, and these periods (windows) may be very short. Animal studies, particularly those involving male reproduction, may be helpful.

Recommendation No. 43: It would be useful to include a discussion of potential uncertainty in the exposure estimates from the Baccarelli study. Serum dioxin levels were only established in a subset of the cohort (approximately 51) at the time of the study while dioxin levels from the main cohort were estimated from data collected from zone of residence (A or B) at a much earlier time.

Response: For derivation of the POD, EPA used the regression modeling in Baccarelli et al. (2008), which was based only on the 51 infants with maternal TCDD measurements taken between 1992 and 1998 and did not depend on prior measurements in the main cohort. All outcomes evaluated for the derivation of the RfD are associated with individual serum concentrations rather than zonal averages. Baccarelli et al. (2008) extrapolated the measured values to the time of conception for each of the 51 pregnancies, which occurred between 1994 and 2005. In Section 4.4, EPA has identified and clarified the qualitative uncertainties associated with deriving an RfD from both of the principal studies (Baccarelli et al., 2008; Mocarelli et al., 2008). EPA has also added Section 4.5. In this section, EPA quantifies the impact of alternative assumptions about the exposures and pharmacokinetic for both the Baccarelli and Mocarelli studies. Also, see response to Recommendation 32.

Recommendations No. 44: While the Panel agrees that the true dioxin-like-compound impact cannot be determined, it might be helpful to provide some general estimates of the variability that may occur at the proposed RfD.

Response: In response to this comment, EPA has added Section 4.5 to the document. In this section, EPA quantifies the impacts of alternative assumptions about the TCDD-only and DLC exposures on the PODs for both the Mocarelli (see Section 4.5.1.1.1) and Baccarelli (see Section 4.5.1.1.2) studies. In Section 4.5.2, EPA has estimated alternative PODs from the NTP (2006) study based on different approaches to modeling TCDD only and the DLCs. In Section 4.5.2, EPA also has estimated potential PODs from several different endpoints identified in Seveso cohort studies (other than those used in developing the RfD) and has estimated the range of potential PODs based on uncertainties encountered in their analyses; these uncertainties included the impacts of DLC background exposures.

A.4.2. Summary of Public Comments and EPA Responses

Comment: Several comments addressed the fact that when determining an RfD, EPA accounted for only 2,3,7,8-TCDD exposures and did not account for exposures to dioxin-like chemicals. The commenters noted that in human epidemiological studies, people are exposed to all

dioxin-like compounds regardless of the sources of their exposures. Specifically, the commenters suggested that EPA did not account for these exposures in the Seveso population when evaluating dose response and, thus, underestimated the reference doses derived from Mocarelli et al. (2008) and Baccarelli et al. (2008).

> ***Response:*** EPA agrees that the human subjects studied in the epidemiological studies were subject to background DLC exposures from many sources. As a component of a sensitivity analysis, EPA has added an analysis of the impact of background DLC exposures on the RfD to the document in Section 4.5. In this analysis, EPA estimates background DLC exposures for several of the Seveso exposure scenarios, including those relevant to the Mocarelli et al. (2008) and Baccarelli et al. (2008) POD estimates. EPA summarizes the results of these sensitivity analyses in Figures 4-6 through 4-9.

Comment: One commenter noted that EPA's qualitative discussion of uncertainty in the reference dose (pp. 4-28 to 4-32) is well written and clearly described. Two commenters felt that the rationale for the selection of the male reproductive effects (Mocarelli et al., 2008) and changes in neonatal thyroid hormone levels (Baccarelli et al., 2008) as critical effects was clearly described and scientifically justified. One commenter felt that the LOAEL selected from the Mocarelli et al. (2008) study was justified. Commenters also felt that EPA's decision not to consider biochemical endpoints (such as CYP induction, oxidative stress, etc.) as potential critical effects for derivation of the RfD for TCDD is clearly described and scientifically justified.

> ***Response:*** No response necessary.

Comment: Several commenters asked EPA to further address the uncertainties associated with deriving an RfD from the Baccarelli et al. (2008) and Mocarelli et al. (2008) studies. Several commenters noted that EPA does not include the use of the data from these studies for dose-response modeling and reference dose derivation with a discussion of the clinical significance of the effects, or the levels of change that represent an adverse effect for each endpoint.

> ***Response:*** In Section 4.4, EPA presents a discussion of the qualitative uncertainties associated with the development of an RfD from these two studies. In response to this and other comments, EPA has expanded the discussion to include the potential clinical significance of the two effects encountered in these epidemiological studies: (1) elevated TSH levels in infants and (2) decreased semen quality in men that experienced elevated TCDD exposures as young boys. Further, in the sensitivity analysis added in Section 4.5, EPA evaluates some quantitative uncertainties in the derivation of PODs from the Baccarelli et al. (2008) and Mocarelli et al. (2008) studies.

Comment: Two commenters noted that the Agency substantially underestimated liver and adipose tissue concentrations in the 2006 National Toxicology Program bioassay (NTP, 2006), resulting in an approximate two-fold overestimate of TCDD potency. EPA ignored reported TCDD concentrations in adipose and liver tissue, which should have been used as the dosimetry endpoints for extrapolation to human equivalent dosages. The use of modeled data is not acceptable for deriving toxicity values used in risk assessment when measured data are available; unnecessary inaccuracies in the derivation of the RfDs are introduced.

Response: In the sensitivity analysis presented in Section 4.5.2, EPA has estimated PODs based on the TCDD adipose concentrations reported in NTP (2006). EPA does not consider the whole liver concentrations to be relevant because they include TCDD bound to CYP1A2, which is not part of the biologically-active TCDD fraction. Because adequate human studies were available, animal studies including the above referenced NTP (2006) were not used to derive the RfD.

Comment: One commenter noted that several studies included in the Report examined the effects of TCDD exposure on serum thyroid hormone concentrations (Crofton et al., 2005; Seo et al., 1995; Sewall et al., 1995), which are toxicologically irrelevant and should be excluded from the analysis.

Response: EPA considers serum thyroid hormone levels to be toxicologically relevant, as indicators of hormonal imbalance and potential thyroid toxicity. EPA does not require the observation of overt clinical effects in this respect.

Comment: A commenter suggested that many of the animal studies, particularly developmental studies, used dosing regimens that cannot be properly extrapolated to chronic exposures and, thus, are inappropriate for derivation of a chronic RfD. The commenter noted that the weight of evidence suggests that peak, rather than average, exposure level is most relevant to assessing the effect of in utero and developmental exposure to TCDD on male rat reproductive system parameters.

Response: EPA defines the RfD as a lifetime protection value that includes all exposures and life stages, not just long-term exposure. If shorter-term exposures over a particular critical window, such as in utero or early childhood, indicate greater susceptibility, the short-term exposures must be considered during the development of an RfD and can be the basis of an RfD. EPA has removed the word "Chronic" from the title of Section 4 in the Reanalysis to avoid confusion. EPA did not distinguish between peak and average exposure levels when evaluating male rat reproductive system effects because administered doses were fairly level, unlike the exposure scenario evaluated for the Seveso cohort.

Comment: A commenter noted that some of the health effects that are addressed in derivation of an RfD are actually precancerous lesions (i.e., hypertrophy and hyperplasia), and as such, are more appropriate for use in cancer risk assessment than for deriving a chronic RfD.

Response: Hypertrophy and hyperplasia are not always considered to be precancerous. For the TCDD assessment, no POD is based solely on either of these effects.

Comment: One commenter noted that in developmental studies, the appropriate unit for statistical analysis is the litter; many of the developmental studies considered by EPA, however, incorrectly used the individual pup as the statistical unit for analysis (e.g., Shi et al., 2007; Hojo et al., 2002; Markowski et al., 2001; Ohsako et al., 2001). The commenter suggested that data from developmental studies that have been incorrectly evaluated using the individual pup should not be used as the basis for derivation of an RfD. Alternatively, the original study data could be reanalyzed using the litter as the statistical unit of analysis.

Response: EPA guidance calls for a litter-based approach for dichotomous outcomes when the data are reported on that basis. All the endpoints in the studies identified by the commenter were continuous measures, to which the guidance does not apply. In addition, all the data were presented only by aggregated exposure groups, so that a litter-based analysis was not possible even if the responses could be dichotomized.

Comment: One commenter noted that some data are derived from guinea pigs, which are known to be substantially more susceptible to the effects of TCDD treatment than humans. Because of the extreme sensitivity, an uncertainty factor of 3 for animal-to-human extrapolation is unfounded for these studies.

Response: There are few data to evaluate the relative sensitivities of guinea pigs and humans to TCDD. As shown in Table 4-5, guinea pigs are not necessarily more sensitive than other species. The use of a three-fold uncertainty factor for the toxicodynamic component of interspecies uncertainty (UF_A) is standard EPA practice when using modeling the toxicokinetic extrapolation component (U.S. EPA, 1994).

Comment: One commenter suggested that several studies included in the analysis are limited by the number of animals used (see Shi et al., 2007; Franc et al., 2001; Sewall et al., 1995) and that the determination of a NOAEL and LOAEL based on the analyses as provided by the authors is not appropriate for deriving a regulatory threshold value.

Response: EPA has indicated such limitations in the animal bioassay evaluations in Table 4-6. While EPA considered these studies as possible POD candidates, the RfD is based on human epidemiological studies, not on data derived from animal bioassays.

Comment: One commenter felt that the LOAELs in the Van Birgelen et al. (1995a; 1995b) and Fattore et al. (2000) studies were incorrectly interpreted. The commenter noted that, in the Van Birgelen et al. (1995a; 1995b) study, the LOAEL should be based only on changes in thymus weight because other changes (i.e., liver retinoid levels) might only be adaptive responses and cannot be considered toxic effects. The commenter also noted that the LOAEL for the Fattore et al. (2000) study should be interpreted as a 1-µg/kg diet (2 µg/day for 13-week old female rats) with a NOAEL of 0.2 µg/kg (0.3 µg/day for 13-week-old female rats) because of the dose-dependent reduction in hepatic vitamin A, with significant reductions at TCDD diet concentrations of 1, 2, and 20 µg/kg, but not at 0.2 µg/kg.

Response: EPA acknowledges that there are uncertainties in the selection of specific effects in these studies but believes that it has appropriately interpreted these study endpoints in its development of candidate RfDs. EPA does not consider depletion of liver retinoid levels to be adaptive in the Van Birgelen et al. (1995a; 1995b) study.

Comment: Several commenters noted that EPA's evaluation of noncancer risk ignored the NAS peer-review conclusions that the evidence for dioxin exposure as a cause of reproductive and hormonal abnormalities is not strong and that there is no convincing evidence of adverse, noncancer effects as a result of dioxin exposure.

Response: In Sections 2 and 4 of the document, EPA identifies a number of additional epidemiology and toxicology studies that support associations between TCDD exposures

and noncancer effects. Several important studies in this group (e.g., Baccarelli et al., 2008; Mocarelli et al., 2008; Bell et al., 2007; NTP, 2006) were published after the NAS report was published.

Comment: Some commenters suggested that there is a significant amount of uncertainty in the Mocarelli et al. (2008) study, given that the reported demographics of the control population were different from those of the exposure groups, and the study authors had no information on TCDD levels in the control group.

> ***Response:*** The analysis in Mocarelli et al. (2008) was performed by grouped exposures across all subjects. The lowest exposure group, being the reference group for the analysis, included individuals from all exposure zones, not just the "control" population (the non-ABR zone) mentioned by the commenter. TCDD serum levels were measured in a subset of the non-ABR population as reported in Needham et al. (1997) and Mocarelli et al. (1991). It is not clear how many, if any, of the individual exposures in the lowest exposure group were assigned a generic value rather than a measured one. Demographic differences among the individuals across all exposure groups were identified and considered as covariates in the analysis by Mocarelli et al. (2008).

Comment: One commenter noted that neither Mocarelli et al. (2008) nor EPA has explained the biological mechanism by which dioxin demonstrated negative effects on sperm concentration in 1- to 9-year-old boys and positive effects on sperm concentration in 10- to 17-year-old boys. Commenters questioned the study's assumption of 10 as a reasonable age for puberty in boys and stated that 12–16 years is the average age at onset of puberty.

> ***Response:*** EPA agrees with the commenter that the mechanism of toxic action for this effect is not known. For the establishment of an RfD, EPA does not require the establishment of a mechanism of toxic action. Neither the study authors nor EPA assume 10 years to be the age of puberty onset; it is simply the age that the study authors used to divide their study population by magnitude of effect.

Comment: In the Baccarelli et al. (2008) and Mocarelli et al. (2008) studies, the populations of interest were small, especially for the high-exposure group. This leads to questions about the overall representativeness of the studies.

> ***Response:*** Both studies refer to specific age groups, specifically newborn infants and young children; therefore, the population is not a representative sample of the general population, but of a potentially sensitive population. In part, because of the small sample size, EPA used a factor of 3, rather than 1, for UF_H to account for the possibility that all sensitive individuals might not be represented.

Comment: One commenter felt that the lack of data on maternal iodine status in the Baccarelli et al. (2008) study could affect the neonatal TSH data. The authors' explanation that potential iodine-related effects would affect all study groups evenly and would not impact the findings was questionable.

> ***Response:*** Baccarelli et al. (2008) discount iodine status in the population as a confounder because exposed and referent populations all lived in a relatively small

geographical area. That an iodine deficiency was present in one and not the other is unlikely based on iodine levels in the soil.

Comment: One commenter stated that EPA used data that were not clinically significant and did not demonstrate a dose-response relationship to derive an RfD. In determining the critical effect, EPA had no information to verify that the persons with the potentially low values were associated with higher exposures to TCDD.

> ***Response:*** EPA does not require PODs used to derive RfDs to be based on effects that have demonstrable clinical significance. EPA has expanded the discussion of the potential significance of elevated neonatal TSH levels in the Reanalysis.

Comment: Several comments suggested that EPA did not acknowledge and address in an appropriate weight-of-evidence evaluation several other credible studies for RfD development. EPA excluded credible studies showing no adverse effect from dioxin, yet failed to address the significant uncertainties associated with the studies used. The commenters felt that EPA should use an approach that includes results from studies that report both positive and negative findings, incorporates an appropriate dose range, and evaluates a biologically plausible endpoint.

> ***Response:*** In response to this comment and others, EPA has added an analysis of the qualitative and quantitative concordance of specific key effects across species in Appendix D.3 as a supplement to the existing discussion of the critical effects in Sections 4.3 and 4.4.

Comment: Commenters noted that some of the animal studies used to support derivation of a chronic RfD evaluate nonadverse endpoints, have not been specifically linked to adverse events, were generally unsuitable, or were of questionable toxicological relevance. See Amin et al. (2000), Cantoni et al. (1981), Fattore et al. (2000), Hojo et al. (2002), Hutt et al. (2008), Kattainen et al. (2001), Keller et al. (2008a; 2008b; 2007), Li et al. (1997), Miettinen et al. (2006), and Van Birgelen et al. (1995a; 1995b).

> ***Response:*** See response to Charge Question 4.4.

Comment: A commenter noted that some of the studies cited in support of EPA's derivation of an RfD report findings that conflict with findings of other studies, thus indicating that the associated responses to TCDD treatment have not been well-elucidated. The commenter also added that the lack of agreement among studies regarding the evaluated responses following TCDD treatment suggests that these endpoints likely are not sensitive indicators of TCDD-mediated effects. Thus, they should not be used to support the derivation of an RfD. (SeeAmin et al., 2000; Gray et al., 1995; Bjerke and Peterson, 1994; Mably et al., 1992.)

> ***Response:*** EPA's methods for developing RfDs do not require that all studies be positive for a given effect and take into account conflicting information when deciding on a critical effect. As mentioned previously in response to other comments, EPA has expanded the discussion of qualitative and quantitative concordance of effects across species and studies (Appendix D.3).

Comment: Several commenters stated that the sperm quality endpoints used for risk assessment were of questionable clinical relevance. EPA failed to present a valid analysis of variability of effects in the control. The commenters felt that the critical effect should not be based on "assumed" effects, but rather, on documented effects of clinical concern and that several scientific and quantitative issues should be addressed regarding the underlying data used to derive an RfD.

> ***Response:*** EPA does not require PODs to be based on effects that have demonstrable clinical significance (see response to SAB charge question 4.4). EPA has framed the concern for the sperm quality endpoints in terms of shifts in the distributions of these measures in the general population. Such shifts could result in decreased fertility in men at the low end of these population distributions. In a new study, Mocarelli et al (2011) report that elevated TCDD exposures during and after pregnancy (via breast-feeding) led to similar sperm quality degradation. EPA has expanded the discussion in Section 4.3.4.2 regarding the significance of this endpoint.

Comment: Some commenters suggested that owing to limitations in control for confounding variables, difficulty in translating exposure scenario to the general population, and relevance of the main outcome measure, the results of the Baccarelli et al. (2008) study are suitable for hypothesis generation but are not strong enough on their own for generation of an RfD. The commenters additionally noted that neither Baccarelli et al. (2008) nor EPA presented any data that shows increasing TSH levels in the population during the years when dioxin exposures were high and decreasing levels in more recent years, specifically the past 20 years.

> ***Response:*** Sections 4.4 and 4.5.1.2 describe and quantify the impacts of important sources of uncertainty in this analysis. In response to the issue of historical infant TSH levels against changing background exposures, EPA has added a discussion of the Goodman et al. (2010) review of this issue in Section 4.3. EPA notes that the SAB agreed with the choice of principal studies, including Baccarelli et al. (2008).

Comment: Several commenters suggested that EPA did not sufficiently address the appropriateness of using the Seveso cohort as a basis to derive an RfD, given that the exposure levels of those nearest the explosion far exceeded what is observed in the general population. Nevertheless, at least one reviewer felt that EPA was justified in using the exposure estimates provided by the study authors to quantify exposure for the dose response.

> ***Response:*** In response to this comment and similar ones, EPA has, in addition to the existing discussion of the Seveso exposure scenarios in Section 4, added a sensitivity analysis in Section 4.5 that investigates in more detail the uncertainties in the exposure modeling.

Comment: Several commenters felt that the exposures in Seveso also included substantial exposure to other confounding chemicals that contribute to the overall TEQ, which was not accounted for in the analysis. They suggested that TCDD comprised only a small fraction of the total TEQ.

Response: The released fluid mixture at Seveso reportedly contained TCDD, sodium trichlorophenate, ethylene glycol, and sodium hydroxide (Mocarelli et al., 2000), but the presence of other dioxin-like compounds was not reported. However, as part of a sensitivity analysis, EPA has evaluated the impact of background DLC exposures for the Seveso population. In Section 4.5.1, EPA analyzes TEQ estimates based on background exposures to DLCs in the Baccarelli et al. (2008) and Mocarelli et al. (2008) studies. In Section 4.5.2, EPA analyzes TEQ estimates based on background DLC exposures for other studies of the Seveso cohort and has concluded that background DLC exposure is relatively small compared to TCDD at the LOAEL POD.

Comment: One commenter noted that, the study by Baccarelli et al. (2008) provided a clear basis for estimating a NOAEL for impacts on neonatal TSH levels. The identification of this robust NOAEL, with substantial support from the weight of evidence from numerous other studies, provides the basis for reduced uncertainty factors in the derivation of the RfD. The commenter outlined an alternative method for deriving the RfD using the principal studies that EPA selected, which included differences in calculating NOAEL/LOAEL values and applied UFs in Baccarelli et al. (2008).

Response: The SAB has agreed with the approach that EPA has taken to derive the RfD from this study. EPA could not define a NOAEL because it is not clear what maternal intake should be assigned to the group below a TSH level of 5 µU/mL. In Section 4.5.1.2, EPA quantifies the impact of sources of uncertainty in a sensitivity analysis that examines the key elements encountered during the derivation of an RfD from Baccarelli et al. (2008), including a potential NOAEL.

Comment: One commenter noted that in the regression analysis plots from Baccarelli et al. (2008) (Figure 2), which EPA cites as the basis of the RfD derivation, if a benchmark of 10 µU/mL had been used rather than 5 µU/mL, the corresponding POD (in terms of a maternal plasma TCDD concentration) would be >1,200 ppt, as compared with 270 ppt. The resulting RfD would be about 5-fold higher. If a 10 µU/mL benchmark was applied to the Baccarelli et al. (2008) regression analysis, there would be little basis for comparing exposures, because no data points exceeded 10 µU/mL.

Response: In Section 4.5.1.2, EPA addresses this issue in a sensitivity analysis of the Baccarelli et al. (2008) study. In this section, EPA estimates PODs based on alternative increases in the neonatal TSH levels reported at different TCDD levels in Baccarelli et al. (2008). The highest TSH level considered for defining an alternate LOAEL was the highest one used by Baccarelli et al. (2008) in their regression model. The overall infant cohort included a number of TSH levels above 10 µU/mL, but no maternal TCDD concentrations were available for those infants. As it is impossible to determine what the regression slope would be had those data points been included, EPA did not evaluate the regression model beyond the highest TSH value in the modeled data set.

Comment: Several commenters suggested changing the uncertainty factors (UFs). One commenter suggested that EPA should reduce the intrahuman uncertainty factor (UF_H) from 3 to 1 as the critical effects observed in the co-principal studies were found in sensitive subpopulations (children, neonates). Another commenter stated that EPA needs to address why

it did not include a UF to account for the unique susceptibility and vulnerability of children and why it chose to use a UF of 3 (instead of 10) to account for human interindividual variability.

> ***Response:*** For human interindividual variability (UF_H), EPA used a factor of 3 ($10^{0.5}$) because the effects were elicited in sensitive populations. A further reduction to 1 was not made because the sample sizes were relatively small, which, combined with uncertainty in exposure estimation, may not fully capture the range of interindividual variability. In addition, chronic effect-levels are not well defined for humans and could possibly be more sensitive. EPA has added text to Table 4-7 and believes that the Report adequately describes the use of UFs.
>
> In the EPA's RfD methodology, there is not a separate UF to account for the unique susceptibility and vulnerability of children. Such differences are accounted for as part of UF_H.

A.5. REFERENCES

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APPENDIX B

Dioxin Workshop Report

January 2012

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

EPA/600/R-09/027
May 2009

Summary of U.S. EPA Dioxin Workshop

February 18−20, 2009

Cincinnati, Ohio

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

DISCLAIMER

This document summarizes the discussions presented at the Dioxin Workshop in February 2009, in Cincinnati, OH, as documented by the Session Co-Chairs. This document is not all inclusive or binding. Conclusions and recommendations to the U.S. EPA may not represent full consensus. The views expressed in this document are those of the Dioxin Workshop Panelists and do not necessarily reflect the views and policies of the U.S. Environmental Protection Agency. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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DIOXIN WORKSHOP TEAM

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INTRODUCTION

This document provides a summary of the Scientific Workshop to Inform EPA's Response to National Academy of Science Comments on the Health Effects of Dioxin in EPA's 2003 Dioxin Reassessment. The U.S. Environmental Protection Agency (U.S. EPA) and Argonne National Laboratories (ANL), through an inter-Agency agreement with the U.S. Department of Energy, convened this scientific workshop ("Dioxin Workshop") on February 18−20, 2009, in Cincinnati, Ohio. The goals of the Dioxin Workshop were to identify and address issues related to the dose-response assessment of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). This report summarizes the discussions and conclusions from this workshop. Previously, at the request of the U.S. EPA, the National Academy of Sciences (NAS) prepared a report, *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment* (NAS, 2006), which made a number of recommendations to improve the U.S. EPA's risk assessment for TCDD (U.S. EPA, 2003). The 3-day Dioxin Workshop was convened specifically to ensure that the U.S. EPA's response to the NAS recommendations focuses on the key issues and reflects the most meaningful science.

The Dioxin Workshop included seven scientific sessions:

(1) Session 1: Quantitative Dose-Response Modeling Issues
(2) Session 2: Immunotoxicity
(3) Session 3A: Dose-Response for Neurotoxicity and Nonreproductive Endocrine Effects
(4) Session 3B: Dose-Response for Cardiovascular Toxicity and Hepatotoxicity
(5) Session 4A: Dose-Response for Cancer
(6) Session 4B: Dose-Response for Reproductive/Developmental Toxicity
(7) Session 5: Quantitative Uncertainty Analysis of Dose-Response

During each session, the U.S. EPA asked a panel of expert scientists to:

- identify and discuss the technical challenges involved in addressing the key NAS comments on the TCDD dose-response assessment in the U.S. EPA Reassessment (U.S. EPA, 2003);
- discuss approaches for addressing the key NAS comments; and
- identify important published, independently peer-reviewed literature, particularly studies describing epidemiologic and *in vivo* mammalian bioassays, which are expected to be most useful for informing the U.S. EPA's response.

The sessions were followed by open comment periods during which members of the audience were invited to address the Panels. At the conclusion of the open comment periods, the Panel Co-Chairs were asked to summarize and present the results of the panel discussions. The summaries could include minority opinions stated by panelists. The main points derived from the session summaries were used to prepare this document. Additionally, this document includes a list of the session panelists and their affiliations and three appendices. Appendix A presents the Dioxin Workshop Agenda. Appendix B identifies the charge questions presented to the Panel. Appendix C describes draft study selection criteria proposed by the Dioxin Workshop Team for consideration by the workshop panelists.

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SCIENTIFIC WORKSHOP TO INFORM THE TECHNICAL WORK PLAN FOR U.S. EPA'S RESPONSE TO NAS COMMENTS ON THE HEALTH EFFECTS OF DIOXIN PRESENTED IN U.S. EPA'S DIOXIN REASSESSMENT

Dioxin Workshop Co-Chairs: Peter W. Preuss and Glenn Rice

The Dioxin Workshop session summaries were prepared by the session panel Co-Chairs with input from the panelists, as requested by the U.S. EPA prior to the workshop. The Co-Chairs subsequently presented these summaries to all of the workshop participants during designated periods at the workshop. In these summaries, the U.S. EPA asked that the Co-Chairs summarize the key issues from the panel discussions. Because the sessions were not designed to achieve consensus among the panelists, the summaries do not necessarily represent consensus opinions; rather, they reflect the essence of the panel discussions. Some of the specific points may represent the views of multiple panelists, while others only the views of a single panelist. Prior to the summarizations, there were opportunities for public comments on the discussion topics. Some Co-Chairs met with their sessions' panelists after their sessions ended to develop these summaries, while others developed reports based on their personal notes. Because Session 5 was the last session of the workshop—with little time provided to develop the summary—the Co-Chairs circulated a draft for comment by the Session 5 panelists after the workshop, prior to finalizing the session summary. The U.S. EPA collected the session summaries and then prepared this document. A draft of this document was distributed to all of the session Co-Chairs to provide them with a final opportunity to comment and make revisions. Finally, it should be noted that U.S. EPA was not prescriptive to the session Co-Chairs with respect to the format of the presentation materials and provided no specific instructions, resulting in unique formats among the session summaries.

SESSION 1: QUANTITATIVE DOSE-RESPONSE MODELING ISSUES

This session discussed the general dose-response modeling issues related to TCDD. Many of these issues were highlighted by NAS (2006). There was a general introductory presentation on TCDD kinetics, including information and uncertainties pertaining to the conversion of administered doses in animals to human body burden (BB) and additivity to background issues. This presentation was followed by a Panel discussion on the state of the science regarding dioxin dose-response modeling issues.

Session 1 Panelists (Session Co-Chairs are identified by asterisk)

- Bruce Allen, Bruce Allen Consulting
- Lesa Aylward, Summit Toxicology
- Roger Cooke, Resources for the Future
- Kenny Crump, Louisiana Tech University
- Mike DeVito, U.S. EPA
- Dale Hattis, Clark University
- Rick Hertzberg, Biomath Consulting
- Rob McDowell, U.S. Department of Agriculture
- Jim Olson, State University of New York, University at Buffalo

- *Lorenz Rhomberg, Gradient
- Woody Setzer, U.S. EPA
- *Jeff Swartout, U.S. EPA

Please note that the use of the term "concluded" or "recommended" in this summary does not mean that a consensus was reached. Session Summaries were written from the material prepared by the non-EPA/ANL Co-Chair and represent a synopsis of the panel discussions.

Key Study Selection Criteria

The Panel discussed the advantages and disadvantages of using key study criteria (Appendix C). They concluded that *a priori* criteria foster transparency and consistency, and could deflect *a posteriori* criticism. However, the Panel also acknowledged that having *a priori* criteria could introduce the potential for excluding useful data. Although the key study criteria provided by the U.S. EPA listed studies using TCDD only as a criterion, the Panel posed the possibility of using closely related dioxin-like compounds (DLCs) as surrogates for TCDD. The criterion for use of data from mammalian studies only was one criterion that received generalized support due to the lack of extrapolation protocols for nonmammalian species. The Panel also discussed the specific exposure-duration criterion and asked if there should be a preference for longer-term rather than acute studies. The Panel made three suggestions to modify U.S. EPA's key study selection criteria:

(1) Define more relevant exposure-level (i.e., dose) cut points using tissue concentrations.
(2) Reword statistical criteria to include do-it-yourself analysis.
(3) Reword the response criteria to clarify "outside of normal range."

Dose Metrics

The Panel discussed the relative merits of various measures of dose for modeling TCDD dose response. One general conclusion was that tissue concentration (TC) is the preferred metric, especially lipid-adjusted TC, because this measure more closely approximates exposures close to the target tissue when compared to administered doses. However, the Panel acknowledged that these data are often unavailable. They further noted that BB, which is defined as the concentration of TCDD in the body (ng/kg body weight) (U.S. EPA, 2003), might be useful as a surrogate for TC provided the two measures were proportional.

The Panel suggested that a linear approach to BB estimation, which was utilized by U.S. EPA (2003), is too simplistic because this approach does not take into account toxicokinetic issues related to TCDD—e.g., sequestration in the liver and fat, age-dependent elimination, and changing elimination rates over time. The Panel recommended the use of kinetic/mechanistic modeling to the extent possible to quantify tissue-based metrics.

The Panel raised the issue of whether the preferred dose metric would be different for different endpoints and exposure durations. This led to the Panel's comment that the peak exposure might be a more important metric than average BB for variable exposure scenarios. Given this discussion about different exposure durations being relevant to a specific endpoint, the Panel suggested that the U.S. EPA also consider peak measures in dose-response modeling.

The last point raised in this part of the discussion centered on the possibility of dose errors in experimental studies. The Panel highlighted the need for the U.S. EPA to consider dose error (i.e., uncertainty in the x-axis of the dose-response curve) when using dose surrogates.

Dose-Response Modeling of Mammalian Bioassays

The Panel considered several issues related to dose-response modeling of mammalian bioassay data for TCDD: supralinearity and incomplete response data ("anchoring"), defining the benchmark response (BMR) level with respect to establishing the point of departure (POD), and the use of threshold modeling—as further explained below.

The Panel discussed the specific issues of supralinearity and anchoring raised by the U.S. EPA with respect to modeling noncancer endpoints. The panel recognized that, for many of the most sensitive endpoints, the response at the lowest dose is high (e.g., quantal responses above 25% and continuous endpoints differ substantially from the mean, often implying 100% incidence in the treated animals). This lack of response anchoring at the low end of the dose-response curve (near the BMR) results in the higher responses determining the shape of the curve.

The Panel asked whether new tools might be needed or whether the current tools could be applied differently. In the context of developing new tools, the Panel emphasized the need for collaboration between biologists and mathematicians. When discussing application, the Panel suggested that the problem with supralinearity might be overcome by simply dropping the requirement for using the lower bound on the Benchmark Dose. In addition, the Panel posed several more approaches for further consideration in dose-response modeling by the U.S. EPA:

(1) Combine similar data sets to fill in data gaps.
(2) Use mechanistic approaches to model the data gaps.
(3) Dichotomize continuous data.

Finally, the Panel acknowledged that, in certain situations, there simply may not be enough information to provide meaningful answers.

The Panel discussed the BMR level for establishing a POD in the context of deriving a Reference Dose (RfD). The Panel generally agreed that, while the effective dose level (ED_{01}) used in the 2003 Reassessment may be useful for comparative analysis across endpoints, the ED_{01} estimates developed for all endpoints considered in the Reassessment were not appropriate for deriving an RfD because they were not based on the effect's adversity. The panel noted that ED_{01} also is much lower than typical EPA BMR levels. The Panel recommended that the U.S. EPA work to define endpoint-specific BMRs based on the consideration of adversity. Given that the same uncertainty factor framework is applied to all PODs, the Panel emphasized the need for consistency in BMRs; numerical consistency is needed for quantal BMRs and consistency in the choice of biological relevance should be applied for continuous BMRs.

The Panel generally discouraged threshold modeling by stating that thresholds are very difficult to pin down and suggested that the lower bound may always be zero.

Dose-Response Modeling of Epidemiological Studies

The Panel noted that many studies have been published with measured concentrations of TCDD that could be used for dose reconstruction. In this discussion, the Panel acknowledged that use of these data would entail dealing with toxicity equivalence (TEQ) issues and pharmacokinetic (PK) modeling. Pertaining to the use of these data for quantitative risk assessment by the U.S. EPA, the Panel posed the question, "At what point does indirect or confounded human data supersede controlled animal bioassay data?", or alternatively, "How much human data uncertainty can we tolerate?" The Panel suggested, at the least, that the epidemiologic data could be used to "ground-truth" the animal bioassay modeling results.

Supporting Information

The Panel acknowledged that Ah receptor (AhR) binding affinities are not necessarily tied to endpoint sensitivity, but they reiterated the need to consider mechanistic modeling to aid in developing appropriate dose metrics or filling in data gaps in the existing dose-response data.

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SESSION 2: IMMUNOTOXICITY

The U.S. EPA plans to consider development of a quantitative dose-response assessment for the immunologic effects associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced immunologic effects.

Session 2 Panelists (Session Co-Chairs are identified by asterisk)

- Roger Cooke, Resources for the Future
- Rob Goble, Clark University
- *Belinda Hawkins, U.S. EPA
- Nancy Kerkvliet, Oregon State University
- Manolis Kogevinas, Centre for Research in Environmental Epidemiology
- Robert Luebke, U.S. EPA
- Paolo Mocarelli, University of Milan
- *Allen Silverstone, State University of New York, Upstate Medical University

- Courtney Sulentic, Wright State University
- Nigel Walker, National Institute of Environmental Health Sciences

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Key Study Selection Criteria

The Panel first addressed the Key Study Selection Criteria proposed by the U.S. EPA (Appendix C). The Panel raised the issue that the key study criteria do not apply to most studies designed to investigate immunotoxicity, including those used to calculate ED_{01}s (U.S. EPA, 2003). The Panel observed that most dioxin immunotoxicity studies are relatively high dose (>200 ng/kg-d) acute studies and/or use parenteral rather than oral administration.

The Panel discussed several studies often considered important for assessing the immunotoxic effects of TCDD exposure. The Oughton et al. (1995) mouse bioassay was discussed and, although the study does meet the proposed criteria, it could not be considered a key study; specifically, the Panel contended that since there were no functional alterations observed or measured in this bioassay, the changes in cellular phenotypes are only "suggestive" of immune alterations and cannot be regarded as having immunopathologic significance.

The Panel discussed two additional studies for further consideration by the U.S. EPA:

- Baccarelli et al. (2002). The Panel discussed this as a potentially key human epidemiological study that should be reviewed and considered further by the U.S. EPA. It measured the level of IgG, demonstrating a significant decline relative to dioxin body burdens.
- Smialowicz et al. (2008). The Panel noted that this study identified the antibody response to sheep red blood cells (SRBCs) as the critical effect, labeling this protocol as a functional assay. The Panel stated that if modeled, the U.S. EPA could calculate the BMR for this endpoint as 1 standard deviation from the control mean.

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SESSION 3A: DOSE-RESPONSE FOR NEUROTOXICITY AND NONREPRODUCTIVE ENDOCRINE EFFECTS

The U.S. EPA plans to consider development of a quantitative dose-response assessment for neurological and/or nonreproductive endocrine effects associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced neurological and/or nonreproductive endocrine effects.

Session 3A Panelists (Session Co-Chairs are identified by asterisk)

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- Mike DeVito, U.S. EPA
- Mary Gilbert, U.S. EPA
- Rob Goble, Clark University
- Nancy Kerkvliet, Oregon State University
- Fumio Matsumura, University of California-Davis
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- *Bernie Weiss, University of Rochester

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What Are the Key Questions Regarding These Endpoints?

The Panel used the following question to initiate discussion: “*Are there identifiable indices of neurotoxicity and nonreproductive endocrine effects in animal studies and human populations?”* Under this discussion topic, the Panel discussed three endpoints: neurotoxicity (with focus on developmental exposures), thyroid dysfunction (e.g., thyroid hormone deficits), and diabetes. The Panel also addressed the relevance of windows of vulnerability to each

endpoint. The Panel acknowledged that, in some cases, the window of exposure may precede the window of expression of toxicity.

Epidemiological Study Selection

Developmental Neurotoxicity

The Panel recognized that an unusual feature for this endpoint is that there are sufficient human data for dose-response modeling (e.g., Dutch children [Huisman et al., 1995; Patandin et al., 1999] and U.S. children [Jacobson and Jacobson, 1996]) and there is an internal dose metric (serum concentrations). Additionally, the Panel discussed recent studies that address this endpoint in humans (from Japan [reference not provided] and Holland [e.g., Koopman-Esseboom et al., 1996; Vreugdenhil et al., 2002]). For continued investigation into this endpoint, the Panel raised two issues to the U.S. EPA:

- Conduct an evaluation of whether a modeled effect can be attributed to TCDD and not some other persistent organic pollutant (POP), although the Panel recognized that it is unlikely U.S. EPA will be able to distinguish among these exposures because other POPs are intrinsic confounders in the Dutch study.
- Allow animal data to inform the dose-response modeling of epidemiological data.

Thyroid Dysfunction

The Panel identified the availability of human data for this endpoint (e.g., Calvert et al., 1999; Koopman-Esseboom et al., 1994). Much of the thyroid dysfunction literature has been published since the 2003 Reassessment (e.g., Wang et al., 2005; Baccarelli et al., 2008). The Panel also noted the availability of an internal dose metric (serum concentrations). Additionally, the Panel discussed the mechanistic studies in animals that link TCDD to thyroid dysfunction. For continued investigation into this endpoint, the Panel raised three issues for the U.S. EPA to consider:

- Consider the newly available human data since the Reassessment.
- Investigate and clarify of the role of TCDD-induced thyroid dysfunction in developmental neurotoxicity.
- Evaluate and determine whether an effect can be attributed to TCDD or other contaminants.

Diabetes

The Panel discussed that data suggest that diabetes incidence in those under 55 years old may be associated with exposure to PCBs. They acknowledged that whether this is a dioxin-like compound (DLC) mediated effect or whether other POPs are responsible is still undetermined. The Panel also acknowledged that no animal model exists for the investigation of xenobiotic-induced diabetes, and that separating the injury dose level from the current body burdens would depend on good pharmacokinetics in humans. For continued investigation into this endpoint, the Panel listed two issues for the U.S. EPA to consider:

- Results from the Anniston study and the Great Lakes Fishermen study (references not provided) should be examined for dose metrics (both studies examine human PCB exposures).

- Changes of adipose tissue status need to be considered, given that dieting can cause release of lipid-soluble contaminants.

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SESSION 3B: DOSE-RESPONSE FOR CARDIOVASCULAR TOXICITY AND HEPATOTOXICITY

The U.S. EPA plans to consider development of a quantitative dose-response assessment for cardiovascular and/or hepatic effects associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced cardiovascular and/or hepatic effects.

Session 3B Panelists (Session Co-Chairs are identified by asterisk)

- Bob Budinksy, Dow Chemical
- Manolis Kogevinas, Centre for Research in Environmental Epidemiology
- Rob McDowell, U.S. Department of Agriculture
- Jim Olson, State University of New York, University at Buffalo
- Marian Pavuk, Agency for Toxic Substances and Disease Registry
- *Jeff Swartout, U.S. EPA
- *Mary Walker, University of New Mexico
- Nigel Walker, National Institute of Environmental Health Sciences

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Key Study Selection Criteria

The Panel initially focused on the draft key study selection criteria offered by the U.S. EPA (Appendix C). The panel recommended that for cardiovascular effects, which are not usually observed in rodents, the use of knockout mouse models (ApoE KO and LDLR KO) be moved to the “primary” column because only these studies establish the cardiovascular toxicity model in mice.

The panel also was concerned that the gavage procedure can increase mouse blood pressure. Consequently, the panel recommended that gavage studies not be used for the blood pressure endpoint (i.e., only dietary dosing studies should be considered).

Human Health Endpoints

In relation to the hepatic endpoint, the Panel acknowledged the large body of dose response information on hepatic effects in rodents and that enzyme (mostly CYP1A1) induction was a sensitive effect. However, the Panel cited the lack of linkage of CYP1A1 to downstream events, which complicates the toxicological interpretation of this endpoint, and concluded that

the more important liver effects in rodents are probably on the "road to cancer." The Panel noted that hepatic effects were not seen in the epidemiological studies, but acknowledged that these studies were not designed to detect them.

In relation to the cardiovascular endpoint, the Panel identified hypertension and ischemic heart disease (IHD) as two key endpoints from the epidemiological studies. The Panel recommended that the U.S. EPA perform a meta-analysis of these data. The Panel also commented that recent animal studies support the observations linking TCDD exposure to IHD and hypertension. In particular, the National Toxicology Program (NTP) study shows inflammatory and structural effects on resistant vascular arterioles (NTP, 2006). Additional evidence from the study suggests that the vascular effects may be CYP1A1-dependent. The Panel suggested that the NTP study data might be used as a surrogate for dose-response modeling of hypertension and that such an approach would be supported by data on the role of AhR in vascular function and remodeling.

POD Issues

The Panel was not supportive of 1% of maximal response (ED_{01}), which was utilized in the 2003 Reassessment. The Panel concluded that the POD should depend on the specific endpoint and recommended the following to the U.S. EPA:

- For continuous measures, base the BMR on difference from control. Consider the adversity level—at what point does the endpoint become adverse?
- For incidence data, set the BMR to a fixed-risk level.

Supporting Information

The Panel posed several suggestions to the U.S. EPA for reducing uncertainty and improving the knowledge base for TCDD toxicity.

- Use in vitro data to define uncertainties, such as the relative sensitivity between rodents and humans and around the definition of a POD.
- Consider studies on dioxin-like compounds (DLCs).
- Use PK modeling to define the dose metric for hepatic effects.
- Use body burden or serum concentrations for cardiovascular endpoints.

Finally, the Panel recommended that U.S. EPA finish the reassessment quickly and establish a definitive plan to review and incorporate new data as they become available.

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SESSION 4A: DOSE-RESPONSE FOR CANCER

The U.S. EPA plans to consider development of a quantitative dose-response assessment for cancer associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced cancer.

Session 4A Panelists (Session Co-Chairs are identified by asterisk)

- Lesa Aylward, Summit Toxicology
- Kenny Crump, Louisiana Tech University
- Dale Hattis, Clark University
- *Janet Hess-Wilson, U.S. EPA
- Karen Hogan, U.S. EPA
- Manolis Kogevinas, Centre for Research in Environmental Epidemiology
- Marian Pavuk, Agency for Toxic Substances and Disease Registry
- Chris Portier, National Institute of Environmental Health Sciences
- Lorenz Rhomberg, Gradient
- Jay Silkworth, General Electric
- *Nigel Walker, National Institute of Environmental Health Sciences

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Key Study Selection

The Panel discussed both human and rodent studies. In reviewing the epidemiological data, the Panel agreed the EPA should focus on four cohort studies (Dutch cohort, NIOSH cohort, BASF accident cohort, and Hamburg cohort) and pointed out that there are numerous updates and reevaluations of data now in the literature and others will be published soon. The Panel stated that it is appropriate for the U.S. EPA to consider the increase in total cancers for modeling human cancer data, however, Non-Hodgkin's lymphoma, and lung tumors are the main TCDD-related cancer types seen in humans exposed to TCDD. The Panel suggested the U.S. EPA focus the quantitative dose-response modeling on the human data.

In reviewing the rat data, the Panel identified four new NTP rodent cancer bioassays with liver and lungs as the main target organs. However, they suggested that dose-response modeling efforts should model "all cancers" from these NTP data sets as well and use tumor incidence—not individual rats as measures.

Key Study Selection Criteria

The Panel discussed whether data for TCDD only should be used or if PCB126 could be used to develop a dose-response curve. From this discussion, the Panel reached a general agreement that limiting the dose-response modeling and cancer assessment to TCDD only would be the best approach.

Regarding the oral dosing regimens, the Panel discussed the differences in results from different bioassays. They concluded that there were insufficient data to pick between oral feed (Kociba et al., 1978) and oral gavage (NTP, 2006) studies, but stated "If all aspects of studies were equal, an oral feed study is preferred." However, given that current data sets are not equal, they agreed that U.S. EPA should consider both feed and gavage studies.

The Panel put forth the recommendation that studies that include initiation-promotion model data and TgAC transgenic model data from oral exposure studies should be excluded from the primary category in the key study selection criteria (Appendix C lists the draft study selection criteria distributed prior to the meeting). Studies from both classifications should be moved to the second tier.

The Panel was also unsupportive of the "response magnitude outside the range of normal variability" criterion, as they did not believe it was applicable to a cancer endpoint.

Critical Endpoints to Consider

The Panel recognized that the MOA for TCDD includes cell growth/differentiation dysregulation, that different endpoints (tumor types) across species may be expected, and that there are differences in tumor sites across species. The Panel further acknowledged that there is insufficient information to determine if rodent tumor types observed are relevant to humans. Thus, the Panel suggests the following:

- U.S. EPA should consider all the observed cancer endpoints in its evaluation.

Nonlinear (aka threshold) Versus Linear Dose-Response Modeling

The Panel agreed that NTP bioassays appear to demonstrate nonlinear dose response, but they expressed concern about using animal data to infer slope and dose response for humans. The Panel pointed out that there are differences in slopes across different bioassays, and specifically, that some appear linear while others appear nonlinear. Given the observation of both nonlinear vs. linear, the Panel concluded that neither could be ruled out for extrapolation below the POD simply based on the available data. One panelist noted that U.S. EPA Cancer Guidelines (U.S. EPA, 2005) state that only if one can demonstrate that the MOA has a threshold dose-response shape, and can exclude all other potential linear MOAs, can one use a nonlinear model. Lastly, the Panel noted that there are data and rationales to support use of both linear and

nonlinear response below POD. From this discussion, the Panel raised one possibility to the U.S. EPA:

- Both linear and nonlinear model functions should be considered in the dose-response analysis.

Dose Metrics

In considering human data, the Panel expressed a preference for lipid-adjusted serum levels over body burden (BB), and they expressed concerns over the assumptions used in the back calculation of the BB in the epidemiologic cohorts. In considering the rat data, the Panel supported the use of BB—especially lipid-adjusted BB. The Panel, however, did express concern over the sequestering of TCDD in liver and then the use of liver levels in BB calculations.

Supporting Information—Biologically-Based Dose-Response (BBDR) Models and MOA

The Panel discussed BBDR. Though once considered an attractive proposition, BBDR models may mask uncertainty within the models, necessitating them to be used with greater caution. The Panel suggested two issues for the U.S. EPA to consider:

- If there is a published model, use it if it is valid—do not generate a new model.
- Focus on the actual experimental data to drive the analysis.

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SESSION 4B: DOSE-RESPONSE FOR REPRODUCTIVE/DEVELOPMENTAL TOXICITY

The U.S. EPA plans to consider development of a quantitative dose-response assessment for reproductive and developmental effects associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced reproductive and developmental effects.

Session 4B Panelists (Session Co-Chairs are identified by asterisk)

- Barbara Abbott, U.S. EPA
- Bruce Allen, Bruce Allen Consulting
- Roger Cooke, Resources for the Future
- George Daston, Procter & Gamble
- Mike DeVito, U.S. EPA
- Rob Goble, Clark University
- *Fumio Matsumura, University of California-Davis
- Paolo Mocarelli, University of Milan
- Brian Petroff, University of Kansas
- *Glenn Rice, U.S. EPA
- Marie Sweeney, National Institute of Occupational Safety and Health
- Mary Walker, University of New Mexico
- Bernie Weiss, University of Rochester

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A Major Question Posed During this Workshop Session was "Are Human Embryos and Infants Less Sensitive to Dioxin Exposures Than Some Experimental Animals?"

The Panel recognized that animal data show a wide range of species sensitivity to dioxin for a given developmental or reproductive endpoint. Presently, there are data for some endpoints that show that human sensitivity is comparable to experimental animals (e.g., semen quality), and for other endpoints the data demonstrate that humans are insensitive compared to other species (e.g., cleft palate). Lastly, the Panel recognized that there are some endpoints for which relative human sensitivity remains uncertain.

Key Study Selection

The Panel reviewed the charge questions (Appendix B), discussed them, and listed two issues for the U.S. EPA to consider:

- Concerning key study determination, use a stepwise approach that is dependent upon the information available and needed to address the question.

- Concerning the key studies informing the POD and the POD endpoint choice, use the POD to depart from what is certain and use a high-confidence study that has found effects at a low enough level at which other effects are protected.

The Panel also developed Table 1, based on the information presented in this session. Table 1 identifies specific reproductive and developmental effects of concern, listing whether an effect has been observed in test animals and epidemiologic cohorts. It also identifies the ED_{10} estimated by the U.S. EPA (2003) for health effects observed in rodent bioassays. If the U.S. EPA did not report an ED_{10} for an effect, the table identifies a study where the effect was reported and the lowest study dose where the effect was observed. Table 1 also identifies the epidemiologic cohort where the specific reproductive and developmental effects were observed.

Epidemiological Study Utility

The Panel reviewed the charge questions (Appendix B), discussed them, and made two suggestions to the U.S. EPA:

- Concerning the ability of epidemiological studies to inform critical effects, start with concordance across species (including humans) for the spectrum of effects.
- Concerning the ability of epidemiological studies to inform dose-response modeling, start with the epidemiology and then go to animal data if the dose response has not been well characterized for an endpoint of interest and compare to animal data as a reality check.

Animal Model Utility

The Panel reviewed and discussed the charge questions (Appendix B). Table 1, which identifies the effects that occur in animals and also have relevance to humans, summarizes much of this discussion. Regarding the influence of mode of action (MOA) on animal model choice, the Panel concluded that by evaluating concordance among health effects reported in epidemiologic and animal bioassay data, the U.S. EPA could identify a set of plausible reproductive and developmental effects to consider. Actual animal and human MOA information is helpful in that it creates comfort with the animal models and in defining the boundaries of possible effects.

TABLE 1

Reproductive/Developmental Effects of Concern for Human Health

Endpoint	Rodent (ED_{10} ng/kg-d)	Human	Notes
Sperm Count/Motility	Yes (6.2−28; 66−200)	Yes	ED_{10} bases Mabley et al. (1992a,b) caudal sperm count and daily sperm production range from 6.2−28; Gray et al. (1997) epididymal sperm count and total testis sperm counts range from 66−200.
Sex Ratio	No	Yes, Seveso	
Delayed Puberty Males	Yes (94)	Yu-cheng	ED_{10} basis rat male puberty delay Gray et al. (1997). Need to qualify epidemiology data because of cohort PCDD/PCDFs exposures.
Delayed Puberty in Females	Yes	No in Seveso	Gray and Ostby (2002) report delayed puberty in female offspring of pregnant rats receiving a single dose of 1 µg TCDD/kg on GD 15.
Cleft Palate	Yes (6300−6400)	No	ED_{10} basis Birnbaum et al. (1989).
Premature Senescence	Yes	No, Seveso	Franczak et al. (2006) report that rats prematurely entered reproductive senescence, after receiving cumulative TCDD doses as low as 1.7 µg TCDD/kg. They considered first occurrence of prolonged interestrous interval (>6 d) as evidence of onset of reproductive senescence.
Hormones E2	Yes	Yes, Males—Seveso	Li et al. (1995) report serum estradiol-17β (E2) concentrations induced by equine Chorionic Gonadotropin injection were significantly elevated in female rats orally administered 10 µg/kg TCDD on PND 22. While E2 decreased dramatically in control animals during the preovulatory LH surge, it did not in TCDD-treated rats.
Low Birth Weight	Yes (190)	Suggestive effect in Seveso in first 8 years after exposure	ED_{10} basis Gray et al. (1997).
Reproductive Cycling (prolongation)	Yes	Yes, Seveso Prepubertal exposure	Franczak et al. (2006) report loss of normal cyclicity in female rats at 8 months of age following a cumulative dose of 1.7 µg TCDD/kg.

Supporting Information

The Panel reviewed the charge questions (Appendix B), discussed them, and made two suggestions to the U.S. EPA:

- Concerning deviation from default approaches for noncancer endpoints, there needs to be a careful assessment of the POD and the application of uncertainty factors in light of PK/pharmacodynamics (PD), population characteristics and variability, and MOA information.
- Concerning the MOA's ability to clarify endpoint and the incorporation of a cascade of cellular event into dose-response for noncancer endpoint, any study that helps inform the dose response should be considered—including studies not specific to dioxins. Complicated mechanistic models need not be developed. Standard dose-response models can be applied. One can look at the cascade of events in a stepwise, simple way.

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Mably, T.A., R.W. Moore, R.W. Goy et al. 1992b. *In utero* and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin. 2. Effects on sexual behavior and the regulation of luteinizing hormone secretion in adulthood. Toxicol. Appl. Pharmacol. 114:108-117.

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SESSION 5: QUANTITATIVE UNCERTAINTY ANALYSIS OF DOSE-RESPONSE

This session addressed the uncertainty analysis to be considered for the dose-response assessments. The session opened with a presentation on current estimates of dioxin exposure levels. Then it focused on the factors to include in the scope of an uncertainty analysis including dioxin kinetics.

Session 5 Panelists (Session Co-Chairs are identified by asterisk)

- Bruce Allen, Bruce Allen Consulting
- Lesa Aylward, Summit Toxicology
- Roger Cooke, Resources for the Future
- Kenny Crump, Louisiana Tech University
- Mike DeVito, U.S. EPA
- Dale Hattis, Clark University
- *Rick Hertzberg, Biomath Consulting
- Nancy Kerkvliet, Oregon State University
- Leonid Kopylev, U.S. EPA
- Rob McDowell, U.S. Department of Agriculture
- Lorenz Rhomberg, Gradient
- Woody Setzer, U.S. EPA
- Marie Sweeney, National Institute of Occupational Safety and Health
- *Linda Teuschler, U.S. EPA

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The Panel summarized the NAS comments regarding uncertainty. Areas for improvement include:

- Ensure “transparency, thoroughness, and clarity in quantitative uncertainty analysis.”
- Describe and define (quantitatively to the extent possible) the variability and uncertainty for key assumptions used for each key endpoint-specific risk assessment, including choices of data set, point of departure, dose-response model, and dose metric.
- Incorporate probabilistic models to represent the range of plausible values.

- Assess goodness-of-fit of dose-response models.
- Provide upper and lower bounds on central tendency estimates for all statistical estimates.
- When quantification is not possible, clearly state it, and explain what would be required to achieve quantification.

Identification of Important Uncertainties

The Panel reviewed the charge questions (Appendix B), discussed them, and listed eight issues for consideration by the U.S. EPA:

- Concerning species and strain differences in the U.S. EPA's Response to NAS, current U.S. EPA procedures do not take this into account when selecting one data set for risk assessment. Issues include "Where are humans in the distribution of potencies that can be generated? How likely is it that human response is similar to the selected data? Can we infer inter-individual variability from these differences?"
- Concerning the use of animal data for cross species extrapolation to humans (PK and PD uncertainties), issues to consider include differences in distribution and responses following bolus doses from those of subchronic and chronic protocols; uncertainty in liver doses due to sequestration; differences in receptor binding affinity among congeners; and age factors (e.g., assumption of a lifetime constant daily dose for a cancer extrapolation).
- Concerning the description of AhR response, biochemical changes occur at lower doses than toxicological changes. There should be an effort to identify the biochemical changes that would mark Ah receptor binding to inform the BMR, and, thus, prevent toxicity.
- Concerning model uncertainty, the mathematical model choice depends on endpoint. There should be an effort towards determining what is the most sensitive endpoint(s) for humans and conducting animal studies to model that endpoint(s).
- Concerning exposure and dose response in human studies, ensure enough similarity to current human exposure profiles (mixture composition) so that a dose-response assessment can be done. Incorporate new epidemiological studies. Evaluate concordance with animal data and consistency across studies. Panel-acknowledged uncertainties include exposure estimates from person to person, shape of human dose-response curve, healthy worker effect, and age dependence.
- Concerning POD determination, uncertainty factors are inherently mathematically inconsistent and that should be conveyed in the discussion of uncertainties when interpreting the POD.
- Concerning dose metric, tissue concentration is preferred. It should be evaluated against a background of variability in AhR-binding expression. There is uncertainty in what level of binding should be considered, in different cell types, tissues, life stage (development). The relationship between dose metric and causation of adverse effects should be examined.

Low-Dose Extrapolation

The Panel reviewed the charge questions and discussed them (Appendix B). The Panel concluded that curve-fitting uncertainty (for a given dataset, dose metric, and model) can be characterized and is useful, but, by itself, it is an incomplete characterization of uncertainty. The Panel acknowledged the difficulty of fully characterizing uncertainty, especially quantitatively. Some panelists argued that the problem is insurmountable and that no meaningful uncertainty analysis is likely to be performable. Other panelists contended that, the difficulties notwithstanding, "good-faith" efforts to do something practical and forthright to characterize uncertainty in low-dose extrapolation would be useful and important. The Panel clarified "good faith" as meaning a characterization that is useful and not misleading to decision makers and is inclusive of approaches that have meaningful support in the scientific community as a whole. Being in "good faith" is more important than being complete (i.e., addressing every uncertain element), especially since completeness is not a realistic goal. From this discussion, the Panel listed four issues for consideration by the U.S. EPA:

- Review alternative data sets, dose metrics, and models to see where consequential uncertainties and impacts on low-dose implications arise.
- Consider the impacts of choices among plausible alternative data sets, dose metrics, models, and other more qualitative choices—issues include how much difference the choices make and also how much relative credence should be put to each alternative as a way of gauging and describing the landscape of imperfect knowledge regarding possibilities for the true dose-response.
    - Hard to do quantitatively, since the factors are not readily expressed as statistical distributions, but can describe the rationale for believing/doubting each alternative in terms of available supporting evidence, contrary evidence, and needed assumptions.
    - Expert judgment methods may be helpful in characterizing the relative weights of scientific credibility among alternatives. The expert judgment process, when conducted systematically, can be thought of as adding data to the assessment of credibility of alternatives, rather than as just an opinion poll.
    - Information on plausibility of alternative low-dose extrapolation approaches can come from external considerations of mode of action, and not just from statistical success at fitting particular (high-dose) data sets.
- Characterizing uncertainty through a variety of approaches could be tried, and their relative merits and shortcomings discussed, as a way forward.
- Consider the sources of potential error, particularly in epidemiological data (e.g., TEF uncertainty and variation in congener mixtures) and if possible quantify their impact on the dose-response assessment.

Considerations for Conducting Uncertainty Analysis

Overall, the Panel was split on whether U.S. EPA should do quantitative uncertainty analyses. The Panel noted that if done on only some of the uncertainties, then results would be misleading and could be misused. Ultimately, the Panel listed seven issues for consideration by the U.S. EPA:

- The Panel recapped what some consider as being the first integrated risk assessment, with structured expert judgment and uncertainty analysis, i.e., the Rasmussen Report (WASH-1400; U.S. Nuclear Regulatory Commission, 1975). In their discussion of the report, the Panel noted that in addition to standard event tree/fault tree modeling, this report also tackled difficult model uncertainty issues involved in accident progression, dispersion of released pollutants in the atmosphere, environmental transport, exposure, health, and economic impacts. And though the Panel also recognized that this method was no longer state-of-the-art, the Panel contended that it represents a good example of a structured approach and methodology that could be built upon.

- The Panel also discussed TEQs used in epidemiological studies, based on intake, and recognized that the key uncertainty in what was measured was not just intake but also involved PK/PD issues. The Panel acknowledged that the TEQ system is regularly used on a concentration basis, but they expressed concern that the qualification becomes lost. TEQs ignore pharmacokinetics and the common practice of rounding to orders of magnitude introduces more error.
- Structure the risk assessment along MOA steps—identify key biochemical measures (~5−10) common across toxic endpoints and identify the degree of meaningful change in effect or effect variance. Make a table with all options for data set, model, etc.; make best estimates/choices and determine which of these choices matter the most to the answer.
- Use expert panels—expert judgment can be collected scientifically (procedures are published). But there are known biases; central tendency estimates work much better than extremes.
- Use supporting studies to fill in critical data gaps—Info filling methods do exist (e.g., PK modeling). Put short-term studies into the "supporting info" category (unless, of course, the risk assessment is for acute exposures, such as chemical spills).
- Be creative in the analysis of uncertainty. Intermediate steps between AhR binding and the end processes can be hypothesized based on data, experiences, and analogies related to other chemicals.
- The 2003 Reassessment presented potency estimates on wide variety of endpoints/models; needed to be more transparent in that discussion. Statistical graphics can be used to convey uncertainties.

Reference

U.S. Nuclear Regulatory Commission. 1975. Reactor Safety Study: An Assessment of Accident Risks in U.S. Commercial Nuclear Power Plants. WASH-1400 (NUREG-75-014). Washington, DC.

APPENDIX A: 2009 U.S. EPA DIOXIN WORKSHOP AGENDA

SCIENTIFIC WORKSHOP
TO INFORM THE TECHNICAL WORK PLAN FOR U.S. EPA'S RESPONSE TO NAS COMMENTS ON THE HEALTH EFFECTS OF DIOXIN PRESENTED IN U.S. EPA'S DIOXIN REASSESSMENT

Cincinnati, OH

Date: February 18–20, 2009

BACKGROUND/WORKSHOP OBJECTIVE

At the request of the U.S. Environmental Protection Agency (U.S. EPA), the National Academy of Sciences (NAS) prepared a report, *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment* (NAS, 2006), that made a number of recommendations to improve the U.S. EPA's risk assessment for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). In response, the U.S. EPA will prepare a technical report that addresses key comments on the dose-response assessment for TCDD. The U.S. EPA intends to develop its response through a transparent process that provides multiple opportunities for input.

To assist in this effort, a Workshop will be held to inform the U.S. EPA's evaluation of the NAS recommendations. The Workshop will be open to the public. At the Workshop, the U.S. EPA will solicit input from expert scientists and the public.

The goal of the Workshop is to ensure that the U.S. EPA's response to the NAS comments focuses on the key issues and reflects the most meaningful science. The three main objectives of the Workshop are to (1) identify and discuss the technical challenges involved in addressing the NAS key comments on the TCDD dose-response assessment in the U.S. EPA Reassessment (U.S. EPA, 2003), (2) discuss approaches for addressing these comments, and (3) identify key published, independently peer-reviewed literature, particularly studies describing epidemiologic and *in vivo* mammalian bioassays, which are expected to be most useful for informing the U.S. EPA response.

Workshop participants will be encouraged to think broadly about the body of scientific information that can be used to inform the U.S. EPA's response and to participate in open dialogue regarding ways in which the science can best be used to address the key dose-response issues. This Workshop is similar to scientific workshops being conducted under the new review process for the National Ambient Air Quality Standards (NAAQS)[1] that assess health-related information for criteria pollutants.

[1] Please see http://www.epa.gov/ttn/naaqs/ for more information on the new NAAQS review process.

The Workshop discussions are expected to build upon two prior publications:

1. Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds (U.S. EPA, 2003). This external review draft provides a comprehensive reassessment of dioxin exposure and human health effects. This "dioxin reassessment" was submitted in October 2004 to the National Academy of Sciences (NAS) for review.
2. *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment* (NAS, 2006).

Workshop participants are encouraged to review both of these documents and other relevant materials (e.g., the National Toxicology Program report on TCDD [NTP, 2006]) before the meeting because they provide important insights into the key questions and challenges. There are a number of open comment periods that are intended to facilitate a broad discussion of the issues.

Scientists with significant expertise and experience relevant to the health effects of TCDD or dioxin-like compounds and associated topics will be asked to serve on "expert panels" for discussions throughout the Workshop. Workshop panelists will include a wide range of experts representing many scientific areas needed to assess TCDD dose-response (e.g., epidemiology, human and animal toxicology, nuclear receptor biology, dose-response modeling, risk assessment, and uncertainty analysis). The Workshop panelists will be asked to highlight significant and emerging research and to make recommendations to the U.S. EPA regarding the design and scope of the technical response to NAS comments on the dose-response analysis for TCDD—including, but not limited to, recommendations for evaluating associated uncertainty. Open comment periods will follow each panel discussion session. Public participation will be encouraged by way of these designated open comment periods and, also, by participation in the scientific poster session planned for the second evening (February 19).

U.S. EPA will use the input received during this Workshop as the foundation for its development of a technical work plan for responding to the NAS comments on the TCDD dose-response analysis. The work plan will outline the schedule, process, and approaches for evaluating the relevant scientific information and addressing the key issues. The work plan also will identify the key literature to be utilized in U.S. EPA's response.

As a follow-on activity to this Workshop, a panel is being established under the Federal Advisory Committee Act (FACA) to guide and review the U.S. EPA's response to NAS comments. The FACA panel will be asked to conduct a consultation with the Agency on the draft technical work plan. At the same time, the public will also have the opportunity to provide comments to the FACA panel on the work plan. The final technical work plan will guide the development of the technical report that will constitute the U.S. EPA's response to NAS comments. During the development of this response, the U.S. EPA will seek advice from the FACA panel and the public several times. Finally, the FACA panel will be asked to review the technical report in a public forum.

The preliminary Agenda presented on the following pages may be revised prior to the Workshop following review by the session Co-Chairs; the dates and general timing of the

sessions, however, will not change. A final Agenda and a set of charge questions, intended to provide general direction for the Workshop discussions, will be posted on the Workshop Internet site (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199923) prior to the meeting.

A poster session will be held on the evening of the second day (February 19). The purpose of this poster session is to provide a forum for scientists to present recent studies relevant to TCDD dose-response assessment and to encourage open discussion about these presentations.

REFERENCES

NAS (National Academy of Sciences). 2006. Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment. National Academies Press, Washington, DC (July). Available at http://www.nap.edu/catalog.php?record_id=11688.

NTP (National Toxicology Program). 2006. Toxicology and Carcinogenesis Studies of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) (CAS No. 1746-01-6) in Female Harlan Sprague-Dawley Rats (Gavage Studies). U.S. Department of Health and Human Services. NTP TR 521. Research Triangle Park, NC (April).

U.S. EPA (U.S. Environmental Protection Agency). 2003. *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds*, NAS review draft, Volumes 1-3 (EPA/600/P-00/001Cb, Volume 1). U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, DC (December). Available at http://www.epa.gov/nceawww1/pdfs/dioxin/nas-review/.

WORKSHOP AGENDA

Day 1

8:00–9:00	**Registration**
9:00–9:30	**Welcome/Purpose of Meeting/Document Development Process**
9:30–9:45	**Panel Comments/Questions on Charge**

9:45–2:45 Session 1: Quantitative Dose-Response Modeling Issues (Hall of Mirrors)

9:45–10:10	**Background/Introductory Remarks**
10:10–10:35	**TCDD Kinetics: Converting Administered Doses in Animals to Human Body Burdens** Presenter: Michael Devito
10:35–11:30	**Panel Discussion**
11:30–1:00	**Lunch**
1:00–2:00	**Panel Discussion cont.**
2:00–2:45	**Open Comment Period**

2:45–3:05 Break

3:05–5:15 Session 2: Immunotoxicity (Hall of Mirrors)

3:05–3:15	**Background/Introductory Remarks**
3:15–4:45	**Panel Discussion**
4:45–5:15	**Open Comment Period**

Day 2

8:00–8:30 **Report-Outs for Sessions 1 and 2 (Hall of Mirrors)**

8:00–8:15 **Report-Out for 1: Quantitative Dose-Response Modeling Issues**

8:15–8:30 **Report-Out for 2: Immunotoxicity**

8:30–11:30 **Sessions 3A and 3B (concurrent sessions)**

8:30–11:30 **Session 3A: Dose-Response for Neurotoxicity and Nonreproductive Endocrine Effects (Hall of Mirrors)**

8:30–8:45 **Background/Introductory Remarks**

8:45–11:00 **Panel Discussion**

11:00–11:30 **Open Comment Period**

8:30–11:30 **Session 3B: Dose-Response for Cardiovascular Toxicity and Hepatotoxicity (Rookwood Room)**

8:30–8:45 **Background/Introductory Remarks**

8:45–11:00 **Panel Discussion**

11:00–11:30 **Open Comment Period**

11:30–1:00 **Lunch**

1:00–2:00 **Report-Outs for Sessions 3A and 3B (Hall of Mirrors)**

The structure of the session report-outs will include the following:

- Summary of session presentation including minority opinion
- Public comments
- Discussion

1:00–1:15 **Report-Out for 3A: Dose-Response for Neurotoxicity and Nonreproductive Endocrine Effects**

1:15–1:30 **Open Comment Period**

1:30–1:45	**Report-Out for 3B: Dose-Response for Cardiovascular Toxicity and Hepatotoxicity**
1:45–2:00	**Open Comment Period**

2:00–5:15 Sessions 4A and 4B (concurrent sessions)

2:00–5:15 Session 4A: Dose-Response for Cancer (Hall of Mirrors)

2:00–2:15	**Background/Introductory Remarks**
2:15–4:45	**Panel Discussion**
4:45–5:15	**Open Comment Period**

2:00–5:15 Session 4B: Dose-Response for Reproductive/Developmental Toxicity (Rookwood Room)

2:00–2:15	**Background/Introductory Remarks**
2:15–4:45	**Panel Discussion**
4:45–5:15	**Open Comment Period**

6:45–8:15 Poster Session (Rosewood Room)

Day 3

8:30–9:30 Report-Outs for Sessions 4A and 4B (Hall of Mirrors)

8:30–8:45	**Report-Out for 4A: Dose-Response for Cancer**
8:45–9:00	**Open Comment Period**
9:00–9:15	**Report-Out for 4B: Dose-Response for Reproductive/Developmental Toxicity**
9:15–9:30	**Open Comment Period**

9:30–3:30	**Session 5: Quantitative Uncertainty Analysis of Dose-Response (Hall of Mirrors)**
9:30–9:40	**Background/Introductory Remarks**
9:40–10:10	**Evidence of a Decline in Background Dioxin Exposures in Americans Between the 1990s and 2000s** Presenter: Matt Lorber
10:10–10:30	**Break**
10:30–11:30	**Panel Discussion**
11:30–1:00	**Lunch**
1:00–2:15	**Panel Discussion cont.**
2:15−2:30	Break
2:30–3:00	**Open Comment Period**
3:00–3:15	**Report-Out for 5: Quantitative Uncertainty Analysis of Dose-Response**
3:15–3:30	**Closing Remarks**
3:30	**Adjourn**

APPENDIX B: 2009 U.S. EPA DIOXIN WORKSHOP QUESTIONS TO GUIDE PANEL DISCUSSIONS

SESSION 1

Dose Metric

Considering all of the endpoints or target tissues, and species that U.S. Environmental Protection Agency (U.S. EPA)'s dose-response modeling might evaluate, what are the best measures of dose (e.g., ingested, tissue concentrations, body burden, receptor occupancy, other surrogate) and why?

Developing Dose-Response Models from Mammalian Bioassays

How best can the point of departure (POD) be determined when the response range is incompletely characterized (i.e., high response at the lowest dose or low response at the highest dose; observed in several key 2,3,7,8-Tetrachlorodibenzo-p-Dioxin [TCDD] studies)?

If considered to be biologically plausible, how can a threshold be incorporated into a dose-response function (e.g., for TCDD cancer data)?

How can nonmonotonic responses be incorporated into the dose-response function?

Developing Dose-Response Models from Epidemiological Studies

How can the epidemiological data be utilized best to inform the TCDD exposure-response modeling? Which epidemiological studies are most relevant?

Supporting Information

For those toxicological endpoints that are Ah receptor-mediated, how would the receptor kinetics influence the shape of the dose-response curve? How would downstream cellular events affect the shape of the dose-response curve? How can this cascade of cellular events be incorporated into a quantitative model of dose-response?

SESSIONS 2, 3A, 3B, 4A, AND 4B

Key Study Selection

For this endpoint, what refinements should be made to the draft criteria for selection of key studies?

What are the specific effects of concern for human health for this endpoint?

Based on the draft criteria for the selection of key studies, what are the key studies informing the shape of the dose-response curve above the POD and the choice of the POD for this endpoint?

Epidemiological Study Utility

How and to what extent do the epidemiological data inform the choice of critical effect?

How can the epidemiological data inform the quantitative dose-response modeling?

Animal Model Utility

Are there types of effects observed in animal models that are more relevant to humans than others? To what extent does information on mode of action (MOA) influence the choice of animal model (species, strain, sex)?

Supporting Information

Are there studies that establish a sufficient justification for departure from the default procedures that address the shape of the dose-response curve below the POD under the cancer guidelines?

Are there studies that establish a sufficient justification for departing from U.S. EPA's default approaches for noncancer endpoints?

To what extent can MOA information clarify the identification of endpoints of concern and dose-response metric for this endpoint? How can the cascade of cellular events for this endpoint be incorporated into a quantitative model of dose response?

SESSION 5

For cancer and noncancer TCDD dose-response assessments, U.S. EPA is interested in developing a quantitative uncertainty analysis addressing both parameter and model uncertainty, if feasible. Uncertainties will include, among others, choice of endpoint; underlying study uncertainties; choice of dose metric; interspecies extrapolations such as kinetic uncertainties; and choice of dose-response model, including threshold models. The U.S. EPA is currently examining techniques and tools for uncertainty analysis—including Bayesian and frequentist approaches.

Identification of Important Uncertainties

What are the major uncertainties pertaining to modeling the animal data?

> Consider the dose metric (species or tissue specificity), vehicle of administration, exposure frequency, exposure duration, and POD determination (e.g., benchmark response selection or no-observed-adverse-effect level/lowest-observed-adverse-effect level identification).

What are the major uncertainties pertaining to dose-response modeling below the POD?

> Consider how receptor kinetics and downstream cellular event information might be used to bound the uncertainties associated with dose-response modeling below the POD.

What are the major uncertainties in cross-species extrapolation (e.g., half-lives, tissue distribution, and toxicodynamics)?

> Consider the primary species dosed with TCDD: mice, hamsters, rats, guinea pigs, and monkeys.

What are the major uncertainties pertaining to intrahuman variability?

> Consider what data sets would be useful to represent sensitive subpopulations.

What are other significant sources of uncertainty for the cancer and noncancer assessments?

Considerations for Conducting Uncertainty Analysis

What data sets could be used to quantify uncertainties in cancer and noncancer TCDD dose-response assessments?

> Consider dioxin-like compound dose-response data.
> Consider MOA information.

What are the appropriate techniques for the TCDD dose-response uncertainty analysis, and what are their respective strengths and weaknesses of these approaches as applied to TCDD?

APPENDIX C: 2009 U.S. EPA DIOXIN WORKSHOP DRAFT SELECTION CRITERIA TO IDENTIFY KEY *IN VIVO* MAMMALIAN STUDIES THAT INFORM DOSE-RESPONSE MODELING FOR 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD)[a]

Study Feature	Selection Rationale		
	Primary[b]	***Secondary***[c]	***Currently Excluded***
Chemical, purity, matrix/medium	TCDD-only doses included, purity specified, matrix in which TCDD is administered is identified	TCDD purity or matrix not clearly identified	Studies of dioxin-like compounds (DLCs) or mixtures
Peer review	Independently peer-reviewed, publicly available	Supplementary materials accompanying peer-reviewed publication	Not formally peer-reviewed; literature not publicly available
Study design, execution, and reporting	Clearly documented and consistent with standard toxicological principles, testing protocols, and practice (i.e., endpoint-appropriate, particularly for negative findings)	Testing protocol provides incomplete coverage of relevant endpoint-specific measures, particularly for negative findings	Studies not meeting standard principles and practices
Study subject: species, strain, and sensitivity for given endpoint; litter; life stage; gender	Mammalian species Strain and gender identified Animal age at beginning of treatment identified Litter confounders (within/between) accounted for	Mammalian species, *in vivo*, but only studying an artificially sensitive subject (e.g., knockout mouse)	Non-mammalian or not *in vivo*
Exposure route	Oral	Parenteral (e.g., intravenous, intramuscular, intraperitoneal, subcutaneous)	Inhalation, dermal, ocular
Dose level	Lowest dose ≤200 ng/kg-d for noncancer endpoints and ≤1 µg/kg-d for cancer	Lowest dose >200 ng/kg-d for noncancer endpoints, or >1.0 µg/kg-d for cancer	
Exposure frequency, duration, and timing	Dosing regimen characterized and explained		Characterization/explanation missing or cannot be determined
Controls	Appropriate and well characterized	Effect reported, but with no negative control	
Response	Effect relevant to human health Magnitude outside range of normal variability	Precursor effects, or adaptive responses potentially relevant to human health	Lethality
Statistical evaluation	Clearly described and appropriate to the endpoint and study design (e.g., per error variance, magnitude of effect)	Limited statistical context	

[a] NAS (2006) commented that the selection of data sets for quantitative dose-response modeling needed to be more transparent. These draft criteria are offered for consideration at the kickoff workshop. These criteria would be used to identify candidate studies of non-human mammals that would be used to define the point-of-departure (POD). These criteria are not designed for hazard identification or weight-of-evidence determinations. Studies addressing data other than direct TCDD dose-response in mammals (including toxicokinetic data on absorption, distribution, metabolism, or elimination; information on physiologically-based pharmacokinetic [PBPK] modeling, and mode of action data) will be evaluated separately.

[b] Presents preliminary draft criteria for evaluating a study being considered for estimating a POD in a TCDD dose-response model.

[c] Presents preliminary draft criteria that could qualify a study as primary with support from other lines of evidence (e.g., PBPK modeling), when no study for an endpoint meets the "primary" criteria.

EPA/600/R-10/038F
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APPENDIX C

Summaries and Evaluations of Cancer and Noncancer Epidemiologic Studies for Inclusion in TCDD Dose-Response Assessment

January 2012

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

CONTENTS—Appendix C: Summaries and Evaluations of Cancer and Noncancer Epidemiologic Studies for Inclusion in TCDD Dose-Response Assessment

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APPENDIX C. SUMMARIES AND EVALUATIONS OF CANCER AND NONCANCER EPIDEMIOLOGIC STUDIES FOR INCLUSION IN TCDD DOSE-RESPONSE ASSESSMENT

C.1. EVALUATION OF EPIDEMIOLOGIC STUDIES FOR DOSE-RESPONSE ASSESSMENT

This appendix summarizes and evaluates studies for potential use in tetrachlorodibenzo-p-dioxin (TCDD) dose-response assessment using the study evaluation considerations and inclusion criteria for epidemiologic data (see Section 2.3.1). Those studies that meet the study inclusion criteria are listed in Section 2 of this document in Tables 2-1 and 2-2, for cancer and noncancer, respectively. The following sections, C.1.1 and C.1.2, for cancer and noncancer studies, respectively, are organized by epidemiologic study population. In Section C.1.1, following a brief summary of each cohort, its associated cancer studies are then summarized chronologically, assessed for methodological considerations relative to epidemiologic cohorts and studies and evaluated for suitability for TCDD dose-response assessment. In Section C.1.2, summaries of the cohorts are not repeated, but are still used as an organizing element for this section. The reader is referred back to the cancer section for the cohort summaries. Following the heading for the cohort, its associated noncancer studies are then summarized chronologically, assessed for methodological considerations relative to epidemiologic cohorts and studies and evaluated for suitability for TCDD dose-response assessment.

Sections C.2 and C.3 of this appendix provide specific details of the study selection criteria results for the cancer and noncancer epidemiologic studies, respectively. This includes a table for each study with information on how each of the five considerations and three criteria were evaluated, and why each study was or was not selected by U.S. Environmental Protection Agency (EPA) for TCDD quantitative dose-response assessment.

C.1.1. Cancer

In the 2003 Reassessment, EPA selected three cohort studies from which to conduct a quantitative dose-response analysis: the National Institute for Occupational Safety and Health (NIOSH) cohort (Steenland et al., 2001b), the BASF cohort (Ott and Zober, 1996b), and the Hamburg cohort (Becher et al., 1998). Although these studies were deemed suitable for a quantitative dose-response analysis, the criteria EPA used to reach this conclusion were unclear.

In this section, the study selection criteria and methodological considerations presented in Section 2.3.1 are systematically applied to evaluate a number of studies to determine their suitability for inclusion in dose-response modeling. In addition to the three cohorts used in previous TCDD quantitative risk assessment, considerations are applied to other relevant TCDD epidemiologic data sets that were identified through a literature review for epidemiologic studies of TCDD and cancer up through 2009. Study summaries and suitability for quantitative dose-response analysis evaluations are discussed below.

C.1.1.1. *Cancer Cohorts*

C.1.1.1.1. *The NIOSH cohort*

In 1978, the NIOSH undertook research that identified workers employed by U.S. chemical companies that made products contaminated with TCDD between 1942 and 1982. TCDD was generated in the production of 2,4,5-trichlorophenol and subsequent processes. This chemical was used to make 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), which was a major component of the widely-used defoliant, Agent Orange. The NIOSH cohort is the largest cohort of occupational workers studied to date, and has been the subject of a series of investigations spanning more than two decades. It is important to note that this cohort consists mostly of male workers that were chronically exposed to TCDD via daily occupational exposure, as compared to an acute accidental exposure scenario seen with other cohorts. The investigations have progressed from a comparison of the mortality patterns of the cohort to the U.S. general population to dose-response modeling using serum-derived estimates of TCDD that have been back-extrapolated several decades. Analyses of cancer data from the NIOSH cohort that are addressed in this section include studies published by Fingerhut et al. (1991a), Steenland et al. (2001b; 1999), Cheng et al. (2006), and Collins et al. (2009).

C.1.1.1.1.1. ***Fingerhut et al. (1991a)***

C.1.1.1.1.1.1. *Study summary*

The investigation of Fingerhut and her colleagues published nearly two decades ago attracted widespread attention (Fingerhut et al., 1991a). This retrospective study examined patterns of cancer mortality for 5,172 male workers who comprised the NIOSH cohort, which combined workers from the company-specific cohorts of Dow Chemical (Ott et al., 1987; Cook,

1981) and the Monsanto Company (Zack and Gaffey, 1983; Zack and Suskind, 1980). These workers were employed at 12 plants producing chemicals contaminated with TCDD. The production processes were assumed to be the same in all 12 plants. Almost all workers in the cohort (97%) had production or maintenance jobs with processes involving TCDD contamination. On average, workers were employed for 2.7 years in specific processes that involved TCDD contamination, and overall, were employed for 12.6 years. Serum TCDD samples were obtained from 253 workers (gender not specified) from two plants (selection criteria and response rates not specified in the study). Due to the high correlation between the logarithm of serum TCDD levels and the logarithm of years of exposure (Pearson correlation coefficient = 0.72), the study used duration of exposure as a surrogate for TCDD exposure. The mortality follow-up began in 1940 and extended until the end of 1987. Vital status was determined using records from the Social Security Administration, the Internal Revenue Service, or the National Death Index. The ascertainment of vital status in the cohort was nearly complete, with less than 1% of the cohort not followed up until death or the end of the study period. Two-hundred two workers were excluded because plant records did not show duration of exposure, and 67 women were excluded. No additional data were presented on study participants to determine how representative they were of the overall study cohort. Comparisons of mortality were made relative to the U.S. male general population and expressed using the standardized mortality ratios (SMRs) and 95% confidence intervals (CIs). Life-table methods were used to generate person-years of risk accrued by cohort members at each plant. Person-years and corresponding deaths were tabulated across age, race, and year of death strata, which permitted the SMRs to be adjusted for the potential confounding influence from these three characteristics. No unadjusted SMRs were presented in the paper. The cross-classification of person-years and deaths was also done across several exposure-related groupings, including duration of employment, years since first exposure, years since last exposure, and duration of exposure. Employment duration was categorized as <5, 5− <10, 10− <15, 15− <20, 20− <25, 25− <30, and ≥30 years. The variable "years since first exposure" (<10, 10− <20, and ≥20 years) was used to evaluate associations for different latency periods. The analysis was jointly stratified by duration of employment and for varying latency intervals to evaluate whether cohort members with higher cumulative TCDD levels had higher cancer mortality rates than those cohort members with lower cumulative levels.

Overall, the cohort of workers had slightly elevated cancer mortality than the general population (SMR = 1.15, 95% CI = 1.02−1.30). Comparisons to the general population, however, yielded no statistically significant excess for any site-specific cancer. Cancer mortality was examined for the subset of workers that worked for at least one year and had a latency interval of at least 20 years (*n* = 1,520). The 1-year cut-point was selected based on analyses of serum levels in a subset of 253 workers which revealed that every worker employed for at least one year had a lipid-adjusted serum level that exceeded the mean (7 ppt). Relative to the U.S. general population, statistically significant excesses in cancer mortality were observed for all cancers (SMR = 1.46, 95% CI = 1.21−1.76), cancers of the respiratory system (SMR = 1.42, 95% CI = 1.03−1.92), and for soft tissue sarcoma (SMR = 9.22, 95% CI = 1.90−26.95) among this subset of 1,520 male workers. The elevated SMR for soft tissue sarcoma, however, was based on only three cases in this subset.

SMRs also were generated across joint categories of duration of exposure and period of latency for deaths from all cancer sites (combined), and cancer of the trachea, bronchus, and lung. Increased SMRs were observed in strata defined by longer duration of exposure and latency, but no statistically significant linear trends were found.

C.1.1.1.1.1.2. *Study evaluation*

This cohort was the largest of four the International Agency for Research on Cancer (IARC) considered in its 1997 classification of TCDD as a Group 1 human carcinogen (IARC, 1997). Duration of employment in processes that involved TCDD contamination was used as a surrogate measure of cumulative exposure. This was based on a high correlation detected between serum TCDD levels and duration of exposure. These 253 workers selected from two plants each had their last exposure 15–37 years prior to evaluation. In using this exposure metric, Fingerhut et al. (1991a) made the implicit assumption that concentrations of TCDD exposures were equivalent at all production plants. Doses for individual cohort members were not reconstructed for these analyses, although they were in subsequent analyses of this cohort.

Workers in this cohort were also exposed to other chemicals, which could have introduced bias if these chemicals were associated with both TCDD exposure and the health outcomes being examined. At one plant, workers were exposed to 4-aminobiphenyl. Previous investigators also reported that workers at another plant were exposed to 2,4,5-T and

2,4-dichlorophenoxyacetic acid (2,4-D) (Bond et al., 1989; 1988; Ott et al., 1987). Although this study did not examine the impact of confounding by other occupational coexposures, subsequent analyses of this cohort showed that associations between cumulative TCDD and all cancer mortality persisted after excluding workers exposed to pentachlorophenols from the analyses (Steenland et al., 1999). Further, the removal of workers who died from bladder cancer did not substantially change the dose-response relationship between TCDD and cancer mortality from all other sites combined. This finding suggests that exposures to 4-aminobiphenyl distort the association between cancer mortality and TCDD exposure. Overall, there is little evidence of confounding by these coexposures among this cohort; however, exposure to other possible confounders, such as dioxin-like compounds (DLCs), was not examined.

The study collected no information on the smoking behaviors of the workers, and therefore, the SMRs do not account for possible differences in the prevalence of smoking that existed between the workers and the general population. For several reasons, however, the inability to take into account smoking is unlikely to have been an important source of bias. First, mortality from other smoking-related causes of death such as nonmalignant respiratory disease were not more common in the cohort than in the general population (SMR = 0.96, 95% CI = 0.54−1.58). Second, stratified analyses of workers with at least a 20-year latency (assuming this subset shared similar smoking habits) revealed that excesses were apparent only among those who were exposed for at least 1 year. Specifically, when compared to the general population, the SMR among workers exposed for at least 1 year with a latency of 20 years was 1.46 (95% CI = 1.21−1.76), while those exposed for less than 1 year had an SMR of 1.02 (95% CI = 0.76−1.36). Third, for comparisons of cancer mortality between blue-collar workers and the general population, smoking is unlikely to explain cancer excesses of greater than 10−20% (Siemiatycki et al., 1988). Finally, the investigators found no substantial changes in the results for lung cancer when risks were adjusted for smoking histories obtained in 1987 from 223 workers employed at two plants. These data were used to adjust for the expected number of lung cancer deaths expected in the entire cohort (Fingerhut et al., 1991a). Following this adjustment, a small change was observed in the SMR for lung cancer in the overall cohort from 1.11 (95% CI = 0.89−1.37) to 1.05 (95% CI = 0.85−1.30). Similarly, only a slight change in the SMR for lung cancer in the higher exposure subcohort was noted from an SMR of 1.39 (95% CI = 0.99−1.89) to 1.37 (95% CI = 0.98−1.87).

The use of death certificate information from the National Death Index is appropriate for identifying cancer outcomes. For site-specific cancers such as soft tissue sarcoma, however, the coding of the underlying cause of death is more prone to misclassification (Percy et al., 1981). Indeed, a review of tissues from four men concluded to have died from soft-tissue sarcoma determined that two deaths had been misclassified (Fingerhut et al., 1991a). A review of hospital data revealed that two other individuals had soft tissue sarcomas that were not identified by death certificate information. The use of death certificate information to derive SMRs for cancer as a whole is likely not subject to significant bias; the same might not hold true, however, for some site-specific cancers such as soft tissue sarcoma.

Using the SMR metric to compare an occupational cohort with the general population is subject to what is commonly referred to as the "healthy worker effect" (Li and Sung, 1999; Choi, 1992). The healthy worker effect is a bias that arises because those healthy enough to be employed have lower morbidity and mortality rates than the general population. The healthy worker effect is likely to be larger for occupations that are more physically demanding (Aittomaki et al., 2005; Checkoway et al., 1989), and the healthy worker effect is considered to be of little consequence in the interpretation of cancer mortality (Monson, 1986; McMichael, 1976). Few cancers are associated with a prolonged period of poor health that would affect employability long before death. Also recognized is that, as the employed population ages, the magnitude of the healthy worker effect decreases as the absolute reduction in mortality becomes relatively smaller (McMichael, 1976). The mortality follow-up of occupational cohorts generally spans several decades, which should minimize the associated healthy worker effect in such studies. Bias could also be introduced in that workers who are healthier might be more likely to stay employed and therefore accrue higher levels of exposure. In the NIOSH cohort, however, mortality was ascertained for those who could have left the workforce or retired by linking subjects to the National Death Index. Although internal cohort comparisons can minimize the potential for the healthy worker effect for the reasons presented above, for cancer outcomes, the SMR statistic is a valuable tool for characterizing whether occupational cohort are more likely to die of cancer than the general population. Moreover, stratified analyses across categories of duration of exposure, or latency periods within a cohort can yield important insights about which workers are at greatest risk. Perhaps most important, subsequent analyses of the NIOSH cohort that presented risk estimates derived from external comparisons using the

SMR were remarkably consistent with rate ratios derived using an internal referent (Steenland et al., 1999).

C.1.1.1.1.1.3. *Suitability of data for TCDD dose-response modeling*

This cohort meets most of the identified considerations for conducting a quantitative dose-response analysis for mortality from all cancer sites combined. The NIOSH cohort is the largest cohort of TCDD-exposed workers, exposure characterization at an individual level is possible but not available in this particular study, and the follow-up period is long enough to evaluate latent effects. Although there is no direct evidence of any important source of bias, confounding may be present due to a lack of consideration of DLCs. For the purpose of quantitative dose-response modeling, it is important to note that subsequent studies of this cohort adopted methods that greatly improved the characterization of TCDD exposure in the NIOSH cohort and increased the follow-up interval (Cheng et al., 2006; Steenland et al., 2001b). As such, for all practical purposes, due consideration for dose-response modeling should focus on the more recently developed data sets.

For quantitative dose-response modeling for individual cancer sites, the data are much more limited. A statistically significant positive association with TCDD was noted only for soft-tissue sarcoma among those with more than 1 year of exposure and 20 years of latency (SMR = 9.22, 95% CI = 1.90−26.95). However there were only three deaths from soft tissue sarcoma among this exposed component of the cohort, and four deaths in total in the overall cohort. Also, misclassification of outcome for soft-tissue sarcoma through death registries is well recognized and supported with additional review of tissue from two of the men. Specifically, tissues from the four men who died of soft-tissue sarcoma revealed that only two of these cases were coded correctly.

Although subsequent analyses of the NIOSH cohort did not show evidence of confounding by other occupational exposures, the design of this initial publication of the NIOSH cohort did not allow for examination of exposures to other possible confounders, such as DLCs. Duration of exposure was used as a surrogate for cumulative TCDD exposure; therefore, effective doses could not be estimated. Therefore, dose-response modeling was not conducted for this study.

C.1.1.1.1.2. ***Steenland et al. (1999)***

C.1.1.1.1.2.1. *Study summary*

A subsequent analysis of the NIOSH cohort extended the follow-up interval of Fingerhut et al. (1991a) by 6 years (i.e., from 1940–1993) and improved the characterization of TCDD exposure (Steenland et al., 1999). A key distinction from the work of Fingerhut et al. (1991a) was the exclusion of several workers that had been included in the previous mortality analyses. The authors excluded 40 workers who were either female, had never worked in TCDD-exposed departments, or had missing date of birth information. An additional 238 workers were excluded as occupational data for characterizing duration of exposure were lacking, preventing their use in a subcohort dose-response analysis. This subcohort was further reduced by excluding workers from four plants (n = 591) because the information on the degree of TCDD contamination in work histories was limited, preventing the characterization of TCDD levels by job type. Thirty-eight additional workers were excluded from the eight remaining plants because TCDD contamination could not be estimated. Finally, 727 workers were excluded because they had been exposed to pentachlorophenol. Exposures were assigned to 3,538 (69%) male members of the overall cohort, a population substantially reduced from the 5,172 on which Fingerhut et al. (1991a) reported. Steenland et al. (1999) also evaluated the mortality experience of a subcohort of 608 workers with chloracne who had no exposure to pentachlorophenol.

For each worker, a quantitative exposure score for each day of work was calculated based on the concentration of TCDD (μg/g) present in process materials, the fraction of the day worked, and a qualitative contact level based on estimates of the amount of TCDD exposure via dermal absorption or inhalation. The authors derived a cumulative measure of TCDD exposure by summing the exposure scores across the working lifetime history for each worker. The authors validated this cumulative exposure metric indirectly by comparing values obtained for workers with and without chloracne. Such a validation is appropriate, given that chloracne is considered a clinical sign of exposure to high doses of dioxin (Ott et al., 1993). The median exposure score among those with chloracne was 11,546 compared with 77 among those without (Steenland and Deddens, 2003).

Cancer mortality was compared using two approaches. As in Fingerhut et al. (1991a), external comparisons were made to the U.S. general population using the SMR statistic. The authors adjusted the SMR statistics for race, age, and calendar time. They also applied life-table

methods to characterize risks across the subcohort of 3,538 workers with exposure data by categorizing the workers into seven cumulative exposure groups. The cut-points for these categories were selected so that the number of deaths in each category was nearly equal to optimize study power. Life-table analyses were extended further to consider a 15-year lag interval, which in a practical sense means that person-years at risk would not begin to accrue until 15 years after the first exposure occurred. The person-years and deaths that occurred in the first 15 years were included in the lowest exposure grouping. The Cox proportional hazards model was used to characterize risk within the cohort. Cox regression was used to provide an estimate of the hazard ratios and the 95% CIs for ischemic heart disease, all cancers combined, lung cancer, smoking related cancers, and all other cancers. The authors also performed Cox regression analyses using the seven categories of exposure, adjusting the regression coefficients for both year of birth and age. The regression models were run for both unlagged and lagged (15 years) cumulative exposure scores.

Overall, when compared with the U.S. general population, a slight excess of cancer mortality (from all sites) was noted in the 5,132 cohort study population (SMR = 1.13, 95% CI = 1.02−1.25). This result did not substantially differ from the earlier finding that Fingerhut et al. (1991a) published (SMR = 1.15, 95% CI = 1.03−1.30). Site-specific analyses revealed statistically significant excesses relative to the U.S. general population for bladder cancer (SMR = 1.99, 95% CI = 1.13−3.23) and for cancer of the larynx (SMR = 2.22, 95% CI = 1.06−4.08). In the chloracne subcohort (*n* = 608), SMRs of 1.25 (95% CI = 0.98−1.57) and 1.45 (95% CI = 0.98−2.07) were found for all cancer sites and for lung cancer, respectively, relative to the general population. The authors also found statistically significant excesses for connective and soft tissue sarcomas (SMR = 11.32, 95% CI = 2.33−33.10) and for lymphatic and hematopoietic malignancies (SMR = 3.01, 95% CI = 1.43−8.52).

External comparisons made by grouping workers into septiles of cumulative TCDD exposure and generating an SMR for each septile using the U.S. population as the referent group suggested a dose-response relationship. For all cancer sites combined, workers in the highest exposure score category had an SMR of 1.60 (95% CI = 1.15−1.82); increases also were observed in the sixth (SMR = 1.34) and fifth (SMR = 1.15) septiles. The two-sided *p*-value associated with the test for trend for cumulative TCDD exposure was statistically significant

(p = 0.02). A similar approach for lung cancer revealed virtually the same pattern. The incorporation of a 15-year latency for the analyses of all cancer deaths, in general, produced slightly higher SMRs across the septiles, although a slight attenuation of effect was noted in the highest septile ($SMR_{unlagged}$ = 1.60 vs. SMR_{lagged} = 1.54). For a 15-year lag, the lung cancer SMRs were mixed compared to the unlagged results with some septile exposure categories increasing and others decreasing relative to the lowest exposure group.

For the internal cohort comparisons using Cox regression analyses, higher hazard ratios were found among workers in the higher exposure categories than those in the lowest. The linear test for trend, however, was not statistically significant (p = 0.10). The associations across the septiles for the unlagged exposure for the internal cohort comparisons were not as strong as for the external cohort comparisons. The opposite was true, however, for cumulative exposures lagged 15 years.

Relative to the lowest septile, stratified analyses revealed increased hazard ratios in the upper septiles of the internal cohort comparisons for both smoking- and nonsmoking-related forms of cancer. The test for linear trend was statistically significant for all other cancers (after smoking-related cancers were excluded). These analyses suggest that the overall cancer findings were not limited to an interaction between TCDD and smoking. Additional sensitivity analyses by the authors indicated the findings for smoking-related cancers were largely unaffected by the exclusion of bladder cancer cases. This observation suggests that exposure to 4-aminobiphenyl, which occurred at one plant and might have contributed to an increased number of bladder cancers, did not substantially bias the relationship between TCDD and all cancers combined.

The investigators also evaluated the dose-response relationship with a Cox regression model separately for each plant using internal cohort comparisons and found some heterogeneity. This finding is not unexpected particularly given the relatively small number of cancer deaths at each plant, and given that exposures were quite low for one plant at which no positive association was found. The variability among plants was taken into account by modeling plant as a random effect measure in the Cox model, which produced little change in the slope coefficient (β = 0.0422 vs. β = 0.0453, respectively).

C.1.1.1.1.2.2. *Study evaluation*

This study represents a valuable extension from that published by Fingerhut et al. (1991a). Internal comparisons were performed to help minimize potential biases associated with using an external comparison group (e.g., healthy worker effect, and differences in other risk factors between the cohort and the general population). That similar dose-response relationships were found for internal and external comparison populations suggests that the bias due to the healthy worker effect in the cohort is minimal for cancer mortality. More importantly, the construction of the cumulative exposure scores provides an improved opportunity to evaluate dose-response relationships compared with the length of exposure and duration of employment metrics that Fingerhut et al. (1991a) used.

A potential limitation of the NIOSH study was the inability to account for cigarette smoking. If cigarette smoking did contribute to the increased cancer mortality rates in this and other cohorts, increased cancer mortality from exposure to TCDD would be expected only for smoking-attributable cancers. This study found associations with TCDD for both smoking- and nonsmoking-related cancers, including a stronger association for nonsmoking-related cancers. Therefore, the data provide evidence that associations between TCDD and cancer mortality are not likely due to cigarette smoking.

The findings regarding latency should be interpreted cautiously as the statistical power in the study to compare differences across latency intervals was limited. Caution also should be heeded, given that latency intervals can vary on an individual basis as they are often dose-dependent (Guess and Hoel, 1977). The evaluation of whether TCDD acts as either an initiating or promoting agent (or both) is severely constrained by the reliance on cancer mortality data rather than incidence data. This constraint is due to the fact that survival time can be quite lengthy and can vary substantially across individuals and by cancer subtype. For example, the 5-year survival among U.S. males for all cancer sites combined ranged between 45 and 60% (Clegg et al., 2002). When only mortality data are available, evaluating the time between when individuals are first exposed and when they are first diagnosed with cancer is nearly impossible.

Starr (2003) suggested that Steenland et al. (1999) focused too heavily on the exposures that incorporated a 15-year period of latency and that those who experienced high exposures would inappropriately contribute person-years to the lowest exposure group "irrespective of how great the workers' actual cumulative exposure scores may have been." Most cancer deaths

would, however, typically occur many years postemployment. Given that the follow-up interval of the cohort was lengthy and the average exposure duration was 2.7 years, at the time of death, person-years for those with high cumulative exposures would be captured appropriately. The median 5-year survival for all cancers is approximately 50% (Clegg et al., 2002), so applying a minimum latency of 5 years when using cancer mortality rather than cancer incidence data is needed to assure that the exposure metric captures exposures before diagnosis. Increasing this latency period, for example to 10 or 15 years, would eliminate consideration of exposures that occur in the period between tumor occurrence and tumor detection (diagnosis), and allows for an appropriate focus on exposures that act either early or late in the pathogenic process. If the association of TCDD with cancer is causal, effects might become apparent only at high exposures and with adequate latency. As such, IARC has concluded that a latency interval of 15 years could be too short (IARC, 1997). EPA considers the Steenland et al. (1999) presentation to be balanced in that they provided the range in lifetime excess risk estimated across the various models used. The authors' finding that the models with a 15-year lag provided a statistically significant improvement in fit based on the chi-square test statistic should not be readily dismissed.

C.1.1.1.1.2.3. *Suitability of data for TCDD dose-response modeling*

This study meets most of the epidemiologic considerations for conducting a quantitative dose-response analysis for mortality from all cancer sites combined. This study excludes a large number of workers who were exposed to pentachlorophenol, thus eliminating the potential for bias from this exposure. Relative to the earlier study by Fingerhut et al. (1991a), improvements were made to the methodology applied to assign TCDD exposures to the workers. This study, however, is superseded by Steenland et al. (2001b), who provide a more detailed presentation and modeling of the NIOSH cohort data. Therefore, dose-response modeling was not pursued for this study, but was for the subsequent NIOSH study by Steenland et al. (2001b).

C.1.1.1.1.3. ***Steenland et al. (2001b)***

C.1.1.1.1.3.1. *Study summary*

In 2001, Steenland et al. (2001b) published a risk analysis using the NIOSH cohort that, for the first time, incorporated serum measures in the derivation of TCDD exposures for

individual workers. The authors applied the same exclusion criteria to the entire cohort of workers across the 12 plants in the Steenland et al. (1999) study, leaving 3,538 male workers for which risk estimates could be calculated. Unlike previous analyses of the NIOSH cohort that considered several different mortality outcomes, the analyses presented in Steenland et al. (2001b) focused exclusively on mortality from all cancers sites combined. The authors observed 256 cancer deaths in the cohort between 1942 and the end of 1993. All risks estimated in the Steenland et al. (2001b) study were based on internal cohort comparisons.

Characterization of TCDD exposure levels among the workers was based on serum measures obtained in 1988 from 199 workers who were employed in one of the eight plants. Only those workers with both TCDD serum measures and previously developed exposure scores (Steenland et al., 1999) were used to estimate the relation between these different exposure metrics. Based on these findings, cumulative TCDD serum levels were estimated on an individual basis for all 3,538 workers following restriction to a subset of 170 workers whose 1988 serum measures were greater than the upper range of background levels (10 ppt) (Steenland et al., 2001b).

The authors developed a regression model estimated the level of TCDD at the time of last exposure for the 170 workers. The model was based on the estimated half-life of TCDD, the known work history of each worker, a pharmacokinetic model for the storage and excretion of TCDD, and exposure scores for each job held by each worker over time. The resulting equation follows:

$$y_{last\ exposure} = y_{1988}\ exp(\lambda \Delta t) \qquad \text{(Eq. C-1)}$$

The first-order elimination rate constant (λ) was based on a half-life of 8.7 years previously reported for the Ranch Hands cohort (Michalek et al., 1996). The background rate of TCDD exposure was assumed to be 6.1 ppt, which was based on the median level in a sample of 79 unexposed workers in the NIOSH cohort (Piacitelli et al., 1992). This value was subtracted when TCDD values were back-extrapolated, and then added again after the back-extrapolation was completed. A background level of 5 ppt also was used in some of the analyses with minimal demonstrable effects on the results. Sensitivity analyses also were incorporated to consider a

7.1-year half-life estimate that had been developed for the earlier Ranch Hands study (Pirkle et al., 1989).

After back-extrapolating to obtain TCDD serums levels at the time of last exposure, the investigators estimated cumulative (or "area under the curve") TCDD serum levels for every cohort member. This estimation procedure was the same method Flesch-Janys et al. (1998) applied to the Hamburg cohort to derive a coefficient for relating serum levels to exposure scores. The "area under the curve" approach integrates time-specific serum levels over the employment histories of the individual workers. The slope coefficient was estimated using a no-intercept linear regression model. This model is based on the assumption that a cumulative score of zero is associated with no serum levels above background.

Cox regression was also used to model the continuous measures of TCDD. A variety of exposure metrics were considered that took into account different lags, nonlinear relationships (e.g., log-transform and cubic spline), as well as threshold and nonthreshold exposure metrics. Categorical analyses were used to evaluate risks across TCDD exposure groups, while different shapes of dose-response curves were evaluated through the use of lagged and unlagged continuous TCDD measures. Categorical analyses of TCDD exposure were conducted using the Cox regression model to derive estimates of relative risk (RR) as described by hazard ratios and 95% CIs. The reference group in this analysis was those workers in the lowest septile cumulative exposure grouping (<335 ppt-years). The septiles were chosen based on cumulative serum levels that considered no lag and also a 15-year lag.

The investigators also conducted dose-response analyses using the toxicity equivalence (TEQ) approach. The TEQ is calculated as the sum of all exposures to dioxins and furans weighted by the potency of each specific compound. In this study, TCDD was assumed to account for all dioxin exposures in the workplace. For background TEQ levels, the investigators used a value of 50 ppt in the dose-response modeling. This is based on the assumption that TCDD accounted for 10% of the toxicity of all dioxins and furans (WHO, 1998), and is equivalent to using a background level of 5 ppt/yr that was used in the derivation of cumulative serum TCDD levels. A statistically significant dose-response pattern was observed for all cancer mortality and TCDD exposure based on log of cumulative TEQs with a 15-year lag. A comparison of the overall model chi-square values indicated that the fit of this model was not as good as that for TCDD.

The hazard ratios among workers grouped by categories of cumulative TCDD exposure (lagged 15 years) suggested a positive dose-response relationship. Steenland et al. (2001b) found statistically significant excesses in the higher exposure categories compared to the lowest septile. The RR was 1.82, (95% CI = 1.18−2.82) for the sixth septile (7,568−20,455 ppt-years) and 1.62, (95% CI = 1.03−2.56) for the seventh septile (>20,455 ppt-years). Cox regression indicated that log TCDD serum concentrations (lagged 15 years) was positively associated with cancer mortality ($\beta = 0.097$, standard error [β] = 0.032, $p < 0.003$). A statistically significant improvement in fit was observed when a 15-year lag interval was incorporated into the model compared to a model with no such lag (Model χ^2 with 4 degrees of freedom = 7.5). Results were similar when using a half-life of 7.1 years rather than 8.7 years. The excess lifetime risk of death from cancer at age 75 for TCDD intake (per 1.0-picogram per kilogram [pg/kg] of body weight [BW] per day) was about 0.05−0.9% above a background lifetime risk of cancer death of 12.4%. The results from the best-fitting models provide lifetime risk estimates within the ranges derived using data from the Hamburg cohort (Becher et al., 1998).

In both categorical and continuous analyses of TCDD based on a linear model, the dose-response pattern tailed off at high exposures suggesting nonlinear effects. This phenomenon could be due to saturation effects (Stayner et al., 2003) or, alternatively, could have resulted from increased exposure misclassification of higher exposures (Steenland et al., 2001b). Specifically, some of the highest exposures might have been poorly estimated as they occurred in workers exposed to short-term high exposures during the clean-up of a spill. The choice of a linear model to develop data from a single time point can also result in exposure misclassification in those individuals that have differences in the length of exposure (Emond et al., 2005). Misclassification would be less likely at low concentrations where dose-dependent elimination is minimal.

C.1.1.1.1.3.2. *Study evaluation*

An important consideration in the Steenland et al. (2001b) study was the use of a small subset of workers ($n = 170$) to infer exposures for the remainder of the cohort. Although there is limited information in the study to determine how representative the 199 workers were of the overall workers in that plant, the authors report that exposures from the plant in which these 170 subjects worked were in the middle of the exposure distribution of the eight U.S. chemical

plants the authors had previously studied.(Steenland et al., 1999) This subset did comprise surviving members of the cohort (in 1988), and therefore, the frequency distribution of their year of birth would have differed from the rest of the cohort. Furthermore, these workers were employed at a single plant that had less detailed work histories than the other plants; thus, the development of the exposure scores differed between this plant and the others. Also, many of the workers at this plant had the same job title and were employed during the same calendar period. The use of serum data from this subset adds a level of uncertainty that is not readily characterized. The study report only states that the serum levels were available for these individuals, but it does not provide any indication of how or why the individuals were selected for serum evaluation or if there were a number of individuals that declined to give samples. Thus, it is hard to gauge how representative this population is of the plant cohort. Despite these limitations, the use of these sera data to derive cumulative measures for all cohort workers seems warranted given the strong correlation observed between the exposure scores, and TCDD serum levels estimates at the time of last exposure (Spearman $r = 0.90$).

The authors performed an extensive series of sensitivity analyses and considered several alternative exposure metrics to the simple linear model. The lifetime excess risk above background was nearly twice as high for the log cumulative serum measures with a 15-year lag when compared to the piecewise linear models with no lag. An important observation was that the exposure metric based on cumulative serum (lagged 15 years) did not fit the data as well as the cumulative exposure score used in earlier analyses (Steenland et al., 1999). A priori, one would expect that a better fit would be obtained with serum-based measures because serum provides a better measure of relevant biological dose. As the authors noted, inaccuracies introduced in estimating the external-based exposure scores could have contributed to a poorer fit of the data. Alternatively, exposure misclassification error could be introduced if serum samples based on the 170 workers were not representative of the entire cohort. Although the serum-based measures did not fit the data as well as the exposures scores, the authors regarded them as providing a reasonable fit based on an improvement in log likelihood of 3.99 (between the log cumulative serum model and the log cumulative exposure score model). Moreover, the serum-based measures enabled better characterization of risk in units (pg/kg-day) that can be used in regulating exposures.

C.1.1.1.1.3.3. *Suitability of data for TCDD dose-response modeling*

This study meets all of the epidemiologic considerations for conducting a quantitative dose-response analysis for mortality from all cancer sites combined. As mentioned previously, the NIOSH cohort is the largest assembled to date for which TCDD-related risks of cancer mortality can be estimated. The use of serum-based measures provides an objective measure of TCDD exposure. Repeated measures in other study populations have provided reasonable estimates of the half-life of TCDD, which permitted exposures to be back extrapolated in this cohort.

The authors have made extensive efforts to evaluate a wide variety of nonlinear and linear models with varying lengths of latency and log transformations. The model chi-square test statistics were fairly similar for the log cumulative serum (15-year lag) (Model $\chi^2_{(4df)} = 11.3$) model and the piecewise linear model (no lag) (Model $\chi^2_{(5df)} = 12.5$). These models, however, produced results with twofold differences in lifetime excess risks. These differences underscore the importance of characterizing uncertainty in modeling approaches when conducting dose-response analysis.

The Steenland et al. (2001b) study characterizes risk in terms of pg/kg of BW per day. Given that tolerable daily intake dioxin levels are typically expressed in pg/kg of BW (WHO, 1998), the presentation of risks using these units is an important advance from the earlier analyses that used exposure scores (Steenland et al., 1999). Many of the Steenland et al. (2001b) findings are consistent with earlier work from this cohort, which is not surprising given that exposures scores were used to derive serum-based levels for the cohort. The findings of excess lifetime risks obtained for the best- fitting model are also consistent with those derived from the Hamburg cohort (Becher et al., 1998). This study meets the epidemiologic considerations noted previously as there is no evidence that the study is subject to bias from confounding due to cigarette smoking or other occupational exposures. Given the considerable efforts to measure effective dose to TCDD among the study participants, this study also meets the requisite dose-response modeling criteria and will be used in quantitative dose-response analyses of cancer mortality.

C.1.1.1.1.4. ***Cheng et al. (2006)***

C.1.1.1.1.4.1. *Study summary*

Cheng et al. (2006) undertook a subsequent quantitative risk assessment of 3,538 workers in the NIOSH cohort using serum-derived estimates of TCDD. This dose-response analysis was published after the 2003 Reassessment document was released. The goal of this study was to examine the relationship between TCDD and cancer mortality (all sites combined) using a new estimate of dose that estimated TCDD as a function of both exposure intensity and age using a kinetic model. This physiologically-based pharmacokinetic model has been termed the "concentration- and age-dependent elimination model" (CADM) and was developed by Aylward et al. (2005b). This model describes the kinetics of TCDD following oral exposure to humans by accounting for key processes affecting kinetics by simulating the total concentration of TCDD based on empirical consideration of hepatic processes (see Section 3.3). An important feature of this kinetic model is that it incorporates concentration- and age-dependent elimination of TCDD from the body; consequently, the effective half-life of TCDD elimination varies based on exposure history, body burden, and age of the exposed individuals. The study was motivated by the reasoning that back-calculations of TCDD using a first-order elimination model and a constant half-life of 7–9 years underestimated exposure to TCDD among workers. This underestimate, in turn, would result in overestimates of the carcinogenic potency of TCDD.

As with the earlier Steenland et al. (2001b) analyses, the cohort follow-up period was extended from 1942 until the end of 1993 and work histories were linked to a job exposure matrix to obtain cumulative TCDD scores. Two cumulative serum lipid exposure metrics (in ppt-years) were constructed using the data obtained from the sample of 170 workers. The first replicated the metric used in a previous analysis of the cohort (Steenland et al., 2001b) and was based on a first-order elimination model with an 8.7-year half-life (Michalek et al., 1996). The second metric was based on CADM and had two first-order elimination processes (Aylward et al., 2005a). This metric assumes that the elimination of TCDD in humans occurs at a faster rate when body concentrations are high and at slower rates in older individuals (Aylward et al., 2005a; 2005b). The model was optimized using individuals for which serial measures of serum TCDD were available. These measures were obtained from 39 adults with initial serum levels between 130 and 144,000 ppt (Aylward et al., 2005b). This group included 36 individuals who had been exposed in the Seveso accident and 3 exposed in Vienna, Austria. In practice, for

serum levels greater than 1,000 ppt, the effective half-life would be less than 3 years, and for serum TCDD levels less than 50 ppt, the effective half-life would be more than 10 years (Aylward et al., 2005b). Results from the model indicate that men eliminate TCDD faster than women do as demonstrated previously by Needham et al. (1994). These age- and concentration-dependent processes were assumed to operate independently on TCDD in hepatic and adipose tissues, and TCDD levels in liver and adipose tissue were assumed to be a nonlinear function of body concentration. Cheng et al. (2006) calibrated CADM using a dose of 156 ng per unit of exposure score and assumed a background exposure rate of 0.01 ng/kg-month. The average TCDD ppt-years derived from CADM with a 15-year lag was 4.5−5.2 times higher than with the first-order elimination model. The two metrics, however, were highly correlated based on a Pearson correlation coefficient of 0.98 ($p < 0.001$). Comparisons of fit between the CADM and first-order elimination model were made using R^2 values and presented in Aylward et al. (2005b).

Cheng et al. (2006) compared the mortality experience of NIOSH workers to the U.S. general population using the SMR statistic. SMR statistics also were generated separately for each of the 8 plants and for all plants combined. Cox regression models were used to analyze internal cohort dose response. These models used age as the time variable, and penalized smoothing spline functions of the CADM metric also were considered. The possible confounding effects of other occupational exposures and other regional population differences were assessed by repeating analyses after excluding one plant at a time. Lagged and unlagged TCDD exposures were analyzed separately, and stratified analyses allowed risk estimates to be compared between smoking- and nonsmoking-related cancers. Cheng et al. (2006) adjusted the slope estimates derived from the Cox model for the potential confounding effects of race and year of birth.

Overall, a statistically significant excess in all cancer mortality in the cohort occurred relative to the general population (SMR = 1.17, 95% CI = 1.03−1.32). The plant-specific SMRs ranged from 0.62−1.87, with a statistically significant excess evident only for plant 10 (SMR = 1.87, 95% CI = 1.35−2.52). For lung cancer mortality, the overall SMR was not statistically significant (SMR = 1.11, 95% CI = 0.89−1.37). A statistically significant excess of lung cancer also was found for plant 10 (SMR = 2.35, 95% CI = 1.44−3.64). The SMRs between

smoking- (SMR = 1.22, 95% CI = 1.01−1.45) and nonsmoking-related cancers (SMR = 1.12, 95% CI = 0.94−1.33) were similar.

For the internal cohort analyses of serum-derived measures, the authors were able to replicate the one-compartmental model used previously (Steenland et al., 2001b). As had been noted by Steenland et al. (2001b), an inverse-dose-response pattern was seen for individuals with high exposures (above 95th percentile); this type of pattern is frequently observed in occupational studies (Stayner et al., 2003). Excluding these data produced a stronger association between TCDD and all-cancer mortality. In fact, only when the upper 2.5% or 5% of observations was removed did a statistically significant positive association become evident with the untransformed, unlagged data. Similarly, when the model incorporated a lag of 15 years, a statistically significant association was noted only for the untransformed TCDD ppt-years with the upper 5% of observations removed. Stratified analyses revealed little difference in the association between TCDD and smoking- and nonsmoking-related cancers, and the removal of one plant at a time from the analyses of TCDD ppt-years changes did not substantially change the slope.

C.1.1.1.1.4.2. *Study evaluation*

The authors reported that CADM provided an improved fit over the one-compartmental model, but presented no evidence regarding any formal test of statistical significance. A comparison of R^2 values presented in Aylward et al. (2005b), however, does reveal that the R^2 value increased from 0.27 (first-order compartmental model with an 8.7-year half-life) to 0.40 for CADM. TCDD exposures estimated using CADM were approximately fivefold higher than the one-compartmental model estimates among cohort members with higher levels of exposure. Differences in exposure estimates between the two metrics were less striking among individuals with lower TCDD exposures. The net effect was that CADM produced a 6- to 10-fold decrease in the estimated risks compared to those previously reported (Steenland et al., 2001b). Nonetheless, the estimates produced by CADM span more than two orders of magnitude under various assumptions. Further uncertainties arise from between-worker variability of TCDD elimination rates, possible residual confounding, and the variability associated with the use of data obtained from other cohorts. Nevertheless, the use of the CADM to estimate TCDD

exposure is considered a significant advantage over the previous first-order body burden calculations.

C.1.1.1.1.4.3. *Suitability of data for TCDD dose-response modeling*

The value of including the NIOSH cohort data has already been established based on investigations by Steenland et al. (2001b; 1999). The decision to include data from the quantitative dose-response analysis by Cheng et al. (2006) relates to the added value that the CADM exposure estimates would provide. The earlier modeling work of Aylward et al. (2005b) provided some support for a modest improvement of the fit of CADM over the first-order compartmental model, and they also confirmed previous studies that found that TCDD elimination rates varied by age and sex. Recent work by Kerger et al. (2006) also demonstrates that the half-life for TCDD is shorter among Seveso children than in adults, and that body burdens influence the elimination of TCDD in humans. That estimates of half-lives among men have been remarkably consistent, with mean estimates ranging between 6.9 and 8.7 years (Needham et al., 2005; Michalek et al., 2002; Flesch-Janys et al., 1996; Pirkle et al., 1989), however, is noteworthy. Based on the underlying strengths of the NIOSH cohort data and efforts by Cheng et al. (2006) to improve estimates of effective dose, these data support further dose-response modeling.

C.1.1.1.1.5. ***Collins et al. (2009)***

C.1.1.1.1.5.1. *Study summary*

In a recent study, Collins et al. (2009) investigated the relationship between serum TCDD levels and mortality rates in a cohort of trichlorophenol workers (gender not specified) exposed to TCDD. These workers were part of the NIOSH cohort having accounted for approximately 45% of the person-years in an earlier analysis (Bodner et al., 2003). The investigators completed an extensive dioxin serum evaluation of workers employed by the Dow Chemical plant in Midland, Michigan, that made 2,4,5-trichlorophenol (TCP) from 1942 to 1979 and 2,4,5-T from 1948 to 1982. Collins et al. (2007) and Aylward et al. (2007) developed historical TCDD exposure estimates for all TCP and 2,4,5-T workers. This study represents the largest group of workers from a single plant ever studied for the health effects of TCDD. Little information on how vital status was ascertained, was provided in this paper or in the Bodner et al. (2003) report

of mortality in this cohort. Although the authors indicate that death certificates were obtained from the states in which the employees died, it is unclear whether vital status was ascertained from company records or through record linkage to the National Death Index is unclear.

The follow-up interval for these workers spanned the period between 1942 and 2003. Thus, the study included 10 more years of follow-up than earlier investigations of the entire NIOSH cohort. Serum samples were obtained from 280 former workers (selection criteria including data on gender were not specified) in 2004−2005. A simple one-compartment first-order pharmacokinetic model and elimination rates as estimated from the BASF cohort were used (Flesch-Janys et al., 1996). The "area under the curve" approach was used to characterize workers' exposures over the course of their working careers and provided a cumulative measure of exposure. Analyses were performed with and without 165 of the 1,615 workers exposed to pentachlorophenol to evaluate the impact of these exposures.

External comparisons of cancer mortality rates to the general U.S. population were made using SMRs. Internal cohort comparisons of exposure-response relationships were made using the Cox regression model. This model used age as the time variable, and was adjusted for year of hire and birth year. Only those causes of death for which an excess was found based on the external comparisons or for which previous studies had identified a positive association were selected for dose-response analyses.

A total of 177 cancer deaths were observed in the cohort. For the external comparison with the U.S. general population, overall, no statistically significant difference was observed in all cancer mortality among all workers (SMR = 1.0, 95% CI = 0.8−1.1). Results obtained after excluding workers exposed to pentachlorophenol were similar (SMR = 0.9, 95% CI = 0.8−1.1). Excess mortality in the cohort was found for leukemia (SMR = 1.9, 95% CI = 1.0−3.2) and soft tissue sarcoma (SMR = 4.1, 95% CI = 1.1−10.5). Although not statistically significant SMRs for other lymphohemopoietic cancers included non-Hodgkin lymphoma (SMR = 1.3, 95% CI = 0.6, 2.5) and Hodgkin disease (SMR = 2.2, 95% CI = 0.2, 6.4).

Internal cohort comparisons using the Cox regression model were performed for all cancers combined, lung cancer, prostate cancer, leukemia, non-Hodgkin lymphoma, and soft-tissue sarcoma. Whether the internal comparisons excluded those workers exposed to pentachlorophenol is not entirely clear from the text or accompanying table, but presumably they do not. The RR was 1.002 (95% CI = 0.991−1.013) for all cancer mortality per 1 ppb-year

increase in cumulative TCDD exposure was not statistically significant. Except for soft tissue sarcomas, no statistically significant exposure-response trends were observed for any cancer site. For soft tissue sarcoma, analyses were based on only four deaths.

C.1.1.1.1.5.2. *Study evaluation*

A key limitation of this study is that SMRs were not derived for different periods of latency for the external comparison group analysis. The original publication on the NIOSH cohort found that SMRs increased when a 20-year latency period was incorporated (Fingerhut et al., 1991a), and similar patterns have been observed in other occupational cohorts (Ott and Zober, 1996a; Manz et al., 1991) and among Seveso residents (Consonni et al., 2008). Additionally, dose-response analyses showed marked increases in slopes with a 15-year latency period (Cheng et al., 2006; Steenland and Deddens, 2003). In this context, the absence of an elevated SMR for cancer mortality is consistent with previous findings of the NIOSH cohort. Additional analyses published subsequently (Collins et al., 2010) found no excess cancer mortality in the cohort relative to the general population when a latency period of 20 years was applied (SMR = 1.0, 95% CI = 0.8−1.1).

Unfortunately, the Collins et al. (2009) study did not include a categorical analysis of TCDD exposure and cancer mortality. This categorical analysis would have enabled an evaluation of whether a nonlinear association exists between TCDD exposure and cancer risk. The analyses of both Cheng et al. (2006) and Steenland et al. (2001b) suggest an attenuation of effects at higher doses, and several investigations have considered log-transformed associations as a means to address nonlinearity. Also, the earlier plant-specific dose-response analyses of Steenland et al. (2001b) are not consistent with the findings for the Midland plant that Collins et al. (2009) presented. In response to the letter by Villeneuve and Steenland (2010) that highlighted the value of characterizing risk across categories of TCDD exposure, Collins et al (2010) reported SMRs across three cumulative exposure levels of 0.1−374.9, 375.0−1,999.9, and 2,000−112,253 ppt-month categories. No excess cancer mortality, as captured by the SMR, was observed in any of the three exposure categories for analyses conducted with no latency and a 20-year latency. Given that excesses were not noted in the NIOSH cohort until approximately 14,000 ppt-months, the upper exposure grouping (2,000-112,253 ppt-months) used by Collins et al. (2010) may not be able to differentiate possible associations at higher exposure levels.

C.1.1.1.1.5.3. *Suitability of data for dose-response modeling*

The Collins et al. (2009) study used serum levels to derive TCDD exposure estimates and does not appear to be subject to important biases. The reliance on data from one plant offers some advantages over the multiplant analyses, as heterogeneity in exposure to other occupational agents would be lower. The number of individuals who provided serum samples (n = 280) is greater than the 170 individuals used to derive TCDD estimates for the NIOSH cohort, but there was no information presented in either study to assess how representative subjects who provided samples were of the larger cohort. The authors found a statistically significant dose-response trend for soft tissue sarcoma mortality and TCDD exposures. Therefore, this study is considered suitable for quantitative dose-response analysis.

C.1.1.1.2. ***The BASF cohort***

In 1953, dioxin contamination occurred as a result of an autoclave accident during the production of trichlorophenol at the BASF plant in Ludwigshafen, Germany. A second dioxin incident occurred in 1988 that was attributed to the blending of thermoplastic polyesters with brominated flame retardants. Of the two events, the one on November 13, 1953, was associated with more severe acute health effects, including chloracne that resulted in immediate hospitalizations for seven workers. These adverse events were not linked to TCDD until 1957 when TCDD was identified as a byproduct of the production of trichlorophenol and was shown to induce chloracne (Zober et al., 1994). Zober and colleagues (1998) noted that with the 1988 accident, affected individuals did not exhibit clinical symptoms or chloracne, but rather were identified through "analytical measures." In both instances, efforts were made to limit the potential for exposure to employees.

C.1.1.1.2.1. ***Thiess and Frentzel-Beyme (1977) and Thiess et al. (1982)***

C.1.1.1.2.1.1. *Study summary*

A study of the mortality of workers employed at the BASF plant was first presented in 1977 (Thiess and Frentzel-Beyme, 1977) with subsequent updates in both 1982 (Thiess et al., 1982), and in 1990 (Zober et al., 1990). In the first published paper (Thiess et al., 1982), 74 employees involved in the 1953 accident were traced and their death certificate information extracted. Of these, 66 suffered from chloracne or severe dermatitis. Observed deaths were

compared to the expected number using three external reference groups: the town of Ludwigshafen (n = 180,000), the district of Rhine-Hessia-Palatinate (n = 1.8 million), and the Federal Republic of Germany (n = 60.5 million). Another comparison group was assembled by selecting age-matched employees taken from other cohorts under study. This additional comparison was aimed at avoiding potential biases associated with healthy worker effect when using an external referent.

During a follow-up interval of up to 26 years (1953−1979), 21 individuals died. Of these, seven deaths were from cancer. The expected number of cancer deaths derived for the three external comparison groups ranged between 4.1 and 4.2, producing an SMR of 1.7 (p-values ranged between 0.12 and 0.14). Excess mortality was found for stomach cancer based on the external comparisons ($p < 0.05$); however, this was based on only three cases. No other statistically significant excesses were found with the external comparisons made to the other cohorts of workers.

C.1.1.1.2.1.2. *Study evaluation*

In the Thiess et al. (1982) study, no TCDD exposures were derived for the workers, thus no dose-reconstruction was performed. The findings from this study are severely limited by the small size of the cohort. The 74 workers followed in this cohort represent the smallest number of workers across the occupational cohorts (McBride et al., 2009a; 2009b; Michalek and Pavuk, 2008; Steenland et al., 2001b; Becher et al., 1998; Hooiveld et al., 1998; Fingerhut et al., 1991b) that have investigated TCDD exposures and cancer mortality. Mechanisms of follow-up were excellent as all individuals were traced, and death certificates were obtained from all deceased workers.

Although the study does compare the mortality experience to other occupational cohorts, the paper provides insufficient information to adequately interpret these findings. For example, a description of these occupations is lacking making it impossible to determine whether these cohorts were exposed to other occupational carcinogens that might have confounded the associations between TCDD exposure and cancer mortality.

C.1.1.1.2.1.3. *Suitability of data for TCDD dose-response modeling*

Subsequent data assembled for the BASF cohort provide more detailed exposure characterization, and also include information for 243 male workers employed at the plant. As such, this study did not meet the considerations for further dose-response analysis.

C.1.1.1.2.2. ***Zober et al. (1990)***

C.1.1.1.2.2.1. *Study summary*

Zober et al. (1990) also examined the mortality patterns of those involved in the 1953 accident at the BASF plant. As detailed in their paper, the size of the original cohort was expanded to 247 workers through efforts to locate all who were exposed in the accident or during the clean-up. Three approaches were followed in assembling the cohort. Sixty-nine cohort members were identified from the company physician's list of employees exposed as a result of the accident (Subcohort C1). Sixty-six of these workers were included in the original study population of workers Thiess et al. (1982) examined. Eighty-four other workers who were potentially exposed to TCDD due to their involvement in demolitions or operations were added to the cohort. This group included 43 firemen, 18 plant workers, 7 bricklayers, 5 whitewashers, 4 mechanics, 2 roofers, and 5 individuals in other occupations (Subcohort C2). The cohort was further augmented through the Dioxin Investigation Program, which sought to locate those who were involved in the 1953 accident and were still alive in 1986. Current and former workers enrolled in the study were asked to identify other current or former coworkers (including deceased or retired) who might have been exposed from the accident. This third component of 94 workers (Subcohort C3) included 27 plant workers, 16 plumbers, 10 scaffolders, 10 professionals, 7 mechanics, 6 transportation workers, 5 bricklayers, 5 laboratory assistant, 3 insulators, and 5 individuals in other occupations. A medical examination was performed for those identified through the Dioxin Investigation Program, and blood measures were obtained for 28 of these workers.

External comparisons of the workers' mortality experience to the general population of the Federal Republic of West Germany were made using SMRs. Person-years were tabulated across strata defined by calendar period, sex, and age-group. Sixty-nine deaths including 23 from cancer were detected among the workers during the 34-year follow-up period (November 17, 1953 through December 31, 1987). Cause-specific death rates for these same strata were

available for the Federal Republic of West Germany. Stratified analyses were conducted to examine variations in the SMRs according to years since first exposure (0−9, 10−19, and ≥20 years) for each of the three subcohorts, as well as 114 workers with chloracne.

Although it was consistent in magnitude with findings from the NIOSH cohort, a statistically significant SMR for all cancer mortality was not observed (SMR = 1.17, 90% CI = 0.80−1.66). The SMRs for each of the three subcohorts varied substantially. For Subcohorts C1, C2, and C3, the SMRs were 1.30 (90% CI = 0.68−2.26), 1.71 (90% CI = 0.96−2.83), and 0.48 (90% CI = 0.13−1.23), respectively. The SMRs increased dramatically when analyses were restricted to those with 20 or more years since first exposure in Subcohort C1 (SMR = 1.67, 90% CI = 0.78−3.13) and Subcohort C2 (SMR = 2.38, 90% CI = 1.18−4.29). Meanwhile, in a subgroup analysis of those with chloracne, for the period of 20 or more years after first exposure, a statistically significant excess in cancer mortality was noted (SMR = 2.01; 90% CI = 1.22−3.15).

C.1.1.1.2.2.2. *Study evaluation*

An important limitation of the study is the manner in which the cohort was constructed. Subcohort C3 was constructed by identifying individuals who were alive in 1986. This resulted in 97 active and retired employees who participated in the program, with 94 included in the analysis. Although these individuals did identify other workers who might have also retired or died, inevitably, some individuals who had died were not included in the cohort. This would serve to underestimate the SMRs that were generated with external comparisons to the German population. Indeed, cancer mortality rates in this subcohort were about half of what would have been expected based on general population rates (SMR = 0.48, 90% CI = 0.13−1.23). Additionally, more than half of Subcohort C2 were firemen (43 of 84), who were likely exposed to other occupational carcinogens. Quantitative analyses of epidemiologic data for firefighters have demonstrated increased cancer risk for several different forms of cancer (Youakim, 2006). Therefore, potential confounding from other occupational exposures of the firefighters could have contributed to the higher SMR in Subcohort C2 cohort and is a concern. Data on cigarette smoking were not available either. No excess for nonmalignant respiratory disease was found, however, suggesting this might not be an important source of bias.

C.1.1.1.2.2.3. *Suitability of data for TCDD dose-response modeling*

As with the Thiess et al. (1982) publication, individual-level estimates of workers' exposures were not made. Lack of exposure estimates precludes a quantitative dose-response analysis using these data. Also, the study design is not well suited to characterization of risk using the SMR statistic. Mortality is likely under-ascertained in the large component of the cohort that was constructed through the identification of surviving members of the cohort.

C.1.1.1.2.3. ***Ott and Zober (1996a)***

C.1.1.1.2.3.1. *Study summary*

Ott and Zober (1996a) extended the analyses of the BASF cohort to include estimates of individual-level measures of TCDD. The researchers also investigated associations with cancer mortality and incidence. The cohort follow-up period of 39 years extended until December 31, 1992, adding 5 years to the previously published study (Zober et al., 1990). Ott and Zober (1996a) identified incident cases of cancer using occupational medical records, death certificates, doctor's letters, necropsy reports, and information from self-reported surveys sent to all surviving cohort members. Self-reported cancer diagnoses were confirmed by contacting the attending physician.

This study characterized exposure by two methods: (1) determining chloracne status of the cohort members, and (2) estimating cumulative TCDD (μg/kg) levels. In 1989, serum measures were sought for all surviving members of the 1953 accident, and serum TCDD levels were quantified for 138 individuals. These serum levels were used to estimate cumulative TCDD concentrations for all 254 members of the accident cohort. Ott et al. (1993) published a description of the exposure estimation procedure, which was a regression model that accounted for the circumstances and duration of individual exposure. The average internal half-life of TCDD was estimated to be 5.8 years based on repeated serum sampling of 29 individuals. The regression model allowed for this half-life to vary according to the percentage of body fat, and yielded half-lives of 5.1 and 8.9 years among those with 20% and 30% body fat, respectively. Previous analyses of this cohort had used a half-life of 7.0 years (Ott et al., 1993).

TCDD half-life has been reported to increase with percentage of body fat in both laboratory mammals (Geyer et al., 1990) and humans (Zober and Papke, 1993). Ott and Zober (1996a) contend that observed correlations with chloracne severity and cumulative estimates of

TCDD exposure indirectly validated this exposure metric. Specifically, the mean TCDD concentration for those without chloracne was 38.4 ppt; for those with moderate and severe forms of chloracne, the mean was 420.8 ppt and 1,008 ppt, respectively.

Unlike the NIOSH cohort, individual-level data were collected for other cancer risk factors. These factors included body mass index at time of first exposure, history of occupational exposure to β-naphthylamine and asbestos, and history of smoking. Smoking data were available for 86% of the cohort. SMRs were based on the external referent population of West Germany. For cancer incidence, Ott and Zober (1996a) generated standardized incidence ratios (SIRs) using incidence rates for the state of Saarland (1970−1991) as the external referent. They calculated SMRs (and SIRs) for three or four categories of cumulative TCDD levels: <0.1 μg/kg, 0.1−0.99 μg/kg and ≥1 μg/kg. The Cox regression model was used to characterize risk within the cohort using a continuous measure of TCDD. These analyses considered the potential confounding influence of age, smoking, and body mass index using a stepwise regression modeling approach. The Cox modeling employed a stratified approach using the date of first exposure to minimize possible confounding between calendar period and exposure. The three first exposure groups were: exposure within the first year of the accident, exposure between 1 year after the accident and before 1960, and exposure after 1959. The Cox regression estimates were presented in terms of conditional risk ratios (i.e., hazard ratios adjusted for body mass index, smoking and age).

Although no statistically significant excess relative to the general population was detected for all cancer mortality, there was some suggestion of an exposure-response relationship. In the 0.1−0.99 μg/kg, 1−1.99 μg/kg, and ≥2.00 μg/kg exposure groups, the all cancer SMRs were 1.2 (95% CI = 0.5−2.3), 1.4 (95% CI = 0.6−2.7) and 2.0 (95% CI = 0.8−4.0), respectively. Higher SMRs for cancer (all sites combined) were also found with an increased interval since exposure first occurred. Specifically, when observed versus expected counts of cancer were compared in the time interval 20 years after first exposure, the SMR in the highest combined exposure group (≥1 μg/kg) was 1.97 (95% CI = 1.05−5.36). An excess in lung cancer also was noted with the same lag in this exposure group (SMR = 3.06, 95% CI = 1.12−6.66). For cancer incidence, a statistically significant increased SIR for lung or bronchus cancer was observed in the highest combined exposure (≥1 μg/kg) category (SIR = 2.2, 95% CI = 1.0−4.3),

but no other statistically significant associations were detected for any other cancer site. No cases of soft-tissue sarcoma were found among the cohort members in this analysis.

Cox regression models also were used to conduct internal cohort comparisons by generating hazard ratios as measures of relative risk for TCDD exposures with adjustment for smoking, age and body mass index. A statistically significant association between TCDD dose (per µg/kg) and cancer mortality was detected (RR = 1.22, 95% CI = 1.00−1.50), but not for cancer incidence (RR = 1.11, 95% CI = 0.91−1.35). Statistically significant findings were observed for stomach cancer mortality (RR = 1.46, 95% CI = 1.13−1.89) and incidence (RR = 1.39, 95% CI = 1.07−1.69).

The Ott and Zober (1996a) study also compared the relationship between TCDD exposure categories and cancer mortality from all sites combined according to smoking status. Associations were noted between increased exposure to TCDD and mortality from cancer among current smokers, but not among never or former smokers.

C.1.1.1.2.3.2. *Study evaluation*

The Ott and Zober (1996a) study characterizes exposure to TCDD at an individual level. Therefore, unlike past studies of this cohort, these data can provide an opportunity for conducting quantitative dose-response modeling. As with the more recent studies involving the NIOSH cohort, serum samples were obtained from surviving cohort members and then used to back-extrapolate TCDD values for all cohort members. In the BASF cohort, however, serum data were available for a much higher percentage of cohort members (54%) than in the NIOSH cohort (5%). An additional study strength was the collection of questionnaire data, which allowed for the potential confounding influence of cigarette smoking and body mass index to be taken into account.

The Ott and Zober (1996a) study also evaluates the relationship between TCDD and cancer incidence. Most cohort studies of TCDD-exposed workers have relied solely on mortality outcomes. The availability of incidence data better allows for period of latency to be described, and moreover, to characterize risks associated with cancers that typically have long survival periods. The authors provide few details on the expected completeness of ascertainment for incident cancer cases, which makes determining any associated bias difficult. They do, however, suggest that nonfatal cancers are more likely to have been missed in the earlier part of the

follow-up. The net result of differential case ascertainment over time makes evaluating differences in risk estimates across different periods of latency impossible.

The small sample size of the cohort (*n* = 243 men) limited the statistical power to detect small associations for some of the exposure measures. This also effectively limited the ability to analyze dose-response relationships quantitatively, particularly across strata such as time since exposure. For site-specific analyses, the cancer site with the most cancer deaths was the respiratory system (*n* = 11). Given the evidence of an exposure-response relationship noted for all cancer sites combined, quantitative dose-response analysis using these cohort data would be limited to the evaluation of this endpoint.

The most important limitation of this study is related to the construction of the third component of the cohort. As mentioned earlier, this cohort was assembled by actively seeking out surviving members of the cohort in the mid-1980s. The mortality experience of this cohort is much lower than that of the general population over the entire follow-up, a result that is expected given that the large component of the cohort was made up of individuals known to be alive as of 1986. The net result is likely an underestimate of the SMR.

C.1.1.1.2.3.3. *Suitability of data for TCDD dose-response modeling*

This study was included in the quantitative dose-response modeling for the 2003 Reassessment (U.S. EPA, 2003). The characterization of exposure data and availability of other risk factor data at an individual level are appropriate for use in quantitative dose-response analyses.

C.1.1.1.3. ***The Hamburg cohort***

The Hamburg cohort has been the subject of several cancer risk assessments. As with the NIOSH and BASF cohorts, analyses have progressed from basic comparisons of mortality rates to those in the general population to more sophisticated internal cohort analyses involving the reconstruction of TCDD exposures using serum measures. This cohort consists of approximately 1,600 workers who were employed in the production of herbicides at a plant in Hamburg, Germany during 1950−1984 (Becher et al., 1998; Flesch-Janys et al., 1995). The herbicides produced included 2,4,5-T, β-hexachlorocyclohexane and lindane. The production of TCP and 2,4,5-T was halted in 1954 following a chloracne outbreak. The plant ceased operations in 1984.

Approximately 20 different working areas were identified, which, in turn, were grouped into five main areas based on putative TCDD exposure levels. One working area was deemed to be extremely contaminated, having TCDD exposures at least 20-fold higher than in other areas. In this section, the studies undertaken in this cohort that have examined cancer mortality are summarized.

C.1.1.1.3.1. ***Manz et al. (1991)***

C.1.1.1.3.1.1. *Study summary*

Manz et al. (1991) investigated patterns of mortality in the Hamburg cohort. The study population consisted of 1,583 workers (1,184 men, 399 women) who were employed for at least three months between 1952 and 1989. Casual workers were excluded as they lack sufficient personal identifying information thereby not allowing for associations with mortality outcomes to be examined. Vital status was determined using community-based registries of inhabitants throughout West Germany. Cause of death until the end of 1989 was determined from medical records for all cancer deaths and classified based on the ninth revision of the International Classification of Diseases (WHO, 1978). Although Manz et al. (1991) present some data on cancer incidence for the cohort, the data are incomplete as information was available on only 12 cases; 103 (93 men and 20 women) cancer deaths were observed in the cohort.

In this study, the authors used information on production processes to group workers into categories of low, medium, or high exposure to TCDD. This information was based on TCDD concentrations in precursor materials, products, waste, and soil from the plant grounds, measured after the plant closed in 1984. The distribution of workers into the low, medium, and high exposure groups was 186 (79 men and 107 women), 901 (636 men and 265 women), and 496 (469 men and 27 women), respectively. The authors examined the validity of the three exposure categories using a separate group of 48 workers not selected for the cohort who volunteered to provide adipose tissue samples. Selection criteria and response rate information for the 48 volunteers were not provided, nor was there any indication that comparisons were made between the 48 volunteers and the individuals included in the study cohort. The median exposure of the 37 volunteers in the high group was 137 ng/kg and 60 ng/kg in the remaining 11. Although the results indicate higher TCDD levels in the high-exposure group, combining the lower two groups precludes separate validation of the two exposure groups. In addition, the

authors reported that some exposure misclassification was likely given that 5 of the 37 workers classified in the high exposure group had adipose levels lower than background (20 ng/kg). Information about chloracne in the cohort was incomplete, and, therefore, was not used as a marker of TCDD exposure. Other surrogate measures of exposure were considered in this study, including duration of exposure and year of first employment. For the latter measure, employment that began after 1954 was assumed to result in much lower exposures given that production of 2,4,5-T and TCP stopped in 1954.

External comparisons of cancer mortality were made by calculating SMRs using the general population of West Germany as a referent. Comparisons of mortality in the cohort also were made to a separate cohort of 3,417 gas supply workers to avoid bias from the healthy worker effect. Vital status and cause of death in the gas supply workers were determined using the same methods as in the Hamburg cohort. SMRs were calculated relative to both referent populations (West Germany and gas supply workers) across low, medium, and high TCDD exposure groups. The comparison of mortality to the gas supply workers, however, extended only until the end of 1985, whereas, comparisons to the general population extended until 1989. Stratified analyses were undertaken to calculate SMRs for each of the three exposure groups for categories of duration of employment (<20 versus ≥20 years) and date of entry into the cohort (≤1954 vs. >1954).

When compared to the general population, overall cancer mortality was elevated in male cohort members (SMR = 1.24, 95% CI = 1.00−1.52) but not in females (SMR = 0.80, 95% CI = 0.60−1.05). A twofold increase in female breast cancer mortality was noted although it did not achieve statistical significance at the alpha level of 0.05 (SMR = 2.15, 95% CI = 0.98−4.09). The SMR among men was further increased when analyses were restricted to workers who were employed for at least 20 years (SMR = 1.87, 95% CI = 1.11−2.95). Analyses restricted to those in the highest exposure group produced an even higher SMR for those with at least 20 years of employment (SMR = 2.54, 95% CI = 1.10−5.00). Statistically significant excesses in risk were detected among those who first worked before 1954, but not afterward. Furthermore, a dose-response trend was observed across increasing exposure categories in the subset of workers employed before 1954. The SMRs using the cohort of gas supply workers as the referent group for the low, medium, and high groups in this subset were 1.41 (95% CI = 0.46−3.28), 1.61 (95% CI = 1.10−2.44), and 2.77

(95% CI = 1.59−4.53), respectively. This finding is consistent with what was known about TCDD exposures levels at the plant, namely, that TCDD concentrations were much higher between 1951 and 1954, with subsequent declining levels after 1954.

Generally speaking, patterns of excess mortality were similar when the cohort of gas workers was used as a reference group. The overall SMR for men was 1.39 (95% CI = 1.10−1.75); and was 1.82 (95% CI = 0.97−3.11) when analyses were restricted to workers with 20 or more years of employment. A dose-response trend also was observed across exposure categories when analyses were restricted to those employed for at least 20 years. In particular, with these analyses, no cancer deaths were observed among those in the lowest exposure group, while the SMRs in the middle and high exposure groups were 1.36 (95% CI = 0.50−2.96) and 3.07 (95% CI = 1.24−6.33).

SMRs also were generated for several site-specific cancers relative to the West German general population and the gas worker cohort. No statistically significant excesses were observed using the general population reference. In contrast, statistically significant excesses were observed for lung cancer (SMR = 1.67, 95% CI = 1.09−2.44) and hematopoietic system cancer (SMR = 2.65, 95% CI = 1.21−5.03) relative to the gas workers cohort.

C.1.1.1.3.1.2. *Study evaluation*

The Manz et al. (1991) findings indicate an excess of all cancer mortality among the workers with the highest exposures, particularly those who worked for at least 20 years and were employed before 1954. The findings across categories of exposure within the subsets of workers employed for at least 20 years and before 1954, particularly using the cohort of gas supply workers, are consistent with a dose-response relationship. These elevated cancer mortality rates found among those employed before 1954 occurred at a time where TCDD exposures were highest. Other carcinogenic coexposures, such as benzene, asbestos, and dimethyl sulfate, could have occurred among this population. Given that no substantial changes in the production processes at the Hamburg plant occurred after 1954, comparable levels of these coexposures would be expected before and after 1954. Exposures to these other chemicals varied across different departments/groups; therefore, confounding was unlikely since a strong association between concentrations of these chemicals and TCDD exposures was not evident. No

information, however, was presented on potential exposure to other DLCs which may confound the associations that were detected.

Detailed information on workers' smoking behaviors was not collected. Limited evidence indicated, however, that smoking prevalence between the Hamburg cohort and the gas supply workers cohort was quite similar. A nonrepresentative sample of 361 workers in the Hamburg cohort and the sample of 2,860 workers in the gas supply cohort found that the self-reported smoking prevalence was 73 and 76% in these two cohorts, respectively. This suggests that the two cohorts are comprised predominantly of smokers. The similarity in overall smoking prevalence suggests that comparisons of cancer mortality between the two groups are not unduly influenced by an inability to adjust for smoking.

C.1.1.1.3.1.3. *Suitability of data for TCDD dose-response modeling*

The data compiled for the Manz et al. (1991) study do satisfy many of the considerations for conducting quantitative dose-response analysis; health outcomes appear to be ascertained in an unbiased manner, and exposure was characterized on an individual-level basis. However, as demonstrated in later studies, there was a large DLC component that was not quantified or assessed in this study. Dose-response associations between TCDD and cancer mortality were detected, with stronger associations observed with increased periods of latency and for those who first worked when TCDD was at higher levels.

The size of the cohort, although not as large as the NIOSH cohort, does offer sufficient statistical power to evaluate TCDD-related risk for all cancers combined. The data are limited, however, for characterizing cancer risks among women; only 20 cancer deaths occurred in the 399 women included in the cohort. It is unlikely that the excess cancer risks using the external reference population are due to uncontrolled effects from smoking since dose-response patterns were strengthened when comparisons were made to the cohort of gas supply workers rather the general population referent where smoking rates were likely lower. The inability to account for other occupational exposure when TCDD exposures were much higher (pre-1955) could result in confounding if these other exposures were related to TCDD and the health outcomes under consideration. This data set would be suitable for quantitative dose-response modeling if the exposure characterization of the cohort could be improved using biological measures of dose.

C.1.1.1.3.2. ***Flesch-Janys et al. (1995)***

C.1.1.1.3.2.1. *Study summary*

In 1995, Flesch-Janys et al. (1995) published an analysis of the male employees from the Hamburg cohort that extended the follow-up to 40 years (1952−1992). Inclusion of these three additional years of follow-up resulted in a sample size of 1,189 male workers.

The authors estimated a quantitative exposure variable for concentrations of TCDD in blood at the end of exposure (i.e., when employment in a department ended) and above German median background TCDD levels. The TCDD exposure assessment defined 14 production departments according to TCDD levels in various products in the plant, in waste products, and in various buildings. The time (in years) each worker spent in each department then was calculated. Concentrations of TCDD were determined in 190 male workers using serum (n = 142) and adipose tissue samples (n = 48). Selection criteria and response rate information was not provided for this subsample. The authors used a first-order kinetic model to calculate TCDD levels at the end of exposure for the 190 workers with available polychlorinated dibenzo-p-dioxin (PCDD) and -furan (PCDF) at various time points. Half-lives were calculated from an elimination study of 48 workers from this cohort, and the median TCDD background level was estimated at 3.4 ng/kg blood fat from the German population (Flesch-Janys et al., 1994; Päpke et al., 1994). Using the one-compartment, first-order kinetic model, the half-life of TCDD was estimated to be 6.9 years (Flesch-Janys, 1997). Increased age and higher body fat percentage were associated with increased TCDD half-life, while smoking was associated with a higher decay rate for most of the congeners examined (Flesch-Janys et al., 1996). Cumulative TCDD exposures for all 1,189 workers were estimated by summing exposures over the time spent in all production departments (expressed in terms of ng/kg of blood fat) in combination with quantitative estimates based on the blood and adipose samples from the 190 workers. The contribution of each working department on overall PCDD exposure was estimated using ordinary least squares regression. The authors also applied a metric of total toxicity equivalence (TOTTEQ) as the weighted sum of all congeners where weights were TEQs that denoted the toxicity of each congener relative to TCDD.

Similar to previous analyses on this cohort, comparisons were made using an external referent group of workers from a gas supply company (Manz et al., 1991). In contrast to previous analyses where SMR statistics were generated using this “external” reference, however,

Flesch-Janys et al. (1995) used Cox regression. The Cox regression models treated the gas worker cohort as the referent group, and six exposure groups were defined from serum-derived cumulative TCDD estimates. The groups were determined by using the first four quintiles with the upper two exposure categories corresponding to the ninth and tenth deciles of the cumulative TCDD. Internal cohort comparisons used those workers in the lowest quintile as the referent group, as opposed to the cohort of gas workers. A similar approach was used to model TEQs. No known TCDD exposures occurred in the gas workers, so they were assigned exposures based on the median background levels in the general population. RRs were calculated based on exposure above background levels; in other words, background levels were assumed to be equivalent across all workers and also for those employed by the gas supply company. The RRs derived using the Cox model were adjusted for total duration of employment, age, and year when employment began.

The Cox regression with the cohort of gas workers as the referent exposure group yielded a linear dose-response relationship between cumulative TCDD exposure and cancer mortality for all sites combined ($p < 0.01$). The RRs for all-cancer mortality were 1.59, 1.29, 1.66, 1.60, 1.70, and 3.30. For four of the six categories (excluding the referent group), the RRs were statistically significant ($p < 0.05$); in the highest TCDD exposure category (344.7−3,890.2 ng/kg) the RR was 3.30 (95% CI = 2.05−5.31). Similar findings were evident with TOTTEQ. A dose-response pattern for all cancer mortality ($p < 0.01$) based on the internal cohort comparisons was also detected.

The authors performed an additional analysis to evaluate the potential confounding role of dimethylsulfate. Although no direct measures of dimethylsulfate were available, the investigators repeated analyses by excluding 149 workers who were employed in the department where dimethylsulfate was present. A dose-response pattern persisted for TCDD and cancer mortality ($p < 0.01$), and those in the highest exposure group (344.7−3,890.2 ng/kg of blood fat) had a RR of 2.28 (95% CI = 1.14−4.59).

C.1.1.1.3.2.2. *Study evaluation*

The Flesch-Janys et al. (1995) study used serum-based measures to determine cumulative exposure to TCDD at the end of employment for all cohort members. They used the standard one-compartment, first-order kinetic model and samples obtained from 190 male workers. This

quantitative measure of exposure permits an examination of a dose-response relationship. However, there is not enough information provided on the selection of these 190 workers to determine how representative they were of the larger cohort. Confounding for other occupational exposures is unlikely to have biased the results. A dose-response relationship persisted after excluding workers exposed to dimethylsulfate. Other potential exposures of interest included benzene and isomers of hexachlorocyclohexane. Exposure to these agents, however, was highest in the hexachlorocyclohexane and lindane department, where TCDD exposures were lower. Confounding was unlikely due to exposure to these chemicals, since a strong association between concentrations of these chemicals and TCDD exposures was not evident (due to considerable variability in concentrations across different departments/groups). As outlined earlier, the study findings are unlikely to be biased for cigarette smoking as the prevalence of smoking in the cohort was similar to that in the comparison population. Moreover, more recent analyses of serum-based TCDD exposure measures found no correlation with smoking status in this cohort (Flesch-Janys et al., 1995)—a necessary condition for confounding to occur.

The authors used an exposure metric that quantified the cumulative TCDD exposure of workers at the time they were last exposed. As a result, the authors were unable to characterize risks associated with this metric for different periods of latency despite a lengthy follow-up period. Subsequent analyses constructed time-dependent measures of cumulative TCDD and accounted for excretion of TCDD during follow-up.

In contrast to most risk assessments of TCDD exposure, this study modeled the relationship between other DLCs and the risk of cancer mortality using the TOTTEQ metric.

C.1.1.1.3.2.3. *Suitability of data for TCDD dose-response modeling*

The data used in this study satisfy most of the considerations developed for performing a quantitative dose-response analysis. However, latency period was not examined in this study. Dose-response analyses were, therefore, limited to a subsequent study of this cohort (Becher et al., 1998), which did examine latency.

C.1.1.1.3.3. ***Flesch-Janys et al. (1998)***

C.1.1.1.3.3.1. *Study summary*

Flesch-Janys et al. (1998) undertook another analysis on this cohort that incorporated additional sera data collected from 275 workers (39 females and 236 males). The follow-up period was the same as that used in the 1995 publication, with mortality follow-up extending until December 31, 1992. Analyses were based on 1,189 males who were employed for at least 3 months from January 1, 1952 onward. The authors continued this dose-response analysis to address limitations in their previous work. One limitation was that the previous method did not account for the elimination of TCDD while exposures were being accrued during follow-up. A second limitation was that the amount of time workers spent in different departments was not considered. In the 1998 study, the "area under the curve" approach was used because it accounts for variations in concentrations over time and reflects cumulative exposure to TCDD. The authors used a first-order kinetic model to link blood levels and working histories to derive department-specific dose rates for TCDD. The TCDD background level of 3.4 ng/kg blood fat for the German population was used (Päpke et al., 1994). The dose rates were applied to estimate the concentration of TCDD at every point in time for all cohort members. A cumulative measure expressed as ng/kg blood fat multiplied by years was calculated and used in the SMR analysis. SMRs were calculated using general population mortality rates for the German population between 1952 and 1992. No lag period was incorporated into the derivation of the SMRs. The SMRs were estimated for the entire cohort and for exposure groups based on quartiles obtained from the area under the curve. Linear trend tests were also performed. The overall SMR for cancer mortality in the cohort was 1.41 (95% CI = 1.17−1.68). This SMR value was higher than the SMR of 1.21 reported for this same cohort with 3 fewer years of follow-up (Manz et al., 1991). In terms of site-specific cancer mortality, excesses were found for respiratory cancer (SMR = 1.71, 95% CI = 1.24−2.29) and rectal cancer (SMR = 2.30, 95% CI = 1.05−2.47). Increased risk for lymphatic and hematopoietic cancer (SMR = 2.16, 95% CI = 1.11−3.17) were also noted largely attributable (SMR = 3.73, 95% CI = 1.20−8.71) to lymphosarcoma (i.e., non-Hodgkin lymphoma). A dose-response relationship was observed across quartiles of cumulative TCDD for all-cancer mortality ($p < 0.01$). The SMRs for these quartiles were 1.24, 1.34, 1.34, and 1.73. Dose-response relationships were not observed for lung cancer or hematopoietic cancers using this same metric. Dose-response relationships were

not observed with cumulative TEQ for any of the cancer sites examined (i.e., all cancers, lung cancer, hematopoietic cancer).

C.1.1.1.3.3.2. *Study evaluation*

The approach used in the Flesch-Janys et al. (1998) study offers a distinct advantage over earlier analyses of the same cohort. The authors used sera data on 275 male and female subjects to estimate department-specific dose rates, although it is unclear whether data on females were used to estimate TCDD levels among the males examined in the cancer mortality analysis. Three more years of follow-up were available, and the characterization of exposure using the "area under the curve" better captures changes in cumulative exposure using a person-years approach when compared to estimates of cumulative TCDD at the time of last exposure. As noted previously, other occupational exposures or cigarette smoking are unlikely to have biased the study findings. A sufficient length of follow-up had accrued, and dose-response relationships were evident. DLCs were evaluated in this study. For TCDD, the mean concentration was 101.3 ng/kg at the time of measurement. For other higher chlorinated congeners, the corresponding mean (without TCDD) was 89.3 ng/kg.

C.1.1.1.3.3.3. *Suitability of data for TCDD dose-response modeling*

The data used in this study satisfy most of the considerations developed for performing a quantitative dose-response analysis. However, latency was not examined in this study. Dose-response analyses were, therefore, limited to a subsequent study of this cohort (Becher et al., 1998) which did examine latency and supersedes the Flesch-Janys et al. (1998) study.

C.1.1.1.3.4. ***Becher et al. (1998)***

C.1.1.1.3.4.1. *Study summary*

The Becher et al. (1998) quantitative cancer risk assessment for the Hamburg cohort was highlighted in the 2003 Reassessment as being appropriate for conducting dose-response analysis. The integrated TCDD concentration over time, as estimated in the Flesch-Janys et al. (1998) study, was used as the exposure variable. Estimates of the half-life of TCDD based on the sample of 48 individuals with repeated measures were incorporated into the model that back-calculated TCDD exposures to the end of the employment (Flesch-Janys et al., 1996). This

method took into account the age and body fat percentage of the workers. In Becher et al. (1998), the analysis used the estimate of cumulative dose (integrated dose or area under the curve) as a time-dependent variable.

Poisson and Cox regression models were used to characterize dose-response relationships. Both models were used to conduct internal comparisons where a person-years offset was used, and to an external comparison where an offset of expected number of deaths was used. The person-years offset was used to account for varying person-time accrued by workers across exposure categories. The use of the expected number of deaths as an offset allows risks to be described in relation to that expected in the general population. Within each classification cell of deaths and person-years, a continuous value TCDD and TEQ levels based on the geometric mean were entered into the Poisson model. For the Cox model, accumulated dose was estimated based on area under the curve for TCDD, TEQ, TEQ without TCDD, and β-hexachlorocyclohexane. These other coexposure metrics were adjusted for in the Cox regression analyses. Other covariates considered included in the models were year of entry, year of birth, and age at entry into the cohort. A background level of 3.4 ng/kg blood fat for the German population was used (Päpke et al., 1994). A variety of latencies was evaluated (0, 5, 10, 15, and 20 years), and attributable and absolute risks were estimated. The unexposed cohort of gas workers was used for most internal analyses.

Internal and external comparisons using the Poisson model found positive associations with TCDD exposure and mortality from all cancers combined. The slope associated with the continuous measure of TCDD (μg/kg blood fat × years) for the internal comparison was 0.027 ($p < 0.001$), which decreased to 0.0156 ($p = 0.07$) after adjusting for age and calendar period. The slope for the external comparison was 0.0163 ($p = 0.055$); this estimate was not adjusted for other covariates. For TEQ, the slopes based on the internal comparisons were 0.0274 ($p < 0.001$) in the univariate model and 0.0107 ($p = 0.175$) in the multivariate model after adjusting for age and calendar period. The external estimate of slope for TEQ was 0.0109 ($p = 0.164$). Cox regression of TCDD across six exposure categories, with a lag of 0 years, found a statistically significant linear trend ($p = 0.03$) and those in the upper exposure group had a RR of 2.19 (95% CI = 0.76−6.29). These estimates were adjusted for year of entry, age at entry, and duration of employment. A similar pattern was observed with the Cox regression analysis of

TEQ; the linear test for trend, however, was not statistically significant at the alpha level of 0.05 ($p = 0.06$).

Cox regression models that included both TCDD and TEQ (excluding TCDD) were applied. In this model, the slope (β) for TCDD was 0.0089 ($p = 0.058$), while the coefficient for TEQ (excluding TCDD) was −0.024 ($p = 0.70$). This suggests that confounding by other DLCs was unlikely and the increased risk of cancer was due to TCDD exposure. For all TEQs combined, the slope was 0.0078 ($p = 0.066$).

The authors used multiple Cox models to evaluate the effect of latency. The slope estimates for both TCDD and TEQ increased dramatically with increasing latency. The slope estimates for TCDD increased from 0.0096 to 0.0160 ($p < 0.05$) when latency was increased from 0 to 20 years. Similar changes in the TEQ slopes were noted (0.0093 to 0.0157). Evaluations of dose-response curves found that the best-fitting curve was concave in shape, thereby yielding higher risk at low exposure. Differences between the fit of the class of models considered [i.e., $RR(x,\beta) = \exp(\beta \log(kx = 1))$], however, were small.

Attributable risks were generated only for TCDD, as the data suggested no effects with other TEQs. The additional lifetime risk of cancer assuming a daily intake of 1 pg TCDD/kg body weight/day was estimated to range between 0.001 and 0.01.

C.1.1.1.3.4.2. *Study evaluation*

The Becher et al. (1998) study represents perhaps the most detailed analyses performed on any cohort to date. The findings were robust, as similar patterns were found with and without using the gas supply worker cohort as the referent group. Exposures to other potential confounding coexposures, such as DLCs, were taken into account, and workers with exposure to other carcinogens (e.g., lindane) were excluded. Furthermore, latency was examined in this study, unlike earlier studies of this cohort. Although the TCDD exposure estimates were derived from a sample of 275 workers with repeated serum measures, the authors indicate that the production department-specific estimates were in agreement with a priori expectations based on an understanding of the chemistry and available industrial hygiene data. The authors also reported no differences in dose rate estimates related to gender or short durations of employment. Similar to other studies, the potential for exposure misclassification based on limited number of

biomarker samples is hard to determine without more information on the representativeness of the participants who provided samples.

C.1.1.1.3.4.3. *Suitability of data for TCDD dose-response modeling*

This study was included in the quantitative dose-response modeling for the 2003 Reassessment (U.S. EPA, 2003). The data in the Becher et al. (1998) study are suitable for conducting quantitative dose-response modeling. The exposure data capture cumulative exposure to TCDD as well as exposures to other DLCs. The length of the follow-up is sufficient, and the study does not appear to be subject to confounding or other types of biases. Therefore, this study is utilized in quantitative dose-response analysis.

C.1.1.1.4. ***The Seveso cohort***

Several studies have evaluated the morbidity and mortality effects of residents exposed to TCDD following a July 10, 1976, accidental release through an exhaust pipe at a chemical plant in the town of Meda near Seveso, Italy. The released fluid mixture contained 2,4,5-T, sodium trichlorophenate, ethylene glycol, and sodium hydroxide. Vegetation in the area showed immediate signs of damage, and in the days following the accident, residents developed nausea, headaches, eye irritation, and dermal lesions, particularly children.

This accident transported TCDD up to 6 km from the plant. Soil samples taken near the plant revealed average levels of TCDD that ranged from 15.5 $\mu g/m^2$ to 580.4 $\mu g/m^2$ in the most contaminated area near the plant (referred to as Zone A) (Bertazzi et al., 2001). Zone A covered 87 hectares and extended 2,200 m south from the plant. Another, more distant contaminated zone (Zone B) covering 270 hectares also had contaminated soil levels, but the TCDD concentration range was much lower (1.7–4.3 $\mu g/m^3$). A reference zone (Zone R), which surrounded the two contaminated areas, had lower TCDD soil levels (range: 0.9–1.4 $\mu g/m^3$) and included approximately 30,000 residents. Following the accident, most residents in Zone A left the area. Although residents in Zone B remained, they were under strict regulations to avoid consuming homegrown products. In total, 736, 4,737, and 31,800 individuals lived in Zones A, B, and R, respectively. Within days of the accident, 3,300 animals (mostly poultry and rabbits) were found dead. Emergency slaughtering was undertaken to prevent TCDD from entering the food chain, and within 2 years more than 80,000 animals had been slaughtered. Mechanisms

were put into place for long-term follow-up of these residents. Unlike the other occupational cohort studies, the follow-up of this population allows for risks to be characterized for females.

The mortality studies from Seveso published to date have not incorporated serum TCDD levels that were measured in individuals. Needham et al. (1997) describe the collection of serum samples from a sample of the exposed population and control subjects in 1976. In 1988, human exposure to TCDD was assessed by measuring small volumes of serum remaining from medical examinations done in 1976. An examination of these data revealed some of the highest serum TCDD levels ever reported, that the half-life of TCDD in this population was between 7 and 8 years, and that half-life varied between women and men. The half-life of TCDD in serum was longer in women (~9 years) than in men (~7 years) (Needham et al., 1994). In this report, the findings of studies that characterized cancer risks in relation to exposure to TCDD from the 1976 accident are highlighted. These studies include comparisons of cancer mortality rates to the general population based on zone of residence at the time of accident (Consonni et al., 2008; Bertazzi et al., 2001). More recent work done by Warner et al. (2002) investigated the relationship between serum-based measures of TCDD and breast cancer among participants in the Seveso Women's Health Study (SWHS).

C.1.1.1.4.1. ***Bertazzi et al. (2001)***

C.1.1.1.4.1.1. *Study summary*

Several studies have reported on the mortality experience of Seveso residents. The more recent publications having a longer follow-up of the cohort are evaluated here. In 2001, the findings from a 20-year mortality study of Seveso residents was published (Bertazzi et al., 2001). The Bertazzi et al. (2001) study was an extension of the 10- and 15-year follow-ups for mortality (Pesatori et al., 1998; Bertazzi et al., 1997; 1989) and the 10-year follow-up for cancer incidence (Bertazzi et al., 1993).

In this cohort, TCDD exposures were assigned to the population using a three-level categorical variable representative of the individual's place of residence (Zones A, B, or R) at the time of the accident or when the person first became a resident of the zone, if that was after 1976. An external comparison to the province of Lombardy was made by generating rate ratios (RR) using Poisson regression techniques. Person-years of follow-up were tabulated across strata defined by age, zone of residence, duration of residence, gender, calendar time, and

number of years that had elapsed since the time of exposure. Mortality rates during the preaccident period also were compared to evaluate potential changes in rates due to the accident and to evaluate whether patterns were consistent before and after the accident.

No overall excess in mortality rates from all cancer sites combined was observed in Zones A or B (combined) when compared to the reference population of Lombardy (*n* = 9 million residents) (RR = 1.0, 95% CI = 0.9−1.2). Analyses of site-specific cancer mortality revealed statistically significant excesses among residents in Zones A or B (combined) for cancer of the rectum (RR = 1.8, 95% CI = 1.0−3.3) and lymphatic and hematopoietic malignancies (RR = 1.7, 95% CI = 1.2−2.5). Lymphatic and hematopoietic malignancies were elevated in women (RR = 1.8, 95% CI = 1.1−3.2) and in men (RR = 1.7, 95% CI = 1.0−2.8).

Analyses stratified by the number of years since first exposure (i.e., 1976) revealed higher risk among men with an increased number of years elapsed. Similar to other studies, the RR for all cancers (combined) was 1.3 (95% CI = 1.0−1.7) among men 15−20 years after first exposure. No such increase after 15 years postexposure, however, was noted in women (RR = 0.8, 95% CI = 0.6−1.2).

C.1.1.1.4.1.2. *Study evaluation*

Ascertainment of mortality appears to be excellent. Vital status was established using similar methods for both the exposed and reference populations. No individual data were collected and, therefore, the possibility that confounding by individual characteristics such as cigarette smoking cannot be entirely dismissed. Bertazzi et al. (2001) do note that the sociodemographic characteristics of residents in the three zones were similar based on independently conducted surveys, and no differences in chronic respiratory disease were found across the different zones. If excess mortality was attributable to cigarette smoking, such excesses would be expected to be evident during the entire study period. Latency analyses revealed elevated risks 15−20 years postaccident. Finally, no excesses were observed for other smoking-related cancers of the larynx, esophagus, pancreas, and bladder. The observed excesses in all cancer mortality do not appear to be attributed to differential smoking rates between the two populations.

To examine potential for bias due to noncomparability in the two study populations, a comparison of cancer mortality rates between the Seveso regions and the reference population of

Lombardy was conducted. Elevated rates for brain cancer mortality were noted in Seveso relative to Lombardy, but the higher rates of leukemia mortality were found in Lombardy relative to Seveso. That no excess was reported for all cancer sites combined lends credence to the hypothesis that the exposure to TCDD from the accident increased rates of cancer after a sufficient period of latency.

Stratified analyses were performed across several categorical variables including gender and time since exposure. The numbers of cancer site-specific deaths are quite small in many of the 5-year increments since first exposure. The study, therefore, has limited statistical power to detect differences in mortality rates among the comparison groups for many cancer sites.

Bertazzi et al. (2001) assigned exposures based on zone of residence. Soil sampling within each zone revealed considerable variability in TCDD soil levels within each zone. Moreover, some individuals would have left the area shortly after the accident, and determining the extent to which individuals in Zone B who were subject to the recommendations near the time of the accident adhered to them is difficult. As a result, exposure misclassification is possible, and the use of individual measures of TCDD level in serum is preferred over zone of residence for determining exposure. As noted by the authors, the study is better suited to "hazard identification" than to quantitative dose-response analysis.

C.1.1.1.4.1.3. *Suitability of data for TCDD dose-response modeling*

Given the variability in soil TCDD levels within each zone and the lack of individual level, no effective dose can be estimated for quantitative dose-response analyses. Uncertainty in identifying the critical exposure window for the Seveso cohort is a key limitation. The evaluation of this study indicates that this study is not suitable for quantitative dose-response analysis.

C.1.1.1.4.2. ***Warner et al. (2002)***

C.1.1.1.4.2.1. *Study summary*

To date, Warner et al. (2002) is the only published investigation of the relationship between serum-based measures of TCDD and cancer in Seveso. Eligible participants from the SWHS (see Section C.1.2.1.4 for details) were women who, at the time of the accident in 1976, were 40 years of age or younger, had lived in one of the most highly contaminated zones (A or

B), and had adequate sera collected soon after the explosion. Enrollment in SWHS was begun in March 1996 and lasted until July 1998. Of the total 1,271 eligible women, 981 agreed to participate in the study. Cancer cases were identified during interview and confirmed through review of medical records. Information on other risk factors including reproductive history and cigarette smoking was obtained through interview.

Serum volumes greater than 0.5 mL collected between 1976 and 1981 were analyzed. Most sera were collected in 1976/77 (*n* = 899); samples were collected in 1978−1981 for 54 women, and in 1996/97 for 28 women. For samples collected after 1977, serum TCDD levels were back-extrapolated using a first-order kinetic model with a 9-year half-life (Pirkle et al., 1989). For 96 women with undetectable values, a serum level that was equal to one-half the detection level was used.

Analyses were based only on women who provided serum samples; no extrapolation of values to a larger population was done. Risks were therefore generated using data collected at an individual level. Serum TCDD was analyzed as both a continuous variable and a categorical variable. The distribution of serum TCDD levels of the 15 cases of breast cancer was examined in relation to the distribution of all women in the SWHS. The median exposure was slightly higher among with the 15 cases of breast cancer (71.8 ppt) compared to those without (55.1 ppt), and the exposure distribution among breast cancer cases appeared to be shifted to the right (i.e., the exposures were higher but followed the same distribution); however, no formal test of significance was conducted.

Warner et al. (2002) used Cox proportional hazards models to evaluate the risk of breast cancer in relation to TCDD serum levels while controlling for a number of potential risk factors. In all, 21 women had been diagnosed with cancer, and of these, 15 cases were cancer of the breast. The analysis revealed that for every 10-fold increase in TCDD log-serum levels (e.g., from 10 to 100 ppt) the risk of breast cancer increased by a factor of 2.1 (95% CI = 1.0−4.6). Risk estimates also were generated across four categories (<20, 20.1−44, 44.1−100, >100 ppt), with the lowest category used as the reference. The RRs estimated in the third and fourth highest exposure categories were 4.5 (95% CI = 0.6−36.8) and 3.3 (95% CI = 0.4−28.0). Although statistical significance was not achieved for either category, likely because of the small number of cases, the greater than threefold risk evident in both categories is worth noting. Given that the reference category had only one incident case underscores the limited inferences that can be

drawn from these analyses. The authors adjusted for numerous potential confounders, but observed no differences between the crude and adjusted results; the authors, therefore, presented unadjusted risks.

C.1.1.1.4.2.2. *Study evaluation*

The findings from the Warner et al. (2002) study differ from reports in earlier studies in which mortality outcomes noted the absence of an SMR association. The design of this study is much stronger than earlier ones, given the improved characterization of exposure, the ability to compare incidence rates within the cohort, the ability to control for potential confounding variables at an individual level, and the availability of incident outcomes. The use of incident cases (versus mortality data) should also help minimize potential bias due to disease survival. Another important advantage was the ability to measure TCDD near the time of the accident, thereby reducing the potential for exposure measurement error.

A potentially important limitation of the Warner et al. (2002) study was that information was collected only from those who were alive as of March 1996. Therefore, TCDD and other relevant risk factor data could not be collected for those who had previously died of breast cancer. Thirty-three women could not participate because they were either too ill or had died. Of these, three died of breast cancer. Given that there were only 15 breast cancer cases, the exclusion of these 3 cases could have dramatically impacted the findings in either direction.

Another limitation was that, at the time of the follow-up, most women were still premenopausal and therefore, most of the cohort (average age = 40.8 years) had not yet attained the age of greater risk of breast cancer (average age at diagnosis among the cases in this cohort was 45.2 years). Although comparable data from Italy were not found, the median age of diagnosis for breast cancer among U.S. women from 2003−2007 was 61 years (Altekruse et al., 2010). An ongoing follow-up of the cohort should be completed by 2010, which should allow for increased number of incident breast cancers to be identified. Given that the current analyses were based only on 15 incident cases, this will substantially improve the statistical power of the study. A secondary benefit is that the increased follow-up will allow for an investigation of possible differential effects according to the age the women were at the time of exposure.

C.1.1.1.4.2.3. *Suitability of data for TCDD dose-response modeling*

Several aspects of the Warner et al. (2002) study are weaknesses in the consideration of this study for further dose-response modeling. Only 15 cases of breast cancer were available, and no increases in risk were found with serum TCDD exposures between 20.1 and 44 ppt (n = 2) when compared to those with <20 ppt (n = 1). The average age at the time of enrollment was 40.8 years while the average age at diagnosis among the cases was 45.2 years. As most women had not yet reached the age when breast cancer cases are typically diagnosed, additional follow-up of the cohort would improve the quantitative dose-response analysis and strengthen this study. A key strength of this study, however, is that Warner et al. (2002) includes an investigation of the relationship between individual serum-based measures of TCDD and cancer in Seveso. Despite the weaknesses, this study meets the evaluation considerations and criteria for inclusion and will be analyzed for quantitative dose-response modeling.

C.1.1.1.4.3. ***Pesatori et al. (2003)***

C.1.1.1.4.3.1. *Study summary*

Pesatori et al. (2003) published a review of the short- and long-term studies of morbidity and mortality outcomes in the Seveso cohort in 2003. This paper presented cancer incidence data from 1977 to 1991 for Seveso males and females residing in Zones A, B and R relative to an external population (i.e., uncontaminated areas). Mortality data are also presented for a 20-year follow-up (1976−1996) relative to the reference population. As in the original Bertazzi et al. (2001) study, RRs were estimated using Poisson regression. No associations were noted for zone of residence and all cancer mortality for either males or females. Although no cases were reported in Zones A and B, soft tissue sarcoma incidence rates were higher among males from Zone R (RR = 2.6, 95% CI = 1.1−6.3). Among males, residence in Zones A and B was associated with lymphatic and hematopoietic cancer (RR = 1.9, 95% CI = 1.1−3.1). This increased risk was due primarily to non-Hodgkin lymphoma, which accounted for 8 of the 15 incident cases (RR = 2.6, 95% CI = 1.3−5.3). Among females, increased incidence of multiple myeloma (RR = 4.9, 95% CI = 1.5−16.1), cancer of the vagina (RR = 5.5, 95% CI = 1.3−23.8), and cancer of the biliary tract (RR = 3.0, 95% CI = 1.1−8.2) was associated with residence in Zones A and B.

C.1.1.1.4.3.2. *Study evaluation*

Limitations of the Pesatori et al. (2003) study included exposure misclassification from the use of an ecological measure of exposure (i.e., region of residency at time of accident) and low statistical power for some health endpoints. For example, all of the RRs presented above for specific cancer mortality among females in the Pesatori et al. (2003) study were based on fewer than five incident cases.

C.1.1.1.4.3.3. *Suitability of data for TCDD dose-response modeling*

As with the studies of mortality among Seveso residents, the Pesatori et al. (2003) study does not capture TCDD exposure on an individual basis, and soil TCDD levels considerably vary within each zone. Therefore, the quality of the exposure data is inadequate for estimating the effective dose needed for quantitative dose-response analysis.

C.1.1.1.4.4. ***Baccarelli et al. (2006)***

C.1.1.1.4.4.1. *Study summary*

Given previous findings from Seveso, Baccarelli et al. (2006) examined t(14;18) translocations in the DNA of circulating lymphocytes of 144 healthy dioxin-exposed individuals. These translocations are associated with the development of cancer, namely follicular lymphomas. The study included 144 individuals selected from a previous population of 211 healthy subjects representative of the Seveso area, and 101 who had developed chloracne. The investigators analyzed data from 72 (52 females and 20 males) high-TCDD plasma level individuals (≥10 ppt) and 72 (41 females and 31 males) low-TCDD plasma levels (<10 ppt), matched for history of chloracne and smoking. A three-level categorical exposure variable was used to evaluate dose response. This variable was developed by dividing those with exposures ≥10 ppt into two groups: 10- <50 ppt, and 50−475.0 ppt. Trained interviewers administered a questionnaire that collected data on demographic characteristics, diet, and residential and occupational history.

The prevalence of t(14;18) was estimated as those individuals having a t(14;18) positive blood sample divided by the t(14;18) frequency (number of copies per million lymphocytes). Baccarelli et al. (2006) found that the frequency of t(14;18) was associated with plasma TCDD levels, but no association between TCDD and the prevalence of t(14;18) was detected.

C.1.1.1.4.4.2. *Study evaluation*

Whether the frequency of t(14;18) associated with plasma TCDD levels translates into an increased risk of lymphoma is uncertain as prospective data of TCDD on those who developed non-Hodgkin lymphoma are lacking. Moreover, the t(14;18) translocation could be an important event in the pre-B stage cell that contributes to tumorigenicity, however subsequent exposure to carcinogenic agents might be necessary for t(14;18) cells to develop into a malignancy (Höglund et al., 2004).

C.1.1.1.4.4.3. *Suitability of data for TCDD dose-response modeling*

Given that current TCDD plasma levels were measured for this study, it is unclear if the effects of lymphocyte translocations may be due to an initial high exposure or are a function of the cumulative exposure accrued over a longer time window. Additionally, whether the frequency of t(14;18) associated with plasma TCDD levels translates into an increased risk of lymphoma is unknown. Dose-response analysis for this outcome, therefore, was not conducted.

C.1.1.1.4.5. ***Consonni et al. (2008)***

C.1.1.1.4.5.1. *Study summary*

Consonni et al. (2008) analyzed cancer mortality in the Seveso cohort with the addition of a 25-year follow up period. Similar analytic methods as Pesatori et al. (2003) were applied with 25 years of follow-up added to the analysis (Consonni et al., 2008). An important addition in this paper was the presentation of RRs for Zone R, which had the lowest TCDD levels. Poisson regression models were used to calculate RRs of mortality using Seregno as the reference population. Cancer deaths observed in Zones A and B were 42 and 244, respectively.

No statistically significant differences in all cancer mortality relative to the reference population were noted in any of the zones (Zone A: RR = 1.03, 95% CI = 0.76−1.39; Zone B: RR = 0.92, 95% CI = 0.81−1.05; Zone R: RR = 0.97, 95% CI = 0.92−1.02). Statistically significant excesses in mortality from non-Hodgkin lymphoma (RR = 3.35, 95% CI = 1.07−10.46) and multiple myeloma (RR = 4.34, 95% CI = 1.07−17.52) were observed in the area with the highest TCDD levels (Zone A). No other statistically significant increases in cancer mortality relative to the reference population were apparent. The absence of elevated breast cancer mortality among women in this study was noteworthy, as this finding differs from

the results of a study of Seveso women for which TCDD exposures were estimated using serum samples (Warner et al., 2002).

C.1.1.1.4.5.2. *Study evaluation*

Although no individual-level data on smoking were available, the potential for confounding is likely minimal. Independent smoking surveys found that smoking prevalence rates in Desio, one of cities affected by the accident, were similar to those in districts just outside the study area (Cesana et al., 1995). As mentioned earlier, one would expect elevated RRs over the entire study period if smoking had biased the study results, and not just after 15–20 years since exposure to TCDD.

C.1.1.1.4.5.3. *Suitability of data for TCDD dose-response modeling*

The lack of individual-level exposure data precludes quantitative dose-response modeling using these data.

C.1.1.1.5. ***Chapaevsk study***

Industrial contamination of dioxin in the Chapaevsk region of Russia has been the focus of research on environmentally-induced cancers and other adverse health effects. The Chapaevsk region is located in the Samara region of Russia and has a population of 83,000. The region is home to a chemical plant that produced lindane and its derivatives between 1967 and 1987, which are believed to be responsible for local dioxin contamination. Soil sampling has demonstrated a strong gradient of increased TCDD concentrations with decreased proximity to the chemical plant (Revich et al., 2001).

C.1.1.1.5.1. ***Revich et al. (2001)***

C.1.1.1.5.1.1. *Study summary*

Revich et al. (2001) used a cross-sectional study to compare mortality rates of Chapaevsk residents to two external populations of Russia and the region of Samara. Mortality rates for all cancers combined among males in Chapaevsk were found to be 1.2 times higher when compared to the Samara region as a whole and 1.3 times higher than Russia. Similar to other studies, a statistically significant excess was noted in men (SMR = 1.8, 95% CI = 1.6–1.9) but not in

women (SMR = 0.9, 95% CI = 0.8−1.1). Among men, the excess was highest for the smoking-related cancers of the lung (SMR = 3.1, 95% CI = 2.6−3.5) and larynx (SMR = 2.3, 95% CI = 1.2−3.8) and urinary organs (SMR = 2.6, 95% CI = 1.7−3.6). Among females, there was no increased SMR for all cancer sites combined, but excesses for breast cancer (SMR = 2.1, 95% CI = 1.6−2.7) and cancer of the cervix (SMR = 1.5, 95% CI = 1.0−3.1) were statistically significant.

Revich et al. (2001) also compared age-standardized cancer incidence rates in Chapaevsk to those in Samara. Although statistical tests examining these differences were not reported, higher incidence rates were observed for all cancers combined, cancer of the lip, cancer of the oral cavity, and lung and bladder cancer among males in Chapaevsk. Considerably lower cancer incidence rates also were observed for prostate cancer, cancer of the esophagus, and leukemia/lymphoma among males from Chapaevsk. Among females, incidence rates were higher in 1998 for all cancers in Chapaevsk when compared to Russia and the Samara region, an observation that appears somewhat counter to the presented SMR of 0.9 for all cancer mortality from 1995−1998. Similar to the mortality findings, rates of breast and cervical cancer incidence among women in Chapaevsk were higher than in Russia. Leukemia/lymphoma rates were higher among women in Chapaevsk than the reference populations of Samara and Russia. This finding is contrary to the results for males where lower rates of leukemia/lymphoma were observed in Chapaevsk.

C.1.1.1.5.1.2. *Study evaluation*

Although the Revich et al. (2001) findings suggest TCDD exposures in Chapaevsk are quite high relative to other parts of the world (Akhmedkhanov et al., 2002), the evaluation of health outcomes to date is based on ecological data. One limitation is that insufficient details are provided by the authors to gauge the completeness and coverage of the cancer registry and mortality data. Given the ecological nature of the data, the authors did not adjust for the influence of other risk factors (e.g., smoking, reproductive characteristics) that could contribute to increased cancer rates for lung cancer in men and breast cancer in women. In addition, occupational exposures may have also contribute to these SMR and SIR differences for cancer outcomes that varied considerably between men and women.

Future research in Chapaevsk includes plans to conduct a breast cancer case-control study. Women who were born from 1940 onward and who have been diagnosed with breast cancer before the age of 55 were included in the study, although the plan to characterize TCDD using serum is uncertain (Revich et al., 2005).

C.1.1.1.5.1.3. *Suitability of data for TCDD dose-response modeling*

This study did not meet most of the study considerations and criteria for inclusion in a quantitative dose-response assessment. Given the lack of exposure data on an individual basis, no effective dose can be estimated for this study population. Therefore, no dose-response modeling was conducted for this study.

C.1.1.1.6. ***The Air Force Health ("Ranch Hands" cohort) study***

Between 1962 and 1971, the U.S. military sprayed herbicides over Vietnam to destroy crops that opposition forces depended upon, to clear vegetation from the perimeter of U.S. bases, and to reduce the ability of opposition forces to hide. These herbicides were predominantly a mixture of 2,4-D; 2,4,5-T; picloram; and cacodylic acid (Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides, 2006). A main chemical sprayed was Agent Orange, which was a 50% mixture of 2,4-D and 2,4,5-T. TCDD was produced as a contaminant of 2,4,5-T and had levels ranging from 0.05 to 50 ppm (Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides, 1994). A series of studies have investigated cancer outcomes among Vietnam veterans. A review of military records to characterize exposure to Agent Orange led Stellman and Stellman (1986) to conclude that assignment of herbicide levels should not be based solely on self-reports or a crude measure such as military branch or area of service within Vietnam. Investigations have been performed on the Ranch Hands cohort, which consisted of those who were involved in the aerial spraying of Agent Orange between 1962 and 1971. More elaborate methods were used to characterize exposures among these individuals, and these studies are summarized below.

C.1.1.1.6.1. ***Akhtar et al. (2004)***

C.1.1.1.6.1.1. *Study summary*

Akhtar et al. (2004) investigated the incidence of cancer in the Ranch Hand cohort. The Ranch Hand Unit was responsible for aerial spraying of herbicides, including Agent Orange, in Vietnam from 1962 to 1971. Cancer incidence in the Ranch Hand cohort was compared to a cohort that included other Air Force personnel who served in Southeast Asia during the same period but were not involved in the spraying of pesticides. Study participation was voluntary, but there was no indication of the participation rate for either the Ranch Hand cohort or the comparison group. Health outcomes were identified during the postservice period that extended from the time each veteran left Southeast Asia until December 31, 1999. The Akhtar et al. (2004) study took into account concerns that both the comparison and spraying cohorts had increased risks of cancer, and addressed the possibility that workers with service in Vietnam or Southeast Asia might have increased cancer risk. The authors addressed the latter concern by adjusting risk estimates for the time spent in Southeast Asia and for the proportion of service time spent in Vietnam.

The Ranch Hand cohort comprised 1,196 men, and the comparison cohort had 1,785 men. The comparison cohort was selected by matching date of birth, race, and occupation (i.e., officer pilot, officer navigator, nonflying officer, enlisted flyer, or enlisted ground personnel). TCDD levels were determined using serum levels collected from veterans who completed a medical examination in 1987. Blood measures also were taken in 1992, 1997, and 2002 for subjects with no quantifiable TCDD levels in 1987, those who refused in 1987, and those new to the study; however, the 2002 data were not available for the Akhtar et al (2004) analyses. For those who did not have a serum measure taken in 1987, but provided one in subsequent years, TCDD levels were back-extrapolated to 1987 using a first-order kinetic model that assumed a half-life of 7.6 years. Those with nonquantifiable levels were assigned a value of the limit of detection divided by the square root of 2. A total of 1,009 and 1,429 individuals in the Ranch Hand and comparison cohorts, respectively, provided serum measures that were used in the risk assessment. Veterans also were categorized according to the time their tours ended. This date corresponded to changes in herbicide use. These categories were before 1962 or after 1972 (no herbicides were used), 1962−1965 (before Agent Orange was used), 1966−1970 (when Agent Orange use was greatest), and 1971−1972 (after Agent Orange was used). Information on

incident cases of cancer in the cohort was determined from physical examinations and medical records. Some malignancies were discovered at death and coded by using the underlying cause of death as detailed on the death certificate. A total of 134 and 163 incident cases of cancer were identified in the Ranch Hand and comparison cohorts, respectively. Akhtar et al. (2004) describe case ascertainment verified by record review as being complete.

External comparisons were made based on the expected cancer experience derived from U.S. national rates by using SIRs and their corresponding 95% confidence intervals. Incident events and person-year contributions per group were tabulated by 5-year calendar and age intervals.

When compared to the general population, no statistically significant excesses in all cancer incidence were observed for either the Ranch Hand (SIR = 1.09, 95% CI = 0.91−1.28) or the comparison cohort (SIR = 0.94, 95% CI = 0.81−1.10). Statistically significant differences were found for three site-specific cancers in the Ranch Hands cohort relative to the general population. Excesses were noted for malignant melanoma (SIR = 2.33, 95% CI = 1.40−3.65) and prostate cancer (SIR = 1.46, 95% CI = 1.04−2.00). In contrast, a reduced SIR was found for cancers of the digestive system (SIR = 0.61, 95% CI = 0.36−0.96). The excess in prostate cancer was also noted in the comparison cohort (SIR = 1.62, 95% CI = 1.23−2.10) relative to the general population. External comparisons were repeated by restricting the cohorts to the period when Agent Orange was used (1966−1970). Again, no statistically significant excesses in all cancer incidence were noted in the Ranch Hand veterans (SIR = 1.14, 95% CI = 0.95−1.37) or in the comparison cohort (SIR = 0.94, 95% CI = 0.80−1.11). Statistically significant excesses persisted for malignant melanoma (SIR = 2.57, 95% CI = 1.52−4.09) and prostate cancer (SIR = 1.68, 95% CI = 1.19−2.33) in the Ranch Hand veterans. No other statistically significant differences were found among Ranch Hands personnel.

For internal cohort analyses, veterans were assigned to one of four exposure categories. Those in the comparison cohort were assigned to the “comparison category.” Ranch Hand veterans that had TCDD serum levels <10 ppt were assigned to the “background” category. Those with a TCDD levels >10 ppt had their TCDD level estimated at the end of their Vietnam service with a first-order kinetic model that used a half-life of 7.6 years. These back-extrapolated values that were less than 118.5 ppt were assigned to a “low” exposure group, while those with values above 118.5 ppt were classified as “high” exposure. Akhtar et al. (2004)

used Cox regression models to describe risks across the exposure groups using the comparison category as the reference. Risks were adjusted for age at tour, military occupation, smoking history, skin reaction to sun exposure, and eye color. Internal cohort analyses were restricted to those who spent no more than 2 years in Southeast Asia and Ranch Hand workers who served exclusively in Vietnam, and the comparison cohort who served exclusively outside of Vietnam.

Statistically significant excesses of cancer incidence (all sites combined) were observed in the highest two exposure groups. A statistically significant trend ($p = 0.04$) was detected based on the RRs for the background, low, and high exposure groups: 1.44 (95% CI = 0.82−2.53); 2.23 (95% CI = 1.24−4.00), and 2.02 (95% CI = 1.03−3.95). For malignant melanoma, a statistically significant trend ($p = 0.004$) was detected, and the RRs across the three increasing exposure categories were 2.99, 7.42, and 7.51, with statistically significant results for the low and high exposure groups. The corresponding risk estimates for prostate cancer were 1.50, 2.17, and 6.04 with statistically significant results only detected for the high exposure group.

C.1.1.1.6.1.2. *Study evaluation*

An important strength of this study is the manner in which TCDD exposure was estimated. Serum data were available for most veterans, and therefore, generalizing exposure from a small sample of cohort members is not a concern as was the case with the NIOSH and Hamburg cohorts. Back-extrapolating to derive past exposures was based on a methodology that has been applied in many of the cohorts, thereby facilitating risk comparisons. An additional strength of the study is the examination of cancer incidence as a measure of disease occurrence rather than mortality. There is limited potential for gauge how representative the study participants were given the lack of information provided on participation rates for either the Ranch Hands or the comparison group. The analysis by Akhtar et al. (2004) was restricted to individuals who spent no more than 2 years in Southeast Asia. Previous research had demonstrated that increased time spent in Southeast Asia was associated with an increased risk of cancer. Confounding might have been introduced given that the comparison cohort spent much more time in Southeast Asia than the Ranch Hands. To illustrate, the median number of days spent in Southeast Asia was 790 for comparison cohort members, and the median days for the Ranch Hand cohort in the background, low, and high exposure groups were 426, 457, and

397, respectively. After restricting to those who spent at most 2 years, statistically significant associations were observed for all cancer sites combined, prostate cancer, and malignant melanoma using the internal cohort comparisons.

Given that 2,4,5-T and 2,4-D were used in equal concentrations in Agent Orange, there is some concern regarding the ability to distinguish independent health effects for TCDD from coexposures to these two herbicides. However, in a large cohort study, called the Agricultural Health Study, these herbicides were 2 of 50 pesticides and herbicides evaluated in a cohort of more than 55,000 (mostly male) pesticide applicators in the United States and more than 33,000 spouses. Although statistically significant associations were shown between prostate cancer and several individual pesticides in this cohort (Alavanja et al., 2005), neither 2,4,5-T nor 2,4-D was associated with prostate cancer in that study (Alavanja et al., 2003); no associations were found for these 2 herbicides and lung cancer either (Alavanja et al., 2004). Therefore, based on these Agricultural Health Study results, the dose-response relationship detected for prostate cancer in the Akhtar et al. (2004) Ranch Hands study seems unlikely to be due to 2,4-D or 2,4,5-T exposures.

C.1.1.1.6.1.3. *Suitability of data for TCDD dose-response modeling*

The ascertainment of incident cases and characterization of exposure to TCDD based on serum measures are strong features of the cohort. Based on findings from another study (Alavanja et al., 2005; 2004; 2003), confounding by 2,4-D and 2,4-T does not appear likely to be responsible for the exposure-response relationships found for prostate cancer and TCDD exposures. Therefore, this study was found suitable for quantitative TCDD dose-response analysis.

C.1.1.1.6.2. ***Michalek and Pavuk (2008)***

C.1.1.1.6.2.1. *Study summary*

Michalek and Pavuk (2008) published an updated analysis of the incidence of cancer and diabetes in the cohort of Ranch Hand veterans. As with the Akhtar et al. (2004) analysis, the study included a comparison cohort of other Air Force veterans who served in Southeast Asia at the same time but were not involved with the spraying of herbicides. This study extended previous analyses (Akhtar et al., 2004; Henriksen et al., 1997) by stratifying the results by the

number of days of herbicide spraying, calendar period of service, and the time spent in Southeast Asia. Veterans who attended at least one of five examinations were eligible for inclusion. Incident cancer cases also were identified from medical records.

The methods used to determine TCDD exposures were as described above in the review of the Akhtar et al. (2004) study. Blood measures taken in 1992, 1997, and 2002 were all included in this new analysis. The study report did not provide the number of men with measurements at the different time points or the number who refused to partake at any time point. TCDD dose at the end of service in Vietnam was assigned to Ranch Hands that had TCDD levels above background using a first-order kinetic model and constant half-life of 7.6 years. Each veteran was then assigned to one of four dose categories: comparison veteran, background (i.e., Ranch Hands with 1987 levels of TCDD ≤10 ppt), low (Ranch Hands with 1987 levels of TCDD >10−91 ppt), and high (Ranch Hands with 1987 levels of TCDD >91 ppt). Serum TCDD estimates were available for 1,597 veterans (men) in the comparison cohort, and 986 veterans (men) in the Ranch Hand cohort. The comparison cohort was selected by matching on date of birth, race, and military occupation of the Ranch Hands.

Michalek and Pavuk (2008) used Cox regression to characterize risks of cancer incidence across the three upper exposure categories using the comparison cohort as the referent group. Risk estimates were adjusted for year of birth, race, smoking, body mass index at the qualifying tour, military occupation, eye color, and skin reaction to sun exposure. Tests for trend for increased risk of cancer were conducted by testing the continuous covariate $\log_{10}$TCDD.

Without stratification, no association between the TCDD exposure categories and RR of all-site cancer incidence was observed. Those in the highest exposure group had an RR of 0.9 (95% CI = 0.6−1.4). Stratified analyses by calendar period of service showed a more pronounced risk for those who served before 1986 (when higher amounts of Agent Orange were used). A statistically significant dose-response trend ($p < 0.01$) was observed for cancer risk and log10TCDD exposure. The RRs for the background, low, and high groups used in these comparisons were 0.7 (95% CI = 0.4−1.3) with $p = 0.26$, 1.7 (95% CI = 1.0−2.9) with $p = 0.03$, and 1.5 (95% CI = 0.9−2.6) with $p = 0.14$. The strongest statistically significant increase, however, was noted when analyses were restricted to those who had served before 1968, had sprayed for at least 30 days before 1967, and had spent less than 2 years in Southeast Asia. A RR of 1.4 (95% CI = 1.1−1.7) per log(TCDD) exposure was detected (trend test $p = 0.005$)

among this subgroup, while categorical exposures also suggested associations in the Low (RR=1.7, 95% CI = 0.8−3.5) and High (RR=2.2, 95% CI = 1.1−4.4) groups relative to the comparison group.

C.1.1.1.6.2.2. *Study evaluation*

Michalek and Pavuk (2008) used the same study population as Akhtar et al. (2004), and so it shares the same basic strengths and limitations as noted above. The follow-up, however, extends an additional 5 years (until the end of 2004), resulting in additional cancer data for analysis and the inclusion of the serum data from 2002. Also, in this study, all analyses were further adjusted for the number of days of spraying, which had not been done before. The findings for the dose-response analyses were not as compelling as the earlier Akhtar et al. (2004) findings, which was due in part to increased cancer risks in 2005 in the comparison cohort with years spent in SEA.

C.1.1.1.6.2.3. *Suitability of data for TCDD dose-response modeling*

As stated above for the Akhtar et al. (2004) study, the ascertainment of incident cases and characterization of exposure to TCDD based on serum measures are strengths of the cohort. In addition, newer data and additional statistical adjustments improved the strength of the analysis. This study, Michalek and Pavuk (2008), was suitable for quantitative dose-response analysis of TCDD.

C.1.1.1.7. ***Other studies of potential relevance to dose-response modeling***

C.1.1.1.7.1. ***Hooiveld et al. (1998)—Netherlands workers***

C.1.1.1.7.1.1. *Study summary*

Hooiveld et al. (1998) reanalyzed the mortality experience of a cohort of workers employed in two chemical plants in the Netherlands using 6 additional years of follow-up from an earlier study (Bueno de Mesquita et al., 1993). The cohort consisted of those employed between 1955 and June 30, 1985, and vital status was ascertained until December 31, 1991 (i.e., 36 years of follow-up). These cohort members were involved in the synthesis and formulation of phenoxy herbicides, of which the main product was 2,4,5-trichlorophenoxyacetic acid and monochloroacetic acid. This cohort, with a shorter follow-up interval than the original study

(t' Mannetje et al., 2005), was included in the IARC international cohort. The cohort consisted of 1,167 workers, of which 906 were alive at the end of the follow-up. The average length of follow-up was 22.3 years, and only 10 individuals were lost to follow-up.

The authors used detailed occupational histories to assign exposures. Workers were classified as exposed to phenoxy herbicides or chlorophenols and contaminants if they worked in selected departments (i.e., synthesis, finishing, formulation, packing, maintenance/repair, laboratory, chemical effluent waste, cleaning, shipping-transport, or plant supervision); were exposed to the accident in 1963; or were exposed by proximity (i.e., if they entered an exposed department at least once a week). The 1963 accident was the result of an uncontrolled reaction in the autoclave in which 2,4,5-trichlorophenol was synthesized; an explosion resulted, with subsequent release of PCDDs that included TCDD. Based on these methods of exposure assignment, 562 workers were deemed to be exposed to phenoxy herbicides or chlorophenols, and 567 were unexposed. Due to limited information, exposure could not be determined for 27 workers.

TCDD exposures also were assigned using serum measured on a sample of workers who were employed for at least 1 year and started working before 1975. DLCs including PCDDs were also measured in the serum samples but were not analyzed for this study. Of the 144 subjects who were invited to provide samples, 94 agreed. TCDD levels were back-extrapolated to the time of maximum exposure using a one-compartment, first-order kinetic model that used a half-life estimate of 7.1 years. The mathematical model used was $\ln(TCDDmax) = \ln(TCDD) + lag \times \ln(2)/7.1$. The lag was defined as the number of years since last exposure for those exposed by virtue of their normal job duties. For those exposed as a result of the accident in 1963, the lag was defined as the number of years since the accident occurred.

The authors made external comparisons of cohort mortality to the Netherlands population using SMRs. Poisson regression was used to perform internal cohort comparisons using unexposed workers as the referent. RRs (measured using rate ratios) generated from the Poisson model also were used to compare mortality based on low, medium, and high TCDD serum-derived categories. The Poisson model included the following covariates as adjustment factors: age, calendar period at end of follow-up, and time since first exposure.

When compared to the general population, workers had an excess mortality from cancer (SMR = 1.5, 95% CI = 1.1−1.9), based on 51 cancer deaths. Generally, no excesses were observed for site-specific cancers. The exception included eight deaths from cancers of the urinary organs (SMR = 3.9, 95% CI = 1.7−7.6). Although not statistically significant, SMRs comparable in magnitude to other studies were detected for non-Hodgkin lymphoma (SMR = 3.8, 95% CI = 0.8−11.0**)** and Hodgkin disease (SMR = 3.2, 95% CI = 0.1−17.6). A statistically significant excess of cancer mortality (*n* = 20 deaths among workers) also was observed relative to the general population when analyses were restricted to those exposed from the 1963 accident (SMR = 1.7, 95% CI = 1.1−2.7). Three deaths from prostate cancer were also noted among these workers (SMR = 5.2, 95% CI = 1.1−15.3), but no excess was observed with any other cancer site.

Internal cohort comparison also demonstrated an increased risk of all cancer mortality among those exposed to phenoxy herbicides, chlorophenols, and contaminants relative to those unexposed (RR = 4.1, 95% CI = 1.8−9.0). A statistically significant increased risk was also noted for respiratory cancer mortality (RR = 7.5, 95% CI = 1.0−56.1). Analyses across categories of TCDD exposure revealed excesses in cancer mortality for all cancer sites combined; however, no dose-response trend was apparent.

C.1.1.1.7.1.2. *Study evaluation*

Several other studies that have characterized cohorts by TCDD levels have used the area under the curve approach and thus have derived an exposure metric that is time dependent. Hooiveld et al. (1998) instead created an exposure metric to capture the maximum exposure attained during the worker's employment. Characterizing risks using this metric assumes that other TCDD exposures accrued during a workers' lifetime are not relevant predictors of cancer risk.

C.1.1.1.7.1.3. *Suitability of data for TCDD dose-response modeling*

One study limitation is that, although DLCs were measured in the serum samples, mortality associations were reported for TCDD only. There is some utility in examining dose-response analyses using the alternative exposure metrics that were constructed for this cohort. However, the small number of identified cancer deaths, exposure assessment limitations

(based on a nonrepresentative sample, and maximum exposure level) and concern over potential confounding by coexposures preclude using these data for a dose-response analysis.

C.1.1.1.7.2. ***t' Mannetje et al. (2005)—New Zealand herbicide sprayers***

C.1.1.1.7.2.1. *Study summary*

t' Mannetje et al. (2005) described the mortality experience of a cohort of New Zealand workers who were employed in a plant located in New Plymouth. The plant produced phenoxy herbicides and pentachlorophenol between 1950 and the mid-1980s. This study population also was included in the international cohort of producers and sprayers of herbicides that was analyzed by IARC (Kogevinas et al., 1997; Saracci et al., 1991). In this 2005 study, analyses were restricted to those who had worked at least 1 month; clerical, kitchen, and field research staff were excluded. The authors followed up 1,025 herbicide producers and 703 sprayers from 1969 and 1973, respectively, until the end of 2000.

The cohort consisted of two components: those involved with the production of herbicides and those who were sprayers. For the herbicide producers, exposures were determined by consulting occupational history records; no direct measures of exposure were available. Each department of employment was assigned to one of 21 codes as in the IARC international cohort (Saracci et al., 1991). Industrial hygienists and factory personnel with knowledge of potential exposures in this workforce classified each job according to potential to be exposed to TCDD, other chlorinated dioxins, and phenoxy herbicides. Exposure was defined as a dichotomous variable (i.e., exposed and unexposed). Among producers, 813 (713 men and 100 women) were classified as exposed, with the remaining 212 (gender not specified) considered unexposed.

The "sprayer" component of the cohort includes those who were registered in the national registry of applicators at any time from January 1973 until the end of 1984. For the sprayers, detailed occupational information was lacking. Exposure was, therefore, based on an exposure history questionnaire completed in a previous study of congenital malformations (Smith et al., 1982). This questionnaire, administered to 548 applicators in 1980 and 232 applicators in 1982, achieved a high response rate (89%). Participants were asked to provide information about 2,4,5-T-containing product use on an annual basis from 1969 up to the year the survey was completed. As the use of 2,4,5-T ceased in the mid-1980s, data on occupational exposure to

TCDD among these workers are fairly complete. Virtually all sprayers (699 [697 men and 2 women] of 703) were deemed to have been exposed to TCDD, higher chlorinated dioxins, or phenoxy herbicides.

Deaths among workers were identified through record linkage to death registrations in the New Zealand Health Information Service. Electoral rolls, drivers' licenses, and social security records also were consulted to confirm identified deaths. External comparisons of mortality were made to the New Zealand population using the SMR statistic. The mortality follow-up for the producers began on January 1, 1969 and extended until December 31, 2000. For the sprayers, the follow-up period extended from January 1, 1973 until December 31, 2000. A total of 43 cancer deaths occurred in the producer group and 35 cancer deaths occurred in the sprayer group in the cohort. Stratified analyses by duration of employment and department were conducted. The departments examined for producers included synthesis, formulation and lab, maintenance and waste, packing and transport, other, and unexposed. SMRs were generated using the New Zealand population as an external referent. A linear test for trend was applied to evaluate dose-response trends according to categories of duration of employment. Stratified analyses also were also done for sprayers who started working before 1973, as TCDD levels in 2,4,5-T produced at the New Zealand plant dropped dramatically after 1973. Although an SMR was presented for female producers, given that only one cancer death was observed, this study can provide no insight on differential risks between the sexes.

Among TCDD-exposed producers, for all cancers combined, no statistically significant excess in mortality was found when compared to the general population (SMR = 1.24, 95% CI = 0.90−1.67). No dose-response trend in the SMRs for all cancers was observed with duration of employment ($p = 0.44$). No statistically significant elevated SMR was observed in any of the duration of employment categories for any of the six specific departments examined. A statistically significant positive linear trend, however, was noted among synthesis workers ($p = 0.04$). There was some suggestion of reduced mortality in the upper exposure levels for workers in the formulation and lab departments. For sprayers, the SMR for all cancer sites combined was not elevated relative to the New Zealand general population (SMR = 0.82, 95% CI = 0.57−1.14), nor was a dose-response pattern observed with increasing duration of employment ($p = 0.86$). Additionally, no statistically significant excess in cancer mortality for all sites combined was evident in workers who were first employed either before 1973

(SMR = 0.75, 95% CI = 0.50−1.07) or from 1973 onwards (SMR = 1.81, 95% CI = 0.59−4.22). For site-specific cancer mortality, an excess of multiple myeloma was observed among production workers relative to the general population (SMR = 5.51, 95% CI = 1.14−16.1). This SMR was based on three deaths. No statistically significant excess (or deficit) of mortality was found for any other cancer site examined in either the sprayers or the producers.

C.1.1.1.7.2.2. *Study evaluation*

The physical activity demands of spraying contribute to a healthy worker effect that manifests itself in a lower SMR based for both external comparisons to the general population as a referent, and that generated relative to the producers in the cohort. The lack of individual-level TCDD data resulted in the analyses being based upon job title and duration of employment. Thus, intra-cohort comparisons were precluded due to a lack of an unexposed group (e.g., the sprayers), limited exposure contrasts and the small number of cancer deaths.

The dose-response pattern with duration of employment coupled with the observation that higher levels of exposure to TCDD occurred among workers in the synthesis department is an important finding. These workers were, however, also exposed to several other contaminants that include processing chemicals, technical products, intermediates, and byproducts (Kauppinen et al., 1993). These included phenoxy herbicides and DLCs such as chlorinated dioxins. Since the dichotomous exposure measure was based on exposure to TCDD, chlorinated dioxins and phenoxy herbicides, the associated dose-response analyses presented in this study should be interpreted cautiously in light of the inability to either characterize or control for these potential confounders. As such, these coexposures might have contributed to the dose-response pattern observed with increased duration of employment in the synthesis workers.

C.1.1.1.7.2.3. *Suitability of data for TCDD dose-response modeling*

Although the study authors completed a subsequent analysis of this cohort using serum-derived TCDD (McBride et al., 2009b), the lack of individual-level TCDD exposures precludes dose-response modeling.

C.1.1.1.7.3. ***McBride et al. (2009b)—New Zealand herbicide sprayers***

C.1.1.1.7.3.1. *Study summary*

McBride et al. (2009b) recently published the mortality experience of the New Zealand cohort in relation to serum estimates of TCDD levels. This study included 1,599 workers who were employed between 1969 and November 1, 1989, which was the date that 2,4,5-T was last used. The study report does not specify how many of the individuals were men or women, but using the percentage that were men lost to follow-up (73% of 1,261 were men) and not lost to follow-up (76% of 338 were men) would indicate 1,001 men and 598 women were included in the original cohort. As in their study published earlier in the same year (McBride et al., 2009a), the follow-up period extended from the first day of employment until December 31, 2004. Vital status was ascertained through record linkage to the New Zealand Health Information Service Mortality Collection and the Registrar General's Index to Deaths for deaths up to 1990.

All current and former workers who lived within 75 km of the plant were invited to provide serum samples. A total of 346 of the eligible workers (68%, gender not specified) provided samples, which represented 22% of the overall study population (346/1,599). Based on the serum measures, 70% (241/346) had been exposed to TCDD. This percentage is similar to the estimated 71% of workers who were deemed to have been exposed based on a review of occupational records. The mean serum TCDD value was 9.9 ppt. The highest exposures were observed for those employed in the trichlorophenol operation (23.4 ppt). Values among unexposed workers averaged 4.9 ppt, which is close to the background level of 3.9 ppt among individuals of similar age in the New Zealand general population (Bates et al., 2004). Details on smoking histories of individuals were also collected for the 346 individuals who provided serum, allowing for an examination of the potential confounding influence that smoking might have on derived risk estimates for TCDD.

Cumulative exposure to TCDD, as a time-dependent metric, was estimated for each worker. A detailed description of the methods used to derive TCDD exposure was described in Aylward et al. (2009). The qualitative TCDD scores available for those with serum measures were used to estimate the cumulative exposures based on a half-life of 7 years. A time-dependent estimate of TCDD exposure was derived and the area under the curve was used to estimate cumulative workplace TCDD exposures above background levels. Model performance appeared modest as the model explained only 30% of the variance (adjusted R^2)

when these TCDD exposure estimates were compared with actual serum levels (Aylward et al., 2009).

As with previous analyses of the cohort (McBride et al., 2009a; t' Mannetje et al., 2005), external comparisons to the New Zealand general population were made using the SMR. The SMR also was used to compare mortality across four exposure groups relative to the general population, as defined by the serum TCDD estimates: 0−68.3, 68.4−475.0, 475.1−2085.7, and ≥2085.8 ppt-month. The proportional hazards model also was used to conduct internal cohort comparisons across these same four exposure groups. In these analyses, age was used as the time variable, and the covariates of date of hire, sex, and birth year were included in the proportional hazards model. The cut-points for these four exposure categories were chosen so that approximately equal numbers of deaths were included in each category.

Consistent with earlier SMR analyses of the same cohort, no increased cancer mortality was observed among "ever" exposed workers when compared to the general population (SMR = 1.1, 95% CI = 0.9−1.4). No statistically significant excess was noted for any of the site-specific cancers, although there was some suggestion of increased risk of soft tissue sarcoma (SMR = 3.4, 95% CI = 0.1–19.5), multiple myeloma (SMR = 2.2, 95% CI = 0.2−8.1), non-Hodgkin lymphoma (SMR = 1.6, 95% CI = 0.3–4.7), and cancer of the rectum (SMR = 2.0, 95% CI = 0.7−4.4). No statistically significant increase in cancer mortality (all sites combined) was found in any of the four exposure categories as measured by the SMR statistic, nor was a dose-response trend noted with increasing exposure categories. No dose-response trends (based on SMR analyses) were noted for five site-specific cancers examined (i.e., digestive organs, bronchus, trachea and lung, soft tissue sarcomas, lymphatic and hematopoietic tissue, and non-Hodgkin lymphoma), although SMRs for three of the four exposure categories exceeded 2.0 for non-Hodgkin lymphoma.

In contrast to the external cohort comparisons, the RRs generated with the proportional hazards model supported a dose-response trend, as rate ratios increased across increasing TCDD exposure categories. The RRs and 95% confidence intervals for all cancer mortality relative to the lowest of the four groups were 1.05 (95% CI = 0.48−2.26), 1.38 (95% CI = 0.64−2.97) and 1.58 (95% CI = 0.71−3.52). Neither the linear (p = 0.29) or quadratic (p = 0.82) test for trend, however, was statistically significant. An increased risk of lung cancer mortality was observed in the highest TCDD exposure category relative to the lowest although the precision of this risk

estimates was poor and was not statistically significant (RR = 5.75, 95% CI = 0.76−42.24). The test for trend for lung cancer also was not statistically significant.

A smoking survey was administered to a sample of surviving workers of this cohort, and smoking prevalence was found to be slightly higher among those with higher cumulative exposure (61%) compared to lower exposures (51−56%). These minor differences in smoking prevalence were unlikely to explain the five-fold increase in risk of lung cancer found in the highest exposure category. Although the smoking data assessment was a strength of the study, it was limited to only sample of workers and was not available for those who died of lung cancer, or other causes of death.

C.1.1.1.7.3.2. *Study evaluation*

Given high rates of emigration, loss to follow-up (21%) was a potential concern in this study. If comparable emigration rates did occur among the general population then the SMRs would be underestimated. It is unclear to what extent emigration occurred among the general population and whether emigration in both the worker and general populations was dependent on health status. If emigration rates were comparable among these two populations, the associated bias from the under-ascertainment of mortality in the lost to follow-up group would likely attenuate a positive association between TCDD and cancer mortality. Among the worker population, there was not much evidence of differential loss to follow-up with respect to exposure as average exposures were lower (3.2 ppt) among those loss to follow up compared to those with complete follow-up (5.7 ppt). Previous studies among this population also found slightly higher loss to follow-up rates among the unexposed (23%) compared to the exposed (17%) workers (t' Mannetje et al., 2005).

McBride et al. (2009b) did not present results using a continuous measure of TCDD exposure (lagged or unlagged) as was done in most other occupational cohorts. Additionally, the modeling did not consider the use of different periods of latency.

C.1.1.1.7.3.3. *Suitability of data for TCDD dose-response modeling*

There was limited evidence of dose-response relationships between TCDD exposure and the cancer outcomes that were examined. There is also no evidence that the authors considered exposure metrics that are consistent with environmental cancer-causing agents such as exposure

modeling that takes latency into account. Given that past occupational cohort studies of TCDD-exposed workers have consistently demonstrated stronger association with lag interval of 15 years, such an approach should be applied to this cohort. This precludes this study from consideration for quantitative dose-response modeling.

C.1.1.1.7.4. ***McBride et al. (2009a)—New Zealand herbicide sprayers***

C.1.1.1.7.4.1. *Study summary*

McBride et al. (2009a) published an updated analysis of the mortality of the New Zealand cohort. The follow-up period was from January 1, 1969 to December 31, 2004 extending the previous study by an additional 4 years. In contrast to the previous study where the cohort comprised individuals employed for at least 1 month prior to 1982 (or 1984) (t' Mannetje et al., 2005), the cohort in this study consisted of all those who worked at least one day between January 1, 1969 and October 1, 2003. This resulted in a cohort of 1,754 workers, of which 247 died in the follow-up interval. Twenty-two percent of the cohort members were lost to follow-up, which could be a source of selection bias if loss to follow-up was related to both the exposure metrics and the health outcome of interest. Previous data from this cohort (t' Mannetje et al., 2005), however, showed fairly comparable loss to follow-up among the unexposed (23%) and the exposed populations (17%).

Comparisons to the New Zealand general population were made using the SMR statistic. Stratified analyses were conducted by duration of employment (<3 months, ≥3 months), sex, latency (<15 years, ≥15 years), and period of hire (<1976, ≥1976). The authors defined latency as the period between the day last worked and the earliest of date of death, date of emigration or loss to follow-up, or December 31, 2004.

The overall SMR for mortality from all cancer sites combined relative to the New Zealand population was 1.01 (95% CI = 0.85−1.10). Although not statistically significant, there was suggestion of an increased risk of rectal cancer (SMR = 2.03, 95% CI = 0.88–4.01). SMRs for lymphatic and hematopoietic cancers (overall SMR = 1.21, 95% CI = 0.52–2.39) included 3.12 (95% CI = 0.08−17.37) for Hodgkin disease, 1.59 (95% CI = 0.43–4.07) for non-Hodgkin lymphoma, and 1.66 (95% CI = 0.20–5.99) for multiple myeloma. No statistically significant excess of cancer mortality was noted among workers employed for <3 months (SMR = 1.19, 95% CI = 0.65−2.00), or for ≥3 months (SMR = 0.98, 95% CI = 0.75−1.26). A statistically

significant excess of digestive cancers was found for those who worked fewer than 3 months relative to the New Zealand population (SMR = 2.52, 95% CI = 1.15−4.78). No excesses were observed for any site-specific cancers when analyses were restricted to those who worked for 3 or more months. No statistically significant elevated SMRs were found for all cancers (combined) either for a latency period of fewer than 15 years (SMR = 1.14, 95% CI = 0.72−1.71) or a latency period of ≥15 years (SMR = 0.96, 95% CI = 0.72−1.26). Similarly, no statistically significant excess in cancer mortality was observed for all cancer sites combined, or any site-specific cancer when analyses were stratified by date of hire (<1976,≥1976) or by sex. The SMR among women who were employed at the site was 0.68 (95% CI = 0.45−1.00).

C.1.1.1.7.4.2. *Study evaluation*

High rates of emigration in New Zealand (9% among workers in the cohort) contributed to a fairly high loss to follow-up (22% among workers) during the study period. The loss to follow-up would reduce the overall mortality estimates among the workers, which could underestimate the SMRs if loss to follow-up (and health status) was not comparable in the general population. For example, it is unclear if workers and the general population who emigrated were less healthy than those who did not. Previous data from the cohort suggests that loss to follow-up rates were slightly higher among those with lower exposures (McBride et al., 2009b; t' Mannetje et al., 2005).

C.1.1.1.7.4.3. *Suitability of data for TCDD dose-response modeling*

This study extended the mortality follow-up of an earlier study and included stratified analyses to investigate effect modification by period of latency, sex, and date of hire. A key limitation was the lack of direct measures of exposure for study participants which precluded estimating effective dose needed for dose-response modeling. As such, this study did not meet the considerations and criteria for inclusion in quantitative dose-response analysis.

C.1.1.2. *Key Characteristics of Epidemiologic Cancer Studies*

Table C-1 summarizes the key characteristics of the available epidemiologic studies of TCDD exposure and cancer. It compares the length of follow-up, latency period used, half-life

for TCDD used, and the fraction of TEQs accounted for by TCDD (when applicable) for each study.

C.1.1.3. *Feasibility of TCDD Cancer Dose-Response Modeling—Summary Discussion by Cohort*

C.1.1.3.1. *Using the NIOSH cohort in dose-response modeling*

It is important to evaluate the NIOSH cohort with respect to its suitability to conduct dose-response modeling of TCDD and cancer. This cohort is the largest assembled to date, direct measures of TCDD based on serum sampling are available, and the lengthy follow-up interval allows for latent effects to be taken into account. Further, although this cohort consists mostly of male workers, these workers were occupationally exposed to TCDD daily, as compared to the acute accidental exposures of other occupational cohorts. Although the most recent analyses of a subset of the NIOSH cohort showed no association between serum TCDD levels and cancer mortality, the exposure category cutpoints did not allow for examination of health effects above levels for which associations had been observed in the larger NIOSH cohort (Collins et al., 2010; 2009).

Most published studies of the NIOSH cohort did not evaluate exposures to DLCs. An exception is the analysis by Steenland et al. (2001b). Although Steenland et al. (2001b) did not incorporate individual-level data on DLCs, based on their previous work (Piacitelli et al., 1992) they assumed that TEQ occupational exposures occurred as a result of TCDD alone in this population. TCDD exposures provided a better fit to the data than the TEQ-based metric, and 15-year latencies improved the fit for both metrics (relative to unlagged exposures). The lifetime risk estimates for an increase in 10 TEQs (pg/kg of body weight/day/sex) ranged from 0.05−0.18%. The value added for this measure is the incorporation of the contribution of other DLCs to the background rates.

Blue collar workers, such as those in the NIOSH cohort, typically have higher rates of smoking than the general population (Lee et al., 2007; Bang and Kim, 2001). This potential source of confounding would be expected to produce a higher SMR for lung cancer mortality, and could contribute to the excess noted in the cohort with longer lag intervals. This bias, however, likely is not large as no statistically significant excess of nonmalignant respiratory mortality was found in these workers. Any associated bias from smoking would be expected to be smaller for comparisons conducted within the cohort, as fellow workers would be expected to

be more homogeneous with respect to their risk factor profile than with an external general population referent group. Stratified analyses using both internal and external comparison groups also did not identify important differences in associations with TCDD exposure between smoking and nonsmoking cancers. Thus, fatal cancer risk estimates reported for workers in the NIOSH cohort appear to provide a reasonable estimate of the carcinogenic potency of TCDD.

Although the Steenland et al. (2001b) study did not directly account for the possible confounding effects of other occupational exposure, the authors did address this source of potential bias. No known occupational exposures to carcinogens occurred, with the exception of 4-aminobiphenyl, which occurred at only one plant. Two deaths from mesothelioma also occurred in the cohort, so some exposure to asbestos was possible (Fingerhut et al., 1991a). The statistical analyses suggested that the inability to control for other occupational exposures would not have unduly affected risk estimates generated from internal cohort comparisons. For instance, the removal of one plant at a time from the analysis did not materially change dose-response estimates generated from the Cox model (Cheng et al., 2006). Moreover, adding a variable to represent each plant in the Cox regression had little impact on the risk estimates. Given that other occupational exposures varied by plant, a change in risk estimates would be expected if such exposures were strong confounders.

The Cheng et al. (2006) analysis provides important information about the impact of applying kinetic models to the data. The CADM TCDD kinetic model resulted in dramatic decreases in the TCDD cancer mortality risk estimates when compared to the one-stage compartmental model that had been applied. Although Cheng et al. (2006) suggested that the CADM provides a better fit to the data than the typically used simple one-compartmental model, statistical comparisons of model fit were not reported. Therefore, there is value in presenting the range in risk estimates across different models when characterizing dose-response relationships.

Finally, the half-life of TCDD is generally recognized to vary according to body fat percentage, and this information was not available for the NIOSH workers. The inability to account for between-worker variability in body fat would introduce exposure measurement error. That body fat percentage would not be expected to correlate with cumulative exposure to TCDD exposure, however, would limit the potential for misclassification bias. The effect of any nondifferential exposure measurement error likely would serve to attenuate the risk estimates of the study.

C.1.1.3.2. *Using the BASF cohort in dose-response modeling*

The availability of blood lipid data for TCDD allows for characterization of cumulative TCDD exposures in the BASF cohort. TCDD blood lipid data were collected for 90% of the surviving members of the cohort (138 of 154) and these serum measures were used to generate TCDD exposure estimates for all 254 cohort members. Therefore, the potential for misclassification error from extrapolating these exposures to the entire cohort is less likely than for the NIOSH cohort where sera data were available for only a small fraction of workers. These BASF serum data were, however, collected long after the accident (36 years) and had to be back-extrapolated to derive the initial exposures.

The data on this cohort included several risk factors such as cigarette smoking and body mass index. One advantage is that cumulative TCDD levels by body mass index can be estimated on an individual-level basis. As expected, the derived cumulative measures appear to correlate well with severity scores of chloracne. The finding that more pronounced risks were found 15−20 years after first exposure are also consistent with findings from several other cohorts (Bertazzi et al., 2001; Fingerhut et al., 1991b; Manz et al., 1991).

A key limitation of the BASF cohort is its relatively small sample size (n = 243), which limits the ability to evaluate dose-response relationships for site-specific cancers. Also, the quality of the ascertainment of cancer incidence cannot be readily evaluated as the geographic area of the cohort is not covered by a tumor registry. Ott and Zober (1996a) state that nonfatal cancers could have been more likely to be missed in early years, which could partially contribute to the higher standardized incidence ratio found for cancer with longer latencies. Commenting on risk differences derived from incident and decedent cancer outcomes is difficult. Among those comprising the cohort, the ascertainment of incident outcomes was recognized to be less complete in early years. Although the ascertainment of mortality outcomes was generally regarded to be good among the 243 workers, some workers who died or moved likely were missed when the cohort was constructed. These deaths would have been more likely to have occurred several years before the second component of the cohort was assembled.

The use of the SMR statistic for this study population is associated with important sources of uncertainties. Deaths were surely missed, particularly for the third component of the cohort that accounts for approximately 38% (94/247) of the entire cohort; this factor would serve to underestimate the overall SMR. As mentioned before, this component of the cohort was

assembled through the recruitment of workers known to be alive in 1986. Despite this limitation, the characterization of exposure data and availability of other risk factor data at an individual level allow the development of quantitative dose-response analyses.

C.1.1.3.3. *Using the Hamburg cohort in dose-response modeling*

The Hamburg cohort lacked data on cigarette smoking, and, therefore, effect estimates could not be adjusted for this covariate. Additional analyses that excluded lung cancers resulted in an even stronger dose-response relationship between all cancer mortality and TCDD. Serum levels of TCDD also were also not associated with smoking status in a subgroup of these workers (Flesch-Janys et al., 1995) suggesting that smoking unlikely confounds the association between all cancer mortality and TCDD.

An important limitation of the cohort is the reliance on blood and tissue measurements of 190 workers that likely represent a highly selective component of the cohort. This subset of workers was identified at the end of the observation period, and therefore, excludes workers who died or could not be traced. There are uncertainties in deriving department- and period-specific estimates for a period that extends over three decades using this number of workers. Additionally, the criteria applied to the reference population could have introduced some bias. Workers were included only in the reference group if they had been employed for at least 10 years in a gas supply industry. The criteria were much different for the workers who were exposed to TCDD (only 3 months of employment). As a result, the reference group likely would be more susceptible to the healthy worker effect. Internal cohort comparisons, which should be void of such bias, however, generally produced results similar to those based on the external comparison population. In summary, the Becher et al. (1998) study meets the criteria and additional epidemiologic considerations which allowed for development of quantitative dose-response analyses.

C.1.1.3.4. *Using the Seveso cohort in dose-response modeling*

Unlike many of the occupational cohorts that were examined, data from the Seveso cohort are representative of a residential population whose primary exposure was from a single TCDD release. A notable exception is the BASF cohort where workers were exposed principally

through two accidents that occurred in the plant. The Seveso data, therefore, might permit cancer dose-response investigations in women and children.

Uncertainty in identifying the critical exposure window for most of the outcomes related to the Seveso cohort is a key limitation. An important feature of the Seveso cohort, however, is that TCDD levels were much lower among those in the highest exposure zones in Seveso (medians range from 56−136 ng/kg) (Eskenazi et al., 2004) than those in the occupational cohorts who had TCDD exposures that were sometimes more than 1,000 ng/kg. Given these dramatic exposure differences in exposures, the standardized mortality ratios (after incorporating a 15−20 year latency period) for all cancer sites combined are remarkably similar between the Seveso and the occupational cohort analyses. Perhaps more importantly, the data from Seveso might be more relevant for extrapolating to lower levels, given that exposures to TCDD are two orders of magnitude higher than background levels (Smith and Lopipero, 2001), and lower than many of the exposures observed in the other occupationally exposed cohorts.

The Warner et al. (2002) study found a positive association between serum levels of TCDD and breast cancer. As noted previously, ascertainment of incident cases for all cancers would allow for a dose-response relationship to be evaluated. Moreover, future breast cancer analyses in this cohort that would increase sample size should strengthen the quantitative dose-response analyses of this specific cancer site. The strengths of the Warner et al. (2002) study outlined earlier suggest that this study should be considered for cancer dose-response modeling.

Earlier Seveso studies likely are unsuitable for conducting quantitative risk assessment. These previous studies used an indirect measure of TCDD exposure, namely, zone of residence. Soil concentrations of TCDD varied widely in these three zones (Zone A: 15.5−580.4 ppt; Zone B: 1.7−4.3 ppt; and Zone R: 0.9−1.4 ppt), which could have resulted in considerable exposure misclassification. The Warner et al. (2002) study greatly improved the characterization of TCDD exposure using serum measures, and also allowed for control of salient risk factors that may have resulted in bias due to confounding.

At this time it is unclear whether any study has examined the relationship between cancer and serum estimates of TCDD among Seveso males exposed from the 1976 accident.

C.1.1.3.5. *Using the Chapaevsk related data in dose-response modeling*

Currently, individual-level exposure data are lacking for residents of this area and there is no established cohort for which cancer outcomes can be ascertained. These limitations, therefore, preclude the inclusion of Chapaevsk data in a quantitative dose-response analysis.

C.1.1.3.6. *Using the Ranch Hands cohort in dose-response modeling*

Study strengths of the Ranch Hand cohort includes a relatively large cohort with individual-level serum measurements taken over time in 1987, 1992, 1997, and 2002. In addition, TCDD levels for later years were back-extrapolated to 1987 using a first-order kinetic model that assumed a half-life of 7.6 years. Although the isolation of TCDD effects from those of other agents found in Agent Orange raised some concerns about confounding, results from a large agricultural cohort found no association between 2,4-D or 2,5-T and prostate cancer or lung cancer (Alavanja et al., 2005; 2004; 2003). It was determined that dose-response analyses would be conducted on this population using both the (Michalek and Pavuk, 2008)) and Akhtar et al. (2004) studies.

C.1.1.4. *Discussion of General Issues Related to Dose-Response Modeling*

C.1.1.4.1. *Ascertainment of exposures*

Several series of epidemiologic data have used serum measures to estimate TCDD exposures. Serum data offer a distinct advantage in that they provide an objective means to characterize TCDD exposure at the individual level. The serum measures in the occupational cohorts, however, are limited in two important ways. First, these samples are generally collected from small subsets of the larger cohorts; therefore, using these measures to extrapolate to the remainder of the cohort could introduce bias due to exposure misclassification. The second limitation is related to estimating the half-life of TCDD. As noted previously, exposures to TCDD were back-extrapolated several decades from the date that serum samples were collected among surviving members of several cohorts. This approach was used in the NIOSH, Ranch Hands, BASF, New Zealand, and Hamburg cohorts. The reported half-life of TCDD among these populations was reported between 7.1 to 9.0 years and the half-life has been shown to vary with several individual characteristics including age, body fat composition, and smoking. The derivation of half-lives from a sample of workers, and application of these estimates to

retrospectively characterize exposure can introduce uncertainty into the lifetime exposure estimates. It is important to note, however, that sensitivity analyses results in several studies have been fairly consistent when evaluating the impact of half-life of TCDD (Steenland et al., 2001b; Flesch-Janys et al., 1995). In addition, the reliance on surviving cohort members for serum samples can introduce bias as it assumes their distribution of TCDD exposures was the same among those who died.

A unique advantage of the Seveso study is that serum measures were taken shortly after the accident, and therefore characterization of TCDD exposure in this population does not depend on assumptions needed to back-extrapolate exposures several decades.

C.1.1.4.2. *Latency intervals*

Many of the epidemiologic studies indicate stronger associations between TCDD and cancer outcomes once a latency period has been considered. Generally, risks are higher when a latency period of 15−20 years is included. As noted previously, this observation is consistent with many other environmental carcinogens such as radon, radiation, and cigarette smoking. That recent exposures do not contribute to increased cancer risk provides some support that the initiation and promotion phases might occur many years before death making recent exposures irrelevant for these analyses. The ability to discriminate between models of varying latency, however, was not possible in many studies. The application of biologically-based modeling could provide additional important insights on which phase(s) of carcinogenesis TCDD exerts an influence. Such modeling, however, would necessitate having data on an individual-level basis. Ideally, this modeling would use cancer incident rather than mortality outcomes given that the median survival time exceeds 5 years for many cancer sites.

C.1.1.4.3. *Use of the SMR metric*

The occupational cohorts and the studies in Seveso and Chapaevsk have relied on the SMR to make inferences regarding the effects of TCDD on mortality. When compared to the general population, the healthy worker effect may result in a downward bias in the SMR. This often can manifest as SMRs less than 1 for several causes of mortality. The effect of this bias is, however, generally smaller for cancer outcomes. Cancer outcomes, whether incidence or death,

typically occur later in life and do not generally affect an individual's ability to work at earlier ages.

There are several approaches that can be taken to minimize potential biases introduced by the healthy worker effect, which would account for workers being healthier than the general population. Comparisons of mortality (or cancer incidence) can be made to other cohorts of similar workers. If done properly, this can allow for some control of characteristics such as sociodemographic characteristics and smoking as the two populations can be matched by these factors. However, it may be the case that other working populations are exposed to other harmful exposures, thereby making it difficult to estimate risk associated with a specific agent (such as TCDD) in the cohort of interest. A second and preferred approach to control for the healthy worker effect, should it prove feasible, is to conduct comparisons of health outcomes in relation to exposure within the cohort. These comparisons are less likely to be influenced by other potential confounding variables such as smoking, socioeconomic status, and other occupational exposures that are generally more homogeneous within the cohort relative to external populations. Moreover, the mechanisms used to identify health outcomes and follow individuals over time are generally applied in the same manner to all cohort members. Taken together, where different comparisons have been made to generate risk estimates, those that have been conducted using internal cohort comparisons are preferable.

In addition to potential bias from the healthy worker effect, the comparison of SMRs between studies is not always straightforward and is not recommended by some (Myers and Thompson, 1998; Rothman, 1986). The SMR is the ratio of the observed number of deaths to the expected number of deaths and is often referred to as the method of indirect standardization. The expected number of deaths is estimated by multiplying the number of person-years tabulated across individuals in the cohort, stratified by age, by rates from a reference population that are available for the same strata. Therefore, each population cohort will have an estimated number of cases derived using a different underlying age structure. As outlined by Rothman (1986), the mortality rates might not be directly comparable to each other, although the impact of such bias will be much less if the age-distribution of the cohorts is similar. While it might be reasoned that the TCDD exposed workers would have similar age distributions this is in fact not the case (Becher et al., 1998; Ott et al., 1993; Thiess et al., 1982). This may be due to exposure occurring both chronically, as well as from acute exposures due to accidental releases that happened at

various times at different plants. This is evident with the Hamburg and the BASF cohorts, as most individuals comprising the BASF cohort were employed at the time of the accident (1953/1954), while most of the Hamburg cohort (852/1048) was employed after 1954; the follow-up of these cohorts ended at approximately the same time.

The method of direct standardization allows for a more meaningful comparison of mortality rates to be made between cohorts. With this approach, weights (usually based on age and sex) are drawn from a standard population and are, in turn, applied to disease rates for the same strata observed in the cohort of interest. A comparison of weighted rates between different cohorts would then be based on the same population standard.

Despite these limitations in comparing SMRs between studies, Armstrong (1995) argues that the comparisons are valid if the underlying stratum specific rates in each exposure grouping are in constant proportion to external rates. Comparisons of the SMRs between studies will be biased only if there is an interaction between age and TCDD (i.e., the RR of disease due to exposure differs by age). For cancer outcomes, the finding that associations become stronger after a period of latency is incorporated into the analyses suggests that this assumption does not hold true. That is, risk estimates would be lower among young workers. Similarly, for noncancer outcomes, some of the data from the Seveso cohort suggests differential effects according to the age at exposure.

The use of the SMR might also be biased in that workers exposed to TCDD could be subject to more intensive follow-up than the general population, and as a result, differential coding biases with cause of death might occur. Moreover, some cohorts (e.g., the BASF cohort) have been assembled, in part, by actively seeking out survivors exposed to accidental releases of dioxins. As such, they would not include persons who have died or who were lost to follow-up. This would result in underascertainment of deaths and SMRs developed from these data. The use of an internal cohort comparison offers distinct advantages to overcome potential sources of selection bias. Given these uncertainties about the comparability across the different studies, conducting a meta-analysis of cancer outcomes for TCDD using the SMR statistic is not warranted for this analysis.

C.1.1.4.4. *All cancers versus site-specific*

An important consideration for quantitative dose-response modeling is the application of models for all cancers combined, or for site-specific cancers. Consistency is often lacking for site-specific cancers, which might be due in large part to the relatively small number of cases identified for site-specific cancers in the cohorts. Although the risk estimates produced for all cancer sites have important limitations and uncertainties, the data are far more consistent in terms of the magnitude of an association and latency intervals. The IARC evaluation has put forth the possibility of a pleuripotential mode of action between TCDD and the occurrence of cancer. Despite the criticism of this assertion by some (Cole et al., 2003), the general consistency of an increased risk for all-cancer mortality across the occupational cohorts when latency intervals have been incorporated, provides adequate justification for dose-response quantification of all cancer sites combined.

C.1.1.4.5. *Summary of epidemiologic cancer study evaluations for dose-response modeling*

All epidemiologic cancer studies summarized above were evaluated for suitability of quantitative dose-response assessment using the TCDD-specific considerations and study inclusion criteria. The results of this evaluation are summarized in a matrix style array (see Table C-2). Table 2-1 in Section 2 of this document summarizes the key epidemiologic cancer studies suitable for further TCDD dose-response analyses.

C.1.2. Noncancer

In this section, the available epidemiologic data that could be used in a dose-response analysis for noncancer endpoints are evaluated. Because many of the key studies also evaluated cancer outcomes, the noncancer studies are presented in the same order as in Section C.1.1. Generally, the strengths and limitations of the cancer studies also apply to the noncancer outcomes. In this section, key features of these studies that have direct relevance to modeling of noncancer outcomes in particular are highlighted. To reduce redundancy, a detailed overview of many of these cohorts and studies are not provided here. Instead, the reader should refer to Section C.1.1.1.

C.1.2.1. *Noncancer Cohorts*

C.1.2.1.1. *The NIOSH cohort*

See general summary of the NIOSH cohort in Section C.1.1.1.1.

C.1.2.1.1.1. ***Steenland et al. (1999)***

C.1.2.1.1.1.1. *Study summary*

The 1999 published report of NIOSH workers exposed to TCDD also conducted external cohort comparisons to the U.S. general population using SMRs for mortality outcomes other than cancer (Steenland et al., 1999). Analyses are based on 3,538 male workers employed at 8 plants from 1942 to 1984. Four of the 12 plants originally analyzed were excluded due to lack of records on the degree of TCDD contamination in the work processes or information was lacking for work histories needed to estimate TCDD exposure. Workers were excluded if they were female (n = 40) or were lacking data to evaluate exposure (n = 238). SMRs were based on a mortality follow-up that was extended until the end of 1993. Cox regression analyses were used to compare mortality risk in relation to TCDD exposure within the cohort.

C.1.2.1.1.1.2. *Study evaluation*

Overall, no statistically significant differences in all-cause mortality (SMR = 1.03, 95% CI = 0.97−1.08) were observed. Mortality from ischemic heart disease (SMR = 1.09, 95% CI = 1.00−1.20) and accidents (SMR = 1.25, 95% CI = 1.03−1.50) was slightly elevated. Based on the external comparison population, the dose-response relationship for ischemic heart disease observed with the SMRs calculated across TCDD exposure septiles was not statistically significant (p = 0.14). Overall, no excess risk was observed for diabetes, cerebrovascular disease, or nonmalignant respiratory disease using the external population comparisons. Internal cohort comparisons using the Cox regression model were performed using 0 and 15-year lag intervals. A dose-response trend was observed for the derived ratios across the unlagged cumulative TCDD exposure septiles for ischemic heart disease (p = 0.05) and diabetes (p = 0.02). For ischemic heart disease mortality, those in the upper two septiles had rate ratios of 1.57 (95% CI = 0.96−2.56) and 1.75 (95% CI = 1.07−2.87), respectively, relative to those in the lowest septile. In contrast, an inverse dose-response relationship was observed for diabetes mortality. The inverse association found for diabetes is inconsistent with the positive association

reported in the Ranch Hands study (Michalek and Pavuk, 2008). However, previous reports have questioned the use of death certificates as the means to ascertain diabetes as these deaths may be under-reported especially among those with diabetes who die from cancer (McEwen et al., 2006).

C.1.2.1.1.1.3. *Suitability of data for TCDD dose-response modeling*

There was no evidence of a dose-response relationship between TCDD exposure and ischemic heart disease mortality in this study or other cohorts. The inverse association with diabetes also precludes dose-response analysis for this outcome. As all outcomes were based on mortality, dose-response modeling was not conducted for this study.

C.1.2.1.1.2. ***Collins et al. (2009)***

C.1.2.1.1.2.1. *Study summary*

Collins et al. (2009) described the mortality experience of Dow employees who worked in Midland, Michigan. This plant produced 2,4,5-trichlorophenol between 1942 and 1979, and 2,4,5-T between 1948 and 1982. The cohort consisted of 1,615 workers (number of each gender not specified) exposed to TCDD from as early as 1942; the follow-up of the cohort extended until 2003.

TCDD exposures were derived using serum samples obtained from 280 surviving individuals (gender and selection criteria not reported). A simple one-compartment, first-order pharmacokinetic model was used to estimate time-dependent TCDD measures. The area under the curve approach was then applied to estimate cumulative TCDD exposure above background. A half-life of 7.2 years for TCDD based on earlier work was incorporated into the exposure estimation (Flesch-Janys et al., 1996).

Collins et al. (2009) made an external comparison of the mortality rates of the cohort to the U.S. general population using the SMR. Noncancer causes of death included all causes, diabetes, cerebrovascular disease, nonmalignant respiratory disease, cirrhosis of the liver, and accidents. Overall, no statistically significant difference in all-cause mortality of these workers was detected when compared to the general population (SMR = 0.9, 95% CI = 0.9−1.0). Except for cirrhosis of the liver (SMR = 0.4, 95% CI = 0.1−0.8), no differences were found for any of the noncancer causes of death relative to the general population.

Internal cohort analyses based on cumulative measures of TCDD were conducted for mortality from diabetes, ischemic heart disease, and nonmalignant respiratory disease using the Cox regression model. These models adjusted for possible confounders such as year of hire and birth year. No statistically significant associations were found between the continuous measure of TCDD exposure and these causes of death.

C.1.2.1.1.2.2. *Study evaluation*

Given that the external comparisons may result in bias from the healthy worker effect, results from the internal cohort comparisons using the Cox regression model are preferred. These analyses were performed for diabetes, ischemic heart disease, and nonmalignant respiratory disease. TCDD levels for these workers were estimated using a simple one-compartment pharmacokinetic model (Aylward et al., 2007). Because participation rates and selection criteria for the 280 individuals providing samples were not reported, it is not possible to determine how representative these individuals are of the larger cohort. The hazard ratios generated from the Cox regression model were not statistically significant for any of the three noncancer outcomes modeled.

C.1.2.1.1.2.3. *Suitability of data for TCDD dose-response modeling*

No increased risks were observed for any of the noncancer outcomes reported in Collins et al. (2009). As all outcomes were based on mortality, dose-response modeling was not conducted for this study.

C.1.2.1.2. ***The BASF cohort***

See general summary of the BASF cohort in Section C.1.1.1.2.

C.1.2.1.2.1. ***Ott and Zober***

C.1.2.1.2.1.1. *Study summary*

In 1996, Ott and Zober (1996a) published a report on the mortality experience of the cohort of 243 BASF male workers who were accidentally exposed to 2,3,7,8-TCDD in 1954 or in the clean up that followed. The mortality follow-up of this cohort extended until the end of 1992. External comparisons of mortality were made with the German population. Internal

cohort comparisons were also made by estimating cumulative TCDD for the cohort using serum measures that were obtained from 138 workers. Ott et al. (1993) provided a detailed account of the methodology to estimate TCDD. The 138 workers were selected based on a set of criteria of duration of exposure (relative to the timing of the accident). There was no indication of the participation rate among these workers, although some employee subgroups were over- and under-represented. Briefly, a cumulative measure of TCDD expressed in µg/kg was derived, by first estimating the half-life of TCDD using individuals who had repeated serum measures; the half-life was estimated to be 5.8 years. Individual-level data on body fat were used to account for the influence of body fat on decay rates. Half-life estimates of TCDD varied (range: 5.1−8.9 years) and were dependent on body fat composition (20% and 30%, respectively). This approach differed from previous analysis of this cohort that used a constant 7-year half-life (Ott et al., 1993). TCDD levels at the time of serum sampling were then estimated as the product of TCDD concentration in blood lipid and the total lipid weight for each worker. Nonlinear models then were applied to estimate the contribution of duration of exposure to TCDD dose extrapolated to the time of exposure.

External comparisons to the German population using the SMR statistic also were examined across dose categories. The noncancer causes of death examined by Ott and Zober (1996a) included all-cause mortality, diseases of the circulatory system, ischemic heart disease, diseases of the digestive system, external causes, suicide, and residual causes of death. Overall, no statistically significant differences in the SMR with the general population for all-causes of death (SMR = 0.9, 95% CI = 0.7−1.1), nor any other causes of death examined were found.

Ott and Zober (1996a) performed internal cohort comparisons using Cox regression. These analyses found no dose-response patterns when cause-specific mortality was examined across increasing cumulative TCDD exposure categories. Although an inverse association for diseases of the respiratory system (SMR = 0.1, 95% CI = 0.0−0.8) was detected, it was based only on 1 reported death. Many comparisons were limited by small sample sizes as only 92 deaths occurred in the cohort, and of these, 31 were from cancer. Also, the third component of the cohort was identified primarily from former employees who were alive in 1986. As a result, the SMR based on the general population was likely underestimated by the exclusion of deceased workers.

C.1.2.1.2.1.2. *Study evaluation*

As noted previously, caution should be exercised in the interpretation of SMR for noncancer outcomes as they could be influenced by the healthy worker effect. Although the mechanism of identifying vital status appears to be excellent and unbiased, SMRs might be underestimated due to the manner in which the cohort was constructed. Specifically, a large component of the cohort was assembled by actively seeking out former workers known to be alive in 1986.

C.1.2.1.2.1.3. *Suitability of data for TCDD dose-response modeling*

No dose-response patterns were observed between TCDD and the noncancer outcomes in the Ott and Zober (1996a) study. Therefore, dose-response modeling was not conducted.

C.1.2.1.3. ***The Hamburg cohort***

See general summary of the Hamburg cohort in Section C.1.1.1.3.

C.1.2.1.3.1. ***Flesch-Janys et al. (1995)***

C.1.2.1.3.1.1. *Study summary*

Flesch-Janys et al. (1995) reported on the mortality experience of a cohort of individuals employed by an herbicide-producing plant in Hamburg, Germany, covering the period 1952 to 1992. As described in more detail in Section C.1.1.1.3, the authors developed a cumulative measure of TCDD using serum measures from 190 workers. Selection criteria and response rates for this subsample were not specified. This study also examined the relationship between total TEQ and mortality. In the study population, the mean TEQ without TCDD was 155 ng/kg, and for the mean TEQ including TCDD was 296.5 ng/kg.

Risks relative to the unexposed referent group of gas workers were estimated using Cox regression across six exposed TCDD groups (i.e., the first four quintiles, and the ninth and tenth deciles). A linear dose-response relationship was found with all causes of mortality and cardiovascular mortality ($p < 0.01$). The RR for all cardiovascular deaths in the upper exposure category was 1.96 (95% CI = 1.15−3.34), although there was no evidence of a linear dose-response trend ($p = 0.27$). The dose-response relationship was strongest for ischemic heart disease, with a RR of 2.48 (95% CI = 1.32−4.66) in the highest exposure group. A dose-response relationship was also observed across TEQ groupings for all cause mortality,

cardiovascular disease mortality, and ischemic heart disease mortality. The authors did not perform joint modeling of TEQ (without TCDD) and TCDD, so determining the extent that DLCs contributed to an increased risk of mortality is not possible.

C.1.2.1.3.1.2. *Study evaluation*

The Flesch-Janys et al. (1995) study lacks information on other potential risk factors for cardiovascular disease, which could result in confounding if those risk factors are also related to TCDD exposure. Dose-response patterns were strong, however, and persisted across numerous TCDD (and TEQ) exposure categories based on the use of an external reference group (i.e., gas workers) or based on the internal comparison. The findings based on the internal comparison are noteworthy in that these groups should be more homogenous with respect to confounding factors. As noted previously, the poor correlation between TCDD and smoking among workers and similar smoking prevalence estimates between the workers and the external gas company workers suggest that smoking was not likely a confounder of the TCDD and cardiovascular disease relationship. No other evaluation of noncancer mortality outcomes has been undertaken in this cohort since 1995.

A strength of the Flesch-Janys et al. (1995) study was that it included the collection of blood serum which provided an objective measure of TCDD exposure. Blood serum data, however, were obtained only for 16% of the cohort. However, the selection criteria and participation rate for individuals providing blood serum is not provided to evaluate how representative these individuals are of the larger cohort. The assumption of the first-order kinetic elimination model is critical, given that measures were taken at the end of follow-up. The model also assumed the half-life of TCDD was 6.9 years. If the kinetics are not first-order, or if the half-life estimate is inaccurate, estimates of TCDD levels during exposure would be biased, particularly for workers having longer periods between exposure and PCDD and PCDF assays. Sensitivity analyses completed by the authors suggest that such bias is not likely to present because the results were unaffected when different model assumptions regarding kinetic and half-lives were examined. The lack of an impact on RR estimates with varying half-life estimates was similar to findings by Steenland et al. (2001b).

C.1.2.1.3.1.3. *Suitability of data for TCDD dose-response modeling*

Despite the aforementioned study strengths, the study focused on fatal outcomes such as all cause mortality, cardiovascular disease mortality, and ischemic heart disease mortality. As all outcomes were based on mortality, dose-response modeling was not conducted for this study.

C.1.2.1.4. ***The Seveso Cohort—SWHS***

Eskenazi et al. (2000) presented an overview of the SWHS. The SWHS is the first comprehensive epidemiologic study of the reproductive health of a female population exposed to TCDD. The primary objective of the SWHS is to investigate the relationship of TCDD and several reproductive endpoints, including endometriosis, menstrual cycle characteristics, birth outcomes, infertility, and age at menopause. A second phase of follow-up that focuses on osteoporosis, thyroid hormone, breast cancer, diabetes, and metabolic syndrome is not yet completed.

Women were eligible for participation in the SWHS if they resided in Zones A and B (the most contaminated areas) at the time of the explosion, were 40 years of age or younger at the time of the explosion in 1976, and samples of their blood were collected and stored between 1976 and 1980. The enrollment of women in the SWHS began in March 1996 and continued until July 1998. Of the 1,271 eligible women, 17 could not be found, 21 had died, and 12 were too ill to participate. Of the 96% remaining women, 80% (n = 981) participated in the study. Participation in the SWHS included a blood draw and an interview by a trained nurse who was blind to subjects' TCDD level and zones of residence at the time of the accident. The interview included detailed information on potential confounders including occupational, medical, and reproductive, and pregnancy history. Women who were premenopausal were also asked to undergo a vaginal ultrasound and pelvic exam and to complete a daily diary on menstruation.

Depending on the health outcome under study, TCDD exposures were characterized for the women at different times. For example, TCDD exposure levels were estimated at the time of the accident for some studies and at the time of conception for others. The SWHS study population has been used to investigate associations between maternal TCDD levels and the following health outcomes: menstrual cycle characteristics (Eskenazi et al., 2002b); endometriosis (Eskenazi et al., 2002a); birth outcomes (Eskenazi et al., 2003); age at menarche (Warner et al., 2004); age at menopause (Eskenazi et al., 2005); uterine leiomyomas (Eskenazi et

al., 2007); and ovarian function (Warner et al., 2007). An evaluation of the studies in chronological order is presented in this section.

C.1.2.1.4.1. ***Eskenazi et al. (2002b)—menstrual cycle characteristics***

C.1.2.1.4.1.1. *Study summary*

Eskenazi et al. (2002b) evaluated serum TCDD exposures in relation to several menstrual cycle characteristics in the SWHS. A total of 981 women who were 40 years of age or younger at the time of the accident comprised the SWHS. The following exclusion criteria was applied 44 years of age or older, women with surgical or natural menopause, those with Turner's syndrome, and those who in the past year had been pregnant, breastfed, or used an intrauterine device or oral contraceptives.

A trained interviewer collected data on menstrual cycle characteristics using a questionnaire. Women were asked to indicate how long their menstrual cycles were, whether the cycles were regular (e.g., irregular cycle defined as length varied by more than 4 days), how many days the menstrual flow lasted, and whether this flow was "scanty, moderate, or heavy." Information was also collected on obstetric and gynecological conditions. TCDD exposures were derived from serum samples collected in 1976−1985. The authors selected the earliest available serum sample, and back-extrapolated to 1976 values using either the Filser model (Kreuzer et al., 1997) for women aged 16 years or younger in 1976 (n = 20) or the first-order kinetic model (n = 6) (Pirkle et al., 1989).

Serum TCDD levels were transformed using the $\log_{10}$ scale, and the relationships between these levels and length of menstrual cycle and days of menstrual flow were examined using linear regression. The authors applied logistic regression to characterize the risk between $\log_{10}$TCDD and heaviness of flow or regularity of cycle. In these analyses, moderate or heavy flow and regular cycle were used as the reference categories. Stratified analysis was performed by menarcheal status at the time of the accident.

Overall, the association with TCDD exposure (per 10-fold increase) and length of menstrual cycle was not statistically significant for premenarcheal (β = 0.93, 95% CI = −0.01, 1.86) women or postmenarcheal women (β = −0.03, 95% CI = −0.61, 0.54). The corresponding estimates found for days of menstrual flow were β = 0.18 (95% CI = −0.15, 0.51) and β = 0.16 (95% CI = −0.18, 0.50), respectively. Reduced flow was not associated with TCDD when

compared to moderate or heavy flow (odds ratio [OR] = 0.84, 95% CI = 0.44, 1.61); effect modification by menarcheal status, however, was evident (p = 0.03). Specifically, women exposed to TCDD who were premenarcheal had lower odds of reduced flow, while those exposed to TCDD who were postmenarcheal did not. Finally, statistically significant ORs were found between serum TCDD levels (per 10-fold increase) and having an irregular cycle (OR = 0.46, 95% CI = 0.23, 0.95). This inverse association was evident in both premenarcheal (OR = 0.50, 95% CI = 0.18, 1.38) and postmenarcheal women (OR = 0.41, 95% CI = 0.15, 1.16).

C.1.2.1.4.1.2. *Study evaluation*

Overall, the Eskenazi et al. (2002b) study reported some associations between TCDD and menstrual cycle characteristics among women exposed before menarche. Exposures to TCDD were well characterized using serum samples available on an individual-level basis, and the design allowed for the influence of other risk factors to be controlled. Analysis of TCDD levels and the length of menstrual cycle in premenarcheal women produced associations that were largely not statistically significant at the alpha level of 0.05, but may have some biological relevance. However, it is unclear whether the endpoints that were measured constitute adverse health outcomes as they are not definitive markers of ovarian dysfunction. Another source of uncertainty is measurement error due to the subjective nature of menstrual flow reporting. Any resulting misclassification of the outcome would be expected to be nondifferential, as the measurement error is unlikely to be dependent on TCDD exposure.

C.1.2.1.4.1.3. *Suitability of data for TCDD dose-response modeling*

Rigon et al. (2010) reported the median age at menarche to be 12.4 in Italian females, which would establish a critical window of susceptibility between birth and about 13 years of age. The determination of a lowest-observed-adverse-effect level (LOAEL) is difficult, as there is no independent measure of an adversity threshold to establish the toxicological significance of a given increase in menstrual cycle length. The study authors did not present data for unexposed premenarcheal girls (in 1976), so an appropriate reference population is not available. However, an approximate LOAEL can be estimated from Figure 1 in Eskenazi et al. (2002b), noting that both the length of the menstrual cycle and its variance increases above TCDD concentrations of

about 1,000 ppt. This study is suitable for further consideration for quantitative dose-response modeling.

C.1.2.1.4.2. ***Eskenazi et al. (2002a)—endometriosis***

C.1.2.1.4.2.1. *Study summary*

The SWHS provided the opportunity to investigate the association between serum TCDD levels and endometriosis (Eskenazi et al., 2002a). The rationale the authors provided for undertaking this study was the experimental animal studies that suggested an association, the high prevalence of endometriosis among infertile women where breast milk concentrations of dioxin are high, and the unknown etiology of endometriosis. The study consisted of 601 women who were younger than 30 years at the time of the Seveso accident. Stored sera that had been collected between 1976 and 1980 were available for these women.

The researchers classified women as having endometriosis based on laparoscopy, symptom report, gynecologic examinations, and vaginal ultrasound. Endometriosis cases were identified by a positive ultrasound or if a woman had endometriosis noted on a laparoscopy or laparotomy. A woman was classified as nondiseased if she had surgery without a finding of endometriosis or if she had a negative ultrasound, exam, and symptom history. Given that laparoscopy could not be performed on women unless clinically indicated, there was less certainty regarding endometriosis diagnoses among those without an ultrasound or prior laparoscopy. These remaining women without clinical confirmation were classified as "uncertain" based solely on positive symptom history.

TCDD was measured in sera in 1976 for 93% of the women. Values for women whose serum TCDD levels were collected after 1977 and had values exceeding 10 ppt were back-extrapolated to 1976 using either the Filser model (<16 years of age) (Kreuzer et al., 1997) or a first-order kinetic model (≥16 years) (Pirkle et al., 1989). These estimates of TCDD were then modeled as both continuous (on a log scale) and categorical (≤20, 20.1−100, and >100 ppt) exposures.

Polytomous logistic regression was applied to generate RRs for internal cohort comparisons. In relation to women in the lowest exposure category, the RR for endometriosis among women in the middle and upper categories was 1.2 (90% CI = 0.3−4.5) and 2.1

(90% CI = 0.5−8.0), respectively. The trend tests were not statistically significant for either the categorical (p = 0.25) or the continuous measures of TCDD (p = 0.84).

C.1.2.1.4.2.2. *Study evaluation*

Based on the results of a validation study they conducted in a clinical population, the study authors found that symptom history was not predictive of disease, but that ultrasound had excellent specificity and sensitivity for ovarian endometriosis. Thus, there was some potential for disease misclassification among the uncertain group who were classified solely on symptom history. Although this disease misclassificationis could have resulted in missed cases of endometriosis, it is unlikely to have biased the study findings. Bias is unlikely to result from differential (by exposure status) symptom reporting for the following reasons: the study interviewers and respondents were unaware of study hypotheses, the interviewers, respondents and investigators who made the diagnoses did not know the TCDD levels, and the Centers for Disease Control and Prevention laboratory had no information about disease. Younger women were likely to be under-represented as those who had never been sexually active could not be examined due to cultural reasons; thus residual confounding by age is a possibility despite statistical adjustment in the regression models. Other DLCs (PCDD, PCDFs, or polychlorinated biphenyls [PCBs]) were not considered because of small serum volumes, but any potential TEQ exposures occurring in the population were thought to be mostly attributable to TCDD in the exposed women. Although individual-level serum samples were available, a biologically-relevant critical exposure window for this effect cannot be established.

C.1.2.1.4.2.3. *Suitability of data for TCDD dose-response modeling*

There were no statistically significant dose-response patterns observed with either log-transformed TCDD exposures or across TCDD exposure categories, and the elevated risks among those with higher exposures had very wide confidence intervals (that included unity). In addition, because of the lack of definitive measures of endometriosis and the inability to define a critical exposure window, quantitative dose-response analysis was not conducted for this outcome.

C.1.2.1.4.3. ***Eskenazi et al. (2003)—birth outcomes***

C.1.2.1.4.3.1. *Study summary*

Eskenazi et al. (2003) examined the relationship between serum TCDD levels and birth outcomes. Analyses were based on 745 of the 981 women from the SWHS who agreed to participate (80% of the cohort) and reported having been pregnant (*n* = 1,822). Many of these pregnancies (888 pregnancies among 510 women) occurred after the accident in 1976. Analysis of spontaneous abortions was restricted to 769 pregnancies among 476 women that did not end in abortion or in ectopic or molar pregnancy. Congenital anomalies were evaluated for the 672 pregnancies that did not end in spontaneous abortion. For the birth outcomes of fetal growth and gestational age, analysis was performed using 608 singleton births from women without hypertensive pregnancy disorders or diabetes.

TCDD exposures were based on serum measures, most of which were taken shortly after the accident. Serum was collected in 1976−1977 for 413 women, between 1978 and 1981 for 12 women, and in 1996 for 19 women whose samples were not viable. For samples collected between 1976 and 1981, the first serum sample collected was used. TCDD exposures based on serum samples collected after 1977 onward were back-extrapolated to 1976 using the Filser toxicokinetic model (Kreuzer et al., 1997).

Statistical analyses were performed on all pregnancies that ended between 1976 and the time of interview. The authors also restricted the analysis to those pregnancies occurring within the first 8 years (1976–1984) or roughly the first TCDD half-life after the explosion (Pirkle et al., 1989), since the expectation was that exposure body burden would be greatest during this period. A continuous measure of $\log_{10}$TCDD (base 10 scale) was used to investigate associations with adverse birth outcomes. Logistic regression was used to characterize the relationship between TCDD exposure spontaneous abortions, small for gestational age, and preterm birth (<37 weeks gestation). Linear regression was used to describe the relationship between TCDD and birth weight (in grams) and gestational age (in weeks) estimates.

The risk estimates were adjusted for various characteristics that included sex of infant, history of low birth weight child, maternal height, maternal body mass index, maternal education, maternal smoking during pregnancy, and parity. No associations were detected between TCDD serum levels and spontaneous abortion for pregnancies between 1976 and 1998 (OR = 0.8, 95% CI = 0.6−1.2), or those between 1976 and 1984 (OR = 1.0, 95% CI = 0.6−1.6).

No statistically significant associations (ORs ranged from 1.2−1.8) were found between $\log_{10}$ TCDD levels and preterm delivery or small for gestational age. The authors also saw no association between TCDD exposure and mean birth weight among the entire population. Although it was not statistically significant, the mean birth weight for pregnancies restricted to between 1976 and 1984 decreased by 92 grams ($\beta = -92$, 95% CI = −204 to 19) for every 10-fold increase in TCDD serum level.

C.1.2.1.4.3.2. *Study evaluation*

This study was well-designed with individual-level exposure data, although there is some uncertainty in extrapolating limited serum data to such narrow critical windows of exposure especially among women who were pregnant many years after the explosion in 1976. While the study lacked exposure data for the fathers, the authors indicated that only a small proportion were believed to have high exposures to TCDD. A key limitation of the study was a reliance on self-reported measures of pregnancy history subject to maternal recall error. For example, birth weight was often reported only to the nearest 100 grams. This measurement error could lead to some misclassification of the birth outcomes. The observation that a large proportion of Seveso women had a voluntary abortion because of fears of possible birth defects due to exposures from the accident suggest that awareness bias is also possible as a result of differential reporting of birth outcomes according to exposure status. Statistically significant associations were not evident, although the mean birth-weight findings among those assumed to have the highest TCDD body burden (exposed during first 8 years (1976–1984)) may have some toxicological significance. As the study authors point out, those who were potentially the most vulnerable at the time of the accident (the youngest) had not yet completed their childbearing years. Thus, further follow-up of this cohort should help elucidate whether subjects with higher TCDD exposures had an increased risk of adverse birth outcomes.

C.1.2.1.4.3.3. *Suitability of data for TCDD dose-response modeling*

No statistically significant associations were found in the study; in addition, possible awareness bias could have influenced the self-reported measures of birth outcomes. The authors did not report TCDD levels at the time of pregnancy and EPA cannot extrapolate serum concentrations measured in 1976 to the times of the pregnancies in these women based on the

information reported in the study. Therefore, quantitative dose-response modeling was not conducted for this study.

C.1.2.1.4.4. ***Warner et al. (2004)—age at menarche***

C.1.2.1.4.4.1. *Study summary*

Warner et al. (2004) examined the relationship between TCDD and age at menarche in the SWHS cohort. As described earlier in this report, the SWHS comprised 981 participants. This study was restricted only to those who were premenarcheal at the time of the accident (n = 282). The proportional hazards model was used to examine the relationship between TCDD exposures and age at menarche. Age at menarche was determined by questionnaire administered by a trained interviewer. Covariates examined as potential confounders included height, weight, body mass index, athletic training at the time of interview, smoking, and alcohol consumption.

TCDD exposures were determined using serum samples collected from 257 (91%) of these women between 1976 and 1977. For the remaining women, TCDD levels were quantified from measures collected between 1978 and 1981 (n = 23, 8%) and in 1996 (n = 2, 1% collected due to inadequate volume of older samples). TCDD levels determined after 1977 were back-extrapolated to the time of the explosion in 1976. TCDD was modeled as both a continuous variable ($\log_{10}$TCDD) and a categorical variable based on quartile values (≤55.9, 56−140.2, 140.3–300, >300 ppt). The lowest group was further subdivided into those with levels ≤20, and >20 ppt; this cut-point represented background levels found in a sample of women living in an unexposed area.

No association (hazard ratio [HR] = 0.95, 95% CI = 0.83−1.09) was detected between age at menarche and a 10-fold increase in serum TCDD concentrations (from 10 ppt to 100 ppt). Analyses restricted to those who were younger than 8 in 1976 produced similar results (HR = 1.08, 95% CI = 0.89−1.30). No dose-response trend was observed with categorical measures of TCDD among all women, as well as those under the age of 8. A 10-fold increase in serum TCDD concentrations were later reported to be associated with an earlier age of menarche (HR = 1.20, 95% CI = 0.98−1.60, p for trend = 0.07) when analyses were restricted to 84 women under the age of 5 at the time of the accident (Warner and Eskenazi, 2005).

C.1.2.1.4.4.2. *Study evaluation*

An important strength of the Warner et al. (2004) study is the ability to characterize TCDD exposures using serum samples that were collected shortly after the accident occurred. The outcome of interest, age at menarche, was determined by asking women "At what age did you get your first menstrual period?" Previous work suggests that self-reported measures of age at menarche decades later have modest agreement with responses provided during adolescence with recall varying by education and by history of an adverse birth outcome (Cooper et al., 2005). Although it seems unlikely, information bias could be introduced in the Seveso study if recall of age of menarche varied according to exposure levels. The results from the analysis in the original paper (Warner et al., 2004) were largely null there was some suggestion of an association between elevated TCDD levels and earlier age of menarche in the follow-on communication (Warner and Eskenazi, 2005). These more recent findings lend some support to the suggestion of Wolff et al. (2005) that the first 5 years of life may be the most relevant exposure period for determination of an effect on age at menarche. However, the actual change in the age at menarche relative to TCDD serum concentrations was not reported and cannot be established from the information presented by the study authors.

C.1.2.1.4.4.3. *Suitability of data for TCDD dose-response modeling*

No major biases were evident, but some sources of uncertainty remain which complicate interpretation of the study results and potential application to dose-response modeling. The study also showed limited evidence of an association between age at menarche and TCDD exposure and little evidence of a dose-response relationship. It remains unclear to what extent age at menarche represents an adverse health effect. Thus, EPA cannot assess the biological significance of this finding and cannot establish a LOAEL for this effect. Therefore, quantitative dose-response assessment was not conducted for this study, but it was included in the reference dose (RfD) uncertainty analysis presented in Section 4.5.2.

C.1.2.1.4.5. ***Eskenazi et al. (2005)—age at menopause***

C.1.2.1.4.5.1. *Study summary*

Eskenazi et al. (2005) evaluated the relationship between the age at onset of menopause and serum levels of TCDD among women in the SWHS. Of the 981 (80% of women contacted)

women who agreed to participate in SWHS, this analysis was restricted to those who had not reached natural menopause before the time of the accident and who were at least 35 years of age at the time of the interview. The recruitment and interview of women occurred approximately 20 to 22 years after the accident (March 1996−July 1998).

The population was divided into quintiles of serum TCDD levels for the categorical analysis. For most women (*n* = 564), TCDD levels were estimated from samples provided in 1976−1977. For the remaining women included in these analyses, TCDD levels were estimated from samples collected between 1978 and 1982 (*n* = 28) and between 1996 and 1997 (*n* = 24; collected due to insufficient volume of earlier sample). As noted previously, exposure levels for women with post-1977 detectable levels of TCDD were back-extrapolated to 1976 using either the first-order kinetic model (Pirkle et al., 1989) (>16 years at time of accident) or the Filser model (<16 years at time of accident) (Kreuzer et al., 1997). Women were classified as premenopausal if they were still menstruating or if they had amenorrhea as a result of pregnancy or lactation (at the time of interview) with an indication of subsequent menstruation based on maintained diaries or further examination. Subjects for which amenorrhea had persisted for at least 1 year with no apparent medical explanation were classified into a natural menopause category. The category, surgical menopause, pertained to women with a medically confirmed hysterectomy or an oophorectomy. Finally, impending menopause was defined for subjects in which menstruation had been absent for 2 months, but who provided evidence of subsequent menstruation, or had a secretory endometrial lining, or indicated less predictable cycles in the previous 2−5 years. If participants' menopausal status could not be determined, they were grouped into the "other" category. This category included those for whom status could not be determined due to current use of oral contraceptives, hormone replacement therapy, or previous cancer chemotherapy.

Statistical analysis was based on both a continuous measure of log-transformed TCDD exposures and categories based on quintiles (<20.4 ppt; 20.4−34.2 ppt; 34.3−54.1 ppt; 54.2−118.0 ppt; >118.0 ppt). The Cox model was used to generate hazard ratios as estimates of relative risks and their 95% confidence intervals examining natural menopause as the outcome. Several covariates previously identified as associated with menopausal status in the literature were considered as potential confounders. These covariates included body mass index, physical

activity, premenopausal smoking, education, marital status, history of heart disease and other medical conditions, and other reproductive characteristics.

A statistically significant association with onset of menopause was not detected (RR = 1.02, 95% CI = 0.8−1.3) based on the logTCDD continuous measure. The RRs were found to increase across the second through fourth quintiles (RRs = 1.1, 1.4, and 1.6, respectively) of serum TCDD categories in relation to those in the lowest category, but not in the upper quintile (RR = 1.0, 95% CI = 0.6−1.8). A statistically significant trend was detected across the first four quartiles (p = 0.04) but not across all five quintiles (p = 0.44). However, when the 24 women who had back-extrapolated TCDD levels from 1996 were excluded, the hazard ratios were slightly larger in magnitude. Compared with women in the lowest quintile, HRs for risk of earlier menopause were 1.2 (p = 0.5) for quintile 2, 1.6 (p = 0.08) for quintile 3, 1.7 (p = 0.05) for quintile 4, and 1.2 (p = 0.5) for quintile 5, with a statistically significant trend (p = 0.02) across the first four quintiles. Eskenazi et al. (2005) suggested that the stronger results following exclusion of 1996 measures may have been due to reduced exposure measurement error and less exposure misclassification.

C.1.2.1.4.5.2. *Study evaluation*

The categorical exposure results from this study support a nonmonotonic dose-related-association for earlier menopause with increased serum TCDD levels up to approximately 118-ppt TCDD serum. Eskenazi et al. (2005) speculated that the inverse "U" shape of the dose-response relationship is explained by the mimicking of hormones at lower doses of a chemical, while at higher levels the toxic effect of a chemical does not have the capacity to either inhibit or stimulate hormonal effects. Similar dose-response relationships have been observed for TCDD for other endpoints in other studies for both humans and rodents (e.g., Mocarelli et al., 2008; NTP, 2006; Steenland et al., 2001a), although none with such a pronounced drop in response at higher exposures. Overall, the findings suggest the possibility of a nonlinear dose-response relationship for age of onset of menopause with TCDD, with increased risks in the 4th quintile and perhaps the 3rd quintile. However, the actual change in the age at menopause relative to TCDD serum concentrations was not reported and cannot be established from the information presented by the study authors. The biological significance of these

findings is unclear. A biologically-relevant critical exposure window for this effect cannot be established.

A study limitation is the potential for residual confounding due to adjustment based on current smoking status and not at the time of onset of menopause. It is unclear to what extent smoking status may differ between these two time periods and whether smoking is related to TCDD exposures in this cohort.

C.1.2.1.4.5.3. *Suitability of data for TCDD dose-response modeling*

Because the critical window of exposure that would cause an effect on age at menopause is not apparent and EPA could not determine with confidence the biological significance of this result for the establishment of a LOAEL, a quantitative dose-response assessment was not conducted for this study in the context of the RfD derivation. However, this study is included in the RfD uncertainty analysis presented in Section 4.5.2.

C.1.2.1.4.6. ***Warner et al. (2007)—ovarian function***

C.1.2.1.4.6.1. *Study summary*

Warner et al. (2007) investigated the association between serum TCDD levels and ovarian function in subjects in the SWHS who were younger than 40 in 1976 and for whom sera collected after the accident had been stored. These women were recruited from March 1996 until July 1998. Ovarian function analysis was limited to 363 women between 20 and 40 years of age and who were not using oral contraceptives. Of these, 310 underwent transvaginal ultrasound and were included in the functional ovarian cyst analysis. Ninety-six women were in the preovulatory stage of their menstrual cycles and were included in the follicle analysis. For the hormone analysis, 126 women who were in the last 2 weeks of their cycle were included.

The authors used logistic regression to examine the relationship between TCDD and the prevalence of ovarian follicles greater than 10 mm. Linear regression models were used to examine the continuous outcomes: number of ovarian follicles >10 mm and diameter of dominant ovarian follicle. Covariates considered for inclusion in the model were age at ultrasound, age at accident, age at menarche, marital status, parity, gravidity, lactation history, current body mass index, age at last birth, and smoking history. For the serum hormone analyses, estradiol and progesterone were measured in blood at the time of interview. Ovulation

status was defined as a dichotomous variable (yes/no) based on a serum progesterone cut-point value of 3 ng/mL.

The adjusted ORs across categories of TCDD exhibited no dose-response trend for the presence of follicles in relation to TCDD in the follicular phase; also, no statistically significant differences were noted in any of the upper exposure categories relative to those in the lowest. The adjusted OR for the continuous measure of $\log_{10}$TCDD was 0.99 (95% CI = 0.4−2.2). A similar nonstatistically significant finding was found for $\log_{10}$TCDD in relation to ovulation in both the luteal (OR = 0.99, 95% CI = 0.5−1.9) and mid-luteal phases (OR = 1.03, 95% CI = 0.4−2.7). Progesterone and estradiol also were not related to serum TCDD levels for either the luteal or mid-luteal phases (p = 0.51 and p = 0.47).

C.1.2.1.4.6.2. *Study evaluation*

The investigators found no relationship between serum TCDD levels and serum progesterone and estradiol levels among women who were in the luteal phase at the time of blood draw. No association with number of ovarian follicles detected from ultrasound. Although no association was found, the authors suggested that the lack of significant results could be because the women in SWHS were all exposed postnatally and the relevant and critical time period for an effect might be in utero.

C.1.2.1.4.6.3. *Suitability of data for TCDD dose-response modeling*

Because of the lack of a defined critical exposure window and absence of associations between TCDD and adverse health effects in this study, quantitative dose-response assessment was not conducted for this study; however, this study is included in the RfD uncertainty analysis presented in Section 4.5.2.

C.1.2.1.4.7. ***Eskenazi et al. (2007)—uterine leiomyoma***

C.1.2.1.4.7.1. *Study summary*

Associations between TCDD exposures and uterine leiomyomata (i.e., fibroids), which are benign estrogen-dependent tumors, were examined among 956 women in the SWHS (Eskenazi et al., 2007). The sample population was based on the original 981 SWHS participants excluding 25 women diagnosed with fibroids before the date of the accident (July 10, 1976).

Women who previously had fibroids were identified both through the administered questionnaire and the review of medical records. Transvaginal ultrasounds were performed for 634 women to determine if they had fibroids at the time of follow-up. Women who had a fibroid diagnosis in their medical records dated after the accident did not need to have an ultrasound. Similar to other SWHS studies, exposure to TCDD was estimated using serum collected from women shortly after the time of the accident, between 1978 and 1981 and in 1996. TCDD levels were back-extrapolated to 1976 levels.

The study authors performed statistical analyses using two definitions of fibroids as outcome measures. The first was fibroids detected before the study, and the second was fibroids detected via ultrasound. A proportional odds method Dunson and Baird (2001) developed was used to model the cumulative odds of onset of fibroids. This method combines historical and current information of diagnoses of fibroids. Continuous and categorical measures of TCDD were modeled. Regression models were adjusted for known or suspected risk factors of fibroids including: parity, family history of fibroids, age at menarche, body mass index, smoking, alcohol use, and education.

Categorical measures of TCDD showed an inverse dose-response relationship with the onset of fibroids. Relative to those with TCDD levels less than 20 ppt, those having TCDD exposures between 20.1 and 75.0 ppt and greater than 75.0 ppt (at time of measurement) had hazard ratios of 0.58 (95% CI = 0.41−0.81), and 0.62 (95% CI = 0.44−0.89), respectively. The hazard ratio was 0.83 (95% CI = 0.65−1.07) for a continuous measure of $\log_{10}$TCDD. The study authors concluded that TCDD may have antiestrogenic effects in the uterine myometrium, in contrast to the suggestion of estrogenic effects previously found in the breast (Warner et al., 2002).

C.1.2.1.4.7.2. *Study evaluation*

The strengths of the Eskenazi et al. (2007) study included the longitudinal design, individual-level serum measures (most taken within 2 years of the accident), and the ability to include outcomes among those who did not take an ultrasound by using an adapted statistical approach. An important limitation was that the differences in risk by the stage of development could not be assessed as all women were exposed postnatally, and only 4 cases were observed among those who were premenarcheal at the time of exposure. The authors found a

statistically-significant reduction in risk for uterine fibroids in SWHS women having TCDD exposures between 20.1 and 75.0 ppt and greater than 75.0 ppt. A biologically-relevant critical exposure window for this effect cannot be established.

C.1.2.1.4.7.3. *Suitability of data for TCDD dose-response modeling*

Although this association is suggestive of anti-estrogenic activity, EPA was unable to establish the biological significance of the findings at any particular exposure level for establishing a LOAEL. Because a LOAEL could not be established for anti-estrogenic activity (Eskenazi et al., 2007), quantitative dose-response modeling was not conducted.

C.1.2.1.5. ***Other Seveso noncancer studies***

See general summary of the Seveso cohort in Section C.1.1.1.4.

C.1.2.1.5.1. ***Bertazzi et al. (1989); Consonni et al. (2008)—mortality outcomes***

C.1.2.1.5.1.1. *Study summary*

Several studies have evaluated the mortality of Seveso residents exposed to TCDD following the 1976 accident. The earlier section of this report described the designs of these studies and discussed their findings as they relate to cancer mortality. In this section, some of the findings for other causes of death are described. A key feature of these studies is that patterns of mortality among Seveso residents were investigated according to their zone of residence at the time of explosion relative to general population rates.

A 10-year mortality follow-up of residents of Seveso was published in 1989 (Bertazzi et al., 1989). Poisson regression was used to derive RRs for those who had lived in Zone A at the time of explosion using a referent group consisting of inhabitants who had lived in the uncontaminated study area. Between 1976 and 1986, no statistically significant difference was observed in all-cause mortality relative to the general population among those who lived in the most highly exposed area (Zone A) at the time of the accident. This finding was evident in both males (RR = 0.86, 95% CI = 0.5−1.4) and females (RR = 1.14, 95% CI = 0.6−2.1). A statistically significant excess in circulatory disease mortality was found among males relative to those in the referent population (RR = 1.75, 95% CI = 1.0−3.2); this increased risk was more pronounced when the follow-up period was restricted to the first 5 years after the accident (1976−1981) (RR = 2.04, 95% CI = 1.04−4.2). Between 1982 and 1986, the RR decreased

substantially and was not statistically significant (RR = 1.19, 95% CI = 0.4−3.5). Among females, a risk similar in magnitude was detected for circulatory disease mortality although it was not statistically significant (RR = 1.89, 95% CI = 0.8−4.2). Contrary to the calendar period-specific findings for males, the excess of circulatory mortality among females occurred between 1982 and 1986 (RR = 2.91, 95% CI = 1.1−7.8) and not between 1976 and 1981 (RR = 1.12, 95% CI = 0.3−4.5). The number of deaths in this cohort with the 10 years of follow-up was relatively small; in Zone A, 16 deaths were observed among males and 11 among females.

The most recently published account of the mortality experience of Seveso residents provides further information on follow-up of these residents until the end of 2001 (25 years after the accident) (Consonni et al., 2008). Three exposure groups were considered: Zone A (very high contamination), Zone B (high contamination), and Zone R (low contamination). The reference population consisted of those residents who lived in unaffected surrounding areas, as well as residents of five nearby towns. The authors used Poisson regression to compare mortality rates for each zone relative to the reference population.

For all causes of death, no excess was found in Zone A, B, or R relative to the reference population. Statistically significant excesses were noted for those who lived in Zone A relative to the reference population for chronic rheumatic heart disease (RR = 5.74, 95% CI = 1.83−17.99) and chronic obstructive pulmonary disease (RR = 2.53, 95% CI = 1.20−5.32). These risks, however, were based on only 3 and 7 deaths, respectively. For those in Zone A, no statistically significant excesses in mortality were noted for diabetes, accidents, digestive diseases, ischemic heart disease, or stroke. Among Zone A residents, stratified analysis by time since accident showed increased rates of circulatory disease 5–9 years since the accident (RR = 1.84, 95% CI = 1.09−3.12). Increased mortality from diabetes relative to the reference population was noted among females who lived in Zone B (RR = 1.78, 95% CI = 1.14−2.77).

C.1.2.1.5.1.2. *Study evaluation*

The ascertainment of mortality in this cohort appears to be nearly complete. Misclassification of some health outcomes, such as diabetes, may occur due to the use of death certificate data.

The characterization of exposure is based on zone of residence. Soil sampling indicated considerable variability in TCDD soil levels, and therefore, the generation of risks based on zone of residence likely does not accurately reflect individual exposure. Exposure misclassification might also occur because residency in the areas does not necessarily reflect whether the individual would have been present in the area at the time the accident occurred. Any exposure misclassification would likely be nondifferential which would tend to bias the risk estimates towards the null.

Although some excess of circulatory disease mortality was found, the finding was not consistent between men and women. Moreover, excess circulatory disease mortality was more pronounced among men within the first 5 years of exposure, while, for women, the excess was more pronounced in years 5–10. Numerous other risk factors for circulatory disease were not controlled for in these analyses and may be confounders if related to TCDD exposure. Taken together, the possibility that TCDD increased circulatory disease mortality based on these data is tenuous at best.

C.1.2.1.5.1.3. *Suitability of data for TCDD dose-response modeling*

There is considerable uncertainty in these data due to the potential for outcome and exposure misclassification. The lack of the individual-level TCDD levels and the examination only of fatal outcomes reported in this study are not a suitable basis for development of an RfD. For these reasons, dose-response analysis for this outcome is not conducted.

C.1.2.1.5.2. ***Mocarelli et al. (2000; 1996)—sex ratio***

C.1.2.1.5.2.1. *Study summary*

A letter to the editor was the first report of a possible change in the sex ratio from dioxin among Seveso residents following the July 10, 1976 accident (Mocarelli et al., 1996). The authors reported that 65% (n = 48) of the 74 total births that had occurred from April 1977 to December 1984 were females. This male to female ratio of 26:48 (35%) is significantly different from the worldwide birth ratio of 106 males:100 females (51%) (James, 1995). Between 1985 and 1994, the Seveso male to female ratio leveled out at 60:64 (48%). The authors suggested that the finding supported the hypothesis that dioxin might alter the sex ratio through several possible mechanistic pathways.

Mocarelli et al. (2000) later reported on an investigation of serum-based TCDD measures in parents and the sex ratio of offspring. In this study, serum samples were collected from mothers and fathers who lived in nearby areas at the time of the explosion, were between the ages of 3 and 45 at the time of the explosion, and produced offspring between April 1, 1977 and December 31, 1996. The study population included 452 families and 674 offspring, and serum measures were available for 296 mothers and 239 fathers. An estimate of TCDD at the time of conception was also examined in relation to male to female birth ratios. TCDD exposure estimates between the years of 1976 and 1996 were estimated using Filser's model (Kreuzer et al., 1997).

Mocarelli et al. (2000) used chi-square test statistics to compare observed sex ratio to an expected value of 0.51 in this Seveso population. Concentrations of TCDD were modeled as categorical variables in several ways. First, a dichotomous variable was used whereby unexposed parents were defined as those who lived outside Zones A, B, and R or had a serum TCDD concentration of less than 15 ppt; parents with exposures of 15 ppt or higher were considered exposed. Second, a trichotomous exposure variable was created that consisted of parents who (1) lived outside Zones A, B, and R or had serum concentrations of less than 15 ppt, (2) had serum concentrations of 15−80 ppt, and (3) had serum concentrations that exceeded 80 ppt. These cut-points were chosen as they represented tertiles based on the distribution of TCDD among parents. Analyses were conducted separately for paternal and maternal TCDD levels.

The overall proportion of 0.49 male births (based on male to female ratio of 328:346) was not significantly different from the expected proportion of 0.51 ($p > 0.05$). Statistically significant differences were found, however, if both parents had TCDD levels >15 ppt (sex ratio = 0.44) or just the father had serum TCDD levels >15 ppt (sex ratio = 0.44). No statistically significant differences were found when the fathers had TCDD levels less than 15 ppt, irrespective of the maternal levels. A dose-response pattern in the sex ratio was found across the paternal exposure categories. That is, the sex ratio decreased with increased paternal TCDD levels (linear test for trend, $p = 0.008$). In the unexposed group, the sex ratio (male to female) was 0.56 (95% CI = 0.49−0.61), while in the highest exposure group (281.0−26,400.0 ppt) the corresponding sex ratio was 0.38 (95% CI = 0.28−0.49).

Stratified analyses by age at paternal exposure revealed that the sex ratio was altered to a greater degree among fathers who were younger than 19 at the time of the explosion. The male to female ratio among the unexposed fathers was 0.56 (95% CI = 0.50−0.62), while it was 0.38 (95% CI = 0.30−0.47) for those younger than 19 when exposed and 0.47 (95% CI = 0.41−0.53) for those exposed after 19. Regardless of the age at the time of exposure, however, fathers who were exposed had a statistically significantly different birth ratio (they were more likely to father girls) than those who were unexposed ($p < 0.05$).

Separate analysis of birth ratios based on paternal TCDD exposure estimated at the time of conception did not show the same dose-response pattern but did show strong evidence of consistently decreased male births relative to females. More specifically, the male to female birth ratios among the four successive quartiles (first through fourth) were 0.41, 0.33, 0.33, and 0.46.

C.1.2.1.5.2.2. *Study evaluation*

Mocarelli et al. (2000) based the characterization of TCDD exposure on serum samples, which is an objective method for characterizing dose. Unlike for the occupational cohorts, serum measures for this study were taken close to the time of the accident, and therefore, back-extrapolation of TCDD exposures is unnecessary. Maternal TCDD levels at the time of conception did not demonstrate a dose-response relationship, but paternal exposures resulted in consistently reduced male to female birth ratios (range: 0.33−0.46). Paternal exposures received before the age of 19 at the time of the explosion were more strongly associated with a reduced male to female ratio than those received after the age of 19.

The methods used to identify births appear to be appropriate. Even if some births were missed, there is no reason to believe that ascertainment would be related to TCDD exposure and the sex of the baby. Therefore, no bias is suspected due to incomplete birth ascertainment. The authors report that the findings did not differ when age at conception was dichotomized (≤ or >35 years). They also state that age at conception was, on average, similar across calendar years. However, some uncertainty remains as to what degree this influenced the sex ratio given that the lowest mean age of conception periods (1973−1976 and 1977–1984) also corresponded with the lowest reported male:female ratios.

C.1.2.1.5.2.3. *Suitability of data for TCDD dose-response modeling*

TCDD exposures were well-characterized, and internal cohort analyses demonstrate an association between paternal TCDD levels and birth ratio, particularly when exposure occurred before 19 years of age. Although the data are suggestive of an effect earlier in life, perhaps even pre-pubertal, the biologically-relevant critical exposure window of susceptibility cannot be defined with any confidence for this endpoint. Quantitative dose-response assessment was not conducted for Mocarelli et al. (2000) in the context of the RfD derivation. However, this study is included in the RfD uncertainty analysis presented in Section 4.5.2.

C.1.2.1.5.3. ***Baccarelli et al. (2004; 2002)—immunologic effects***

C.1.2.1.5.3.1. *Study summary*

The relationship between TCDD and immunological effects was evaluated in a sample of Seveso residents (Baccarelli et al., 2004; Baccarelli et al., 2002). Both studies were based on findings from 62 individuals who were randomly selected during December 1992 and March 1994 from Zones A and B. An additional randomly selected 59 subjects were chosen from the surrounding noncontaminated areas during the same time period. Residency was based on where subjects lived at the time of the accident (July 10, 1976) (Landi et al., 1998). Frequency matching ensured that the two groups of subjects were similar with respect to age, sex, and cigarette smoking status.

TCDD levels were determined by mass spectrometric analysis of plasma samples. TCDD levels at the time of sampling were obtained, and estimates of levels at the time of the accident also were estimated by assuming an 8.2-year half-life (Landi et al., 1998). Exposure to other DLCs for both the TCDD contaminated and noncontaminated areas were reported to be at background levels. The plasma was also used to characterize levels of the immunoglobulins (Ig) IgG and IgM and the complement components C3 and C4. One subject was excluded due to lack of an immunological evaluation. Analyses are, therefore, based on 58 subjects in the noncontaminated areas and 62 individuals from the contaminated areas.

Nonparametric tests were applied to test for differences between the two groups. Multiple regression also was used to describe the relationship between the variables. Adjustment was made for several potentially confounding variables that were collected via questionnaire.

An inverse association was noted with TCDD levels and plasma IgG levels; this result remained statistically significant after adjusting for other potential confounding variables in the regression models. Specifically, the regression coefficient and *p*-value for the unadjusted ($\beta = -0.35$; $p = 0.0002$) and adjusted model were noted to be similar. In the 2004 analysis, the authors present IgG, IgM, IgA, C3, and C4 median and interquartile values across TCDD exposure quintiles. Decreased levels of IgG were observed in the highest exposure groups. Specifically, the median values across the five quintiles (for lowest to highest) were 1,526; 1,422; 1,363; 1,302; and 1,163. The Kruskal-Wallis test for differences across the TCDD categories was statistically significant ($p = 0.002$), which is consistent with the findings for the continuous measures of TCDD. This finding persisted after excluding those subjects with inflammatory diseases and those who used antibiotics or nonsteroidal anti-inflammatory drugs. For the other plasma measures, no dose-response relationship was apparent based on median values for IgM, IgA, C3, or C4 across TCDD quintiles. The authors highlight the need for additional research, particularly given the excess of lymphatic tumors noted in the area.

C.1.2.1.5.3.2. *Study evaluation*

Both TCDD exposure and health outcome measures are relatively well characterized. TCDD exposures, however, are based on concurrent serum measures and are far-removed from the initial peak-exposure event. Therefore, back-extrapolation to earlier time periods of exposure would be highly uncertain. EPA cannot determine with confidence whether the health outcome is a result of current exposure or longer-term continuous exposure to elevated TCDD levels. Furthermore, EPA cannot determine what effect the much higher initial peak exposure might have had on the outcome observed 17 years later. A dose-response relationship between TCDD and IgG was evident in the unadjusted model, but no details are provided on any changes that may be present when other covariates were added to the model.

Interpreting the inverse association between TCDD exposure and IgG in terms of clinical significance is not possible. The 24% reduction in IgG at the highest exposures cannot be linked to any adverse health outcome without more specific testing. The IgG values reported are much higher than those associated with antibody immunodeficiency disorders, as discussed by Baccarelli et al. (2002). The biologically-relevant critical window of TCDD exposure associated

with possible IgG impacts is uncertain, because it is unclear whether the current serum TCDD levels or the higher prior TCDD serum levels are associated with these impacts.

C.1.2.1.5.3.3. *Suitability of data for TCDD dose-response modeling*

Although the data support an inverse dose-response relationship between IgG and TCDD, the biological significance of the findings are too uncertain to define a LOAEL or a NOAEL. Further the critical window of exposure that would cause an effect on IgG levels is not known and thus does not allow for estimation of the effective TCDD exposure. For these reasons, these data were not suitable for quantitative dose-response modeling.

C.1.2.1.5.4. ***Landi et al. (2003)—gene expression***

C.1.2.1.5.4.1. *Study summary*

The impact of TCDD on the aryl hydrocarbon receptor (AhR) was evaluated by Landi et al. (2003) in a population-based study of Seveso residents. AhR, a mechanistically based biomarker of dioxin response, must be present for manifestation of most of the toxic effects of TCDD, including tumor promotion and immunological and reproductive system effects (Puga et al., 2000; Safe, 1986). AhR activates the transcription of several metabolizing enzymes in addition to certain genes (Whitlock, 1999). The primary objective of the study was to determine whether plasma levels of TCDD and TEQ are associated with the AhR-dependent pathway in lymphocytes among Seveso residents. The genes involved in the pathway that were examined included: AhR, aryl hydrocarbon receptor nuclear translocator, CYPA1A1 and CYP1B1 transcripts, and CYP1A1-associated 7-ethoxyresorufin O-deethylase (EROD).

Study recruitment occurred from December 1992 to March 1994. A total of 62 subjects were randomly chosen from the highest exposed zones in Seveso (Zones A and B), while 59 were chosen from the noncontaminated area (non-ABR). Those chosen from the noncontaminated zone were matched by age, sex, and smoking. Assignment of zones was based on place of residence where subjects lived at the time of the accident in 1976. Subjects provided data via questionnaire on a variety of sociodemographic and behavioral risk factors, including cigarette smoking. Multivariate models were adjusted for a variety of confounders including: age, gender, date of assay, actin expression, postculture viability, experimental group, and cell growth.

TCDD levels were determined using high-resolution gas chromatography, and 21 other dioxins, or DLCs, were measured to examine TEQ. Eleven measurements taken on the 121 subjects were deemed inadequate and excluded, but no further information was provided on these exclusions. Nine subjects from Zone B and fourteen subjects from Zone ABR had TCDD levels below detection, and were assigned a value equal to the lipid-adjusted detection limit divided by the square root of 2. The toxic equivalent for the mixture of DLCs (i.e., TEQ) was calculated by summing the products of the concentration of each congener by its specific toxic equivalency factor.

The subjects provided between 5 and 50 mL of whole blood, which was centrifuged to separate mononuclear cells. The cells were frozen and later thawed. Cells were cultured, removed from the culture medium, and resuspended in a stimulation medium, 14 mL of which was used for RNA analysis. Reverse transcription-PCR was conducted and EROD was assayed. Differences in gene expression and EROD activity observed for various cell culture conditions were compared using paired t-tests. The unpaired Student's t-test was applied to test for differences between groups, while a Bonferroni factor was used to account for multiple comparisons. Data for continuous variables were log-transformed.

TCDD accounted for 26% of the TEQ among the study subjects, but varied by zone (35% in zone A and 18% in zone non-ABR). After adjusting for confounding, AhR was inversely related to plasma TCDD levels in uncultured cells ($p < 0.03$) and in mitogen-stimulated cells ($p < 0.05$). EROD was lower in cells cultured from subjects with higher plasma TCDD and TEQ levels, and the corresponding continuous measure of EROD was statistically significant ($p < 0.05$). No statistically significant associations with TCDD or TEQ were found with ARNT or CYP1B1 in uncultured cell medium, nor with CYP1A1 or CYP1B1 in mitogen-stimulated cells. In general, females had lower AhR transcripts and higher levels of dioxin.

Collectively, the findings suggest that TCDD exposure might reduce AhR expression in unstimulated cells. Therefore, TCDD could exert an influence on the AhR pathway regulation.

C.1.2.1.5.4.2. *Study evaluation*

The study used biologically-based measures of both TCDD exposures and biomarkers or AhR. Subjects were randomly selected from the larger cohort; some individuals with severe medical illnesses were excluded (Landi et al., 1998). Although few details are provided on the

number of subjects excluded for these reasons, given the objective nature of the biomarker outcomes that were evaluated, such exclusions are unlikely to be an important source of bias. The exclusion rates were also reported to be low and comparable across the zones (five subjects from the noncontaminated zone non-ABR and four subjects from zone B).

A strength of the study was the examination of other DLCs via the TEQ analysis. A limitation of the study included the relatively small number of subjects which resulted in the grouping of several covariates, including TCDD exposures, into a small number of categories. As such, slope coefficients derived from modeling continuous measures were emphasized in the data presentation. Another key limitation of the study is the uncertainty of how effects on AhR translate into subsequent development of cancer and other chronic health effects.

C.1.2.1.5.4.3. *Suitability of data for TCDD dose-response modeling*

It is unclear how associations between AhR biomarkers and TCDD levels translate into an increased risk of adverse health effects. Dose-response analysis for this outcome, therefore, was not conducted.

C.1.2.1.5.5. ***Alaluusua et al. (2004)—developmental dental defects***

C.1.2.1.5.5.1. *Study summary*

Alaluusua et al. (2004) examined the relationship between TCDD and dental defects, dental caries, and periodontal disease among Seveso residents who were children at the time of the accident. Subjects were randomly selected from those individuals who had previously provided serum samples in 1976, which was shortly after the accident. A total of 65 subjects who were less than 9.5 years of age at the time of the accident, and who lived in Zones A, B, or R were invited to participate. Recruitment was initiated 25 years after the time of the Seveso accident. An additional 130 subjects from the surrounding area (outside Zones A, B, or R or "non-ABR zone") having the same age restriction were recruited. Subjects were frequency matched by age, sex, and education. Questionnaires were administered to these individuals to collect detailed information on dental and medical histories, education, and smoking behaviors. Ten subjects who had completed at least high school were randomly excluded from the non-ABR zone to create groups with similar educational profiles. Participation rates for the ABR and non-ABR zones were 74% and 58%, respectively.

One dentist who was blind to the patients' TCDD exposure levels assessed dental aberrations. Dental caries were assessed using recommendations of the World Health Organization (WHO). Periodontal status was described following a detailed evaluation of the surfaces of the teeth. A radiographic examination was done to identify missing teeth, alveolar bone loss, deformities in the roots, and jaw cysts.

Comparisons of the presence of dental enamel defects according to exposure status were made using logistic regression. Chi-square test statistics were applied to compare the distributions in the prevalence of dental defects across several categorical covariates (i.e., education, age, and serum TCDD level). For those who were younger than 5 at the time of the accident, dental defects were more prevalent among patients in zone ABR (42%) than those in the non-ABR zone (26%) ($p = 0.14$). Zone ABR is characterized by higher levels of soil TCDD levels relative to non-ABR. Serum levels permitted an improved characterization of risk as they were available at an individual level, rather than using a zone of residence. The continuous measure of serum TCDD was associated with developmental dental defects ($p = 0.007$) and hypodontia ($p = 0.05$). The authors classified less-exposed individuals in the non-ABR zones as the reference population and also examined exposure tertiles for the ABR residents. The prevalence of dental effects for the reference group was 26% (10/39). The prevalence of dental effects in the 1st, 2nd and 3rd tertile exposure groups was 10% (1/10), 45% (5/11) and 60% (9/15), respectively. A total of 12.5% of the zone ABR subjects had missing permanent teeth (lateral incisors and second premolars) compared with 4.6% of the zone non-ABR residents. For zone ABR subjects, missing teeth were more frequent with higher serum TCDD levels.

C.1.2.1.5.5.2. *Study evaluation*

TCDD exposures were characterized using serum measures for those who resided in zone ABR in 1976 (within a year of the accident). Alaluusua et al. (2004), however, provide few details about the sampling frame used to identify these participants. Despite this, it is important to note that a dose-response pattern was observed between TCDD exposure and presence of developmental dental defects in the ABR population alone ($p = 0.016$). This finding is based on 27 subjects with developmental dental defects. This positive association provides support for a quantitative dose-response modeling of developmental dental defects. The numbers of such subjects are small, however, with one, five, and nine subjects having defects in the exposure

tertiles ; the concentration ranges in the 1st, 2nd and 3rd tertiles were 31−226, 238−592, and 700−26,000 ng/kg TCDD, respectively.

C.1.2.1.5.5.3. *Suitability of data for TCDD dose-response modeling*

The considerations for conducting a dose-response analysis have been satisfied with the study population. A critical window of exposure can be defined for the subjects with individual-level serum samples. The enamel defects combined with the prevalence of missing permanent teeth in the higher-exposed subjects allows for a LOAEL to be established for the 2nd tertile exposure range. A NOAEL is evident for the 1st tertile and a NOAEL and LOAEL could be established. Dose-response analyses were conducted for this outcome.

C.1.2.1.5.6. ***Baccarelli et al. (2005)—chloracne***

C.1.2.1.5.6.1. *Study summary*

Baccarelli et al. (2005) published findings from a case-control study of 110 chloracne cases and 211 controls. The authors collected information on pigment characteristics and an extensive list of diseases. This study was performed to yield information about the health status of chloracne cases, TCDD-chloracne exposure response, and factors that could modify TCDD toxicity. TCDD was measured from plasma from subjects recruited during 1993 to 1998. Following adjustment for confounding, TCDD was associated with chloracne (OR = 3.7, 95% CI = 1.5−8.8), and the risk of chloracne was considerably higher in subjects younger than 8 at the time of the accidents (OR = 7.4, 95% CI = 1.8−30.3). Among individuals with lighter hair, the association between TCDD and chloracne was stronger than among those with darker hair.

C.1.2.1.5.6.2. *Study evaluation*

Statistical power was limited in this study especially to assess potential interactions. Study strengths included unique distribution of age and sex of chloracne cases, characterization of individual-level TCDD exposures using sera samples, and the availability of both clinical and epidemiologic data. Although a dose-response relationship was observed, chloracne is a rare health outcome likely only to occur among those highly exposed.

C.1.2.1.5.6.3. *Suitability of data for TCDD dose-response modeling*

Given the very high TCDD levels needed to cause chloracne (Ott et al., 1993), this health endpoint would not be considered as the basis for the RfD. Therefore, dose-response analyses for the Baccarelli et al. (2005) study were not conducted.

C.1.2.1.5.7. ***Baccarelli et al. (2008)—neonatal thyroid hormone levels***

C.1.2.1.5.7.1. *Study summary*

Baccarelli et al. (2008) investigated the relationship between thyroid function and TCDD among offspring of women who were of reproductive age at the time of the 1976 accident. This health endpoint is relevant because thyroid function is important for energy metabolism and nutrients and for stimulating growth and development of tissues. Neonatal thyroid function at birth is evaluated through blood thyroid-stimulating hormone (b-TSH). Two related analyses were conducted as part of this investigation: (1) the Residence-Based Population Study and (2) the Plasma Dioxin Population Study.

For the Residence-Based analysis, the study population of 1,772 women was selected based on the following criteria: having lived in the highly contaminated areas (Zones A or B) at the time of the accident or between July 10, 1976 and December 31, 1947; were of fertile age (born after 1947); and were alive as of January 1, 1994. A random sample of 1,772 unexposed women who lived in the reference area was selected from the 55,576 eligible female participants using frequency matching by year of birth to the exposed women and residency in the reference area at the time of the accident. The reference area represents the noncontaminated areas that surround the three zones of decreasing exposure (Zones A, B and R). Population registry offices (n = 472) were contacted to detect children born to these women. Records could be traced for virtually all subjects (1761/1772 exposed; 1762/1772 unexposed). Children born outside the Lombardy area (n = 156) were excluded as b-TSH could not be obtained for them. The analyses were based on the remaining 56, 425, and 533 singletons born between January 1, 1994 and June 30, 2005 in Zone A, B, and from the reference area, respectively.

Thyroid function is tested in all newborns by b-TSH measures in the region of Lombardy where Seveso is located. These measures were obtained from blood samples taken 72 hours after birth using a standardized protocol. The b-TSH levels were log transformed to approximate a normal distribution. Linear regression analysis was used to conduct test for trends in mean

b-TSH levels across different covariates. Logistic regression was used to assess associations between elevated b-TSH levels defined by the cutpoint of 5 μU/mL and residence in particular zones of contamination. The 5 μU/mL cutpoint for thyroid stimulating hormone (TSH) measurements in neonates was recommended by WHO (1994) for use in neonatal population surveillance programs. Although WHO established the standard for increased neonatal TSH in the context of iodine deficiency disease, the toxicological implications are the same for TCDD exposure and include increased metabolism and clearance of thyroxine (T4). Fisher's exact tests, Wilcoxon nonparametric tests, and generalized estimating equations were used to adjust the standard errors of the regression coefficients due to correlation between siblings.

Results from the Residence-Based analysis indicate that mean levels of b-TSH were positively associated with average soil TCDD concentrations in the three areas (Zone A: 1.66 μU/mL; Zone B: 1.35 μU/mL; and Zone R: 0.98 μU/mL) ($p < 0.001$). Plasma TCDD levels also were shown to be much higher in a group of 51 newborns that had b-TSH levels >5 μU/mL. Compared to the reference population, adjusted ORs were elevated for Zone B (OR = 1.90, 95% CI = 0.94−3.86) and Zone A (OR = 6.63, 95% CI = 2.36−18.6). These ORs were adjusted for gender, birth weight, birth order, maternal age at delivery, hospital, and type of delivery. The adjusted ORs however differed only slightly from those that were unadjusted (Zone B OR = 1.79, 95% CI = 0.92−3.50; Zone A OR = 6.60, 95% CI = 2.45−17.8). Of the risk factors considered, only gender and birth weight were identified as independent predictors of neonatal b-TSH levels.

The Plasma Dioxin Population analysis included children born to 109 women who were part of the Seveso Chloracne Study (Baccarelli et al., 2005). A total of 51 children were born to 38 of these women, of these 12 lived in Zone A, 10 in Zone B, 20 in Zone R, and 9 from the reference population. All children in this analysis from zones A and B were also part of the Residence-Based population study (which included all zone A and B women), while none of the children from zone R and the reference area were sampled in the Residence-Based population study. Several congeners including TCDD were measured in maternal plasma collected from December 1992 to September 1998. TCDD levels were extrapolated to the date of delivery using a first-order pharmacokinetic model (Michalek et al., 1996). The elimination rate used was 9.8 years based on the mean half-life estimate from a previous study of women in the Seveso region (Michalek et al., 2002). TEQs were calculated for a mixture of DLCs by multiplying the

concentration of each congener by its toxicity equivalence factor. The maternal average TEQ was 44.8 ppt (range: 11.6−330.4) among 51 mothers. The measurement of noncoplanar PCBs occurred only later in the study (1996) and, therefore, total mean TEQs (i.e., including the sum of PCDDs, PCDFs, coplanar PCBs, and noncoplanar PCBs) are available only on a subset (n = 37) of the population. DLCs were examined as earlier studies suggested associations between the sum of PCBs, or individual congeners having decreased thyroxine (Sandau et al., 2002; Longnecker et al., 2000), and increased TSH (Alvarez-Pedrerol et al., 2008; Chevrier et al., 2007). The following confounders were examined by the authors in the plasma dioxin models: maternal body mass index, smoking habits, alcohol consumption, and neonatal age in hours at the time of the b-TSH measurement.

For the Plasma Dioxin analysis, the authors used a linear regression model to examine the association between maternal TCDD levels and b-TSH. The standardized regression coefficient obtained from this model was 0.47 ($p < 0.001$). For the evaluation of TEQs, a similar association was noted for PCDDs, PCDFs, and coplanar PCBs ($n = 51$, $\beta = 0.45$, $p = 0.005$) but not with noncoplanar PCBs ($n = 37$, $\beta = 0.16$, $p = 0.45$). Statistically significant associations between b-TSH with plasma TCDD, PCDDs, PCDFs, and coplanar PCBs, but not with noncoplanar PCBs, were found based on multivariate regression models adjusted for gender, birth weight, birth order, maternal age at delivery, hospital, and type of delivery. No association was detected for the sum of all total TEQs from the measured compounds ($n = 37$, $\beta = 0.31$, $p = 0.14$).

C.1.2.1.5.7.2. *Study evaluation*

The Baccarelli et al. (2008) study satisfies the epidemiologic considerations and criteria for determining whether dose-response modeling should be pursued. The outcome is well defined, and a dose-response pattern was observed. The study also contained a substudy that characterized TCDD and exposures to other DLCs and used serum measures for a sample of mothers. Results were consistent among the zone of residence analysis and the substudy based on plasma measures. Although they examined potential confounding factors, a study limitation was that this assessment was based on statistical significance alone.

C.1.2.1.5.7.3. *Suitability of data for TCDD dose-response modeling*

Given the potential for exposure misclassification due to variability in TCDD soil levels within each zone, modeling should rely on individual-level TCDD exposures derived from the plasma sampling substudy. Data from this study population provide an opportunity for quantitative dose-response analyses as the critical exposure window of 9 months can be used for exposure assessment purposes.

C.1.2.1.5.8. ***Mocarelli et al. (2008)—sperm effects***

C.1.2.1.5.8.1. *Study summary*

Mocarelli et al. (2008) examined the relationship between TCDD and endocrine disruption and semen quality in a cohort of Seveso men. Study participants included 397 of the eligible 417 males (<26 years old in 1976) from Zone A and nearby contaminated areas who had serum TCDD levels measured in 1976. Frozen serum samples collected from 1976 to 1977 were used to derive TCCD exposures. In addition, 372 healthy blood donors not living in the TCCD-contaminated area were invited to participate. The researchers collected a health questionnaire and semen samples from participants. Analyses were based on 257 individuals in the exposed group and 372 in the comparison group. Of the 257 exposed men, 135 (53%) without disease agreed to participate, while 184 of the 372 (49%) recruited men in the comparison group participated. Semen samples were collected postmasturbatory at home. Ejaculate volume, sperm motility, and sperm concentration were measured on these samples. Fasting blood samples also were collected from the subjects for reproductive hormone analyses, including 17β-estradiol (E_2), follicle stimulating hormone (FSH), inhibin B, LH, and testosterone.

The researchers estimated serum concentrations of TCDD from samples provided in 1976−1977, and also in 1997−1998 for individuals whose earlier samples had TCDD values that exceeded 15 ppt. Serum concentrations for the comparison group were assumed to be less than 15 ppt in 1976 and 1977 and <6 ppt in 1998/2002 on the basis of serum results for residents in uncontaminated areas. The exposed and comparison groups were divided into three groups based on their age in 1976: 1−9, 10−17, and 18−26 years. Mocarelli et al. (2008) applied a general linear model to the sperm and hormone data and included exposure status, age, smoking

status, body mass index, and occupational exposures as covariates. The study authors addressed the potential for confounding factors.

Men exposed between the ages of 1 and 9 had reduced semen quality 22 years later. Reduced sperm quality included decreases in sperm count ($p = 0.025$), progressive sperm motility ($p = 0.001$), and total number of motile sperm ($p = 0.01$) relative to the comparison group. The opposite pattern was observed for several indices of semen quality among those aged 10−17 at the time of the accident; this included a statistically significant increase in sperm count ($p = 0.042$). The clinical significance of this increase is unknown. For the hormone analyses, those in the exposed group had lower serum E_2 levels, and higher follicle stimulating hormone concentrations. Neither testosterone levels nor inhibin B concentrations were associated with TCDD exposure.

C.1.2.1.5.8.2. *Study evaluation*

The findings of the Mocarelli et al. (2008) study support the hypothesis that exposure to TCDD in infancy/prepuberty reduces sperm quality. The changes in serum E_2 and FSH concentrations are of unknown clinical significance, and it is unclear whether they represent adverse health endpoints. Further, it may be noted that the collection of a single semen sample is not suitable for accurate evaluation of semen effects in an individual, but is less of a concern for evaluation of the population average. Although most semen analysis studies have low compliance rates in general population samples (20−40%) (Muller et al., 2004; Jørgensen et al., 2001), the compliance rate in this study was much higher (60%). Given that the compliance rates were similar between the exposed and comparison groups and the strong differences detected across the two age groups, selection bias appears unlikely in this study.

C.1.2.1.5.8.3. *Suitability of data for TCDD dose-response modeling*

The health outcomes are well defined in the Mocarelli et al. (2008) study, and exposures are well characterized using serum data. Because the men exposed to elevated TCDD levels between the ages of 1 and 9 had reduced semen quality 22 years later, it is difficult to identify the relevant time interval over which TCDD dose should be considered. Specifically, it is difficult to discern whether this effect is a consequence of the initial high exposure between 1 and 9 years of age or a function of the cumulative exposure for this entire exposure window beginning at the

early age. However, the differences between these two dose estimates (the initial high exposure versus the cumulative exposure for the 9 year window) are minimal (i.e., within an order of magnitude). Despite the uncertainty in estimating the critical window of exposure, dose-response analysis for this outcome was conducted.

C.1.2.1.6. *The Chapaevsk study*

See general summary of the Chapaevsk study in Section C.1.1.1.5.

C.1.2.1.6.1. ***Revich et al. (2001)—mortality and reproductive health***

C.1.2.1.6.1.1. *Study summary*

Revich et al. (2001) describe a series of investigations that have evaluated adverse health outcomes among residents of Chapaevsk where ecological measures of TCDD have been noted to be higher than expected. In the earlier cancer section of this report, the cross-sectional comparisons of mortality that the authors carried out between Chapaevsk residents and a general population reference were described. Although the general focus of this paper is on cancer, the authors examined other adverse health outcomes.

For all-cause mortality, rates were found to be higher in Chapaevsk relative to the Samara region and other nearby towns. The magnitude of this increase, however, was not quantified in the review by Revich et al. (2001) Cardiovascular mortality accounted for nearly two-thirds of women's deaths and almost half of those among men. The rates of cardiovascular mortality among Chapaevsk men have been reported to be 1.14 times higher than those in Russia.

Revich et al. (2001) also reported on the occurrence of adverse reproductive events. Although the authors indicated that official medical information was used to make comparisons between regions, no details were provided about data quality, completeness, or surveillance differences across areas. The presented rates for reproductive health outcomes should be interpreted cautiously. A higher rate of spontaneous abortions (24.4 per 100 pregnancies finished by delivery) was found in Chapaevsk women relative to rates that ranged between 10.6 and 15.2 found in five other areas. The frequency of preeclampsia also was found to be higher in Chapaevsk women (44.1/100) relative to other towns, as was the proportion of low birth-weight babies and preterm births. The percentage of newborns with low birth weight was slightly larger in Chapaevsk (7.1%) when compared to other towns in Samara (5.1−6.2%); observed differences, however, were not statistically significant. The authors also reported on the sex ratio

of newborns born between 1983 and 1997. These ratios (boys:girls) were highly variable and ranged between 0.79 and 1.29. Given the annual variability of this ratio on a year-to-year basis, it is unclear if this is largely due to natural fluctuations and to what extent this may result from prior TCDD (or other contaminants) exposure TCDD and other contaminants.

C.1.2.1.6.1.2. *Study evaluation*

The review by Revich et al. (2001) highlights analyses that have been undertaken using largely cross-sectional data. Although soil sampling measures appear to demonstrate decreasing levels of TCDD in the soil with increasing distance from the plant, at this time, no individual-level TCDD exposure data are available. Increased rates of mortality relative to the Samara region in Russia were observed among Chapaevsk men for all cancer sites combined; this excess risk however, was not observed among women. Although the authors provide compelling evidence of increased adverse events among residents of Chapaevsk, the study lacks a discussion about the validity of comparing health data across regions, and suffers from inherent limitations from ecological studies such as exposure misclassification and potential for confounding.

C.1.2.1.6.1.3. *Suitability of data for TCDD dose-response modeling*

Insufficient details are provided by the authors to gauge the completeness and coverage of the cancer registry and mortality data. Health outcomes were studied on the basis of information in the official medical statistics. As with the cancer outcomes presented in this study, the data for noncancer outcomes are limited by the absence of TCDD levels on an individual-level basis and information on other potential confounding variables that could have biased the results. The cross-sectional nature of the data that were presented does not provide the necessary level of detail needed to estimate effective dose given the lack of individual-level exposure data. Therefore, a quantitative dose-response analysis was not conducted.

C.1.2.1.7. ***The Air Force Health ("Ranch Hands" cohort) study***

See general summary of the Ranch Hands cohort in Section C.1.1.1.6.

C.1.2.1.7.1. ***Henriksen et al., (1997)***

C.1.2.1.7.1.1. *Study summary*

Henriksen et al. (1997) investigated the relationship between TCDD exposure and diabetes among participants of the Air Force Health Study (AFHS). This study included veterans of Operation Ranch Hand who served in Southeast Asia between 1962 and 1971 and were exposed to high levels of dioxin from the spraying of Agent Orange during flight operations and the maintenance of aircraft and herbicide spray equipment. In addition, it included a comparison group of other Air Force veterans who also served in Southeast Asia during the same period, but were not actively involved in the spraying of herbicides. This comparison group was selected by matching to the Ranch Hands on the basis of age, race, and military occupation. Data from physical examinations in 1982, 1985, 1987, and 1992 were used for the study. The cohort initially consisted of 1,108 Ranch Hands and 1,494 veterans in the control cohort.

Incident diabetes from the end of the tour of duty through June 1995 was identified based responses provided from questionnaires administered from at least one of the four examinations, followed by verification of medical records and laboratory results. Study subjects were classified as diabetics if they had a verified history of diabetes mellitus by medical diagnosis or if they exhibited a 2-hour postprandial glucose laboratory value of ≥200 mg/dL. A total of 315 incident cases of diabetes were identified; of these, 169 occurred in the comparison cohort. The authors also examined associations between TCDD and the following health outcomes: severity of diabetes, time to onset of diabetes, and glucose abnormalities. Diabetes severity was determined based on a review of the medical records, and questionnaire responses and classified as insulin therapy, oral medication, diet only, or no control. Fasting glucose and 2-hour postprandial glucose were used to identify glucose abnormalities. The 100-gm glucose load for the postprandial assay was not given to known diabetics. The outcome time-to-onset of diabetes was defined as the number of years between the end of the last tour of duty in Southeast Asia, and initial diagnosis of diabetes. For those without diabetes, the time to onset of diabetes was the number of years since the end of tour of duty and the last physical examination; this time-to onset value was right-censored.

Serum dioxin levels were first estimated using high resolution gas chromatography/high resolution mass spectrometry using samples collected in the 1987 interview. Those whose

dioxin levels were not quantifiable in 1987 and those who refused or were new to the study were asked to provide serum in 1992 to measure dioxin. Dioxin levels were then estimated for the Ranch Hands at the end of the tour of duty by assuming a constant half-life of 8.7 years. The Ranch Hands were classified on the basis of this TCDD exposure estimate into one of three groups (Background, Low, or High). The study excluded those with a history of diabetes before service in Southeast Asia, those with no measure of dioxin, and those in the comparison group with a dioxin level that exceeded 10 ppt which was regarded as the threshold level for background exposure. The analyses of diabetes mellitus and TCDD exposure were based on 2,265 veterans (989 Ranch Hands, 1276 Comparison veterans).

The relative risk (and confidence intervals) of diabetes was estimated using the ratio of the prevalence of diabetes in Ranch Hands veterans relative to the comparison group using the method of Rothman (1986). The risk of diabetes was associated with TCDD exposure, and Ranch Hands in the highest exposure group had a relative risk of 1.5 (95% CI = 1.2, 2.0) relative to those in the comparison cohort. A subsequent analysis of this cohort further adjusted for the effects of triglycerides, which slightly attenuated this risk estimate (RR = 1.4, 95% CI = 1.1−1.8) (Michalek et al., 1998). The severity of diabetes was associated with dioxin exposure. For example, among those who required insulin therapy for the management of their diabetes, the relative risk was among those in the High dioxin exposure group relative to those in the lowest 2.4 (95% CI=0.9 – 6.4). Time to onset of diabetes was found to be inversely related to exposure to dioxin, and this association persisted across veterans stratified by body fat percentage. Serum insulin abnormalities, as determined by the 2-hour postprandial glucose measure, were positively associated with dioxin exposure in nondiabetics. Specifically, among Ranch Hands in the High dioxin exposure category, the prevalence of those with abnormal insulin values was 8.4% compared to 2.5% among those in the comparison cohort (RR=3.4, 95% CI=1.9 – 6.1).

C.1.2.1.7.1.2. *Study evaluation*

A strength of this study is its relatively large sample size of 2,265 veterans, and identified cases of diabetes (*n* = 315). Moreover, there is a large range in exposure to TCDD across the study population (i.e., the comparison cohort as well as veterans of the Operation Ranch Hands). The study was able to achieve a high level of participation, and lengthy follow-up interval with

data from four physical examinations. As documented by Michalek et al (2001c), few veterans were lost to attrition over the four physical examinations.

The methods used to identify newly diagnosed cases of diabetes following the tour of duty were valid, and the study evaluated several different measures associated with diabetes. The associations observed between these different health measures (i.e., diabetic status, time to onset of diabetes, severity of diabetes, and insulin abnormalities) were consistent, and therefore, strengthen the argument that exposure to TCDD may contribute to the development of insulin resistance and diabetes.

The use of serum measures to estimate TCDD exposure was also a strength of the study. The authors estimated dioxin levels in veterans at the end of their tour of duty using a constant half-life of 8.7 years, and conducted additional sensitivity analyses across strata of subjects grouped by body fat percentages. These results produced similar associations.

Unlike the subsequently published study by Longnecker and Michalek (2000) which is an essentially cross-sectional analysis of the comparison cohort, the analysis presented in this study is longitudinal. The dramatically higher exposure to TCDD among the Ranch Hand component of the cohort during their tour of duty allows for diabetes prevalence, severity, time to onset, as well as glucose abnormalities among nondiabetics to be compared across groups that differed by TCDD exposure before these health outcomes were determined.

An important limitation of the study was raised by Slade (1998) who noted that interactions between plasma lipid fractions, dioxin, and diabetes could produce a spurious association between dioxin and diabetes. In her letter, she noted that hyperinsulinemia, insulin resistance, impaired glucose tolerance and diabetes are all associated with lipid abnormalities, and the corresponding change in lipid fractions may elevate dioxin levels. As exposure to TCDD was estimated in 1987, and in some cases 1992, it is possible that these lipid abnormalities may have distorted the back-extrapolation of TCDD exposure estimates at the end of the tour of duty in Vietnam. The authors were not able to directly evaluate the magnitude of this source of measurement error because no lipid samples were stored for this cohort that would allow for dioxin to be measured. Subsequent analysis to respond to these comments found little change in the risk estimates for diabetes after adjusting for triglycerides (Michalek et al., 1998). However, dioxins have also been shown to affect triglyceride levels in both animals and in humans, and

therefore the influence of triglycerides may be responsible for a noncausal association between dioxin and the health outcomes in this study.

C.1.2.1.7.1.3. *Suitability of data for TCDD dose-response modeling*

The use of the individual-level TCDD serum measures and the identification of diabetes through medical records and objectively-based serum tests are strengths. TCDD levels were estimated based on samples collected in 1987, and in some cases 1992; the study authors note that these samples were collected 20 to 30 years after the TCDD exposures. If there are diabetogenic effects of TCDD, it is unclear whether TCDD-mediated diabetes onset might be a consequence of an elevated TCDD exposure event over a relatively short period of exposure (during service) or chronic TCDD exposure over a longer window of time. Estimation of peak exposures 20 years earlier is highly uncertain. Also, the longer potential exposure window occurred during a time period of decreasing exposure to TCDD and DLCs (Lorber and Phillips, 2002) further impeding the ability to estimate effective exposures. The uncertainty in identifying a critical period of exposure precluded the estimation of an effective TCDD exposure. Therefore, a quantitative dose-response analysis was not conducted for this study.

C.1.2.1.7.2. ***Longnecker and Michalek (2000)***

C.1.2.1.7.2.1. *Study summary*

Longnecker and Michalek (2000) evaluated the relationship between serum levels of TCDD and the incidence of diabetes and levels of serum glucose and insulin among veterans in the AFHS. However, unlike the earlier work on diabetes by Henriksen et al. (1997), and Michalek et al. (2003), this study did not include those in operation Ranch Hand that were more highly exposed to TCDD from the spraying of Agent Orange. Instead, this study was restricted to the comparison group of male veterans in the AFHS who were never in contact with dioxin-contaminated herbicides, and whose serum TCDD levels were thought to fall within the same range as the background levels found in the United States. These veterans included air and ground personnel who participated in aircraft missions in Southeast Asia between August 1961 and May 1972. The manner in which this cohort of nonsprayers was assembled was originally described by Wolfe et al. (1990). A total of 1,667 comparison group veterans (i.e., non-Ranch hands) were invited to participate in AFHS examinations in 1982. Subsequent examinations

were also conducted in 1985, 1987, and 1992. Participation rates were high (>70%) among this comparison group of veterans, with 1,197 subjects available for analyses.

Incident diabetes following each veteran's tour of duty was the primary health outcome under study. This outcome was defined by either (i) self-reported physician diagnosis of diabetes at any of the examinations (1982, 1987, and 1992) with subsequent verification of medical records through June 1995, or (ii) by a postchallenge glucose test using 100 g of glucose (positive status ≥200 mg/dL) in 1992. All incident cases of diabetes were type II. Levels of serum and insulin were also measured using fasting, and 2-hour postchallenge tests in nondiabetics.

Serum dioxin levels were estimated using high resolution gas chromatography/high resolution mass spectrometry using samples collected in the 1987 interview. For a small number of veterans (n = 21) dioxin levels were estimated using serum collected in 1997. For the 108 subjects with TCDD levels below the level of detection (1.25 ng/kg lipid), they were assigned a TCDD level of 0.625 mg/kg. Those with serum TCDD levels above 10 ng/kg were excluded as were those who lacked complete data for the covariates of interest. The covariates that were examined as potential confounders included age, dioxin, body mass index, waist size, and family history of diabetes, postchallenge glucose, and triglycerides. Analyses were based on the remaining 1,197 veterans, and among these 169 incident cases of diabetes were identified.

Logistic regression was used to estimate the odds ratios and 95% confidence intervals of diabetes across quartiles of serum TCDD levels, as well as in relation to a linear increase in 4.0 ng/kg of TCDD. The natural logarithm of serum-insulin levels was modeled again TCDD levels using linear regression. Results were adjusted for year of birth, race, military occupation, body mass index at 1992, body mass index at time of TCDD measurement and waist size in 1992. Ordinary least squares regression was used to evaluate associations between serum glucose or insulin measures and quartiles of TCDD exposure. Adjustment was made for the same covariates used in the logistic regression analysis.

The adjusted odds ratio for diabetes increased with higher serum TCDD levels. Specifically, an increase of 4.0 ng/kg of serum TCDD yielded an adjusted odds ratio of 1.55 (95% CI = 1.09−2.20). After further adjustment for serum triglyceride levels, the corresponding odds ratio remained positive but was attenuated (OR = 1.37, 95% CI = 0.96−1. 97). Associations were also observed between serum TCCD and serum glucose (and insulin) levels, although some

of these were not statistically significant following adjustment for confounding. This implies that TCDD may contribute to increased insulin resistance and increased glucose levels among those not satisfying the formal criteria for the diagnosis of diabetes. The addition of serum triglycerides to this model weakened these associations. The findings for both the outcomes of diabetes and serum glucose were essentially unchanged after excluding subjects whose serum TCDD was measured after 1987.

C.1.2.1.7.2.2. *Study evaluation*

A strength of this study is the relatively large sample size (*n* = 1197) and corresponding number of incident cases of diabetes (*n* = 169). However, while exposure levels are well characterized using serum-based measure of TCDD, the primary limitation of this study is that the analysis is essentially cross-sectional. The measurement of serum levels of TCDD occurred following onset of diabetes for many of the veterans. On the other hand, associations between dioxin exposure and diabetes during the most recent follow-up interval were dependent on serum based TCDD exposures taken much earlier in 1987. In short, the findings did not account for the timing of the exposure in relation to when diabetes was diagnosed. Therefore, the associations may be noncausal. As noted by the authors, the onset of diabetes may have affected dioxin levels via the increased solubility of dioxides within increased serum triglycerides. Diabetes is recognized to increase triglyceride levels, and adjustment for triglycerides attenuated the findings in this study. Unlike the earlier study by Henriksen et al. (1997), this study excluded the Ranch Hand workers that had considerably higher exposures. The much smaller range in exposures along with the potential for serum triglycerides to affect dioxin levels implies that there is a greater potential for exposure misclassification across the groups used in this study than those used by Henriksen et al (1997).

The ascertainment of incident diabetes relied on either a self-reported measure with confirmation through medical records, or a postglucose challenge serum test. These are valid methods to identify cases of diabetes mellitus. The possibility existed that those with lower dioxin levels may have been less likely to participate in the follow-up examination, thereby, leading to an under-ascertainment of diabetes among those with lower dioxin level. However, given a positive association was noted based on 1992 examination alone, and that participation

rates among those with 1987 dioxin less than the median was 91%, this potential source of bias would likely be modest.

C.1.2.1.7.2.3. *Suitability of data for TCDD dose-response modeling*

The use of the individual-level TCDD serum measures and the identification of diabetes through medical records and objective serum tests are strengths of this study, however, the potential noncausal role of serum triglycerides cannot be dismissed. Additionally, there is uncertainty in determining the critical window of exposure. This was essentially a cross-sectional analysis of diabetes in relation to a single point-in-time measure of TCDD background exposure level that may have occurred over an approximate 20-year interval. Considering the uncertainty in estimating the biologically relevant exposure window and the uncertainty in estimating peak exposures 20 years prior to measurement, a quantitative dose-response analysis was not conducted.

C.1.2.1.7.3. ***Michalek et al. (2001a)***

C.1.2.1.7.3.1. *Study summary*

Michalek et al. (2001a) examined the relationship between TCDD exposure and hematopoietic effects among veterans in the Air Force Health Study. A description of the overall study design has been described earlier, and can be found in the paper by Wolfe et al (1990). This study included both veterans in the Ranch Hand unit, as well as those in a comparison cohort who were not involved in the spraying of herbicides.

The study used data collected from medical examinations and self-reported questionnaires completed in 1982, 1985, 1987, and 1992. TCDD levels were estimated using serum collected in 1987, with some additional samples taken in 1992 for those who lacked TCDD measurements. In total, TCDD was assayed for 2,198 veterans. TCDD levels below the limit of detection were assigned a value of 0 ppt. The study excluded veterans with no TCDD measure, those with TCDD levels above the level of detection but below the level of quantification, and comparison subjects whose TCDD levels exceeded 10 ppt serum lipid (threshold for background exposure). A first order kinetics model with a constant half-life of 8.7 years was used to estimate the initial TCDD dose at the end of the veterans' tours of duty in Southeast Asia. Veterans were classified into four dioxin exposure groups: comparison cohort,

Ranch Hand—Background (<10 ppt), Ranch Hand—Low (10− ≤94 ppt), and Ranch Hand—High (>94 ppt).

At each of the four physical examinations, the following hematological characteristics were measured: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, white blood cell count, platelet count and erythrocyte sedimentation rate. Veterans who participated in at least one examination, and who had a TCDD measurement were included unless they had a fever (body temperature greater than 100°F) or they tested positive for human immunodeficiency virus.

Michalek et al. (2001a) applied a linear regression model (adjusted for other covariates) to calculate estimated mean differences in the various hematological measures among the comparison group and the three other exposure groups. An adjusted test for trend was also applied to the restricted group of Ranch Hand veterans. Logistic regression was used to estimate the adjusted odds ratio for abnormally high or low hematological characteristics across TCDD exposure categories. The measures of association were adjusted for the percentage of body fat, year of birth, race, military occupation, and life-time smoking patterns. A secondary analysis of mean corpuscular volume adjusted for current alcohol consumption was undertaken.

There were no statistically significant differences in the mean values for red blood cell counts, hematocrit, and white blood cell counts across the TCDD exposure categories in any of the four examination periods. For three of the four examination periods, there was no association observed between TCDD and hemoglobin. Relative to the comparison group, the mean corpuscular volumes were elevated among those in the highest exposure category in all examination periods, while platelet counts were higher in three of the four periods. Overall, corpuscular volumes were about 1% higher among the most highly exposed Ranch Hands compared to the comparison cohort, while the corresponding increase was 4% with platelet counts.

Logistic regression analysis of abnormal red blood cell counts across TCDD exposure categories was hampered by small sample sizes. Typically, there were fewer than four abnormalities in each of the four examination periods. In contrast, there was some evidence for abnormally high platelet counts, abnormally high mean corpuscular volume, and abnormally high hematocrit in the highest Ranch Hand exposure group in some, but not all examination periods.

Michalek et al. (2001a) suggested that the increased corpuscular volumes may be explained by the noncausal effects of TCDD on serum triglycerides. Other possible explanations are also available for these associations, such as increased gamma-glutamyl transferase.

C.1.2.1.7.3.2. *Study evaluation*

Strengths of the study included an assessment of dioxin at an individual-level using serum based measures, a lengthy follow-up period that extended 30 years postservice, multiple physical examination, and the use of valid methods of hematological function. There are some uncertainties in the estimation of TCDD exposure given serum was drawn decades after the exposure period. Exposure misclassification may have been introduced from measurement error in exposure estimates due to variations in metabolism, use of an assumed half-life of TCDD, and calculations based on first-order decay. The authors note considerable uncertainty in the classification of the Background Ranch Hand veteran group as it comprised a mixture of exposed and unexposed individuals. However, it is hard to gauge whether any exposure misclassification would be differential by the health endpoints that were examined.

For the most part, there were no associations between hematological measures and TCDD exposure. As noted by the authors, the associations between TCDD and mean corpuscular volume may not be causally related. It may be a spurious association due to the influence of TCDD on triglycerides levels which in turn affect corpuscular volume, or be due to an increased prevalence of liver impairment previously noted in the cohort (Grubbs et al., 1995). The positive association between TCDD and platelet count cannot be attributed directly to TCDD given that many health conditions, which were not controlled for in the analysis, may have influenced platelet levels. Furthermore, the relationships identified are not supported by other animal or epidemiologic literature, making interpretation of the associations difficult.

C.1.2.1.7.3.3. *Suitability of data for TCDD dose-response modeling*

There was no consistent association between TCDD serum levels and the hematological measures of red and white blood cell counts, hemoglobin, hematocrit, and erythroctyes. While corpuscular volume and platelet counts were both positively associated with TCDD levels at multiple examinations, evaluations of the data did not determine whether increases in these measures were due to TCDD exposure during the Vietnam War. These increases may be due to

noncausal associations from increased levels of triglycerides, or increased prevalence of mild liver abnormalities among those with higher exposures (Grubbs et al., 1995), or the presence of other comorbid health conditions that were not controlled for in the analysis. The findings of associations that were small in magnitude between hematological function and TCDD likely have little clinical relevance, but could provide some insight on biological mechanism of disease from exposure to dioxin.

This study analyzes the potential for associations between point-in-time measures of TCDD serum levels and changes in hematological measures that may have occurred at any time over approximately a 30-year interval, which precludes estimation of an effective TCDD exposure over time. EPA is uncertain whether TCDD-mediated changes in hematological measures are the consequence of an elevated TCDD exposure event over a relatively short period of exposure (during service) or chronic TCDD exposure over a longer window of time due to slow TCDD elimination rates. Also, the long potential exposure window occurred during a time period of decreasing background exposure to TCDD and DLCs (Lorber and Phillips, 2002) likely decreasing the accuracy of the estimated exposure levels. Given the uncertainty in defining the critical window of exposure and the inability to estimate an effective TCDD exposure over time, quantitative dose-response analysis was not conducted for this study.

C.1.2.1.7.4. ***Michalek et al. (2001b)—hepatic health outcomes***

C.1.2.1.7.4.1. *Study summary*

Michalek et al. (2001b) investigated the association between TCDD and the prevalence of liver disease, and other indices of hepatic function in the Air Force Health Study. The study population included both Ranch Hands, as well as a comparison group of veterans. A detailed description of the study design and methods is provided in earlier sections, as well as the paper by Wolfe et al. (1990).

This study relied on data collected at physical examinations conducted in 1982, 1985, 1987, and 1992. TCDD levels were estimated using serum collected in 1987, with some additional samples taken in 1992 for those who lacked TCDD measurements. In total, TCDD was assayed for 2,198 veterans. TCDD levels below the limit of detection were assigned a value of 0 ppt. The study excluded veterans with no TCDD measure, those with TCDD levels above the level of detection but below the level of quantification, and comparison subjects whose

TCDD levels exceeded 10 ppt serum lipid (threshold for background exposure). A first order kinetics model with a constant half-life of 8.7 years was used to estimate the initial TCDD dose at the end of the veterans' tours of duty in Southeast Asia. Veterans were classified into four dioxin exposure groups: (i) Comparison cohort, (ii) Ranch Hand—Background (<10 ppt), (iii) Ranch Hand—Low (10− ≤94 ppt), and (iv) Ranch Hand—High (>94 ppt).

At each examination, participants were asked whether (1) a physician had informed them that they had an enlarged liver, cirrhosis, or other liver condition (2) a physician had determined presence or absence of hepatomegaly by palpitation, or (3) the presence or absence of liver function test abnormalities through laboratory examination. All self-reported cases of liver disease were confirmed through verification of medical records through 1993. In 1992, several indices of liver function were measured using serum. These include: alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, lactic dehydrogenase, alkaline phosphatase, and total bilirubin

Michalek et al. (2001b)conducted statistical analysis for the measures of liver function collected during the 1992 examination, since they state that "the liver function test results for 1992 were not consistently different from those of previous examination." Mean values of liver function were compared across the four categories of exposure using a linear model with a log-transformation of liver function measures to enhance normality. An adjusted test for trend was also applied to the restricted cohort of Ranch Hands veterans. All analysis was adjusted for the history of liver disease, percentage of body fat, year of birth, race, military occupation, lifetime industrial chemical exposure, lifetime degreasing chemical exposure, as well as life-time smoking and alcohol consumption. Enlisted Ranch Hands who had served in the ground crew were analyzed separately because this subgroup was found to have the highest TCDD exposure. The numbers of veterans included in the analysis of liver function tests across Comparison, Background, Low and High TCDD exposure groups were 1195, 398, 262, and 264, respectively. Logistic regression was used to evaluate the association between TCDD exposure and the prevalence of liver diseases. These analyses were done among those who volunteered for at least one examination, with valid dioxin measures, and excluded those with a history of liver disease before their service in Southeast Asia. The numbers of veterans included in the analysis of liver disease prevalence across Comparison, Background, Low and High TCDD exposure groups was 1,266; 420; 284; and 283, respectively.

There was no association between TCDD exposure and hepatomegaly, or nonalcoholic chronic liver disease (p-value linear test for trend=0.6). TCDD exposure was found to be associated with other liver disorders. Compared to non-Ranch Hand veterans, the adjusted odds ratio in the "high" exposure group was 1.6 (95% CI = 1.2−2.1). Laboratory measures associated with these disorders were also found to be increased. An increased level(s) of transaminase or lactate dehydrogenase was found in veterans in the "high" exposure group (OR = 2.7, 95% CI = 1.4−5.1), and a dose-response trend was noted across exposure categories ($p = 0.03$). Additionally, an increased odds ratio for nonspecific liver abnormalities was found in the same "high" exposure group (OR = 1.4, 95% CI = 1.0−2.0), while no association was noted for hepatomegaly. There were no statistically significant dose-response trends between TCDD and any of the mean hepatic measures (AST, ALT, GGT, LDH, Alkaline phosphatase, or total bilirubin) based on the 1992 serum data, although p-values for tests of trends for alkaline phosphatase and γ-glutamyltransferase (GGT) were 0.06. Statistically significant increases ($p < 0.05$) in mean GGT levels were noted among those in the highest TCDD exposure group relative to the comparison cohort. No consistent patterns were detected when results were stratified by drinking history or current alcohol use, but GGT levels tended to increase across current drinking levels,

C.1.2.1.7.4.2. *Study evaluation*

Strengths of this study include the high rate of participation, low attrition rate, appropriately matched comparison group, and the decade long follow-up period. Within some of the exposure categories, relatively few cohort members were diagnosed with several of the liver conditions following their tours of duty. For example, there were only 10 veterans in the high exposure group diagnosed with hepatomegaly, and only 5 diagnosed with nonalcoholic liver disease and cirrhosis. As such, the statistical power to detect some associations that may be present was limited.

C.1.2.1.7.4.3. *Suitability of data for TCDD dose-response modeling*

The results do not unequivocally support a relationship between liver damage and TCDD exposure. Confounding and reverse causality cannot be eliminated as possible explanations of the study results, and the clinical significance of the results (which were small in magnitude) is

unclear. Additionally, there is uncertainty in determining the critical window of exposure. This study analyzes the potential for associations between point-in-time measures of TCDD serum levels and possible changes in hepatic measures that may have occurred at any time over approximately a 30-year interval. Thus, it is unclear whether the differences in serum enzyme levels and liver function measures potentially affected by TCDD exposures are the consequence of an elevated TCDD exposure event over a relatively short period of exposure (during service) or chronic TCDD exposure over a longer window of time due to slow TCDD elimination rates. Also, the long potential exposure window occurred during a time period of decreasing background exposure to TCDD and DLCs (Lorber and Phillips, 2002) further impeding the ability to estimate dose accurate. Considering the uncertainty in estimating the biologically relevant exposure window and the uncertainty in estimating peak exposures 20 years prior to measurement, a quantitative dose-response analysis was not conducted.

C.1.2.1.7.5. ***Michalek et al. (2001c)—peripheral neuropathy***

C.1.2.1.7.5.1. *Study summary*

Michalek et al. (2001c) studied the relationship between TCDD exposure and peripheral neuropathy among veterans in the Air Force Health Study. The study included the Ranch Hands who were involved in the spraying of herbicides in Southeast Asia, as well as a comparison cohort of veterans. The study population and design has been described earlier in this section, and is detailed in the publication by Wolfe et al. (1990).

This study relied on data collected at physical examinations conducted in 1982, 1985, 1987, 1992 and 1997. TCDD levels were estimated using serum collected in 1987, with some additional samples taken in 1992 for those who lacked measures. In total, TCDD was assayed for 2,198 veterans. TCDD levels below the limit of detection were assigned a value of 0 ppt. The study excluded veterans with no TCDD measure, those with TCDD levels above the level of detection but below the level of quantification, and comparison subjects whose TCDD levels exceeded 10 ppt serum lipid (i.e., the threshold for background exposure). A first-order kinetics model with a constant half-life of 8.7 years was used to estimate the TCDD levels at the end of the veterans' tours of duty in Southeast Asia. Veterans were classified into four dioxin exposure groups: (i) Comparison cohort, (ii) Ranch Hand—Background (<1 ppt), (iii) Ranch Hand—Low (10− ≤94 ppt), and (iv) Ranch Hand—High (>94 ppt).

Blinded neurological examinations were conducted on volunteers at each of the five examinations by staff who were blinded to the veterans' exposure levels. These neurological examination included evaluations of cranial nerves, muscle strength in both lower and upper limbs, sensory perception of pain, light touch, vibration, proprioception, activity of deep tendon reflexes, stance, gait, hand and foot coordination, and tremor. Velocities of nerve conduction were conducted in 1982, while vibrotactile thresholds of the left and right toes were measured in 1992 and 1997. The study excluded veterans with a history of neurological disorders prior to their service in Southeast Asia. The analysis also excluded veterans with disorders that could interfere with peripheral nerve assessments. These conditions included: quadriplegia, injuries or amputations, and alcohol-related disorders. Diabetes status was also determined as described by Longnecker and Michalek (2000). Michalek et al. (2001c) analyzed data using main effects logistic and linear regression models. An adjusted test for trend was also applied. All measures of association were adjusted for body mass index, year of birth, height, and alcohol consumption. As in the Michalek et al. (2001b) study, enlisted Ranch Hands who had served in the ground crew were analyzed separately. Diabetics and nondiabetics were also analyzed separately. Furthermore, the data was analyzed in two rounds, with the second round excluding veterans with neurologic conditions with known causes unrelated to dioxin exposure, which could impact the neurological findings.

No association was observed between TCDD and nerve conduction velocities in 1982, and there were no statistically significant associations found for 'any symmetrical peripheral abnormalities' in 4 of the 5 examinations. However, based on the 1997 examination, those in the highest exposure category had an increased risk of any symmetrical peripheral abnormality (OR = 1.8, 95% CI = 1.2−2.7). These associations were stronger for 'probable' symmetrical peripheral neuropathy than they were for those designated as possible. There was no evidence of effect measure modification by diabetes status for TCDD associations with probable peripheral neuropathy in the 1997. An interaction was found between diabetes status and current dioxin exposure for diagnosed neuropathy in 1997. Additional restrictions excluding veterans with diseases, disorders or other exposures that may have produced neuropathic symptoms resulted in groups that were too small to further analyze.

C.1.2.1.7.5.2. *Study evaluation*

The strengths of this study are the same as described for the Michalek et al. (2001a; 2001b) studies. Uncertainty in the critical window of exposure, as well as uncertainty in exposure classification present in the Michalek et al. (2001b), are also weaknesses of this study. The Michalek et al. (2001c) study attempts to characterize risks of neuropathy while accounting for the possible modifying influence of diabetes. While the associations are strong, they are limited by the relatively small number of cases in the "high" exposure group. Moreover, associations were for the most part, confined to only one of the five examination intervals. A large number of comparisons were conducted in this study using multiple measures of neuropathy that were assessed at up to 5 examination periods. As a result, the multiple comparisons performed increase the chance of detecting a false-positive association due to the number of statistical hypothesis tests performed.

C.1.2.1.7.5.3. *Suitability of data for TCDD dose-response modeling*

The dose-response relationship between TCDD exposure and peripheral neuropathy is strong, and supported by several important strengths. However, associations were not consistent across the different examinations, and further work is needed to evaluate the relationship between diabetes and peripheral neuropathy in this cohort. Some comparisons are limited by a small number of outcomes particularly in the highest exposure group. Additionally, there is uncertainty in the critical window of exposure. This study analyzes the potential for associations between peripheral neuropathy and point-in-time measures of TCDD serum levels that may have occurred at any time over approximately a 30-year interval, making it difficult to calculate a TCDD effective dose over time. Thus, it is unclear whether the peripheral neuropathies are the consequence of an elevated TCDD exposure event over a relatively short period of exposure (during service) or chronic TCDD exposure over a longer window of time due to slow TCDD elimination rates. Also, the long potential exposure window occurred during a time period of decreasing background exposure to TCDD and DLCs (Lorber and Phillips, 2002) further impeding the ability to estimate dose accurately. For these reasons, a quantitative dose-response analysis was not conducted for this study.

C.1.2.1.7.6. ***Pavuk et al. (2003)—thyroid health endpoints***

C.1.2.1.7.6.1. *Study summary*

Pavuk et al. (2003) published an analysis that examined the effects of TCDD exposure on thyroid function among veterans enrolled in the AFHS. A summary of the design of the AFHS study and methods have been already described in this section, and are provided in greater detail in the paper by Wolfe et al. (1990). This current study included both those involved with Operation Ranch Hand, as well as a comparison cohort of other veterans who served in Southeast Asia but who were not involved with spraying of herbicides. The objective of this study was to examine associations between TCDD levels estimated in 1987 and several measures of thyroid function, as well the incidence of six different thyroid diseases following the completion of the veterans' tours of duty.

The study used data collected from medical examinations and self-reported questionnaires completed in 1982, 1985, 1987, 1992, and 1997. TCDD levels were estimated using serum collected in 1987, with some additional samples taken in 1992 and 1997 for those who lacked measures. For those with serum measures taken in 1992 or 1997, a first order kinetics model with a constant half-life of 8.7 years was used to extrapolate values to 1987. Veterans were classified into four dioxin exposure groups: comparison cohort, Ranch Hand—Background (<10 ppt), Ranch Hand—Low (10− ≤94 ppt), and Ranch Hand—High (>94 ppt).

Thyroid diseases that occurred following the veterans' tours of duty were identified through self-report of physician diagnosis at any of the five physical examinations and verified from medical records. The following conditions were considered: unspecified goiter, nontoxic nodular goiter, thyrotoxicosis, acquired hypothyroidism, thyroiditis, and other disorders of the thyroid. Congenital hypothyroidism was not examined as this condition would have prevented individuals from entering the military. Serum samples were used to obtain measures of thyroid function. T4 and TSH were estimated at each of the five examinations, while triiodothyronine percent (T3%) was determined in 1982, 1985, and 1987. The free thyroxine index (FTI) was only estimated in 1982. Veterans who participated in at least one examination, and who had a TCDD measurement were included unless they were being treated with thyroid medication, had a previous thryroidectomy or irradiation, or were diagnosed with a thyroid disease before their service had ended.

For each physical examination, cross-sectional analysis was performed to compare the mean levels of TSH, T4, T3%, and FTI across the four TCDD exposure categories. A repeated measures linear model was used to compare mean TSH, T4, and T3% values across exposure categories using data from all five examinations combined. This model took into account the repeated nature of the data by using an autoregressive order one covariance structure. Logistic regression was used to estimate the OR of thyroid diseases across TCDD exposure categories, as well as abnormally high TSH levels across the five examinations. These models were adjusted for confounding by age, race, and military occupation.

No association was found between TCDD and any of the six thyroid diseases that were examined. In four of the five examinations, higher TSH values were observed in the higher TCDD exposure categories. A dose-response relationship was observed in the longitudinal analyses of these data ($p = 0.002$). The ORs of an abnormally high TSH among the high exposure Ranch Hand group ranged from 1.4 to 1.9 relative to the comparison group, but was not statistically significant in any of the five examinations ($p > 0.05$). No significant associations were reported with either the cross-sectional or longitudinal analyses of the total T4 levels (mean), T3% uptake, or FTI.

C.1.2.1.7.6.2. *Study evaluation*

The overall size of the cohort was relatively large as analyses were based on 1,009 Ranch Hands, and 1,429 comparison veterans. However, there were relatively few thyroid disorders identified among these veterans following their tour of duty. Specifically, there were only 188 such veterans, and therefore, analyses of the relationship between these six different disorders and the four categories of TCDD exposure was limited by statistical power.

Strengths of this study include the estimation of TCDD levels using serum, and the consideration of several different outcome measures of thyroid disorders from questionnaire data, as well as serum TSH, T3% uptake, T4, and FTI measurements. Thyroid function was assessed multiple times using serum-based measures that are valid and widely used. While the authors did not take into account the timing of disease onset for the thyroid conditions examined, the serum-based measures of TCDD in 1987 allowed for veterans to be classified according to exposure status prior to onset of disease. In particular, these exposure levels among the Ranch

Hands could be attributed to exposure received during their tours in Southeast Asia, and only thyroid conditions that occurred following the tour of duty were considered.

There was no association found between serum-based measures of TCDD and any of the six thyroid conditions examined (unspecified goiter, nodular goiter, hyperthyroidism, thyroiditis, or other thyroid disease). The only thyroid measure that was associated with TCDD levels was TSH. Higher levels of TSH were observed among those in the higher exposure categories, and a dose-response relationship was observed when data across all examinations were modeled. However, those in the highest exposure group did not have a statistically significant increased risk of abnormal TSH levels irrespective of when the examination date. Taken together, the findings suggest that TCDD may increase TSH levels which are a marker for an underactive thyroid. Lower TSH levels over the long term may increase the risk of hypothyroidism, or indicate thyroid hormone resistance. However, the clinical implications are unclear in light of the absence of an association between TCDD and any of the six thyroid conditions that were examined. As noted by the authors, this cohort may not yet be old enough to determine whether TCDD exposure increases the risk of developing thyroid disease.

C.1.2.1.7.6.3. *Suitability of data for TCDD dose-response modeling*

There was no association between TCDD exposure and any of the six thyroid diseases that were examined. Further, there was no association between cross sectional or longitudinal analyses of TCDD and T4, T3% uptake, or FTI. While a dose-response trend was observed with TCDD and TSH levels, evidence of a statistically significant increase in abnormally high TSH levels was not observed among veterans in the highest exposure group. Additionally, there is uncertainty in the critical window of exposure. This study examined associations between thyroid conditions and measures of thyroid disorders with point-in-time measures of TCDD serum levels that may have occurred at any time over approximately a 30-year interval. As a whole, these analyses do not support an association between TCDD exposure and comprised thyroid function, and therefore, a quantitative dose-response analysis was not conducted for this study.

C.1.2.1.7.7. ***Michalek and Pavuk (2008)—diabetes***

C.1.2.1.7.7.1. *Study summary*

Michalek and Pavuk (2008) examined both the incidence of cancer and the prevalence of diabetes in the cohort of Ranch Hand workers exposed to TCDD. As noted previously, these veterans were responsible for aerial spraying of Agent Orange in Vietnam between 1962 and 1971. Exposure to TCDD was estimated using serum collected from (1) participants in 1987 or (2) participants in 1992, 1997, and 2002 for those who had no quantifiable TCDD result in 1987, those who refused in 1987, and those subjects who were new to the study. Exposure to TCDD was estimated using a first-order pharmacokinetic model with a half-life of 7.6 years and provided an estimate of TCDD at the end of the tour of duty in Vietnam. Veterans were grouped into four categories: comparison, background, low, and high. Diabetes was identified from diagnoses during the post-Vietnam era from medical records. Overall, no differences were shown in the RR of diabetes between the Ranch Hand unit and the reference group (RR = 1.21, $p = 0.16$). Stratified analyses by days of spraying (<90 days, ≥90 days), however, revealed a significant increase in risk of diabetes (RR = 1.32, $p = 0.04$) among those who sprayed for at least 90 days. A dose-response relationship was also evident when $\log_{10}$TCDD was modeled in the combined cohort. Also, stratification by calendar period showed a dose-response relationship for those whose last year of service was during or before 1969.

C.1.2.1.7.7.2. *Study evaluation*

The Michalek and Pavuk (2008) study provides an opportunity to characterize risks of diabetes as the study is not subject to some of the potential bias of case ascertainment based on death certificates (D'Amico et al., 1999). The quality of the TCDD exposure estimates is good, given that serum data were available at an individual-level basis for all Ranch Hand and comparison veterans used in the cohort. However, there is significant uncertainty in the biologically-relevant critical window of exposure. Also, the long lag between initial exposure and sera measurements limits the estimation of peak exposures 20 years earlier.

C.1.2.1.7.7.3. *Suitability of data for TCDD dose-response modeling*

The reported dose-response relationship between TCDD and diabetes in the Michalek and Pavuk (2008) study is supported by study strengths, including the use of the individual-level

TCDD serum measures and the identification of diabetes through medical records. However, it is unclear whether the diabetes cases are the consequence of an elevated TCDD exposure event over a relatively short period of exposure (during service) or chronic TCDD exposure over a longer window of time due to slow TCDD elimination rates. In addition, the long potential exposure window occurred during a time period of decreasing background exposure to TCDD and DLCs (Lorber and Phillips, 2002) further impedes the ability to estimate dose accurately. For these reasons, a quantitative dose-response analysis was not conducted for this study.

C.1.2.1.8. *Other noncancer studies of TCDD*

See general summaries of the Netherlands and New Zealand cohorts in Section C.1.1.1.7.

C.1.2.1.8.1. ***Ryan et al. (2002)—sex ratio***

C.1.2.1.8.1.1. *Study summary*

Ryan et al. (2002) conducted an investigation on the sex ratio in offspring of pesticide workers who were involved with the production of trichlorophenol and the herbicide 2,4,5-T in Ufa, Bashkortostan, Russia. Ufa was the site of a state agrochemical plant that has been in operation since the 1940s. Between 1961 and 1988, the plant employed more than 600 workers, most in their early 20s. Females, however, accounted for about 15% of the workforce that produced 2,4,5-T and 30% for 2,4,5-trichlorophenol.

Serum samples previously taken in 1992 among 60 men, women, and children from the factory and city of Ufa showed TCDD exposures that were approximately 30 times higher than background levels (Ryan and Schecter, 2000). Blood data were subsequently measured on a sample of 20 workers between 1997 and 2000, and on 23 2,4,5-trichlorophenol workers between 1997 and 2001. In all, 84 individuals (67 men and 19 women) who provided blood samples formed the basis of the analysis in this study. Of these, 55 (43 men and 12 women) were exposed to 2,4,5-T and 29 (22 men and 7 women) were exposed to 2,4,5-trichlorophenol. There is no indication on how the individuals that were asked to provide and those who did provide serum samples were selected. Ryan et al. (2002) reviewed company records for these workers to determine the number, sex, and date of birth of any children; birth data were available for 198 workers (150 men and 48 women). Awareness of the study led other workers who had not

provided serum to provide information on births that occurred 9 months after the time of first employment in the factory.

The authors calculated descriptive statistics for the 198 workers and compared them to values for the city of Ufa between 1959 and 1996. Tests of statistical significance were made using the z-test, and the chi-square test. The observed proportion of male births (0.40) among the factory workers was much lower than that for the city of Ufa (0.51) ($p < 0.001$). Stratified analyses revealed that this lower ratio was observed only among those paternally exposed to TCDD. Specifically, the proportion of male births among exposed fathers was 0.38 and among exposed mothers was 0.51. This pattern was observed in both the workers exposed to 2,4,5-T (proportion of male births = 0.40) and 2,4,5-trichlorophenol (proportion of male births = 0.35).

C.1.2.1.8.1.2. *Study evaluation*

The Ryan et al. (2002) findings are consistent with earlier work completed for Seveso residents (Mocarelli et al., 2000). Although individual-level serum measures were available for 84 individuals, exposure-response relationships with birth ratios were not performed on these data. This approach would have been preferred and consistent with that which Mocarelli et al. (2000) used. All comparisons were made using an external comparison group, namely the sex ratio observed in Ufa between 1959 and 1996.

Although serum measures were used to describe TCDD exposure for a sample of the workers (selection criteria for these workers was not provided), individual-level dose estimates were not calculated for the study population. Specifically, exposures were characterized many years after exposure, and no attempt was made to back-extrapolate to the time of conception. The two groups of workers in the study also reportedly had high exposure levels of 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin. So, the group level exposure classification (by plant) did not allow consideration of potential confounding due to other DLCs. Another limitation of the study is that the study population is likely nonrepresentative of all workers employed at the plant. Participants included only those willing to provide serum samples and those who volunteered to participate in the study after learning about it in a public forum. If participation was dependent on TCDD exposures and the reproductive health of these subjects, then bias may have occurred.

C.1.2.1.8.1.3. *Suitability of data for TCDD dose-response modeling*

The findings are notable in their consistency with those found in Seveso residents by Mocarelli et al. (2000). For the Ryan et al. (2002) study, serum data were quantified at an individual-level basis. Risk estimates, however, were not derived in relation to these exposures but instead in two separate subgroups (2,4,5-T and 2,4,5-trichlorophenol workers). Because of this important limitation and the uncertainty in the biologically-relevant critical window of exposure, a quantitative dose-response analysis was not conducted for this study.

C.1.2.1.8.2. ***Kang et al.(2001)—long-term health effects***

C.1.2.1.8.2.1. *Study summary*

Kang et al. (2001) investigated the relationship between self-reported health measures and serum-based measures of TCDD in a group of 1,499 Vietnam veterans and a control group of 1,428 non-Vietnam veterans. The study subjects were identified from (1) reports of Army Chemical Corps detachments in Vietnam between 1966 and 1971, (2) personnel records of individuals involved in chemical operations who were on active duty between 1971 and 1974, and (3) class rosters of personnel who were trained at Fort McClellan in Alabama between 1965 and 1973. The comparison group was selected so that branch of service, time period, and military occupation were similar to those of the subjects with the exception that they did not serve in Vietnam. Although 2,872 Vietnam veterans and 2,732 non-Vietnam veterans were identified as potential subjects, those who were deceased as of December 1998 and those who had previously participated in a pilot study were excluded. The study targeted 2,247 Vietnam and 2,242 non-Vietnam veterans.

Exposure to TCDD was characterized for subsets of the study population that provided blood samples, specifically 795 of 1,085 (73%) Vietnam veterans and 102 of 157 (65%) non-Vietnam veterans. Details on these individuals selected for participation in the serum dioxin study were not presented. The authors did state, however, that due to economic constraints, only 897 serum samples could be analyzed. Blood specimens were collected in 1999–2000 at individuals' homes. TCDD concentrations were analyzed by laboratory staff blind to the group status (i.e., Vietnam or non-Vietnam) of the study subjects.

Prevalent health outcomes were ascertained by self-reported information on selected conditions diagnosed by a medical doctor. The following conditions were included: diabetes,

hepatitis (all types combined), heart disease, all cancer, nonmalignant chronic respiratory diseases, and hypertension. Health-related quality of life was evaluated using the SF-36 survey instrument (Ware et al., 1993).

Eligible veterans whose current residences (4,119 total) could be identified were contacted for study participation. Survey participation rates were 73% for Vietnam veterans, yielding data for 1,499 individuals, and 69% for non-Vietnam veterans, yielding data for 1,428 non-Vietnam veterans. The survey data showed that, relative to non-Vietnam veterans, Vietnam veterans were more likely to be regular smokers and to be obese. They also were more likely to be enlisted personnel, and a much higher proportion was 51 years of age or older (83% vs. 58%). After adjusting for age, race, smoking status, rank, and body mass index, the prevalence of self-reported health conditions was found to be statistically significantly higher in the Vietnam group. The adjusted ORs were as follows: diabetes, OR = 1.16 (95% CI = 0.91, 1.49); hepatitis, OR = 1.85 (95% CI = 1.30, 2.64); heart condition, OR = 1.09 (95% CI = 0.87, 1.38); all cancer, OR = 1.46 (95% CI = 1.02, 2.10); nonmalignant respiratory condition, OR = 1.41 (95% CI = 1.13, 1.76); and hypertension, OR = 1.06 (95% CI = 0.89, 1.27).

For those with Vietnam service, the mean serum TCDD concentrations were higher among those who reported spraying herbicides (4.3 ppt) than those who did not (2.7 ppt) ($p < 0.001$). The investigators did not back-extrapolate serum levels to the time when individuals last sprayed. The adjusted ORs (adjusted for age, cigarette smoking, body mass index, rank, and race) for most chronic health conditions examined revealed increased prevalence among Vietnam sprayers relative to non-Vietnam sprayers. These ORs included: diabetes, OR = 1.49 (95% CI = 1.10, 2.02); hepatitis, OR = 1.40 (95% CI = 0.92, 2.12); heart condition, OR = 1.41 (95% CI = 1.06, 1.89); all cancer, OR = 1.36 (95% CI = 0.91, 2.04); nonmalignant respiratory condition, OR = 1.57 (95% CI = 1.20, 2.07); and hypertension, OR = 1.26 (95% CI = 1.00, 1.58).

The investigators also examined the possibility of over-reporting of chronic health conditions by comparing the prevalence of self-reported conditions among 357 Vietnam sprayers who mean serum TCDD levels of 2.5 ppt compared to those who had levels less than 2.5 ppt. Prevalence of diabetes, heart condition, and hypertension, was higher among those with mean serum TCDD levels of 2.5 ppt, although no levels of statistical significance were reported. Data for cancer were not presented.

C.1.2.1.8.2.2. *Study evaluation*

Data were collected from only half of the individuals in the study target population, so there is some potential for selection bias in this study. First, the study excluded those who had died before 1999, excluding potentially important TCDD-related adverse health effects that could result in death more than two decades after veterans had been actively spraying. Survey participation rates were 73% for Vietnam veterans and 69% for non-Vietnam veterans. If those in poorer health were less inclined to participate, the prevalence of the selected chronic health conditions would be understated. Selection bias due to study participation could also be possible if, for example, those in poorer health also had higher (or lower) exposures than those not participating in the study. The lack of direct evidence of differential participation and reports of comparable prevalence rates of hypertension and diabetes to other general populations suggests that selection bias may be minimal.

Because the data collected are cross-sectional, they are not well suited for evaluating the relationship between the timing of exposure and the onset of disease. Whether any of the data could help identify when the chronic health conditions were diagnosed is unclear. Given the long period covered by the study, many of the self-reported health conditions likely were diagnosed some time ago, perhaps closer to the time of potential TCDD exposure. Such detail is needed to characterize health risks associated with specific TCDD levels, particularly given that TCDD levels have been demonstrated to decrease from time of last exposure.

An important strength of the study is the availability of blood sera for a subset of the study population, which allows for individual-level estimates of TCDD exposure. Serum TCDD levels were available for only 897 subjects, however, which limits the ability to examine the relationship between measures of TCDD and prevalence of health outcomes without restricting the sample size or extrapolating exposure levels to the whole study population. For example, among sprayers with available TCDD exposure data only 60 cases of diabetes and 69 cases of heart disease were examined relative to exposure. Also, the small number of cancers precluded a site-specific cancer analysis. Moreover, whether these TCDD levels are representative of the larger eligible population is difficult to gauge, given that deceased veterans and those whose current residences could not be determined were excluded.

The study relied on self-reported measures of disease prevalence. The ascertainment of chronic health conditions using self-reported data can be fraught with difficulties. For example,

the sensitivity of self-reported data when compared to medical diagnosis has been shown to be poor for conditions such as diabetes and hypertension (Okura et al., 2004). As Kang et al. (2006) state, prevalence studies are not be well suited to examine rare diseases with short survival times such as cancer. In addition, self-report of physician-diagnosed cancers by study subjects often lacks the sensitivity needed in most epidemiologic studies as they can be influenced by a variety of factors including age and education (Navarro et al., 2006).

The potential for biases in the reporting of health outcomes between the sprayers and the non-Vietnam veterans (i.e., differential by TCDD exposure status) is plausible, given the public attention that spraying of Agent Orange has received. Although the authors examined whether over-reporting was related to outcome prevalence among herbicide sprayers (prior to collection and determination of actual TCDD serum levels), the possibility exists that these subjects reporting could be influenced by their perceived level of exposure from herbicide spraying. The authors also examined the potential for misreported diabetes by conducting a medical records review of 362 veterans. Seventy-nine percent of the self-reported diabetes cases were confirmed with medical records. The documentation rate was also comparable between the Vietnam veterans and the non-Vietnam veterans suggesting that differential reporting was not an issue for this health outcome.

Because the Vietnam veterans group comprised professional sprayers, it is not unreasonable to assume that they would have been exposed to other potentially harmful agents either during their service in Vietnam, or from the end of their service to when they provided data in 1999–2000. This study did not control for other, potentially relevant occupational exposures.

C.1.2.1.8.2.3. *Suitability of data for TCDD dose-response modeling*

Although the study demonstrates increased prevalence of several chronic health conditions, these findings should be interpreted with caution due to the potential for selection and recall biases. Because of the lack of demonstrated dose-response relationships with cancer or other outcomes and uncertainty in the biologically-relevant critical exposure window, a quantitative dose-response analysis was not conducted for this study.

C.1.2.1.8.3. ***McBride et al. (2009a) —noncancer mortality***

C.1.2.1.8.3.1. *Study summary*

The McBride et al. (2009a) mortality study of New Zealand workers employed as producer or sprayers with potential exposure to TCDD was described earlier in this report. These individuals were employed at a plant that manufactured 2,4,-dichlorophenoxyacetic acid, and later 2,4,5-T and 4-chloro-2-methyphenoxyacetic acid. In 1987, the plant closed and 2,4,5-T production ceased in 1988.

The cohort consisted of 1,754 individuals who were employed for at least one day at the New Plymouth site between January 1, 1969, and October 1, 2003. Vital status was determined until the end of 2004, and 247 deaths occurred during this time period. Comparisons of mortality were made to the New Zealand general population. Exposure was characterized by duration of employment. Person-years of follow-up were tabulated across strata defined by age, calendar period, duration of employment, sex, latency, and period of hire. Analyses were stratified to compare risks by duration of employment (<3 or ≥3 months), latency (<15 or ≥15 years), and period of hire (<1976 or ≥1976).

Overall, no statistically significant differences in all-cause mortality relative to the general population were found among those who worked for at least 3 months (SMR = 0.92, 95% CI = 0.80−1.06) or for less than 3 months (SMR = 1.23, 95% CI = 0.91−1.62). No statistically significant excesses were found for mortality from diabetes, cerebrovascular disease, heart disease, or accidents. The incorporation of a latency period of 15 years revealed no statistically significant excesses for these same causes of death. Similarly, no excesses for any cause of death were noted among those who were hired either before or after 1976.

In subsequent analyses of the same cohort that used estimated TCDD levels from serum samples, McBride et al. (2009b) found no excesses for all-cause mortality or mortality from diabetes or heart disease.

C.1.2.1.8.3.2. *Study evaluation*

For the McBride et al. (2009a) study, the size of the cohort is large enough to characterize mortality risks relative to the general population for most common causes of deaths. An important limitation of this study is the loss to follow-up of a substantial percentage of workers (22%). This would have impacted statistical power by reducing the number of deaths among the

workers. If this incomplete ascertainment of mortality outcomes did not occur in a similar fashion with the general population then the results may also be biased.

For noncancer causes of death, the use of the SMR statistic is more likely to be influenced by the healthy-worker effect. Therefore, the findings obtained for these outcomes should be interpreted with caution. Subsequent analyses published by the same authors (McBride et al., 2009a) provide improved characterization of TCDD exposure using serum samples.

C.1.2.1.8.3.3. *Suitability of data for dose-response analysis*

Overall, no associations were evident between surrogate measures of TCDD (duration of employment, year of hire) and noncancer mortality outcomes. As all outcomes were based on mortality, dose-response modeling was not conducted for this study.

C.1.2.1.8.4. ***McBride et al. (2009b)—noncancer mortality***

C.1.2.1.8.4.1. *Study summary*

McBride et al. (2009b) further analyzed the cohort of New Zealand workers to include estimates of TCDD exposure based on serum samples. Current and former employees who were still alive and living within 75 km of the site were asked to provide serum samples. Samples were collected from 346 workers representing 22% (346/1599) of the entire study population. These serum measures were used to estimate cumulative TCDD levels for all workers. The exposure assessment approach by Flesch-Janys et al. (1996) was used to estimate time-dependent exposures based on area under the curve models. This was based on a one-compartment first-order kinetic model with a half-life of 7.2 years.

Comparisons of mortality were made to the general population using the SMR. The Cox proportional hazards model was used to conduct an internal cohort analysis across four categories of cumulative TCDD levels for diabetes and ischemic heart disease mortality. The RRs generated from these models were adjusted for sex, hire year, and birth year. No diabetes deaths were observed among women, and therefore, analysis of this outcome was limited to men.

Relative to the general population, no difference in the all-cause mortality experience was observed in exposed cohort members (SMR = 1.0, 95% CI = 0.9−1.2). Similarly, no excess in

these workers was observed for heart disease (SMR = 1.1, 95% CI = 0.9−1.5); cerebrovascular disease (SMR = 1.1, 95% CI = 0.6−1.9); diabetes (SMR = 0.7, 95% CI = 0.2−2.2); or nonmalignant respiratory disease (SMR = 0.8, 95% CI = 0.4−1.4). For the internal cohort analysis, the RR associated with cumulative categorical TCDD measure was 1.0 for both diabetes and ischemic heart disease.

C.1.2.1.8.4.2. *Study evaluation*

The McBride et al. (2009b) study extends their earlier work in two ways. First, serum measures were used to estimate cumulative TCDD with methodology that has been applied to several other cohorts of workers exposed to TCDD. Second, they used regression analyses that examined individual-level TCDD exposures in relation to various outcomes as part of the internal cohort comparisons. For noncancer outcomes, no dose-response associations with TCDD were observed with the internal comparisons. Also, as found with earlier analyses of this same cohort, no excess noncancer mortality relative to the New Zealand general population was observed.

Associations between TCDD and diabetes have been found previously in TCDD-exposed populations, most notably in the Ranch Hands cohort (Michalek and Pavuk, 2008). In this cohort, only five deaths from diabetes were identified, and of these, only three occurred among those who were exposed to TCDD. The study, therefore, has limited statistical power to characterize associations between TCDD and mortality from diabetes. Further, the identification of diabetes deaths is subject to misclassification errors due to under-reporting (McEwen et al., 2006).

C.1.2.1.8.4.3. *Suitability of data for TCDD dose-response modeling*

McBride et al. (2009b) found no statistically significant associations in any of the noncancer causes of death. As all outcomes were based on mortality, dose-response modeling was not conducted for this study.

C.1.2.2. *Feasibility of Dose-Response Modeling for Noncancer*

Relatively few study populations permit quantitative dose-response modeling to be performed for noncancer outcomes. The serum collected among Seveso men and women

provide an opportunity to characterize risks for several health conditions in relation to TCDD exposure. The collection of these serum samples, shortly after the accident does not require the back-extrapolation of TCDD levels as in the occupational cohorts, which should reduce the exposure assessment uncertainty and minimize the potential for exposure misclassification.

An added feature of the SWHS is the detailed collection of other risk factor data from trained interviewers. These data allow for risk estimates to be adjusted for potential confounding variables. For the evaluations of reproductive health outcomes, this adjustment is critical given there are various documented risk factors for the different outcomes that were examined. For some health outcomes, continued follow-up of the cohort is needed, given that several of the Seveso studies suggest that those exposed at a very young age might be more susceptible to subsequent adverse health effects.

The findings of positive associations and dose-response relationships with serum-based measures of TCDD suggest several noncancer health outcomes could be associated with TCDD exposure. These health outcomes include neonatal thyroid function, sex ratio, diabetes, and semen quality. Although findings have suggested an association between TCDD and age at menopause, they were not statistically significant and no dose-response trend was observed. Weak or nonstatistically significant associations have been noted for endometriosis and menstrual cycle characteristics and do not support quantitative dose-response analyses.

Associations between TCDD exposure and cardiovascular disease have been noted in some, but not all, of the occupational cohorts, and also shortly after the accident among Seveso residents. Findings from the cohort studies based on external comparisons using the SMR statistic should be interpreted cautiously due to potential bias from the healthy worker effect. Because the magnitude of the healthy worker bias is recognized to be larger for cardiovascular diseases than for cancer outcomes, risk estimates in some occupational cohorts might be underestimated for cardiovascular outcomes. Information on cardiovascular risk factors generally was not captured in these studies, and sensitivity analyses were generally designed to examine risk estimates generated for cancer outcomes.

C.1.2.3. *Summary of Epidemiologic Noncancer Study Evaluations for Dose-Response Modeling*

All epidemiologic noncancer studies summarized above were evaluated for suitability of quantitative dose-response assessment using the TCDD-specific considerations and study

inclusion criteria. The results of this evaluation are summarized in a matrix style array (see Table C-3). The key epidemiologic noncancer studies suitable for further TCDD dose-response assessment are presented in Table 2-2 in Section 2 of this document.

Table C-1. Summary of epidemiologic cancer studies (key characteristics)

Publication	Length of follow-up	Latency period	Half-life for TCDD	Fraction of TEQs accounted for by TCDD
NIOSH Cohort				
Fingerhut et al. (1991a)	1942−1987	0, 20 years	N/A	N/A
Steenland et al. (1999)	1942−1993	0, 15 years	N/A	N/A
Steenland et al. (2001b)	1942−1993	0, 15 years	8.7 years (Michalek et al., 1996)	TCDD accounted for all occupational TEQ; 10% of background
Cheng et al. (2006)	1942−1993	0, 10, 15 years	8.7 years (Michalek et al., 1996), and CADM (Aylward et al., 2005a)	N/A
Collins et al. (2009)	1942−2003	None	7.2 years (Flesch-Janys et al., 1996)	N/A
BASF Cohort				
Thiess et al. (1982)	1953−1980	None	N/A	N/A
Zober et al. (1990)	1953−1987	Years since first exposure: 0−9, 10−19, and 20+	N/A	N/A
Ott and Zober (1996a)	1953−1991	None	5.8 years	N/A
Hamburg Cohort				
Manz et al. (1991)	1952−1989	None, used duration of employment (<20, >20 years)	N/A	N/A
Flesch-Janys et al. (1995)	1952−1992	None	7.2 years Flesch-Janys et al. (1994)	Mean TEQ without TCDD was 155 ng/kg; mean TEQ with TCDD was 296.5 ng/kg
Flesch-Janys et al. (1998)	1952−1992	None	7.2 years Flesch-Janys et al. (1996), also used decay rates that were function of age and fat composition	Mean concentration of TCDD was 101.3 ng/kg; for TEQ (without TCDD) mean exposure was 89.3 ng/kg
Becher et al. (1998)	1952−1992	0, 5, 10, 15 and 20 years	7.2 years Flesch-Janys et al. (1996) took into account age and fat composition	Not described

Table C-1. Summary of epidemiologic cancer studies (key characteristics) (continued)

Publication	Length of follow-up	Latency period	Half-life for TCDD	Fraction of TEQs accounted for by TCDD
Seveso Cohort				
Bertazzi et al. (2001)	1976−1996	Periods postexposure: 0, 0−4, 5−9, 10−14, 15−19 years	N/A	N/A
Warner et al. (2002)	1976−1998	None	8 years (Pirkle et al., 1989)	N/A
Pesatori et al. (2003)	1976−1996	Period postexposure: 20 years	N/A	N/A
Baccarelli et al. (2006)	1976−1998	Period postexposure: 22 years	N/A	N/A
Consonni et al. (2008)	1976−2001	Periods postexposure: 0, 0−4, 5−9, 10−14, 15−19, 20−24 years	N/A	N/A
Chapaevsk Cohort				
Revich et al. (2001)	Cross-sectional study (1995−1998)	N/A	N/A	N/A
Ranch Hand Cohort				
Akhtar et al. (2004)	1962−1999	None	N/A	N/A
Michalek and Pavuk (2008)	1962−2004	None, but stratified by period of service	7.6 years	N/A
New Zealand Cohort				
t'Mannetje et al. (2005)	1969−2000 (herbicide producers); 1973−2000 (herbicide sprayers)	N/A	N/A	N/A
McBride (2009b)	1969−2004	None	N/A	N/A
New Zealand Cohort (continued)				
McBride et al. (2009b)	1969−2004	None	7 years	N/A
Dutch Cohort				
Hooiveld et al. (1998)	1955−1991	Postexposure periods: 0−19 years, >19 years	7.1 years	N/A

Table C-2. Epidemiologic cancer study selection considerations and criteria

	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect	Individual-level exposures	Study size and follow-up adequate	Published in peer-reviewed literature.	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
Cancer	**Considerations**					**Criteria**			**Y/N**
NIOSH Cohort									
Fingerhut et al. (1991a) all cancer sites, site-specific analyses	√	X	X	X	√	√	X	√	N
Steenland et al. (1999) all cancer sites combined, site-specific analyses	√	√	√	√	√	√	√	√	N[a]
Steenland et al. (2001b) all cancer sites combined	√	√	√	√	√	√	√	√	Y
Cheng et al. (2006) all cancer sites combined	√	√	√	√	√	√	√	√	Y
Collins et al. (2009) all cancer sites combined, site-specific analyses	√	√	√	√	√	√	√	√	Y
BASF Cohort									
Thiess et al. (1982) all cancer sites combined, site-specific analyses	√	X	X	X	X	√	X	X	N

Table C-2. Epidemiologic cancer study selection considerations and criteria (continued)

Cancer	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect,	Individual-level exposures	Study size and follow-up adequate	Published in peer-reviewed literature.	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
	Considerations					Criteria			Y/N
BASF Cohort (continued)									
Zober et al. (1990) all cancer sites combined, site-specific analyses	√	√	X	X	X	√	X	X	N
Ott and Zober (1996a) all cancer sites combined	√	√	√	√	√	√	√	√	Y
Hamburg Cohort									
Manz et al. (1991) all cancer sites combines, site-specific analyses	√	√	√	√	√	√	X	√	N
Flesch-Janys et al. (1995) all cancer sites combined	√	√	√	√	√	√	√	X	N
Flesch-Janys et al. (1998) all cancer sites combined, site-specific analyses	√	√	√	√	√	√	√	√	N[b]
Becher et al. (1998) all cancer sites combined	√	√	√	√	√	√	√	√	Y
Seveso Cohort									
Bertazzi et al. (2001) all cancer sites combined, site-specific analyses	√	√	√	X	√	√	√	X	N
Warner et al. (2002) - SWHS breast cancer incidence	√	√	√	√	√	√	√	√	Y
Pesatori et al. (2003) all cancer sites combined, site-specific analyses	√	√	X	X	√	√	X	X	N
Baccarelli et al. (2006) - SWHS site specific analysis	√	√	X	√	√	√	√	√	N[c]

Table C-2. Epidemiologic cancer study selection considerations and criteria (continued)

Cancer	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect,	Individual-level exposures	Study size and follow-up adequate	Published in peer-reviewed literature.	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
	Considerations					Criteria			Y/N
Consonni et al. (2008) all cancer sites combined, site-specific analyses	√	√	√	X	√	√	√	X	N
Chapaevsk Cohort									
Revich et al. (2001) all cancer sites combined, site-specific analyses	X	X	X	X	√	√	X	X	N
Ranch Hands Cohort									
Akhtar et al. (2004) all cancer sites combined, site-specific analyses	√	√	√	√	√	√	√	√	Y
Michalek and Pavuk (2008) all cancer sites combined	√	√	√	√	√	√	√	√	Y
Dutch Cohort									
Hooiveld et al. (1998) all cancer sites combined, site-specific analyses	√	X	√	√	X	√	√	X	N
New Zealand Cohort									
t' Mannetje et al. (2005) all cancer sites combined, site-specific analyses	√	X	√	√	√	√	X	X	N
McBride et al. (2009b) all cancer sites combined, site-specific analyses	√	√	X	√	√	√	√	X	N
McBride et al. (2009a) all cancer sites combined, site-specific analyses	√	X	X	√	X	√	X	X	N

Table C-2. Epidemiologic cancer study selection considerations and criteria (continued)

[a]This study has been superseded and updated by Steenland et al. (2001b).
[b]Becher et al. (1998) assessed this same cohort taking cancer latency into account, thereby superseding this study.
[c]It is unknown whether the frequency of t(14;18)translocations in lymphocytes relates specifically to an increased risk of non-Hodgkin lymphoma. Given this lack of obvious adverse effect, dose-response analyses for this outcome were not conducted.

√ = Consideration/criterion satisfied; X = Consideration/criterion not satisfied.

Table C-3. Epidemiologic noncancer study selection considerations and criteria

	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect	Individual-level exposures	Study size and follow-up adequate		Published in peer-reviewed literature	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
Noncancer	**Considerations**						**Criteria**			**Y/N**
NIOSH Cohort										
Steenland et al. (1999) mortality (noncancer) -ischemic heart disease	√	X	√	√	√		√	√	X	N
Collins et al. (2009) mortality (noncancer)	√	√	X	√	√		√	√	X	N
BASF Cohort										
Ott and Zober (1996a) mortality (noncancer)	√	√	X	√	√		√	√	X	N
Hamburg Cohort										
Flesch-Janys et al. (1995) mortality (noncancer)	√	√	√	√	√		√	√	X	N
Seveso Cohort–SWHS										
Eskenazi et al. (2002b) menstrual cycle characteristics	√	√	√	√	√		√	√	√	Y
Eskenazi et al. (2002a) endometriosis	√	√	X	√	X		√	√	X	N

Table C-3. Epidemiologic noncancer study selection considerations and criteria (continued)

Noncancer	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect	Individual-level exposures	Study size and follow-up adequate	Published in peer-reviewed literature	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
	Considerations					Criteria			Y/N
Seveso Cohort–SWHS (continued)									
Eskenazi et al. (2003) birth outcomes	X	X	X	√	√	√	√	X	N
Warner et al. (2004) age at menarche	√	√	X	√	√	√	√	√	N[a]
Eskenazi et al. (2005) age at menopause	√	√	X	√	√	√	√	X	N
Warner et al. (2007) ovarian function	√	√	X	√	√	√	√	X	N
Eskenazi et al. (2007) uterine leiomyoma	√	√	√	√	√	√	√	X	N
Seveso Cohort–Other Studies									
Bertazzi et al. (2001) mortality (noncancer)	√	√	X	X	√	√	√	X	N
Consonni et al. (2008) mortality (noncancer)	√	√	X	X	√	√	√	X	N
Seveso Cohort–Other Studies (continued)									
Mocarelli et al. (2000) sex ratio	√	√	√	√	√	√	√	X	N
Baccarelli et al. (2004; 2002) immunological effects	√	√	X	√	√	√	√	X	N
Landi et al. (2003) gene expression	√	√	X	√	X	√	√	X	N
Alaluusua et al. (2004) developmental dental defects	√	√	√	√	√	√	√	√	Y
Baccarelli et al. (2005) chloracne	√	√	√	√	√	√	√	√	N[b]
Baccarelli et al. (2008) neonatal thyroid function	√	√	√	√	√	√	√	√	Y

Table C-3. Epidemiologic noncancer study selection considerations and criteria (continued)

	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect	Individual-level exposures	Study size and follow-up adequate		Published in peer-reviewed literature	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
Noncancer	**Considerations**						**Criteria**			**Y/N**
Mocarelli et al. (2008)										
semen quality	√	√	√	√	√		√	√	√	Y
Chapaevsk Study										
Revich et al. (2001) mortality (noncancer) and reproductive health	X	X	X	X	√		√	X	X	N
Ranch Hands Cohort										
Henriksen et al. (1997) diabetes	√	X	√	√	√		√	√	X	N
Longnecker and Michalek (2000) diabetes	√	X	√	X	√		√	√	X	N
Michalek et al. (2001a) hematological effects	√	X	X	√	√		√	√	X	N
Michalek et al. (2001b) hepatic abnormalities	√	X	√	√	√		√	√	X	N
Michalek et al. (2001c) peripheral neuropathy	√	X	√	√	X		√	√	X	N
Pavuk et al. (2003) thyroid function and disorders	√	√	X	√	X		√	√	X	N
Michalek and Pavuk (2008) diabetes	√	√	√	√	√		√	√	X	N
Ufa Cohort										
Ryan et al. (2002) sex ratio	X	X	X	X	√		X	X	X	N
Vietnam Veterans Cohort										
Kang et al. (2001) long-term health consequences	X	X	X	√	√		√	X	X	N
New Zealand Cohort										
McBride et al. (2009a) mortality (noncancer)	√	X	X	√	√		√	X	X	N

Table C-3. Epidemiologic noncancer study selection considerations and criteria (continued)

	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect	Individual-level exposures	Study size and follow-up adequate		Published in peer-reviewed literature	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
Noncancer	**Considerations**						**Criteria**			**Y/N**
McBride et al. (2009b)										
mortality (noncancer)	√	√	X	√	X		√	√	X	N

[a]EPA cannot assess the biological significance of this finding and cannot establish a LOAEL for this effect.
[b]Chloracne is considered to be an outcome associated with high TCDD exposures; thus this study was not considered further in RfD derivation.
√ = Consideration/criterion satisfied. X = Consideration/criterion not satisfied.

C.2. EVALUATION TABLES FOR CANCER STUDIES

C.2.1. NIOSH Cohort Studies

Table C-4. Fingerhut et al. (1991a)—All cancer sites, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The data sources to ascertain vital status and cause of death information were the Social Security death files, the National Death Index, and the Internal Revenue Service. Vital status could be determined for 98% of the cohort.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. While the authors provide compelling arguments that suggest risks are not unduly biased by lack of cigarette smoking data, they acknowledge potential biases that could exist for other occupational exposure (e.g., asbestos) for which data were lacking.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. There was not a statistically significant linear trend of increasing mortality with increased duration of exposure.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. This study used duration of exposure, at an individual level, as a surrogate measure of TCDD. Duration of exposure determined by number of years workers were involved in processes involving TCDD contamination. Exposure was determined by reviewing, at each plant, operating conditions, job duties, records of TCDD levels in industrial hygiene samples, intermediate reactants, products, and wastes. Exposure assessment was limited and the uncertainty related to exposure measures not fully addressed.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. This is the largest of the occupational cohorts that has been exposed to TCDD. The cohort consisted of 5,172 workers and a total of 265 cancer deaths. Site-specific mortality analyses, including soft tissue sarcoma (n = 4), was limited by small numbers.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. New England Journal of Medicine, 1991; 324:212–218. Authors address the possibility of bias from lack of control for potential confounders such as smoking and other occupational exposures. They address limitations of using death certificates for identifying certain causes of deaths, and limitations of using duration of employment as an exposure metric.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Since this study used duration of exposure as the exposure metric, dose-response relationships cannot be quantified.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Models incorporated period of latency, and a surrogate measure of cumulative TCDD exposure was modeled. The follow-up interval was sufficiently long (1942–1987).
Conclusion	Overall, quantitative exposure data are lacking on an individual-level basis. Further dose-response analysis should consider updated data for this cohort that includes serum-based measures of TCDD, in addition to an extension of the follow-up period. Given these limitations, this study is not further evaluated for TCDD dose-response assessment.

Table C-5. Steenland et al. (1999)—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The study evaluated mortality from all cancer sites (combined). As described in the paper, the sources of vital status and cause of death information were received from the Social Security death files, the National Death Index, and the Internal Revenue Service. Vital status was known for 99.4% of the cohort members, cause of death information is available for 98% of the decedents.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Occupational exposure to asbestos and 4-aminobiphenyl contributed to some excess cancer, but no evidence of confounding for the relationship between TCDD and all cancer mortality was detected following removal of workers who died of bladder cancer. No information is available for cigarette smoking, although dose-response patterns were stronger for nonsmoking related cancers. This finding suggests that smoking is not responsible for excess cancer risk that was observed in the cohort.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. When a 15-year lag interval was incorporated into the exposure metric a statistically significant dose-response pattern was observed for all cancer sites combined with both a continuous measure of TCDD ($p = 0.05$) as well as one that was log-transformed ($p < 0.001$).
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The study conducted detailed sensitivity analyses and evaluated different assumptions regarding latency, log-transformed TCDD exposures, and half-life values for TCDD.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. This is the largest of the occupational cohorts with exposures to TCDD. The cohort consisted of 5,132 male workers and a total of 377 cancer deaths. This permits characterization of risk for all cancer sites (combined).
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Journal of the National Cancer Institute, 1999; 91(9):779–786. The authors discussed the potential for bias from smoking, and other occupational exposures for which data for both were lacking at an individual basis.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Exposure scores assigned on an individual level using a job-exposure matrix (JEM). The job-exposure matrix was based on estimated factor of contact with TCDD in each job, level of TCCD contamination of materials at each plant over time, and proportion of day worker could be in contact with materials. These factors were multiplied together to derive a daily exposure score, which was accumulated over the working history of each worker to obtain a cumulative measure of TCDD.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. The follow-up of the cohort extended from 1942 until the end of 1993. Greater than 25 years of follow-up have accrued in cohort allowing for latency to be examined. Different assumptions on the half-life of TCDD were evaluated and produced similar results. Latency intervals were incorporated, with strongest associations noted with an interval of 15 years.
Conclusion	This study meets the criteria and considerations noted above but has been superseded and updated by Steenland et al.(2001b). Therefore, this study was not considered for further dose-response analyses.

Table C-6. Steenland et al. (2001b)—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The study evaluated mortality from all cancer sites (combined). As described by Steenland et al. (1999) the sources of vital status and cause of death information were received from the Social Security death files, the National Death Index, and the Internal Revenue Service. Vital status was known for 99.4% of the cohort members, cause of death information is available for 98% of the decedents.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Occupational exposure to asbestos and 4-aminobiphenyl contributed to some excess cancer, but no evidence of confounding for the relationship between TCDD and all cancer mortality was detected following removal of workers who died of bladder cancer. No information is available for cigarette smoking, although dose-response patterns were similar between smoking and nonsmoking related cancers. There is no available information in the study to determine how representative the 199 workers were of the overall workers in that plant, or the potential for this to result in exposure misclassification.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Increased risk estimates were observed in the higher cumulative exposure categories. The dose-response curve was not linear at higher doses.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Exposure metrics considered included cumulative TCDD, log10TCDD, average exposure, and a cubic spline model was also evaluated. Exposure response relationships were also evaluated using TEQs. Exposure scores were assigned on an individual level using a job-exposure matrix. The job-exposure matrix was based on estimated factor of contact with TCDD in each job, level of TCCD contamination of materials at each plant over time, and proportion of day worker could be in contact with materials. Serum levels were measured in 199 workers at one of 8 plants in 1998. Different estimate of the half-life of TCDD were used, and similar results were produced. The paper presented a range in risk estimates thereby conveying the range of uncertainties in risk estimates derived using different measures of exposure.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. This is the largest of the occupational cohorts with exposures to TCDD. The cohort consisted of 3,538 male workers and a total of 256 cancer deaths.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 2001, 154(5):451–458. However, additional details to assess uncertainties associated with characterizing serum data in a subset of workers to remainder of cohort are lacking.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. The metrics considered included cumulative TCDD, log10TCDD, average exposure, and a cubic spline model was also evaluated. Exposure response relationships were also evaluated using TEQs. Serum lipid TCDD measurements from 170 workers whose TCDD levels were greater than 10 ppt (the upper ranges of a background level) were used along with JEM information, work histories, and a pharmacokinetic elimination model to estimate dose rates per unit exposure score. In this regression model, the estimated TCDD level at the time of last exposure was modeled as a function of exposure scores. The coefficient relating serum levels and exposure scores was then used to estimate serum TCDD levels over time from occupational exposure (minus the background level) for all 3,538 workers. Time-specific serum levels were then integrated over time to derive a cumulative serum lipid concentration due to occupational exposure for each worker.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Greater than 25 years of follow-up have accrued in cohort allowing for latency to be examined. Different assumptions on the half-life of TCDD were evaluated producing similar results.

Conclusion	Overall, criteria have been satisfied. This study was modeled in the 2003 Reassessment and is considered for further dose-response evaluations herein.

Table C-7. Cheng et al. (2006)—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The study evaluated cancer mortality. The vital status and the information regarding the cause of death were extracted from the Social Security death files, the National Death Index, and the Internal Revenue Service (Steenland et al., 1999). Vital status was known for 99.4% of the cohort members, while cause of death information is available for 98% of the decedents.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. This is the same data set used in the Steenland et al. (2001b) paper. Occupational exposure to asbestos and 4-aminobiphenyl contributed to some excess cancer, but no evidence of confounding for the relationship between TCDD and all cancer mortality was detected following removal of workers who died of bladder cancer. No information is available for cigarette smoking, although dose-response patterns were similar between smoking and nonsmoking related cancers.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Slope coefficients are available for all cancers combined under a varying set of assumptions. Little evidence of an association was found when lag interval was not taken into account. Associations strengthened with incorporation of a 10 to 15 year lag interval. Dose response was nonlinear at higher exposures, suggesting a nonlinear relationship or increased exposure misclassification at higher levels.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Compared to the 1st order models, the CADM provided a better fit for the serum sampling data. CADM exposure estimates are higher than those based on an age only, constant 8.7-year half-life model. As discussed by Aylward et al. (2005b), model exposure estimates are influenced not only by choice of elimination model, but also by choices in regression procedure (e.g., log transformation, use of intercept, and incorporation of background dose term). Other limitations or uncertainties in exposure assessment include the following Job-exposure matrix based on limited sampling data, and subjective judgment on contact times and factors Inability to take into account interindividual variability in TCDD elimination kinetics Dose-rate regressions are based on a small sample of the cohort with serum measures; therefore, regression results may not be representative of remainder of the cohort.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Largest cohort of TCDD exposed workers. The risk estimates are based on a total of 256 cancer deaths.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Risk Analysis, 2006; 4:1,059–1,071. Additional details to assess uncertainties associated with characterizing serum data can be found in Aylward et al. (2005b); Risk Anal. 25(4):945–956.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Cumulative serum lipid concentrations were estimated for each worker. No other DLCs were assessed in this analysis.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Concentration and age-dependence of TCDD elimination and two compartments (hepatic and adipose tissue) were taken into account when estimating TCDD exposures. Nearly 50 years of follow-up were available permitting an evaluation of latency.
Conclusion	This study met the main criteria and considerations. The study is considered for further dose-response analyses.

Table C-8. Collins et al. (2009)—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Vital status complete for all but two workers.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. No information collected on smoking status, but no excess in lung cancer or nonmalignant respiratory diseases noted. Analyses took into account potential for exposure to pentachlorophenol.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. No dose-response pattern was observed with all cancer sites combined, however, a dose-response pattern was observed with soft tissue sarcoma. The study found no association between TCDD and death from most types of cancer.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The authors used serum from 280 former TCP workers to estimate historical exposure levels of TCDD, furans, and polychlorinated biphenyls (PCBs) for all 1,615 workers. Exposure assessment included detailed work history, industrial hygiene monitoring, and the presence of chloracne cases among groups of workers. This data was integrated into a 1-compartment, first-order pharmacokinetic to determine the average TCDD dose associated with jobs in each group, after accounting for the presence of background exposures estimated from the residual serum TCDD concentration in the sampled individuals. The authors did not evaluate departures from linearity, or examine skewness at higher exposures. Exposure levels were not provided.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Largest study of workers employed in one center, and a total of 177 deaths from cancer were observed. Limited precision in the relative risk estimate was noted for soft tissue sarcoma and TCDD exposures.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in Am J Epidemiol, 2009, 170(4):501–506. The authors discuss limitations of using death certificates for identifying deaths from soft tissue sarcoma for which a positive association was noted, assumptions in exposure characterization, and effects of cigarette smoking.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. This study has the largest number of serum samples obtained from a specific plant.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Although specific analyses of latency were not reported, this cohort had a sufficient length of follow-up for cancer mortality outcomes.
Conclusion	The authors found a statistically significant dose-response trend for soft tissue sarcoma mortality and TCDD exposures. The all-tumor results are not amenable to dose-response analysis because they found no effect. Therefore, this study is considered for quantitative dose-response analysis for the soft tissue sarcoma mortality results, only.

C.2.2. BASF Cohort Studies

Table C-9. Zober et al. (1990)—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. A large component of the cohort (94 out of 247 workers) was assembled by actively seeking out workers who were alive in 1986 through the "Dioxin Investigation Programme." As a result, it is likely a number of deaths were missed due to the recruitment of survivors. This underascertainment is supported by much lower all cancer SMR one component of the cohort (SMR = 0.48, 95% CI = 0.13–1.23) relative to the general population.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. See above discussion of underascertainment in mortality for some of the cohort members. Although it is likely that other coexposures occurred (e.g., among firefighters), confounding could only occur if these coexposures were associated with both the endpoint and exposure (TCDD) being considered.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Workers were not categorized on the basis of their exposure, but rather their mortality experience compared to control cohort and the general population. The design of the study does not allow for dose response to be examined.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. Although years since first exposure was examined, exposure assessment was based on working in various occupational cohorts. Since there was no quantitative assignment of TCDD exposures, the associated uncertainties could not be evaluated.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied. There were only 23 cancer deaths in the entire cohort. As such, this study lacked adequate statistical power to detect cancer mortality differences that were moderate in magnitude.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Int Arch Occup Environ Health, 1990, 62:139–157. The authors address issues related to the healthy worker effect, multiple comparisons, smoking, and small size of the cohort.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Risks were derived by comparing mortality rates of the three cohort subsets relative to a control cohort and the general population by time since first exposure categories. Workers were not assigned exposures. There were no quantitative estimates of TCDD exposure.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. While the study was able to indirectly look at variations in risk estimates related to latency by using time since exposure, there were no quantitative estimates of TCDD exposure.
Conclusion	This study is not suitable for dose-response analysis, as it failed the inclusion criteria. Most notably, the lack of exposure data does not permit the use of these data for a dose-response analysis.

Table C-10. Ott and Zober (1996a)—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Mortality ascertainment appeared to be fairly complete. The ascertainment of cancer incidence is more difficult to judge as geographical area not covered by a cancer registry.
2. Consideration	Risk estimates are not susceptible to important biases.

Response	Consideration satisfied. Information was collected on smoking status, body mass index (BMI), and other occupational exposures, however a large portion of the cohort was firefighters who may have been exposed to other occupational carcinogens. However, the recruitment of survivors may results in under-ascertainment of mortality.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Increased cancer incidence was observed in the highest TCDD cumulative exposure category. Risks were most pronounced when a period of 20 years since first exposure was incorporated into the model.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Cumulative measure of TCDD expressed was derived from serum measures. Exposure was also estimated by chloracne status of the cohort members. The authors have not addressed the potential implication of deriving TCDD exposure estimates for the whole cohort using sera data that were available for only about half of the cohort.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 31 deaths. It is the smallest of the occupational cohorts, but the deaths can be grouped into quartiles to allow for evaluation of dose-response relationships.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Occupational and Environmental Medicine, 1996, 53:606–612. A large component of the cohort (94 out of 247 workers) was assembled by actively seeking out workers who were alive in 1986 through the "Dioxin Investigation Programme." As a result, it is likely a number of deaths were missed due to the recruitment of survivors. This underascertainment is supported by much lower all cancer SMR one component of the cohort (SMR = 0.48, 95% CI = 0.13–1.23) relative to the general population (Zober et al., 1990).
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum samples, taken in 1989, were available for 138 surviving workers out of 254 and allowed for cumulative TCDD levels to be estimated using regression techniques in the remainder of the cohort.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Exposure assignment took into the affect that body mass index had on TCDD half-lives. TCDD levels estimates through back-extrapolation of serum levels based on half-life estimates obtained from previous studies. Latency was considered with stronger association observed in external comparisons incorporating a latency of 20 years. The follow-up of the cohort was lengthy (>50 years).
Conclusion	Given a part of the cohort was based solely on survivors in the in the mid-1980s, the SMR statistic derived from this study underestimates excess mortality relative to the general population. The cohort also includes some firefighters who are recognized to be exposed to other carcinogenic agents—these exposures may be confounding the associations that were reported. However, exposure to TCDD was quantified and the effective dose and oral exposure estimable. Overall, criteria have been satisfied. This study was modeled in the 2003 Reassessment and is considered for further dose-response evaluations herein.

C.2.3. The Hamburg Cohort

Table C-11. Manz et al. (1991)—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Deaths were identified through medical records of the cohort members. A review of death certificates of the identified cancer deaths found a high degree of concordance (51/54). One of the 136 noncancer death certificates examined indicated an "occult" neoplasm.

2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Smoking data were similar between exposed and nonexposed cohort based on independent samples. Occupational exposures for which individual data are lacking are unlikely to explain dose response with TCDD. The potential impacts of any exposure misclassification is hard to gauge, but the authors reported that some misclassification was likely given that 5 of the 37 workers classified in the high exposure group had adipose levels lower than background (20 ng/kg).
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Dose-response patterns across three levels of exposure observed among those who started work before 1954, and among those who worked for 20 years or longer. Dose-response patterns not evident across whole cohort, among those with less than 20 years of employment, or among those who started after 1954.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures..
Response	Consideration satisfied. Categorical exposures were based on TCDD concentrations in precursor materials, products, waste, and soil from the plant grounds, measured after the plant closed in 1984. Exposure uncertainty examined using a separate group of 48 workers who provided adipose tissue samples. Other surrogate measures of exposure were considered in this study, including duration of exposure and year of first employment.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 65 cancer deaths for the comparison to the comparison cohort of gas workers. The study is underpowered to look at site-specific cancers.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Lancet 1991, 338:959–964. The authors discussed the potential for misclassification from the use of death certificates, the healthy worker effect and the related use of a comparison cohort of gas supply workers, other occupational exposures present at the plant, potential impact and the lack of smoking data.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Exposure consisted of a large DLC component that was not quantified. Given crude TCDD exposure categorization data, no quantitative exposure metric was derived.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Exposure metrics were constructed that took into account duration of exposure, and periods when exposure was highest. However, exposure estimates did not consider lagged exposure.
Conclusion	This study is not amenable to further TCDD dose-response analysis and is not considered further here because it consisted of a large DLC component that was quantified and no quantitative exposure metric was derived. The dose-response patterns of risks observed across the three exposure groups provide compelling support for an association between TCDD and cancer mortality, particularly, given the associations observed when analyses restricted to those who were hired when TCDD exposures were known to be much higher, and among those who worked for at least 20 years. Subsequent studies improved the exposure assessment through the use of serum measures.

Table C-12. Flesch-Janys et al. (1995); Flesch-Janys et al. (1996) erratum—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Medical records used to identify deaths over the period 1952–1992.
2. Consideration	Risk estimates are not susceptible to important biases.

Response	Consideration satisfied. Similarity in smoking rates between control cohort and the exposed workers was similar based on independent surveys. Occupational exposures to benzene, and dimethyl sulfate were unlikely to bias dose-response pattern observed as these exposures occurred in production departments with low-medium levels of exposure.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Dose-response relationship observed across 6 exposure categories, with the cohort of gas supply workers used as the referent.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 124 deaths in the exposed cohort, and 283 in the cohort of gas supply workers. No site-specific cancers were examined in this paper.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 1995, 1442:1165–1175. The authors discuss the potential role of other occupational exposures (i.e., dimethyl sulfate, solvents, and benzene), smoking, and suitability of the comparison cohort of gas supply workers.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum and adipose tissues were used to estimate TCDD exposure in 190 workers. A one-compartment first-order kinetic model was used to estimate exposure at end of exposure for these workers. Regression methods were then used to estimates TCDD exposures for all workers.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Exposure was based on half-life estimates from individuals with repeated serum measures. Other dioxin-like compounds were considered with the TOTTEQ of polychlorinated dibenzo-p-dioxins and furans exposure metric. No consideration, however, was given to latency or lagged exposures.
Conclusion	The exposure data used within this study are well-suited to a dose-response analysis given the associations observed, the characterization of exposure using serum, and quality of ascertainment of cancer outcomes. However, subsequent methods have been applied to the cohort to derive different exposures to TCDD using area under the curve approaches, which updates the analysis herein. Therefore, subsequent studies (i.e., Becher et al., 1998) will supersede this evaluation.

Table C-13. Flesch-Janys et al. (1998)—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Mortality follow-up was extended until the end of 1992, an increase in 3 years from previous analyses of the cohort.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Exposure was well characterized using sera data. While serum samples provided only from a subsample of surviving workers, these levels were consistent with expected levels in different production departments. The authors examined other potential occupational coexposures (e.g., β-hexachlorocyclohexane) and indirectly examined the potential effect of smoking on the associations that were detected.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. A dose-response relationship across quartiles of TCDD was observed with cancer mortality based on the SMR statistic (SMRs = 1.24, 1.34, 1.34, 1.73), and a linear test for trend was statistically significant (p = 0.01).

4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The exposure measure was an integrated TCDD concentration over time estimate that back-calculated TCDD exposures to the end of the employment. Categorical and continuous TCDD exposures were examined in relation to the health outcome. These efforts improve the exposure assessment of earlier studies.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 124 cancer deaths.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environ Health Perspect, 1998, 106(2):655–662. The authors address uncertainties in the estimation of exposure, describe the potential for confounding from β-2,4,5-T, hexachlorocyclohexane, and cigarette smoking. In fact, they showed that blood levels of TCDD were not associated with smoking in a subsample suggesting little bias from lack of smoking data.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum samples, taken from 190 workers were used to derive TCDD levels for the entire cohort. Methods used to estimate exposure took into account elimination of TCDD during employment periods when exposure took place, and the methods of the area under the curve was used as it takes into account variations in concentration over time, and reflects cumulative exposure.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Exposure estimated based on half-lives observed in individuals with repeated samples. Area under the curve approach was used which is an improvement from past characterizations of exposure in this cohort.
Conclusion	The study provides data suitable for dose-response modeling. Derivation of exposure was done using current understanding of elimination of TCDD. Estimates of risks were derived from external comparisons to the general population that are unlikely to be biased by healthy worker effect, but risks generated using internal cohort comparisons would be preferable. Becher et al., (1998) assessed this same data taking cancer latency into account, therefore Flesch-Janys et al., (1998) will not be further considered for dose-response modeling.

Table C-14. Becher et al. (1998)—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Medical records used to identify deaths over the period 1952–1992. The follow-up interval was lengthy.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Risks adjusted for exposures to TEQ, β-hexachlorobenzene, and employment characteristics. Smoking was shown to be similar to the comparison cohort of gas workers.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. A variety of exposure measures for both TCDD and TEQs found positive associations with cancer mortality.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The exposure measure was an integrated TCDD concentration over time estimate that back-calculated TCDD exposures to the end of the employment. Categorical and continuous TCDD exposures were examined in relation to the health outcome. Different models explored the shape of the dose-response curve. These efforts improve the exposure assessment of earlier studies.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 124 cancer deaths.
1. Criteria	Study is published in the peer-reviewed scientific literature.

Response	Criteria satisfied. Environ Health Perspect, 1998, 106(2):663–670. The authors discuss uncertainties associated with their use of exposure metrics, inability to evaluate effects for PCDD/ PCDF other than dioxin due to high correlations with β-HCH, and inability to characterize risks associated with exposures in children.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. The authors derived a measure of cumulative dose as a time-dependent variable ("area under curve") using serum measures available in a sample of 275 workers.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. TCDD levels estimates through back-extrapolation of serum levels based on half-life estimates obtained from previous studies. Latency was considered, and a variety of exposure metrics including nonlinear relationships were evaluated.
Conclusion	In this paper, a variety of exposure metrics were found to be positively associated with cancer mortality. The additional lifetime risk of cancer corresponded to a daily intake of 1pg ranged between .01 and 0.001. This study was modeled in the 2003 Reassessment and is considered for further dose-response evaluations herein.

C.2.4. The Seveso Cohort Studies

Table C-15. Bertazzi et al. (2001)—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Mortality appears to be well captured from the vital statistics registries in the region (99% complete). Vital status was ascertained using similar methods for both the exposed and reference populations. Both cancer and noncancer mortality outcomes were evaluated. Ideally, would have evaluated incident rather than decedent outcomes for cancer.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Individual-level data on potential confounders (i.e., age, calendar period, and gender) were adjusted for. Information from other independent surveys suggests similarity between smoking behaviors across the regions. Comparison of cancer mortality rates before the time of the accident between the regions also revealed no differences.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied (for all cancers combined). No statistically significant excesses noted in Zone A, or Zone B relative to reference area. Evidence of an exposure-response relationship was detected for lymphatic and hematopoietic tissues by number of years since first exposure.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. Subjects were assigned to one of the zones (A, B, R, or reference) based on official residence on the day of the accident or at entry into the area. Exposure misclassification is likely and lack of individual-level data precludes an examination of this source of error.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. In total, 27, and 222, cancer deaths were found among residents of Zones A, and B, respectively. This allowed examined of gender-specific effects.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 2001 Jun 1; 153(11):1031–1044. Authors discuss completeness of mortality ascertainment, diagnostic accuracy of death certificates particularly with respect to diabetes, limited available of blood dioxin measures that did not permit estimation of TCDD dose on an individual-level basis.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.

Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying wherever excesses occurred among highly exposed populations, it is not precise enough to conduct a quantitative dose-response analysis.
Conclusion	The lack of individual-level exposure data precludes quantitative dose-response modeling using these data.

Table C-16. Pesatori et al. (2003)—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Mortality was ascertained from 1977−1996, and, as reported in other related manuscripts, appears to be well captured from the vital statistics registries in the region (99% complete). Cancer incidence data was available from 1977−1991.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Individual-level data on potential confounders (i.e., age, calendar period, and gender) were adjusted for.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Although risk of all cancer mortality was not associated with zone of residence, increased risk of cancer incidence was observed in Zone A. Among men, excess lymphatic and hematopoietic cancer incidence was observed in Zone A (primarily to non-Hodgkin lymphoma). Soft tissues sarcoma cancer incidence was also associated with residence in Zone R among males, but not the more highly exposed zones (A and B). Among females living in Zones A and B, higher rates were observed for multiple myeloma (RR = 4.9, 95% CI = 1.5−16.1), cancer of the vagina (RR = 5.5, 95% CI = 1.3−23.8), and cancer of the biliary tract (RR = 3.0, 95% CI = 1.1−8.2).
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. Subjects were assigned to one of the zones (A, B, R, or reference) based on official residence on the day of the accident or at entry into the area. Exposure misclassification is likely and lack of individual-level data precludes an examination of this source of error.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied for some endpoints, although several of the cancer specific mortality results among women were based on very small number of deaths (i.e., <5).
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Occup Environ Med, 1998; 55:126–131. Authors discuss limitations such as residency-based exposure assignment, absence of smoking, differential and death certification in exposed versus nonexposed areas.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.

Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying wherever excesses occurred among highly exposed populations, it is not precise enough to conduct a quantitative dose-response analysis.
Conclusion	No dose-response patterns evident in the study, and the study lacked quantifiable measures of TCDD at an individual-level basis. The data are not well suited for dose-response analysis.

Table C-17. Consonni et al. (2008)—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Mortality appears to be well captured from the vital statistics registries in the region (99% complete). Both cancer and noncancer mortality evaluated, although diagnostic accuracy of death certificates is likely low. Ideally, would have evaluated incident rather than decedent outcomes for cancer.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Individual-level data on potential confounders (i.e., age, calendar period, and gender) were adjusted for. Comparison of cancer mortality rates before the time of the accident between the regions also revealed no differences. Information from other independent surveys suggests similarity between smoking behaviors across the regions.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied for some outcomes. For all cancer sites combined, no evidence of dose response was observed relative to general population across Zones A, B and R. Only statistically significant excess found in Zone A was for chronic rheumatic disease but based on only three deaths. Higher cancer excesses were found in Zone A after a latency period was incorporated; however, no dose-response relationship observed with this latency period. Evidence of an exposure-response relationship was detected for lymphatic and hematopoietic tissues by zone of residence.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. Subjects were assigned to one of the zones (A, B, R, or reference) based on official residence on the day of the accident or at entry into the area. Exposure misclassification is likely and lack of individual-level data precludes an examination of this source of error.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. In total, 42, 244, and 1,848 cancer deaths were found among residents of Zones A, B, and R respectively.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 2008, 167:847–858. Authors discuss potential for selection bias, limitation of residential based measure of exposure, similarities of mortality ascertainment in exposed and referent populations, and multiple testing.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.

Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying wherever excesses occurred among highly exposed populations, it is not precise enough to conduct a quantitative dose-response analysis.
Conclusion	The lack of individual-level exposure data precludes quantitative dose-response modeling using these data.

Table C-18. Baccarelli et al. (2006)—Site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Polymerase chain reaction methods were used to describe outcome measures. The prevalence of t(14; 18) was estimated as those individuals having a t(14; 18) positive blood sample divided by the t(14; 18) frequency (number of copies per million lymphocytes).
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Questionnaire data were used to collect information on cigarette smoking. Other potential confounders (age, smoking status, and duration of smoking). In addition, both exposure and outcome were objectively and accurately measured.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Associations were detected between the frequency of t(14; 18) and plasma TCDD levels as well as zone of residence at the time of the explosion. No association was detected for these exposure measures and prevalence of t(14; 18). A dose-response trend was detected for TCDD and the mean number of t(14;18) translocations/10^6 lymphocytes, however the relevance of t(14; 18) in lymphocytes to non-Hodgkin lymphoma is uncertain.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The authors highlight that exposure metrics represent both past and current body burdens. They employ several different exposure metrics of TCDD: place of residence (Zone A, B, R or reference), categorical serum measures, a linear term, log (base 10) transformed TCDD, and individuals with chloracne diagnosed after the accident.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Analyses are made using 72 highly exposed, and 72 low exposed individuals.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Carcinogenesis, 2006, 27(10):2001–2007. The authors discuss the limitation of using t(14; 18) translocations as an outcome measure, and the uncertain role it plays in the development of non-Hodgkin lymphoma.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. A total of 144 subjects were included in the study. This included 72 subjects who had low exposures, and 72 who had high exposures based on serum concentrations.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. A variety of measures were employed including current TCDD levels, as well as surrogates of exposure at the time of the accident.
Conclusion	While an association was observed with the frequency of t(14; 18) translocation, it is uncertain whether this translates into an increased risk of non-Hodgkin lymphoma. Given the speculative nature of this endpoint and lack of demonstrated adverse effect, dose-response analyses for this outcome were not conducted.

Table C-19. Warner et al. (2002)—Breast cancer incidence

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Diagnoses of incident breast cancer were based on interview and information from medical records appears thorough. Of the 15 cases of breast cancer, 13 were confirmed by pathology and the remaining 2 by surgery report only. Three cases of breast cancer were excluded which represents a large proportion of the total cases identified. This would reduce sample size and could result in bias if the exclusion was association with TCDD exposure.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Information was collected on an extensive series of risk factors by using an interviewer administered questionnaire. Participation rates for the survey were fairly good (80%).
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Limited evidence (not statistically significant) of a dose response when TCDD was analyzed as a categorical variable; only one breast cancer case was in the referent exposure category. In the analysis of TCDD as a continuous measure ($\log_{10}$TCDD), the hazard ratio associated with a 10-fold increase in TCDD serum levels was 2.1 (95% CI = 1.0–4.6).
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures..
Response	Consideration satisfied. Different exposure metrics were considered in these analyses (categorical, continuous, measures on a log-scale). Exposure data are of high quality as they are based on serum samples taken among women near the time of the accident. As such, exposure assignment is not dependent on as many assumption as used in occupational cohorts were back-extrapolation for many years had to be performed.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration somewhat satisfied. Inadequate follow-up for cancer limited the number of cases available. Sample size also limited the conclusions draw from the categorical analysis based on very few cases for some exposure categories.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Paper published in Environ Health Perspect, 2002 Jul, 110(7):625–628. A major limitation of the study is the small number of incident cases of breast cancer (*n* = 15), important strengths of the study include characterization of TCDD using serum collected near the time of the accident.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum was used to estimate TCDD levels in 981 of 1,271 eligible women who had lived in either of the two contaminated sites in 1976. Data represent an objective measure of TCDD near the time of the exposure. Data obtained near the time of exposure which minimized the potential for exposure misclassification.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Exposure characterized using serum measures obtained close to the time of the accident.
Conclusion	While characterization of exposure and availability of other risk factor data at an individual-level basis are important strengths of this study, small sample size (*n* = 15 cases) based on inadequate follow-up is a key limitation. Quantitative dose-response analyses were conducted using this study, but continued follow-up of the study population or consideration of all cancer outcomes would be valuable.

C.2.5. The Chapaevsk Study

Table C-20. Revich et al. (2001)—All cancer sites combined, and site-specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration cannot be evaluated. Insufficient details are provided in the paper to gauge the completeness and coverage of the cancer registry and mortality data. Health outcomes were examined on the basis of information in the official medical statistics.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Given the aforementioned limitations of this ecological study, it is unclear to what extent the results may be subject to bias
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Dose response was not evaluated as exposure was based on residency in the region vs. no residency.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. No individual-level exposure estimates were used.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. A total of 476 cancer deaths were observed among males, and 376 cancer deaths observed among females. The precision of the SMRs is demonstrated with fairly narrow confidence intervals for many causes of death.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in Chemosphere, 2001, 43(4–7):951–966. Authors do not address the completeness of the mortality follow-up, and whether there are differences in mortality surveillance between regions. The authors do acknowledge, however, that new investigations being undertaken would characterize exposure using serum-based measures.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. It is a cross-sectional study that compares mortality rates between regions. No individual-level exposure data available.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. No individual-level exposure estimates were used in the study.
Conclusion	These cancer data are cross-sectional in nature; therefore, dose-response analyses were not conducted for this study.

C.2.6. The Air Force Health ("Ranch Hands") Study

Table C-21. Akhtar et al. (2004)—All cancer sites combined and site-specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Cancer incidence and mortality based on information from repeated medical examinations, medical records and death certificate.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. The risk estimates were adjusted for a number of factors measured on an individual level, including smoking.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. There is evidence of a dose response for all cancers and for some site-specific cancers (i.e., malignant melanoma, and prostate cancer).
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.

Response	Consideration satisfied. High quality exposure data for most veterans was collected, so extrapolation to other members of the cohort was not required. The serum dioxin measurements also correlated well with reported skin exposure to herbicide in Vietnam, but collection of the samples 25 years later required back-extrapolation.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. In total, 117 incidence cancers identified in the Ranch Hands cohort. For those sites with a dose-response association, malignant melanoma and prostate cancer, there were 16 and 34 incident cases, respectively.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in J Occup Environ Med, 2004, 46(2):123–136. Authors highlight that this is only cancer incidence study in US veterans, and the lengthy interval of follow-up (35-40 years)—both important strengths of the study. They addressed potential bias from healthy-worker effect, and uncertainties surrounding the estimation of TCDD exposure (extrapolation 30 years after exposure), as well as exposure to other chemical exposures. Study uses incident outcomes for cancer.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Individual exposure estimates are based on measurements of dioxin serum lipid concentrations. They were available for 1,009 Ranch Hands and 1,429 in the comparison cohort.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. TCDD exposures at the end of duty were estimated by back-extrapolating 1987 serum values.
Conclusion	This study is suitable for TCDD dose-response modeling of cancer outcomes data.

Table C-22. Michalek and Pavuk (2008)—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Cancer incidence was ascertained through the use of medical records. Death certificate were used to identify some malignancies. Little data is provided on the number of individuals lost to follow-up, however the same mechanisms of case ascertainment were applied to both the comparison and Ranch Hand cohorts.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Information collected from repeated physical examinations allowed for the adjustment of risk factors such as smoking and exposure related factors such military occupation and number of years served.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied for some comparisons. Statistically significant associations were noted with cancer incidence and TCDD when analyses were restricted to workers who served at most two years in Southeast Asia and those who sprayed more than 30 days before 1967.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Initial TCDD dose were estimated at the end of the tour of duty for the Ranch Hands. Individual-level serum dioxin measurements correlated well with correlated with days of spraying and calendar period of service, but collection of the samples roughly 20 years later required back-extrapolation.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. A total of 347 incident cases of cancer were used in the analyses. For stratified analyses, statistical power is more limited. For example, only 67 incident cancer in the subset of workers who spent less than 2 years in Southeast Asia, and sprayed for at least 30 days before 1967.
1. Criteria	Study is published in the peer-reviewed scientific literature.

Response	Criteria satisfied. J Occup Environ Med 2008; 50:330–340. The authors discuss issues related to exposure misclassification error, and suggest approaches for improving characterization of days of spraying. Congener specific data were unavailable, thereby not allowing for congener specific risks or adjustments to be made.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. TCDD data was available for 986 veterans in the Ranch Hand cohort, and 1,597 members of the comparison cohort.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. TCDD exposures at the end of duty were estimated by back-extrapolating 1987 serum values.
Conclusion	This study is suitable for TCDD dose-response modeling of cancer outcomes.

C.2.7. Other Studies of Potential Relevance to Dose-Response Modeling

Table C-23. 't Mannetje et al. (2005)—All cancer sites combined, site specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. National records for death registrations through the New Zealand Health Information Service. Subjects not registered as having died during the study period were confirmed to be actually alive and resident in New Zealand using the New Zealand Electoral Roll, drivers' license, and social security records.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Seventeen percent of workers were lost to follow up but it is unclear if bias resulted. The dichotomous exposure measure was based on exposure to TCDD, chlorinated dioxins and phenoxy herbicides, so confounding is a possibility by these coexposures.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Dose-response evidence for duration of employment and elevated mortality noted only in synthesis workers.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Exposure measures were limited to duration of employment and exposed/unexposed.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 43 cancer deaths among the production workers, and 35 such deaths among the sprayers. Site-specific cancer analyses are limited by small sample sizes.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria not satisfied. Occup Environ Med, 2005; 62:34–40. A high percentage of the cohort was lost to follow-up (17%). The authors fail to mention this important limitation in this paper.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. This study used duration of exposure, at an individual level, as a surrogate measure of TCDD.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Exposure was defined according to duration, and not concentrations of TCDD. Latency intervals were not evaluated.
Conclusion	Overall, quantitative exposure data are lacking for TCDD and limited dose-response relationships were observed across duration of exposure categories. Furthermore, confounding by coexposures is a possibility. Taken together, these data are not suitable for inclusion in a dose-response analysis

Table C-24. McBride et al. (2009a)—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The New Zealand Health Information Service Mortality Collection and the Registrar-General's Index to Deaths. Additional searches were based on the last known address from the work record; the electoral roll and the habitation index; the telephone book; the internet; and Terranet property information database. An additional search was carried out through the Births, Deaths, and Marriages office of the New Zealand Department of Internal Affairs. Lastly, automated personnel and pension records were also used to locate past New Plymouth workers and identify some deaths.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Considerable amount of workers were lost to follow up (22%), but it is unclear if bias resulted. The dichotomous exposure measure was based on exposure to TCDD, chlorinated dioxins and phenoxy herbicides, so confounding is a possibility by these coexposures.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Some SMRs for site-specific cancers were elevated but not statistically significant. There was no examination of dose-response effects.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Dichotomous exposure (exposed/unexposed) and duration of employment were examined from job exposure classification assessed via occupational history records industrial hygienists/factory personnel knowledge and questionnaires. Authors discuss limitations in the assignment of exposure among cohort members.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied. A low number of deaths (n = 76) may have limited ability to detect effects small in magnitude and exposure-response relationships.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in Occup Medicine, 2009; 59(4):255–263. The authors highlight cohort lost to follow-up (22%), the limited size of the cohort, differences in cohort definitions between sprayers and producers, and the potential for other exposures during employment at the plant.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. TCDD exposures were not quantified.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Effective dose could not be estimated given the lack of individual-level TCDD exposure data.
Conclusion	The study lacks the quantification of exposures at an individual level, precluding dose-response analysis. This study is not considered further in the dose-response modeling analysis.

Table C-25. McBride et al. (2009b)—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The New Zealand Health Information Service Mortality Collection and the Registrar-General's Index to Deaths were used to identify deaths. Additional searches were based on the last known address from the work record; the electoral roll and the habitation index; the telephone book; the internet; and several other public databases in New Zealand. An additional search was carried out through the Births, Deaths, and Marriages office of the New Zealand Department of Internal Affairs. Lastly, automated personnel and pension records were also used to locate past New Plymouth workers and identify some deaths.

2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Workers lost to follow-up (21%) were an unlikely source of bias since there was no evidence that this loss was differential in the internal analyses of workers. Confounding by sex, hire year, and birth year was addressed by adjustment in regression models. Potential confounding by other coexposures (e.g., 2,4,6-TCP) unlikely to have resulted in bias, due to presumed poor correlation with TCDD.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Although not statically significant, elevated SMRs (≥1.6) were noted for soft tissue sarcoma, non-Hodgkin Lymphoma, multiple myeloma and rectal cancer. The linear test for trend for TCDD exposure was not statistically significant for all cancer sites (combined), as well as lung cancer mortality. Dose-response relationships were not apparent across quartiles of TCDD exposure for all cancer sites combined, digestive cancers, lung cancer, soft tissue sarcomas or non-Hodgkin Lymphoma.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Cumulative exposure to TCDD as a time-dependent metric was estimated for each worker from serum samples, but the authors did not examine a continuous measure of TCDD exposure (lagged or unlagged).
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. The adequate statistical power to detect associations that were present was a strength of the study owing to the large sample size (*n* = 1,599 workers), extensive follow-up period (35 years) and considerable exposure gradient.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in J Occup Environ Med 51:1049−1056. This paper discussed the strengths and limitation of the study
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum measures available for 346 workers were used to derive TCDD exposures for the entire cohort using the area under the curve approach.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Although, effective dose could be estimated from serum-derived cumulative exposure estimates, the exposure models did not consider different latency periods.
Conclusion	Given that no dose-response relationships were found, the data are not suited to dose-response analysis.

Table C-26. Hooiveld et al. (1998)—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Outcomes were mortality. Few deaths expected to be missed since only 5% of the cohort was lost to follow-up or had emigrated.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Although dioxin-like compounds (PCDDs, PCDFs, and PCBs) were measured in the serum samples, these were not incorporated into the analysis. Therefore, confounding cannot be ruled out as an explanation of the reported association.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. A dose-response pattern was observed for internal cohort comparison for all cancer mortality, with RRs of 5.0 and 5.6 for the medium and high exposure, respectively. Dose-response patterns evident for lung cancer as well.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures..

Response	Consideration satisfied. Detailed occupational histories to assign dichotomous exposures (exposed/unexposed) based on maximum exposure levels. Although serum data also collected for TCDD and other coexposures (PCDDs, PCDFs, and PCBs), study only presents data for TCDD exposure. TCDD exposures at time of maximum exposure were extrapolated from measured serum.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied for internal cohort comparisons in either men or women. Among men, only 7 cancer deaths were observed among those in the unexposed part of the cohort, and 51 among exposed workers. For external cohort comparisons, a total of 20 deaths were observed.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 1998, 147:891–901. The authors address potential limitations of estimating TCDD exposure from a subsample of surviving workers, lack of smoking data, the healthy worker effect, and relevance of other occupational exposures.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum samples were obtained from 94 of 144 subjects who were asked to participate in serum measurement study. Of these, a further 44 excluded due to absence due to holiday or work (n = 22), and nonexposed workers excluded because matching exposed worker not participating (n = 20). TCDD levels were extrapolated to the time of maximum exposure.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Exposures assigned based on levels at maximum exposure. Assignment of exposure based on nonrepresentative sample of 50 survivors among the occupational cohort.
Conclusion	The small number of identified cancer deaths, limitations in terms of the exposure assignment (based on nonrepresentative sample, and maximum exposure level) and concern over potential confounding by coexposures preclude using these data for a dose-response analysis.

C.3. EVALUATION TABLES FOR NONCANCER STUDIES

C.3.1. NIOSH Cohort

Table C-27. Steenland et al. (1999)—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased..
Response	Consideration satisfied. The study evaluated mortality from all cancer sites (combined). As described in the paper, the sources of vital status and cause of death information were received from the Social Security death files, the National Death Index, and the Internal Revenue Service. Vital status was known for 99.4% of the cohort members, cause of death information is available for 98% of the decedents.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. External comparisons for all-cause and cardiovascular mortality do not appear to be affected by the “healthy worker effect” as similar patterns were observed with internal cohort comparisons. Nonetheless, internal cohort comparisons are unable to adjust for many of the individual-level risk factors for cardiovascular disease.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. A dose-response relationship was observed with ischemic heart disease (linear test for trend p = 0.05), and with TCDD on a log-transformed scale the p-value was <0.001.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The study conducted detailed sensitivity analyses and evaluated different assumptions regarding latency, log-transformed TCDD exposures, and half-life values for TCDD. Associations were stronger for log-transformed values, and latency intervals of 15 years.

5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. This is the largest of the occupational cohorts with exposures to TCDD. The cohort consisted of 5,132 male workers and a total of 456 deaths from ischemic heart disease. This permits characterization of risk for all cancer sites (combined).
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Journal of the National Cancer Institute, 1999, 91(9):779–786. The authors discussed the potential for bias from smoking, and other occupational exposures for which data for both were lacking at an individual basis.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Exposure scores assigned at an individual level based on JEM. The JEM was based on estimated factor of contact with TCDD in each job, level of TCCD contamination of materials at each plant over time, and proportion of day worker could be in contact with materials. These factors were multiplied together to derive a daily exposure score, which was accumulated over the working history of each worker to obtain a cumulative measure of TCDD.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. The follow-up of the cohort extended from 1942 until the end of 1993. Greater than 25 years of follow-up have accrued in cohort allowing for latency to be examined. Different assumptions on the half-life of TCDD were evaluated and produced similar results. Latency intervals were incorporated, with strongest associations noted no lag. Suggests mechanisms occur at the same time as exposure. However, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	TCDD exposures were quantified in this study, and a dose-response relationship was observed with ischemic heart disease mortality. The sample size was sufficient, and the follow-up interval was lengthy. However, no individual-level data were available for cardiovascular conditions, and the inability to adjust for these exposures introduces considerable uncertainty into the risk estimates. Furthermore, noncancer mortality is not considered a viable endpoint for dose-response analysis.

Table C-28. Collins et al. (2009)—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Vital status complete for all but two workers.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. No information collected on smoking status, but no excess in lung cancer or nonmalignant respiratory diseases noted. Analyses took into account potential for exposure to pentachlorophenol. External cohort comparisons should be interpreted cautiously due to healthy worker effect, but internal cohort comparisons should not be influence by this bias.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. No statistically significant mortality excess for any noncancer mortality outcome evaluated. This included ischemic heart disease, stroke, nonmalignant respiratory disease, ulcers, cirrhosis, and external causes of death (accidents). Modeling of continuous measure of TCDD was not related to diabetes, ischemic heart disease, or nonmalignant respiratory mortality.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.

Response	Consideration satisfied. The authors used serum samples from 280 former TCP workers to estimate historical exposure levels of TCDD, furans, and polychlorinated biphenyls for all 1,615 workers. Exposure assessment included detailed work history, industrial hygiene monitoring, and the presence of chloracne cases among groups of workers. This data was integrated into a 1-compartment, first-order pharmacokinetic to determine the average TCDD dose associated with jobs in each group, after accounting for the presence of background exposures estimated from the residual serum TCDD concentration in the sampled individuals. The authors did not evaluate departures from linearity, or examine skewness at higher exposures. No presentation of exposure levels was provided.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. A total of 662 deaths were observed. Of these, 218 were from ischemic heart disease, and 16 from diabetes (two outcomes for which associations have been noted elsewhere).
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in Am J Epidemiol, 2009, 170(4):501–506. The authors discuss potential for exposure misclassification, large size of the cohort, lengthy follow-up interval, and large number of workers who provided serum from which TCDD exposures were estimated.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. This study has the greatest number of serum samples obtained from a specific plant.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusions	No dose-response associations were noted for noncancer mortality outcomes. The data are, therefore, not suited for dose-response modeling.

C.3.2. BASF Cohort

Table C-29. Ott and Zober (1996a)—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Mortality ascertainment appeared to be fairly complete.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Information was collected on smoking status, body mass index, and other occupational exposures, however a large portion of the cohort was firefighters who may have been exposed to other occupational carcinogens. However, the recruitment of survivors may results in under-ascertainment of mortality.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. For external cohort comparisons across the three TCDD exposure categories, there was no dose-response pattern observed for any of the noncancer causes of death. Cox regression risk estimates for all cause or circulatory disease mortality when TCDD was modeled as a continuous variable were not statistically significant.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Cumulative measure of TCDD expressed was derived from serum measures. Exposure was also estimated by chloracne status of the cohort members. The authors have not addressed the potential implication of deriving TCDD exposure estimates for the whole cohort using sera data that were available for only about half of the cohort.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all causes of death, there were 92 deaths, while 37 circulatory deaths. Many of the cause-specific death had less than 5 deaths in the upper exposure category.

1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Occup Environ Med, 1996, 53:606–612. A large component of the cohort was assembled by actively seeking out workers who were alive in the mid 1980s. As a result, it is likely a number of deaths were missed. This is supported by much lower SMRs in this component of the cohort published in earlier studies of the cohort. This underascertainment of mortality results in biased SMR statistics (underestimated). The authors do highlight the value of the serum based measures to estimate TCDD exposure
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum samples, taken in 1989, were available for 138 surviving workers out of 254 and allowed for cumulative TCDD levels to be estimated using regression techniques in the remainder of the cohort.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Exposure assignment took into the affect that body mass index had on TCDD half-lives. TCDD levels estimates through back-extrapolation of serum levels based on half-life estimates obtained from previous studies. Latency was considered with stronger association observed in external comparisons incorporating a latency of 20 years. The follow-up of the cohort was lengthy (>50 years). However, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	No associations noted with any noncancer deaths. External comparisons should be treated cautiously especially for cardiovascular mortality which is recognized to often be biased by the healthy-worker effect. In the absence of any outcome with an association with TCDD exposure, dose-response analyses of these data were not undertaken.

C.3.3. Hamburg Cohort

Table C-30. Flesch-Janys et al. (1995); Flesch-Janys et al. (1996) erratum—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Medical records used to identify deaths over the period 1952−1992.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Similarity in smoking rates between control cohort and the exposed workers was similar based on independent surveys. Occupational exposures to benzene, and dimethyl sulfate were unlikely to bias dose-response pattern observed as these exposures occurred in production departments with low to medium levels of TCDD exposure.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Dose-response relationship observed for all-cause mortality, cardiovascular mortality, and ischemic heart disease mortality across 6 exposure categories, with the cohort of gas supply workers used as the referent. The linear tests for trend for these three outcomes were all statistically significant ($p < 0.05$).
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The exposure measures was an integrated TCDD concentration over time estimate that back-calculated TCDD exposures to the end of the employment. Categorical and continuous TCDD exposures were examined in relation to the health outcome. These efforts improve the exposure assessment of earlier studies.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all causes of death combined, there were 414 deaths in the exposed cohort, and 943 in the cohort of gas supply workers. A total of 157 and 76 deaths from cardiovascular disease, and ischemic heart disease were noted. The corresponding number in the cohort of gas supply workers was 459, and 205, respectively.
1. Criteria	Study is published in the peer-reviewed scientific literature.

Response	Criteria satisfied. Am J Epidemiol, 1995, 1442:1165–1175. The authors discuss the potential role of other occupational exposures (i.e., dimethyl sulfate, solvents, benzene), smoking, and suitability of the comparison cohort of gas supply workers.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum and adipose tissues were used to estimate TCDD exposure in 190 workers. A one-compartment first-order kinetic model was used to estimate exposure at end of exposure for these workers. Regression methods were then used to estimates TCDD exposures for all workers.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Exposure based on half-life estimates from individuals with repeated serum measures. Other DLCs were considered with the TOTTEQ exposure metric. Noncancer mortality, however, is not a viable endpoint to consider for further dose-response analysis.
Conclusion	Although, the exposure data used within this study are well-suited to a dose-response analysis for all-cause and cardiovascular mortality given the associations observed, use of noncancer mortality endpoint is not amenable for further dose-response analysis.

C.3.4. The Seveso Women's Health Study

Table C-31. Eskenazi et al. (2002b)—Menstrual cycle characteristics

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Information was also obtained from medical records for all obstetric and gynecologic conditions. Information on menstrual cycles was obtained from questionnaires. Women were asked about length of cycles, regularity, how many days flow lasted, and heaviness of menstrual flow (scanty, moderate, or heavy). Measurement error is likely for the subjective nature of self-reported menstrual parameters but specificity and sensitivity is difficult to ascertain due to lack of validation data for these measures.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Detailed risk factor information was collected from questionnaire, allowing for the potential confounding influence of many risk factors to be controlled for. The length of cycle study findings may have been affected by the presence of a few outliers.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. A positive dose-response relationship was found with TCDD among women who were premenarcheal at time of the explosion and longer menstrual cycle. Increased TCDD exposure was associated with a lower relative risk of scanty menstrual flow. No association was noted with these two outcomes among postmenarcheal women. A decreased risk of irregular cycles was also observed with higher TCDD levels.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Cohort was large enough as analyses were conducted on 301 women.
1. Criteria	Study is published in the peer-reviewed scientific literature.

Response	Criteria satisfied. Am J Epidemiol, 2002; 156(4) 383−392. Limitations included an inability to assess affects on menstrual cycle at time body burdens were the highest (at time of the accident). Also, TCDD was estimated for 1976, not concurrent with their cycles in the previous year, and a large number of women were excluded due to intrauterine device or oral contraceptive use. Strengths included population-based nature of study, with characterization of exposure using serum, and levels of other polychlorinated dibenzo-*p*-dioxins and dibenzofurans were at background levels. Findings for length of menstrual cycle may be unduly influenced by the presence of some outliers.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. The study population was based on 301 women as those who were over the age of 44 were excluded, as well as women with surgical of natural menopause, women with Turner's syndrome, those who had been pregnant or breastfed in the past year, and those who had used an intrauterine device or oral contraceptives. For 272 women, TCDD levels were based on serum data provided in 1976; TCDD levels were back-extrapolated to 1976 levels for the other 29 women.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Ideally, TCDD exposures would be concurrent with reporting of cycle characteristics. Herein, TCDD exposures were based on levels in 1976; however, given the long half-life of TCDD and the same follow-up interval for all women, TCDD exposures in 1976 should correlate well with levels near the time of interview. Further, the critical window of exposure can be estimated for the women that were premenarcheal at the time of the accident (12 years).
Conclusion	This study meets all of the criteria and considerations for further dose-response analysis. Although it is difficult to define the biologically relevant critical window of exposure for quantitative exposure calculations, the critical window of susceptibility is assumed to occur between birth and 13 years of age.

Table C-32. Eskenazi et al. (2002a)—Endometriosis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Results of a pilot study showed that ultrasounds had excellent specificity and sensitivity for ovarian endometriosis. Those with uncertain case status were analyzed separately from cases.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Although more than half of the women were classified as 'uncertain' with respect to endometriosis disease status, these subjects were analyzed separately from those with endometriosis detected by laparoscopy or ultrasound. Bias is unlikely since disease misclassification is not likely to be differential with respect to TCDD exposure status.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. While an increased risk of endometriosis was observed across the 3 TCDD categories, these risks were not statistically significant relative to the lowest exposure category. The test for trend based on a continuous measure ($\log_{10}$TCDD) was also not statistically significant.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied. Only a total of 19 cases of endometriosis were identified, and more than half of the subjects were listed as uncertain regarding endometriosis incidence.
1. Criteria	Study is published in the peer-reviewed scientific literature.

Response	Criteria satisfied. Environ Health Perspect 2002; 110(7) 629–634. Author's highlight that this is the first study to examine the relationship between TCDD and endometriosis, and the availability of sera data to estimate TCDD levels. Limitations included the small number of women with endometriosis, and inability to confirm disease status for those without ultrasound or laparoscopy. Finally, young women may have been underrepresented due to cultural difficulties in examining women who had never been sexually active.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Eligible study subjects were women between 1 month and 40 years of age at time of accident. These analyses excluded virgins, those with Turner's syndrome, and women who refused the examination of ultrasound. Serum data were available for the 601 participants on which the analyses are based. Of these, 559 had serum measures taken in 1976/77, 25 between 1978 and 1981, and 17 women in 1996.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. TCDD exposure was estimated at the time of "conception attempt" using serum measures, with extrapolation from 1976 levels using half-life assumptions. It is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis. The critical window of exposure is unknown.
Conclusion	Various reasons preclude the use of these data to conduct dose-response analysis. This includes the lack of a statistically significant association, the large number of women for which endometriosis disease status was "uncertain", and uncertainty in estimating the critical period of exposure.

Table C-33. Eskenazi et al. (2003)—Birth outcomes

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration not satisfied. Outcomes were identified through self-reported questionnaires and subject to measurement error. Although there is no direct evidence of bias from differential reporting, women tended to over-report birth weight, and underreport birth defects in children. As a large number of women in Seveso underwent voluntary abortion in the first year after the explosion, an awareness bias may have contributed to differential reporting of pregnancy histories.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. See above.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. There was no association between spontaneous abortions and $\log_{10}$TCDD, or with small for gestational age. There was some suggestion of decreased mean birth weight and increased ORs for small for gestational age with TCDD exposure among pregnancies occurring in the first eight years following the accident; however, none of these achieved statistical significance at $p < 0.05$.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For spontaneous abortions there were 769 pregnancies. Fetal growth and gestational age analysis was carried out on 608 singleton births that occurred postexplosion.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environ Health Perspect, 2003, 111(7):947–953. The authors highlight potential limitation of reliance on self-reported data to ascertain pregnancy outcomes. They also address the relevance of paternal exposures to TCDD on the developing fetus—such exposure data were not considered in this study.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.

Response	Criteria satisfied. A total of 745 women in the SWHS had reported getting pregnant, of these 510 women were pregnant after the explosion (888 pregnancies). Analyses of spontaneous abortions based on 476 women (excludes those with voluntary abortion, ectopic pregnancy, or molar pregnancy). TCDD measured for 413 women in 1976/77, 12 women between 1978 and 1981, and 1996 for 19 women.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. TCDD exposures were extrapolated to 1976 values. However, there is considerable uncertainty in estimating exposure levels for narrow critical windows of exposure (e.g., trimesters during pregnancy) especially for pregnancies that occurred many years after the explosion in 1976.
Conclusion	The findings of the study are somewhat limited due to the reliance on self-reported information for pregnancy outcomes and possible awareness bias. The findings were not statistically significant. Considered together with the uncertainty in estimating exposure levels for narrow critical windows of exposure, dose-response analyses for this study were not conducted.

Table C-34. Warner et al. (2004)—Age at menarche

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. In this study age at menarche was based on retrospective recall 5 to 19 years before the interview. Previous work suggests moderate to high correlations between actual and recalled menarche, misclassification of outcome would bias risk estimates towards the null (assuming nondifferential misclassification).
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Data collected from self-reported questionnaires allow for the potential confounding influence of many risk factors to be taken into account. Some misclassification of outcome may bias risk estimates towards the null.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. There was no association between TCDD levels and the age at menarche with either the continuous or categorical measures of TCDD in the primary publication, However, suggestive evidence of an association between serum TCDD concentrations and earlier age of menarche (HR = 1.20, 95% CI = 0.98−1.60, *p* for trend = 0.07) among 84 women under the age of 5 at the time of the accident was noted in a follow-up communication from Warner & Eskenazi (2005)to be when analyses were restricted. The consideration is not satisfied because, in the context of the RfD derivation, considerable uncertainty remains as to whether associations with age at menarche represent an adverse health effect.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Cohort was large enough as analyses were performed using 282 women who were premenarcheal at the time of the explosion.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environ Health Perspect, 2004, 112:1289–1292. Authors discuss use of pooled serum from residents of the unexposed zone, and that those in lowest exposure group had high exposures relative with contemporary levels for the area. Strengths of study include use of serum to estimate TCDD exposure.

2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. The SWHS included women between 1 month and 40 years of age at time of accident who attempted to get pregnant after the explosion (n = 463). This study is restricted to those who were premenarcheal at the time of the explosion (n = 282). Serum was collected for these women, primarily in 1976–1977 (n = 257), between 1978 and 1981 for 23, and in 1996–1997 for the 2 remaining women.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. TCDD exposures in 1976 were estimated by extrapolation serum levels obtained after this date using the Filser model. Both categorical and continuous measures of exposure were modeled. In utero measures of exposure are likely most relevant exposure based on findings from animal studies.
Conclusion	No association between TCDD levels and age at menarche was reported in the primary publication; however, a follow-up communication from Warner & Eskenazi (2005) reported a 10-fold increase in serum TCDD concentrations to be associated with an earlier age of menarche (HR = 1.20, 95% CI = 0.98−1.60, p for trend = 0.07) when analyses were restricted to 84 women under the age of 5 at the time of the accident. The TCDD exposure characterization of study subjects was based on serum data, and no major biases were introduced from the study design or analytical methods that were used. In the context of the RfD derivation, considerable uncertainty remains as to whether associations with age at menarche represents an adverse health effect, Therefore, dose-response analyses were not conducted for this study.

Table C-35. Eskenazi et al. (2005)—Age at menopause

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Outcome measures were obtained based on self-reported data collected from questionnaires. Studies have shown that self-reports of age at menopause are reported with accuracy and reliability, and among women with surgical menopause, the self-reported age correlated well with that on the medical records.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Data obtained from the questionnaire allow for the potential confounding influence of several potential confounders to be examined.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Risks of earlier menopause increased in the first four quintiles, with a statistically significant trend. No increased risk was noted in the highest exposure category (HR = 1.0 relative to lowest exposure group). The study authors suggest this is due to the "inverted U" dose response often seen with hormonally active compounds. Additionally, no statistically significant association was noted with $\log_{10}$TCDD for the individual quintiles. More importantly, the biological significance of this result for the establishment of a LOAEL (that is needed in the context of the RfD derivation) could not be determined with confidence.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although the critical exposure window is uncertain.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. The study included 616 women. Of these, 260 were premenopausal, 169 classified as natural menopause, 83 as surgical menopause, 24 as impending menopause, 33 as premenopausal, and 58 in an "other" category.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environ Health Perspect, 113:858–862 (2005). The authors highlight that this is first study to look at relationship between dioxin and age at menopause. Limitations of the study were that the lowest exposure group (≤20.4 ppt) included exposure levels that are far higher than background, and age at menopause was based on retrospective recall. A strength of study is ability to characterize TCDD using serum measures.

2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. The Seveso Women's Health Study collected serum sample which allowed TCDD exposures to be characterized. Those women (*n* = 616) who had not reached natural menopause at the time of the accident were included in the study. Serum measures collected in 1976/77 were available for 564 women, for 28 women, sera was collected between 1978 and 1981, while for 24 women, sera was collected in 1996/97.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. TCDD levels were estimated at the time of the explosion using available information on TCDD half-life. However, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis. The critical window of exposure can be estimated but is large and highly uncertain.
Conclusion	The biological significance of this result for the establishment of a LOAEL (that is needed in the context of the RfD derivation) could not be determined with confidence. Therefore, dose-response analyses were not conducted for this study.

Table C-36. Warner et al. (2007)—Ovarian function

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Ovarian cyst analysis based on women who underwent ultrasound (*n* = 310). Ovarian follicle analysis based on self-report on menstrual cycle and done in women in preovulatory cycle (*n* = 96) at time of ultrasound. Hormonal analysis based on women in last 14 days of cycle (*n* = 129).
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Data collected from self-reported questionnaires allow for the potential confounding influence of many risk factors to be taken into account. Some misclassification of outcome based on self-reports of menstrual cycle may bias risk estimates towards the null.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. There was no association between serum TCDD levels and the number or size of ovarian follicles. TCDD was also not associated with the odds of ovulation.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Cohort was large enough as analyses were performed using 129 women for ovulation outcome, and hormone analyses based on 87 women in luteal, and 55 in midluteal phases.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environ Health Perspect, 2007,115:336–340. An important limitation cited by the authors was that women may not have been exposed at critical period (prenatally). Phases of the cycle may also have been misclassified as this was based on self-reported data. Strength, first study to have examined ovarian function and TCDD exposures.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. The SWHS included women between 1 month and 40 years of age at time of accident who were between 20–40 years of age and not using oral contraceptives at follow-up (*n* = 363). Of these, serum was collected for 330 women between 1976 and 1977, between 1978 and 1982 for 25 women, and between 1996 and 1997 for 8 women.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. There is a lack of a defined critical window of exposure in this study.

Conclusion	Because of the lack of a defined critical exposure window and absence of associations between TCDD and adverse health effects in this study, quantitative dose-response assessment was not conducted for this study. For these reasons, dose-response analyses were not conducted for this study.

Table C-37. Eskenazi et al. (2007)—Uterine leiomyoma

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Outcomes were determined using two definitions: current fibroids, or past diagnosis of fibroids. For past diagnosis of fibroids, self-reported data and medical records were used to determine whether women were previously diagnosed with fibroids, these were confirmed with medical records. A total of 25 women indicated they had never been diagnosed with fibroids. Medical records indicate a past diagnosis for these women, and they were classified as such. For current fibroids, this was determined at the time of the interview for 634 women using transvaginal ultrasound examinations.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. In the SWHS questionnaires were administered to the participants and detailed data for reproductive characteristics, smoking, body mass index, and alcohol use were collected so risks could readily be adjusted for these covariates.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied, but inverse associations reported. An inverse dose-response pattern with the percentage of women diagnosed (current and past history—combined) with fibroids across 3 categories of exposure. Namely, the percentages of women with fibroids in the≤20, 20.1 –75.0, and >75.0 ppt categories were 41.1%, 26.8%, and 20.0%, respectively.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. A variety of different exposure metrics were considered including linear, categorical, splines, and $\log_{10}$TCDD.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. A total of 251 women were found to have fibroids, and there were 62, 110, and 79 women with fibroids diagnosed in the 3 TCDD exposure categories.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 2007, 166:79–87. In this study, the authors found an inverse association between TCDD and uterine leiomyoma risk. The authors highlighted strengths of the study that included the longitudinal design, serum measures taken at an individual-level basis and most taken within 2 years of the accident, ability to include outcomes among those who did not take an ultrasound by using an adapted statistical approach. An important limitation that was the differences in risk by the stage of development could not be assessed as all women were exposed postnatally, and only 4 cases were observed among those who were premenarcheal at the time of exposure.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Final sample consisted of 956 women in the Seveso Women's Health Study without a history of fibroids. For 872 of these women, serum was collected in 1976 and 1977. For 56 women, TCDD was measured in women between 1978 and 1981, and for 28 women the serum was collected in 1996.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. TCDD exposures were back extrapolated to expected levels in 1976 (at the time of the accident). However, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis. The critical window of exposure is uncertain.
Conclusion	Because the critical window of exposure is uncertain, dose-response analyses were not conducted for this study.

C.3.5. Other Seveso Noncancer Studies

Table C-38. Mocarelli et al. (2008)—Semen quality

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Serum levels of TCDD were measured on an individual basis for men in exposed areas; pooled samples from men in uncontaminated areas were measured to assess background TCDD exposure levels.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. While compliance rates may have introduced some possible bias, this does not seem likely as different effects noted between the 22–31 and 32–39 year old age groups. Information collected for other risks factors, which have been used as adjustment factors in the models.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Figure 3 (Mocarelli et al., 2008) suggests dose-response relationship among those aged 1–9 at the time of the accident for sperm concentration and motility.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Analyses are based on 135 males exposed to TCDD.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environmental Health Perspective s, 2008, 116(1):70–77. The authors describe strengths associated with characterization of exposure (using serum samples), and representativeness of study population. Limitation of study includes low compliance (but high for semen sample studies), namely, 60% among a group of healthy men. The compliance rate was higher among exposed group (69%).
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Involved males, <16 years old at time of accident.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. TCDD exposures were based on serum samples. Serum samples were drawn (in 1997/1998) from participants whose 1976 samples were above 15 ppt. Pooled samples obtained in 1997/98 were used to describe background TCDD levels in uncontaminated areas. The associated between TCDD exposure and semen quality was found statistically significant for the boys with 1 and 9 years of age at the time of the accident. This provides a critical window of exposure to estimate TCDD concentration.
Conclusion	Health outcomes are exposures are well characterized using serum data. However, the men exposed between the ages of 1 and 9 to elevated TCDD levels had reduced semen quality 22 years later. It is difficult to discern whether this effect is a consequence of the initial high exposure between 1 and 9 years of age or a function of the cumulative exposure for this entire exposure window beginning at the early age. Nonetheless, dose-response analyses for this outcome were conducted.

Table C-39. Mocarelli et al. (2000)—Sex ratio

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Birth records examined for those who lived in parents who lived in the area and who provided serum samples.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied.

3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Paternal TCDD exposures were associated with an increased probability of female births ($p = 0.008$).
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum samples were used to estimate maternal and paternal TCDD levels. No discussion of exposure levels in reference population.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Statistically significant findings achieved.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. The Lancet, 2000, 355:1858–1863.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum levels of TCDD were obtained from parents using samples provided in 1976/77. Serum measures available for 296 mothers and 239 fathers.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Serum based measures of TCDD were obtained shortly after the accident. TCDD levels were also extrapolated to the time of conception. Although paternal pubertal exposures may be a key critical window for sex differentiation, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis.
Conclusion	The data from this study demonstrate a positive dose-response relationship with pubertal and pre-pubertal paternal TCDD levels at the time of the accident and increased likelihood for female births. However, it is difficult to identify the relevant time interval over which TCDD dose should be considered; specifically, it is difficult to discern whether this effect is a consequence of the initial high exposure during childhood or a function of the cumulative exposure for this entire exposure window beginning at the early age. Dose-response analysis for this outcome was not conducted, because EPA could not define the critical exposure window.

Table C-40. Baccarelli et al. (2008)—Neonatal thyroid function

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Measures of b-TSH are taken using a standardized protocol 72 hours after birth. These b-TSH measures are taken on all newborns born in the region of Lombardy which includes Seveso.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. For the comparisons involving place of residence at the time of the accident, exposure misclassification is likely given variability in soil TCDD exposure levels within these areas. For the individual TCDD measures ($n = 51$) reported in the study figures, exposure misclassification is unlikely.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Mean neonatal b-TSH was 0.98µU/ml [0.90–1.08] in the reference area, 1.35µU/ml [1.22–1.49] in zone B, and 1.66µU/ml [1.19–2.31] in zone A ($p < 0.001$). The plotted frequency distributions have similar shapes, but have shifted to the right for areas of higher exposures. Neonatal b-TSH was correlated with current maternal plasma TCDD (β-0.47, $p < 0.001$) in the 51 newborns for which individual maternal serum TCDD values were available.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. TEQs were measured among the 38 women for which serum samples were available and were defined for a mixture of dioxin-like compounds. Maternal mean total TEQs (PCDDs, PCDFs, coplanar PCBs, and noncoplanar PCBs) was 41.8 ppt. Two measures of exposure included place of residence at time of accident and plasma samples obtained from mothers at the time of delivery. Similarities in positive dose-response relationships give stronger weight to the findings.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.

Response	Consideration satisfied. For plasma based estimate of maternal TCDD there were 51 mother-child pairs. Only seven children in total were found to have b-TSH levels in excess of 5 μU/mL.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. PLOS Medicine 2008; 5(7)1133–1142. The authors discuss the strength of the study related to characterization of exposure using serum sampling, and ability to adjust for factors related to b-TSH or TCDD levels (gender, birth weight, birth order, maternal age, hospital and type of delivery). They also highlight that a limitation of study was that the influence of mother-child dioxin transfer through colostrum could not be assessed because no information on breast-feeding before b-TSH measurement was available.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. In the population-based study, eligible women who resided in zones A and B at the time of the accident (n = 1,772) were matched to nonexposed women. In the study based on plasma dioxin measurements, participants were the 51 children born to 38 women from zones A, B, R, or a reference zone for which plasma dioxin measurements were available.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Maternal TCDD levels were estimated at the time of delivery based on plasma samples, and the critical window of exposure was assumed to be the 9-month gestational period.
Conclusion	The data provide an opportunity for conducting dose-response analyses.

Table C-41. Alaluusua et al. (2004)—Developmental dental defects

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Ascertainment of dental health was done blind to place of residence, used standard protocol for caries developed by the WHO, and the clinical examination supplemented by radiographic examination.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Additional risk factor information was collected on questionnaires. These factors were considered as adjustment factors. The potential for participation bias is not possible to ascertain given the available information. The potential impact of exposure misclassification is also unknown, but the there is some suggestion that some individuals in the non-ABR zone may higher TCDD levels than expected based on background exposure concentrations.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Increased prevalence of developmental enamel effects found with increased TCDD serum measures. Namely, prevalence in unexposed region was 26%, whereas in the low, middle, and high TCCD groups the prevalence was 10%, 40%, and 60%, respectively.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. TCDD exposure level based on serum lipids. No discussion of exposure levels in reference population.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Despite small numbers, statistically significant findings were achieved.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environmental Health Perspectives, 2004, 112(13):1313–1318. Authors mention two important strengths of the study: characterization of TCDD exposure using serum collected shortly after the time of the accident, and the fact that developmental defects are permanent in nature. Therefore, they represent a health outcome can evaluated years later. Little discussion was made of the impact of differential compliance rates between the exposed (74%) and nonexposed (58%) groups. Authors mention two important strength of the study: characterization of TCDD exposure using serum collected shortly after the time of the accident, and the fact that developmental defects are permanent in nature. Therefore, they represent a health outcome can evaluated years later. Little discussion was made of the impact of differential compliance rates between the exposed (74%) and nonexposed (58%) groups.

2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum levels of TCDD could be estimated for children in exposed areas. No serum levels were available for reference group of children, and assumption of zero exposure was made. This seems reasonable.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. It is difficult to discern whether this effect is a consequence of the initial high exposure during childhood or a function of the cumulative exposure of the entire exposure window beginning at early age. However, assumptions can be made regarding the critical window of exposure and the relevant dose can be calculated.
Conclusion	The considerations for conducting a dose-response analysis have been satisfied with the study population of only those subjects who lived in the ABR zone at the time of the accident; exposure data are unavailable for those in the referent area. While is difficult to identify the relevant time interval over which TCDD dose should be considered, dose-response analyses were conducted for this outcome.

Table C-42. Bertazzi et al. (2001)—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. For some causes of death methods highly specific mortality appears to be well captured from the vital statistics registries in the region (99% complete). Some health outcomes (e.g., diabetes) are subject to misclassification using death certificate data.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Although individual-level data for individual risk factors are not available, the potential for confounding is likely minimal. For e.g., independent surveys suggests similarity between smoking behaviors across the regions. Exposure misclassification based on place of residency likely to bias risk estimates towards the null.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. While a dose-response relationship was observed for chronic obstructive pulmonary disease across Zones A, and B, this relationship was not.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. Exposure classification was based on the address of the residence on the date of the accident or when the person first entered the area. Although TCDD blood levels were also measured, these were not examined with respect to health outcomes. The lack of individual-level data also precluded an examination of these uncertainties.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. A total of 494 noncancer deaths were found among residents of Zones A, and B, respectively. This allowed examined of gender-specific effects.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 2001, 153:1031–1044. Authors discuss lack of individual-level exposure data and other risk factors (e.g., smoking), difficulties in extrapolating to background levels, diagnostic accuracy of using death certificates. Strengths included similarities between exposed and comparison population for several risk factors, completeness of follow-up, and consistent methods to identify mortality outcomes in the exposed and comparison populations.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.

Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying whether excesses occurred among highly exposed populations, it is not precise enough to conduct dose-response analyses. Furthermore, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	Study is not suitable for dose-response analysis due to mortality as endpoint and lack of individual-level exposure data.

Table C-43 Consonni et al. (2008)—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. For some causes of death detection methods were highly specific; mortality appears to be well captured from the vital statistics registries in the region (99% complete). Some health outcomes (e.g., diabetes) are subject to misclassification using death certificate data.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Although individual-level data for individual risk factors are not available, the potential for confounding is likely minimal. For e.g., information from other independent surveys suggests similarity between smoking behaviors across the regions. Exposure misclassification based on place of residency is likely to bias risk estimates towards the null.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Statistically significant association noted in most highly exposed area for chronic rheumatic disease and chronic obstructive pulmonary disease. Dose-response pattern noted across Zones A, B and R for circulatory disease mortality 5–9 years after the accident.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. Lack of individual-level data precludes an examination of these uncertainties.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. However, only three deaths from diabetes occurred among residents of Zone A. The limitation related to statistical power is exacerbated for stratified analyses carried out by number of years since the accident.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 2008, 167:847–858. Authors discuss potential for selection bias, limitation of residential based measure of exposure, similarities of mortality ascertainment in exposed and referent populations, and multiple testing.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying whether excesses occurred among highly exposed populations, it is not precise enough to conduct dose-response analyses. Furthermore, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	Study is not suitable further dose-response evaluation due to noncancer morality endpoint.

Table C-44. Baccarelli et al. (2005)—Chloracne

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Chloracne cases identified using standardized criteria.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Important potential confounders were included in the quantitative analyses conducted by the study authors.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Plasma TCDD was associated with an increased risk of chloracne. The odds ratios increased in a dose-response pattern across zone of residence.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Authors discussed implications of differential elimination rates by age and body growth.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. A total of 101 chloracne cases were identified, and 211 controls were selected. Statistically significant findings were observed in several comparisons, although statistical power was limited to assess potential interactions.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. British Journal of Dermatology, 2005, 152, 459–465. The authors detail the limited statistical power they had available in the study. They also highlight study strengths that included uniqueness of age and sex distribution of chloracne cases, characterization of TCDD that could be done using sera samples, and availability of both clinical and epidemiologic data.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. TCDD was estimated in both chloracne cases and control using serum measures.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Serum based measures of TCDD were obtained shortly after the accident. Chloracne is thought to be caused by the initial high exposure.
Conclusion	Exposure to TCDD at sufficiently high levels is recognized to cause chloracne. This study provides limited relevance to dose-response modeling of TCDD as exposure levels typically observed in the general population are much lower.

Table C-45. Baccarelli et al. (2004; 2002)—Immunological effects

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Common methods were used to describe blood levels of plasma immunoglobulins (IgA, IgG, and IgM) and complement components (C3 and C4).
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Both exposure and outcome were objectively and accurately measured.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. While plasma IgG levels were inversely related with TCDD, it is uncertain whether this outcome is adverse.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Both categorical (quintiles) and continuous measures of TCDD were examined in the dose-response analysis.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Analyses are made using 72 highly exposed, and 72 low exposed individuals.
1. Criteria	Study is published in the peer-reviewed scientific literature.

Response	Criteria satisfied. Toxicology letters, 2004, 149:287–293 and Environ Health Perspect, 2002, 110(12):1169–1173. The authors highlight that few studies have looked at immunological effects of TCDD in humans, that the current study was able to exclude those with concurrent medical conditions, and the ability to characterize exposure using serum measures. Limitations addressed were the uncertainty about the clinical relevance of the dose-response pattern found, and the relatively small size of the study population.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. A total of 120 subjects were included in the study. This included 62 randomly selected from the high exposed zone, and 58 selected from the reference area.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Dose-response relationships were examined using current TCDD levels. However, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis.
Conclusion	An inverse dose-response relationship between IgG and TCDD was observed. However, the biological significance of a decrease in IgG for the establishment of a LOAEL (needed in the context of the RfD derivation) could not be determined with confidence. Further the critical window of exposure that would cause an effect on IgG levels is not known and thus does not allow for estimation of the effective TCDD exposure. Therefore, dose-response analyses were not conducted for this outcome.

C.3.6. Chapaevsk Study

Table C-46. Revich et al. (2001)—Mortality (noncancer) and reproductive health

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration not satisfied. Insufficient details are provided in the paper to gauge the completeness and coverage of the cancer registry and the mortality data. Health outcomes were examined on the basis of information in the official medical statistics.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Given the aforementioned limitations of this ecological study, it is unclear to what extent the results may be subject to bias.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Dose response was not evaluated as exposure was based on residency in the region vs. no residency.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. No individual-level exposure estimates were used.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Population-based data over several years were used to make comparisons at the ecological level.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in Chemosphere, 2001, 43(4–7):951–966.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. It is a cross-sectional study that compares mortality rates between regions. No individual-level exposure data available.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. No individual-level exposure estimates were used in the study.
Conclusion	These cancer data are cross-sectional in nature; therefore, dose-response analyses were not conducted for this study.

C.3.7. Air Force Health ("Ranch Hands") Study

Table C-47. Henriksen et al. (1997)—Diabetes

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Newly diagnosed cases of diabetes following the completion of the veterans' tours of duty were identified from self-reported questionnaire data with verification from medical records, or by using a postchallenge glucose serum test. Disease severity was determined based on questionnaire, and review of medical records. Fasting glucose and 2-hour postprandrial glucose tests were used to identify glucose abnormalities among nondiabetics.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Adjustment was made for a number of risk factors related to diabetes (e.g., BMI, family history, smoking). However, variations in the solubility of dioxin due to between-subject differences in lipid fractions may account for the positive association observed. Many of the health outcomes under study (i.e., diabetes, impaired glucose tolerance, insulin resistance) are associated with lipid abnormalities.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. There were statistically significant positive associations noted between TCDD and diabetes, as well as changes in serum glucose levels, reduced time to onset of diabetes, severity of diabetes, and glucose abnormalities among nondiabetics. While many of the comparisons are based on small numbers, overall, the associations are consistent across the outcomes that were examined.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The methods used to estimates TCDD levels are clearly described, and capture exposure at an individual-level many years before the health outcome was determined. The authors describe the limitations of the exposure assessment within the paper. Sensitivity analyses were undertaken for several of the key associations. The key limitation is that the associations may be caused by differences in lipid fractions between individuals.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. There were a total of 2,265 veterans and 315 cases of diabetes. There was very little attrition across the four physical examinations performed in 1982, 1985, 1987 and 1992.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. The paper was published in Epidemiology 1997;8:252-258. The discussion contains an appropriate discussion of the strengths and weaknesses of the study.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum was used to characterize TCDD exposure. While the quantification of TCDD levels at the time the tour of duty ended may be misspecified due to between-subject differences in lipid fractions, the methods used were able to reasonably discriminate between those veterans with high and low exposures.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. The nature of the data preclude identification of the critical window of exposure to be examined and a effective dose to be calculated for this endpoint.
Conclusion	While the health outcomes and TCDD exposures were characterized using valid methods, the nature of the data preclude identification of the critical window of exposure to be examined. Thus, dose-response modeling was not conducted for this study.

Table C-48. Longnecker and Michalek (2000)—Diabetes

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Newly diagnosed cases of diabetes following the completion of the veterans' tours of duty were identified from self-reported questionnaire data with verification from medical records, or by using a postchallenge glucose serum test. Glucose and insulin measures were obtained among nondiabetics using fasting and 2-yr post challenge serum test.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Adjustment was made for a number of risk factors related to diabetes (e.g., BMI, family history, smoking). However, the analysis was cross-sectional in nature, and therefore was unable to take into account the timing of exposure in relation to diagnosis of diabetes. The increased solubility of dioxin in triglycerides, whose levels are higher in diabetics, may account for the positive association observed.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. There were statistically significant positive associations noted between TCDD and diabetes, as well between TCDD and serum glucose and insulin levels.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. The methods used to estimate TCDD levels are clearly described and are able to determine exposures at an individual level. However, the range of exposures is small given the exclusion of the more highly exposed Ranch Hand veterans. It is possible that between-subject difference in lipids and triglycerides may introduce an important source of exposure measurement error. The authors describe the limitations of the exposure assessment within the paper. The key limitations include the cross-sectional nature of the data, and the noncausal associations that may be caused by triglycerides.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. There were a total of 1,197 veterans and 169 cases of diabetes. Levels or participation across the multiple physical examinations were high.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. The paper was published in Epidemiology 2000;11(1):44-48. The discussion contains an appropriate discussion of the strengths and weaknesses of the study.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum-based measures are an objective and valid method to determine TCDD exposure levels.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. The diabetes cases were identified over a nearly 25-year interval. The nature of the data and analysis preclude identification of the critical window of exposure and estimation of an effective dose for this study.
Conclusion	While the health outcomes and TCDD exposures were characterized using valid methods, the data are essentially cross-sectional and thus are unable to evaluate associations between TCDD and diabetes that can take into account the timing of the exposure. Given the narrow range in TCDD exposures in this study, particularly given the Ranch Hand workers were excluded, these between-subject differences may introduce an important source of bias. Further, the nature of the analysis precludes identification of the critical window of exposure. Thus, dose-response modeling was not conducted for this study.

Table C-49. Michalek et al. (2001a)—Hematological effects

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Hematological measures were determined from serum samples obtained across four physical examinations.
2. Consideration	Risk estimates are not susceptible to important biases.

Response	Consideration not satisfied. Associations between TCDD and platelet counts may be influenced by other health conditions not accounted for by the study design. The positive association noted between TCDD and mean corpuscular volume may be noncausal. Specifically, this association may be due to raised triglycerides levels or increased prevalence of liver impairment among those more highly exposed to TCDD.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Most hematological measures were not consistently associated with TCDD across the different physical examination periods. While positive associations between TCDD and platelet counts and mean corpuscular volumes were observed, they were not consistent with a dose-response relationship as statistically significant differences, relative to those in the lowest exposure group, were observed only among those in the highest exposure group.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The methods used to estimate TCDD exposure are clearly described, and capture exposure at an individual level prior to the diagnosis of the health outcome under study. The authors describe the limitations of the exposure assessment within the paper.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Continuous measures of hematological function approximately 2,200 veterans at four physical examinations. The study lacked adequate statistical power to perform the secondary analysis of the relationship between TCDD and abnormally high red blood cell counts.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. The paper was published in Archives of Environmental Health, 2001; 56(7):396-405.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum was used to characterize TCDD exposure at end of tour of duty. Given exposures dropped dramatically for the Ranch Hands following their tours of duty, exposure to TCDD prior to disease onset is reasonably characterized, though some misclassification between those in the comparison group and those in the lowest Ranch Hand exposure grouping is inevitable. Serum-based measures of hematological function were obtained at multiple examinations which permitted dose-response relationships to be evaluated at four time intervals.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. There is uncertainty in the critical window of exposure. This study analyzes the potential for associations between point-in-time measures of TCDD serum levels and changes in hematological measures that may have occurred at any time over approximately a 30-year interval. The clinical relevance of reported outcomes also is uncertain.
Conclusion	While the health outcomes and TCDD exposures were characterized using valid methods, most hematological measures were not associated with TCDD. For corpuscular volume and blood platelet levels an association with TCDD was detected. However, this association may be noncausal and the influence of other confounders cannot be entirely ruled out. The clinical relevance of these outcomes is also uncertain. Further, no dose-.response trend was observed with either of these two hematological measures. Additionally, there is uncertainty in the critical window of exposure. For these reasons, dose-response modeling was not conducted for this study.

Table C-50. Michalek et al. (2001b)—Hepatic abnormalities

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Hepatic function measures were determined from serum samples obtained across four physical examinations, and the prevalence of liver disorders was determined using self-reported data verified by medical records.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Associations between TCDD and liver function may be influenced by other health conditions not accounted for by the study design.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.

Response	Consideration satisfied. No dose-response trend was observed with most measures of liver function. There was no association between TCDD and hepatomegaly or nonalcoholic chronis liver disease and cirrhosis. However, an association between TCDD was observed with γ-glutamyltransferase, and increased odds ratios of several hepatic disorders were observed among those in the highest TCDD exposure group relative to the comparison cohort.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The methods used to estimate TCDD exposure are clearly described, and capture exposure at an individual level prior to the diagnosis of the health outcome under study. The authors describe the limitations of the exposure assessment within the paper.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Continuous measures of liver function approximately 2,200 veterans during the 1992 physical examination. For some liver conditions, there were few prevalent cases across the exposure categories, however, statistically significant differences were observed for many conditions when comparisons where made between those in the highest exposure group relative to the lowest.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. The paper was published in Annals of Epidemiology 2001; 11:304-311.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum was used to characterize TCDD exposure at end of tour of duty. Given exposures dropped dramatically for the Ranch Hands following their tours of duty, exposure to TCDD prior to disease onset is reasonably characterized, though some misclassification between those in the comparison group and those in the lowest Ranch Hand exposure grouping is inevitable. Serum-based measures of liver function were obtained at the 1992 examination which permitted dose-response relationships to be examined.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. There is uncertainty in the critical window of exposure. This study analyzes the potential for associations between point-in-time measures of TCDD serum levels and liver disease that may have occurred at any time over approximately a 25-year interval the clinical relevance of the health endpoints that were examined is uncertain.
Conclusion	The results do not unequivocally support a relationship between liver damage and TCDD exposure. Confounding and reverse causality cannot be eliminated. Additionally, there is uncertainty in the critical window of exposure. This study analyzes the potential for associations between point-in-time measures of TCDD serum levels and liver disease that may have occurred at any time over approximately a 25-year interval, making it difficult to calculate a cumulative TCDD effective dose over time. For these reasons, dose-response modeling was not conducted for this study.

Table C-51. Michalek et al. (2001c)—Peripheral Neuropathy

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The outcomes were determined using a standardized neurological exam conducted by a board certified neurologist blinded to exposure status. A number of difference measures of peripheral neuropathy were obtained over multiple physical examinations.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Some of the observed associations may be due to residual confounding by diabetes.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.

Response	Consideration satisfied. For some measures of peripheral neuropathy, the data were suggestive of a dose-response relationship, particularly for probable symmetrical peripheral neuropathy. However, only data from the 1997 examination yielded statistically significant increased odds ratio in the highest exposure category relative to the comparison cohort. Associations between TCDD and diagnosed peripheral neuropathy were evident in both 1992 and 1997, however, there were very few veterans diagnosed with this condition.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The methods used to estimate TCDD exposure are clearly described, and capture exposure at an individual level prior to the diagnosis of the health outcome under study. The authors describe the limitations of the exposure assessment within the paper.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied. There were very few cases of peripheral neuropathy, particularly in the most highly exposed groups. Statistical significance was only achieved in a few instances, and in some cases, the odds ratios could not be estimated.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Neurotoxicology 2001: 22:479-490.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum was used to characterize TCDD exposure at end of tour of duty. Given exposures dropped dramatically for the Ranch Hands following their tours of duty, exposure to TCDD prior to disease onset is reasonably characterized, though some misclassification between those in the comparison group and those in the lowest Ranch Hand exposure grouping is inevitable.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. There is uncertainty in the critical window of exposure which impacts the ability to calculate an effective TCDD over time. This study analyzes the potential for associations between point-in-time measures of TCDD serum levels and peripheral neuropathy that may have occurred at any time over approximately a 30-year interval.
Conclusion	While an association was noted between peripheral neuropathy and TCDD levels, these comparisons were limited by a small number of outcomes particularly within the highest exposure group. Statistical significance was only achieved for some measures of peripheral neuropathy using data from the 1997 examination, but not in the other 4 examination periods. Residual confounding by undiagnosed diabetes may have distorted the measures of association, and this bias cannot be fully dismissed. Additionally, there is uncertainty in the critical window of exposure which precludes calculation of a cumulative TCDD effective dose over time. Multiple comparisons arising from conducting statistical tests of significant over multiple time periods, and measure of neuropathy raise the possibility of detecting a false-positive (spurious) association. For these reasons, dose-response modeling was not conducted for this study.

Table C-52. Pavuk et al. (2003) —Thyroid function and disorders

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Thyroid diseases among veterans in the Air Force Health Study were identified using questionnaire data collected in up to five examinations that were verified by a review of medical records. Measures of thyroid function were also determined using serum samples.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Exposure to TCDD was assessed using serum, and reasonably classified veterans based on their exposure prior to disease onset. Appropriate methods were used to analyze the data both longitudinally and cross-sectionally.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.

Response	Consideration not satisfied. There were no statistically significant associations between TCDD and thyroid diseases. No associations were noted between serum-based measures of thyroid function (T4, T3%, or FTI) and TCDD levels. While the data suggest a dose-response relationship between TCDD and TSH levels, the clinical implications are unclear. There were no statistically significant increased risks of abnormal TSH levels among those in the highest exposure group relative to the lowest for any of the five examination periods.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The methods used to estimate TCDD exposure are clearly described, and capture exposure at an individual level prior to the diagnosis of the health outcome under study. The authors describe the limitations of the exposure assessment within the paper.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied. There were 188 veterans who were diagnosed with a thyroid condition following their tour of duty, and comparisons between 6 different thyroid diseases and four TCDD exposure categories had poor statistical power. While there was a suggestion of increased TSH abnormalities among Ranch Hand in the highest exposure group, these findings did not achieve statistical significance for any of the 5 examination periods. Further follow-up of this cohort is needed as the age distribution of the cohort may be too young to detect associations between TCDD and thyroid function.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. The paper was published in Annals of Epidemiology 2003; 13:335-343. The authors have discussed the strengths and limitations of the study.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum was used to characterize TCDD exposure as of 1987. Given exposures dropped dramatically for the Ranch Hands following their tours of duty, exposure to TCDD prior to disease onset is reasonably characterized. Serum-based measures of thyroid function were obtained at multiple examinations which permitted dose-response relationships to be evaluated both cross sectionally and longitudinally.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. There is uncertainty in the critical window of exposure which impacts the ability to calculate an effective TCDD over time. This study analyzes the potential for associations between point-in-time measures of TCDD serum levels and thyroid conditions and measures of thyroid disorders that may have occurred at any time over approximately a 30-year interval.
Conclusion	While the health outcomes and TCDD exposures were characterized using valid methods, no associations were observed between TCDD and any of the six thyroid conditions studied. Additionally, no associations were noted with T4, FTI, or T3% in either cross-sectional or longitudinal analyses. There is some support for a dose-response relationship between TCDD and TSH, however, no statistically significant increase in abnormal TSH levels were observed among those in the highest exposure group at any of the 5 examinations. Therefore, the clinical implications of this dose-response relationship are unclear, particularly in light of the lack of associations between TCDD and any of the thyroid disorders examined. Additionally, there is uncertainty in the critical window of exposure, which precludes calculation of a cumulative TCDD effective dose over time. For these reasons, dose-response modeling was not conducted for this study.

Table C-53. Michalek and Pavuk (2008)—Diabetes

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Prevalent diabetes identified from medical records from repeated medical check-ups. Preferred method of ascertaining outcome relative to use of death certificates.
2. Consideration	Risk estimates are not susceptible to important biases.

Response	Consideration satisfied. Adjustment was made for a number of risk factors related to diabetes (e.g., BMI, family history, smoking) and other factors likely strongly associated with TCDD exposure (e.g., last calendar year of service, occupation, etc.).
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. The RR for an increase in 10 units was 1.29 ($p < 0.001$), and the risks across the background, low and high exposure categories, relative to the unexposed were 0.86, 1.45, and 1.68.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Initial TCDD dose were estimated at the end of the tour of duty for the Ranch Hands. Individual-level serum dioxin measurements correlated well with correlated with days of spraying and calendar period of service, but collection of the samples roughly 20 years later required back-extrapolation.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. There were a total of 439 cases of diabetes identified.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. J Occup Environ Medicine, 2008, 50:330–340. The authors address strengths and limitations related to the accuracy of the one-compartment pharmacokinetic model, impact of the covariate time spent in Southeast Asia, and potential exposure misclassification on days sprayed.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. TCDD estimates were derived using serum samples.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. The nature of the data did not allow for latency or critical windows of exposure to be determined.
Conclusion	Because the nature of the data did not allow for the critical windows of exposure to be identified, dose-response modeling was not conducted for this study.

C.3.8. Other Noncancer Studies of Dioxin

Table C-54. McBride et al. (2009b)—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The New Zealand Health Information Service Mortality Collection and the Registrar-General's Index to Deaths were used to identify deaths. Additional searches were based on the last known address from the work record; the electoral roll and the habitation index; the telephone book; the internet; and Terranet property information database. An additional search was carried out through the Births, Deaths, and Marriages office of the New Zealand Department of Internal Affairs. Lastly, automated personnel and pension records were also used to locate past New Plymouth workers and identify some deaths.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Workers lost to follow-up (21%) were an unlikely source of bias since there was no evidence that this loss was differential in the internal analyses of workers. Confounding by sex, hire year, and birth year was addressed by adjustment in regression models. Potential confounding by other coexposures (e.g., 2,4,6-TCP) unlikely to have resulted in bias, due to presumed poor correlation with TCDD.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. No associations were detected for mortality and the TCDD exposure surrogates. No dose-response trend was observed across the exposure categories of TCDD.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.

Response	Consideration satisfied. Cumulative exposure to TCDD as a time-dependent metric was estimated for each worker from serum samples, but the authors did not examine a continuous measure of TCDD exposure (lagged or unlagged).
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied. Although the study had a large sample size (n=1,599 workers), extensive follow-up period (35 years) and considerable exposure gradient, a limited number noncancer deaths occurred. As such, mortality for some outcomes such as diabetes (based on 5 deaths) did not have adequate statistical power to examine potential associations. T he loss to follow-up of 21% of workers was also substantial. This would have impacted statistical power by reducing the number of deaths among the workers.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in J Occup Environ Med, 2009, 51:1049–1056. The other studies in the cohort highlight the 21% of the cohort lost to follow-up and the potential for other exposures during employment at the plant.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum measures available for 346 workers were used to derive TCDD exposures for the entire cohort using the area under the curve approach.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Effective dose could be estimated from serum-derived cumulative exposure estimates. Also, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	A considerable portion of the cohort was lost to follow-up, and no dose-response associations were reported. In addition, since all outcomes were based on mortality, dose-response modeling was not conducted for this study

Table C-55. McBride et al. (2009a)—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The New Zealand Health Information Service Mortality Collection and the Registrar-General's Index to Deaths were used to identify deaths. Additional searches were based on the last known address from the work record; the electoral roll and the habitation index; the telephone book; the internet; and Terranet property information database. An additional search was carried out through the Births, Deaths, and Marriages office of the New Zealand Department of Internal Affairs. Lastly, automated personnel and pension records were also used to locate past New Plymouth workers and identify some deaths.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Considerable amount of workers were lost to follow up (22%), but it is unclear if bias resulted. The dichotomous exposure measure was based on exposure to TCDD, chlorinated dioxins and phenoxy herbicides, so confounding by these coexposures is possible.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. There was no associations detected for mortality and the TCDD exposure surrogates. Because no individual exposure estimates were available for these analyses, dose response could also not be evaluated.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Dichotomous exposure (exposed/unexposed) and duration of employment were examined from job exposure classification assessed via occupational history records industrial hygienists/factory personnel knowledge and questionnaires. Authors discuss limitations in the assignment of exposure among cohort members.

5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. The size of the cohort is large enough to characterize mortality risks relative to the general population for most common causes of deaths. A limitation of this study is the loss to follow-up of a substantial percentage of workers (22%). This would have impacted statistical power by reducing the number of deaths among the workers.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in Occup Medicine, 2009, 59(4):255–263. The authors highlight cohort lost to follow-up, the limited size of the cohort, differences in cohort definitions between sprayers and producers, and the potential for other exposures during employment at the plant.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. TCDD exposures were not quantified. The dichotomous exposure measure was based on exposure surrogates of TCDD, chlorinated dioxins and phenoxy herbicides.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Effective dose could not be estimated given the lack of individual-level exposure data. Noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	The study lacks the quantification of exposures at an individual level, and a considerable portion of the cohort was lost to follow-up. In addition, since all outcomes were based on mortality, dose-response modeling was not conducted for this study.

Table C-56. Ryan et al. (2002)—Sex ratio

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration not satisfied. Company records were used to identify births, the date of birth, and the sex of the child. No information was provided on the expected completeness of identifying births in this manner. Moreover, the study was expanded to include workers who heard about the study in a public forum. Therefore, the study could be influenced by participation bias.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. See above.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. The study compared birth ratios among men and women employed at the plant to the general population. No categories of exposure were examined.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. This is not relevant as no analyses were done in relation to exposure levels.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For the categories of exposure used (yes/no), and the stratified analyses by sex and subcohort, the study allows for the birth ratios to be estimated with sufficient precision.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria not satisfied. Published in Environ Health Perspect, 2002, 110(11):A699–A701. The authors discussed the limitations of using serum collected many years after they stopped working to estimate TCDD exposures when the preferred metric would be TCDD levels at the time of conception. They did not address issues about the representativeness of the study participants to the entire cohort of workers, nor did they address the limitation of not being able to conduct dose-response analyses using individual-level TCDD data.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. While serum measures were available for 84 of the 198 participants of the study, birth ratios were compared between the cohort of 2,4,5-T and 2,4,5-trichlorphgenol workers relative to the city of Ufa. There was no attempt to derive birth ratios in relation to exposure levels. The serum data were only used to demonstrate that these workers, on average, had TCDD levels 30 times higher than Ufa residents.

3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. TCDD exposures were based on serum measures taken in some cases many years after children were born; no attempt was made to back-extrapolate to the time of conception.
Conclusion	Risk estimates have not been derived in relation to TCDD exposure levels. Uncertainties exist about the representativeness of the participants in relation to the cohort as a whole, and insufficient details are provided to evaluate the extent in which all births were identified. While these data could not be used for quantitative dose-response modeling, the much lower male:female birth ratio among exposed fathers is consistent with the finding by Mocarelli et al, and lends support to those findings. Dose-response modeling was not conducted for this study.

Table C-57. Kang et al. (2001)—Long term health consequences

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration not satisfied. Data collected from only half of the individuals in the study target population, thus, there is some potential for selection bias in this study. The study excluded those who had died before 1999, excluding potentially important TCDD-related adverse health effects that could result in death more than two decades after veterans had been actively spraying. Survey participation rates were modest: 72.9% for Vietnam veterans and 69.2% for non-Vietnam veterans. If those in poorer health were less inclined to participate, the prevalence of the selected chronic health conditions would be understated. The study relied on self-reported measures of disease prevalence increasing the possibility of recall bias.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. See above.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. The data collected are cross-sectional, they are ill-suited for evaluating the relationship between the timing of exposure and the onset of disease.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum TCDD levels were available for 897 subjects, although the entire study population consisted of a group of 1,499 Vietnam veterans and a control group of 1,428 non-Vietnam veterans.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Size of study population likely provided sufficient study power to observe effects.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in Chemosphere in 2001. The authors discussed the limitations of using collected sera.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. While serum TCDD measures were available for some of the study participants, there was no analysis of other contaminant exposures in the study population.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. The critical exposure window could not be identified for the study.
Conclusion	A number of potential biases are present in this study. There is also potential confounding of results from exposures to other contaminants that have not been evaluated in the population. The critical exposure window cannot be determined. Dose-response modeling was not conducted for this study.

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APPENDIX D

Summaries and Evaluations of Cancer and Noncancer In Vivo Animal Bioassays for Inclusion in TCDD Dose-Response Assessment

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National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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APPENDIX D. SUMMARIES AND EVALUATIONS OF CANCER AND NONCANCER IN VIVO ANIMAL BIOASSAYS FOR INCLUSION IN TCDD DOSE-RESPONSE ASSESSMENT

D.1. SUMMARY OF ANIMAL BIOASSAY STUDIES INCLUDED FOR TCDD DOSE-RESPONSE MODELING

This appendix summarizes studies that have already met the in vivo animal bioassay 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) study inclusion criteria (see Section 2.3.2). These studies are identified and described in a tabular form in Section 2.4.2 of the main document in Tables 2-3 and 2-4, for cancer and noncancer, respectively. Section D.2 of this appendix also provides lists of the animal bioassays that met and did not meet the study inclusion criteria. Sections D.2.1 and D.2.2 describe the results for the cancer and noncancer studies, respectively. Table D-1 presents the noncancer studies that met the study inclusion criteria, and Table D-2 identifies the noncancer studies that were excluded, along with the criteria that were not met for those studies. The following study summary sections are organized by reproductive studies, developmental studies, and general toxicity studies (subdivided by duration). They summarize the experimental protocol, the results, and the no-observed-adverse-effect levels (NOAELs) and LOAELs U.S. Environmental Protection Agency (EPA) has identified for each included study.

To evaluate and discuss studies consistently, doses were converted to nanograms per kilogram body weight per day (ng/kg-day) and were also adjusted for continuous exposure. Some doses were adjusted based on daily dietary intake and body weight. For these studies, EPA uses 10% of an animal's body weight as the daily feed rate. More commonly, doses were adjusted from 5 days/week to a 7 days/week standard adjustment, in which case administered doses were multiplied by 5 and divided by 7 to obtain continuous doses. To adjust for weekly dosing, the weekly administered doses were multiplied by the administration frequency per week (in days) and divided by 7 to give continuous doses.

Other exposure protocols used a single loading dose followed by weekly maintenance doses. To adjust these doses, the loading dose was added to the maintenance doses multiplied by the administration frequency, and this sum was divided by the exposure duration to give a continuous dosing rate. The doses administered in single dose studies were not averaged over the observation period.

D.1.1. Reproductive Studies

D.1.1.1. *Bowman et al. (1989a; 1989b) [and related Schantz and Bowman (1989); Schantz et al. (1986); Schantz et al. (1992)]*

Female rhesus monkeys (6 to 10 years old; 8 per treatment) were exposed to 0 or 5 ppt (for 3.5 years), or 25 ppt (for 4 years) TCDD (purity not specified) (Schantz et al., 1992; Bowman et al., 1989a; Bowman et al., 1989b; Schantz and Bowman, 1989; Schantz et al., 1986). Female monkeys were mated to unexposed males after 7 months (Cohort I) and 27 months (Cohort II) of exposure, and, then again 10 months postexposure (Cohort III). The average daily doses to mothers were equivalent to 0, 0.12, and 0.67 ng/kg-day. The 0.67 ng/kg-day dose group had reduced reproductive rates in both Cohorts I ($p < 0.001$) and II (Bowman et al., 1989b). The mean number of days of offspring survival ($p < 0.023$) also decreased. No effects on birth weight or growth, or physical evidence of toxicity (Bowman et al., 1989a) were observed. Behavioral effects were observed in the offspring (Cohort I: 7, 6, and 0 offspring, respectively; Cohort II: 3, 5, and 0 offspring, respectively; Cohort III: 6, 7, and 3, respectively). In the 0.67 ng/kg-day dose group, the number of offspring was insufficient to form a group in either Cohorts I or II. Offspring in the 0.12 ng/kg-day dose group had alterations in social behavior of the mother-infant pairs (mothers had increased care giving, which appeared to be an effect of the infants and not due to the treatment of the mother) and peer group of the offspring after weaning (Bowman et al., 1989a). The performance of learning tasks was inversely related to the level of TCDD in the body fat. Schantz and Bowman (1989) examined effects using discrimination-reversal learning (RL) and delayed spatial alteration (DSA). RL detected effects in the 0.12 ng/kg-day group as measured by retarded learning of the shape reversal ($p < 0.05$), but DSA did not. In another behavioral study, Schantz et al. (1992) placed two offspring (one male, one female) from the 0.12 ng/kg-day dose group of Cohort I into each of three peer groups that also consisted of two control monkeys tested in a large playroom for 1.5 hours/day, 5 days/week. Patterns of behavior were then watched beginning on the second day of socialization 4 days/week for 9 weeks. Play behavior, displacement, and self-directed behavior were significantly altered in the TCDD-exposed offspring. In a second experiment by Schantz et al. (1992) utilizing offspring from Cohort III (i.e., born after the cessation of maternal exposure to TCDD), four offspring from mixed treatment groups (i.e., control and 0.12 and 0.67 ng/kg-day dose groups; varying numbers of males and females per group) and 3–4 offspring

from the same treatment groups were placed into peer groups and assessed similarly as described above. Behavioral changes were observed in peer groups containing only TCDD-exposed offspring, but behavior was not altered in TCDD-exposed offspring socializing with control monkeys. Additionally, Schantz et al. (1986) combined the cohorts and looked at 5, 5, and 3 mother-infant pairs in the 0, 0.12, and 0.67 ng/kg-day groups, respectively. They found that TCDD-exposed mother-infant pairs spent more time in close, social contact compared with the controls (mutual ventral contact, $p < 0.025$; nipple contact, $p < 0.01$) and infants had reduced locomotor activity ($p < 0.05$), but the dose effect was complex. Of note, the control groups contained fewer males than did the TCDD-exposed groups.

From these reproductive studies in monkeys, a lowest-observed-adverse-effect level (LOAEL) of 0.12 ng/kg-day is established for significantly altered social behavior in offspring from TCDD-exposed females (Schantz et al., 1992). A NOAEL cannot be determined. However, there are several issues associated with these data that confound their interpretation. For example, there were a small number of TCDD-exposed offspring (only one male and one female) in a limited number of observed peer groups (only three). The subjective nature of the experimental design (e.g., observing and scoring the various social interactions and other behaviors among the offspring, the schematic of the playroom apparatus, etc.) also contributes uncertainty to the data analysis. Additionally, the biological significance of the alteration in social behaviors among the TCDD-exposed offspring (e.g., increased initiation of social play as it pertains to overall social adjustment) is difficult to assess. Furthermore, in a follow-up report by Rier et al. (2001b), DLC levels were quantified in the sera of some of the maternal monkeys from the aforementioned studies 13 years after termination of TCDD treatment. Rier et al. (2001b) reported that the animals had elevated serum polychlorinated biphenyl (PCB)77 and PCB126 levels and an increased serum toxicity equivalence (TEQ). Although the cause of the elevated PCB levels was unclear, the study authors speculated that "accumulation of PCBs in TCDD-treated animals may have resulted from PCB exposure during TCDD administration due to a contaminated TCDD solution or other inadvertent source." They also inferred that all the animals may have been exposed to PCBs in their feed or other environmental sources. Taken together, the multitude of confounding factors greatly decreases the confidence in the dose-response data from aforementioned reproductive studies in monkeys.

D.1.1.1.1. *Supplemental published information on these rhesus monkeys [Rier et al. (1995; 1993)]*

Rier et al. (1995; 1993) examined the impact of chronic TCDD exposure on endometriosis. Female rhesus monkeys (eight animals per treatment group) were exposed to 0, 5, or 25 ppt TCDD (purity not specified) in feed for 4 years. Previously, Bowman et al. (1989a) determined that these dietary concentrations were equivalent to 0, 0.12, and 0.67 ng/kg-day, respectively. Ten years after termination of TCDD treatment, the presence of endometriosis was determined via laparoscopic surgical procedure, and the severity of the disease was assessed. The study authors reported that three monkeys in the 0.67 ng/kg-day exposure group died at 7, 9, and 10 years after termination of TCDD treatment. Autopsy results attributed the deaths to widespread and severe peritoneal endometriosis (all three monkeys) along with obstruction of the colon (one monkey) and blockage of the jejunum (one monkey). Other deaths also occurred in the control group (1 death from birthing complications and another from an unknown cause); in the 0.12 ng/kg-day dose group (1 death due to natural causes with no endometriosis), and in the 0.67 ng/kg-day dose group (1 death due to a breeding fight with no incidence of endometriosis). At study termination, 17 live animals and the 3 that had previously died of endometriosis were evaluated (total $n = 20$).

Incidence of endometriosis was significantly ($p < 0.05$) higher than in the control group with 71 and 86% incidence rates in the 0.12 and 0.67 ng/kg-day dose groups, respectively, compared with 33% in the control group. Severity of endometriosis was also significantly ($p < 0.001$) correlated with TCDD dose. Staging by rAFS indicated that untreated control animals had either minimal or no incidence of endometriosis. In comparison, endometriosis was absent in 2 of the 7 monkeys in the 0.12 ng/kg-day dose group, while only 1 of the 7 animals in the high-dose group was disease free. Moderate-to-severe disease was observed in 3 of the 7 animals in the 0.12 ng/kg-day dose group and 5 of the 7 animals in the 0.67 ng/kg-day dose group. Moderate-to-severe disease was not observed in the control group. The authors also compared the incidence and severity of endometriosis in TCDD-exposed animals with 304 normal, nonneutered females with no dioxin exposure and reported that the disease was not present in monkeys that were less than 13 years of age, while the disease rate was 30% among animals 13 years of age or older. The study authors report that these findings are in agreement with human and rhesus studies demonstrating that the prevalence of detectable endometriosis can increase with advanced age.

In a follow-up report, Rier et al. (2001b) examined the DLC and TCDD levels in sera collected from 9 treated (n = 6, 0.12 ng/kg-day dose group; n = 3, 0.67 ng/kg-day dose group) and 6 control female monkeys surviving from the Rier et al. (1995; 1993) study and 13 years after termination of TCDD treatment. Additional studies were conducted on four monkeys that died 7 to 11 years after TCDD exposure. Rier et al. (2001b) reported that treated animals in this study had elevated serum TCDD, PCB77, and PCB126 levels, as well as an increased serum TEQ; the fractional contribution of serum TCDD levels to total serum TEQ was 30% in treated animals. Although the severity of endometriosis in the 15 monkeys examined was determined previously (Rier et al., 1995; Rier et al., 1993), it was reevaluated and disease status was similar between laparoscopies. Endometriosis severity corresponded to the serum PCB77 concentrations rather than total TCDD. As stated previously, the study authors speculated that "accumulation of PCBs in TCDD-treated animals may have resulted from PCB exposure during TCDD administration due to a contaminated TCDD solution or other inadvertent source." They also inferred that all the animals may have been exposed to PCBs in their feed or other environmental sources. Thus, in these studies, it is not possible to determine the contribution of TCDD, alone, to the endometriosis due to the background contamination. These studies (Rier et al., 1995; Rier et al., 1993), were not selected for TCDD dose-response modeling because exposures were not to TCDD only.

D.1.1.2. *Franc et al. (2001)*

To study the effects of subchronic, low-dose exposure to TCDD on the regulation and expression of the aryl hydrocarbon receptor (AhR), Franc et al. (2001) used rodent models with varying sensitivities to TCDD. Female Sprague-Dawley rats, inbred Long-Evans rats, and outbred Han/Wistar rats (eight per dose group) were dosed via oral gavage with 0, 140, 420, or 1,400 ng/kg TCDD (>99% purity) dissolved in corn oil once every 2 weeks for 22 weeks (0, 10, 30, and 100 ng/kg-day average daily doses). Animals were sacrificed 10 days after the final dosing. Body weights were recorded biweekly and just before sacrifice. After sacrifice, liver and thymus weights were determined. Liver tissue samples were removed and either frozen for RNA isolation followed by semiquantitative reverse transcription polymerase chain reaction (RT-PCR) or homogenized and prepared for subcellular fraction analysis. Radioligand binding and immunoblotting techniques were used to measure AhR levels, and RT-PCR analysis was

used to assess mRNA levels of AhR, aryl hydrocarbon nuclear receptor (ARNT), and cytochrome P450 (CYP)1A1.

Long-Evans rats exhibited significant ($p < 0.001$) decreased weight gain over time as compared with the Sprague-Dawley and Han/Wistar rats as determined by repeated measures analysis of variance (ANOVA). Because body-weight gain varied indirectly with TCDD exposure, liver and thymus tissue weights were normalized to body weight for data analysis. TCDD exposure led to a significant ($p < 0.05$) increase in relative liver weights at all three TCDD doses and in all three rat strains, compared with the control groups. At the upper end of the TCDD dose range, Sprague-Dawley rats dosed with 100 ng/kg-day showed the greatest increase in relative liver weights (160% of the control values), while the relative liver weights in Long-Evans and Han/Wistar rats were similar to each other, and also were elevated above control values by 10–20%. At the 30 and 100 ng/kg-day doses, the relative thymus weights were significantly lower ($p < 0.05$) in all rat strains compared with their corresponding controls, but the 10 ng/kg-day dose did not produce a statistically significant effect in any strain. However, absolute thymus weight was higher at all doses in Han/Wistar rats, which also had a higher control thymus weight.

Supporting observed differences in baseline TCDD sensitivity among the rat strains, liver AhR levels in the control groups as measured by radioligand binding were similar for Sprague Dawley and Han/Wistar rats, but were approximately twofold higher for Long-Evans rats. A significant ($p < 0.05$) twofold, dose-dependent increase in radioligand binding of liver AhR was observed at all TCDD doses relative to the control in Sprague-Dawley rats. At the 30 ng/kg-day dose, the AhR level for Long-Evans rats was significantly ($p < 0.05$) increased to approximately 250% of the control level.

AhR protein levels measured in the liver cytosol by immunoblotting were highest in the 10 and 30 ng/kg-day TCDD dose groups for all three rat strains. Significant ($p < 0.05$) increases in AhR levels were observed in the Sprague-Dawley rats that received 30 ng/kg-day, and in Long-Evans rats that received either 10 or 30 ng/kg-day. A significant ($p < 0.05$) decrease in AhR protein level was observed only at the 100 ng/kg-day dose in Han/Wistar rats. Liver AhR protein was not detectable by immunoblotting in nuclear extracts for any strain or dose. The study authors assert that AhR levels measured in cytosol correspond to measures in whole-tissue lysates as demonstrated in their previous work.

Based on RT-PCR analysis, all three rat strains showed similar responses in liver AhR mRNA following TCDD exposure. Liver AhR mRNA levels increased significantly ($p < 0.05$) as compared with control levels in all rat strains at 10 and 30 ng/kg-day and in Long-Evans rats at 100 ng/kg-day. The study authors observed that statistically significant increases in AhR mRNA levels in the liver were not always associated with statistically significant increases in AhR levels for a given strain and dose, but that the opposite (increases in AhR levels associated with increases in AhR mRNA levels) was always true. Changes in liver ARNT mRNA levels tended to increase with increasing TCDD dose, and the increases were significant ($p < 0.05$) in the 30 ng/kg-day dose groups of Long-Evans and Han/Wistar rats. At the 100 ng/kg-day TCDD dose, all rat strains showed a decrease in ARNT mRNA in the liver relative to controls with significant ($p < 0.05$) differences for the 100 ng/kg-day TCDD dose groups of Sprague-Dawley and Han/Wistar rats. Liver CYP1A1 mRNA induction was not detectable in control animals. A significant ($p < 0.05$) increase in liver CYP1A1 mRNA was observed in all rat strains administered 10 or 30 ng/kg-day TCDD. Liver CYP1A1 mRNA levels also were significantly ($p < 0.05$) elevated above controls in the 100 ng/kg-day groups although not to the same extent as in the 30 ng/kg-day groups. For all rat strains, the largest up-regulation for AhR and ARNT mRNA levels occurred in the 30 ng/kg-day TCDD dose groups.

The NOAEL for TCDD identified in this study is 10 ng/kg-day TCDD. At 10 ng/kg-day TCDD, the change in relative liver weight, while significantly ($p < 0.05$) increased in Sprague-Dawley rats, was determined (Franc et al., 2001) to be less than 10% and judged by EPA not to be biologically relevant. Also, at 10 ng/kg-day TCDD, the change in relative thymus weight, was not statistically significantly decreased in Sprague-Dawley, Han-Wistar or Long-Evans rats. The study LOAEL is 30 ng/kg-day based on statistically and biologically significant increases in relative liver weight in Sprague-Dawley and Long-Evans rats and statistically and biologically significant decreases in relative thymus weight in Sprague-Dawley, Han-Wistar, and Long-Evans rats.

D.1.1.3. *Hochstein et al. (2001)*

Adult female mink (12/treatment group) were administered dietary concentrations of 0.0006 (control), 0.016, 0.053, 0.180, or 1.40 ppb TCDD (purity >99.8%) for 132 days (Hochstein et al., 2001). This dose is estimated to be equivalent to 0.03 (control), 0.8, 2.65, 9,

and 70 ng/kg-day assuming a food consumption of 5% of body weight per day. Females were mated with unexposed males beginning on treatment Day 35. Females were allowed to mate every fourth day during a 29-day mating period or until a confirmed mating. Mated females were presented with a second male either the day after initial mating or 8 days later. In the 70 ng/kg-day group, the treated animals were lethargic after 4 to 5 weeks, with several having bloody (tarry) stools near the end of the trial. Two animals in the 70 ng/kg-day dose group died prior to study termination. These animals had lost a large percentage of their body weight (24−43%), and had pale yellow livers and intestinal hemorrhages. Histopathology from both mink indicated marked diffuse hepatocellular vacuolation. The mean body weight decreased in all treatment groups including the control (losing an average of 3.29% of initial body weight), compared to a dose-dependent loss of up to 26% in the 70 ng/kg-day group. Mating and reproduction were considered subnormal in all groups. The number of females that gave birth in the 0.03 (control), 0.8, 2.65, 9, and 70 ng/kg-day dose groups were 5/12, 0/12, 3/12, 8/12, and 0/11, respectively. The study authors speculated that the subnormal breeding and reproductive performances in the control females likely were due to the indoor environment in which the mink were housed. In the three groups that gave birth, there was a dose-dependent decrease in kit body weight at birth, which was significant ($p < 0.05$) in the 9 mg/kg-day group compared with the controls. The body weight in the kits was not significantly different at 3 or 6 weeks after birth. The 3-week survival rates of 71, 47, and 11% were recorded for kits in the 0.03 (control), 2.65, and 9 ng/kg-day dose groups, respectively. Six-week kit survival rates were 62, 29, and 11% in the 0.03 (control), 2.65, and 9 ng/kg-day dose groups, respectively.

In the adult females, clinical signs of toxicity were noted in the 70 ng/kg-day group near the end of the study and included alopecia and notably thickened, deformed, and elongated toenails. There was a dose-dependent decrease in plasma total solids, total protein, and osmolality that reached statistical significance ($p < 0.05$) in the two highest exposure groups. Anion gap was significantly decreased ($p < 0.05$) and alanine aminotransferase was significantly increased in the 70 ng/kg-day group compared to the controls. At terminal sacrifice, there was a dose-related decrease in body weight. There was a dose-related increase in liver weight that reached statistical significance ($p < 0.05$) in the 70 ng/kg-day dose group. The brains of 42% of the animals in the 70 ng/kg-day dose group had localized accumulation of lymphatic cells within the meninges with mild extension into the adjacent neuropil and mild gliosis. Of the 10 mink

surviving to study termination in the 70 ng/kg-day group, 3 had periportal hepatocellular vacuolation. These same brain and liver lesions were not observed in the control mink.

As there were no litters produced in the low-dose group and pregnancy outcomes were not dose related, the 0.8 ng/kg-day exposure level does not inform the choice of NOAEL or LOAEL. Thus, the LOAEL for this study is 2.65 ng/kg-day (132-day maternal exposure duration) based on reduced kit survival (47% of control at 6 weeks). A NOAEL cannot be determined for this study.

D.1.1.4. *Hutt et al. (2008)*

Hutt et al. (2008) conducted a 3-month study investigating changes in morphology and morphogenesis of preimplantation embryos as a result of chronic exposure to TCDD in female rats. The study authors administered 0 or 50 ng/kg TCDD (>99% purity) in corn oil via oral gavage to groups of three pregnant Sprague-Dawley rats on gestation days (GDs) 14 and 21 and on postnatal days (PNDs) 7 and 14. The resulting female pups were divided into groups of 3 and administered 0 or 50 ng/kg TCDD (>99% purity) in corn oil (equivalent TCDD doses of 0 and 7.14 ng/kg-day) on PND 21 and weekly thereafter until they reached 3 months of age. Pups were then mated, fertilization was verified, and preimplantation embryos were harvested 4.5 days later. Preimplantation embryos were examined using immunofluorescence microscopy to determine blastomere abnormalities.

No significant difference as compared with the control in preimplantation embryotoxicity was observed following exposure to TCDD. Morphologically normal preimplantation embryos were significantly ($p < 0.05$) reduced in the 50 ng/kg TCDD exposed rats (15 of 41, 36.6%) compared with the control group (31 of 39, 79.5%). Preimplantation embryos of TCDD-exposed rats included irregularities in mitotic spindles (13 of 18 were monopolar), chromosome patterns in metaphase, blastomere size, and shape, blastomere nuclei shape in interphase, f-actin, and cytokinesis. The study authors concluded that the compaction stage of preimplantation embryogenesis is the most sensitive following exposure to TCDD.

A LOAEL for this study is 50 ng/kg (7.14 ng/kg-day adjusted dose) for a significantly ($p < 0.05$) lower proportion of morphologically normal preimplantation embryos during compaction stage in female Sprague-Dawley pups weekly for 3 months. A NOAEL cannot be determined for this study.

D.1.1.5. *Ikeda et al. (2005b)*

Ikeda et al. (2005b) studied the effect of repeated TCDD exposure to F0 dams on the male gonads of F1 generation and sex ratio in the F2 generation. Twelve female Holtzman rats were treated with a single dose of 400 ng/kg TCDD (≥98% purity) orally, via gavage, followed by weekly treatment doses of 80 ng/kg TCDD (16.5 ng/kg-day adjusted for continuous exposure of 10 weeks; specified 2 weeks premating, assumed 1 week for successful mating, 3 weeks of gestation, and specified 4 weeks to weaning) during mating, pregnancy, and lactational periods (total exposure duration approximately 10 weeks). Corn oil served as the control in another group of 12 dams. Four dams were sacrificed on GD 20 to evaluate the in utero toxicity of TCDD. Litter sizes from the remaining eight dams were examined on PND 2, and some of the F1 offspring were sacrificed to estimate TCDD tissue concentrations. The remaining offspring were weaned on PND 28. Some of the F1 (number not specified) offspring were mated with untreated females on PND 98, following which, litter size, sex ratio, weight, and anogenital distance of F2 pups were examined on PND 2. Mated and unmated F1 males were sacrificed and the testes, epididymis, seminal vesicle, and the ventral prostate were weighed; the cauda epididymis was weighed and examined for sperm count.

All fetuses in the control and TCDD group as a result of in utero exposure in the F0 generation survived. Litter size, sex ratio, and anogenital distance in the F1 generation on PND 2 were not altered as a result of in utero TCDD exposure. Pup weight was significantly ($p < 0.05$) lower in the TCDD-treated group than in controls. TCDD concentration in the adipose tissue of the F0 dams on GD 20 was significantly ($p < 0.05$) higher than in the liver. Adipose TCDD was significantly ($p < 0.01$) reduced at weaning, however, compared to concentrations on GD 20. F1 pup liver TCDD concentration increased significantly ($p < 0.01$) and was higher on PND 28 than PND2. The liver weight in F1 males increased by 14-fold at PND 28 compared to PND 2, implying a transfer of approximately 850 pg of TCDD from the dam to the F1 pup livers during lactation. TCDD also was detected in pup adipose tissue on PND 28. Body weight of TCDD-exposed F1 males was significantly ($p < 0.001$) lower than control males at weaning (PND 28). No significant differences in testis and cauda epididymis weights were observed between the control and treated groups. Ventral prostate weight in the F1 males exposed to TCDD, however, was approximately 60% lower than controls. No change in weight of the body, brain, testes, cauda epididymis, or seminal vesicle was observed at

PND 120. Ventral prostate weight, however, was 16% lower than that of the control group ($p < 0.001$). Sperm count in the cauda epididymis of the F1 males was not affected by TCDD exposure.

Examination of F2 generation litters indicated no significant differences in litter size, pup body weight, and anogenital distance between TCDD-treated or vehicle control groups. The percentage of male F2 pups born to maternally and lactationally TCDD-exposed males was significantly ($p < 0.05$) lower (38%) than those sired by control group males (52%). Every female mated with maternally TCDD-exposed F1 males delivered more female than male pups.

A LOAEL for TCDD of 16.5 ng/kg-day for an estimated 10 week exposure duration in F0 rat dams is identified in this study for decreased development of the ventral prostate in the F1 generation (60% lower than controls) and for significantly ($p < 0.05$) altered sex ratio (decreased percentage of males) in the F2 generation. A NOAEL cannot be determined for this study.

D.1.1.6. *Ishihara et al. (2007)*

Ishihara et al. (2007) examined the effect of repeated TCDD exposure of F0 males on the sex ratio of F1 offspring. Seven-week-old male ICR mice ($n = 127$) were divided into three groups and treated via gastric intubation with an initial loading dose of either 2 or 2,000 ng TCDD/kg body weight(BW) or an equivalent volume of sesame oil (vehicle) as control, followed by a weekly maintenance doses of 0, 0.4, or 400 ng/kg until the animals were 12 weeks old. One week after the last exposure, the animals were mated with untreated female mice. On the day a vaginal plug was identified, F0 male mice were sacrificed and major organs including testes, epididymis, and liver were removed and weighed. Organ tissues also were examined for histopathological and immunohistochemical changes. Treatment levels, averaged over the 6 week period from start of treatment to mating (five maintenance doses), were 0, 0.095, and 950 ng/kg-day for the control, low dose and high dose groups, respectively.

All TCDD-treated males successfully impregnated untreated females and yielded viable offspring. Mortality, pup weights, and mating and fertility indices were not affected by TCDD exposure. There were no significant differences in body weights or in relative weights of testes, epididymis, or livers in the TCDD-treated F0 males compared to the control group. The livers of some animals (number not specified) in the high-dose group, however, were larger and heavier

than in the controls or the low-dose group. Hence, tissues from the high-dose animals were selected for detailed immunohistochemical examination.

General histopathological findings in the TCDD-treated groups showed no changes in cell morphology in germ, Sertoli, and Leydig cells of the testes. Arrangement of the germ cells was normal and there was no difference in the epididymis spermatozoon number in either of the TCDD-treated groups compared to controls. Livers of some of the animals in the high-dose group however, showed enlarged and vacuolated areas in the centrilobular area when compared to the low-dose group and the control group. Immunohistochemical and quantitative immunohistological findings showed a marked increase in staining intensity for CYP1A1 in the cytoplasm of the hepatocytes in the centrilobular area of the high-dose TCDD group compared to the cells in the low-dose and the control groups. In addition, proportions of immunoreactive CYP1A1 areas in the liver sections of the high-dose group were higher than in the low-dose and control groups. The proportions of immunoreactive CYP1A1 also varied across animals (n = 33) in the high-dose group.

In addition to the above findings, there was a dose-related decrease in the male/female sex ratio. The proportion of male offspring of the high-dose group was significantly lower ($p < 0.05$) than that observed in controls (46.2% vs. 53.1%, respectively). Hepatic immunoreactive CYP1A1 staining levels in individual F0 males were strongly correlated with the sex ratio of their offspring.

A LOAEL for TCDD of 950 ng/kg-day for a 6 week exposure duration of F0 male mice is identified for significantly ($p < 0.05$) decreased male/female sex ratio (i.e., higher proportion of female offspring) in the F1 generation. The NOAEL is 0.095 ng/kg-day.

D.1.1.7. *Latchoumycandane and Mathur (2002) [and related: Latchoumycandane et al. (2003, 2002a; 2002b)]*

Latchoumycandane and Mathur (2002) conducted a study to determine whether treatment with vitamin E protected rat testes from TCDD-induced oxidative stress. Groups of albino male Wistar rats (n = 6) were administered an oral dose of 0 (vehicle alone) 1, 10, or 100 ng TCDD/kg-day for 45 days, while another group of animals (n = 6) was coadministered TCDD at the same doses, along with vitamin E at a therapeutic dose of 20 mg/kg-day for 45 days. At study termination, animals were fasted overnight, weighed, and sacrificed. Testis, epididymis,

seminal vesicles, and ventral prostate were removed, weighed, and preserved for further examination. The left testis was used to determine daily sperm production, while the right testis was used for biochemical studies. Superoxide dismutase (SOD), catalase, glutathione reductase, and glutathione peroxidase activity were measured in the testes, along with production of hydrogen peroxide and lipid peroxidation. In a separate exposure protocol, groups of albino male Wistar rats (n = 4) were administered an oral dose of 0 (vehicle alone) 100, 1,000, or 10,000 ng/kg-day TCDD for 4 consecutive days (Latchoumycandane et al., 2003 see summary in Appendix H); .

Body weights of TCDD-treated rats did not differ significantly from the control group. Testis, epididymis, seminal vesicle, and ventral prostate weights in the TCDD-treated groups, however, decreased significantly ($p < 0.05$) when compared with controls. None of these changes were observed in the TCDD-exposed groups receiving vitamin E. There was a dose-related decrease in daily sperm production ($p < 0.05$) in all three TCDD-treated groups when compared with the control group. In contrast, the TCDD-treatment groups that also received vitamin E did not show any significant changes in daily sperm production compared to the controls. The TCDD-treated groups also showed significantly ($p < 0.05$) lower activities of the antioxidant enzymes (superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase) than the control group. Levels of hydrogen peroxide and lipid peroxidation increased significantly ($p < 0.05$) in the testes of the rats treated with TCDD compared to the corresponding controls. The TCDD-treated groups that had been coadministered vitamin E show no difference in antioxidant enzyme activities or in reactive oxygen species production when compared with controls.

A LOAEL for TCDD of 1.0 ng/kg-day for a 45-day exposure duration in rats is identified in this study for significantly ($p < 0.05$) reduced sperm production and significantly ($p < 0.05$) decreased reproductive organ weights. A NOAEL cannot be determined for this study.

D.1.1.8. *Murray et al. (1979)*

Male (10−16 per treatment) and female (20−32 per treatment) Sprague-Dawley rats were administered diets containing TCDD (purity >99%) to achieve daily dosages of 1, 10, or 100 ng/kg-day through three generations. After 90 days of treatment, F0 rats were mated to produce F1a offspring. Thirty-three days after weaning of the last F1a litter, the F0 rats were

mated again to produce F1b offspring. Some F0 rats were mated a third time for a cross-mating study. The F1b and F2 rats were mated at about 130 days of age to produce the F2 and F3 generations. No clinical signs of toxicity or changes in body weight or food consumption were observed in F0 rats during the 90 days of treatment before mating. The 100 ng/kg-day group was discontinued due to the lack of offspring. In the three surviving offspring (all males), no changes in appearance, body weight, or food consumption occurred. A dose of 10 ng/kg-day caused a consistent decreased body weight in both sexes of F1 and F2 rats, which was associated with decreased food consumption. A significant ($p < 0.05$) decrease in the fertility in the F1 and F2 rats occurred in the 10 ng/kg-day group—but not in F0 rats. The number of live pups and gestational survival index were significantly ($p < 0.05$) decreased in the 100 ng/kg-day F0 rats and in the 10 ng/kg-day F1 and F2 rats. The gestational survival index also was significantly ($p < 0.05$) decreased in F2 rats administered 1 ng/kg-day. Postnatal survival was significantly ($p < 0.05$) reduced only in F2 rats administered 10 ng/kg-day. Growth (as measured by body weight) was affected in the 10 ng/kg-day group only in the third generation. In the 10 ng/kg-day group, a significant ($p < 0.05$) decrease in relative thymus weight and increase in liver weight also occurred in F3 rats (weights were not measured in F2 rats). Additionally, mating 100 ng/kg-day TCDD-treated females with untreated males increased the percent of implants resorbed as assessed by uterine histopathology.

The reproductive LOAEL is 10 ng/kg-day based on a significant ($p < 0.05$) decrease in fertility (33−37% lower than controls); decrease in the number of live pups (18−27% lower than controls); decrease in gestational survival (10−11% lower than controls); decrease in postnatal survival (32% lower than controls); and decreased postnatal body weight (14−19% lower than controls at weaning) in one or more generations. The reproductive NOAEL is 1 ng/kg-day.

D.1.1.9. *Shi et al. (2007)*

Pregnant Sprague-Dawley rat dams (3 per treatment group) were administered 0, 1, 5, 50, or 200 ng/kg TCDD (purity >99%) in corn oil by gavage on GD 14 and GD 21 and on PND 7 and PND 14 for lactational exposure to pups (Shi et al., 2007). Ten female pups per treatment were selected and administered TCDD weekly at the same dose levels through their reproductive lifespan (approximately 11 months). The corresponding equivalent daily TCDD doses are 0, 0.14, 0.71, 7.14, and 28.6 ng/kg-day. Vaginal opening was slightly—but significantly

($p < 0.05$)—delayed in the 28.6 ng/kg-day females. Vaginal opening was also delayed—but not significantly—in the 0.14 and 7.14 ng/kg-day females. Reproductive senescence with normal cyclicity was significantly ($p < 0.05$) accelerated beginning at 9 months in 7.14 and 28.6 ng/kg-day females. Serum estradiol concentrations were decreased at all time points across the estrous cycle in a dose-dependent manner with a statistically significant decrease ($p < 0.05$) in all but the lowest dose group. TCDD exposure, however, did not affect the number or size distribution of ovarian follicles; responsiveness of the pituitary gland to gonadotropin-releasing hormone, or serum profiles of follicle stimulating hormone (FSH), luteinizing hormone (LH), or progesterone.

A LOAEL for TCDD of 0.71 ng/kg-day for an 11-month exposure duration was identified in this study based on significantly ($p < 0.05$) decreased estradiol levels in offspring. The NOAEL for this study is 0.14 ng/kg-day.

D.1.1.10. *Yang et al. (2000)*

Yang et al. (2000) studied the impact of TCDD exposure on the incidence and severity of endometriosis in female rhesus monkeys. Groups of 7- to 10-year old nulliparous cynomolgus monkeys were treated with 0 ($n = 5$), 1, 5, or 25 ($n = 6$ per group) ng/kg BW TCDD 5 days per week via gelatin capsules for 12 months. Because the monkeys received 1 capsule 5 days per week, the doses adjusted for continuous exposure were 0, 0.71, 3.57, and 17.86 ng/kg-day. Prior to TCDD administration, all animals had endometriosis induced during Days 12–14 of the menstrual cycle by auto-transplantation of endometrial-strips in multiple abdominal sites. All TCDD-treated and control groups were laparoscopically examined during months 1, 3, and 6 to monitor the survival of endometrial implantations and to obtain peritoneal fluid to determine the concentration and immunotype of endometrial growth regulator cytokines interleukin-6 (IL-6) and interleukin-6 soluble receptor (IL-6sR). Because insufficient peritoneal fluids were present in the treated and control monkeys, however, the study authors collected blood samples at 6 and 12 months during laparoscopy for routine hematology and to assess the circulating levels of IL-6 and IL-6sR. All animals were sacrificed at 12 months, and circulating levels of gonadal steroids also were measured at the time of necropsy.

No changes were observed among treatment levels in general toxicological endpoints such as body weight changes, food consumption, hematological endpoints, general activity

levels, and caretaker interaction. In addition, TCDD did not impact circulating levels of gonadal steroids measured during necropsy. Similarly, there were no differences in the number of menstrual cycles, the length of the menstrual cycle, or bleeding intervals. Endometrial implants were found in at least one site in all TCDD-treated and control monkeys during the first laparoscopic examination. Follow-up laparoscopies revealed that there was a continuous loss of endometrial implants over time in each dose group. At the 1-, 3-, and 6-month examination, the number of endometrial losses was not significantly different among different dose groups. At the 12-month examination, however, a significantly ($p < 0.05$) higher rate of survival of endometrial implants was observed in the 3.57 and 17.86 ng/kg-day dose groups compared to the control group. The highest rate of endometrial implant survival was observed in the ovaries regardless of the dose group. In contrast, all lesions disappeared from the left broad ligament, whereas two on the right broad ligament and one on the uterine fundus survived. There was a dose-dependent divergence in the growth response of endometrial implants following TCDD exposure. Both the maximum and minimum implant diameters in the 17.86 ng/kg-day dose group were significantly ($p < 0.05$) larger compared to controls. In contrast, the maximum and minimum implant diameters in the 0.71 ng/kg-day dose group were significantly ($p < 0.05$) smaller compared to controls. TCDD did not impact implant diameters in the 3.57 ng/kg-day dose group when compared to controls. Histological examinations revealed that endometrial glands and stromal cells were present in all surviving implants. Sections examined in the 17.86 ng/kg-day of TCDD possessed cystic endometrial glands that were more frequently observed in this dose group compared to other groups including controls. In addition, the circulating levels of IL-6 were significantly ($p < 0.05$) lower in monkeys exposed to 17.86 ng/kg-day TCDD both at 6 and 12 months compared to the control group. In contrast, the circulating levels of IL-6sR were significantly ($p < 0.05$) higher in animals treated with 3.57 and 17.86 ng/kg-day TCDD at 6 months, while the levels were higher only in the 17.86 ng/kg-day TCDD group at 12 months.

A LOAEL for TCDD of 17.86 ng/kg-day for a 1 year exposure duration was identified in this study for significantly ($p < 0.05$) increased endometriosis induced by endometrial implant survival, significantly ($p < 0.05$) increased maximum and minimum implant diameters, and growth regulatory cytokine dysregulation (as assessed by significantly decreased IL-6 levels, $p < 0.05$). A NOAEL of 3.57 ng/kg-day is identified in this study.

D.1.2. Developmental Studies

D.1.2.1. *Amin et al. (2000)*

Amin et al. (2000) studied the impact of in-utero TCDD exposure on the reproductive behavior in male pups. Groups of pregnant Harlan Sprague-Dawley rats (n = 108 divided into 4 cohorts; number of animals in the TCDD treatment group is ~3 per dose group) were dosed via gavage with 0, 25, or 100 ng/kg-day TCDD (purity >98%) in corn oil on GDs 10−16. On the day of birth (PND 0), pups were examined for gross abnormalities and the number of live pups, their weights, and sex were recorded from each litter. Litters consisting of more than eight pups were reduced to eight, composed of four males and four females when possible. Litters consisting of fewer than five pups were excluded from the study to minimize between-litter differences in growth rate, maternal behavior, and lactational exposure. After this exclusion, approximately 10 to 11 litters per exposure group remained. All pups were weaned on Day 21 and one male and one female were retained to assess reproductive development, play behavior, reproductive behavior, and saccharin preference behavior. Both male and female pups were tested for saccharin preference between 189 and 234 days of age. A saccharin preference test was conducted for 8 days. For the first 4 days, rats were provided bottles containing tap water, and on Days 5 and 6 the animals were provided a bottle containing water and a bottle containing 0.25% saccharin solution. On Days 7 and 8, the animals were provided water and a bottle containing 0.50% of saccharin solution. A 0.50% saccharin solution was used because previous studies have reported that male rats exhibited a greater reduction in preference for this saccharin concentration compared to females, hence the sex difference in preference is more marked at this saccharine dose.

None of the treated dams exhibited any signs of toxicity as a result of exposure to TCDD. Gestational body weight, liver weight, litter size, and percent live births were all comparable to the corresponding control group. Birth rate and weaning weight of the pups also were not affected by TCDD exposure. Sex-related water consumption, however, was significantly ($p < 0.001$) affected during the first 4 days with female pups drinking more water per 100 g of body weight compared to the respective male counterparts. Saccharin consumption was significantly ($p < 0.001$) affected, with females consuming greater amounts of saccharin solution per 100 g body weight compared with the corresponding males. Additionally, both male and

female pups drank significantly ($p < 0.001$) more of the 0.25% saccharin solution compared with the 0.50% saccharin solution. Females of all exposure groups consumed less of both the 0.25 and 0.50% saccharin solution compared to the same-sex control group. Comparisons of each exposure group to the control group indicated that only the high TCDD exposure group (100 ng/kg-day) different significantly ($p < 0.05$) compared to control in the consumption of 0.25% saccharin solution. In contrast, for the 0.50% saccharin solution, both the low- and high-TCDD-dose groups differed significantly ($p < 0.05$ and $p < 0.01$, respectively) compared to the control group. The saccharin preference of TCDD-exposed male rats did not differ from that of the male control group. The TCDD-exposed females' preference for saccharin solution, however, was significantly reduced in both the 25 ($p < 0.05$) and the 100 ng/kg-day ($p < 0.005$) dose group compared to that of the female controls. The study authors state that the reduction in saccharin consumption and preference in females could be due to the antiestrogenic action of TCDD and that recent research reports suggest that TCDD can decrease the level of estrogen receptor (ER) mRNA by blocking the ability of ER to transactivate from the estrogen response element.

A LOAEL for TCDD of 25 ng/kg-day for 7 days of gestational exposure is identified for significantly ($p < 0.05$) decreased preference in the consumption of 0.25% saccharin solution. A NOAEL cannot be determined for this study.

D.1.2.2. *Bell et al. (2007c)*

Bell et al. (2007c) examined the reproductive effects of TCDD in rats exposed during development. Female CRL:WI (Han) rats were treated with TCDD (99% purity; dissolved in acetone) in the diet at concentrations of 0 (acetone alone; $n = 75$), 28, 93, or 530 ($n = 65$/group) ng TCDD/kg diet, which provided average doses of 0, 2.4, 8, or 46 ng/kg-day, respectively. Rats were exposed to TCDD 12 weeks prior to mating, during mating, and through pregnancy. Dams were switched to the control diet after parturition. Litters from pregnant dams were reduced to a maximum size of eight on PND 4 and to five males (if possible) on PND 21. These males were left untreated until sacrificed (25/group, one/litter) on PND 70, while all remaining animals were sacrificed on PND 120. All sacrificed animals were necropsied and received a seminology examination. Prior to sacrifice, during Weeks 12 and 13, 20 animals from each dose group were tested for learning ability and motor activity, and were

also administered a functional observation battery. During postnatal Week 16, groups of 20 male F1 rats from each treatment group were paired with untreated virgin females for 7 days, and mated females were killed on GD 16 and examined for terminal body weights, pregnancy status, number of corpora lutea, and number of intrauterine implantations.

The study authors found no evidence of direct maternal toxicity from exposure to TCDD. In the high-dose groups, 8 of 27 dams suffered complete litter loss compared with 3 dams in the control group, but the difference was not statistically significant. Pup survival at PND 4 was also lower in the high-dose group, but the difference again was not statistically significant.

A dose-related decrease in mean pup body weight was observed on PND 1, and this trend continued throughout the lactation period. High-dose male pups had lower body weights when compared to controls at PND 21, with this trend continuing over the course of the study. Balanopreputial separation (BPS) was significantly ($p < 0.05$) delayed compared to controls in all three treatment groups by 1.8, 1.9, and 4.4 days in the low-, medium-, and high-dose groups, respectively. The study authors reported that adjustment for lower body weights observed at PND 21 and PND 42 did not affect the estimate of delay in BPS. No adverse effects from maternal treatment were observed on learning or in functional observational battery performance. Offspring in the high-dose group exhibited less activity when compared to controls ($p < 0.05$) when they were subjected to a test of motor activity for 30 minutes.

The median precoital time was 2−3 days for all 20 F1 males that were mated during postnatal Week 16. The uterine and implantation data were similar in all dose groups and there were no significant differences in the proportion of male offspring between groups. Epididymal sperm counts and sperm motility did not differ significantly between dose groups in animals sacrificed during postnatal Week 10. The mean number of spermatids was significantly lower (14%; $p < 0.05$), and the proportion of abnormal sperm was significantly ($p < 0.05$) higher in the high-dose group when compared to controls on PND 70. These effects, however, were not seen in animals sacrificed on PND 120.

Terminal body weights were significantly ($p < 0.05$) decreased in the high-dose group (6.9 %) compared to controls on PND 120, while the depression in body weight in the medium-dose group (5.5%) was not statistically significant. At PND 70, the relative and absolute testis weight of the high-dose group was less than the controls (12 and 18%, respectively). Absolute spleen weight in the high-dose group was significantly higher (8%) on

PND 70, and increased significantly ($p < 0.05$) by 1−3% on PND 120 in all dose groups compared to controls. Kidney weight in the low and medium-dose groups was significantly ($p < 0.05$) greater than in controls (~2%) at PND 120. In addition to these organs, ventral prostate (9.4%) and relative liver (~4.5%) weights were significantly ($p < 0.05$) higher than controls on PND 120 in the medium- and low- and high-dose groups, respectively. On PND 120, absolute brain weight was significantly ($p < 0.05$) less than the control in the medium-dose group, while relative brain weight was significantly ($p < 0.05$) higher than the control in the low- and high-dose group. Histological examination revealed no unusual findings.

A LOAEL for TCDD of 2.4 ng/kg-day following an estimated 17-week exposure duration of dams was identified in this study for significantly ($p < 0.05$) delayed BPS. A NOAEL was not identified in this study.

D.1.2.3. *Franczak et al. (2006)*

Franczak et al. (2006) examined the impact of chronic TCDD exposure on the onset of reproductive senescence in female rats. Pregnant Sprague-Dawley rats (n = 2–3/dose group) were fed 50 or 200 ng/kg TCDD (>99% purity) or corn oil vehicle (4 mL/kg) orally on GD 14 and 21 and PND 7 and 14 to provide in utero and lactational exposure to TCDD. On PND 21, female pups (n = 7/dose group) were weaned and were subsequently given weekly doses of either 50 or 200 ng/kg-week TCDD by gavage (7.14 or 28.6 ng/kg-day adjusted for continuous exposure; administered doses divided by 7) or corn oil vehicle. Exposure continued for up to 8 months, and the animals were observed for changes in estrus cycle at 4, 6, and 8 months. Rats were sacrificed at 8 months of age when the TCDD-treated animals had entered the transition to reproductive senescence. Following sacrifice, diestrus concentrations of serum LH, FSH, progesterone, and estradiol were measured, and the ovaries were collected for examination.

Estrus cycles at 4 months exhibited normal cyclicity in both TCDD-exposed groups and did not differ significantly from the control group. At 6 months, however, there was a tendency ($p < 0.1$) toward loss of normal estrus cyclicity in animals treated with TCDD. At the 8 month observation, estrus cyclicity was significantly ($p < 0.05$) different in both dioxin-exposed groups compared to controls (cumulative TCDD exposure is reported as 1.7 and 8 μg/kg for the 50 and 200 ng/kg dose groups, respectively). The study authors noted that although the low-dose animals showed an increased prevalence of prolonged cycles, persistent estrus or diestrus was

observed in only 10% of the rats. Conversely, approximately 50% of the rats exhibited loss of cyclicity in the high-dose group. There were no changes in the number and size distribution of ovarian follicles or the number of corpora lutea at either dose. Progesterone levels at 8 months tended to be higher ($p < 0.08$) in animals receiving either 7.14 or 28.6 ng/kg-day TCDD compared to controls, while serum estradiol concentrations were significantly ($p < 0.03$) lower at diestrus. Serum LH levels in TCDD-treated animals were comparable to those in the control group, while FSH levels were elevated in rats receiving 7.14 ng/kg-day TCDD—but not in the 28.6 ng/kg-day dose group.

A LOAEL for TCDD of 7.14 ng/kg-day for an 8-month exposure duration was identified for significantly ($p < 0.03$) decreased serum estradiol levels. A NOAEL cannot be determined for this study.

D.1.2.4. *Hojo et al. (2002) [and related: Zareba et al. (2002)]*

Hojo et al. (2002) studied the impact of prenatal exposure to TCDD on sexually dimorphic behavior in rats. Thirty-six pregnant Sprague-Dawley rats were assigned according to a randomized block design to groups receiving 0, 20, 60, or 180 ng/kg TCDD (98% purity) on GD 8. Litters from pregnant dams were culled to 5 females and 5 males on PND 4 and allowed to wean normally, at which time 5, 5, 6, and 5 litters from the 0, 20, 60, and 180 ng/kg TCDD treatment groups, respectively, were maintained for examination of behavioral response. Offspring were exposed to TCDD (from a single maternal exposure) for about 35 days through gestation and lactation. After weaning at PND 21, offspring were fed ad libitum until PND 80, at which time a fixed amount of food was supplied daily to maintain constant body weights. At 90 days old, the rats in these treatment groups were trained to press a lever to obtain food pellets using two operant behavior procedures. Initially, each lever press was reinforced. The fixed ratio (FR) requirement was then increased every fourth session from the initial setting of 1 to values between 6 and 71. The responses for 30 days were studied under a multiple schedule combining FR 11 and another schedule requiring a pause of at least 10 seconds between responses (differential reinforcement of low rate, or DRL 10-seconds)

Pup and dam body weights were not affected by TCDD exposure, and all pups were successfully trained in the lever-press response within 3–4 days. Analyses of the FR procedure data indicated that the male pups responded at a lower rate at all TCDD doses when compared to

the control group. In case of female pups, all TCDD-treated groups responded at a higher rate than controls. None of these results was, by itself, however, statistically significant. Examination of the FR 11 and DRL 10-second data indicated that when considering the FR component of this multiple procedure, males from all three treatment groups responded at lower rates when compared to the controls. Conversely, all female pups responded at higher rates than controls. In addition, the treatment-by-sex interaction was significant ($p = 0.036$), with the 60 ng/kg female pups responding at a higher rate than the 60-ng/kg male pups. Examination of the delayed response component in the multiple FR 11 and DRL 10-seconds procedures indicated that almost all TCDD treatment groups were affected. Like the FR component, male pups at all TCDD dose groups responded at a lower rate compared to controls, while female pups at all dose groups responded at a higher rate than controls. There was also a significant ($p = 0.001$) sex-by-treatment interaction for the DRL 10-seconds similar to the FR component. Following behavioral testing, the animals were sacrificed and cortical depth measurements were taken in selected right and left brain regions. Reduced cortical thickness and altered brain morphometry were observed in both male and female offspring in the 180-ng/kg exposure group when compared to controls (Zareba et al., 2002).

A nominal LOAEL for TCDD of 20 ng/kg for a single exposure on GD 8 is established for this study based on abrogation of sexually dimorphic neurobehavioral responses. A NOAEL cannot be derived for this study.

D.1.2.5. *Kattainen et al. (2001)*

Pregnant Line A, B, and C rats derived from Han/Wistar and Long-Evans rats (4−8 pregnant dams/strain/treatment group) were administered a single gavage dose of 0, 30, 100, 300, or 1,000 ng/kg TCDD (purity >99%) in corn oil on GD 15 (Kattainen et al., 2001). On PND 1, the litters were culled to three males and three females. Offspring were weaned on PND 28. Female pups were sacrificed on PND 35 and male pups were sacrificed on PND 70. TCDD treatment did not affect body weight or cause clinical signs of toxicity in the dams. In Line B offspring, body weights in the 1,000 ng/kg group were slightly decreased during PND 1−7, while Line C offspring had slightly decreased body weights throughout the study period (data were not provided). The development of the third molar was affected the most in Line C offspring. In 5 of 10 Line C females and 6 of 10 Line C males treated with 1,000 ng/kg

TCDD, the lower third molar did not develop. In comparison, 1 of 19 Line A females and 1 of 18 Line B females administered 1,000 ng/kg TCDD lacked the third molar at sacrifice. Third molars were present in all the controls and all male Line A and B offspring administered 1,000 ng/kg. Due to the lack of eruption of the third molar in the majority of Line B and C control females (only 30% erupted), however, the effects of TCDD on third molar eruption could only be evaluated in Line A female offspring (with 94% eruption). There was a dose-dependent decrease in the eruption of the lower third molar in Line A female offspring with a significant ($p < 0.05$) decrease observed in the 300 and 1,000 ng/kg dose groups. In the male offspring, any third molar that developed erupted by PND 70. The mesiodistal length of the existing lower third molar was reduced in a dose-dependent manner in both genders of all three rat lines. In Line A and C females, the decrease was significant ($p < 0.05$) at all doses. The size of the second molars was also significantly decreased with 1,000 ng/kg ($p < 0.05$) in all but Line C males.

A developmental LOAEL for TCDD of 30 ng/kg for maternal exposure on GD 15 is established for this study, based on impaired tooth development (significantly reduced mesiodistal length of the lower third molar by approximately 12% to 38% [$p < 0.05$]). A NOAEL could not be determined.

D.1.2.6. *Keller et al. (2008a; 2008b; 2007c)*

Keller et al. (2008a; 2008b; 2007c) conducted three separate experiments to assess the impact of TCDD on molar tooth development using different mouse strains. In Experiment 1, Keller et al. (2007c) used six inbred mouse strains (C57BL/6J, BALB/cByJ, A/J, CBA/J, C3H/HeJ, and C57BL/10J) known to possess high affinity ligand-binding aryl hydrocarbon receptor alleles (*b*), two with *b1* alleles (C57BL/6J and CBA/J), and four with *b2* alleles (BALB/cByJ, A/J, C3H/HeJ, and CBA/J). Females (number not specified) from each strain were mated with males of the same strain. On GD 13, each pregnant female was assigned to one of the four dose groups and treated with 0, 10, 100, or 1,000 ng TCDD/kg BW via oral gavage. The control group received corn oil. GD 13 was chosen for dosing because the first morphological signs of tooth development occur on GD 11. The first visible signs of the M1 (molar) occur on GDs 13–14 followed by final cuspal morphology, which is determined on GD 15. The F1 offspring of females from each strain were weaned and separated by sex at PND

28 and were euthanized at PND 70. Each F1 mouse was examined for the presence or absence of both maxillary (M^3) and mandibular third molars (M_3) on both the left and right sides. In addition, all mice were scored as either normal or variant in M_1 morphology for both molar rows.

In Experiment 2 (Keller et al., 2008b), dams from six inbred mouse strains (C57BL/6J, BALB/cByJ, A/J, CBA/J, C3H/HeJ, and C57BL/10J) were orally dosed on GD 13 with 0, 10, 100, or 1,000 ng TCDD/kg BW in corn oil. GD 13 was used as the dosing day because it coincided with the formation of Meckel's cartilage (a major signal center) in the mouse mandible that is followed shortly by intramembranous bone formation on GD 15. The A/J mouse strain was abandoned because the authors had difficulty rearing the offspring from this strain. All offspring (n = 4 or 5 per treatment group) from the remaining strains were euthanized at 70 days of age. Mandible size and shape from all selected offspring were examined using geometric morphometric methods to assess the impact of TCDD exposure.

In Experiment 3 (Keller et al., 2008a), dams from six inbred mouse strains (C57BL/6J, BALB/cByJ, A/J, C3H/HeJ, CBA/J, and C57BL/10J) were treated with a single oral dose of 0, 10, 100, or 1,000 ng TCDD/kg-BW in corn oil. GD 13 was chosen as the dosing day because the first visible signs of the first molar (M_1) occurs on GDs 13–14 and the final cuspal morphology (the pattern of projections on the chewing surface of the tooth) is not determined until after GD 15. Similar to Experiment 2, the A/J mouse strain was abandoned due to difficulty in rearing offspring. All offspring (n = 107–110 in each of the five strains for all treatment groups) were euthanized at 70 days of age and their molar size, shape, and asymmetry traits were examined using geometric morphometric methods.

In Experiment 1, all four M_3s were present in all dose groups in mice from C57BL/6J, BALB/cByJ, and C57BL/10J strains. A similar response was observed in the A/J strain mice with only 3 of 51 F1 mice exhibiting missing third molars. Approximately one-third of the mice from the CBA/J and C3H/HeJ strains, however, were missing at least one M^3 or M_3 molar. The numbers of CBA/J mice missing one or both M_3 or M^3 molars were 0/29, 2/21, 6/29, and 30/30 in the 0, 10, 100, and 1,000 ng/kg groups, respectively. In the C3H/Hej animals, the numbers missing one or both molars were 1/24, 3/28, 1/26, and 30/36, respectively.

Maternal TCDD exposure was also found to affect the frequency of M_1 variants, but only in the C57BL/10J strain, and the dose-response relationship was nonmonotonic. The proportions

of variants observed in the 0, 10, 100, and 1,000 ng/kg dose groups were 33, 68, 59, and 58%, respectively.

A LOAEL for TCDD of 10 ng/kg maternal exposure on GD 13 is identified for this study for increased incidence (33%) of the M_1 variant in the C57BL/10J mouse strain. A NOAEL cannot be determined in this study.

In Experiment 2, TCDD exposure of dams did not affect offspring survival or 10-week body weight in any of the inbred mouse strains used. ANOVA indicated that although mandible size in both male and female offspring varied significantly ($p < 0.0001$) among strains, it was not affected by TCDD exposure. In contrast, analysis of covariance indicated that TCDD exposure significantly ($p = 0.0033$) decreased the mandible size in male offspring in the C3H/HeJ strain at all treatment groups. The mean mandible size was similar across all treatment groups in both sexes in all strains with male offspring exhibiting larger mandibles compared to females. Males in the C3H/HeJ strain exhibited a significant (level not reported) downward trend in mandible size throughout all treatment groups. Females in the C3H strain also showed a similar trend in mandible size—but the trend was not significant. ANOVA on mandible shape indicated that males had significantly ($p < 0.0001$) different mandible shape in strain × treatment groups. In contrast, in female offspring, although the mandible shape was significantly ($p < 0.0001$) different due to strains, treatment groups, and litter, the strain × treatment interaction was not significant. Male offspring from the C3H/HeJ and C57BL/6J mouse strains appear to be more sensitive to TCDD than BALB/cByJ or CBA/J mice, with the C57BL/10J strain exhibiting intermediate sensitivity. In addition to these analyses, Procrustes distance analysis also indicated that C3H/HeJ mice had the greatest response to the highest dose of TCDD, followed by the C57BL/6J strain. Female offspring in the C3H/HeJ and C57BL/6J strains also exhibited the largest change in Procrustes distance with TCDD exposure. This trend, however, was not statistically significant ($p = 0.29$).

A LOAEL for TCDD of 10 ng/kg maternal exposure on GD 13 was identified for this study for significantly ($p = 0.0033$) decreased mandible shape and size in male C3H/HeJ mice. A NOAEL cannot be determined in this study.

In Experiment 3, the effect of TCDD exposure on offspring survival or body weight was not reported. Three-way ANOVA results showed significant ($p < 0.0001$) differences in molar size among strains, sexes, and litters—but not among treatment groups. Molar size difference in

sex × strain interaction was significant ($p = 0.03$), whereas differences in sex × treatment and sex × strain × treatment were not significant. Additionally, molar size in treatment × strain interaction also was not statistically significant. Based on these results, the authors reported that molar size varied significantly ($p < 0.0001$) among all five strains tested, with all strains exhibiting similar trends in all four treatment groups. Strain differences in molar size were more apparent in male offspring. A hormesis-like trend in molar size was observed in all strains (except in BALBc/ByJ) and sexes with an increase at the 100 ng/kg dose and a decrease in the 1,000 ng/kg dose. In addition to lack of difference in molar size for all treatment groups in all strains, fluctuating asymmetry in molar size also did not increase with increasing doses of TCDD.

In contrast to these results on molar size, the Procrustes ANOVA indicated that molar shape was significantly ($p < 0.0001$) affected by strain, sex, treatment, and litter size. Molar shape in sex × strain and sex × strain × treatment interactions was also highly significant ($p < 0.0001$). Based on these results, the authors concluded that differences between males and females varied based on the strain, and that the effect of TCDD exposure on each strain also differed for male and female offspring. Because molar shape in treatment × strain interaction was significant ($p < 0.0001$), differences in molar shape between the three treatment groups and the control group were analyzed for each strain using nonorthogonal contrasts. In male offspring, contrasts between the control group and 1,000 ng/kg were statistically significant only in the C3H/HeJ ($p < 0.0001$) and CBA/J ($p < 0.03$) strains. These results suggest that these two strains are most susceptible to TCDD effect on molar shape, and similar results were observed in female offspring of these two strains. The contrast in molar shape between the control and the 100 ng/kg treatment group for the female C57BL/6J mice also was statistically significant ($p = 0.0096$). On the whole, when considering Procrustes distance results for molar shape, the C3H/HeJ male offspring had the largest response at the low and high doses, while the female offspring had the largest response at low and mid doses. This observation in male C3H/HeJ mice is consistent with that of TCDD-induced changes in mandible size from Keller et al. (2008b).

A LOAEL for TCDD of 10 ng/kg maternal exposure on GD 13 is identified for this study for significant ($p < 0.0001$) differences in molar shape in male C3H/HeJ mice. A NOAEL cannot be determined in this study.

D.1.2.7. *Kuchiiwa et al. (2002)*

Kuchiiwa et al. (2002) studied the impact of in utero and lactational TCDD exposure on serotonin-immunoreactive neurons in raphe nuclei on F1 male mouse offspring. Twenty-one adult female ddY mice (seven per treatment group) were administered TCDD (99.1% purity) by oral gavage once per week, for 8 weeks, at doses of 0, 4.9, or 490 ng/kg (0, 0.7, or 70 ng/kg-day average daily dose; administered doses divided by 7) or an equivalent volume of olive oil vehicle (6.7 mL/kg) by gavage. Immediately following the final treatment, the mice were housed with untreated male mice for mating. At approximately 20–21 days after mating, 3 female mice from each dose group, including the control group gave birth to 10–12 offspring. One day after birth, each litter was culled to 10 offspring to accommodate similar lactational TCDD exposure. On PND 28, the offspring were weaned, and three offspring from each TCDD exposed group and the control group were selected for an immunocytochemical examination at 42 days of age. Following sacrifice of these offspring, the brain of each animal was removed and every second serial section of the brain was processed for immunocytochemistry. In addition to the serial sections of the brain, cells from 18 offspring (6 males per treatment group) were used to assess the number of cells in the dorsal and median raphe nucleus, the supralemniscal area, and the Nucleus raphe magnus.

Examination of external morphology, birth, and postnatal body weights indicated that there were no differences between the male TCDD-exposed offspring and the control male offspring. TCDD-exposed males, however, were aggressive toward other normal mice and were also hypersensitive to soft touch.

Serotonin-immunoreactive neurons were found to be distributed throughout the entire brainstem in 42-day-old males, and the general pattern in the TCDD-exposed animals was consistent with those observed in control male offspring. Serotonergic neurons were identified and counted in the caudal linear nucleus, the median and dorsal raphe nucleus, Nucleus raphe pontis, interpeduncular nucleus, supralemniscal area, pedunculopontine segmental nuclei, deep mensencephalic nucleus, Nucleus raphe magnus, pallidus, and obscurus, dorsal and medial to the facial nucleus and the ventrolateral medulla. Results from computerized cell counts (n = 6) showed an average of 1,573.3 immunoreactive neurons in the raphe nuclei from the control group versus 716.3 and 419.8 neurons in the low- and high-dose offspring, respectively. The

numbers of immunoreactive neurons in the individual raphe nuclei (dorsalis, medianus, magnus, and B9) from the TCDD-exposed offspring were significantly ($p < 0.01$) lower than control values, with the degree of reduction being dose-related.

A LOAEL of 0.7 ng/kg-day for an 8-week exposure duration is identified in this study for a significantly ($p < 0.01$) lower number of serotonin-immunoreactive neurons in the raphe nuclei of male offspring. A NOAEL cannot be determined for this study.

D.1.2.8. *Li et al. (2006)*

Pregnant and pseudopregnant (obtained by mating normal estrous female mice with vasectomized male mice) NIH mice (10 per treatment group) were exposed to 0, 2, 50, or 100 ng/kg-day of TCDD (purity 99%) during early gestation (GDs 1–8), preimplantation (GDs 1−3), or peri-implantation to postimplantation (GDs 4–8) (Li et al., 2006). On GD 9, animals were evaluated. The two highest TCDD doses (50 and 100 ng/kg-day) caused significant ($p < 0.05$) early embryo loss independent of gestational exposure time. At 100 ng/kg-day, however, the embryo loss was greater when administered during GDs 1–8 or GDs 1–3 compared to GDs 4–8 ($p < 0.01$). Uterine weight was significantly decreased in the pseudopregnant mice when administered 50 or 100 ng/kg-day TCDD during GDs 1–8 ($p < 0.001$) or 1–3 ($p < 0.01$), but was only decreased at 100 ng/kg-day in pseudopregnant mice when administered during GDs 4–8 ($p < 0.01$). Estradiol levels were increased at all TCDD treatment levels (100% at the lowest dose), but statistical significance was not indicated. All doses at all treatment times resulted in a significant reduction ($p < 0.01$) in serum progesterone levels, with a 45% decrease at the lowest dose. Because the hormone effects were observed following 4 days of treatment, the nominal doses were averaged over the entire test period of 8 days prior to measurement. The resulting average daily doses of TCDD were 0, 1, 25, and 50 ng/kg-day.

A LOAEL of 2 ng/kg-day administered for 4 to 8 days is established in this study for a significant ($p < 0.01$) decrease in progesterone (45% above control) and an approximate twofold increase in estradiol levels (significance not indicated). A NOAEL cannot be determined.

D.1.2.9. *Markowski et al. (2001)*

Pregnant Holtzman rats (4–7 per treatment group) were administered a single gavage dose of 0, 20, 60, or 180 ng/kg TCDD (purity not specified) in olive oil on GD 18 (Markowski et al., 2001). One female rat from each liter (4–7 per treatment group) was assigned to training on a wheel apparatus to respond on a lever for brief opportunities to run. Once animals responded to an FR1 schedule of reinforcement, the requirement for lever pressing was increased to FR2, FR5, FR10, FR20, and FR30 schedules. After each training session, the estrous cycle stage was determined. Maternal body weight, length of gestation, number of pups per litter, and sex distribution within litters were unaffected by treatment. For each of the FR schedules, there was a significant dose-related ($p = 0.0001$) decrease in the number of earned run opportunities, lever response rate, and total number of revolutions in the wheel in the adult female offspring. There was no correlation between estrous cycle and responding for access to wheel running.

The developmental LOAEL for this study is a single dose of 20 ng/kg administered on GD 18 for neurobehavioral effects. A NOAEL cannot be determined for this study.

D.1.2.10. *Miettinen et al. (2006)*

Miettinen et al. (2006) administered a single oral dose of 0, 30, 100, 300, or 1,000 ng/kg TCDD (purity >99%) in corn oil on GD 15 to pregnant Line C rats. The offspring (24–32 per treatment group) were assigned to a sugar-rich cariogenic diet (via feed and drinking water) and were orally inoculated three separate times with fresh cultures of *Streptococcus mutans*. Three control groups varied with regard to TCDD exposure and administration of a cariogenic diet. Two of the control groups received no TCDD, and the offspring were either maintained on a normal diet without inoculation with *S. mutans* (C1; $n = 48$) or were given the cariogenic diet with *S. mutans* inoculation (C2; $n = 42$). The final control group was maternally exposed to 1,000 ng/kg TCDD with offspring fed a normal diet without *S. mutans* inoculation (C3; $n = 12$). TCDD did not affect the maternal or offspring body weight. Survival of the offspring was reduced in the 1,000 ng/kg dose group (50–58% survival compared to 83–95% in C1 and C2, respectively). All offspring administered 1,000 ng/kg were missing all lower third molars. Two animals (8%) in the 100 ng/kg group were missing one of their lower third molars. All doses—except the 100 ng/kg dose— caused a significant ($p < 0.05$) increase in the number of caries lesions compared to group C2 (60, 79, 76, 83, and 91% in the C2, 30, 100, 300, and

1,000 ng/kg groups, respectively). Group C3 (1,000 ng/kg TCDD exposure, normal diet) animals also had increased caries lesions compared to C1 (8 vs. 0%, respectively). There were no detectable changes in tooth mineral composition that could explain the increase in caries susceptibility.

The developmental LOAEL from this study is a single dose of 30 ng/kg administered on GD 15 based on the significant ($p < 0.05$) increase in dental caries in pups (30% above control). A NOAEL cannot be determined from this study.

D.1.2.11. *Nohara et al. (2000b)*

Pregnant Holtzman rats were administered 0, 12.5, 50, 200, or 800 ng/kg TCDD in corn oil by gavage on GD 15 (Nohara et al., 2000b). On PND 2, five males were randomly selected from each litter and dose group. TCDD was detected in the thymus, spleen, and bone marrow of the male pups on PND 21 and PND 49. TCDD was still detected in the thymus and spleen on PND 120 but the levels decreased over time. The TCDD concentration was highest in the thymus at all time points. There were no changes in the body, thymus, or spleen weights of the male offspring on PND 5, PND 21, PND 49, or PND 120. On PND 5, there was a 200-fold increase in CYP1A1 in the thymus of the high-dose male pups. CYP1A1 was only slightly increased in the spleen. This induction decreased through PND 49. There was a slight (not statistically significant) dose-dependent decrease in thymus cellularity in the male offspring at PND 120. Spleen cellularity at PND 49 decreased in a dose-dependent manner (15–50% of the control), with a statistically significant ($p < 0.05$) decrease observed in the high-dose group. A slight but not significant reduction in spleen cellularity was noted in the high-dose group at PND 21. The same effect was not observed at PND 120, nor was there any change in the percent of B or T cells in the spleen. No changes in cytokine levels were observed in the 800-ng/kg group.

Although a change in spleen cellularity on PND 49 (puberty) was observed, this effect was transient, and there were no coexisting changes in the percentage of splenic lymphocytes, spleen weight, and cytokine levels. Therefore, a developmental NOAEL of a single dose of 800 ng/kg administered on GD 15 is identified for this study. A LOAEL is not established.

D.1.2.12. *Ohsako et al. (2001)*

Pregnant Holtzman rats (6 per treatment group) were administered 0, 12.5, 50, 200, or 800 ng/kg TCDD (purity >99.5%) in corn oil by gavage on GD 15 (Ohsako et al., 2001). On PND 2, five males were randomly selected from each litter. Two male offspring from each litter were sacrificed on PND 49 and PND 120. Neither maternal nor male offspring body weight was affected by TCDD treatment. TCDD was detected in both the fat and testes at all dose levels (including controls) with highest levels found in fat. There were no apparent treatment-related effects on testicular weight, epididymal weight, daily sperm production, cauda epididymal sperm reserves, luteinizing hormone, follicle stimulating hormone, or testosterone levels. There was, however, a clear dose-dependent decrease in urogenital complex weight and ventral prostate weight at both PND 49 and PND 120. For male offspring, statistically significant ($p < 0.05$) decreases were noted in urogenital complex weight at PND 120 in the 200 and 800 ng/kg groups, in ventral prostate weight at PND 49 in 800 ng/kg group, and at PND 120 in the 200 and 800 ng/kg groups. There was also a dose-dependent decrease in anogenital distance (the length between the base of the genital tubercle and the anterior edge of the anus); the decrease was not statistically significant at PND 49. At PND 120, however, male offspring in all but the lowest dose group had significantly ($p < 0.05$) reduced anogenital distance compared to the control animals. There was also a dose-dependent increase in 5αR-II mRNA expression in the ventral prostate on PND 49 with significant increases ($p < 0.05$) in the 200 and 800 ng/kg animals. There was a significant ($p < 0.01$) decrease in the androgen receptor mRNA in the ventral prostate on PND 49 at all doses tested. Similar effects were not observed on PND 120 or in the caput epididymis on PND 49.

The developmental LOAEL for this study is a single dose of 50 ng/kg administered on GD 15 for significantly ($p < 0.01$) reduced anogenital distance in male offspring (approximately 14%). The NOAEL for this study is 12.5 ng/kg.

D.1.2.13. *Schantz et al. (1996)*

Schantz et al. (1996) studied the impact of in utero TCDD exposure on spatial learning in male and female pups. Groups of pregnant Harlan Sprague-Dawley rats (n = 108, divided into 4 cohorts; number of animals in each TCDD group approximately 4 per treatment group) were dosed via gavage with 0, 25, or 100 ng/kg-day TCDD (purity >98%) in corn oil on GDs 10−16.

On the day of birth (PND 0), the pups were examined for gross abnormalities and the number of live pups, weight, and sex were recorded for each litter. On PND 2, litters were culled to eight animals and were balanced to include four males and four females whenever possible. To minimize litter-size effects, litters with fewer than five pups were excluded from the study. The exclusion of these litters resulted in 10−11 litters per treatment group. Pups were weaned on PND 21 and one male and one female pup from each litter were maintained for the learning tests. Pups were tested 5 days per week for spatial learning and memory in a radial arm maze and a T-maze. A radial arm maze working memory test and a T-maze DSA task were used a part of the testing process.

TCDD treatment did not affect dam gestational weight gain, dam liver weight, gestation length, litter size, percentage of live births, birth weight, or postnatal growth of the pups observed during the course of the study. Exposed pups, however, exhibited some signs of toxicity in all exposure groups. Thymus weight was decreased and liver weight was increased in the 100 ng/kg-day TCDD dose group. Also, liver microsomal 7-ethoxyresorufin-O-deethylase (EROD) activity was markedly induced in pups from both the 25 and 100 ng/kg-day dose groups. In the radial maze test, rats from all TCDD exposure groups displayed a significant ($p < 0.01$) learning behavior as shown by progressively fewer errors from the first block of sessions through the fourth session. The treatment by sex and treatment by session block interactions were not significant. Comparisons between the average number of errors per session block in the TCDD-exposed and control group indicated that both the 25 and the 100 ng/kg-day dose groups made significantly ($p < 0.05$ and $p < 0.001$, respectively) fewer errors compared to the control group. TCDD did not significantly affect adjacent arm selection behavior as measured by C statistic; hence the reduction in errors observed did not appear to be accounted for by an increased tendency to run into adjacent arms. Female pups had a significant ($p < 0.05$) shorter radial arm maze latency, however, compared to the male pups. In the T-maze test, TCDD did not significantly affect the percent of correct performance. All exposure groups performed best at the shortest delay, which showed a decline as the length of the intertrial delay interval was increased. Additionally, all treated groups improved their performance over a three-block session period. This finding indicated that animals in all groups could learn the task. These observations were confirmed by a highly significant main effect of delay ($p < 0.001$) and highly significant main effect of session blocks ($p < 0.001$). At the shortest 15-second delay,

average percent correct performance increased from 75 to 92%, while at the longest 40-second delay, the average percent correct performance increased from 62 to 82%. A significant ($p < 0.05$) main effect of exposure was evident in latency to respond in the T-maze. Comparisons of the exposed group to control group, however, indicated that none of the individual exposure groups differed significantly from the controls. Because no clear pattern was observed in the various exposure groups, differences in latency to respond had no impact on learning of the task.

Based on these results, the study authors state that the fact TCDD seems to have a facilitatory effect on radial arm maze learning in rats should be interpreted with caution and needs further evaluation using different and more varied learning tasks. No toxicologically adverse endpoints were concurrently examined. Thus, a LOAEL and a NOAEL cannot be determined for this study.

D.1.2.14. *Seo et al. (1995)*

To study developmental effects of TCDD on thyroid hormone levels, time-mated female Sprague-Dawley rat dams (n = 10−14/treatment group) were administered either 25 or 100 ng/kg-day of TCDD (>98% pure) in corn oil via gavage from GDs 10–16. Vehicle controls received equivalent amounts of corn oil. The study also investigated PCB treatment outcomes. At birth, pups were weighed and grossly examined for abnormalities. At 2 days of age, litters with fewer than 5 pups were excluded from the analysis and the remaining litters were culled to 4 males and 4 females. Each treatment group contained 10 or 11 litters. Pups remained with the dams until weaning. At weaning, 4−6 pups were retained for neurobehavioral tests (which were not reported as part of this study). The remaining offspring were sacrificed, which provided 5−9 litters per treatment group. Data were collected from one male and one female when possible. No signs of toxicity were evident in the dams; measurements on dams included gestational weight gain, liver weight, litter size, and live births. Pup birth weight and weaning weight were unaffected by treatment. In pups sacrificed at weaning (21 days old), a significant ($p < 0.05$) decrease occurred in thymus weight for the high-dose group, but not in thyroid, liver, or brain weight. A significant ($p < 0.05$) decrease (20.4%) was observed in thyroxine (T4) in high-dose females. Thyroid stimulating hormone and triiodothyroxine (T3) were unaffected by treatment. Uridine diphosphate (UDP)-glucuronosyltransferase activity towards 4-nitrophenol

significantly ($p < 0.05$) increased in both treatment groups over control values, and the increase in the high-dose group was significantly ($p < 0.05$) greater than in the low-dose group. Liver microsomal EROD activity was significantly ($p < 0.05$) increased in both treatment groups, but is considered to be an adaptive response and not adverse.

A LOAEL of 100 ng/kg-day for decreased thymus weights and decreased thyroxine is identified for this study. A NOAEL of 25 ng/kg-day is established.

D.1.2.15. *Sparschu et al. (1971)*

Sparschu et al. (1971) studied the teratogenic and developmental effects of TCDD exposure in rats. Groups of pregnant Sprague-Dawley rats were dosed via gavage with 0 (n = 31), 30, 125, 500, 2,000, or 8,000 (n = 10-14 per group) ng/kg-day TCDD (purity 91%) in corn oil on GDs 6−15. Maternal body weights were assessed on GD 0, 6, 13, and 20, and all dams were observed for clinical signs of toxicity throughout the test period. On GD 20, the dams were sacrificed and evaluated for the numbers of pregnancies, implantation sites, corpora lutea, and viable and dead fetuses. All removed fetuses were individually weighed, sexed, and examined for external malformations as well as intestinal hemorrhage. One-third of the fetuses were examined for skeletal alterations, and two-thirds for visceral abnormalities.

Clinical signs of toxicity in the dams included vaginal hemorrhage at ≥2,000 ng/kg-day at various intervals throughout gestation. The study authors described dams in the 8,000 ng/kg-day dose group as “thin” and showing “signs of debilitation.” Maternal body weight gain was significantly ($p < 0.01$) reduced compared to control values at doses ≥500 ng/kg-day on GD 13, as well as at 500 ($p < 0.01$), 2,000 ($p < 0.001$), and 8,000 ng/kg-day ($p < 0.001$) on GD 20. No significant differences were observed in fertility or the number of implantation sites or corpora lutea at any dose tested. The mean number of viable fetuses per litter was significantly ($p < 0.05$) decreased at 500 ng/kg-day compared to control. Only 7 viable fetuses were found and occurred in 4 of the 11 total litters examined in the 2,000 ng/kg-day dose group, and there were no viable fetuses in the 8,000 ng/kg-day dose group. The mean number of resorption sites per litter was significantly increased at 500 ($p < 0.05$), 2,000 ($p < 0.001$), and 8,000ng/kg-day ($p < 0.001$).

No significant differences were observed in the fetal sex ratios at any dose tested. Mean fetal body weight was significantly decreased compared to control values at 125 ($p < 0.01$), 500

($p < 0.05$), and 2,000 ng/kg-day ($p < 0.001$) for males, and at 125 ($p < 0.01$) and 2,000 ng/kg-day ($p < 0.001$) for females. Incidence of intestinal hemorrhage was increased on a per-fetus and per-litter basis at doses ≥125 ng/kg-day. The incidence of tail and limb malformations was not consistently increased over that of control. With respect to soft tissue abnormalities, subcutaneous edema was observed at doses ≥125 ng/kg-day on a per fetus basis. Skeletal abnormalities included delayed ossification of sternebrae and skull bones and wavy thirteenth ribs, but these findings occurred throughout the various groups independent of dose and also in controls.

The developmental LOAEL for TCDD of 125 ng/kg-day was identified for decreased body weight in dams and male fetuses, as well as fetal intestinal hemorrhage and subcutaneous edema. The developmental NOAEL in this study is 30 ng/kg-day. The maternal NOAEL and LOAEL were 125 and 500 ng/kg-day, respectively, for decreased body weight gain.

D.1.2.16. *Smith et al. (1976)*

Smith et al. (1976) studied the teratogenic and developmental effects of TCDD exposure in mice. Groups of pregnant CF-1 mice were dosed via gavage with 0, 1.0, 10, 100, 1,000, or 3,000 (n = 14−41 per group) ng/kg-day TCDD (purity not specified) in corn oil on GDs 6−15. Maternal body weights were assessed on GD 6, 10, 16, and 18, and all dams were observed for clinical signs of toxicity throughout the test period. On GD 18, the dams were sacrificed and evaluated for the number of live, dead, and resorbed fetuses, and the livers were also removed and weighed. All removed fetuses were individually weighed, sexed, measured, and examined for external malformations. One-third of each litter was examined for soft tissue anomalies, and all the fetuses were examined for skeletal anomalies. The litter was considered the experimental unit of treatment and observation.

No significant differences were observed in maternal body weight at any time during gestation at any dose tested. Relative liver weight in dams was significantly ($p < 0.05$) increased in the 3,000 ng/kg-day dose group (13%) compared to control, but absolute liver weights were not significantly changed at any dose tested. The percentage of resorptions per implantations was significantly ($p < 0.05$) increased only at the 1,000 ng/kg-day dose compared to control. There were no significant differences from control values at any dose in implantation sites per litter, percentage of litters with resorptions, sex ratio, fetal body weight, and fetal length.

With respect to fetal anomalies among the litters, there was a significantly ($p < 0.05$) increased incidence of cleft palate in the 1,000 and 3,000 ng/kg-day dose groups compared to that of control. Additionally, there was a significantly ($p < 0.05$) increased incidence of litters with bilateral dilated renal pelvis in the 3,000 ng/kg-day group compared controls. Although not statistically significant, the incidence of exencephaly was greatest at the lowest dose level (1.0 ng/kg-day). Because of this observation, an additional group of 30 mice were run through the GD 6−15 treatment protocol at 1.0 ng/kg-day with another control group run concurrently ($n = 24$). In this exposure, the incidence of exencephaly in the litters from treated dams was comparable to that in the controls. The percentage of resorptions per implantations was increased (12%, $p = 0.048$) over that of controls (8%); however, this effect was not observed in the original 1.0 ng/kg-day exposure and the incidence was similar to that of the original control animals (11%).

A maternal LOAEL of 3,000 ng/kg-day was identified for increased relative liver weight in mouse dams. The maternal NOAEL is 1,000 ng/kg-day. A developmental LOAEL of 1,000 ng/kg-day was identified for increased incidence of cleft palate. The developmental NOAEL is 100 ng/kg-day.

D.1.2.17. *Simanainen et al. (2004b)*

Simanainen et al. (2004b) studied the impact of in utero and lactational TCDD exposure on the male reproductive system in three rat lines that are differentially sensitive to TCDD. Groups of 5 to 8 pregnant Line A, B, and C C57BL/6N CYP1A2 dams were given a single dose of 0, 30, 100, 300, or 1,000 ng/kg of TCDD (purity >99%) in corn oil on GD 15 via oral gavage. Control animals were similarly dosed with a corn oil vehicle. One day after birth, litters were randomly culled to include three males and three females to allow uniform postnatal exposure. Offspring were weaned on PND 28. Dam and pup viabilities were monitored throughout the study. Pup body weights were determined on PNDs 1, 4, 7, 14, and 28. Anogenital distance and crown-to-rump length were measured on PNDs 1 and 4. On Day 70, pups were sacrificed and trunk blood was collected. Serum was collected for testosterone analysis. The testes, cauda of the right epididymis, ventral prostrate, seminal vesicles, and thymus was dissected and weighed. Absolute and relative organ weights were determined, and cauda epididymis and testes were also preserved for sperm count analysis.

TCDD caused no mortality or overt signs of toxicity to the dams. Pup survival from implantation to the day after birth also was not affected by TCDD exposure. Survival from the day of implantation to the day after birth, however, was uncharacteristically lower in control Line B rats (41%), resulting in a significant difference compared with the two lowest doses (30 and 100 ng/mg TCDD). The average survival percentage in the controls for Line A, B, and C rats was 85% (range 80−86%); 64% (41−86%); and 74% (63−85%); respectively. Percentage of male pup survival in each line between PND 1 and PND 28 was 99% except for Line B males exposed to 30 ng/kg TCDD and Line C males exposed to 30 or 100 ng/kg, where male survival rate averaged 81% (range 81−83%). On PND 70, a significant ($p < 0.05$) reduction in body weight was observed only in Line B and C rats at 1,000 ng/kg. In pups exposed to 1,000 ng/kg TCDD, both absolute and relative weight of the ventral, anterior, and dorsolateral prostrate decreased in all three lines at most postnatal time points measured. The change was most consistent and significant ($p < 0.05$) in the ventral lobe. Animals exposed to 1,000 ng/kg TCDD had an average decrease in absolute weight of the anterior prostrate of 37, 32, and 34% in Lines A, B and C, respectively. Additionally, the average dorsolateral prostrate weight was also decreased by 34, 28, and 39% in Lines A, B, and C, respectively. The effect on the ventral prostrate was reversible with the only significant ($p < 0.05$) decrease in weight observed in Line B rats at PND 70 in the 1,000 ng/kg TCDD dose group. The authors reported that TCDD had no consistent effects on the weight of seminal vesicles. The absolute weights of the testis and epididymis showed a significant ($p < 0.05$) increase on PNDs 28−49, but the relative testis, epididymis, and cauda epididymis weights remained unchanged. In pups exposed to 1,000 ng/kg TCDD, severe malformation, including small caput and cauda and degeneration of corpus epididymis, was observed. Malformations in the epididymis were observed in 6 of 44 Line C male rat offspring and 3 of 47 Line A male rat offspring. In Line A, B, and C rats at PND 70in the 1,000 ng/kg TCDD dose group, daily sperm production was reduced by 9, 25, and 36% and cauda epididymal sperm reserves were reduced by 18, 42, and 49%, respectively. Daily sperm reduction (17%) was significant ($p < 0.05$) in Line C rats at a TCDD dose of 300 ng/kg and in Line B and C rats at 1,000 ng/kg. A reduction in cauda epididymal sperm reserves (25%) was significant ($p < 0.05$) in Line C rats at 300 and 1,000 ng/kg TCDD.

A LOAEL for TCDD of 300 ng/kg is identified for reduction in daily sperm production and cauda epididymal sperm reserves in Line C rats. A NOAEL of 100 ng/kg is identified for this study.

D.1.2.18. *Sugita-Konishi et al. (2003)*

Sugita-Konishi et al. (2003) examined the immunotoxic effects of lactational exposure to TCDD in newborn mice. Eight pregnant female C57BL/6NCji mice were administered 0, 1.8, or 18 ng/L of TCDD via drinking water from parturition to weaning of the offspring (for a total of 17 days). Based on an average water intake of 14–16 mL/day, the average daily intake of TCDD for the dams was 1.14 and 11.3 ng/kg-day in the low- and high-dose groups, respectively. In male offspring sacrificed at weaning (21 days after birth), there was a statistically significant ($p < 0.05$) decrease in relative spleen weight and a statistically significant ($p < 0.005$) increase in thymic CD4+ cells in the high-dose group. The changes in relative spleen weight and thymic CD4+ cells were dose related, but effects in the low-dose group did not achieve statistical significance. Changes in spleen weight and CD4+ cell numbers were not observed in the female offspring. In a separate experiment, offspring infected with *Listeria monocytogenes* following lactational TCDD exposure exhibited a statistically significant increase in serum tumor necrosis factor alpha (TNF-α) 2 days after infection in both sexes in the low- ($p < 0.05$) and high-dose ($p < 0.005$) groups. There was also a statistically significant increase in serum interferon gamma in *Listeria*-infected high-dose females ($p < 0.05$). The number of bacteria in the spleen was also significantly increased ($p < 0.05$) 2 days after infection in the high-dose females compared to the controls, but not in males. *Listeria* levels in the spleen returned to control levels by 4 days after infection in both sexes.

Based on these results, a LOAEL for TCDD of 11.3 ng/kg-day following a 17 day exposure to dams was identified for significantly ($p < 0.05$) decreased spleen weight (in male pups), a significant ($p < 0.005$) increase in thymic CD4+ cells (in male pups), and for increased susceptibility to *Listeria monocytogenes* (in male and female pups). The NOAEL for this study is 1.14 ng/kg-day.

D.1.3. Acute Studies

D.1.3.1. *Burleson et al. (1996)*

Burleson et al. (1996) studied the impact of TCDD exposure on mice that were challenged with the influenza virus 7 days after treatment with TCDD. Groups of 8-week-old female B6C3F$_1$ mice (n = 20, 2 replicate groups) were treated one time with 0, 1, 5, 10, 50, 100, or 6,000 ng/kg TCDD (purity >99%, dissolved in corn oil) via oral gavage. In addition to the treated groups, randomly selected animals were assigned as a sentinel group and screened for numerous pathogens. Results of all tests performed on this sentinel group were negative. Seven days after TCDD treatment, all animals were lightly anesthetized and infected intranasally with a highly lethal influenza A/Hong Kong/8/68 virus (H3N1; passage 14). The animals were infected with sufficient H3N1 virus to achieve a 30% mortality rate in the control animals. Animals were observed for mortality and morbidity for 21 days following viral infection. Six mice from each treatment group were sacrificed on Days 3, 9, and 12 postinfection, and body, thymus, and wet lung weights were recorded. Influenza viral titers were examined by sacrificing eight mice each at 2 hours and at 1, 4, 6, 7, 8, 9, 10, and 11 days post infection.

Exposure to TCDD resulted in significantly ($p < 0.05$) increased mortality in the 10, 50, and 100 ng/kg dose groups. No statistically significant difference in the percentage alive was observed between these dose groups. TCDD doses of 1 and 5 ng/kg did not alter mortality in influenza infected animals. A time-related increase in the wet weights of the lungs in infected mice as a result of increased edema also was reflected in an increase in the lung weight-to-body-weight ratio. The study authors stated that this ratio was not altered as a result of TCDD exposure. TCDD-only exposures at 1, 10, or 100 ng/kg did not affect thymus weight. Similarly, animals infected with the influenza virus following TCDD exposure also showed no loss in thymic weight. Enhanced mortality in TCDD-treated animals was not correlated with an increase in influenza virus titers. Additionally, animals treated with 1, 10, 100, or 1,000 ng/kg did not affect pulmonary viral titer assays on Days 6, 7, and 8 postinfection. The authors also concluded that TCDD did not alter Hong Kong virus replication or clearance.

Although these results support immunotoxic effects induced by TCDD, the findings were not reproduced by Nohara et al. (2002a) using the identical study design, and the translation of these findings to humans is dubious. Thus, no LOAEL/NOAEL was established. A lowest-observed-adverse level (LOEL) for TCDD of 10 ng/kg for a single exposure is identified

for significantly ($p < 0.05$) increased mortality in mice infected 7 days later with the influenza virus. The no-observed-effect level (NOEL) for this study is 5 ng/kg.

D.1.3.2. *Crofton et al. (2005)*

Crofton et al. (2005) studied the impact of TCDD exposure in addition to the impact of mixtures of thyroid disrupting chemicals and PCBs on serum total thyroxine (TT4) concentration. Groups of female Long-Evans rats were dosed via oral gavage with 0, 0.1, 3, 10, 30, 100, 300, 1,000, 3,000, or 10,000 ng/kg-day TCDD (purity >99%) in corn oil (n = 14, 6, 12, 6, 6, 6, 6, 6, 6, and 4, respectively) for 4 consecutive days. On the day following the last dose, animals were sacrificed, trunk blood was collected, and serum obtained via centrifugation was assayed for TT4 concentration using standard radioimmunoassay methods.

No visible signs of toxicity or changes in animal body weight as a result of TCDD exposure were observed. Serum T4 levels showed a dose-dependent decrease, with the levels dropping sharply beginning at 100 ng/kg-day dose. Percent serum T4 levels were 96.3, 98.6, 99.8, 93.3, 70.9, 62.5, 52.7, 54.7, and 49.1% in the 0.1, 3, 10, 30, 100, 300, 1,000, 3,000, and 10,000 ng/kg-day groups, respectively.

A LOAEL for TCDD of 100 ng/kg-day for 4 consecutive days of exposure is identified in this study for a reduction in serum T4 levels (70.9% compared to 100% in controls). The NOAEL for this study is 30 ng/kg-day.

D.1.3.3. *Kitchin and Woods (1979)*

Female Sprague-Dawley rats (nine per control and four per treatment group) were administered a single dose of 0, 0.6, 2, 4, 20, 60, 200, 600, 2,000, 5,000, or 20,000 ng/kg TCDD (purity >99%) in corn oil. Animals were sacrificed 3 days after treatment and CYP level and benzo[*a*]pyrene hydroxylase activity in the liver were measured. A significant ($p < 0.05$) increase in cytochrome P450 levels occurred with doses of 600 ng/kg or greater and in benzo[*a*]pyrene hydroxylase activity with doses of 2 ng/kg or greater. Cytochrome P450 was significantly ($p < 0.05$) higher 1 month after a single exposure of 2,000 ng/kg (the only dose measured), but not after 3 or 6 months. Aryl hydrocarbon hydralase (AHH; $p < 0.05$) and EROD

($p < 0.01$) were both significantly increased through 3 months after treatment, and although elevated at 6 months, the results were not significant.

CYP induction alone is not considered a significant toxicologically adverse effect given that CYPs are induced as a means of hepatic processing of xenobiotic agents. Thus, no LOAEL or NOAEL was established for this study because adverse endpoints (e.g., indicators of hepatotoxicity) were not measured. The acute LOEL, however, is 2 ng/kg based on a significant ($p < 0.05$) increase in benzo[*a*]pyrene hydroxylase activity (37% above control). The NOEL is 0.6 ng/kg.

D.1.3.4. *Li et al. (1997)*

Female Sprague-Dawley rats (22 days old; 10 per treatment) were administered a single oral dose of TCDD (>98% pure) in corn oil via gavage at doses of 3, 10, 30, 100, 300, 1,000, 3,000, 10,000, or 30,000 ng/kg. Vehicle controls received equivalent amounts of corn oil, while naïve controls were sham-treated only. In a preliminary time-course study, animals received a single dose of 10,000 ng/kg and were sacrificed at 1, 2, 4, 8, 16, 24, 48, and 72 hours. The time-course study showed two peaks in LH and FSH levels at 1 hour and 24 hours, with a decrease to control values by 48 hours. Thus, in the dose-response study, animals were sacrificed at 1 or 24 hours after treatment, blood was collected, and serum FSH and LH were measured. The dose-response study demonstrated that the peak at 1 hour was related to the vehicle as the peak also occurred in the vehicle controls, but did not occur in the naïve controls. At 24 hours, FSH was increased at 10 ng/kg and higher (>fourfold increase at 10 ng/kg). Doses of 10 to 1,000 ng/kg showed similar increases (not all reached statistical significance; $p < 0.05$). A dose-dependent increase occurred for doses ≥3,000 ($p < 0.05$) with a maximum increase of 20-fold over the vehicle control. At 24 hours, the LH response significantly ($p < 0.05$) increased only for doses ≥300 ng/kg with a maximum increase of 15-fold above the vehicle control. The study authors calculated an effective dose eliciting 50 percent response of 500 ng/kg for gonadotropin increase. The dose-dependent release of LH was confirmed in in vitro studies, but did not occur with the same magnitude. The increase did not occur in calcium-free medium and was unrelated to gonadotropin releasing hormone.

Based on the increase in serum FSH, the LOAEL was 10 ng/kg and the NOAEL was 3 ng/kg.

D.1.3.5. *Lucier et al. (1986)*

Adult female Sprague-Dawley rats (six per treatment) were administered a single gavage dose of TCDD (purity not specified) in either corn oil or contaminated soil at doses of 15, 40, 100, 200, 500, 1,000, 2,000, 5,000 (corn oil), or 5,500 (contaminated soil) ng/kg. Animals were sacrificed 6 days later and livers were removed for analysis. No clinical signs of acute toxicity or changes in body weight were observed at any dose. AHH increased in a dose-dependent manner with significant ($p < 0.05$) increases observed at 15 ng/kg or greater in corn oil or 40 ng/kg or greater in contaminated soil. Cytochrome P450 was significantly ($p < 0.05$) increased with doses of 1,000 ng/kg or greater in corn oil or 500 ng/kg or greater in contaminated soil. A dose-dependent increase was observed for UDP glucoronyltransferase (significance of individual doses not reported), with the results twice as high with corn oil than with contaminated soil. The authors state that the results indicate bioavailability from soils is 50%.

Because the association between AHH activity and TCDD-mediated hepatotoxicity is unknown and no adverse endpoints were measured, a LOAEL or NOAEL was not determined for this study. The acute LOEL for this study is 15 ng/kg, based on the significant ($p < 0.05$) increase (80% above control) in AHH. No NOEL is established.

D.1.3.6. *Nohara et al. (2002a)*

Male and female B6C3F$_1$ (C57BL/6 × C3H), BALB/c, C57BL/6N, and DBA2 mice (10−40 per treatment group) were administered a single dose of 0, 5, 20, 100, or 500 ng/kg TCDD in corn oil via gavage. Seven days following TCDD treatment, mice were infected with a mouse-adapted strain of influenza (A/PR/34/8; H1N1) at a plaque forming unit dose designed to target approximately 30% mortality in each strain. TCDD did not affect the body weight or survival in any of the infected mouse strains at any dose.

Therefore, no LOAEL is established in this study. The NOAEL is 500 ng/kg.

D.1.3.7. *Simanainen et al. (2003)*

Simanainen et al. (2003) studied the short-term effects of TCDD exposure to determine the efficacy and potency relationships among three differentially susceptible rat lines. The three rat lines used were A, B, and C, and they were selectively bred from TCDD-resistant Han/Wistar

and TCDD-sensitive Long-Evans rats. The study authors reported that Line A rats were most resistant to TCDD acute lethality followed by Line B and C. Groups of five or six randomly selected rats (sex not specified) were treated with a single oral dose of TCDD (purity >99%) in corn oil by oral gavage. The dose of TCDD was reported to range between 30 ng/kg and 3,000 µg/kg for Line A, 30 ng/kg and 1,000 µg/kg in Line B, and 30 ng/kg and 100 µg/kg for Line C. Control animals were similarly dosed with a corn oil vehicle. Rats were sacrificed on Day 8 postexposure, and trunk blood was collected and serum separated. Liver and thymus were removed and weighed, and liver samples were collected and preserved. Liver EROD activity, serum aspartate aminotransferase (ASAT) activity, free fatty acid (FFA) concentration, and total bilirubin concentration were determined. Teeth were also examined.

Relative thymus weights were reduced 25% at 300 ng/kg relative to controls in Line B rats. Liver enzyme (CYP1A1) induction, as measured by EROD activity, was evident at all exposure levels; CYP induction is considered to be an adaptive effect and not adverse in itself. No other endpoints were affected below 1 µg/kg in any of the three rat lines.

A LOAEL for TCDD of 300 ng/kg is identified for decreased relative thymus weight in Line B rats. A NOAEL of 100 ng/kg is identified for this study.

D.1.3.8. *Simanainen et al. (2002)*

To study the short-term effects of TCDD on hormone levels, adult female Long-Evans (TCDD-sensitive) and Han/Wistar (TCDD-resistant) rats (n = 9−11/treatment) were administered a single dose of TCDD (>99% pure) in corn oil via gavage at doses ranging from 30 ng/kg to 100 µg/kg. Vehicle controls received an equivalent amount of corn oil. The study also examined other polychlorinated dibenzo-*p*-dioxins outcomes. Rats were sacrificed on Day 8 postexposure, and trunk blood was collected and serum separated. Liver and thymus were removed and weighed, and liver samples were collected and preserved. Liver EROD activity, serum ASAT activity, FFA concentration, and total bilirubin concentration were determined. Teeth were also examined.

Neither FFA nor ASAT levels in Han/Wistar rats showed a dose-response relationship. In Long-Evans rats, however, a significant ($p < 0.05$) dose-dependent increase in FFA occurred at 300 ng/kg TCDD. Serum ASAT sharply increased in Long-Evans rats between 3,000 and 10,000 ng/kg. Body weight change and relative thymus weights were significantly decreased

($p < 0.05$) in Han/Wistar rats with doses ≥10,000 ng/kg and in Long-Evans rats with doses ≥1,000 ng/kg. Liver EROD activity was significantly ($p < 0.05$) increased with all doses in both strains. Serum T4 was significantly ($p < 0.05$) decreased in Long-Evans rats at concentrations ≥300 ng/kg, but were not significantly affected in Han/Wistar rats. Serum bilirubin was significantly ($p < 0.05$) increased with doses ≥10,000 ng/kg in Long-Evans rats and ≥30,000 ng/kg in Hans/Wistar rats. Both strains of rat showed a dose-dependent increase in mean severity of incisor tooth defects. The results indicate that TCDD was the most potent congener tested in both rat strains.

A LOAEL of 300 ng/kg for decreased T4 in the Long-Evans rat is identified for this study. A NOAEL of 100 ng/kg is established.

D.1.3.9. *Smialowicz et al. (2004)*

Smialowicz et al. (2004) examined the impact of TCDD exposure on immunosuppression in mice. Groups of female (number not specified) C57BL/6N CYP1A2 (+/+) wild-type mice were administered a single dose of 0, 30, 100, 300, 1,000, 3,000, or 10,000 ng/kg TCDD (purity >99%) in corn oil via oral gavage. Control animals were similarly dosed with a corn oil vehicle. To assess immune function, 7 days after TCDD administration, all mice were immunized with sheep red blood cells (SRBCs) via injection into the lateral tail vein. Five days after immunization, mice were sacrificed, blood was collected, and enzyme-linked immunosorbant assays were performed. Additionally, spleen, thymus, and liver weights also were measured.

Body and spleen weights of the wild-type mice were unaffected by the TCDD exposure. A decrease in thymus weights of the mice appeared to be dose related. Only mice treated with 10,000 ng/kg TCDD, however, showed a statistically significant ($p < 0.05$) decrease in thymus weights compared to corresponding controls. Liver weights also showed a dose-related increase with only animals treated with 3,000 and 10,000 ng/kg TCDD showing statistical significance ($p < 0.05$) compared to the control group. The antibody response to SRBCs indicated a dose-related suppression in the wild-type mice, with animals treated with 1,000, 3,000, and 10,000 ng/kg TCDD showing statistically significant ($p < 0.05$) suppression compared to the controls.

A LOAEL for TCDD of 1,000 ng/kg is identified in female C57BL/6N CYP1A2 (+/+) wild-type mice for significant ($p < 0.05$) suppression of SRBCs. The NOAEL for this study is 300 ng/kg.

D.1.3.10. *Vanden Heuvel et al. (1994)*

Vanden Heuvel et al. (1994) examined the dose-response relationship between TCDD exposure and induction of hepatic mRNA. Groups of 10-week-old female Sprague-Dawley rats were administered TCDD (purity ~99%) in corn oil once at 0, 0.1, 0.05, 1, 10, 100, 1,000, or 10,000 ng/kg-BW. Four days after TCDD treatment, animals were sacrificed and livers were excised and preserved. Total hepatic RNA was extracted using guanidine thiocyanate and DNA was removed using standard phenol-chloroform-isoamyl alcohol partitioning procedures. Quantitative competitive RNA-PCR method was used to analyze CYP1A1, UDP-glucuronosyltransferase I (UGT1), plasminogen activator inhibitor 2 (PAI2), β-actin, and transforming growth factor α (TGFα). In addition to hepatic mRNA levels, microsomal protein was assayed for EROD activity and livers were tested for TCDD concentration.

CYP1A1 mRNA induction levels in the TCDD-treated groups were low in the low-dose region and sharply increased to plateaus at higher doses. The lowest dose that showed a statistically significant ($p < 0.05$) difference compared to controls was the 1 ng/kg dose, which showed a threefold increase in CYP1A1 mRNA levels. In contrast, a 130-fold increase occurred at 100 ng/kg and a 4,000- and 7,000-fold increase occurred at 1,000 and 10,000 ng/kg, respectively. A slight increase in the CYP1A1/β-actin levels was observed in the 0.1 ng/kg group, but this increase was not significant. EROD activity exhibited a pattern similar to CYP1A1 activity. EROD activity, however, was approximately 100-fold less sensitive compared to mRNA levels in TCDD-treated groups. Statistical significance (*p*-value not provided) in CYP1A1 level was observed at the 100 ng/kg dose compared to the 1 ng/kg dose. The study authors reported that, despite this difference in CYP1A1 and EROD activity, the correlation between CYP1A1 enzyme activity and mRNA levels was good. Dose-response relationships for the induction of UGT1, PAI2, and TGFα mRNA differed from what had been observed for CYP1A1 mRNA. UGT1 mRNA was induced, but at the much higher dose of 1,000 ng/kg. Additionally, the fivefold maximum induction of UGT1 mRNA was much less than the 7,000-fold induction observed for CYP1A1 mRNA at the 10,000 ng/kg dose. The

authors state that this could be a result of the constitutive level of UGT1, which is much higher than CYP1A1, which makes detecting induction of UGT1 in the low dose regions more difficult. PAI2 and TGFα mRNA were not affected by TCDD in rat liver in the dose range tested. These results indicate that dioxin-inducible genes have a quite dissimilar dose-response relationship.

Induction of CYP1A1 expression is not considered an adverse effect, as the role of CYP1A1 in TCDD-mediated hepatotoxicity is unsettled. Therefore, in the absence of other indicators of hepatotoxicity, a NOAEL/LOAEL cannot be determined for this study. A LOEL for TCDD of 1 ng/kg for a single exposure was identified for statistically significant ($p < 0.05$) increase in CYP1A1 mRNA levels. The NOEL for this study is 0.1 ng/kg.

D.1.3.11. *Weber et al. (1995)*

Weber et al. (1995) studied the effects of TCDD on intermediary metabolism in inbred mice. Following establishment of dose ranges via lethal dose eliciting 50 percent response (LD50) studies, male C57BL/6 inbred mice (4-7 per dose group) were administered a single gavage dose of 0, 30, 100, 300, 1,000, 3,000, 9,400, 37,500, 75,000, 100,000, 133,00, or 235,000 ng/kg TCDD (purity not specified) dissolved in corn oil (on Day 0 of the experiment). Male DBA/2 inbred mice (4−7 per dose group) were treated with 0, 1,000, 10,000, 97,500, 375,000, 1,500,000, 1,950,000, or 3,295,000 ng/kg TCDD delivered in two gavage doses (on Days -1 and 0). All mice were sacrificed and weighed on Day 8 after dosing, trunk blood was collected and pooled for each dose group for serum preparation, and livers and kidneys were removed, weighed, and snap frozen. In both strains of mice, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G-6-Pase) activities were measured in the liver, and EROD activity was measured in the liver and kidneys. Liver tryptophan 2,3-dioxygenase (TdO) activity and serum tryptophan levels were measured in C57BL/6 mice. Additionally, glucose concentrations and T4 and T3 levels were measured in the pooled serum of both mouse strains.

On Day 8 after dosing, the study authors reported that food consumption and body weight were unchanged from control values in C57BL/6 mice at any dose tested, but a significant ($p < 0.05$) reduction in food consumption and body weight at doses ≥1,500,000 ng/kg-day in DBA/2 mice (data not shown). Relative liver weight was significantly ($p < 0.05$) increased above control values at doses ≥ 3,000 ng/kg-day in C57BL/6 mice and ≥97,500 ng/kg-day in

DBA/2 mice. Relative kidney weight was not affected by any dose of TCDD in C57BL/6 mice, but was significantly ($p < 0.05$) decreased at 1,950,000 and 3,295,000 ng/kg in DBA/2 mice (data not shown).

In both mouse strains tested, basal EROD activities in the kidneys were only about one-tenth of those in the liver. In the liver of C57BL/6 mice, EROD activity was significantly ($p < 0.05$) induced over control values at doses ≥300 ng/kg-day. Maximum induction occurred at 37,500 ng/kg-day (58-fold), but then decreased by 28% in mice exposed at higher doses. Kidney EROD activity in C57BL/6 mice was significantly ($p < 0.05$) induced over control values at doses ≥ 37,500 ng/kg-day, and no decrease was observed at the higher doses. In the liver of DBA/2 mice, EROD activity was significantly ($p < 0.05$) induced over control values at doses ≥10,000 ng/kg-day. Maximum induction occurred at 375,000 ng/kg-day, but then decreased by 57% in mice exposed at higher doses. Kidney EROD activity in DBA/2 mice was significantly ($p < 0.05$) induced over control values at doses ≥375,000 ng/kg-day, with a 3% and 29% decrease below the level of maximum induction (1,500,000 ng/kg-day) at the two highest doses, respectively. Liver PEPCK activity was significantly ($p < 0.05$) decreased below control values at doses ≥100 ng/kg-day in C57BL/6 mice, and ≥10,000 ng/kg-day in DBA/2 mice. In contrast to the PEPCK dose response, liver G-6-Pase activity was significantly ($p < 0.05$) decreased below control values at doses ≥75,000 ng/kg-day in C57BL/6 mice, and ≥375,000 ng/kg-day in DBA/2 mice. Liver TdO activity in C57BL/6 mice increased by ~20% over that of control at 300 ng/kg-day, and this magnitude of induction did not change throughout doses tested.

With respect to serum measurements, there were no dose-dependent changes in tryptophan levels in either mouse strain tested. Serum glucose levels followed the course of PEPCK activity in both strains of mice, with sharp decreases observed only in the high dose range. Thyroid hormone (T3 and T4) levels exhibited a dose-dependent decrease over the entire dose range in both strains of mice; the lowest T3 and T4 levels were 35% of controls at the 133,000 ng/kg-day dose in C57BL/6 mice, and 40% (T3) and 20% (T4) of controls at the highest dose in DBA/2 mice.

TCDD-induced hepatic and renal enzyme alterations are not considered significant toxicologically adverse effects in and of themselves. Additionally, because the serum determinations were performed in pooled serum samples, statistical analysis could not be performed. Thus, this precludes these effects from being used to identify a NOAEL or LOAEL.

However, a LOAEL for TCDD of 3,000 ng/kg-day was identified for increased relative liver weight in C57BL/6 mice. The NOAEL is 1,000 ng/kg-day for C57BL/6 mice in this study. In DBA/2 mice, a LOAEL for TCDD of 97,500 ng/kg-day was identified for increased relative liver weight, and the NOAEL is 10,000 ng/kg-day for this mouse strain.

D.1.4. Subchronic Studies

D.1.4.1. *Chu et al. (2001)*

Adult female Sprague-Dawley rats (five per treatment group) were administered TCDD (purity >99%) in corn oil by gavage at doses of 0, 2.5, 25, 250, or 1,000 ng/kg-day for 28 days (Chu et al., 2001). The 1,000 ng/kg-day dose of TCDD caused a significant ($p \leq 0.05$) decrease in body weight gain (36% lower than the control), increase in relative liver weight (40% greater than the control), and decrease in relative thymus weight (50% lower than the control). There was a significant ($p \leq 0.05$) increase in EROD activity, methoxy resoufin-O-deethylase (MROD) activity, and UDP-glucuronosyltransferase activity in the liver of female rats receiving 250 or 1,000 ng/kg-day TCDD. In addition, significant ($p \leq 0.05$) increases in serum cholesterol were observed in the 250 and 1,000 ng/kg-day dose groups, and liver ascorbic acid (AA) also was significantly increased in the 1,000 ng/kg-day dose group. There was ~1.5-fold increase in liver glutathione-*S*-transferase (GST), which was not statistically significant. Other significant ($p \leq 0.05$) findings for the 1,000 ng/kg-day group included a decrease in liver vitamin A (51% lower than the control), an increase in kidney vitamin A (15.5-fold increase above the control), an increase in liver benzyloxy resoufin-O-deethylase (BROD, 30-fold increase above control), a decrease in liver pentoxyresoufin-O-deethylase (PROD, 37% lower than the control), increase in serum albumin (18% above the control), and a decrease in mean corpuscular hemoglobin (MCH, 7% below the control) and mean corpuscular volume (MCV, 7% below the control).

Based on the numerous significant ($p \leq 0.05$) liver-related biochemical changes and significant ($p \leq 0.05$) increased relative liver weight, as well as significantly decreased body weight and relative thymus weight, the LOAEL for 28 days of exposure in this study is 1,000 ng/kg-day and the NOAEL is 250 ng/kg-day.

D.1.4.2. *Chu et al. (2007)*

Chu et al. (2007) examined the potential impact of TCDD on various organs and the toxicological impacts as a result of interactions between TCDD and PCBs in rats. Groups of female Sprague-Dawley rats (n = 5 per treatment group) were treated daily for 28 days via gavage with 0, 2.5, 25, 250, or 1,000 ng/kg-day TCDD (purity not specified) dissolved in corn oil. Body weights were determined three times per week, and clinical observations were made daily. At study termination, all animals were sacrificed and blood was analyzed for various biochemical and hematological parameters. Liver, spleen, heart, thymus, brain, and kidneys were removed and weighed. A small portion of the liver was homogenized and assayed for BROD; EROD; MROD; and PROD. UGT, GST, and ascorbic acid levels also were measured. Vitamin A levels in the liver, kidney, and lungs were analyzed as free retinol (vitamin A), and histopathological analysis was conducted on various tissues.

Growth rate and thymic weights in rats treated with 1,000 ng/kg-day TCDD were significantly ($p \leq 0.05$) inhibited compared to the control group. Enzyme analysis indicated that measured levels of TCDD in the liver correlated with hepatic microsomal enzyme activity. The authors reported that liver microsomal EROD and MROD activities were significantly ($p < 0.05$ for EROD activity, significance level for MROD not reported) increased in the 250 and 1,000 ng/kg-day TCDD dose groups compared to the control group. UGT levels were significantly (significance level not reported) increased in the 250 and 1,000 ng/kg-day TCDD dose groups compared to the controls. Serum albumin levels were significantly ($p < 0.05$) increased in the 1,000 ng/kg-day TCDD dose group compared to the control group. Serum cholesterol levels were significantly (level not reported) increased compared to the control group at 250 ng/kg-day TCDD dose, while liver ascorbic acid concentrations were significantly (level not reported) increased in the 1,000 ng/kg-day dose group. Hematological analysis indicated that hemoglobin, packed cell volume, MCH, MCV, and platelet values were decreased in the 1,000 ng/kg-day TCDD dose group. Significant ($p \leq 0.05$) differences were observed only in MCH and MCV levels compared to the control. Vitamin A levels in the liver and kidney were significantly ($p < 0.05$) lower in the 1,000 ng/kg-day TCDD group compared to the control group. Histopathological evaluation of various tissues indicated that liver, thyroid, and thymus were the target organs. No TCDD-related affects were found in other tissues. A dose-dependent alteration in the thymus consisted of reduced thymic cortex and increased medullar volume with

more animals exhibiting these changes at the 250 and 1,000 ng/kg-day dose level compared to the control group. Alterations in thyroid included reduced follicles, reduced colloid density, and increased epithelial height. A dose-dependent change in the thyroid was observed, with the highest impact evident in reduced follicles and reduced colloid density beginning at a dose of 25 ng/kg-day TCDD. Changes in liver were characterized by accentuated hepatic zones, anisokaryosis of hepatocytes, increased cytoplasmic density, and vacuolation. These changes were also dose dependent, with more animals exhibiting these histopathological changes with increasing TCDD dose. Based on these results, the study authors concluded that exposure to TCDD resulted in a wide range of adverse effects with the thyroid proving to be most sensitive.

A LOAEL for TCDD of 25 ng/kg for a 28-day exposure is identified for alterations in thyroid, thymus, and liver histopathology. The NOAEL for this study is 2.5 ng/kg-day.

D.1.4.3. *DeCaprio et al. (1986)*

Hartley guinea pigs (10 per sex per dose) were administered TCDD (purity not specified) in the diet for 90 days at concentrations of 0, 2, 10, 76, or 430 ppt (equivalent to 0, 0.12, 0.61, 4.9, and 26 ng/kg-day in males and 0, 0.12, 0.68, 4.86, and 31 ng/kg-day in females calculated by the study authors using food consumption and body weights). Other animals were administered the high-dose diet (i.e., 430 ppt) for 11, 21, or 35 days and then administered the control diet (i.e., no exposure) for the remainder of the 90 days for recovery analysis. Four high-dose males died and two were sacrificed moribund by Day 45; the remaining four animals were sacrificed on Day 46 for necropsy. Four high-dose females also died and two were sacrificed moribund by Day 55 with the remaining females sacrificed on Day 60 for necropsy. Animals in the 76- and 430-ppt groups had significantly ($p < 0.05$) reduced body weights. Organ weights were not obtained in the 430-ppt group due to the early sacrifice, but in the 76-ppt group a significant decrease in relative thymus weight ($p < 0.05$) was observed, and relative liver ($p < 0.01$) and brain ($p < 0.05$) weights in males increased. Although a similar trend occurred in the females, the results were not statistically significant. Males administered 76 ppt in the diet also had a 53% increase in triglycerides ($p < 0.05$). The same increase was observed in females, but was not statistically significant. In the recovery groups, mortality during the recovery period after 11 or 21 days of treatment was 10% and after 35 days of treatment was 70%. Animals lost

weight during the treatment period. Although the body weight increased during the recovery period, the body weight remained low compared to the control for the study duration.

The LOAEL from this study is 4.9 ng/kg-day for 90 days of exposure, based on decreased body weight (12−15%; $p < 0.05$) and changes in organ weights (10−30%, significant only in the males). The NOAEL is 0.61 ng/kg-day.

D.1.4.4. *Devito et al. (1994)*

Female $B6C3F_1$ mice (5 per treatment) were administered 0, 1.5, 4.5, 15, 45, or 150 ng/kg TCDD (98% pure) in corn oil via gavage, 5 days a week, for 13 weeks. This dose is equivalent to 0, 1.07, 3.21, 10.7, 32.1, 107 ng/kg-day (adjusted for continuous exposure, administered dose multiplied by 5 and divided by 7). Body weight was recorded weekly and animals were sacrificed 3 days after the last treatment. Examinations were performed on the lung, skin, uterus, and liver. No differences were observed in the liver or uterus weights or in the estrogen receptor levels in these two tissues. A dose-dependent increase in EROD activity (an indicator of CYP1A1 [CYP] induction) in the lung, skin, and liver was observed, with significant ($p < 0.05$) increases even at the lowest dose. The TCDD doses used did not achieve maximal EROD induction. A significant ($p < 0.05$) increase in liver acetanilide-4-hydroxylase (ACOH; an indicator of CYP1A2 induction) also was observed with all doses. A maximum induction of ACOH occurred with doses of 3.21 ng/kg-day and greater. A dose-dependent increase in specific phosphotyrosyl protein (pp) levels also was observed. Levels of pp34 and pp38 were significantly ($p < 0.05$) increased even at the lowest dose, while pp32 reached statistical significance ($p < 0.05$) with doses of 4.5 ng/kg-day and above.

The role of CYPs and phosphorylated pp32, pp34, and pp38 in TCDD-mediated toxicity is unknown, and changes in the activity or function of these proteins are not considered adverse. Therefore, no LOAEL or NOAEL is established. The 13-week LOEL is 1.07 ng/kg-day, based on a significant ($p < 0.05$) increase in EROD, ACOH, pp34, and pp38 levels (all increased by at least twofold). No NOEL is established for this study.

D.1.4.5. *Fattore et al. (2000)*

Fattore et al. (2000) examined TCDD-induced reduction of hepatic vitamin A levels in a subchronic rat bioassay on Sprague-Dawley rats. Four experiments were conducted; Experiments 1, 2, and 3 were conducted in both male and female rats, while Experiment 4 was conducted only in female rats. The dosing regimens for each experiment were as follows:

Experiment 1—Groups of six Iva:SIV 50 rats (male and female) were maintained on a diet consisting of 0, 200, 2,000, or 20,000 ng TCDD/kg diet and 3-µg vitamin A/kg diet for 13 weeks. Assuming food consumption of 10% of body weight per day, the average daily doses are 0, 20, 200, and 2,000 ng/kg-day TCDD.

Experiment 2—Groups of six male and female rats were treated with 0 or 200 ng TCDD/kg-day and 3 µg vitamin A/kg diet for 13 weeks.

Experiment 3—Groups of six male and female rats were fed 0, 200, or 1,000 ng TCDD/kg-day and 3 µg vitamin A/kg diet for 13 weeks.

Experiment 4—Groups of female rats (number not specified; IVA;SIV 50 Sprague-Dawley strain) were treated with TCDD for 26 and 39 weeks in addition to a 13-week dietary treatment with 0 or 100 ng TCDD/kg-day and 3 µg vitamin A/kg diet for 13 weeks.

For a 13-week exposure duration employed in all four experiments, male and female rats were treated at 0, 20, 100 (females only), 200, 1,000, or 2,000 ng/kg-day. In all four experiments, the livers from the control and treated animals were analyzed at termination for free retinol content to determine hepatic vitamin A levels.

Results

Experiment 1—Liver and body weights in both treated males and females were significantly affected at all but the lowest dose tested (20 ng/kg-day). Liver injury was severe, particularly in female rats treated with 2,000 ng TCDD/kg-day. Dietary intake of vitamin A in male rats was comparable to intake in controls—except in the 2,000 ng/kg-day group, which showed a reduction of 16% in the dietary intake of vitamin A compared to controls. There was no effect of TCDD on vitamin A intake in female rats. Hepatic vitamin A levels showed a dose-dependent reduction with levels dropping sharply in the 200 and 2,000 ng/kg-day dose groups, particularly in treated females. The reduction was significant at 200 ng/kg-day ($p < 0.05$) and 2,000 ng/kg-day ($p < 0.01$) in males and at 200 ng/kg-day ($p < 0.5$) and 2,000 ng/kg-day ($p < 0.001$) in females. The reductions ranged from 68–99% in males and 72–99% in females when compared to corresponding controls.

Experiment 2—Changes in liver and body weights were not reported. Hepatic vitamin A level in males and females were reduced by 70% and 99%, respectively, compared to controls, in rats receiving 20 ng/kg-day (significance level in females: $p < 0.01$).

Experiment 3—Similar to the results of Experiments 1 and 2, a dose-related trend of significantly ($p < 0.001$) reduced hepatic vitamin A level was observed in both males and females, with males exhibiting a particularly sharp drop at the 1,000 ng/kg-day dose compared to controls.

Experiment 4—Females treated with 100 ng/kg-day showed significant reductions in hepatic vitamin A levels ($p < 0.05$–0.001) at all three treatment durations (13, 26, and 39 weeks).

A LOAEL for TCDD of 20 ng/kg-day for a 13-week subchronic exposure was identified in this study for decreased hepatic vitamin A levels (27 and 24% lower than the corresponding control in female and male rats, respectively). This LOAEL is determined using data from Experiment 1. A NOAEL was not identified in this study.

D.1.4.6. *Fox et al. (1993)*

Sprague-Dawley rats (6 per sex per dose) were gavaged with TCDD (purity not specified) in corn oil using a dose-loading regime to achieve and maintain steady-state levels of 0.03, 30, or 150 ng/g in the liver. The regime consisted of an initial loading dose of 5, 2,500, or 12,000 ng/kg followed every 4 days with a maintenance dose of 0.9, 600, or 3,500 ng/kg. Averaging the doses over the 14 days provides average daily doses of 0.55, 307, and 1,607 ng/kg-day (e.g., 5 ng/kg-day on Day 1 and 0.9 ng/kg-day on Days 5, 9, and 13 is $5 + 0.9 + 0.9 + 0.9/14 = 0.55$ ng/kg-day). Body weight, liver weight, and liver gene expression were measured at 7 and 14 days. A significant ($p < 0.05$) decrease in body weight occurred in high-dose males (at 14 weeks only) and females (at 7 and 14 days). A significant ($p < 0.05$) increase in absolute and relative liver weights was observed in mid- and high-dose males and females at both 7 and 14 days. Although the liver of treated animals indicated moderate vacuolization and swelling, there was no indication of necrosis. An increase in gene expression (clone 1, CYP1A1, CYP1A2, and albumin) was observed in the mid- and high-dose groups. A significant ($p < 0.05$) decrease in labeling index (indication of cell proliferation) occurred in both females (all doses) and males (high-dose only) during Week 1—but not during Week 2.

The 14-day LOAEL is 307 ng/kg-day for significant ($p < 0.05$) increases in absolute and relative liver weights (25─34%). The NOAEL is 0.55 ng/kg-day.

D.1.4.7. *Hassoun et al. (1998)*

Female B6C3F$_1$ mice (number not specified) received TCDD (>98% pure) in corn oil 5 days per week for 13 weeks via gavage at doses of 0, 0.45, 1.5, 15, or 150 ng/kg (equivalent to 0, 0.321, 1.07, 10.7, and 107 ng/kg-day adjusted for continuous exposure; administered dose multiplied by 5 and divided by 7). Three days after the final dose, animals were sacrificed and their brains were removed for oxidative stress testing. Biomarkers for oxidative stress included production of superoxide anion (SA), lipid peroxidation, and DNA single-strand breaks (SSBs). A significant ($p < 0.05$) increase was observed in superoxide anion production, lipid peroxidation as measured by thiobarbituric acid-reactive substances (TBARS), and DNA single-strand breaks with all doses tested.

No other indicators of brain pathology were assessed, and it is unfeasible to link the markers of oxidative stress to a TCDD-induced toxicological outcome in the brain. Thus, no LOAEL/NOAEL was established. The subchronic (13-week) LOEL is 0.32 ng/kg-day, based on significant ($p < 0.05$) increases in superoxide anion production (80% above control); lipid peroxide production (25% above the control); and DNA single-strand breaks (twofold over the control). No NOEL is established.

D.1.4.8. *Hassoun et al. (2000)*

Hassoun et al. (2000) examined the effect of subchronic TCDD exposure on oxidative stress in hepatic and brain tissues. Groups of 8-week-old female Harlan Sprague-Dawley rats (6 rats/group) were administered TCDD (98% purity, dissolved in 1% acetone in corn oil) via gavage at 0, 3, 10, 22, 46, or 100 ng/kg-day, 5 days/week, for 13 weeks (0, 2.14, 7.14, 15.7, 32.9, or 71.4 ng/kg-day adjusted for continuous exposure; administered doses were multiplied by 5 and divided by 7 days/week). Animals were sacrificed at the end of the study period, and the brain and liver tissues were collected and used to determine the production of reactive oxygen species, lipid peroxidation, and DNA SSBs.

A dose-dependent effect was observed in both the liver and brain tissue as a result of TCDD treatment. Based on the maximal induction of superoxide anion by various doses, more production of superoxide anion was observed in the liver tissue when compared with the brain tissue with an observed increase of 3.1- and 2.2-fold respectively, when compared to the control group. A similar dose-dependent effect was observed in the induction of lipid peroxidation in TCDD-treated animals with an approximately 1.8-fold increase in lipid peroxidation in both tissues relative to the corresponding controls. A dose-dependent relationship was also observed for DNA SSBs in both the hepatic and brain tissues at all TCDD-treated doses compared to controls. Increases were statistically significant ($p \leq 0.05$) beginning at the lowest administered dose.

Similar to the statement above, because no adverse endpoints were measured, no LOAEL/NOAEL was established. However, a LOEL for TCDD of 2.14 ng/kg-day for a 13-week exposure duration was identified in this study for significant increases ($p \leq 0.05$) in superoxide anion, lipid peroxidation, and DNA SSBs in the liver and brain tissues. A NOEL cannot be determined for this study.

D.1.4.9. *Hassoun et al. (2003)*

Hassoun et al. (2003) examined the role of antioxidant enzymes in TCDD-induced oxidative stress in various regions of the rat brain after subchronic exposure. Groups of 8-week-old female Harlan Sprague-Dawley rats (12 rats/group) were administered TCDD (98% purity, dissolved in 1% acetone in corn oil) via gavage at 0, 10, 22, or 46 ng/kg-day (0, 7.14, 15.7, or 32.9 ng/kg-day adjusted for continuous exposure; administered doses were multiplied by 5 and divided by 7) daily for 13 weeks. Animals were sacrificed at the end of the study period and the brain was immediately removed and dissected to the following regions: cerebral cortex (Cc), hippocampus (H), cerebellum (C), and brain stem including midbrain, pons, and medulla. Four pooled samples from each region per dose (i.e., 3 animals/pooled sample) were used in the study. Dissected regions were subsequently assayed for lipid peroxidation (TBARS), superoxide dismutase, catalase, and glutathione peroxidase. Because the cytochrome c reduction method was used to determine SA production in brain tissues, SOD was added to some of the brain tissue samples that had the highest SA production (tissue homogenates from Cc and H from rats treated with 46 ng/kg-day TCDD).

A dose-dependent increase in the production of SA was observed in the Cc and H, but significant changes in SA production were not observed in either the C or the mid-brain, pons, or medulla brain stem cells. Similar to SA production, there was a dose-dependent increase in the production of TBARS in the Cc and H regions of the brain, but no significant changes were observed in either the C or the B sections of the brain. The study authors also measured the activities of various enzymes as a result of TCDD treatment and reported a dose-dependent increase in SOD activity in the C and B sections, while there was dose-dependent suppression in SOD activity in Cc and H. In contrast, catalase activity was significantly ($p < 0.05$) increased in H and Cc at the 10 ng/kg-day TCDD dose level compared to controls and the mid- and high-dose animals. Catalase activity also was increased in a dose-dependent manner in the C section, but no significant changes in the activity of this enzyme were observed in the B section at any of the three TCDD tested doses. The effects of subchronic exposure to different doses of TCDD on glutathione stimulating hormone peroxidase (GSH-Px) showed a different response compared to other enzymes. There was a dose-dependent increase in the activity of this enzyme in the C and B regions of the brain, while a significant increase in the activity of GSH-Px occurred in Cc and H only at the 10 ng/kg-day TCDD dose. In addition, the activity of this enzyme was suppressed in a dose-dependent manner in the Cc and H at 22 and 46 ng/kg-day TCDD doses. Based on these results, the study authors concluded that induction of oxidative stress by TCDD in the rat brain occurs mainly in the Cc and H regions.

Similar to the statement above, because no adverse endpoints were measured, no LOAEL/NOAEL was established. However, a LOEL for TCDD of 7.14 ng/kg-day for a 13-week exposure duration was identified for this study for increases in superoxide anion and lipid peroxidation production, as well as increased activity in SOD, catalase, and GSH-Px.

D.1.4.10. *Kociba et al. (1976)*

Adult Sprague-Dawley rats (12 per sex per treatment group) were administered TCDD (purity not reported) in corn oil via gavage 5 days per week at doses of 0, 1, 10, 100, or 1,000 ng/kg-day (equivalent to 0, 0.71, 7.14, 71.4, or 714 ng/kg-day averaged over 7 days; 5/7 of dose). Five animals per group were sacrificed at the end of treatment, and the remaining animals were observed over 13 weeks post treatment (only initial results for the post-treatment period were provided in the report). Body weights and food consumption were measured semiweekly.

Hematology and clinical chemistry were measured after 36−37 or 85−86 days of treatment and 59−60 days after termination of treatment. Forty-eight hour urine samples were collected from select rats from 85−89 days of treatment and 52−56 days after cessation of treatment. Gross and histopathological exams were conducted on the tissues.

Four high-dose females died during treatment. Two high-dose females and two high-dose males died during the post-treatment period. Animals treated with 714 ng/kg-day were less active during the treatment period, which became less evident during the posttreatment period. Yellow discoloration of the external pinnae also was noted in this group, both during treatment and during the post-treatment period. A significant ($p < 0.05$) reduction in body weight and food consumption was observed in the 71.4 and 714 ng/kg-day groups. The following significant ($p < 0.05$) hematology changes were observed in the high-dose (714 ng/kg-day) males at all measured time points: decreased packed cell volume, decreased red blood cells, decreased hemoglobin, increased reticulocytes, and decreased thrombocytes. Significant ($p < 0.05$) changes also occurred in the high-dose females, but the only consistent observation was a decrease in thrombocytes and increased leukocytes. Significant changes in clinical chemistry ($p < 0.05$) and urinalysis ($p < 0.05$) were more consistent between the sexes in the high-dose group and included increases in total and direct serum bilirubin; increase in serum alkaline phosphatase; decreased urinary creatinine; and increased urinary coproporphyrin, uroporphyrin, and delta-amino-levulinic. The following significant ($p < 0.05$) changes were observed in the 71.4 ng/kg-day group: decreased packed cell volume (4−9%) in males; decreased red blood cells (2−10%) in males; decreased hemoglobin (2−13%) in males; increased urinary coproporphyrin (2.2-fold increase during treatment) in females; increased urinary delta-amino-levulinic (47% increase during treatment) in females; increased total and direct serum bilirubin (48−61%) in females; and increased serum alkaline phosphatase (twofold) in females. The following significant ($p < 0.05$) changes in relative organ weights were observed increased brain weight in 714 ng/kg-day males and females; increased liver weight in males (71.4 and 714 ng/kg-day) and females (7.14, 71.4, and 714 ng/kg-day); increased spleen weight in 714-ng/kg-day males and females; decreased thymus weight in 71.4 and 714 ng/kg males and females; and increased testes weight in 714 ng/kg-day males. Microscopic changes were observed in the thymus, and in other lymphoid tissues, and in the liver in rats treated with 71.4 ng/kg-day or greater.

The subchronic (13-week) LOAEL is 71.4 ng/kg-day, based on the numerous changes noted in body weight, hematology, clinical chemistry, urinalysis, and histopathology. The NOAEL is 7.14 ng/kg-day.

D.1.4.11. *Mally and Chipman (2002)*

Female F344 rats (3 per treatment group) were administered TCDD at concentrations of 0, 2.5, 25, or 250 ng/kg in corn oil via gavage for either 3 consecutive days or 2 days per week for 28 days (Mally and Chipman, 2002). The average daily doses for the 28-day study when adjusted for 7 days a week were 0, 0.71, 7.1, and 71 ng/kg-day (i.e., 2/7 of administered dose). No clinical signs of toxicity were observed. Histological examination of the liver revealed no abnormalities. All doses of TCDD reduced the number of connexin (Cx) 32 plaques and Cx32 plaque area in the liver, which was considered the target tissue. The reductions were not statistically significant after the 3-day treatment, but were significant after the 28-day treatment ($p < 0.05$). TCDD also caused a reduction in the Cx32 plaque number and area in the thyroid after 28 days, but the results were not statistically significant. Although the reduction in Cx32 plaque number and plaque area in the liver and thyroid occurred at all dose levels, there was no relation to dose. TCDD did not induce hepatocyte proliferation.

In the absence of additional indicators of hepatotoxicity, changes in Cx32 plaques are not clearly linked to TCDD-mediated hepatotoxicity, nor are they considered an adverse effect. Additionally, no toxicologically relevant endpoints were examined. Therefore, a NOAEL or LOAEL cannot be determined. A 28-day LOEL at the lowest dose of 0.71 ng/kg-day for significantly ($p < 0.05$) decreased Cx32 plaque area is evident (approximately 70% of the controls).

D.1.4.12. *Slezak et al. (2000)*

Slezak et al. (2000) studied the impact of subchronic TCDD exposure on oxidative stress in various organs of $B6C3F_1$ female mice. Groups of 8- to 10-week-old female $B6C3F_1$ mice (number not specified) were administered TCDD (purity >98%, dissolved in corn oil) via gavage at 0, 0.15, 0.45, 1.5, 15, or 150 ng/kg-day (0, 0.11, 0.32, 1.07, 10.7, or 107.14 ng/kg-day adjusted for continuous exposure) 5 days per week for 13 weeks. Three days after the last treatment, the

animals were sacrificed and organs were removed for the measurement of oxidative stress indicators including SA, lipid peroxidation (TBARS), AA, and total glutathione stimulating hormone (GSH). Tissue TCDD concentrations also were measured.

The study authors reported that TCDD dose range resulted in overlapping tissue concentrations for liver, lung, kidney, and spleen. Liver had the highest TCDD concentration, with each tissue demonstrating a dose-dependent increase in TCDD concentration. Compared to controls, SA production in the liver was significantly ($p < 0.05$) lower at the 0.15 ng/kg-day TCDD dose, while it was significantly ($p < 0.05$) higher at 15 and 150 ng/kg-day. A dose-dependent increase in hepatic TBARS production was observed, although the rate of production was significant ($p < 0.05$) only at the highest TCDD administered dose (150 ng/kg-day) compared to controls. AA also followed the same pattern observed for hepatic SA and TBARS with AA production significantly ($p < 0.05$) increased at the 15 and 150 ng/kg-day TCDD doses. Contrary to the SA, TBARS, and AA responses, liver GSH levels were decreased at 0.15 ng/kg-day, were increased at 0.45 and 150 ng/kg-day, and did not change at 1.5 or 15 ng/kg-day when compared to the control group. Unlike the liver, there was no significant increase in SA production in the lung at any of the TCDD tested doses; a dose dependent reduction, however, was observed at 0.45, 15, and 150 ng/kg-day compared to controls. GSH and AA production in the lung was decreased at 0.15 ng/kg-day, while AA production was significantly ($p < 0.05$) increased at 15 and 150 ng/kg-day. Kidney SA production showed a statistically significant ($p < 0.05$) increase only at the 15 and 150 ng/kg-day doses. GSH, like in the liver and the lung, exhibited a decrease in production in the kidney following treatment at 0.15 ng/kg-day with this trend continuing at 0.45 and 1.5 ng/kg-day. AA levels in the kidney were significantly ($p < 0.05$) lower at all subchronic doses, except at 1.5 ng/kg-day dose. SA levels in the spleen differed little from the control group at any of the TCDD doses. Total GSH in the spleen was higher only at the 150 ng/kg-day dose level, while the AA levels were significantly ($p < 0.05$) decreased at 0.15, 1.5, and 150 ng/kg-day.

Similar to the statements regarding the Hassoun et al. studies above, because no adverse endpoints were measured, no LOAEL/NOAEL was established. Therefore, a NOAEL or LOAEL cannot be determined. However, a NOEL and LOEL of 1.07 and 10.7 ng/kg-day, respectively, are identified in this study for increases in superoxide anion in the liver.

D.1.4.13. *Smialowicz et al. (2008)*

Female B6C3F$_1$ mice (8–15 per treatment group) were administered TCDD (purity >98%) in corn oil by gavage at doses of 0, 1.5, 15, 150, or 450 ng/kg-day, 5 days a week, for 13 weeks (1.07, 10.7, 107, or 321 ng/kg-day, adjusted for continuous exposure; i.e., 5/7 of the dose) (Smialowicz et al., 2008). Mice were immunized 3 days after the final TCDD exposure with an intravenous injection of an optimal concentration of 4×10^7 SRBCs and sacrificed 4 days later. No TCDD-related effects on body weight were observed. There was a dose-related decrease in relative spleen weight (9–19% lower than control values) with statistically significant ($p < 0.05$) decreases at all but the lowest dose. Additionally, there was a statistically significant ($p < 0.05$) increase in relative liver weight (5–21%) in all treatment groups compared to controls. Statistically significant dose-dependent decreases were observed in the antibody response to SRBCs (24–89% lower than control values), as measured by both the number of plaque forming cells per 10^6 cells and plaque forming cells per spleen.

The 13-week LOAEL for this study is 1.07 ng/kg-day based on a significant ($p < 0.05$) increase in relative liver weight (10%) and a significant ($p < 0.05$) decrease in antibody response to SRBCs (24%). A NOAEL cannot be determined for this study.

D.1.4.14. *Van Birgelen et al. (1995a; 1995b)*

Van Birgelen et al. (1995a; 1995b) studied the impact of TCDD exposure on various biochemical endpoints in rats. In Van Birgelen et al.(1995b) groups of 7-week-old female Sprague-Dawley rats ($n = 8$ per treatment group) were treated with 0, 200, 400, 700, 5,000, or 20,000 ng/kg TCDD (purity >99%) in the diet for 13 weeks. Daily TCDD intake based on food consumption, diet level, and mean weight was estimated to be 0, 14, 26, 47, 320, or 1,024 ng/kg-day. Blood samples were collected from treated animals and assayed for retinol (vitamin A), triiodothyronine, and TT4 and free thyroxine (FT4). At study termination, the animals were sacrificed, and the liver, thymus, spleen, and kidneys were removed and weighed. Parts of the liver were homogenized and assayed to determine EROD; CYP1A1; CYP1A2; and UGT activity. Liver samples also were analyzed for retinol content. Van Birgelen et al. (1995a) analyzes in greater detail the effects of TCDD on thyroid hormone metabolism, and both papers are based on the same materials and methods.

TCDD-treated animals showed a dose-related decrease in food consumption. Animals treated with 1,024 ng/kg-day TCDD consumed 32% less food compared to controls. Similarly, a

dose-related decrease in body weight gain was observed in all animals treated with TCDD. Animals treated with ≥47 ng/kg-day of TCDD showed a statistically significant ($p < 0.05$) decrease in body weight gain. Relative liver weights were significantly ($p < 0.05$) increased in the 320 and 1,024 ng/kg-day TCDD dose groups compared to the controls. Absolute and relative thymus weights were significantly ($p < 0.05$) decreased at all TCDD dose groups compared to the control group. Relative kidney and spleen weights were significantly ($p < 0.05$) higher in animals dosed with ≥47 ng/kg-day of TCDD compared to the control group, with the greatest increase occurring in animals treated with 1,024 ng/kg-day TCDD (121 and 173% higher than controls for kidney and spleen, respectively). Cytochrome P450 enzymes, including EROD, CYP1A2, CYP1A1, and UGT, exhibited statistically significant ($p < 0.05$) increases in activity at all TCDD dose groups compared to the control group. TT4 and FT4 thyroid hormone concentrations were statistically significantly ($p < 0.05$) decreased only at TCDD doses ≥47 ng/kg-day. A dose-dependent increase was observed in the plasma retinol concentrations with significant ($p < 0.05$) increases occurring at ≥47 ng/kg-day TCDD after a 13-week exposure. A dose-dependent reduction in liver retinoid levels also was observed after 13 weeks of TCDD exposure with the levels dropping significantly ($p < 0.05$) at all TCDD-treated doses compared to the control group.

A LOAEL for TCDD of 14 ng/kg for a 13-week exposure is identified for significantly ($p < 0.05$) decreased absolute and relative thymus weights and significantly ($p < 0.05$) decreased liver retinoid levels. A NOAEL cannot be determined for this study.

D.1.4.15. *Vos et al. (1973)*

Vos et al. (1973) conducted a study to examine the immune response in laboratory animals treated with TCDD. In one experiment, 10 female Hartley strain guinea pigs were orally treated with 8 weekly doses of 0, 8, 40, 200, and 1,000 ng/kg TCDD in corn oil (purity of TCDD not specified) (0, 1.14, 5.71, 28.6, and 143 ng/kg-day adjusted for continuous exposure; administered dose divided by 7). At study termination, the animals were sacrificed, and heart blood was used to determine total leukocyte and differential leukocyte counts. In another experiment, the effect of TCDD on humoral immunity was determined by injecting 0.1 mL of tetanus toxoid into the right hind-foot pad on Day 28 (1 left foot tetanus toxoid, aluminum phosphate-adsorbed) and again on Day 42 (1 left foot tetanus toxoid, unadsorbed). Blood was

collected (n = 10) on Days 35 and 49, and the serum tetanus-antitoxin concentrations were determined using a modified single radial immunodiffusion technique.

All guinea pigs receiving 1,000 ng/kg-day TCDD either died or were killed when moribund between 24 and 32 days. These animals showed severe weight loss, lymphopenia, and depletion of the lymphoid organs, especially the thymus. Microscopic observations revealed severe atrophy of the thymic cortex with substantial destruction of lymphocytes, with the nuclear debris being engulfed by macrophages. Large cystic Hassall bodies, filled with polymorphonuclear leukocytes, were observed in the medulla. All animals treated with 0, 8, 40, or 200 ng/kg-day TCDD survived until study termination. Body weight gain was significantly ($p < 0.01$) lower in the 200 ng/kg-day group. Absolute thymus weight was significantly reduced in the 40 and 200 ng/kg-day treatment groups ($p < 0.01$ and $p < 0.05$, respectively). In contrast, relative thymus weight was significantly ($p < 0.01$) reduced only in the 200 ng/kg-day dose group. The absolute weight of the superficial cervical lymph nodes was significantly ($p < 0.05$) decreased in the 200 ng/kg-day group, while the relative adrenal weight was significantly ($p < 0.05$) increased in the 200 ng/kg-day dose group. Total leukocyte count was significantly ($p < 0.05$) decreased in the 40 ng/kg-day dose group and total lymphocyte count was significantly decreased at 8, 40, and 200 ng/kg-day ($p < 0.01$, $p < 0.05$, and $p < 0.05$, respectively). A significant (p-values not provided) monotonic dose-response relationship was determined for body weight (decrease), relative thymus weight (decrease), relative adrenal weight (increase), and total leukocyte and lymphocyte count (decrease). Microscopic examination of the lymphoid organs and adrenals showed no effects, while slight cortical atrophy of the thymus was observed at the 200 ng/kg-day dose.

Animals receiving the tetanus toxoid injection showed a small but significant increase in serum tetanus antitoxin concentrations at the 8 and 40 ng/kg-day dose ($p < 0.05$ and $p < 0.01$, respectively). Measurement at Days 49 and 56 indicated that serum antitoxin levels had decreased sharply and the significant ($p < 0.05$ on Day 49 and $p < 0.01$ on Day 56) effect was seen only at the 200 ng/kg-day dose level.

A LOAEL for TCDD of 5.71 ng/kg-day for an 8-week exposure is identified in this study for significantly ($p < 0.01$) reduced absolute thymus weight, significantly ($p < 0.05$) reduced leukocyte and lymphocyte count, and significantly ($p < 0.01$) increased serum tetanus antitoxin concentration. The NOAEL for this study is 1.14 ng/kg-day.

D.1.4.16. *White et al. (1986)*

White et al. (1986) studied the impact of TCDD exposure on serum complement levels. Groups of female (C57BL/6 × C3H)F1(B6C3F$_1$) mice were treated for 14 consecutive days with TCDD in corn oil (purity of TCDD not specified) at doses of 0, 10, 50, 100, 500, 1,000 or 2,000 ng/kg-day via gastric intubation (n = 6−8). At study termination, blood was collected from anesthetized animals and assayed for serum complement activity and complement component C3 levels.

Serum complement activity between the 10 and 100 ng/kg-day doses was between 69 and 59% compared to the vehicle control group, with all treatment groups being significantly ($p < 0.05$) low compared to the vehicle control. In contrast, C3 levels were comparable to the vehicle control with levels ranging between 98 and 94% of the control group. The higher doses of 500, 1,000, and 2,000 ng/kg-day, however, produced a marked decrease of the component hemolytic activity (45, 35, and 19% of the vehicle control) and of C3 levels (91, 81, and 74% of the vehicle control, respectively; significance level at $p < 0.05$).

A LOAEL for TCDD of 10 ng/kg-day for a 14-day exposure is identified in this study for significantly ($p < 0.05$) lower serum complement activity. A NOAEL cannot be determined for this study.

D.1.5. Chronic Studies (Noncancer Endpoints)

D.1.5.1. *Cantoni et al. (1981)*

CD-COBS rats (4 per treatment) were orally administered TCDD (purity not specified) dissolved in acetone:corn oil (1:6) at doses of 0 (vehicle alone), 10, 100, or 1,000 ng/kg per week (equivalent to 1.43, 14.3, and 143 ng/kg-day adjusted for continuous exposure, administered dose by dividing the dose by 7) for 45 weeks. Urine was collected several times during treatment and tested for porphyrin excretion. Twenty-four hours after the final dose, animals were sacrificed and their livers, spleens, and kidneys were removed for analysis of total porphyrins. All treatment groups had a significant ($p < 0.05$) increase in coproporphyrin excretion beginning at 6, 3, or 2 months, respectively. Uroporphyrin excretion was significantly ($p < 0.05$) increased in the 14.3 ng/kg-day group at 10 months and in the 143 ng/kg-day group

beginning at 6 months. The high-dose group also had a significant ($p < 0.05$) increase in excretion of heptacarboxylic methyl ester beginning at 6 months. The high-dose group had a marked porphyric state beginning at 8 months as indicated by a 70-fold increase above controls in total urinary porphyrin excretion. This group also had a significant ($p < 0.05$) increase in total porphyrins in the liver, kidneys, and spleen.

The 45-week LOAEL for this study is 1.43 ng/kg-day, based on a two- to threefold increase in urinary coproporphyrin excretion. No NOAEL was established for this study.

D.1.5.2. *Croutch et al. (2005)*

Croutch et al. (2005) examined the impact of TCDD exposure on body weight via insulin-like growth factor (IGF) signaling. Female Sprague-Dawley rats were randomly assigned in groups of five to initial loading doses of TCDD (purity >98.5%, dissolved in corn oil) at 0, 12.5, 50, 200, 800, or 3,200 ng/kg-day, followed by treatment with maintenance doses equivalent to 10% of the initial loading dose every third day to maintain a pharmacokinetic steady state throughout the entire study (equivalent to 14-day average = 0, 1.25, 5, 20, 80, or 320 ng/kg-day; 28-day average = 0, 0.85, 3.4, 13.6, 54.3, or 217 ng/kg-day; 63-day average = 0, 0.60, 2.4, 9.5, 38, or 152 ng/kg-day; and 128-day average dose = 0, 0.51, 2.0, 8.1, 32.5, or 130 ng/kg-day). Following 2, 4, 8, 16, 32, 64, or 128 days of initial dosing, the animals were sacrificed, the livers were removed and weighed, and the trunk blood was collected to analyze glucose content. Rat liver PEPCK mRNA and protein levels also were analyzed, and PEPCK activity was measured.

Body weights of TCDD-treated animals decreased after the second week of the 3,200 ng/kg-day TCDD loading dose, with significant differences beginning at Week 9. There was also a statistically significant ($p \leq 0.05$) difference in body weights at Weeks 10, 11, 13, 18, and 19 at the highest loading dose (3,200 ng/kg-day). PEPCK activity in the liver was also decreased in a dose-dependent manner following TCDD administration at approximately 16 days. PEPCK inhibition was statistically significant ($p \leq 0.05$) on Day 4 in rats treated with either 800 or 3,200 ng/kg-day TCDD when compared to animals treated with a loading dose of 200 ng/kg-day. A similar statistically significant change was observed in animals treated with 3,200 ng/kg-day on Day 16 when compared to the 200 ng/kg-day treatment group. In contrast, differences in PEPCK activity at other doses or time points were not statistically significant. In TCDD-treated animals, there was also a dose-dependent decrease in PEPCK mRNA expression

along with a decrease in PEPCK protein levels in the liver. In addition to body weight and PEPCK activity changes, animals treated with 3,200 ng/kg-day TCDD showed a sharp decline in circulating IGF-I levels on Day 8 compared to the control group (corn oil) and TCDD-treated animals at lower doses. In the highest dose animals, IGF-I levels continued to decline to 42% of the control group by Day 16 of the study. The IGF-I levels at the highest dose plateaued at an average decrease of 66% through Day 128 when compared to controls. Beginning at Day 8, the decrease in IGF-I was statistically significant at every time point through Day 128 compared to the control group, as well as groups treated with either 12.5 or 50 ng/kg-day TCDD. Similar statistically significant decreases also were observed for the 800 ng/kg-day TCDD-treated groups with an initial decrease of 37% on Day 16 followed by a further decline to approximately 45% thereafter compared to controls and the 12.5, 50, and 200 ng/kg-day dose groups. In contrast to these results, circulating levels of insulin and glucose were unaffected by TCDD treatment, while the active or phosphorylated form of AMPK-α protein increased with dose as a result of TCDD treatment.

A LOAEL for TCDD of 217 ng/kg-day for a 28-day exposure duration (because this represented the most sensitive time for elicitation of effects) was identified in this study for decreased body weight, significant ($p \leq 0.05$) inhibition of PEPCK activity, and reduced IGF-I levels (42% lower than the control group). A NOAEL of 54.3 ng/kg-day was identified in this study.

D.1.5.3. *Hassoun et al. (2002)*

Hassoun et al. (2002) examined the potential of TCDD and other dioxin-like chemicals to induce oxidative stress in a chronic rat bioassay. Groups of six Harlan Sprague-Dawley female rats were treated with 0, 3, 10, 22, 46, or 100 ng/kg-day TCDD (98% purity), 5 days a week via gavage for 30 weeks. The administered doses adjusted for continuous exposure were 0, 2.14, 7.14, 15.7, 32.9, and 71.4 ng/kg-day, respectively (administered doses were multiplied by 5 and divided by 7). At study termination, hepatic and brain tissues from all treated rats were divided into two portions and examined for the production of reactive oxygen species and SSBs in DNA.

When compared to controls, there was a dose-dependent increase in the production of superoxide anion in TCDD-treated animals ranging from 21–998% and 66–257% in hepatic and brain tissues, respectively. Hepatic tissues had statistically significant ($p < 0.05$) increases in

superoxide anion production at doses ≥7.14 ng/kg-day, while the brain tissue had a statistically significant ($p < 0.05$) increase over controls at all doses. Similarly, increases in lipid peroxidation were observed in hepatic and brain tissues with a 481% increase ($p < 0.05$) at 71.4 ng/kg-day in the hepatic tissue when compared to controls. The increase in lipid oxidation in brain tissue ranged from 33–188% ($p < 0.05$) in the 2.14–71.4 ng/kg-day dose groups. DNA SSBs were also observed in both hepatic and brain tissue in all treated groups. When compared to the control group, there was a dose-dependent statistically significant ($p < 0.05$) increase in DNA SSBs ranging from 58–322% and 29–137% in hepatic and brain tissues, respectively. Nonmonotonic dose-response relationships were observed for superoxide production and lipid peroxidation in liver tissues, with greater-than-linear increases in effect between the two highest dose levels.

As stated above, because no adverse endpoints were measured, no LOAEL/NOAEL was established. However, a LOEL for TCDD of 2.14 ng/kg-day for a 30-week exposure duration is identified in this study for significant ($p < 0.05$) increases in superoxide anion, lipid peroxidation production, and DNA SSBs in the liver and brain tissues. A NOEL cannot be determined for this study.

D.1.5.4. *Hong et al. (1989)*

Hong et al. (1989) studied the immunotoxic effects associated with chronic exposure to TCDD in rhesus monkeys. Female rhesus monkeys (seven to eight animals per treatment group) were exposed to 0, 5, or 25 ppt TCDD (purity not specified) in feed for 4 years. As described previously (Bowman et al., 1989a; 1989b), these dietary concentrations were equivalent to 0, 0.12, and 0.67 ng/kg-day, respectively. These adult females were tested for immune abnormalities 4 years after cessation of exposure. Additionally, offspring from exposed mothers born into Cohort I (n = 7, 6, and 1, respectively), Cohort II (n = 5, 6, and 2, respectively), and Cohort III (n = 6, 6, and 3, respectively) (as described by Bowman et al. (1989b)) were also tested. Monoclonal antibodies with flow cytometry were used to enumerate cells in the various leukocyte populations. A proliferative response to mitogens (phytohemagglutinin, pokeweed, concanavalin A) as well as allo- and xeno-transplantation antigens was measured. Natural killing capacity and a T cell dependent response to immunization with tetanus toxoid was also

assessed. The range of normal immune responses in rhesus monkeys was obtained from 45 healthy animals unrelated to the TCDD exposure studies.

In adult monkeys, an increased number of T lymphocytes were observed in the 0.67 ng/kg-day dose group. However, there was not a proportional increase in each of the T cells subsets, which was represented by increased numbers of cytotoxic/suppressor cells and decreased numbers of helper/inducer cells. Although this resulted in a lower helper/suppressor ratio in the 0.67 ng/kg-day group, the values were within the measured normal range. Peak antibody level and antibody response to tetanus toxoid immunization was not altered compared to control values at either dose tested. Macrophage depletion in the 0.12, and 0.67 ng/kg-day groups resulted in the absence of amplification in a mixed lymphocyte response assay, compared to a fivefold amplification in control monkeys. As previously reported, the 0.67 ng/kg-day dose group had reduced reproductive rates (Bowman et al., 1989b) and the mean number of days of offspring survival also decreased.

The surviving offspring from the TCDD-exposed mothers were examined using the same immune panel used on the mothers and described above. The only material finding was an immune hyperresponsiveness to tetanus toxoid immunization which correlated with TCDD tissue levels (r = 0.40). However, this effect seems to be driven by only two of the offspring, and its biological significance is unknown. There was no correlation between TCDD body burdens in the offspring with a mother monkey's TCDD dose (i.e., offspring with the highest TCDD tissue levels were born as often to mothers exposed to 0.12 ng/kg-day as 0.67 ng/kg-day).

In the absence of any relevant immunotoxicity endpoints or functional decrements of immune function following TCDD exposure, neither a NOAEL nor a LOAEL can be established for this study.

D.1.5.5. *Kociba et al. (1978)*

Sprague-Dawley rats (50 per sex per treatment group) were administered TCDD (purity >99%) in the diet at doses of 0, 1, 10, or 100 ng/kg-day for 2 years. Body weights and food consumption were routinely measured. Hematology, clinical chemistry, and urinalysis were measured after 3, 12, or 23 months of treatment. Animals were routinely palpitated for tumors. Gross and histopathological exams were conducted on the tissues of dead or dying animals or at terminal sacrifice. Specific organs also were weighed.

The high-dose females had a statistically significant ($p < 0.05$) increase in mortality compared to the controls during the second half of the study. Mortality changes in males were variable and of questionable toxicological significance. A significant ($p < 0.05$) reduction in body weight occurred in the 100 ng/kg-day males and females beginning at 6 months. Mid-dose females also had reduced body weight, but to a lesser degree during the same time frame. There were no consistent changes in food consumption. The following significant ($p < 0.05$) hematology changes were observed in the high-dose animals: decreased packed cell volume in males after 3 months and in females after 1 year, decreased red blood cells in females after 1 year and in males at terminal sacrifice, decreased hemoglobin in males after 3 months and in females after 1 year, and decreased total white blood cell count in females after 1 year. Changes in clinical chemistry ($p < 0.05$) occurred only in high-dose females and consisted of an increase in serum alkaline phosphatase and gamma glutamyl transferase. Significant changes in urinalysis occurred only in females and included increased urinary coproporphyrin in the mid- and high-dose groups, increased urinary uroporphyrin in the mid- and high-dose groups, and increased urinary delta-amino-levulinic acid in the high-dose group. Significant ($p < 0.05$) changes in relative organ weights were observed, including increased liver weight in mid- and high-dose females and decreased thymus weight in high-dose females. Mid- and high-dose rats showed hepatocellular degeneration and inflammatory and necrotic changes in the liver. Thymic and splenic atrophy were noted in high-dose females. An increase in non-neoplastic lung lesions was noted in mid-dose females and high-dose males and females. High-dose females had an increase in uterine changes. High-dose males had a significant ($p < 0.05$) increase in the incidence of stratified squamous cell carcinomas of the tongue. High-dose males and females had a significant ($p < 0.05$) increase in the incidence of squamous cell carcinomas of the hard palate/turbinates.

The chronic (2-year) LOAEL is 10 ng/kg-day, based on the numerous significant ($p < 0.05$) changes noted in coproporphyrin excretion (67% increase above control) and an increase in liver and lung lesions in female rats. The NOAEL is 1 ng/kg-day.

D.1.5.6. *Maronpot et al. (1993)*

An initiation-promotion study was performed in female Sprague-Dawley rats (8–10 rats per group). The rats were initiated with saline (S) or diethylnitrosamine (DEN), followed

2 weeks later by promotion with biweekly administration of TCDD (purity not specified) in corn oil via gavage for 30 weeks. The doses were stated to be equivalent to 3.5, 10.7, 35.7, or 125 ng/kg-day. The rats were sacrificed 7 days after the final treatment. A significant ($p < 0.05$) decrease in body weight occurred in the 125 ng/kg-day group. A significant ($p < 0.05$) increase in relative liver weight occurred in the 35.7 and 125 ng/kg-day groups. There was a significant ($p < 0.05$) increase in the labeling index in the 125 ng/kg-day group, but only with DEN initiation. In the TCDD-alone group, a twofold increase in labeling index occurred in the 125 ng/kg-day group that did not reach statistical significance. A significant ($p < 0.05$) trend test for increased alkaline phosphatase levels was observed in TCDD-treated animals; despite a 50% increase in the highest dose group, the increase was not statistically significant from controls via a pairwise comparison. Total cholesterol and triglycerides were significantly ($p < 0.05$) higher in the 125 ng/kg-day TCDD-alone group. A significant ($p < 0.05$) increase in 5'-nucleotidase occurred in the 35.7 and 125 ng/kg-day TCDD-alone groups. A dose-dependent increase in the incidence and severity of liver toxicity as measured by microscopic lesions was observed.

The 30-week LOAEL is 35.7 ng/kg-day, based on a significant ($p < 0.05$) increase in relative liver weight (12%, accompanied by increases in incidence and severity of liver lesions). The 30-week NOAEL is 10.7 ng/kg-day.

D.1.5.7. *National Toxicology Program (1982)*

National Toxicology Program (NTP, 1982) conducted a carcinogenic bioassay of TCDD on rats and mice. Fifty male and female Osborne-Mendel rats and male and female $B6C3F_1$ mice were treated twice per week with TCDD (purity not specified) in corn oil via oral gavage at doses of 0, 5, 25, or 250 ng/kg for rats and male mice (1.4, 7.1, 71 ng/kg-day adjusted for continuous exposure; administered doses multiplied by 2 and divided by 7) and 0, 20, 100, or 1,000 ng/kg for female mice (5.7, 28.6, or 286 ng/kg-day adjusted for continuous dosing; administered doses multiplied by 2 and divided by 7) for 104 weeks. Seventy-five rats and mice of each sex served as vehicle controls. One untreated control group of 25 rats and mice of each sex was present in the TCDD treatment room and one untreated control group consisting of 25 rats and mice of each sex were present in the vehicle-control room. Animals surviving until

study termination were sacrificed at 105 or 108 weeks. A complete histopathological evaluation was conducted on all animals.

Survival rates were not affected by TCDD exposure in rats or mice of either sex. Male rats exhibited a dose-related depression in mean body weight after Week 55, while the females exhibited a dose-related body-weight depression after 45 weeks of TCDD exposure. However, the magnitude of the body weight response is not indicated. Mean body weights in male and female mice were comparable to the vehicle control group throughout the bioassay. Noncancer histopathologic findings included increased incidences of liver lesions (termed toxic hepatitis) from TCDD exposure, and were detected in the high-dose rats and high-dose mice of each sex.

A LOAEL for TCDD of 1.4 ng/kg-day for a 104-week exposure duration is identified for increased incidences of liver lesions in mice of both sexes. A NOAEL cannot be determined for this study.

D.1.5.8. *National Toxicology Program (2006)*

Female Sprague-Dawley rats (81 control; 82 treatment group) were administered TCDD (purity >98%) in corn oil:acetone (99:1) via gavage at doses of 0, 3, 10, 22, 46, or 100 ng/kg-day, 5 days per week for 105 weeks (0, 2.14, 7.14, 15.7, 32.9, or 71.4 ng/kg-day, adjusted for continuous exposure) (NTP, 2006). In addition to this primary group, a stop group of 50 animals was administered 100 ng/kg-day TCDD in corn oil:acetone (99:1) via gavage for 30 weeks and then just the vehicle for the remainder of the study. Up to 10 rats per dose group were sacrificed and evaluated at 14, 31, or 53 (n = 8) weeks for biologically noteworthy changes in the incidences of neoplasms or non-neoplastic lesions in the liver, lung, oral mucosa, uterus, pancreas, thymus, adrenal cortex, heart, clitoral gland, ovary, kidney, forestomach, bone marrow, mesentery gland, and pituitary gland. All interim sacrifice animals also received a complete necropsy and microscopic examination, and the following organs were weighed: the left kidney, liver, lung, left ovary, spleen, thymus (14 weeks only), and thyroid gland. Out of 53 control animals and 53 or 54 animals per treatment group not used for interim sacrifice analyses, at study termination the number of surviving animals had declined to 25 in the control group and to 21, 23, 19, 22, and 21 in five treatment groups, respectively, due to accidental deaths, moribund animals, or death due to natural causes.

Survival rate was not affected by TCDD treatment. Mean body weights in the high dose primary study group and the 100 ng/kg stop group were less than the vehicle control group after

Week 13 of the study. The mean body weights of animals in the 46 ng/kg-day group were less than in the vehicle control at study termination (2 years), whereas animals in the 22 ng/kg-day had lower mean body weights compared to controls during the last 10 weeks of study. In addition to body weight changes, liver weights were also impacted as a result of TCDD exposure. Absolute and relative liver weights were significantly (either $p \leq 0.01$ or $p \leq 0.05$) higher in all dose groups compared to controls at the 14- and 31-week evaluation period, whereas the relative liver weights were significantly (either $p \leq 0.01$ or $p \leq 0.05$) higher only at ≥10 ng/kg-day at 53 weeks.

No clinical findings associated with TCDD treatment were observed. TCDD caused changes in thyroid hormone levels at 14, 31, and 53 weeks. The following changes were statistically significant ($p \leq 0.05$) compared to the vehicle control: decrease in TT4 at doses ≥22 ng/kg-day at 14 and 31 weeks and at doses ≥46 ng/kg-day at 53 weeks; decrease in FT4 at doses ≥22 ng/kg-day at 14 and 31 weeks; increase in total T_3 at doses ≥46 ng/kg-day at 14 and 31 weeks and at doses ≥10 ng/kg-day at 53 weeks; and increase in TSH at doses ≥46 ng/kg-day at 14 weeks. There was a statistically significant ($p \leq 0.05$) increase in hepatocyte proliferation at 14 weeks (22 ng/kg-day group only); 31 weeks (all doses); and 53 weeks (≥46 ng/kg-day). There were statistically significant ($p \leq 0.01$) dose-dependent increases in liver (includes EROD [CYP1A1-associated] activity; 7-PROD [CYP2B-associated] activity; and acetanilide-4-hydroxylase [CYP1A2-associated] activity) and lung (EROD) cytochrome P450 enzyme activities in all treatment groups at all three evaluation periods compared to the vehicle control group. The largest effect was an 82-fold induction of hepatic EROD activity in the 46 ng/kg-day group at 31 weeks.

TCDD was detected at the greatest concentration in the liver, followed by fat tissue, with tissue concentration increasing in both of these tissues in a dose-dependent manner. TCDD tissue levels generally remained constant after the first measurement at Week 14. Pathological examination at Week 14 revealed increased incidences of hepatocellular hypertrophy in animals administered ≥10 ng/kg-day TCDD. Examinations at Weeks 31 and 53 indicated that incidence and or severity of hepatocellular hypertrophy was increased at all treatment doses although incidences were statistically significant ($p \leq 0.05$) only at ≥10 ng/kg-day doses. The incidence of non-neoplastic hepatic lesions (including inflammation, necrosis, multiple eosinophilic focus, diffuse fatty change, pigmentation, toxic hepatopathy) in the liver increased at doses

≥22 ng/kg-day beginning at 14 weeks. The severity of the lesions increased at 14 weeks at doses ≥46 ng/kg-day, but lesions were also observed at lower dose levels during later evaluation periods (31 and 53 weeks). By terminal sacrifice, numerous non-neoplastic changes were noted in TCDD treated rats, even at the lowest dose tested.

Noncancer cardiovascular and pulmonary effects were evident after 2 years of TCDD exposure. Significantly increased incidences of minimal to mild cardiomyopathy were seen in male and female rats at ≥10 ng/kg-day. In the lung, there was a significant ($p \leq 0.01$) dose-dependent increase, when compared to the vehicle control, in the incidence of bronchiolar metaplasia of the alveolar epithelium at all dose groups in the primary study.

A LOAEL for TCDD of 2.14 ng/kg-day adjusted dose for a 105-week exposure duration is identified in this study for significantly (either $p \leq 0.01$ or $p \leq 0.05$) increased absolute and relative liver weights, increased incidence of hepatocellular hypertrophy, and increased incidence of alveolar to bronchiolar epithelial metaplasia. A NOAEL cannot be determined for this study.

D.1.5.9. *Sewall et al. (1993)*

Sewall et al. (1993) examined the impact of TCDD exposure on the hepatic epidermal growth factor receptor (EGFR) as a critical effect in hepatocarcinogenicity. In two separate experiments, groups of 6- to 8-week-old female Sprague-Dawley rats were randomly assigned to the following groups: control group, receiving saline and corn oil; a promoted group that received four different doses of TCDD along with saline; a DEN-only initiated control group; and a DEN and TCDD initiated and promoted group that received four different doses of TCDD. DEN was administered via intraperitoneal injection at a dose of 175 mg/kg [S vehicle] as the initiating agent to animals that were 70 days old. The control animals received saline only. In the first experiment, each treatment group (S/TCDD and DEN/TCDD) that included sham-operated or ovariectomized and intact animals were treated with TCDD (purity >98%) at 125 ng/kg-day. In the second dose-response experiment, DEN-initiated and saline control treatment groups (intact animals, 84 days old) were administered TCDD (purity >98%) in corn oil via oral gavage once every 2 weeks for 30 weeks at doses equivalent to 0, 3.5, 10.7, 35.7, or 125 ng/kg-day ($n = 9$). A week after the last treatment, all animals were sacrificed and livers were harvested and fixed for immunohistochemistry. Sections of the fixed liver were tested for

EGFR binding, EGFR autophosphorylation, immunolocalization of EGFR, and hepatic cell proliferation.

In the first experiment, intact animals treated with 125 ng/kg-day TCDD exhibited a 65% reduction in EGFR binding capacity. In contrast, the EGFR equilibrium maximum binding capacity (B_{max}) of the ovariectomized rats was not statistically different from the ovariectomized control rats, and no changes in the dissociation constant (K_d) were detected in any treatment group. In the dose-response experiment with intact animals, a significant ($p < 0.05$) TCDD dose-dependent decrease in the B_{max} of EGFR was shown. A two-factor, five-level ANOVA indicated that the effect of TCDD exposure on EGFR B_{max} was significant ($p = 0.0001$), whereas, the effect of DEN treatment on EGFR B_{max} was not significant. Comparative analysis using Fisher's protected least significant difference test indicated that the lowest TCDD dose resulting in a statistically significant ($p < 0.05$) decrease in the EGFR B_{max} was 10.7 ng/kg-day S/TCDD group. At the highest TCDD dose of 125 ng/kg-day, the EGFR B_{max} was reduced by 38% compared to controls in both the DEN initiated and noninitiated groups. A two-factor, five-level ANOVA showed no significant effect on EGFR K_d in either the DEN- or the TCDD-treated groups. The EGFR autophosphorylation assay indicated that, with increasing TCDD dose, the amount of EGFR autophosphorylation in DEN/TCDD-treated animals decreased. The study authors state that this decrease is similar to the dose-response alterations observed for the EGFR B_{max}. Additionally, EGFR autophosphorylation in control and 125 ng/kg-day noninitiated animals was similar to the corresponding dose levels for the DEN-treated animals, suggesting that DEN treatment did not affect the EGFR or the EGFR response to TCDD under the experimental conditions. The immunolocalization assay indicated that staining was more apparent in the centrilobular and midzonal regions of the liver in the DEN initiated control animals, whereas, the amount of hepatocyte plasma membrane staining in DEN/TCDD treated animals substantially decreased. The cell proliferation assay showed a decrease in the cell labeling index in the 3.5 ng/kg-day DEN/TCDD dose group that was statistically less ($p \leq 0.05$) than the labeling index for the control group. In contrast, the labeling index for the 125 ng/kg-day DEN/TCDD treatment group was significantly ($p \leq 0.05$) higher compared to controls. Except for the low-dose (3.5 ng/kg-day) group, a clear dose-response trend (two mid-level doses were not statistically significant) was observed in the other three TCDD treated groups.

The role of EGFR in TCDD-mediated hepatotoxicity is unknown, and as such, this endpoint cannot be unequivocally linked to TCDD-induced hepatotoxicity nor labeled as adverse. Thus, no LOAEL/NOAEL was established. A LOEL for TCDD of 3.5 ng/kg-day for a 30-week exposure duration was identified in this study for a significant (p = 0.0001 using ANOVA) decrease in EGFR B_{max} levels. A NOEL cannot be determined for this study.

D.1.5.10. *Sewall et al. (1995a)*

Sewall et al. (1995a) studied the dose-response relationship for thyroid function alterations in female rats as a result of TCDD exposure. Groups of female Sprague-Dawley rats were initiated with DEN at 70 days of age at a dose of 175 mg/kg in a saline vehicle via an i.p. injection. DEN was administered as a liver-initiating agent for a concurrent study to determine TCDD promotion of hepatic preneoplastic foci. Saline-treated animals served as controls. At 84 days of age, both the DEN-initiated and the saline-noninitiated groups of animals were administered TCDD (purity >98%) or corn oil vehicle via oral gavage once every 2 weeks for 30 weeks at dose levels equivalent to 0, 0.1, 0.35, 1.0, 3.5, 10.7, 35.7, or 125 ng/kg-day (n = 9 per group). One week after the last TCDD treatment, the animals were sacrificed and the thyroid was removed and fixed for further analysis. Blood was drawn from the abdominal aortic vein, and the serum was isolated and preserved for hormone analysis. Liver was also removed and prepped for further analysis. Thyroid hormone analysis was performed to determine serum TSH, T3, and T4 levels using radioimmunoassay kits. Histological examination was conducted on eosin-stained sections of the thyroid tissue. RNA level in the hepatic tissue was determined using a RT-PCR technique.

TCDD treatment did not affect thyroid weight. A dose-dependent decrease in serum T4 levels was observed in both noninitiated and DEN-initiated animals with T4 levels dropping significantly ($p < 0.05$) at the 35 and 125 ng/kg-day TCDD doses in the noninitiated group. Compared to the noninitiated control group, DEN alone did not significantly affect T4 levels. Serum T3 level in the 125 ng/kg-day treatment group was slightly elevated but was not significantly different from levels in the control group. TSH levels in DEN initiated rats were increased at a dose of 3.5 ng/kg-day. In the noninitiated group, TSH level in the 125 ng TCDD/kg-day group was 3.27 ± 0.34 ng/mL (n = 9) compared to 1.3 ± 0.18 ng/mL in the corn oil control group (n = 7). This result, in conjunction with the T4 data, demonstrates that TCDD

had a similar effect on thyroid hormone levels in both the noninitiated and DEN initiated groups. Histological sections examined for nodular lesions or neoplasms exhibited thyroid follicular adenoma in one DEN/corn oil control animal. The DEN/TCDD-treated animals exhibited diffuse follicular hyperplasia, with the size of colloidal follicles decreasing with TCDD treatment. Other qualitative DEN/TCDD-related changes included increased frequency of abnormally shaped follicles. The study authors reported that image analysis demonstrated a significant ($p = 0.013$) TCDD dose-related decrease in mean follicle size along with a significant ($p = 0.001$) TCDD dose-related increase in parenchymal area. Additionally, like T4 and TSH levels, DEN treatment alone or in combination with TCDD did not influence thyroid follicular or C-cell morphology.

RT-PCR results for UGT1 and CYP1A1 mRNA levels indicated that the amount of UGT1 mRNA at the 125 ng/kg-day dose was approximately 2.5-fold higher compared to the concurrent controls. The study authors also stated that the maximal response for the UGT1 mRNA levels was reached at a dose between 1.0 and 3.5 ng TCDD/kg-day. In contrast, the maximum induction of CYP1A1 mRNA was 260-fold higher at the 125 ng/kg-day compared to the concurrent controls.

A LOAEL for TCDD of 35 ng/kg-day for a 30-week exposure duration was identified in this study for a significant ($p < 0.05$) decrease in T4 levels. The NOAEL for this study is 10.7 ng/kg-day.

D.1.5.11. *Toth et al. (1979)*

Toth et al. (1979) examined the impact of TCDD exposure on the formation of liver tumors in male mice. Ten-week-old, outbred Swiss/H/Riop male mice were administered sunflower oil or TCDD (purity not specified; in sunflower oil) at 0, 7, 700 or 7,000 ng/kg (0, 1, 100, or 1,000 ng/kg-day adjusted for continuous dosing; administered dose divided by 7; $n = 38$, 44, 44, and 43, respectively) once per week via gastric tube for 1 year. Once exposure had ceased, animals were followed for the rest of their lives. After spontaneous death or when mice were moribund, autopsies were performed and all organs were examined histologically.

Average life span in the 1,000 ng/kg-day dose group decreased considerably (72%) when compared to the control group. TCDD also caused dose-dependent, severe chronic and ulcerous skin lesions (12, 30, and 58% in the 1, 100, and 1,000 ng/kg-day dose groups, respectively) that

was followed by generalized lethal amyloidosis (12, 23, and 40% in the 1, 100, and 1,000 ng/kg-day dose groups, respectively).

A LOAEL for TCDD of 1 ng/kg-day for 1-year exposure duration was identified in this study for severe chronic and ulcerous skin lesions (12% higher than controls), and generalized lethal amyloidosis (12% higher than controls). A NOAEL cannot be determined for this study.

D.1.5.12. *Tritscher et al. (1992)*

An initiation-promotion study was performed in female Sprague-Dawley rats (at least nine rats per group). Rats were initiated with an i.p. injection of diethylnitrosamine (DEN, 175 mg/kg) or saline, followed 2 weeks later by promotion with biweekly administration of TCDD (purity not specified) in corn oil via gavage for 30 weeks. The doses were stated to be equivalent to 3.5, 10.7, 35.7, or 125 ng/kg-day; control animals received corn oil. Rats were sacrificed 7 days after the final treatment and the livers were removed for further analysis. Liver TCDD concentrations were analyzed in DEN-initiated rats by gas chromatography-mass spectrometry. Hepatic cytochrome P450 levels (CYP1A1 and CYP1A2) and EROD activity were quantified in DEN/TCDD-treated rats, and immunohistochemical detection of CYP1A1 and CYP1A2 in liver was also conducted.

A linear relationship between administered dose of TCDD and liver TCDD concentration on a wet weight (r = 0.999) and lipid-adjusted basis (r = 0.993) was observed. A significant ($p < 0.01$) dose-response trend for increased CYP1A1 and CYP1A2 protein in the liver (hepatic microsomes) was observed in initiated and noninitiated rats. However, there were higher constitutive levels of the two CYP isozymes in nonintiated rats which produced a lower magnitude of induction by TCDD compared to the TCDD-alone group; there were no statistically significant differences between initiated and noninitiated rats at any dose tested. A strong relationship between liver TCDD concentration and CYP1A1 and CYP1A2 protein levels and EROD activity was also observed in DEN/TCDD-treated rats. Immunohistochemical staining of the serial liver sections for CYP1A1 and CYP1A2 protein from initiated and noninitiated rats exhibited a dose-dependent increase consistent with that observed via microsomal quantification. Immunolocalization and pattern of induction were also similar for both CYP isozymes. However, distribution pattern of positive immunoreactivity of the two CYP isozymes was varying, with the most intense staining observed around central veins.

CYP induction alone is not considered a significant toxicologically adverse effect given that CYPs are induced as a means of hepatic processing of xenobiotic agents. Thus, no LOAEL or NOAEL was established for this study because adverse endpoints (e.g., indicators of hepatotoxicity) were not measured.

D.1.6. Chronic Studies (Cancer Endpoints)

D.1.6.1. *Della Porta et al. (1987)*

Della Porta et al. (1987) studied the long-term carcinogenic effects of TCDD in $B6C3F_1$ (C57BL/6JDp × C3Hf/Dp) mice. Six-week-old male and female mice (initially about 15/sex/dose, and increased by approximately 30 to 40 per group within a few weeks) were administered 0, 2,500, and 5,000 ng/kg TCDD (purity not provided) in corn oil by oral gavage once per week for 52 weeks (0, 357, and 714 ng/kg-day adjusted for continuous exposure). At ages 31 to 39 weeks, 41 male mice and 32 female mice in the 2,500 ng/kg dose group were mistakenly administered a single dose of 25,000 ng/kg TCDD. TCDD treatment for the 2,500 ng/kg dose group was halted for 5 weeks (beginning the week after the 25,000 ng/kg dose was administered in error) and resumed until exposure was terminated at 57 weeks. Mortality was observed and body weights recorded at unspecified intervals until 110 weeks of age, when all surviving animals were sacrificed and necropsied. Histopathological analysis was conducted on the following organs and tissues: Harderian glands, pituitary, thyroid, adrenals, tongue, esophagus, and trachea; lungs, liver, pancreas; spleen, kidneys, and bladder; testes, ovaries, and uterus, mesenteric lymph nodes, small intestine, and all other organs with presumed pathological changes.

The body weights of both male and female mice exposed to 2,500 and 5,000 ng/kg TCDD were markedly lower than in the corresponding control groups (statistical significance not reported). Relative to the controls, a significant ($p < 0.001$), dose-related decrease in survival occurred in animals treated with either dose of TCDD. In the subset of animals treated inadvertently with a single dose of 25,000 ng/kg TCDD, mortality in male mice increased shortly after this treatment; females, however, did not show a mortality increase following the inadvertent treatment. This mortality in male mice was associated with subcutaneous edema, degenerative hepatocyte changes, and bile duct hyperplasia. The incidence of non-neoplastic lesions (such as amyloidosis of the liver, spleen, adrenals, and pancreas), liver necrosis, and

nephrosclerosis, was increased in mice exposed to TCDD compared to controls (statistical significance not reported).

The study authors used two statistical tests to analyze tumor incidence. Because of the increased mortality in treated groups compared to controls, one test, which assumes all tumors are fatal, overestimated the differences between the treated and control groups. The second test assumes that all tumors are incidental and resulted in an underestimation of TCDD effects. Both tests were used to analyze the results for nonthymic lymphomas and hepatic adenomas and carcinomas. Incidence of nonthymic lymphomas (6/45, 4/51, and 3/50 in the 0, 2,500, and 5,000 ng/kg dose groups, respectively in males and 17/49, 21/42, and 17/48 in the 0, 2,500, and 5,000 ng/kg dose groups, respectively in females) was significantly ($p < 0.05$ in males and $p < 0.01$ in females) higher in TCDD-treated animals compared to the corresponding controls using the fatal tumor test. However, the incidental tumor test showed that this higher incidence was not significant. Similarly, a significantly ($p < 0.001$) higher incidence of hepatocellular adenomas occurred in male mice using the fatal tumor test (10/43, 11/51, and 10/50 in the 0, 2,500, and 5,000 ng/kg dose groups, respectively), but the incidence was not significant when assessed using the incidental tumor test. Hepatocellular carcinomas in males were significant, ($p < 0.001$) using either the fatal or incidental tumor tests (5/43, 15/51, and 33/50 in the 0, 2,500, and 5,000 ng/kg dose groups, respectively). In female mice, hepatocellular adenomas were significant using both the fatal ($p < 0.01$) and incidental ($p < 0.001$) tumor tests (2/49, 4/42, and 11/48 in the 0, 2,500, and 5,000 ng/kg dose groups, respectively). Similar results for female mice were obtained for incidence of hepatocellular carcinomas (1/49, 12/42, and 9/48 in the 0, 2,500, and 5,000 ng/kg dose groups, respectively), which also were significant using both the fatal ($p < 0.01$) and incidental ($p < 0.05$) tumor tests. TCDD-related incidences of other tumor types in both sexes were uniformly low and comparable in the treatment and control groups.

These results indicate that TCDD is carcinogenic in male and female $B6C3F_1$ mice, causing hepatocellular adenomas and carcinomas in both sexes.

In addition to the long term bioassay results in mice described by Della Porta et al. (1987), carcinogenic effects of TCDD in a neonatal bioassay were reported in the same publication. Briefly, groups of male and female $B6C3F_1$ and B6CF1 (C57/BL6J × BALB/c) mice were treated with 0, 1,000, 30,000 or 60,000 ng/kg BW TCDD via i.p. injection beginning at PND 10. Animals were treated once weekly for 5 weeks and then observed until 78 weeks of

age. However, because this study utilized i.p. injection as the route of TCDD exposure, it does not qualify for further consideration based on the study selection criterion that the study design consist of orally administered TCDD.

D.1.6.2. *Kociba et al. (1978)*

As discussed above, Kociba et al. (1978) conducted a lifetime (2-year) feeding study of male and female Sprague-Dawley rats using doses of 0, 1, 10, and 100 ng/kg-day. There were 50 males and 50 females in each group.

With respect to the cancer endpoints examined, the most significant finding was an increase in hepatocellular hyperplastic nodules and hepatocellular carcinomas in female rats. The incidence of hepatocellular carcinomas was significantly elevated above the control incidence at the 100 ng/kg-day dose, whereas increased incidence of hyperplastic nodules was evident in the 10 ng/kg-day dose group.

There have been two reevaluations of slides of liver sections from the Kociba et al. study (Goodman and Sauer, 1992; Sauer, 1990; Squire, 1990). The Squire Review was requested by EPA as an independent review of the slides. The Sauer Review was carried out using refined criteria for the diagnosis of proliferative hepatocellular lesions (Maronpot et al., 1989; Maronpot et al., 1986). Liver tumor incidences for the three evaluations are compared in Appendix F. Although there are some quantitative differences between the evaluations, the lowest detectable effect for liver tumor incidence is consistently observed at 10 ng/kg-day.

In the 10 ng/kg-day dose group, significant increases in the incidence of hyperplastic nodules of the liver were observed in female rats (18/50 in the Kociba evaluation, 27/50 in the Squire evaluation). Two females (2/50) had hepatocellular carcinomas. In the 1990 reevaluation (Goodman and Sauer, 1992; Sauer, 1990), nine females (9/50) were identified with hepatocellular adenomas and none with carcinomas; thus only one-third of the previously observed “tumors” were identified when using the refined diagnostic criteria. As discussed below, the tumor reclassification of Goodman and Sauer (1992) was used in the dose-response modeling for the Kociba et al. (1978) data set.

In addition to nodules in the liver, increased incidence of stratified squamous cell carcinoma of the tongue and nasal turbinates/hard palate, and keratinizing squamous cell carcinoma of the lung were also observed in female rats in the 100 ng/kg-day dose group.

One possible cause for the induction of lung tumors in the Kociba feeding study may have been the aspiration of dosed feed into the lungs. However the promotion of lung tumors has been observed in mice treated systemically by i.p. injections of TCDD (Beebe et al., 1995). In addition the induction of hyperplastic and metaplastic lesions in rats has been observed following chronic oral gavage treatment with TCDD (Tritscher et al., 2000). More recently, chronic oral exposure to heptachlorodibenzodioxin (HpCDD) resulted in the induction of lung tumors in treated female rats (Rozman, 2000). These data indicate that the induction of lung tumors in the Kociba study was most likely primarily the result of systemic chronic dietary exposure to TCDD rather than due to a localized exposure to aspired dosed feed.

There was no detectable increase in liver tumor incidences in male rats in any of the dose groups. The mechanism responsible for dioxin-mediated sex specificity for hepatocarcinogenesis in rats is not clear, but may involve ovarian hormones (Lucier et al., 1991).

Although there was no increase in liver tumors in male rats in this study, in the 100 ng/kg-day group, there was an increased incidence of stratified squamous cell carcinoma of the hard palate/nasal turbinate, stratified squamous cell carcinoma of the tongue, and adenoma of the adrenal cortex.

Kociba et al. (1978) had reported that chemically related increases in preneoplastic or neoplastic lesions were not found in the 1 ng/kg-day dose group. However, Squire identified two male rats in the 1 ng/kg-day dose group with squamous cell carcinoma of the nasal turbinates/hard palate, and one of these male rats had a squamous cell carcinoma of the tongue. These are both rare tumors in Sprague-Dawley rats, and these sites are targets for TCDD, implying that 1 ng/kg-day may not represent a NOEL. However, no dose-response relationships were evident for tumors at these sites (Huff et al., 1991).

There is considerable controversy concerning the possibility that TCDD-induced liver tumors are a consequence of cytotoxicity. Goodman and Sauer (1992) have extended the reevaluation of the Kociba slides to include liver toxicity data and have reported a correlation between the presence of overt hepatotoxicity and the development of hepatocellular neoplasms in female rats. With the exception of two tumors in controls and one each in the low- and mid-dose groups, all liver tumors occurred in livers showing clear signs of toxicity. However, male rat livers exhibit cytotoxicity in response to high TCDD doses, yet they do not develop liver tumors. Moreover, both intact and ovariectomized female rats exhibit liver toxicity in response to TCDD,

yet TCDD is a more potent promoter in intact but not ovariectomized rats (Lucier et al., 1991). Therefore, if cytotoxicity is playing a role in liver tumorigenesis, other factors must also be involved. Also, there is little information on the role of cytotoxicity in TCDD-mediated cancer at other sites such as the lung and thyroid.

D.1.6.3. *Toth et al. (1979)*

In a study of 10-week-old outbred male Swiss/H/Riop mice, Toth et al. *(1979)* administered oral gavage TCDD doses of 0, 7, 700, and 7,000 ng/kg-day in sunflower oil weekly for 1 year (0, 1, 100, or 1,000 ng/kg-day adjusted for continuous dosing; see details above). All mice (100/group) were followed for their entire lives. The study authors identified the effective number of mice in each group to be the number of surviving animals when the first tumor-bearing animal was identified. The average lifespan of the control, low, mid and high dose groups was 588, 649, 633, and 424 days, respectively.

In the 100 ng/kg-day dose group, liver tumor incidence was twice that of the control group and was statistically significant ($p < 0.01\%$). A dose-related increase in liver tumor incidence was observed (18, 29, 48, and 30% in the control and three TCDD-treated groups, respectively) in all treated mice. Increases were not statistically significant, however, at 1 and 1,000 ng/kg-day. The study authors also stated that spontaneous and induced liver tumors were not histologically different. Additionally, the ratio of benign hepatomas to hepatocellular carcinomas in the control group was not affected by treatment and an increase was observed only in the absolute number of liver tumors. Cirrhosis was not observed with the tumors.

D.1.6.4. *NTP (1982)*

As discussed above, the NTP (1982) study was conducted using Osborne-Mendel rats and B6C3F$_1$ mice (NTP, 1982). Groups of 50 male rats, 50 female rats, and 50 male mice received TCDD as a suspension in corn oil:acteone (9:1) by gavage twice each week at doses of 0, 5, 25, or 250 ng/kg-day (daily averaged doses of 0, 1.4, 7.1, or 71 ng/kg-day for rats and male mice and doses of 0, 5.7, 28.6, or 286 ng/kg-day for female mice.

There were no statistically significant dose-related decreases in survival in any sex-species group. TCDD-induced malignant liver tumors occurred in the high-dose female rats

and in male and female mice. These can be considered to result from TCDD exposure because they are relatively uncommon lesions in control Osborne-Mendel rats (male, 1/208; female, 3/208), are seen in female rats and mice of both sexes, and their increasing incidence with increasing dose is statistically significant (Cochran-Armitage trend test, $p = 0.004$). Because liver tumors were increased in both sexes of mice, this effect is not female-specific as was observed in rats. Interestingly, liver tumor incidences were decreased in female rats in both the NTP and Kociba low doses (not statistically significant compared with controls). For example, the combined control incidence data were 11/161 (7%) compared with 4/99 (4%) in the low-dose group.

The incidences of thyroid gland (follicular cell) tumors were increased in all three dose groups in male rats. Because the responses in the two highest dose groups are highly significant, the statistically significant elevation of incidence in the lowest dose group (Fisher exact *p*-value = 0.042) is considered to be caused by exposure to TCDD, suggesting that thyroid tumor incidence may be the most sensitive site for TCDD-mediated carcinogenesis. Because 71 ng/kg-day is above the maximum tolerated dose (MTD) (Huff et al., 1991), thyroid tumors occur at doses more than 50 times lower than the MTD.

TCDD-induced neoplasms of the adrenal gland were observed in the 7.1 ng/kg-day/dose group in male rats and in high-dose female rats. Fibrosarcomas of the subcutaneous tissue were significantly elevated in high-dose female mice and female rats. One additional tumor type, lymphoma, was seen in high-dose female mice. Lung tumors were elevated in high-dose female mice; the increase was not statistically significant when compared with concurrent controls, but the increase was dose related (Cochran-Armitage trend test, $p = 0.004$).

Huff (1992) concluded, based on the NTP bioassay results, that TCDD was a complete carcinogen and induced neoplasms in rats and mice of both sexes. As was observed in the Kociba study (1978), liver tumors were observed with greater frequency in treated female rats, but in male rats the thyroid appears to be the most sensitive (increased tumor incidence at doses as low as 1.4 ng/kg-day).

D.1.6.5. *NTP (2006)*

As discussed above, female Sprague-Dawley rats (53 control; 53 or 54 animals per treatment group) were administered TCDD (purity >98%) in corn oil:acetone (99:1) via gavage

at doses of 0, 3, 10, 22, 46, or 100 ng/kg-day, 5 days per week for 105 weeks (0, 2.14, 7.14, 15.7, 32.9, or 71.4 ng/kg-day, adjusted for continuous exposure) (NTP, 2006). In addition to this primary group, a stop-dose group of 50 animals was administered 100 ng/kg-day TCDD in corn oil:acetone (99:1) via gavage for 30 weeks and then just the vehicle for the remainder of the study. At study termination, the number of surviving animals had declined to 25 in the control group and to 21, 23, 19, 22, and 21 in five treatment groups, respectively, due to accidental deaths, moribund animals, or death due to natural causes.

Incidence of hepatocellular adenomas was significantly ($p < 0.001$) increased in the 100 ng/kg-day dose group in the primary study and exceeded incidences seen in historical vehicle control range at study termination. A dose-related increase in the incidence of cholangiosarcoma was seen in the primary study group in animals receiving 22 ng/kg-day or higher doses of TCDD. The high dose group of 100 ng/kg-day had the highest incidence of cholangiosarcoma with a significant ($p < 0.001$) number of animals exhibiting multiple cholangiosarcomas. Such an incidence was not seen in historical vehicle controls. In contrast, only two cholangiosarcomas and hepatocellular adenomas were seen in the 100 ng/kg-day group in the stop-exposure study.

In the lung, at 2 years, there was a significantly ($p = 0.002$) increased incidence of cystic keratinizing epithelioma in the 100 ng/kg-day dose group of the primary study, while there were no epitheliomas in the 100 ng/kg-day group of the stop-exposure study. There was also a significant ($p \leq 0.01$) dose-dependent increase, when compared to the vehicle control, in the incidence of bronchiolar metaplasia of the alveolar epithelium at all dose groups in the primary study. Squamous metaplasia was also present in the 46 and 100 ng/kg-day dose groups in the primary study, and was also observed in the 100 ng/kg-day dose group in the stop-exposure study.

A positive trend in the incidence of gingival squamous cell carcinoma of the oral cavity was seen at all doses (except 22 ng/kg-day), with the incidence significantly ($p = 0.007$) high in the 100 ng/kg-day dose group. In addition, the occurrence of this lesion in the 46 and 100 ng/kg-day group of the primary study and 100 ng/kg-day group of the stop-exposure study exceeded the historical control range. The incidence of gingival squamous hyperplasia was significantly (either $p \leq 0.01$ or $p \leq 0.05$) increased in all dose groups of the primary study as well as the 100 ng/kg-day group of the stop-exposure study.

In the uterus, at 2 years, there was a significantly (p = 0.032) higher rate of squamous cell carcinoma in the 46 ng/kg-day group compared to vehicle controls. In addition there were two squamous cell carcinomas in the 100 ng/kg-day group of the stop-exposure study. No squamous cell carcinomas have been reported in historical vehicle controls.

These results indicate that TCDD is carcinogenic to female Sprague-Dawley rats and causes tumors at multiple sites.

D.2. EVALUATION OF STUDIES

Based on the results of EPA's literature search and collection activities (see Section 2.2 and Figure 2-1), a total of 1,441 studies were examined for their potential to be used in TCDD quantitative dose-response analysis (see Figure 2-4 of the main document). Of the 1,441 studies, 49 were epidemiologic cancer or noncancer studies (see Appendix C for their summaries and evaluations). In addition, there were 637 studies eliminated from consideration because they were not suitable study types; these included, in vitro bioassays, review articles, PBPK modeling studies, and studies that evaluated PCBs or other dioxin-like compounds other than TCDD. A list of these studies is not provided in this appendix; results of the initial literature review can be found online at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199923#Download.
A total of 755 animal studies were evaluated (4 studies contained both cancer and noncancer endpoints). The results are shown and discussed in the remainder of this Section D.2.

D.2.1. Evaluation of Animal Cancer Bioassays

A total of eight animal cancer bioassays were available for evaluation (see Figure 2-4) using EPA's study inclusion criteria (see Section 2.3.2 and Figure 2-3). Table 2-3 of the main document presents the six studies that met these criteria and comprise the preliminary list of cancer bioassays considered suitable for quantitative TCDD dose-response modeling. Only two of the available animal cancer bioassays did not meet EPA's study selection criteria, and, therefore, are not summarized in this appendix. These include Eastin et al. (1998), because a genetically altered mouse strain was tested, and Rao et al. (1988), because an intraperitoneal injection was used instead of oral route of exposure.

D.2.2. Evaluation of Animal Noncancer Bioassays

Table D-1 provides the final list of 78 studies that were selected as key studies for TCDD noncancer dose-response analyses. These studies are peer-reviewed, noncancer, in vivo mammalian bioassays that assessed TCDD dose response, and they meet EPA's study inclusion criteria (see Section 2.3.2 and Figure 2-3). Information on each of these studies is provided in Section D.1 of this appendix and in Table 2-4 of the main document.

An additional 637 studies were excluded from analysis based on one or more of the following reasons (see Figure 2-4): (1) 66 studies used genetically altered animals; (2) 370 studies had a lowest tested dose that was too high (i.e., greater than 30 ng/kg-day); (3) 142 studies tested chemicals that were not TCDD-only or used an unspecified TCDD dose; and (4) 135 studies employed a nonoral dosing method. Table D-2 shows these studies and identifies the study inclusion criteria that were not met. For many studies, more than one reason for exclusion was found. Conversely, in some cases at least one criterion was not met and was identified, but, given that the study had already been excluded based on one criterion, not all of the other criteria for exclusion were further evaluated and identified.

D.3. CROSS-SPECIES CONCORDANCE OF SELECTED HEALTH ENDPOINTS

This appendix presents a cross-species comparison of NOAELs and LOAELs for selected endpoints from the animal bioassay and human epidemiology studies that passed the noncancer study selection criteria outlined in Section 2. The tables and figures are intended to illustrate the degree of qualitative and quantitative concordance of effects across species and the consistency of observation of those effects across studies within species. Tables D-3 through D-8 provide these comparison for male reproductive, female reproductive, thyroid, developmental dental, immune system, and neurological effects, respectively (also illustrated in Figures D-1 through D-6). This analysis goes beyond the one presented in Section 4 (see Tables 4-3 and 4-5) in that effects at doses higher than the study LOAELs (for most sensitive effect) are included. Quantitative concordance is considered in terms of modeled equivalent human exposures, as displayed on the figures, and actual administered doses (tables only). Results from animal bioassays that did not pass the low-dose-maximum selection criterion are not included here, but may provide additional relevant information.

The endpoints evaluated here were chosen because they have been observed in both human epidemiologic studies and animal bioassays (i.e., male and female reproductive effects, thyroid hormone levels, and developmental dental effects) and quantified by EPA for reference dose (RfD) point of departure (POD) consideration, or are sensitive effects in animals but not in humans (i.e., immunological and neurological effects). Hepatic effects, which are not included here, are evident in all rodent studies that looked for them and are often severe; hepatic effects reported for humans were not as severe (Michalek et al., 2001b). Diabetes may be a sensitive health effect in humans(Michalek and Pavuk, 2008), but no animal bioassays included in this analysis address diabetes or glucose metabolism. Other animal studies that did not meet the dose-limit selection criterion may show effects of interest at higher doses.

Male reproductive effects have been reported in all species (mice, rats and humans) in which they were evaluated (see Table D-3 and Figure D-1). Sperm effects, one of the co-critical effects in humans selected for the RfD, is observed in more than one rat study, but not in mice, in the studies selected for this analysis. Altered sex ratios (i.e., decreased proportion of male offspring) have been reported for both mice and rats and in one human study (Mocarelli et al., 2000); the human study was not considered for a POD (see Appendix C for study evaluation details), and thus is not included in Figure D-1.

Female reproductive effects also have been reported for all species (mice, rats, monkeys and humans) in which they were evaluated (see Table D-4 and Figure D-2). Of particular note are the more severe effects (i.e., reduced fertility, embryo loss, and reduced offspring survival; see Table D-4) that have been observed in animal species as compared to humans. Adverse birth outcomes were not observed for the Seveso Women's Cohort as reported by Eskenazi et al. (2003). Other female reproductive effects observed in humans included lengthened menstrual cycle reported by Eskenazi et al., (2002) which is the only study that passed the selection criteria (and is shown in Figure D-2). Other female reproductive effects were unable to be evaluated for RfD POD consideration because a critical exposure window could not be identified for these effects (see Appendix C); these other health outcomes included early menopause (Eskenazi et al., 2005) and possible anti-estrogenic effects (Eskenazi et al., 2007).

Effects of TCDD on thyroid hormones have been reported for rats and humans (see Table D-5 and Figure D-3) but have not been evaluated in other species in the selected data sets.

Increased neonatal TSH, the other co-critical effect for the RfD, has only been evaluated for humans; rat studies have reported decreased serum levels of T3 and T4 in adults.

Developmental dental defects have also been observed in mice, rats and humans (see Table D-6 and Figure D-4) but are not a particularly sensitive endpoint for humans, as they are for mice and rats. Other relatively sensitive endpoints reported in animal bioassays, such as immunotoxicity (see Table D-7 and Figure D-5) and neurotoxicity (see Table D-8 and Figure D-6) do not appear to be sensitive human health outcomes associated with TCDD exposure. Baccarelli et al. (2004; 2002) reported decreased IgG levels for some individuals in the Seveso cohort and concluded that the levels were far above those associated with immunodeficiency disorders. Michalek et al. (2001c) found no evidence of peripheral neuropathy in Vietnam veterans exposed to TCDD during operation Ranch Hand.

Overall, the analysis presented here supports the conclusion that there is a substantial amount of qualitative concordance of effects between laboratory animal species and humans, but lower quantitative concordance.

Table D-1. Noncancer animal studies selected for TCDD dose-response analyses

Author (year)	Title of study
Amin et al. (2000)	Gestational and Lactational Exposure to TCDD or Coplanar PCBs Alters Adult Expression of Saccharin Preference Behavior in Female Rats
Bell et al. (2007c)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Developing Male Wistar(Han) Rat. II: Chronic Dosing Causes Developmental Delay
Bowman et al. (1989a)	Behavioral Effects in Monkeys Exposed to 2,3,7,8-TCDD Transmitted Maternally During Gestation and for Four Months of Nursing
Bowman et al. (1989b)	Chronic Dietary Intake of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) at 5 or 25 ppt in Monkey: TCDD Kinetics and Dose-effect Estimate of Reproductive Toxicology
Burleson et al. (1996)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Influenza Virus Host Resistance in Mice
Cantoni et al. (1981)	Porphyrogenic Effect of Chronic Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Female Rats. Dose–Effect Relationship Following Urinary Excretion of Porphyrins
Chu et al. (2001)	Mixture Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Polychlorinated Biphenyl Congeners in Rats
Chu et al. (2007)	Combined Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Polychlorinated Biphenyl Congeners in Rats
Crofton et al. (2005)	Thyroid-Hormone-Disrupting Chemicals: Evidence for Dose-Dependent Additivity or Synergism
Croutch et al. (2005)	2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and 1,2,3,4,7,8-Hexachlorodibenzo-*p*-Dioxin (HxCDD) Alter Body Weight by Decreasing Insulin-Like Growth Factor I (IGF-I) Signaling
DeCaprio et al. (1986)	Subchronic Oral Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Guinea Pig: Comparisons with a PCB-containing Transformer Fluid Pyrolysate
DeVito et al. (1994)	Dose-response Relationships in Mice Following Subchronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: CYP1A1, CYP1A2, Estrogen Receptor, and Protein Tyrosine Phosphorylation
Fattore et al. (2000)	Relative Potency Values Derived from Hepatic Vitamin A Reduction in Male and Female Sprague-Dawley Rats Following Subchronic Dietary Exposure to Individual Polychlorinated Dibenzo-*p*-dioxin and Dibenzofuran Congeners and a Mixture Thereof
Fox et al. (1993)	Gene Expression and Cell Proliferation in Rat Liver After 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure
Franc et al. (2001)	Persistent, Low-dose 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure: Effect on Aryl Hydrocarbon Receptor Expression in a Dioxin-Resistance Model
Franczak et al. (2006)	Effects of Acute and Chronic Exposure to the Aryl Hydrocarbon Receptor Agonist 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on the Transition to Reproductive Senescence in Female Sprague-Dawley Rats
Hassoun et al. (1998)	Induction of Oxidative Stress in Brain Tissues of Mice after Subchronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
Hassoun et al. (2000)	The Relative Abilities of TCDD and its Congeners to Induce Oxidative Stress in the Hepatic and Brain Tissues of Rats After Subchronic Exposure
Hassoun et al. (2002)	Induction of Oxidative Stress in the Tissues of Rats after Chronic Exposure to TCDD, 2,3,4,7,8-Pentachlorodibenzofuran, and 3,3',4,4',5-Pentachlorobiphenyl

Table D-1. Noncancer animal studies selected for TCDD dose-response analyses (continued)

Author (year)	Title of study
Hassoun et al. (2003)	The Role Of Antioxidant Enzymes In TCDD-Induced Oxidative Stress in Various Brain Regions of Rats After Subchronic Exposure
Hochstein et al. (2001)	Chronic Toxicity of Dietary 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin to Mink
Hojo et al. (2002)	Sexually Dimorphic Behavioral Responses to Prenatal Dioxin Exposure
Hong et al. (1989)	Immune Abnormalities Associated With Chronic TCDD Exposure in Rhesus
Hutt et al. (2008)	The Environmental Toxicant 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Disrupts Morphogenesis of the Rat Pre-implantation Embryo
Ikeda et al. (2005b)	Repeated In Utero and Lactational 2,3,7,8-TCDD Exposure Affects Male Gonads in Offspring, Leading to Sex Ratio Changes in F2 Progeny
Ishihara et al. (2007)	Does Paternal Exposure to 2,3,7,8-TCDD Affect the Sex Ratio of Offspring?
Kattainen et al. (2001)	In Utero/Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure Impairs Molar Tooth Development in Rats
Keller et al. (2007)	Qualitative Effects of Dioxin on Molars Vary Among Inbred Mouse Strains
Keller et al. (2008a)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Molar Development Among Non-resistant Inbred Strains of Mice: A Geometric Morphometric Analysis
Keller et al. (2008b)	Genetic Differences in Sensitivity to Alterations of Mandible Structure Caused by the Teratogen 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin
Kitchin and Woods (1979)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Effects on Hepatic Microsomal Cytochrome P-448-mediated Enzyme Activities
Kociba et al. (1976)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD): Results of a 13-week Oral Toxicity Study in Rats
Kociba et al. (1978)	Results of a Two-year Chronic Toxicity and Oncogenicity Study of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Rats. Long-term Toxicologic Studies of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Laboratory Animals
Kuchiiwa et al. (2002)	In Utero and Lactational Exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin Decreases Serotonin-immunoreactive Neurons in Raphe Nuclei of Male Mouse Offspring
Latchoumycandane and Mathur (2002)	Effects of Vitamin E on Reactive Oxygen Species-mediated 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Toxicity in Rat Testis
Latchoumycandane et al.(2002b)	Induction of Oxidation Stress in Rat Epidermal Sperm After Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
Latchoumycandane et al. (2002a)	The Effect of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on the Antioxidant System in Mitochondrial and Microsomal Fractions of Rat Testis
Latchoumycandane et al. (2003)	2,3,7,8-Tetrachlorodibenzo-*p* -dioxin (TCDD) Induces Oxidative Stress in the Epididymis and Epididymal Sperm of Adult Rats
Li et al. (1997)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Increases Release of Luteinizing Hormone and Follicle-Stimulating Hormone from the Pituitary of Immature Female Rats In Vivo and In Vitro
Li et al. (2006)	The Early Embryo Loss Caused by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin May be Related to the Accumulation of this Compound in the Uterus
Lucier et al. (1986)	Ingestion of Soil Contaminated with 2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin (TCDD) Alters Hepatic Enzyme Activities in Rats
Mally and Chipman (2002)	Non-genotoxic Carcinogens: Early Effects on Gap Junctions, Cell Proliferation and Apoptosis in the Rat
Markowski et al. (2001)	Altered operant Responding for Motor Reinforcement and the Determination of Benchmark Doses Following Perinatal Exposure to Low-level 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

Table D-1. Noncancer animal studies selected for TCDD dose-response analyses (continued)

Author (year)	Title of study
Maronpot et al. (1993)	Dose Response for TCDD Promotion of Hepatocarcinogenesis in Rats Initiated with DEN: Histologic, Biochemical, and Cell Proliferation Endpoints
Miettinen et al. (2006)	The Effect of Perinatal TCDD Exposure on Caries Susceptibility in Rats
Murray et al. (1979)	Three-generation Reproduction Study of Rats Given 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in the Diet
Nohara et al. (2000b)	The Effects of Perinatal Exposure to Low Doses of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Immune Organs in Rats
Nohara et al. (2002a)	Effect of Low-dose 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Influenza A Virus-induced Mortality in Mice
NTP (1982)	NTP Technical Report on Carcinogenesis Bioassay of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in Osborne-Mendel Rats and B6C3F$_1$ Mice (Gavage Study)
NTP (2006)	NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Female Harlan Sprague-Dawley Rats (Gavage Studies)
Ohsako et al. (2001)	Maternal Exposure to a Low Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Suppressed the Development of Reproductive Organs of Male Rats: Dose-Dependent Increase of mRNA Levels of 5a-reductase Type 2 in Contrast to Decrease of Androgen Receptor in the Pubertal Ventral Prostate
Schantz and Bowman (1989)	Learning in Monkeys exposed Perinatally to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)
Schantz et al. (1986)	Maternal Care by Rhesus Monkeys of Infant Monkeys Exposed to Either Lead or 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)
Schantz et al. (1992)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Behavior of Monkeys in Peer Groups
Schantz et al. (1996)	Effects of Gestational and Lactational Exposure to TCDD or Coplanar PCBs on Spatial Learning
Seo et al. (1995)	Effects of Gestational and Lactational Exposure to Coplanar Polychlorinated Biphenyl (PCB) Congeners or 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Thyroid Hormone Concentrations in Weanling Rats
Sewall et al. (1993)	TCDD-mediated Changes in Hepatic Epidermal Growth Factor Receptor May be a Critical Event in the Hepatocarcinogenic Action of TCDD
Sewall et al. (1995a)	Alterations in Thyroid Function in Female Sprague-Dawley Rats Following Chronic Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
Shi et al. (2007)	Ovarian Endocrine Disruption Underlies Premature Reproductive Senescence Following Environmentally Relevant Chronic Exposure to the Aryl Hydrocarbon Receptor Agonist 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin
Simanainen et al. (2002)	Structure-Activity Relationships and Dose Responses of Polychlorinated Dibenzo-*p*-dioxins for Short-Term Effects in 2,3,7,8- Tetrachlorodibenzo-*p*-dioxin-Resistant and -Sensitive Rat
Simanainen et al. (2003)	Dose-response Analysis of Short-term Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Three Differentially Susceptible Rat Lines
Simanainen et al. (2004b)	Pattern of Male Reproductive System Effects After In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Exposure in Three Differentially TCDD-Sensitive Rat Lines
Slezak et al. (2000)	Oxidative Stress in Female B6C3F$_1$ Mice Following Acute and Subchronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)
Smialowicz et al. (2004)	CYP1A2 is Not Required for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Immunosuppression

Table D-1. Noncancer animal studies selected for TCDD dose-response analyses (continued)

Author (year)	Title of study
Smialowicz et al. (2008)	Relative Potency Based on Hepatic Enzyme Induction Predicts Immunosuppressive Effects of a Mixture of PCDDS/PCDFS and PCBS
Smith et al. (1976)	Teratogenicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in CF-1 Mice
Sparschu et al. (1971)	Study of the Teratogenicity of 2,3,7,8-Tetrachiorodibenzo-*p*-dioxin in the Rat
Sugita-Konishi et al. (2003)	Effect of Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on the Susceptibility to *Listeria* Infection
Tritscher et al. (1992)	Dose-response Relationships for Chronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in a Rat-tumor Promotion Model: Quantification and Immunolocalization of CYP1A1and CYP1A2 in the Liver
Toth et al. (1979)	Carcinogenicity Testing of Herbicide 2,4,5-Trichlorophenoxyethanol Containing Dioxin and of Pure Dioxin in Swiss Mice
Van Birgelen et al. (1995a)	Subchronic Dose-response Study of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Female Sprague-Dawley Rats
Van Birgelen et al. (1995b)	Subchronic Effects of 2,3,7,8-TCDD or PCBs on Thyroid Hormone Metabolism: Use in Risk Assessment
Vanden Heuvel et al. (1994)	Dioxin-responsive Genes: Examination of Dose-response relationships Using Quantitative Reverse Transcriptase-polymerase Chain Reaction
Vos et al. (1973)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on the Immune System of Laboratory Animals
Weber et al. (1995)	Correlation Between Toxicity and Effects on Intermediary Metabolism in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Male C57BL/6L and DBA/2J Mice
White et al. (1986)	Modulation of Serum Complement Levels Following Exposure to Polychlorinated Dibenzo-*p*-dioxins
Yang et al. (2000)	Subchronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Modulates the Pathophysiology of Endometriosis in the Cynomolgus Monkey
Zareba et al. (2002)	Sexually Dimorphic Alterations of Brain Cortical Dominance in Rats Prenatally Exposed to TCDD

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Abbott and Birnbaum (1989)	TCDD Alters Medial Epithelial Cell Differentiation During Palatogenesis	-	X	-	-
Abbott and Birnbaum (1990)	Effects of TCDD on Embryonic Ureteric Epithelial EGF Receptor Expression and Cell Proliferation	-	X	-	-
Abbott and Probst (1995)	Developmental Expression of Two Members of a New Class of Transcription Factors: II. Expression of Aryl Hydrocarbon Receptor Nuclear Translocator in the C57BL/6N Mouse Embryo	-	-	X	-
Abbott et al. (1987b)	TCDD Alters the Extracellular Matrix and Basal Lamina of the Fetal Mouse Kidney	-	X	-	-
Abbott et al. (1987a)	TCDD-Induced Hyperplasia of the Ureteral Epithelium Produces Hydronephrosis in Murine Fetuses	-	X	-	-
Abbott et al. (1999a)	AhR, ARNT, and CYP1A1 mRNA Quantitation in Cultured Human Embryonic Palates Exposed to TCDD and Comparison with Mouse Palate In Vivo and in Culture	-	X	-	-
Abbott et al. (1999b)	RT-PCR Quantification of AHR, ARNT, GR, and CYP1A1 mRNA in Craniofacial Tissues of Embryonic Mice Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Hydrocortisone	-	X	-	-
Abbott et al. (2003)	EGF and TGF-α Expression Influence the Developmental Toxicity of TCDD: Dose Response and AhR Phenotype in EGF, TGF-α , and EGF+ TGF- α Knockout Mice	-	X	-	-
Abernethy et al. (1985)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Promotes the Transformation of C3H/10T1/2 Cells	-	-	-	X
Abraham et al. (1988)	Pharmacokinetics and Biological Activity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. 1. Dose-dependent Tissue Distribution and Induction of Hepatic Ethoxyresorufin *o*-deethylase in Rats Following a Single Injection	-	-	-	X
Ackermann et al. (1989)	Selective Inhibition of Polymorphonuclear Activity by 2,3,7,8-Tetracholordibenzo-*p*-dioxin	-	X	-	-
Adamsson et al. (2008)	The Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Fetal Male Rat Steroidogenesis	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Agrawal et al. (1981)	3,4,3N,4N-Tetrachlorobiphenyl Given to Mice Prenatally Produces Long-term Decreases in Striatal Dopamine and Receptor Binding Sites in the Caudate Nucleus	-	-	X	-
Aitio et al. (1979)	Different Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Glucuronide Conjugation of Various Aglycones: Studies in Wistar and Gunn Rats	-	X	-	-
Albro et al. (1978)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Lipid Profiles in Tissues of the Fischer Rat	-	X	-	-
Allen and Carstens (1967)	Light and Electron Microscopic Observations in *Macaca mulatta* Monkeys Fed Toxic Fat	-	X	-	-
Allen and Leamy (2001)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Affects Size and Shape, but Not Asymmetry, of Mandibles in Mice	-	X	-	-
Alsharif and Hassoun (2004)	Protective Effects of Vitamin A and Vitamin E Succinate Against 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-induced Body Wasting, Hepatomegaly, Thymic Atrophy, Production of Reactive Oxygen Species and DNA Damage in C57BL/6J Mice	-	X	-	-
Alsharif et al. (1990)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-induced Decrease in the Fluidity of Rat Liver Membranes	-	X	-	-
Alsharif et al. (1994b)	Oxidative Stress Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin is Mediated by the Aryl Hydrocarbon (Ah) Receptor Complex	-	X	-	-
Alsharif et al. (1994c)	Stimulation of NADPH-dependent Reactive Oxygen Species Formation and DNA Damage by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin TCDD in Rat Peritoneal	-	X	-	-
Alsharif et al. (1994a)	The Effects of Ani-TNF-alpha Antibody and Dexamethasone on 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Oxidative Stress in Mice	-	X	-	-
Altmann et al. (1995)	Maternal Exposure to Polychlorinated Biphenyls Inhibits Long-term Potentiation in the Visual Cortex of Adult Rats	-	-	X	-
Altmann et al. (1998)	Inhibition of Long-term Potentiation in Developing Rat Visual Cortex but Not Hippocampus by In Utero Exposure to Polychlorinated Biphenyls	-	-	X	-
Andersson et al. (2002)	A Constitutively Active Dioxin/Aryl Hydrocarbon Receptor (AhR) Induces Stomach Tumors	X	-	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Aoa et al. (2009)	Comparison of Immunotoxicity Among Tetrachloro-, Pentachloro-, Tetrabromo- and Pentabromo-dibenzo-*p*-dioxins in Mice	-	-	X	-
Aragon et al. (2008a)	In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure: Effects on Fetal and Adult Cardiac Gene Expression and Adult Cardiac and Renal Morphology	-	X	-	-
Aragon et al. (2008b)	Perinatal 2,3,7,8-TCDD Exposure Sensitizes Offspring to Angiotensin II-induced Hypertension	-	X	-	-
Ashida et al. (1996)	Protective Action of Dehydroascorbic Acid on the Ah Receptor-dependent and Receptor-independent Induction of Lipid Peroxidation in Adipose Tissue of Male Guinea Pig Caused by TCDD Administration	-	-	-	X
Ashida et al. (2000)	2,3,7,8-TCDD-induced Changes in Activities of Nuclear Protein Kinases and Phosphatases Affecting DNA Binding Activity of c-Myc and AP-1 in the Livers of Guinea Pigs	-	X	-	X
Astroff et al. (1987)	6-Methyl-1,3,8-Trichlorodibenzofuran as a 2,3,7,8-TCDD Antagonist: Inhibition of the Induction of Rat Cytochrome P-450 Isozymes and Related Monooxygenase Activities	-	-	-	X
Aubert et al. (1985)	Ontogeny of Hypothalamic Luteinizing Hormone-releasing Hormone (GnRH) and Pituitary GnRH Receptors in Fetal and Neonatal Rats	-	-	-	X
Aulerich et al. (2001)	Short Communications: Dietary Exposure to 3,3',4,4',5 -Pentachlorobiphenyl (PCB 126) or 2,3,7,8-TCDD Does Not Induce Proliferation of Squamous Epithelium or Osteolysis in Jaws of Weanling Rats	-	X	-	-
Badawi et al. (2000)	Effect of Chlorinated Hydrocarbons on Expression of Cytochrome P450 1A1, 1A2 and 1B1 and 2- and 4-Hydroxylation of 17β-estradiol in Female Sprague-Dawley Rats	-	X	-	-
Badesha et al. (1995)	Immunotoxic Effects of Prolonged Dietary Exposure of Male Rats to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Bagchi et al. (1993)	Time-dependent Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Serum and Urine Levels of Malondialdehyde, Formaldehyde, Acetaldehyde, and Acetone in Rats	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Bagchi et al. (2002)	Comparative Effects of TCDD, Endrin, Naphthalene and Chromium (VI) on Oxidative Stress and Tissue Damage in the Liver and Brain Tissues of Mice	-	X	-	-
Bars and Elcombe (1991)	Dose-dependent Acinar Induction of Cytochromes P450 in Rat Liver. Evidence for a Differential Mechanism of Induction of P4501A1 by Beta-naphthaflavone and Dioxin	-	-	-	X
Barsotti et al. (1979)	Hormonal Alterations in Female Rhesus Monkeys Fed a Diet Containing 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Barter and Klaassen (1992)	UDP-glucuronosyltransferase Inducers Reduce Thyroid Hormone Levels in Rats by an Extrathyroidal Mechanism	-	-	X	-
Bastomsky (1977)	Enhanced Thyroxine Metabolism and High Uptake Goiters in Rats After a Single Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Beckett et al. (2005)	Squamous Epithelial Lesion of the Mandibles and Maxillaw of Wild Mink Naturally Exposed to Polychlorinated Biphenyls	X	-	-	X
Beebe et al. (1995)	Promotion of N-nitrosodimethylamine-initiated Mouse Lung Tumors Following Single or Multiple Low Dose Exposure to 2,3,7,8- Tetrachlorodibenzo-*p*-dioxin	-	-	-	X
Beguinot et al. (1985)	Phorbol Esters Induce Internalization Without Degradation of Unoccupied Epidermal Growth Factor Receptors	-	-	X	-
Bell et al. (2007b)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Developing Male Wistar(Han) Rat. I: No Decrease in Epididymal Sperm Count after a Single Acute Dose	-	X	-	-
Bell et al. (2007a)	Relationships Between Tissue Levels of 2,3,7,8-Tetrachlorodibenzop-dioxin (TCDD), mRNAs, and Toxicity in the Developing Male Wistar(Han) Rat	-	X	-	-
Bemis et al. (2007)	TCDD-Induced Alterations in Gene Expression Profiles of the Developing Mouse Paw Do Not Influence Morphological Differentiation of This Potential Target Tissue	-	-	-	X
Besteman et al. (2005)	Tetrachlorodibenzo-*p*-Dioxin (TCDD) Inhibits Differentiation and Increases Apoptotic Cell Death of Precursor T-Cells in the Fetal Mouse Thymus	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Besteman et al. (2007)	2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) or Diethylstilbestrol (DES) Cause Similar Hematopoietic Hypocellularity and Hepatocellular Changes in Murine Fetal Liver, but Differentially Affect Gene Expression	-	X	-	-
Biegel et al. (1989)	2,2N4,4N5,5N-Hexachlorobiphenyl as a 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Antagonist in C57BL/6 Mice	-	X	-	-
Birnbaum et al. (1985)	Toxic Interaction of Specific Polychlorinated Biphenyls and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: Increased Incidence of Cleft Palate in Mice	-	-	X	-
Birnbaum et al. (1986)	Synergistic Interaction of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Hydrocortisone in the Induction of Cleft Palate in Mice	-	X	-	-
Birnbaum et al. (1987a)	Teratogenic Effects of Polychlorinated Dibenzofurans in Combination in C57BL/6N Mice	-	-	X	-
Birnbaum et al. (1987b)	Teratogenicity of Three Polychlorinated Dibenzofurans in C57BL/6N Mice	-	-	X	-
Birnbaum et al. (1989)	Retinoic Acid and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Selectively Enhance Teratogenesis in C57BL/6N Mice	-	X	-	-
Birnbaum et al. (1990)	Differential toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in C57Bl/6 mice congenic at the Ah locus	-	X	-	-
Birnbaum et al. (1991)	Teratogenic Effects of 2,3,7,8-Tetrabromodibenzo-*p*-dioxin and Three Polybrominated Dibenzofurans in C57BL/6N Mice	-	-	X	-
Bjerke and Peterson (1994)	Reproductive Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Male Rats: Different Effects of In Utero Versus Lactational Exposure	-	X	-	-
Bjerke et al. (1994a)	Effects of In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure on Responsiveness of the Male Rat Reproductive System to Testosterone Stimulation in Adulthood	-	X	-	-
Bjerke et al. (1994b)	Partial Demasculinization and Feminization of Sex Behavior in Male Rats by In Utero and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin is Not Associated with Alterations in Estrogen Receptor Binding or Volumes of Sexually Differentiated Brain	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Blaylock et al. (1992)	Exposure to Tetrachlorodibenzo-*p*-dioxin (TCDD) Alters Fetal Thymocyte Maturation	-	X	-	-
Bohn et al. (2005)	Increased Mortality Associated with TCDD Exposure in Mice Infected with Influenza A Virus is Not Due to Severity of Lung Injury or Alterations in Clara Cell Protein Content	-	X	-	-
Boverhof et al. (2005)	Temporal and Dose-Dependent Hepatic Gene Expression Patterns in Mice Provide New Insights into TCDD-Mediated Hepatotoxicity	X	-	-	-
Boverhof et al. (2008)	Inhibition of Estrogen-Mediated Uterine Gene Expression Responses by Dioxin	-	X	-	-
Bowers et al. (2006)	Short Report: 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Reduces Leishmania Major Burdens In C57Bl/6 Mice	-	X	-	-
Brewster et al. (1987)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on the Guinea Pig Heart Muscle	-	-	-	X
Brewster and Matsumura (1984)	TCDD (2,3,7,8-Tetrachlorodibenzo-*p*-dioxin) Reduces Lipoprotein Lipase Activity in the Adipose Tissue of the Guinea Pig	-	-	-	X
Brouillette and Quirion (2008)	The Common Environmental Pollutant Dioxin-induced Memory Deficits by Altering Estrogen Pathways and a Major Route of Retinol Transport Involving Transthyretin	-	X	-	X
Brouwer and van den Berg (1983)	Early Decrease in Retinoid Levels in Mice After Exposure to Low Doses of Polychlorinated Biphenyls	-	-	X	-
Brouwer and van den Berg (1984)	Early and Differential Decrease in Natural Retinoid Levels in C57Bl/Rij and DBA/2 Mice by 3,4,3N,4N-Tetrachlorobipheny	-	-	X	-
Brouwer et al. (1985)	Time and Dose Responses of the Reduction in Retinoid Concentrations in C57BL/Rij and DBA/2 Mice Induced by 3,4,3N,4N-Tetrachlorobiphenyl	-	-	X	-
Brown and Lamartiniere (1995)	Xenoestrogens Alter Mammary Gland Differentiation and Cell Proliferation in the Rat	-	X	-	-
Brunnberg et al. (2006)	The Constitutively Active Ah Receptor (CA-AhR) Mouse as a Potential Model for Dioxin Exposure—Effects in Vital Organs	-	X	-	-
Bryant et al. (1997)	Effects of TCDD on Ah Receptor, ARNT, EGF, and TGF-alpha Expression in Embryonic Mouse Urinary Tract	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Bryant et al. (2001)	Teratogenicity of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) in Mice Lacking the Expression of EGF and/or TGF-alpha	X	X	-	-
Buchmann et al. (1994)	Effects of 2,3,7,8-Tetrachloro- and 1,2,3,4,6,7,8-Heptachlorodibenzo-*p*- dioxin on the Proliferation of Preneoplastic Liver Cells in the Rat	-	-	X	-
Bushnell and Rice (1999)	Behavioral Assessments of Learning and Attention in Rats Exposed Perinatally to 3,3',4,4',5-Pentachlorobiphenyl (PCB 126)	-	-	X	-
Byers et al. (2006)	Association Between the Levels of Biogenic Amines and Superoxide Anion Production in Brain Regions of Rats After Subchronic Exposure to TCDD	-	X	-	-
Calfee-Mason et al. (2002)	Vitamin E Inhibits Hepatic NF-kB Activation in Rats Administered the Hepatic Tumor Promoter Phenobarbital	-	-	X	-
Camacho et al. (2004)	Effect of 2,3,7,8-TCDD on Maternal Immune Response During Pregnancy	-	X	-	-
Cantoni et al. (1984)	Different Susceptibility of Mouse Tissues to Porphyrogenic Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Carney et al. (2004)	2,3,7,8-TCDD Activation of the AHR/AHR Nuclear Translocator Pathway Causes Developmental Toxicity Through a CYP1-A-independent Mechanism in Zebrafish	X	-	-	-
Chaffin et al. (1996)	In Utero and Lactational Exposure of Female Holtzman Rats to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: Modulation of the Estrogen Signal	-	X	-	-
Chaffin et al. (1997)	Alterations to the Pituitary-gonadal Axis in the Female Rat Exposed In Utero and Through Lactation to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Chahoud et al. (1989)	Reproductive Toxicity and Pharmacokinetics of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. I. Effects of High Doses on the Fertility of Male Rats	-	-	-	X
Chapman and Schiller (1985)	Dose-related Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in C57BL/6J and DBA/2J Mice	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Chen et al. (1993)	In Utero Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Does Not Impair Testosterone Production by Fetal Rat Testis	-	X	X	-
Chen et al. (2001)	Disposition of Polychlorinated Dibenzo-*p*-dioxins, Dibenzofurans, and Non-ortho Plychlorinated Biphenyls in Pregnant Long Evans Rats and the Transfer to Offspring	-	-	X	-
Chen et al. (2002)	A Mixture of Polychlorinated Dibenzo-*p*-dioxins (PCDDs), Dibenzofurans (PCDFs), and Non-ortho Polychlorinated Biphenyls (PCBs) Changed the Lipid Content of Pregnant Long Evans rats	-	-	X	-
Chen et al. (2003)	The Effect of 2,3,7,8-TCDD on Chorionic Gonadotrophin Activity in Pregnant Macaques	-	X	-	-
Cheng et al. (2002)	2,3,7,8-TCDD Treatment Induces c-Fos Expression in the Forebrain of the Long-Evans Rat	-	X	-	-
Cho et al. (2006)	Enhanced Expression of Plasma Glutathione Peroxidase in the Thymus of Mice Treated with TCDD and its Implication for TCDD-induced Thymic Atrophy	-	X	-	-
Choi et al. (2006)	In Utero Exposure to 2,3,7,8-TCDD Induces Amphiregulin Gene Expression in the Developing Mouse Ureter	-	-	-	X
Choi et al. (2008)	Effect of 2,3,7,8-TCDD on Testicular Spermatogenesis-related Panels and Serum Sex Hormone Levels in Rats	-	X	-	-
Chou et al. (1979)	Neuropathology of "Spinning Syndrome" Induced by Prenatal Intoxication with a PCB in Mice	-	-	X	-
Clark et al. (1981)	Enhanced Suppressor Cell Activity as a Mechanism of Immunosuppression by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	-	X
Clark et al. (1991a)	Tumor necrosis Factor involvement in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-mediated Endotoxin Hypersensitivity in C57Bl/6 Mice Congenic at the Ah Locus	-	X	-	-
Clark et al. (1991b)	Tumor Promotion by TCDD in Female Rats. In: Biological Basis for Risk Assessment of Dioxins and Related Compounds	-	X	-	X
Cohen et al. (1979)	Anticarcinogenic Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Benzo[a]pyrene and 7,12-Dimethylbenz[a]anthrene Tumor Initiation and its Relationship to DNA Binding	-	-	-	X

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Collins and Capen (1980)	Fine Structural Lesions and Hormonal Alterations in Thyroid Glands of Perinatal Rats Exposed In Utero and by the Milk to Polychlorinated Biphenyls	-	-	X	-
Collins et al. (2008)	2,3,7,8-Tetracholorodibenzo-*p*-Dioxin Exposure Disrupts Granule Neuron Precursor Maturation in the Developing Mouse Cerebellum	-	X	-	-
Comer and Norton (1982)	Effects of Perinatal Methimazole Exposure on a Developmental Test Battery for Neurobehavioral Toxicity in Rats	-	-	X	-
Courtney (1976)	Mouse Teratology Studies with Chlorodibenzo-*p*-dioxins	-	X	-	-
Courtney and Moore (1971)	Teratology Studies with 2,4,5-Trichlorophenoxyacetic Acid and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	X
Couture et al. (1989)	Developmental Toxicity of 2,3,4,7,8-Pentachlorodibenzofuran in the Fischer 344 Rat	-	-	X	-
Couture et al. (1990)	Characterization of the Peak Period of Sensitivity for the Induction of Hydronephrosis in C57BL/6N Mice Following Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Crofton and Rice (1999)	Low-frequency Hearing Loss Following Perinatal Exposure to 3,3',4,4',5-Pentachlorobiphenyl (PCB 126) in Rats	-	-	X	-
Cummings et al. (1996)	Promotion of Endometriosis by 2,3,7,8- Tetrachlorodibenzo-*p*-dioxin in Rats and Mice: Time-Dose Dependence and Species Comparison	-	X	-	-
Dalton et al. (2001)	Dioxin Exposure Is an Environmental Risk Factor for Ischamic Heart Disease-IP injection	-	-	-	X
D'Argy et al. (1984)	Teratogenicity of TCDD and Congener 3,3N,4,4N-Tetrachloroazoxybenzene in Sensitive and Nonsensitive Mouse stRains After Reciprocal Blastocyst Transfer	-	X	-	-
Davies et al. (2008)	Essential Role of the AH Receptor in the Dysfunction of Heme Metabolism Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Davis et al. (2000)	Ovarian Tumors in Rats Induced by Chronic 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Treatment	-	X	-	-
de Heer et al. (1995)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) to the Human Thymus after Implantation in SCID Mice	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Dearstyne and Kerkvliet (2002)	Mechanism of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-induced Decrease in Anti-CD3-activated CD4+ T cells: the Roles of Apoptosis, Fas, and TNF	-	X	-	-
Devito et al. (1992)	Antiestrogenic Action of 2,3,7,8-Tetrachloro- dibenzo-*p*-dioxin: Tissue Specific Regulation of Estrogen Receptor in CD1 Mice	-	-	-	X
Dhar and Setty (1990)	Changes in Testis, Epididymis and Other Accessory Organs of Male Rats Treated with Anandron During Sexual Maturation	-	-	X	-
Dienhart et al. (2000)	Gestational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Induces Developmental Defects in the Rat Vagina	-	X	-	-
Diliberto et al. (1999)	Effects of CYP1A2 on Disposition of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, 2,3,4,7,8-Pentachlorodibenzofuran, and 2,2',4,4',5,5'-Hexachlorobiphenyl in CYP1A2 Knockout and Parental (C57BL/6N and 129/Sv) Strains of Mice	-	X	-	-
Dong et al. (2002)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Zebra Fish Embryo: Local Circulation Failure in the Dorsal Midbrain is Associated with Increased Apoptosis	X	-	-	-
Dong et al. (2004)	Role of Aryl Hydrocarbon Receptor in Mesencephalic Circulation Failure and Apoptosis in Zebrafish Embryos Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	X	-	-	-
Dragan et al. (1991)	An initiation-promotion assay in rat liver as a potential complement to the 2-year carcinogenesis bioassay	-	-	X	-
Dragan et al. (1992)	Characterization of the Promotion of Altered Hepatic Foci by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Female Rat	-	-	-	X
Dragin et al. (2006)	For Dioxin-induced Birth Defects, Mouse or Human CYP1A2 in Maternal Liver Protects whereas Mouse CYP1A1 and CYP1B1 Are Inconsequential	X	X	-	-
Dunlap and Matsumura (2000)	Analysis of Difference In Vivo Effects of TCDD Between c-src +/+ mice, c-src Deficient, -/+ and -/- B6, 129-Srctm l sor Mice and their Wild-type Littermates-IP Injection	X	-	-	-
Dunlap et al. (1999)	Differential Toxicities of TCDD In Vivo Among Normal, c-src Knockout, Geldanamycin-, and Quercetin-treated Mice	X	-	-	X

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Dunlap et al. (2002)	Effects of Src-deficiency on the Expression of In Vivo Toxicity of TCDD in a Strain of c-src Knockout Mice Procured Through Six Generations of Backcrossings to C57BL/6 Mice-IP Injection	X	-	-	X
Ebner et al. (1988)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Serum Insulin and Glucose Levels in the Rat	-	-	-	X
Eckle et al. (2004)	Immunohistochemical Detection of Activated Caspases in Apoptotic Hepatocytes in Rat Liver	X	-	-	-
Elder et al. (1976)	The Effect of Porphyrogenic Compound, Hexachlorobenzene, on the Activity of Hepatic Uroporphyrinogen Decarboxylase in the Rat	-	-	X	-
El-Sabeawy et al. (1998)	Treatment of Rats during Pubertal Development with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Alters Both Signaling Kinase Activities and Epidermal Growth Factor Receptor Binding in the Testis and the Motility and Acrosomal Reaction of Sperm-IP injection	-	-	-	X
El-Tawil and Elsaieed (2005)	Induction of Oxidative Stress in the Reproductive System of Rats after Subchronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Enan et al. (1992)	TCDD Causes Reduction in Glucose Uptake Through Glucose Transporters on the Plasma Membranes of the Guinea Pig Adipocyte	-	-	-	X
Enan et al. (1998)	Mechanism of Gender-Specific TCDD-induced Toxicity in Guinea Pig Adipose Tissue	-	X	-	X
Eriksson et al. (1991)	Neonatal Exposure to 3,3N,4,4N-Tetrachlorobiphenyl: Changes in Spontaneous Behavior and Cholinergic Muscarinic Receptors in the Adult Mouse	-	-	X	-
Esser et al. (2005)	Effects of a Single Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, Given at Post-puberty, in Senescent Mice	-	-	-	X
Evans and Andersen (2000)	Sensitivity Analysis of a Physiological Model for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD): Assessing the Impact of Specific Model Parameters on Sequestration in Liver and Fat in the Rat	X	-	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Faith and Moore (1977)	Impairment of Thymus-dependent Immune Function by Exposure of the Developing Immune System to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Fan and Rozman (1994)	Relationship Between Acute Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and Distribution of Intermediary Metabolism in the Long-Evans Rat	-	X	-	-
Fan et al. (1996)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Humoral and Cellmediated Immunity in Sprague-Dawley Rats	-	X	-	-
Faqi et al. (1998)	Reproductive Toxicity and Tissue Concentrations of Low Doses of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Male Offspring Rats Exposed Throughout Pregnancy and Lactation	-	-	-	X
Fernandez-Salguero et al. (1995)	Immune System Impairment and Hepatic Fibrosis in Mice Lacking the Dioxinbinding Ah Receptor	X	-	-	-
Fernandez-Salguero et al. (1996)	Aryl-hydrocarbon Receptor-Deficient Mice Are Resistant to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-Induced Toxicity	-	-	-	X
Fetissov et al. (2004)	Expression of Hypothalamic Neuropeptides After Acute TCDD Treatment and Distribution of Ah Receptor Repressor	-	X	-	-
Fine et al. (1989)	Lymphocyte Stem Cell Alterations Following Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	X
Fine et al. (1990)	Prothymocyte Activity is Reduced by Perinatal 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure	-	X	-	X
Fisher et al. (2005)	Aryl Hydrocarbon Receptor-dependent Induction of Loss of Mitochondrial Membrane Potential in Epididydimal Spermatozoa by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	-	-	X
Flaws et al. (1997)	In Utero and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Induces Genital Dysmorphogenesis in the Female Rat	-	X	-	-
Fletcher et al. (2001)	Hepatic Vitamin A Depletion is a Sensitive Marker of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Exposure in Four Rodent Species	-	X	-	-
Fletcher et al. (2005a)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Alters the mRNA Expression of Critical Genes Associated with Cholesterol Metabolism, Bile Acid Biosynthesis, and Bile Transport in Rat Liver: A Microarray Study	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Fletcher et al. (2005b)	Altered Retinoid Metabolism in Female Long-Evans and Han/Wistar Rats following Long-Term 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD)-Treatment-Subcutaneous administration	-	-	-	X
Flodstrom and Ahlborg (1992)	Relative Tumor Promoting Activity of Some Polychlorinated Dibenzo-*p*-dioxin-, Dibenzofuran-, and Biphenyl Congeners in Female Rats	-	-	-	X
Foster et al. (1997)	Morphologic Characteristics of Endometriosis in the Mouse Model: Application to Toxicology	-	-	-	X
Frericks et al. (2006)	Transcriptional Signatures of Immune Cells in Aryl Hydrocarbon Receptor (AHR)-proficient and AHR-deficient Mice	X	X	-	X
Fritz et al. (2005)	In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure: Effects on the Prostate and Its Response to Castration in Senescent C57BL/6J Mice	-	X	-	-
Fujimaki et al. (2002)	Effect of a Single Oral Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Immune Function in Male NC/Nga Mice	-	X	-	-
Fujiwara et al. (2008)	Morphological and Immunohistochemical Studies on Cleft Palates Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Mice	-	X	-	-
Funatake et al. (2005)	Cutting Edge: Activation of the Aryl Hydrocarbon Receptor by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Generates a Population of CD4+ CD25+ Cells with Characteristics of Regulatory T Cells	X	X	-	-
Funseth et al. (2002a)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Trace Elements, Inflammation and Viral Clearance in the Myocardium During Coxsackievirus B3 Infection in Mice	-	-	-	X
Funseth et al. (2002b)	Effects of Coxsackievirus B3 Infection on the Acute-phase Protein Metallothionein and on Cytochrome P-4501A1 Involved in the Detoxification Processes of TCDD in the Mouse	-	-	-	X
Galijatovic et al. (2004)	The Human CYP1A1 Gene Is Regulated in a Developmental and Tissue-specific Fashion in Transgenic Mice	-	-	-	X
Gallo et al. (1986)	Interactive Effects of Estradiol and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Hepatic Cytochrome P-450 and Mouse Uterus	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Gao et al. (2000)	Gonadotropin-releasing Hormone (GNRH) Partially Reverses the Inhibitory Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Ovulation in the Immature Gonadotropin-treated Rat	-	X	-	-
Gao et al. (2001)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Decreases Responsiveness of the Hypothalamus to Estradiol as a Feedback Inducer of Preovulatory Gonadotropin Secretion in the Immature Gonadotropin-Primed Rat	-	X	-	-
Gao et al. (2004)	Lactational Exposure of Han/Wistar Rats to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Interferes with Enamel Maturation and Retards Dentin Mineralization	-	X	-	-
Garrett and Gasiewicz (2006)	The Aryl Hydrocarbon Receptor Agonist 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Alters the Circadian Rhythms, Quiescence, and Expression of Clock Genes in Murine Hematopoietic Stem and Progenitor Cells	-	X	-	-
Gasiewicz and Rucci (1984)	Cytosolic Receptor for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. Evidence for a Homologous Nature Among Various Mammalian Species	-	-	-	X
Gasiewicz et al. (1983)	Distribution, Excretion, and Metabolism of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in C57BL/6J, DBA/2J and B6D2F1/J Mice	-	-	-	X
Gasiewicz et al. (1986)	Changes in Hamster Hepatic Cytochrome P-450, Ethoxycoumarin *o*-deethylase, and Reduced NAD(P): Menadione Oxidoreductase Following Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. Partial Dissociation of Temporal and Dose-response Relationships From Elicited Toxicity	-	-	-	X
Gehrs and Smialowicz (1999)	Persistent Suppression of Delayed-type Hypersensitivity in Adult F344 Rats after Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Gehrs et al. (1997)	Alterations in the Developing; Immune System of the F344 Rat After Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. II. Effects on the Pup and the Adult	-	X	-	-
Genter et al. (2006)	Comparison of Mouse Hepatic Mitochondrial Versus Microsomal Cytochromes P450 Following TCDD Treatment	-	-	-	X

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Geusau et al. (2005)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Impairs Differentiation of Normal Human Epidermal Keratinocytes in a Skin Equivalent Model	X	-	-	-
Ghafoorunissa (1980)	Undernutrition and Fertility of Male Rats	-	-	X	-
Giavini et al. (1982)	Rabbit Teratology Studies With 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Giavini et al. (1983)	Embryotoxic Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Administered to Female Rats Before Mating	-	X	-	-
Goldey and Crofton (1998)	Thyroxine Replacement Attenuates Hypothyroxinemia, Hearing Loss, and Motor Deficits Following Developmental Exposure to Aroclor 1254 in Rats	-	-	X	-
Goldstein and Linko (1984)	Differential Induction of Two 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-inducible Forms of Cytochrome P-450 in Extrahepatic Versus Hepatic Tissues	-	-	-	X
Goldstein et al. (1973)	Hepatic Porphyria Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Mouse	-	X	-	-
Goldstein et al. (1982)	Induction of Porphyria in the Rat by Chronic Versus Acute Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Gonzalez et al. (1995)	Xenobiotic Receptor Knockout Mice	X	-	-	-
Gordon and Miller (1998)	Thermoregulation in Rats Exposed Perinatally to Dioxin: Core Temperature Stability to Altered Ambient Temperature, Behavioral Thermoregulation, and Febrile Response to Lipopolysaccharide	-	X	-	-
Gordon et al. (1995)	Temperature Regulation and Metabolism in Rats Exposed Perinatally to Dioxin: Permanent Change in Regulated Body Temperature	-	X	-	-
Gordon et al. (1996)	Autonomic and Behavioral Thermoregulation in Golden Hamsters Exposed Perinatally to Dioxin	-	X	-	-
Gorski and Rozman (1987)	Dose-response and Time Course of Hypothyroxemia and Hypoinsulinemia and Characterization of Insulin Hypersensitivity in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-treated Rats	-	-	-	X
Gorski et al. (1990)	Reduced Gluconeogenesis in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-treated Rats	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Gray et al. (1995b)	Exposure to TCDD During Development Permanently Alters Reproductive Function in Male Long Evans Rats and Hamsters: Reduced Ejaculated and Epididymal Sperm Numbers and Sex Accessory Gland Weights in Offspring With Normal Androgenic Status	-	X	-	-
Gray et al. (1995a)	Functional Developmental Toxicity of Low Doses of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and a Dioxin-like PCB (169) in Long Evans Rats and Syrian Hamsters: Reproductive, Behavioral and Thermoregulatory Alterations	-	X	-	-
Gray et al. (1997a)	A Dose-response Analysis of the Reproductive Effects of Single Gestational Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Male Long Evans Hooded Rat Offspring	-	X	-	-
Gray et al. (1997b)	In Utero 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Alters Reproductive Morphology and Function in Female Rat Offspring	-	X	-	-
Gray et al. (1997b)	In Utero Exposure to Low Doses of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Alters Reproductive Development of Female Long Evans Hooded Rat Offspring	-	X	-	-
Greenlee et al. (1985)	Evidence for Direct Action of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Thymic Epithelium	X	-	-	-
Greig and DeMatteis (1973)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Drug Metabolism and Hepatic Microsomes of Rats and Mice	-	X	-	-
Guo et al. (2000)	Effect of TCDD on Maternal Toxicity and Chorionic Gonadotropin: Bioactivity in the Immediate Post-implantation Period of Macaque	-	X	-	-
Guo et al. (2007)	Toxic Effects of TCDD on Osteogenesis Through Altering IGFBP-6 gene Expression in Osteoblasts	-	X	-	X
Guo et al. (2008)	Anti-estrogenic Effect of Dioxin on Rat Skeleton Development	-	X	-	-
Haag-Gronlund et al. (1997)	Promotion of Altered Hepatic Foci by 2,3',4,4',5-Pentachlorobiphenyl in Sprague-Dawley Female Rats	-	-	-	X
Haake et al. (1987)	Aroclor 1254 as an Antagonist of the Teratogenicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Haavisto et al. (2001)	Prenatal Testosterone and Luteinizing Hormone Levels in Male Rats Exposed During Pregnancy to 2,3,7,8-TCDD and Diethylstilbestrol	X	-	-	-
Haavisto et al. (2006)	The Effects of Maternal Exposure to 2,3,7,8-TCDD on Testicular Steroidogenesis in Infantile Male Rats	-	X	-	-
Hahn et al. (1988)	The Role of the Ah Locus in Hexachlorobenzene-induced Porphyria: Studies in the Congenic C57BL/6J Mice	-	-	X	X
Håkansson and Hanberg (1989)	The Distribution of [14C]-2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and its Effect on Vitamin A Content in Parenchymal and Stellate Cells of Rat Liver	-	X	-	-
Håkansson et al. (1989a)	2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin (TCDD)-induced Alterations in the Vitamin A Homeostasis and in the 7-Ethoxyresorufin *o*-deethylase (EROD)-activity in SD Rats and Hartley Guinea Pigs	-	X	-	-
Håkansson et al. (1989b)	Hepatic Vitamin A Storage in Relation to Paired Feed Restriction and TCDD-treatment	-	X	-	-
Håkansson et al. (1990)	Vitamin A Storage in Rats Subchronically Exposed to PCDDs/PCDFs	-	-	X	-
Håkansson et al. (1991)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on the Vitamin A Status of Hartley Guinea Pigs, SD Rats, C57Bl/6 Mice, DBA/2 Mice, and Golden Syrian Hamsters	-	-	-	X
Håkansson et al. (1994)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on the Hepatic 7-Ethoxyresorufin *o*-deethylase Activity in Four Rodent Species	-	-	-	X
Hamm et al. (2000)	In Utero and Lactational Exposure to 2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin Alters Postnatal Development of Seminal Vesicle Epithelium	-	X	-	-
Hamm et al. (2003)	A Mixture of Dioxins, Furans, and Non-ortho PCBs Based Upon Consensus TEQ Factors Produces Dioxin-like Reproductive Effects	-	-	X	-
Hanson and Smialowicz (1994)	Evaluation of the Effect of Low-level 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure on Cell Mediated Immunity	-	-	-	X

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Hany et al. (1999)	Behavioral Effects Following Single and Combined Maternal Exposure to PCB 77 (3,4,3',4'-Tetrachlorobiphenyl) and PCB 47 (2,4,2',4'- Tetrachlorobiphenyl) in Rats	-	-	-	X
Harper et al. (1991)	Ah Receptor in Mice Genetically "Nonresponsive" for Cytochrome P4501A1 Induction: Cytosolic Ah Receptor, Transformation to the Nuclear Binding State, and Induction of Aryl Hydrocarbon Hydroxylase by Halogenated and Nonhalogenated Aromatic Hydrocarbons in Embryonic Tissues and Cells	X	-	-	-
Harper et al. (1994a)	An Enzyme-linked Immunosorbent Assay (ELISA) Specific for Antibodies to TNP-LPS Detects Alterations in Serum Immunoglobulins and Isotype Switching in C57BL/6 and DBA/2 Mice Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Related Compounds	X	-	-	-
Harper et al. (1994b)	Inhibition of Estrogen-induced Progesterone Receptor in MCF-7 Human Breast Cancer Cells by Aryl Hydrocarbon (Ah) Receptor Agonists	X	-	-	-
Harris et al. (1973)	General Biological Effects of TCDD in Laboratory Animals	X	X	-	-
Hart (1972)	Manipulation of Neonatal Androgen: Effects on Sexual Responses and Penile Development in Male Rats	-	-	X	-
Harvey et al. (1993)	Spontaneous and Carcinogen-induced Tumorigenesis in P53 Deficient Mice	X	-	-	-
Hassoun et al. (1984a)	Teratogenicity of 2,3,7,8-Tetrachloro-dibenzofuran in BXD Recombinant Inbred Strains	-	-	X	X
Hassoun et al. (1984b)	Teratological Studies on the TCDD Congener 3,3N,4,4N-Tetrachloro-azoxybenzene in Sensitive and Nonsensitive Mouse Strains: Evidence for Direct Effect on Embryonic Tissues	-	-	X	-
Hassoun et al. (1995)	Evidence of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-Induced Tissue Damage in Fetal and Placental Tissues and Changes in Amniotic Fluid Lipid Metabolites of Pregnant CF1 Mice	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Hassoun et al. (1997)	Modulation of TCDD-induced Fetotoxicity and Oxidative Stress in Embryonic and Placental Tissues of C57BL/6J Mice by Vitamin E Succinate and Ellagic Acid	-	X	-	-
Hassoun et al. (2001)	Production of Superoxide Anion, Lipid Peroxidation and DNA Damage in the Hepatic and Brain Tissues of Rats after Subchronic Exposure to Mixtures of TCDD and its Congeners	-	-	X	-
Hassoun et al. (2004)	The Modulatory Effects of Ellagic Acid and Vitamin E Succinate on TCDD-Induced Oxidative Stress in Different Brain Regions of Rats after Subchronic Exposure	-	X	-	-
Hassoun et al. (2006)	The Effects of Ellagic Acid and Vitamin E Succinate on Antioxidant Enzymes Activities and Glutathione Levels in Different Brain Regions of Rats After Subchronic Exposure to TCDD	-	X	-	-
Hebert et al. (1990)	Relative Toxicity and Tumor-promoting Ability of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), 2,3,4,7,8-Pentachlorodibenzofuran (PCDF), and 1,2,3,4,7,8-Hexachlorodibenzofuran (HCDF) in Hairless Mice	-	-	-	X
Heimler et al. (1998)	Dioxin Perturbs, in a Dose- and Time-Dependent Fashion, Steroid Secretion, and Induces Apoptosis of Human Luteinized Granulosa Cells	X	-	-	-
Hemming et al. (1993)	Relative Tumor Promoting Activity of Three Polychlorinated Biphenyls in Rat Liver	-	-	-	X
Hemming et al. (1995)	Liver Tumor Promoting Activity of 3,4,5,3',4'-Pentachloro-biphenyl and its Interaction with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
Henck et al. (1981)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: Acute Oral Toxicity in Hamsters	-	X	-	-
Henry and Gasiewicz (1987)	Changes in Thyroid Hormones and Thyroxine Glucuronidation in Hamsters Compared with Rats Following Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	-	X
Henry et al. (2006)	A Potential Endogenous Ligand for the Aryl Hydrocarbon Receptor Has Potent Agonist Activity In Vitro and In Vivo	X	-	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Herbet et al. (1990)	Relative Toxicity and Tumor-promoting Ability of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), 2,3,4,7,8-Pentachlorodibenzofuran (PCDF), and 1,2,3,4,7,8-Hexachorodibenzofuran (HCDF) in Hairless Mice	-	-	-	X
Hermsen et al. (2008)	In Utero and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Affects Bone Tissue in Rhesus Monkeys	-	-	-	X
Herr et al. (1996)	Developmental Exposure to Aroclor 1254 Produces Low-frequency Alterations in Adult Rat Brainstem Auditory Evoked Responses	-	-	X	-
Herzke et al. (2002)	Kinetics and Organotropy of Some Polyfluorinated Dibenzo-*p*-dioxins and Dibenzofurans (PFDD/PFDF) in Rats	-	-	-	X
Hinsdill et al. (1980)	Immunosuppression in Mice Induced by Dioxin (TCDD) in Feed	-	X	-	-
Hochstein et al. (1998)	Effects of Dietary Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Adult Female Mink (*Mustela vison*)	-	X	-	-
Hoegberg et al. (2005)	Retinoid Status and Responsiveness to 2,3,7,8,-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Mice Lacking Retinoid Binding Protein or Retinoid Receptor Forms- Exp 3	X	X	-	-
Hofer et al. (2004)	Simultaneous Exposure of Rats to Dioxin and Carbon Monoxide Reduces the Xenobiotic but Not the Hypoxic Response	-	X	-	-
Hoffer et al. (1996)	Dioxin Induces Transcription of Fos and Jun Genes by Ah Receptor-dependent and -Independent Pathways	X	-	-	-
Hogaboam et al. (2008)	The Aryl Hydrocarbon Receptor Affects Distinct Tissue	-	X	-	-
Hojo et al. (2006)	Sex-specific Alterations of Cerebral Cortical Cell Size in Rats Exposed Prenatally to Dioxin	-	X	-	-
Holcomb and Safe (1994)	Inhibition of 7,12-Dimethylbenzanthracene-induced Rat Mammary Tumor Growth by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
Holene et al. (1995)	Behavioral Effects of Pre- and Postnatal Exposure to Individual Polychlorinated Biphenyl Congeners in Rats	-	-	X	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Holladay et al. (1991)	Perinatal Thymocyte Antigen Expression and Postnatal Immune Development Altered by Gestational Exposure to Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Holman et al. (2000)	Low-dose Responses to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Single Living Human Cells Measured by Synchrotron Infrared Spectromicroscopy	X	-	-	-
Hood et al. (2006)	Gestational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure Effects on Sensory Cortex Function	-	X	-	-
Hook et al. (1975)	Induction and Suppression of Hepatic and Extrahepatic Microsomal Foreign-compound-metabolizing Enzyme Systems by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
House et al. (1990)	Examination of Immune Parameters and Host Resistance Mechanisms in B6C3F$_1$ Mice Following Adult Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	-	X
Hung et al. (2006)	Protective Effects of Tea Melanin against 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-Induced Toxicity: Antioxidant Activity and Aryl Hydrocarbon Receptor Suppressive Effect	-	X	-	-
Hurst et al. (2000)	Acute Administration of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Pregnant Long Evans Rats: Association of Measured Tissue Concentrations with Developmental Effects	-	X	-	-
Hurst et al. (2002)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Disrupts Early Morphogenetic Events That Form the Lower Reproductive Tract in Female Rat Fetuses	-	X	-	-
Hushka et al. (1998)	Characterization of 2,3,7,8-Tetrachloro-dibenzofuran-dependent Suppression and AH Receptor Pathway Gene Expression in the Developing Mouse Mammary Gland	-	-	X	-
Huuskonen et al. (1994)	Developmental Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in the Most TCDD-resistant and -Susceptible Rat Strains	-	X	-	-
Hwang et al. (2004)	Panax Ginseng Improves Survival and Sperm Quality in Guinea Pigs exposed to 2,3,7,8-TCDD	-	-	-	X

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Iba et al. (2001)	Pulmonary CYP1A1 and CYP1A2 Levels and Activities in Adult Male and Female Offspring of Rats Exposed During Gestation and Lactation to 2,3,7,8-TCDD	-	X	-	X
Ikeda et al. (2005a)	In Utero and Lactational Exposure to 2,3,7,8-TCDD in Rats Disrupts Brain Sexual Differentiation	-	X	-	-
Inouye et al. (2005)	T cell-derived IL-5 Production is a Sensitive Target of 2,3,7,8-TCDD	-	X	-	-
Ioannou et al. (1983)	Toxicity and Distribution of 2,3,7,8-Tetrachlorodibenzofuran in Male Guinea Pigs	-	-	X	-
Ishida et al. (2004)	Reduction of the Toxicity of 2,3,7,8-TCDD in Mice Using an Antiulcer Drug, Geranylgeranylacetone	-	X	-	-
Ishimura et al. (2002)	Increased Glycogen Content and Glucose Transporter 3 mRNA Level in the Placenta of Holtzman rats After Exposure to 2,3,7,8-TCDD	-	X	-	-
Ishimura et al. (2006)	Suppressive Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Vascular Remodeling That Takes Place in the Normal Labyrinth Zone of Rat Placenta during Late Gestation	-	X	-	-
Ishizuka et al. (2003)	Perinatal Exposure to Low Doses of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Alters Sex-Dependent Expression of Hepatic CYP2C11	-	-	X	-
Ito et al. (1980)	The Effects of Various Chemicals on the Development of Hyperplastic Liver Nodules in Hepatectomized Rats Treated with N-nitrosodiethylamine or N-2-fluorenylacetamide	-	-	X	-
Ito et al. (2002)	Mechanism of TCDD-Induced Suppression of Antibody Production: Effect on T Cell-Derived Cytokine Production in the Primary Immune Reaction of Mice	-	-	X	-
Ito et al. (2008)	TCDD Exposure Exacerbates Atopic Dermatitis-related Inflammation in NC/Nga Mice	-	X	-	-
Jain et al. (1998)	Expression of ARNT, ARNT2, HIF1 Alpha, HIF2 Alpha and Ah Receptor mRNAs in the Developing Mouse	-	-	X	-
Jamsa et al. (2001)	Effects of 2,3,7,8-tetrachlorodibenzo-*p*-Dioxin on Bone in Two Rat Strains with Different Aryl Hydrocarbon Receptor Structures (subcutaneous exposure)	-	-	-	X

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Jang et al. (2007)	Antiteratogenic Effects of Alpha-naphthoflavone on 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Exposed Mice In Utero	-	X	-	-
Jang et al. (2008)	Antiteratogenic Effect of Resveratrol in Mice Exposed In Utero to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Janz and Bellward (1996)	In Ovo 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure in Three Avian Species	X	-	-	-
Jean-Faucher et al. (1982)	The Effect of Preweaning Under-nutrition Upon the Sexual Development of Male Mice. Biol Neonate 41:45-51	-	-	X	-
Jeong et al. (2008)	Accumulation of M1dG DNA Adducts After Chronic Exposure to PCBs, but Not From Acute Exposure to Polychlorinated Aromatic Hydrocarbons-mixtures Study	-	-	X	-
Jin et al. (2008a)	Enhanced TGF-β1 is Involved in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Induced Oxidative Stress in C57BL/6 Mouse Testis	-	X	-	-
Jin et al. (2008b)	In Utero Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Affects the Development of Reproductive System in Mouse-IP Injection	-	-	-	X
Jin et al. (2008c)	Toxic Effects of Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Development of Male Reproductive System: Involvement of Antioxidants, Oxidants, and p53 Protein	-	X	-	-
Jinno et al. (2006)	Induction of Cytochrome P450-1A by the Equine Estrogen Equilenin, a New Endogenous Aryl Hydrocarbon Receptor Ligand	-	-	X	X
Johnson et al. (1992)	Reduced Leydig Cell Volume and Function in Adult Rats Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Without a Significant Effect on Spermatogenesis. Toxicology 76(2):103-118	-	X	-	X
Johnson et al. (1994)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Reduces the Number, Size, and Organelle Content of Leydig Cells in Adult Rat Testes	-	X	-	X
Johnson et al. (1997)	Promotion of Endometriosis in Mice by Polychlorinated Dibenzo-*p*- dioxins, Dibenzofurans, and Biphenyls	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Johnson et al. (2000)	Sensitivity of the SRBC PFC Assay Versus ELISA for Detection of Immunosuppression by TCDD and TCDD-like Congeners	-	X	-	-
Jones and Greig (1975)	Pathological Changes in the Liver of Mice Given 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Kakeyama et al. (2001)	Changes in Expression of NMDA Receptor Subunit mRNA by Perinatal Exposure to Dioxin	-	X	-	-
Kakeyama et al. (2003)	Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Alters Activity-dependent Expression of BDNF mRNA in the Neurocortex and Male Rat Sexual Behavior in Adulthood	-	X	-	-
Kakeyama et al. (2008)	Perinatal Exposure of Female Rats to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Induces Central Precocious Puberty in the Offspring	-	X	-	-
Kamath et al. (1997)	Evidence for the Induction of Apoptosis in Thymocytes by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin In Vivo	-	-	-	X
Kamath et al. (1999)	Role of Fas-Fas Ligand Interactions in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-induced Immunotoxicity: Increased Resistance of Thymocytes From Fasdeficient (lpr)and Fas Ligand-defective (gld) Mice to TCDD-induced Toxicity	-	-	-	X
Katz et al. (1984)	Characterization of the Enhanced Paw Edema Response to Carrageenan and Dextran in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Rats	-	-	X	-
Kedderis et al. (1991)	Disposition of 2,3,7,8-tetrabromodibenzo-*p*-dioxin and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Rat: Biliary Excretion and Induction of Cytochromes CYP1A1 and CYP1A2	-	-	-	X
Keller et al. (2007a)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Affects Fluctuating Asymmetry of Molar Shape in Mice, and an Epistatic Interaction of Two Genes for Molar Size	-	X	-	-
Keller et al. (2007b)	The Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Molar and Mandible Traits in Congenic Mice: A Test of the Role of the Ahr Locus	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Kelley et al. (1998)	Use of Model-based Compartmental Analysis to Study Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Vitamin A Kinetics in Rats	-	X	-	-
Kelley et al. (2000)	Mobilization of Vitamin A Stores in Rats After Administration of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: a Kinetic Analysis	-	X	-	-
Kelling et al. (1985)	Hypophagia-induced Weight Loss in Mice, Rats, and Guinea Pigs Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Kelling et al. (1987)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin treatment on Mechanical Function of the Rat Heart	-	X	-	-
Kerkvliet and Brauner (1990)	Flow Cytometric Analysis of Lymphocyte Subpopulations in the Spleen and Thymus of Mice Exposed to an Acute Immunosuppressive Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Kerkvliet and Oughton (1993)	Acute Inflammatory Response to Sheep Red Blood Cell Challenge in Mice Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD): Phenotypic and Functional Analysis of Peritoneal Exudate Cells	-	X	-	-
Kerkvliet et al. (1990)	Role of the Ah Locus in Suppression of Cytotoxic T Lymphocyte (CTL) Activity by Halogenated Aromatic Hydrocarbons (PCBs and TCDD): Structure-activity Relationships and Effects in C57Bl/6 Mice	-	X	-	-
Kerkvliet et al. (1996)	Inhibition of TC-1 Cytokine Production, Effector Cytotoxic T Lymphocyte Development and Alloantibody Production by 2,3,7,8- Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Kerkvliet et al. (2002)	T Lymphocytes Are Direct, Aryl Hydrocarbon Receptor (AhR)-Dependent Targets of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD):AhR Expression in Both CD4+ and CD8+ T Cells Is Necessary for Full Suppression of a Cytotoxic T Lymphocyte Response by TCDD	-	X	-	-
Khera (1992)	Extraembryonic Tissue Changes Induced by 2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin and 2,3,4,7,8-Pentachlorodibenzofuran with a Note on Direction of Maternal Blood Flow in the Labyrinth of C57BL/6N Mice	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Khera and Ruddick (1973)	Polychlorodibenzo-*p*-dioxins: Perinatal Effects and the Dominant Lethal Test in Wistar rats. In: Chlorodioxins—Origin and Fate. Blair, EH, ed. Washington, DC: American Chemical Society; pp. 7084	-	X	-	-
Kim et al. (2003a)	Area Under the Curve as a Dose Metric for Promotional Responses Following 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure	-	X	-	-
Kim et al. (2003b)	Effects of Benzo[a]pyrene, 2-Bromopropane, phenol and 2,3,7,8-TCDD on IL-6 Production in Mice After Single or Repeated Exposure-IP Injection	-	-	-	X
Kimmig and Schultz (1957)	Chlorierte Aromatische Zyklische Äther Als Ursache Der Sogenannten Chlorakne	-	-	-	X
Kitajima et al. (2004a)	Expression of the Arylhydrocarbon Receptor in the Peri-implantation Period of the Mouse Uterus and the Impact of Dioxin on Mouse Implantation-subcutaneous Injection	-	-	-	X
Kitajima et al. (2004b)	Histomorphometric Alteration and Cell-type Specific Modulation of Arylhydrocarbon receptor and Estrogen Receptor Expression by 2,3,7,8-TCDD and 17β-estradiol in Mouse Experimental Model of Endometriosis-subcutaneous Injection	-	-	-	X
Kitamura et al. (2006)	Mechanistic Investigation of the Cause for Reduced Toxicity of TCDD in wa-1 homozygous TGFα Mutant Strain of Mice as Compared its Matching Wild-type Counterpart, C57BL/6J Mice-IP Injection	-	-	-	X
Kleeman et al. (1990)	Inhibition of Testicular Steroidogenesis in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Rats: Evidence That the Key Lesion Occurs Prior to or During Pregnenolone Formation	-	X	-	-
Ko et al. (2002)	In Utero and Lactational Exposure to 2,3,7,8-TCDD in the C57BL/6J Mouse Prostate: Lobe-specific Effects on Branching Morphogenesis	-	X	-	-
Ko et al. (2004)	Evidence that Inhibited Prostatic Epithelial Bud Formation in 2,3,7,8-TCDD-exposed C57BL/6J Fetal Mice is Not Due to Interruption of Androgen Signaling in the Urogenital Sinus	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Kopec et al. (2008)	Comparative Toxicogenomic Examination of the Hepatic Effects of PCB126 and TCDD in Immature, Ovariectomized C57BL/6 Mice	-	X	-	-
Kopf et al. (2008)	Hypertension, Cardiac Hypertrophy, and Impaired Vascular Relaxation Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin are Associated With Increased Superoxide	-	X	-	-
Korenaga et al. (2007)	Long-term Effects of Subcutaneously Injected 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on the Liver of Rhesus Monkeys-subcutaneous Injection	X	-	-	-
Korte et al. (1990)	Induction of Hepatic Monooxygenases in Female Rats and Offspring in Correlation with TCDD Tissue Concentrations After Single Treatment During Pregnancy	-	-	-	X
Kozak (1997)	ARNT-deficient Mice and Placental Differentiation	-	-	X	-
Kransler et al. (2007a)	Comparative Developmental Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Hamster, Rat, and Guinea Pig	-	X	-	-
Kransler et al. (2007b)	Gestational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Alters Retinoid Homeostasis in Maternal and Perinatal Tissues of the Holtzman Rat	-	X	-	-
Kransler et al. (2008)	Effects of Helicobacter infection on Developmental Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Holtzman rats	-	X	-	-
Kransler et al. (2009)	Lung Development in the Holtzman rat is Adversely Affected by Gestational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Kronenberg et al. (2000)	Generation of αβ T-cell receptor+ CD4- CD8+ cells in Major Histocompatibility Complex Class-I-deficient Mice Upon Activation of the Aryl Hydrocarbon Receptor by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-IP Injection	-	-	-	X
Krowke et al. (1989)	Pharmacokinetics and Biological Activity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. 2. Pharmacokinetics in Rats Using a Loading-Dose/Maintenance-dose Regime With High Doses	-	-	-	X
Kruger et al. (1990)	Induction of Caffeine-demethylations by 2,3,7,8-TCDD in Marmoset Monkeys Measured with a 14CO2-breath Test	-	-	-	X

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Kwon et al. (2004)	Protective Effects of Ursodeoxycholic Acid Against 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Testicular Damage in Mice-subcutaneous Injection	-	-	-	X
Laiosa et al. (2002)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Causes Alteration in Lymphocyte Development and Thymic Atrophy in Hemopoietic Chimeras Generated from Mice Deficient in ARNT2-IV Injection	-	-	-	X
Lakind et al. (2000)	Methodology For Characterizing Distributions Of Incremental Body Burdens Of 2,3,7,8-TCDD And DDE From Breast Milk In North American Nursing Infants	X	-	-	-
Lakshman et al. (1988)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on De Novo Fatty Acid and Cholesterol Synthesis in the Rat	-	X	-	-
Lakshman et al. (1989)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Lipid Synthesis and Lipogenic Enzymes in the Rat	-	-	-	X
Lakshman et al. (1991)	Mechanism of Action of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Intermediary Metabolism in the Rat	-	X	-	-
Latchoumycandane and Mathur (2002)	Effects of Vitamin E on Reactive Oxygen Species-mediated 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Toxicity in Rat Testis	-	-	X	-
Laurent et al. (2002)	Portal Absorption of 14C After Ingestion of Spiked Milk With 14C-Phenanthrene, 14C-Benzo[a]pyrene or 14C-TCDD in Growing Pigs	-	X	-	-
Lawrence and Vorderstrasse (2004)	Activation of the Aryl Hydrocarbon Receptor Diminishes the Memory Response to Homotypic Influenza Virus Infection but Does Not Impair Host Resistance	-	X	-	-
Lawrence et al. (2000)	Fewer T lymphocytes and Decreased Pulmonary Influenza Virus Burden in Mice Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Lawrence et al. (2006)	Aryl Hydrocarbon Receptor Activation Impairs the Priming but Not the Recall of Influenza Virus-Specific CD8_ T Cells in the Lung	-	X	-	-
Lee et al. (2007)	Panax Ginseng Effects on DNA Damage, CYP1A1 Expression and Histopathological Changes in Testes of Rats Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-IP Injection	-	-	-	X

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Lensu et al. (2006)	Assessment by c-Fos Immunostaining of Changes in Brain Neural Activity Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Leptin in Rats	X	-	-	-
Lewis et al. (2001)	In Utero and Lactational Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Impairs Mammary Gland Differentiation but Does Not Block the Response to Exogenous Estrogen in the Postpubertal Female Rat	-	X	-	-
Li et al. (1995a)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Estrous Cyclicity and Ovulation in Female Sprague-Dawley Rats	-	X	-	-
Li et al. (1995b)	Reproductive Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Female Rats: Ovulation, Hormonal Regulation, and Possible Mechanism(s)	-	X	-	-
Li et al. (1995c)	Toxicokinetics of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Female Sprague-Dawley Rats Including Placental and Lactational Transfer to Fetuses and Neonates	-	X	-	-
Lilienthal and Winneke (1991)	Sensitive Periods for Behavioral Toxicity of Polychlorinated Biphenyls: Determination by Cross-fostering in Rats	-	-	X	-
Lilienthal et al. (1997)	Effects of Maternal Exposure to 3,3',4,4'-Tetrachlorobiphenyl or Propylthiouracil in Rats Trained to Discriminate Apomorphine From Saline	-	-	X	-
Lim et al. (2006)	Dihydroxy-, Hydroxyspirolactone-, and Dihydroxyspirolactone-urochlorins Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Liver of Mice	-	X	-	-
Lin et al. (1991)	The Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on the Hepatic Estrogen and Glucocorticoid Receptors in Congenic Strains of Ah Responsive and Ah Nonresponsive C57BL/6 Mice	-	X	-	-
Lin et al. (2001)	Role of the Aryl Hydrocarbon Receptor in the Development of Control and 2,3,7,8- Tetrachlorodibenzo-p-dioxin-Exposed Male Mice	-	X	-	-
Lin et al. (2002a)	Critical Window of Vulnerability for Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Prostate and Seminal Vesicle Development in C57BL/6 Mice	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Lin et al. (2002b)	Effects of Aryl Hydrocarbon Receptor Null Mutation and In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure on Prostate and Seminal Vesicle Development in C57BL/6 Mice	-	X	-	-
Linden et al. (2005)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and Leptin on Hypothalamic mRNA Expression of Factors Participating in Food Intake Regulation in a TCDD-Sensitive and a TCDD-Resistant Rat Strain	-	X	-	-
Liu et al. (2003)	Induction of Aryl Hydrocarbon Receptor and CYP1A1 mRNA by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Rat Liver-IP Injection	-	-	-	X
Loertscher et al. (2002)	In Utero Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Causes Accelerated Terminal Differentiation in Fetal Mouse Skin	-	X	-	-
Lucier et al. (1973)	TCDD-induced Changes in Rat Liver Microsomal Enzymes	-	X	-	-
Lucier et al. (1975a)	Nature of the Enhancement of Uridine Diphosphate Glucuronyltransferase Activity by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Rats	-	X	-	-
Lucier et al. (1975b)	Postnatal Stimulation of Hepatic Microsomal Enzymes Following Administration of TCDD to Pregnant Rats	-	X	-	-
Lucier et al. (1991)	Ovarian Hormones Enhance 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-mediated Increases in Cell Proliferation and Preneoplastic Foci in a Two-stage Model for Rat Hepatocarcinogenesis	-	-	X	-
Luebeck et al. (2000)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Initiation and Promotion of GST-P-Positive Foci in Rat Liver: A Quantitative Analysis of Experimental Data Using a Stochastic Model-subcutaneous injection	-	-	-	X
Luebke et al. (1994)	Assessment of Host Resistance to *Trichinella spiralis* in Mice Following Pre-infection Exposure to 2,3,7,8-TCDD	-	-	-	X
Luebke et al. (1995)	Host Resistance to *T. spiralis* infection in Rats Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	-	-	X
Luebke et al. (1999)	Effects of Aging on Resistance to *Trichinella spiralis* Infection in Rodents Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Luebke et al. (2001)	Suppression of Allergic Immune Responses to House Dust Mites in Rats Exposed to 2,3,7,8-TCDD-IP Injection	-	-	-	X
Luebke et al. (2002)	Mortality in Dioxin-exposed Mice Infected With Influenza: Mitochondrial Toxicity (Reye's Like Symptoms) Versus Enhanced Inflammation as a Mode of Action-IP Injection	-	-	-	X
Lundberg et al. (1990)	Effects of 2,3,7,8-Tetrachlorodibenzo- *p*-dioxin (TCDD) Treatment In Vivo on Thymocyte Functions in Mice After Activation In Vitro	-	X	-	-
Luster et al. (1980)	Examination of Bone Marrow, Immunologic Parameters and Host Susceptibility Following Pre- and Postnatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Luster et al. (1985)	Acute Myelotoxic Responses in Mice Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Ma et al. (2007)	Mouse Lung CYP1A1 Catalyzes the Metabolic Activation of 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-IP Injection	-	-	-	X
Mably et al. (1990)	Hypergastrinemia is Associated With Decreased Gastric Acid Secretion in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Treated Rats	-	X	-	-
Mably et al. (1991)	The Male Reproduction System is Highly Sensitive to In Utero and Lactational TCDD Exposure	-	X	-	-
MacLusky et al. (1998)	Hormonal Interactions in the Effects of Halogenated Aromatic Hydrocarbons on the Developing Brain	-	-	X	-
Madhukar et al. (1984)	Effects of In Vivo Administered 2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin on Receptor Binding of Epidermal Growth Factor in the Hepatic Plasma Membrane of Rat, Guinea Pig, Mouse and Hamster	-	-	-	X
Madhukar et al. (1988)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Causes an Increase in Protein Kinases Associated With Epidermal Growth Factor Receptor in the Hepatic Plasma Membrane	-	-	-	X
Mann (1997)	Selected Lesions of Dioxin in Laboratory Rodents	-	-	-	X
Mantovani et al. (1980)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Macrophage and Natural Killer Cell Mediated Cytotoxicity in Mice	-	-	-	X

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Markowski et al. (2002)	Impaired Cued Delayed Alternation Behavior in Adult Rat Offspring Following Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on GD 15	-	X	-	-
Marks (1985)	Exposure to Toxic Agents: the Heme Biosynthetic Pathway and Hemoproteins as Indicator	-	-	X	-
Marks and Staples (1980)	Teratogenic Evaluation of the Symmetrical Isomers of Hexachlorobiphenyl (HCB) in the Mouse. In: Proceedings of the 20th Annual Meeting of the Teratology Society, Portsmouth, NH, June 1980, p. 54A	-	-	X	-
Marks et al. (1981)	Influence of Symmetrical Polychlorinated Biphenyl Isomers on Embryo and Fetal Development in Mice	-	-	X	-
Massart and Meucci (2007)	Environmental Thyroid Toxicants and Child Endocrine Health	X	-	-	-
Matsumura et al. (1997)	Altered In Vivo Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in c-src Deficient Mice	-	-	-	X
Max and Silbergeld (1987)	Skeletal Muscle Glucocorticoid Receptor and Glutamine Synthetase Activity in the Wasting Syndrome in Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
McConnell and Moore (1979)	Toxicopathology Characteristics of Halogenated Aromatic Hydrocarbons	-	-	X	-
McConnell et al. (1978)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Rhesus Monkeys (*Macaca mulatta*) Following a Single Oral Dose	-	X	-	-
McGrath et al. (1995)	Alternative Models for Low Dose-response Analysis of Biochemical and Immunological Endpoints for Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
McKinley et al. (1993)	The Effect of Pretreatment on the Biliary Excretion of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, 2,3,7,8-Tetrachlorodibenzofuran, and 3,3',4,4'-Tetrachlorobiphenyl in the rat	-	-	X	-
McKinney et al. (1985)	Molecular Interactions of Toxic Chlorinated Dibenzo-*p*-dioxins and Dibenzofurans with Thyroxine Binding Prealbumin	-	-	X	-
McNulty (1977)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin for Rhesus Monkeys: Brief Report	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
McNulty (1984)	Fetotoxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) for Rhesus Macaques (*Macaca mulatta*)	-	X	-	-
McNulty (1985)	Toxicity and Fetotoxicity of TCDD, TCDF and PCB Isomers in Rhesus Macaques (*Macaca mulatta*)	-	-	X	-
McNulty et al. (1982)	Persistence of TCDD in Monkey Adipose Tissue	-	-	X	-
Mebus et al. (1987)	Depression of Rat Testicular 17-Hydroxylase and 17,20-Lyase After Administration of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Meulenbelt and de Vries (2005)	Toxicity of Dioxins in Humans	-	-	X	-
Meyer (2002)	Incidence of CTCL in Vietnam Veterans	-	-	X	-
Michalek (2008)	Diabetes and Cancer in Veterans of Operation Ranch Hand After Adjustment for Calendar Period, Days of Spraying, and Time Spent in Southeast Asia	-	-	X	-
Michalek et al. (2001a)	Relation of Serum 2,3,7,8-Tetrachloro-*p*-dioxin (TCDD) Levels to Hematological Examination Results in Veterans of Operation Ranch Hand	-	-	X	-
Michalek et al. (2001c)	Serum Dioxin and Hepatic Abnormalities in Veterans of Operation Ranch Hand	-	-	X	-
Miettinen et al. (2002)	Effect of In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure on Rat Molar Development: The Role of Exposure Time	-	-	X	-
Miettinen et al. (2004)	Effects of Epidermal Growth Factor Receptor Deficiency and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Fetal Development in Mice	-	-	X	-
Miettinen et al. (2005)	Effects of In Utero and Lactational TCDD Exposure on Bone Development in Differentially Sensitive Rat Lines	-	-	X	-
Miller (1985)	Congenital PCB Poisoning: a Reevaluation	-	-	X	-
Miller et al. (1986)	Teratologic Evaluation of Hexabrominated Naphthalenes in C57BL/6N Mice	-	-	X	-
Mimura et al. (1997)	Loss of Teratogenic Response to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Mice Lacking the Ah (dioxin) Receptor	-	-	X	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Mitchell and Lawrence (2003a)	Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Renders Influenza Virus-Specific CD8_ T Cells Hyporesponsive to Antigen	-	-	X	-
Mitchell and Lawrence (2003b)	T cell Receptor Transgenic Mice Provide Novel Insights Into Understanding Cellular Targets of TCDD: Suppression of Antibody Production, but Not the Response of CD8+ T Cells, During Infection with Influenza Virus	X	-	-	-
Mitchell et al. (2006)	Sustained Aryl Hydrocarbon Receptor Activity Attenuates Liver Regeneration	-	-	X	-
Mitrou et al. (2001)	Toxic Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Related Compounds	-	-	X	-
Mitsui et al. (2006)	Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Suppresses Contextual Fear Conditioning-accompanied Activation of Cyclic AMP Response Element-binding Protein in the Hippocampal CA1 Region of Male Rats	-	-	X	-
Mittler et al. (1984)	Changes in Testosterone Hydroxylase Activity in Rat Testis Following Administration of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
Mizuyachi et al. (2002)	Alteration in Ovarian Gene Expression in Response to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: Reduction of Cyclooxygenase-2 in the Blockage of Ovulation	-	-	X	-
Mocarelli (2001)	Seveso a Teaching Story	-	-	X	-
Moennikes et al. (2004)	A Constitutively Active Dioxin/Aryl Hydrocarbon Receptor Promotes Hepatocarcinogenesis in Mice	-	-	X	-
Moolgavkar et al. (1996)	Quantitative Analysis of Enzyme-altered Liver Foci in Rats Initiated with Diethylnitrosamine and Promoted with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin or 1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin	-	-	-	X
Moon et al. (2004)	Effect of TCDD on Corpus Cavernosum Histology and Smooth Muscle Physiology-IP Injection	-	-	X	-
Moon et al. (2008)	A Single Administration of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin that Produces Reduced Food and Water Intake Induces Long-lasting Expression of Corticotropin-releasing Factor, Arginine Vasopressin, and Proopiomelanocortin in Rat Brain	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Moore and Peterson (1985)	Enhanced Catabolism and Elimination of Androgens do Not Cause the Androgenic Deficiency in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Rats	-	-	X	-
Moore et al. (1973)	Postnatal Effects of Maternal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Moore et al. (1976)	Tissue Distribution of [14C] Tetrachlorodibenzo-*p*-dioxin in Pregnant and Neonatal Rats	X	-	-	-
Moore et al. (1979)	Comparative Toxicity of Three Halogenated Dibenzofurans in Guinea Pigs, Mice, and Rhesus Monkeys	-	-	X	-
Moore et al. (1985)	Enhanced Catabolism and Elimination of Androgens do Not Cause the Androgenic Deficiency in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Rats	-	-	X	-
Moore et al. (1989)	Plasma Concentrations of Pituitary Hormones in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Male Rats	-	-	X	-
Moore et al. (1991)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Inhibits Steroidogenesis in the Rat Testis by Inhibiting the Mobilization of Cholesterol to Cytochrome P450_scc 1	-	X	-	-
Moore et al. (1985)	Androgenic Deficiency in Male Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Moore et al. (1992)	In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Exposure Decreases Androgenic Responsiveness of Male Sex Organs and Permanently Inhibits Spermatogenesis and Demasculinizes Sexual Behavior in Rats	-	X	-	-
Moos et al. (1994)	Acute Inflammatory Response to Sheep Red Blood Cells in Mice Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: the Role of Proinflammatory Cytokines, IL-1 and TNF	-	-	X	-
Moran et al. (2001)	Effect of Dioxin on Ovarian Function in the Cynomolgus Macaque (*M. fascicularis*)	X	X	-	-
Moriguchi et al. (2003)	Distinct Response to Dioxin in an Arylhydrocarbon Receptor (AHR)-humanized Mouse-IP Injection	-	-	X	-
Morris et al. (1992)	Enhanced Suppression of Humoral Immunity in DBA/2 Mice Following Subchronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Morrissey et al. (1992)	Limited PCB Antagonism of TCDD-induced Malformations in Mice	-	X	-	-
Morse et al. (1993)	Interference of polychlorinated biphenyls in hepatic and brain thyroid hormone metabolism in fetal and neonatal rats	-	-	X	-
Morse et al. (1996)	Alterations in rat brain thyroid hormone status following pre- and postnatal exposure to polychlorinated biphenyls (Aroclor 1254)	-	-	X	-
Moshammer and Neuberger (2000)	Sex ratio in the children of the Austrian chloracne cohort	-	X	-	-
Mukai et al. (2008)	Behavioral Rhythmicity of Mice Lacking AhR and Attenuation of Light-Induced Phase Shift by 2,3,7,8-Tetrachlorodibenzo- *p*-Dioxin	-	X	X	-
Murante and Gasiewicz (2000)	Hemopoietic Progenitor Cells Are Sensitive Targets of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in C57BL/6J Mice	-	X	-	-
Mustafa et al. (2008)	An Enhanced Postnatal Autoimmune Profile in 24 Week-old C57BL/6 Mice Developmentally Exposed to TCDD	-	X	-	-
Myllymaki et al. (2005)	In Utero and Lactational Exposure to TCDD; Steroidogenic Outcomes Differ in Male and Female Rat Pups	-	X	-	-
Nagarkatti et al. (1984)	Sensitivity of Suppression of Cytotoxic T Cell Generation by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is Dependent on the Ah Genotype of the Murine Host	X	-	-	-
Nayyar et al. (2007)	Developmental Exposure of Mice to TCDD Elicits a Similar Uterine Phenotype in Adult Animals as Observed in Women with Endometriosis	-	X	-	-
Neff-LaFord et al. (2003)	Fewer CTL, Not Enhanced NK Cells, are Sufficient for Viral Clearance From the Lungs of Immunocompromised Mice	-	X	-	-
Negish et al. (2006)	Gestational and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Affects Social Behaviors Between Developing Rhesus Monkeys (*Macaca mulatta*)	-	X	-	-
Ness et al. (1993)	Effects of Perinatal Exposure to Specific PCB Congeners on Thyroid Hormone Concentrations and Thyroid Histology in the Rat	-	-	X	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Neubert et al. (1990)	Polyhalogenated Dibenzo-*p*-dioxins and Dibenzofurans and the Immune System 1. Effects on Peripheral Lymphocyte Subpopulations of a Non-human Primate (*Callithrix jacchus*) After Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	-	-	X
Nienstedt et al. (1979)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Hepatic Metabolism Of Testosterone in the Rat	-	X	-	-
Niittynen et al. (2003)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-Induced Accumulation of Biliverdin and Hepatic Peliosis in Rats	-	X	-	-
Niittynen et al. (2007)	Differences in Acute Toxicity Syndromes of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and 1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin in Rats	-	X	-	-
Niittynen et al. (2008)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Heme Oxygenase-1, Biliverdin IXα Reductase and δ-aminolevulinic Acid Synthetase 1 in Rats with Wild-type or Variant AH Receptor	X	X	-	-
Nikolaidis et al. (1990)	TCDD Inhibits the Support of B-cell Development by the Bursa of Fabricius	X	-	-	-
Nilsson et al. (2000)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Increases Serum and Kidney Retinoic Acid Levels and Kidney Retinol Esterification in the Rat	-	X	-	-
Nishijo et al. (2007)	Effects of Maternal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Fetal Brain Growth and Motor and Behavioural Development in Offspring Rats	-	X	-	-
Nishimura et al. (2001)	Induction of Metallothionein in the Livers of Female Sprague-Dawley Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Nishimura et al. (2002)	Immunohistochemical Localization of Thyroid Stimulating Hormone Induced by a Low Oral Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Female Sprague-Dawley Rats	-	X	-	-
Nishimura et al. (2003)	Rat Thyroid Hyperplasia Induced by Gestational and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Nishimura et al. (2005a)	Altered Thyroxin and Retinoid Metabolic Response to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Aryl Hydrocarbon Receptor-null Mice	-	X	-	-
Nishimura et al. (2005b)	Disruption of Thyroid Hormone Homeostasis at Weaning of Holtzman Rats by Lactational but Not In Utero Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin	-	X	-	-
Nishimura et al. (2006)	Localization of Cytochrome P450 1A1 in a Specific Region of Hydronephrotic Kidney of Rat Neonates Lactationally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Nishimura et al. (2008)	Critical Role of Cyclooxygenase-2 Activation in Pathogenesis of Hydronephrosis Caused by Lactational Exposure of Mice to Dioxin	-	X	-	-
Nishiumi et al. (2008)	Involvement of SREBPs in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Disruption of Lipid Metabolism in Male Guinea Pig-IP Injection	-	-	-	X
Nohara et al. (2000a)	Alterations of Thymocyte Development, Thymic Emigrants and Peripheral T Cell Population in Rats Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Nohara et al. (2002b)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on T Cell-derived Cytokine Production in Ovalbumin (OVA)-Immunized C57Bl/6 Mice	-	X	-	-
Nohara et al. (2008)	Arsenite-Induced Thymus Atrophy is Mediated by Cell Cycle Arrest: A Characteristic Downregulation of E2F-Related Genes Revealed by a Microarray Approach-IP injection	X	-	-	X
Nottebrock et al. (2006)	Effects of 2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin on the Extracellular Matrix of the Thymus in Juvenile Marmosets (*Callithrix jacchus*)-Subcutaneous Exposure	-	-	-	X
Novelli et al. (2005)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Impairment of Glucose-stimulated Insulin Secretion in Isolated Rat Pancreatic Islets-IP Injection	-	-	-	X
Ohbayashi et al. (2008)	Occurrence of Two Different Types of Glutathione S-Transferase Placental Form-Positive Hepatocytes after a Single Administration of 2,3,7,8-Tetrabromodibenzo-pdioxin in Rats	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Ohsako et al. (2002)	Developmental Stage-Specific Effects of Perinatal 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure on Reproductive Organs of Male Rat Offspring	-	X	-	-
Ohyama (2006)	Disorders of Sex Differentiation Caused by Exogenous Hormones	-	-	X	-
Ohyama et al. (2007)	Maternal Exposure of Low Dose of TCDD Modulates the Expression of Estrogen Receptor Subunits of Male Gonads in Offspring-subcutaneous Exposure	-	-	-	X
Okey et al. (1989)	Detection and Characterization of a Low-affinity Form of Cytosolic Ah Receptor in Livers of Mice Nonresponsive to Induction of Cytochrome P1-450 by 3-Methylcholanthrene	X	-	-	-
Olson (1980)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Golden Syrian Hamster	-	X	-	-
Olson and McGarrigle (1990)	Characterization of the Developmental Toxicity of 2,3,7,8-TCDD in the Golden Syrian Hamster	-	X	-	-
Olson and McGarrigle (1992)	Comparative Developmental Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Olson et al. (1990)	Developmental Toxicity of 2,3,7,8-TCDD in the Rat and Hamster	-	X	-	-
Operana et al. (2007)	Human CYP1A1^GFP Expression in Transgenic Mice Serves as a Biomarker for Environmental Toxicant Exposure-IP Injection	-	-	-	X
Paajarvi et al. (2005)	TCDD Activates Mdm2 and Attenuates the P53 Response to DNA Damaging Agents	-	X	-	-
Pan et al. (2004)	Evaluation of Relative Potencies of PCB126 and PCB169 for the Immunotoxicities in Ovalbumin (OVA)-immunized Mice	-	X	-	-
Pande et al. (2005)	Aspects of Dioxin Toxicity Are Mediated by Interleukin 1-Like Cytokines-IP injection	-	-	-	X
Park et al. (2006)	The Therapeutic Effect of Tissue Cultured Root of Wild Panax ginseng C.A. Mayer on Spermatogenetic Disorder-IP injection	-	-	X	-
Parkinson et al. (1983)	Differential Time Course of Induction of Rat Liver Microsomal Cytochrome P450 Isozymes and Epoxide Hydrolase by Arochlor 1254	-	-	X	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Partanen et al. (1998)	Epidermal Growth Factor Receptor as a Mediator of Developmental Toxicity of Dioxin in Mouse Embryonic Teeth	-	-	-	X
Patterson et al. (2003)	Induction of Apoptosis by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Following Endotoxin Exposure	-	X	-	-
Peraino et al. (1981)	Early Appearance of Histochemically Altered Hepatocyte Foci and Liver Tumors in Female Rats Treated with Carcinogens 1 Day After Birth	-	-	X	-
Perucatti et al. (2006)	Increased Frequencies of Both Chromosome Abnormalities and SCEs in Two Sheep Flocks Exposed to High Dioxin Levels During Pasturage	X	-	-	-
Pesonen et al. (2006)	Effects of In Utero and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Rat Follicular Steroidogenesis	-	X	-	-
Peters and Wiley (1995)	Evidence that Murine Preimplantation Embryos Express Aryl Hydrocarbon Receptor	-	-	X	-
Peters et al. (1999)	Amelioration of TCDD-induced Teratogenesis in Aryl Hydrocarbon Receptor (AhR)-null Mice	X	X	-	-
Petroff et al. (2000)	Interaction of Estradiol and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in an Ovulation Model: Evidence for Systemic Potentiation and Local Ovarian Effects	-	X	-	-
Petroff et al. (2001)	The Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Weight Gain and Hepatic Ethoxyresorufin-*o*-deethylase (EROD) Induction Vary with Ovarian Hormonal Status in the Immature Gonadotropin-primed Rat Model	-	X	-	-
Petroff et al. (2002)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Serum Inhibin Concentrations and Inhibin Immunostaining During Follicular Development in Female Sprague-Dawley Rats	-	X	-	-
Pitt et al. (2000)	Adrenocoricotropin (ACTH) and Corticosterone Secretion by Perifused Pituitary and Adrenal Glands From Rodents Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Plüess et al. (1988)	Subchronic Toxicity of Some Chlorinated Dibenzofurans (PCDFs) and a Mixture of PCDFs and Chlorinated Dibenzodioxins (PCDDs) in rats	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Pohjanvirta et al. (1988)	Hepatic Ah-receptor Levels and the Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Hepatic Microsomal Monooxygenase Activity in a TCDD-susceptible and -resistant Rat Strain	X	-	-	-
Pohjanvirta et al. (1989)	The Central Nervous System May be Involved in TCDD Toxicity	-	-	-	X
Pohjanvirta et al. (1990)	Effects of TCDD on Vitamin A Status and Liver Microsomal Enzyme Activities in a TCDD-susceptible and a TCDD-resistant Rat Strain	-	-	-	X
Pohjanvirta et al. (1993)	Comparative Acute Lethality of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), 1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin and 1,2,3,4,7,8- Hexachlorodibenzo-*p*-dioxin in the most TCDD-susceptible and the Most TCDD-resistant Rat Strain	X	-	-	-
Pohjanvirta et al. (1998)	Point Mutation in Intron Sequence Causes Altered Carboxyl-terminal Structure in the Aryl Hydrocarbon Receptor of the most 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-resistant Rat Strain	X	-	-	-
Pohjanvirta et al. (2006)	Evaluation of Various Housekeeping Genes for Their Applicability for Normalization of mRNA Expression in Dioxin-treated Rats	-	X	-	-
Poland and Glover (1990)	Characterization and Strain Distribution Pattern of the Murine Ah Receptor Specified by the Ahd and Ahb-3 Alleles	-	-	X	-
Poland et al. (1982)	Tumor Promotion by TCDD in Skin of HRS/J Mice	-	-	-	X
Pollenz et al. (1998)	Female Sprague-Dawley Rats Exposed to a Single Oral Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exhibit Sustained Depletion of Aryl Hydrocarbon Receptor Protein in Liver, Spleen, Thymus, and Lung	-	X	-	-
Porterfield et al. (2000)	Thyroidal Dysfunction and Environmental Chemicals -- Potential Impact on Brain Development	-	-	X	-
Potter et al. (1983)	Hypothyroxinemia and Hypothermia in Rats in Response to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Administration	-	X	-	-
Potter et al. (1986a)	Relationship of Alterations in Energy Metabolism to Hypophagia in Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Potter et al. (1986b)	Thyroid Status and Thermogenesis in Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Powers et al. (2005)	Tetrachlorodibenzo-*p*-dioxin Exposure Alters Radial Arm Maze Performance and Hippocampal Morphology in Female AhR+/- Mice	X	X	-	-
Prell et al. (2000)	CTL Hyporesponsiveness Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: Role of Cytokines and Apoptosis	-	X	-	-
Puhvel and Sakamoto (1988)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Murine Skin	-	-	-	X
Puhvel et al. (1982)	Hairless Mice as Models for Chloracne: a Study of Cutaneous Changes Induced by Topical Application of Established Chloracnegens	X	-	-	X
Puhvel et al. (1991)	Vitamin A Deficiency and the Induction of Cutaneous Toxicity in Murine Skin by TCDD	-	-	-	X
Ramakrishna et al. (2002)	Decrease in K-ras p21 and Increase in Raf1 and Activated Erk1 and 2 in Murine Lung Tumors Initiated by N-nitrosodimethylamine and Promoted by 2,3,7,8-TCDD-IP Injection	-	-	-	X
Randerath et al. (1988)	Organ-specific Effects of Long-term Feeding of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and 1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin on I-compounds in Hepatic and Renal DNA of Female Sprague-Dawley Rats	-	X	-	-
Render et al. (2000)	Proliferation of Periodontal Squamous Epithelium in Mink Fed 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Render et al. (2001)	Squamous Epithelial Proliferation in the Jaws of Mink Fed Diets Containing 3,3',4,4',5-Pentachlorobiphenyl (PCB 126) or 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Rhile et al. (1996)	Role of Fas Apoptosis and MHC Genes in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-induced Immunotoxicity of T Cells	-	X	-	-
Rice (1997)	Effect of Postnatal Exposure to a PCB Mixture in Monkeys on Multiple Fixed Internal-fixed Ratio Performance	-	-	X	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Rice (1999)	Effect of Exposure to 3,3',4,4',5-Pentachlorobiphenyl (PCB 126) Throughout Gestation and Lactation on Development and Spatial Delayed Alternation Performance in Rats	-	-	X	-
Rice and Hayward (1998)	Lack of Effect of 3,3'4,4',5-Pentachlorobiphenyl (PCB 126) Throughout Gestation and Lactation on Multiple Fixed Interval-fixed Ratio and DRL Performance in Rats	-	-	X	-
Rice and Hayward (1999)	Effects of Exposure to 3,3',4,4',5-Pentachlorobiphenyl (PCB 126) Throughout Gestation and Lactation on Behavior (Concurrent Random Interval-random Interval and Progressive Ratio Performance) in Rats	-	-	X	-
Riecke et al. (2002)	Low Doses of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Increase Transforming Growth Factor [TGF] β and Cause Myocardial Fibrosis In Marmosets (*Callithrix jacchus*)-Subcutaneous Exposure	-	-	-	X
Rier et al. (1993)	Endometriosis in Rhesus Monkeys (*Macaca mulata*) Following Chronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
Rier et al. (1995)	Immunoresponsiveness in Endometriosis: Implications of Estrogenic Toxicants	-	-	X	-
Rier et al. (2001a)	Increased Tumor Necrosis Factor-α Production by Peripheral Blood Leukocytes from TCDD-exposed Rhesus Monkeys	-	X	-	-
Rifkind and Muschick (1983)	Benoxaprofen Suppression of Polychlorinated Biphenyl Toxicity Without Alteration of Mixed Function Oxidase Function	-	-	X	-
Roby (2001)	Alterations in Follicle Development, Steroidogenesis, and Gonadotropin Receptor Binding in a Model of Ovulatory Blockade	-	X	-	-
Roman and Peterson (1998)	In Utero and Lactational Exposure of the Male Rat to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Impairs Prostate Development	-	X	-	-
Roman et al. (1995)	In Utero and Lactational Exposure of the Male Rat to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: Impaired Prostate Growth and Development Without Inhibited Androgen Production	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Roman et al. (1998)	In Utero and Lactational Exposure of the Male Rat to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Impairs Prostate Development. 1. Effects on Gene Expression	-	X	-	-
Roman et al. (1998)	In Utero and Lactational Exposure of the Male Rat to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Impairs Prostate Development. 2. Effects on Growth and Cytodifferentiation	-	X	-	-
Romkes and Safe (1988)	Comparative Activities of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Progesterone as Antiestrogens in the Female Rat Uterus	-	-	-	X
Rosenthal et al. (1989)	Characteristics of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Induced Endotoxin Hypersensitivity: Association with Hepatotoxicity	-	X	-	-
Rozman et al. (1984)	Effect of Thyroidectomy and Thyroxine on 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-induced Toxicity	-	-	X	-
Russell et al. (1988)	Hypothalamic Site of Action of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	-	-	X
Russo and Russo (1978)	Developmental Stage of the Rat Mammary Gland as Determinant of its Susceptibility to 7,12-Dimethylbenz[a]anthracene	-	-	X	-
Ryo et al. (2006)	Germ-line Mutations at a Mouse ESTR (Pc-3) Locus and Human Microsatellite Loci-IP Injection	-	-	-	X
Salisbury and Marcinkiewicz (2002)	In Utero and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and 2,3,4,7,8-Pentachlorodibenzofuran Reduces Growth and Disrupts Reproductive Parameters in Female Rats	-	X	-	-
Sanders et al. (1988)	Thyroid and Liver Trophic Changes in Rats Secondary to Liver Microsomal Enzyme Induction Caused by an Experimental Leukotriene Antagonist (L-649,923)	-	-	X	-
Santostefano et al. (1998)	A Pharmacodynamic Analysis of TCDD-induced Cytochrome P450 Gene Expression in Multiple Tissues: Dose- and Time-dependent Effects	-	X	-	-
Schantz et al. (1979)	Toxicological Effects Produced in Nonhuman Primates Chronically Exposed to Fifty Parts per Trillion 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Schantz et al. (1991)	Effects of Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Spatial Learning and Memory and Locomotor Activity in Rats	-	X	-	-
Schantz et al. (1995)	Spatial Learning Deficits in Adult Rats Exposed to Ortho-substituted PCB Congeners During Gestation and Lactation	-	-	X	-
Schantz et al. (1997)	Long-term Effects of Developmental Exposure to 2,2',3,5',6-Pentachlorobiphenyl (PCB 95) on Locomotor Activity, Spatial Learning and Memory and Brain Ryanodine Binding	-	-	X	-
Schrenk et al. (1994)	Promotion of Preneoplastic Foci in Rat Liver with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, 1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin and a Defined Mixture of 49 Polychlorinated Dibenzo-*p*-dioxins	-	-	-	X
Schulz et al. (2000)	Identification of Theta-class Glutathione S-transferase in Liver Cytosol of the Marmoset Monkey	-	-	X	-
Schuur et al. (1997)	Extrathyroidal Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Thyroid Hormone Turnover in Male Sprague-Dawley Rats	-	-	-	X
Scott et al. (2001)	Exposure to the Dioxin 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Induces Squamous Metaplasia in the Endocervix of *Cynomolgus Macaques*	-	X	-	-
Seefeld and Peterson (1984)	Digestible Energy and Efficiency of Feed Utilization in Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Seefeld et al. (1979)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Indocyanine Green Blood Clearance in Rhesus Monkeys	-	X	-	-
Seefeld et al. (1984a)	Body Weight Regulation in Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Seefeld et al. (1984b)	Characterization of the Wasting Syndrome in Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Seegal et al. (1990)	Lightly Chlorinated Ortho-substituted PCB Congeners Decrease Dopamine in Nonhuman Primate Brain and in Tissue Culture	-	-	X	-
Seegal et al. (1997)	Effects of In Utero and Lactational Exposure of the Laboratory Rat to 2,4,2',4'- and 3,4,3',4'-Tetrachlorobiphenyl on Dopamine Function	-	-	X	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Senft et al. (2002)	Mitochondrial Reactive Oxygen Production is Dependent on the Aromatic Hydrocarbon Receptor-IP Injection	-	-	-	X
Seo and Meserve (1995)	Effects of Maternal Ingestion of Aroclor 1254 (PCB) on the Developmental Pattern of Oxygen Consumption and Body Temperature in Neonatal Rats	-	-	X	-
Seo et al. (1999)	Learning and Memory in Rats Gestationally and Lactationally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Seo et al. (2000)	Radial Arm Maze Performance in Rats Following Gestational and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Sewall et al. (1995b)	TCDD Reduces Rat Hepatic Epidermal Growth Factor Receptor: Comparison of Binding, Immunodetection, and Autophosphorylation	-	X	-	-
Shepherd et al. (2000)	The Effects of TCDD on the Activation of Ovalbumin (OVA)-Specific DO11.10 Transgenic CD4+ T-cells in Adoptively Transferred Mice	-	X	-	-
Shepherd et al. (2001)	Anti-CD40 Treatment of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-Exposed C57Bl/6 Mice Induces Activation of Antigen Presenting Cells Yet Fails to Overcome TCDD-Induced	-	X	-	-
Shirota et al. (2007)	Internal Dose-effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Gonadotropin-primed Weanling Rat Model	-	X	-	-
Shiverick and Muther (1982)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Serum Concentrations and the Uterotrophic Action of Exogenous Estrone in Rats	-	X	-	-
Shiverick and Muther (1983)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Effects on Hepatic Microsomal Steroid Metabolism and Serum Estradiol of Pregnant Rats	-	X	-	-
Shon et al. (2002)	Effect of Chitosan Oligosaccharide on 2,3,7,8-Tetrachlorodibenzop-dioxin-Induced Oxidative Stress in Mice	-	X	-	-
Silkworth and Antrim (1985)	Relationship Between Ah Receptor-mediated Polychlorinated Biphenyl (PCB)-induced Humoral Immunosuppression and Thymic Atrophy	-	-	X	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Silkworth et al. (1984)	Correlations Between Polychlorinated Biphenyl Immunotoxicity, the Aromatic Hydrocarbon Locus, and Liver Microsomal Enzyme Induction in C57Bl/6 and DBA/2 Mice	-	-	X	-
Silkworth et al. (1989)	Teratology of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in a Complex Environmental Mixture From the Love Canal	-	-	X	-
Silkworth et al. (1997)	Tumor responses, PCB Tissue Concentrations and PCB Hepatic Binding in S-D Rats Fed Aroclors 1016, 1242, 1254 or 1260	-	-	X	-
Sills et al. (1994)	Tumor-Promoting Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin and Phenobarbital in Initiated Weanling Sprague-Dawley Rats: A Quantitative, Phenotypic, and ras p21 Protein Study	-	-	X	-
Simanainen et al. (2004a)	Adult 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) Exposure and Effects on Male Reproductive Organs in Three Differentially TCDD-Susceptible Rat Lines	-	X	-	-
Slezak et al. (1999)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-Mediated Oxidative Stress in CYP1A2 Knockout (CYP1A2-/-) Mice	-	X	-	-
Slezak et al. (2002)	TCDD-Mediated Oxidative Stress in Male Rat Pups Following Perinatal Exposure	-	X	-	-
Sloop and Lucier (1987)	Dose-dependent Elevation of Ah Receptor Binding by TCDD in Rat Liver	-	X	-	-
Smialowicz et al. (1997)	Opposite Effects of 2,2',4,4',5,5'-Hexachlorobiphenyl and 2,3,7,8-TCDD on the Antibody Response to Sheep Erythrocytes in Mice	-	-	X	-
Smith et al. (1981)	Hepatic Toxicity and Uroporphyrinogen Decarboxylase Activity Following a Single Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin to Mice	-	X	-	-
Smith et al. (1998)	Interaction Between Iron Metabolism and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Mice with Variants of the AhR Gene: a Hepatic Oxidative Mechanism	-	-	X	-
Sommer et al. (2005)	Early Developmental 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin Exposure Decreases Chick Embryo Heart Chronotropic Response to Isoproterenol but Not to Agents Affecting Signals Downstream of the Beta-Adrenergic Receptor	X	-	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Staples et al. (1998)	Thymic Alterations Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin are Strictly Dependent on Aryl Hydrocarbon Receptor Activation in Hematopoietic Cells	-	-	-	X
Stohs et al. (1983)	Lipid Peroxidation as a Possible Cause of TCDD Toxicity	-	X	-	-
Sugihara et al. (2001)	Aryl Hydrocarbon Receptor (AhR)-Mediated Induction of Xanthine Oxidase/Xanthine Dehydrogenase Activity by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Sweeney et al. (1979)	Iron Deficiency Prevents Liver Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	X	-	-	-
Takagi et al. (2000)	Pathogenesis of Cleft Palate in Mouse Embryos Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Tani et al. (2004)	Follicular Epithelial Cell Hypertrophy Induced by Chronic Oral Administration of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Female Harlan Sprague-Dawley Rats	-	X	-	-
Teske et al. (2005)	Activation of the Aryl Hydrocarbon Receptor Increases Pulmonary Neutrophilia and Diminishes Host Resistance to Influenza A Virus	-	X	-	-
Thackaberry et al. (2005a)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin on Murine Heart Development: Alteration in Fetal and Postnatal Cardiac Growth, and Postnatal Cardiac Chronotropy	-	X	-	-
Thackaberry et al. (2005b)	Toxicogenomic Profile of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in the Murine Fetal Heart: Modulation of Cell Cycle and Extracellular Matrix Genes	-	X	-	-
Theobald and Peterson (1997)	In Utero and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-rho-dioxin: Effects on Development of the Male and Female Reproductive System of the Mouse	-	X	-	-
Theobald et al. (2000)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Inhibits Lumen Cell Differentiation and Androgen Responsiveness of the Ventral Prostate Without Inhibiting Prostatic 5α-Dihrdrotestosterone or Testicular Androgen Production in Rat Offspring	-	X	-	-
Thigpen et al. (1975)	Increased Susceptibility to Bacterial Infection as a Sequela of Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Thomas and Hinsdill (1979)	The Effect of Perinatal Exposure to Tetrachlorodibenzo-*p*-dioxin on the Immune Response of Young Mice	-	X	-	-
Thornton et al. (2001)	Mutagenicity of TCDD in Big Blue® Transgenic Rats	-	X	-	-
Thornton et al. (2004)	The Dioxin TCDD Protects Against Aflatoxin-induced Mutation in Female Rats, but Not in Male Rats	-	X	-	-
Thunberg (1984)	Effects of TCDD on Vitamin A and its Relation to TCDD Toxicity	-	X	-	-
Thunberg and Hakansson (1983)	Vitamin A (retinol) Status in the Gunn Rat: the Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	X	-	-	-
Thunberg et al. (1979)	Vitamin A (Retinol) Status in the Rat After a Single Oral Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Tilson et al. (1979)	The Effects of Polychlorinated Biphenyls Given Prenatally on the Neurobehavioral Development of Mice	-	-	X	-
Timms et al. (2002)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Interacts with Endogenous Estradiol to Disrupt Prostate Gland Morphogenesis in Male Rat Fetuses	-	X	-	-
Tomar and Kerkvliet (1991)	Reduced T helper Cell Function in Mice Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Tritscher et al. (1995)	Persistence of TCDD-induced Hepatic Cell Proliferation and Growth of Enzyme Altered Foci After Chronic Exposure Followed by Cessation of Treatment in DEN Initiated Female Rats	-	X	-	-
Tritscher et al. (1996)	Increased Oxidative DNA Damage in Livers of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Treated Intact but Not Ovariectomized Rats	-	X	-	-
Tritscher et al. (1999)	TCDD-induced Lesions in Rat Lung After Chronic Oral Exposure. Dioxin '99: 19th International Symposium on Halogenated Environmental Organic Pollutants and POPs	-	X	-	-
Tritscher et al. (2000)	Induction of Lung Lesions in Female Rats following Chronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Truelove et al. (1982)	Polychlorinated Biphenyl Toxicity in the Pregnant Cynomolgus Monkey: A Pilot Study	-	-	X	-
Tsutsumi (2000)	Effects of Endocrine Disruptors on Preimplantation Embryo Development	X	-	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Tucker et al. (1986)	Suppression of B Cell Differentiation by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Tuner and Collins (1983)	Liver Morphology in Guinea Pigs Administered Either Pyrolysis Products of a Polychlorinated Biphenyl Transformer Fluid or 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
Unkila et al. (1994a)	Characterization of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Induced Brain Serotonin Metabolism in Rat	-	X	-	-
Unkila et al. (1994b)	Dose Response and Time Course of Alterations in Tryptophan Metabolism by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in the Most TCDD- susceptible and the Most TCDD-resistant Rat Strain: Relationship with TCDD Lethality	-	X	-	-
Unkila et al. (1995)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Tryptophan and Glucose Homeostasis in the Most TCDD-susceptible and the Most TCDD-resistant Species, Guinea Pigs and Hamsters	-	X	-	-
Unkila et al. (1998)	Body Weight Loss and Changes in Tryptophan Homeostasis by Chlorinated Dibenzo-*p*-dioxin Congeners in the Most TCDD-Susceptible and the Most TCDD-resistant Rat Strain	X	-	-	-
Ushinohama et al. (2001)	Impaired Ovulation by 2,3,7,8 Tetrachlorodibenzo-*p*-dioxin (TCDD) in Immature Rats Treated with Equine Chorionic Gonadotropin	-	X	-	-
Van Birgelen et al. (1996)	Synergistic Effect of 2,2',4,5,5'-Hexachlorobiphenyl and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Hepatic Porphyrin Levels in the Rat	-	X	-	-
Van Birgelen et al. (1999b)	Dose and Time-response of TCDD in Tg.AC Mice After Dermal and Oral Exposure. Dioxin '99: 19th International Symposium on Halogenated Environmental Organic Pollutants and POPs	-	X	-	-
Van Birgelen et al. (1999a)	Toxicity of 3,3',4,4'-Tetrachloroazobenzene in Rats and Mice	-	X	-	-
Van den Berg et al. (1987)	Transfer of Polychlorinated Dibenzo-*p*-dioxins and Dibenzofurans to Fetal and Neonatal Rats	-	-	X	-
Vanden Heuvel (1994)	Accumulation of Polychlorinated Dibenzo-*p*-dioxins and Dibenzofurans in Liver of Control Laboratory Rats	-	-	X	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Van der Kolk (1992)	Interactions of 2,2',4,4',5,5'- Hexachlorobiphenyl and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in a Subchronic Feeding Study in the Rat	-	-	X	-
Van Logten et al. (1980)	Role of the Endocrine System in the Action of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on the Thymus	-	X	-	-
Van Miller et al. (1977)	Increased Incidence of Neoplasms in Rats Exposed to Low Levels of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Vecchi et al. (1983)	Immunosuppressive Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Strains of Mice with Different Susceptibility	-	X	-	X
Vezina et al. (2008)	Dioxin Causes Ventral Prostate Agenesis by Disrupting Dorsoventral Patterning in Developing Mouse Prostate	-	X	-	-
Viluksela et al. (1995)	Tissue-specific Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on the Activity of Phosphoeno/Pyruvate Carboxykinase (PEPCK) in Rats	-	X	-	-
Viluksela et al. (1997b)	Subchronic/Chronic Toxicity of 1,2,3,4,6,7,8-Heptachlorodibenzop-dioxin (HpCDD) in Rats: Part I. Design, General Observations, Hematology, and Liver Concentrations	-	X	-	-
Viluksela et al. (1997a)	Subchronic/Chronic Toxicity of 1,2,3,4,6,7,8-Heptachlorodibenzop-dioxin (HpCDD) in Rats: Part II. Biochemical Effects	-	X	-	-
Viluksela et al. (1998)	Subchronic/Chronic Toxicity of Four Chlorinated Dibenzo-*p*-dioxins in Rats. Part I. Design, General Observations, Hematology, and Liver Concentrations	-	-	X	-
Viluksela et al. (1999)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Liver Phosphoenolpyruvate Carboxylase (PEPCK) Activity, Glucose Homeostasis and Plasma Amino Acid Concentrations in the Most TCDD-susceptible and the Most TCDD-resistant Rat Strains	-	X	-	-
Viluksela et al. (2000)	Liver Tumor-promoting Activity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in TCDD-sensitive and TCDD-resistant Rat Strains	X	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Vogel et al. (2003)	The Use of c-src Knockout Mice for the Identification of the Main Toxic Signaling Pathway of TCDD to Induce Wasting Syndrome	-	-	-	X
Vogel et al. (2007)	Modulation of the Chemokines KC and MCP-1 by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Mice	-	-	-	X
Vorderstrasse and Kerkvliet (2001)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Affects the Number and Function of Murine Splenic Dendritic Cells and Their Expression of Accessory Molecules	-	X	-	-
Vorderstrasse and Lawrence (2006)	Protection Against Lethal Challenge with Streptococcus Pneumoniae is Conferred by Aryl Hydrocarbon Receptor Activation but is Not Associated with an Enhanced Inflammatory Response	X	-	-	-
Vorderstrasse et al. (2001)	Aryl Hydrocarbon Receptor-deficient Mice Generate Normal Immune Responses to Model Antigens and are Resistant to TCDD-induced Immune Suppression	X	X	X	-
Vorderstrasse et al. (2003)	Examining the Relationship Between Impaired Host Resistance and Altered Immune Function in Mice Treated with TCDD	X	-	-	-
Vorderstrasse et al. (2004)	Developmental Exposure to the Potent Aryl Hydrocarbon Receptor Agonist 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin Impairs the Cell-Mediated Immune Response to Infection with Influenza A Virus, but Enhances Elements of Innate Immunity	-	X	-	-
Vorderstrasse et al. (2006)	A Dose-response Study of the Effects of Prenatal and Lactational Exposure to TCDD on the Immune Response to Influenza A Virus	-	X	-	-
Vos and Moore (1974)	Suppression of Cellular Immunity in Rats and Mice by Maternal Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Vos et al. (1974)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in C57B1/6 Mice	-	X	-	-
Vos et al. (1978)	Studies on 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Immune Suppression and Decreased Resistance to Infection: Endotoxin Hypersensitivity, Serum Zinc Concentrations and Effect of Thymosin Treatment	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Waern et al. (1991)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in the Lactating Rat on Maternal and Neonatal Vitamin A Status and Hepatic Enzyme Induction: A Dose-Response Study	-	-	-	X
Wagner et al. (2001)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Natural Immunity: Lack of an Effect on the Complement System in a Guinea Pig Model	-	-	-	X
Wahba et al. (1988)	Induction of Hepatic DNA Single Strand Breaks in Rats by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Wahba et al. (1989)	Factors Influencing the Induction of DNA Single Strand Breaks in Rats by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Wahba et al. (1990a)	Altered Hepatic Iron Distribution and Release in Rats After Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Wahba et al. (1990b)	Desferrioxamine-induced Alterations in Hepatic Iron Distribution, DNA Damage, and Lipid Peroxidation in Control and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Rats	-	-	X	-
Walisser et al. (2004)	Patent Ductus Venosus and Dioxin Resistance in Mice Harboring a Hypomorphic ARNT Allele	-	X	-	-
Walker et al. (1995)	Rat CYP1B1: an Adrenal Cytochrome P450 that Exhibits Sex-dependent Expression in Livers and Kidneys of TCDD-treated Animals	-	X	-	-
Walker et al. (1997)	Hepatocarcinogenesis in a Sprague-Dawley Rat Initiation/Promotion Model Following Discontinuous Exposure to TCDD	-	X	-	-
Walker et al. (1998a)	Differences in Kinetics of Induction and Reversibility of TCDD-Induced Changes in Cell Proliferation and CYP1A1 Expression in Female Sprague-Dawley Rat Liver	-	X	-	-
Walker et al. (1998b)	Induction and Localization of Cytochrome P450 1B1 (CYP1B1) Protein in the Livers of TCDD-treated Rats: Detection Using Polyclonal Antibodies Raised to Histidine-tagged Fusion Proteins Produced and Purified From Bacteria	-	X	-	-
Walker et al. (1999)	Characterization of the Dose-response of CYP1B1, CYP1A1, and CYP1A2 in the Liver of Female Sprague-Dawley Rats Following Chronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	-	X

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Walker et al. (2004)	Persistent Suppression of Contact Hypersensitivity, and Altered T-cell Parameters in F344 Rats Exposed Perinatally to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Warren et al. (2000)	Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Suppresses the Humoral and Cell-mediated Immune Responses to Influenza A Virus Without Affecting Cytolytic Activity in the Lung	X	-	-	-
Weber and Birnbaum (1985)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and 2,3,7,8-Tetrachlorodibenzofuran (TCDF) in Pregnant C57BL/6 Mice: Distribution to the Embryo and Excretion	-	X	-	X
Weber et al. (1985)	Teratogenic Potency of TCDD, TCDF and TCDD-TCDF Combinations in C57BL/6N Mice	-	X	-	X
Weber et al. (1994)	Reduced Activity of Tryptophan 2,3,-Dioxygenase in the Liver of Rats Treated with Chlorinated Dibenzo-*p*-dioxins (CDDs): Dose-responses and Structure-activity Relationship	-	X	-	-
Weinand-Harer et al. (1997)	Behavioral Effects of Maternal Exposure to an Ortho-chlorinated or a Coplanar PCB Congener in Rats	-	-	X	-
Weinstein et al. (2008)	Mid-gestation Exposure of C57BL/6 Mice to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Causes Postnatal Morphologic Changes in the Spleen and Liver	-	X	-	-
Weissberg and Zinkl (1973)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Upon Hemostasis and Hematologic Function in the Rat	-	X	-	-
Wheatley (1968)	Enhancement and Inhibition of the Induction by 7,12-Dimethylbenz(a)anthracene of Mammary Tumors in Female Sprague-Dawley Rats	-	-	X	-
Widholm et al. (2003)	Effects of Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin on Spatial and Visual Reversal Learning in Rats	-	X	-	-
Wolf et al. (1999a)	Administration of Potentially Antiandrogenic Pesticides (Procymidone, Linuron, Iprodione, Chlozolinate, *p*,*p*'-DDE, and Ketoconazole) and Toxic Substances (Dibutyl- and Diethylhexyl Phthalate, PCB 169, and Ethane Dimethane Sulphonate) During Sexual Differentiation Produces Diverse Profiles of Reproductive Malformations in the Male Rat	-	-	X	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Wolf et al. (1999b)	Gestational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Severely Alters Reproductive Function of Female Hamster Offspring [In Process Citation]	-	X	-	-
Wu et al. (2004)	Exposure of Mouse Preimplantation Embryos to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Alters the Methylation Status of Imprinted Genes H19 and Igf2	X	-	-	-
Wyde et al. (1999)	Influence of Ovariectomy and 17 ß-Estradiol on the Promotion of Altered Hepatocellular Foci by TCDD. Dioxin '99: 19th International Symposium on Halogenated Environmental Organic Pollutants and POPs	X	-	-	-
Wyde et al. (2000)	Toxicity of Chronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Diethylnitrosamine-initiated Ovariectomized Rats Implanted with Subcutaneous 17 Beta-estradiol Pellets	X	-	-	-
Wyde et al. (2001a)	Induction of Hepatic 8-Oxo-deoxyguanosine adducts by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Sprague-Dawley Rats is Female-specific and Estrogen-dependent	X	-	-	-
Wyde et al. (2001b)	Regulation of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Tumor Promotion by 17 Beta-estradiol in Female Sprague-Dawley Rats	X	-	-	-
Wyde et al. (2002)	Promotion of Altered Hepatic Foci by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and 17Beta-estradiol in Male Sprague-Dawley Rats	-	-	X	-
Wyde et al. (2004)	Oral and Dermal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Induces Cutaneous Papillomas and Squamous Cell Carcinomas in Female Hemizygous Tg.AC Transgenic Mice	-	X	-	-
Yang and Foster (1997)	Continuous Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Inhibits the Growth of Surgically Induced Endometriosis in the Ovariectomized Mouse Treated with High Dose Estradiol	X	-	-	X
Yang et al. (1983)	Effects of Halogenated Dibenzo-*p*-dioxins on Plasma Disappearance and Biliary Excretion of Ouabain in Rats	-	X	-	-
Yang et al. (1994)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Pulmonary Influenza Virus Titer and Natural Killer (NK) Activity in Rats	-	X	-	-

Table D-2. Noncancer animal studies not selected for TCDD dose-response analyses and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Yang et al. (2005)	Inhibitory Effects of vitamin A on TCDD-induced Cytochrome P-450 1A1 Enzyme Activity and Expression	-	X	-	-
Yasuda et al. (1999)	Palatal rugae Anomalies Induced by Dioxins in Mice	-	X	-	-
Ye and Leung (2008)	Effect of Dioxin Exposure on Aromatase Expression in Ovariectomized Rats	-	X	-	-
Yoon et al. (2000)	Teratological Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD): Induction of Cleft Palate in the DDY and C57BL/6 Mouse	-	X	-	-
Yoon et al. (2001a)	Hemopoietic Cell Kinetics After Intraperitoneal Single Injection of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Mice-IP Injection	-	-	-	X
Yoon et al. (2001b)	Transgene Expression of Thioredoxin (TRX/ADF) Protects Against 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD)-Induced Hematotoxicity-IP injection	-	-	-	X
Yoon et al. (2006)	Gene Expression Profile by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Liver of Wild-type (Ahr +/+) and Aryl Hydrocarbon Receptor Deficient (Ahr -/-) Mice-IP Injection	-	-	-	X
Zhu et al. (2008)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Administration and High-fat Diet on the Body Weight and Hepatic Estrogen Metabolism in Female C3H/HeN Mice-IP Injection	-	-	-	X
Zingeser (1979)	Anomalous Development of the Soft Palate in Rhesus Macaques (*Macaca mulatta*) Prenatally Exposed to 3,4,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
Zinkl et al. (1973)	Hematologic and Clinical Chemistry Effects of 2,3,7,8-Tetrachlorodi-benzo-*p*-dioxin in Laboratory Animals	-	X	-	-
	Totals	66	370	140	135

Table D-3. Cross-species concordance of male reproductive effects

Study	Species	Specific endpoint	Endpoint category	Administered dose (ng/kg-day)		Human-equivalent dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(1) Bell et al. (2007c)	Rat	Delayed balanopreputial separation	Altered sexual development	2.40E+00	8.00E+00	8.85E-02	3.23E-01
		Increased ventral prostate weight	Organ weight changes	2.40E+00	8.00E+00	8.85E-02	3.23E-01
		Higher proportion of abnormal sperm	Sperm effects	8.00E+00	4.60E+01	3.23E-01	2.05E+00
(2) Ishihara et al. (2007)	Mouse	Altered sex ratio (decreased percentage of males)	Altered sex ratio	1.00E-01	1.00E+02	4.91E-05	4.96E-01
(3) Ikeda et al. (2005b)	Rat	Decreased ventral prostate weight	Organ weight changes	–	1.65E+01	–	2.75E+00
		Altered sex ratio (decreased percentage of males)	Altered sex ratio	–	1.65E+01	–	2.75E+00
(4) Kociba et al. (1976)	Rat	Increased testes weight	Organ weight changes	7.14E+01	7.14E+02	3.03E+00	3.19E+01
(5) Latchoumycandane and Mathur (2002)	Rat	Decreased daily sperm production	Sperm effects	–	1.00E+00	–	1.62E-02
		Decreased testis, epididymis, seminal vesicle, and ventral prostate weights	Organ weight changes	–	1.00E+00	–	1.62E-02
(6) Mocarelli et al. (2008)	Human	Decreased sperm count, progressive sperm motility, and total number of motile sperm	Sperm effects	–	–	–	2.01E-02
(7) Ohsako et al. (2001)	Rat	Decreased anogenital distance	Altered sexual development	1.25E+01	5.00E+01	2.74E-02	1.78E-01
		Decreased urogenital complex and ventral prostate weights	Organ weight changes	5.00E+01	2.00E+02	1.78E-01	1.04E+00
(8) Simanainen et al. (2004b)	Rat	Decreased daily sperm production	Sperm effects	1.00E+02	3.00E+02	4.33E-01	1.70E+00
		Decreased ventral prostate weight	Organ weight changes	3.00E+02	1.00E+03	1.70E+00	6.92E+00
		Epididymal degeneration	Organ toxicity	3.00E+02	1.00E+03	1.70E+00	6.92E+00

[a] Human equivalent dose (HED) for rat and mouse studies based on Emond rodent and human PBPK models described in Section 3.3.6.

Table D-4. Cross-species concordance of female reproductive effects

Study	Species	Specific endpoint	Endpoint category	Administered dose (ng/kg-day)		Human-equivalent dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(1) Bowman et al.(1989a; 1989b)	Monkey	Reduced reproductive rate	Reduced fertility	1.20E-01	6.70E-01	8.22E-03[b]	4.59E-02 [b]
		Decreased days of offspring survival	Decreased offspring survival	1.20E-01	6.70E-01	8.22E-03[b]	4.59E-02 [b]
(2) Eskenazi et al. (2002).	Human	Increased length of menstrual period	Altered menstrual cycle	–	–	–	3.11E+02
(3) Franczak et al. (2006)	Rat	Altered estrus cyclicity	Altered menstrual cycle	–	7.14E+00	–	3.18E-01
(4) Hutt et al. (2008)	Rat	Lower proportion of morphologically normal preimplantation embryos	Early embryo loss	–	7.14E+00	–	2.52E-01
(5) Li et al. (1997)	Rat	Increased serum FSH	Altered hormone levels	3.00E+00	1.00E+01	2.90E-03	1.67E-02
		Increased serum LH	Altered hormone levels	1.00E+02	3.00E+02	3.78E-01	1.48E+00
(6) Li et al. (2006)	Mouse	Increased serum estradiol, decreased serum progesterone	Altered hormone levels	–	2.00E+00	–	1.58E-03
		Early embryo loss	Early embryo loss	2.00E+00	5.00E+01	1.58E-03	1.31E-01
		Decreased uterine weight	Organ weight changes	2.00E+00	5.00E+01	1.58E-03	1.31E-01
(7) Murray et al. (1979)	Rat	Reduced fertility	Reduced fertility	1.00E+00	1.00E+01	2.89E-02	3.79E-01
		Reduced neonatal survival	Decreased offspring survival	1.00E+00	1.00E+01	2.89E-02	3.79E-01
(8) Shi et al. (2007)	Rat	Decreased serum estradiol	Altered hormone levels	1.43E-01	7.14E-01	4.47E-03	2.69E-02
		Accelerated reproductive senescence with normal cyclicity	Altered menstrual cycle	7.14E-01	7.14E+00	2.69E-02	3.18E-01
		Delayed vaginal opening	Altered sexual development	7.14E+00	2.86E+01	3.18E-01	1.34E+00
(9) Smith et al. (1976)	Mouse	Increased percentage of resorptions per implantations	Late embryo loss	1.00E+02	1.00E+03	5.24E-01	7.61E+00
(10) Sparschu et al. (2008; 1971)	Rat	Decreased mean number of viable fetuses per litter	Late embryo loss	1.25E+02	5.00E+02	1.73E+00	8.03E+00

[a] HED for rat and mouse studies based on Emond rodent and human PBPK models described in Section 3.3.6.
[b] HED based on 1st order body burden model described in Section 3.3.4.2.

Table D-5. Cross-species concordance of thyroid effects

Study	Species	Specific endpoint	Endpoint category	Administered dose (ng/kg-day)		Human-equivalent dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(1) Baccarelli et al. (2008)	Human	Elevated blood TSH in male and female neonates	Altered hormone levels	–	–	–	2.00E-02
(2) Chu et al. (2007)	Rat	Reduced follicles, reduced colloid density, and increased epithelial height in females	Histopathological lesions	2.50E+02	1.00E+03	7.03E+00	2.96E+01
(3) Crofton et al. (2005)	Rat	Reduced serum T4 levels in females	Altered hormone levels	3.00E+01	1.00E+02	1.69E-01	7.43E-01
(4) NTP (2006)	Rat	Reduced serum free and total T4 levels at 14 and 31 weeks	Altered hormone levels	7.14E+00	1.57E+01	4.09E-01	9.14E-01
		Increased serum total T3 levels at 53 weeks	Altered hormone levels	7.14E+00	1.57E+01	4.34E-01	9.63E-01
		Follicular cell hypertrophy at 2 years	Histopathological lesions	7.14E+00	1.57E+01	4.53E-01	9.98E-01
		Increased serum TSH levels in females	Altered hormone levels	1.57E+01	3.29E+01	9.98E-01	2.09E+00
(5) Seo et al. (1995)	Rat	Decreased serum T4 and thymus weight	Altered hormone levels	2.50E+01	1.00E+02	1.67E-01	9.15E-01
(6) Sewall et al. (1995a)	Rat	Decreased serum T4	Altered hormone levels	5.16E+00[b]	3.57E+01	1.80E-01[b]	1.71E+00
		Increased serum TSH levels in females	Altered hormone levels	3.57E+01	1.25E+02	1.71E+00	6.30E+00
(7) Simanainen et al. (2002)	Rat	Decreased serum T4	Altered hormone levels	1.00E+02	3.00E+02	4.26E-01	1.67E+00
(8) VanBirgelen et al. (1995a)	Rat	Reduced serum free and total T4 levels in females	Altered hormone levels	2.64E+01	4.69E+01	1.05E+00	1.93E+00

[a] HED for rat and mouse studies based on Emond rodent and human PBPK models described in Section 3.3.6.
[b] Benchmark dose lower confidence bound (BMDL) used instead of NOAEL.

Table D-6. Cross-species concordance of developmental dental effects

Study	Species	Specific endpoints	Endpoints category	Administered dose (ng/kg-day)		Human-equivalent dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(1) Alaluusua et al. (2004)	Human	Developmental dental defects	Enamel defects	–	–	4.06E-02	9.00E-01
(2) Kattainen et al. (2001)	Rat	Reduced mesiodistal length of the lower third molar in males and females	Altered tooth morphology	–	3.00E+01	–	9.01E-02
(3) Keller et al. (2008a; 2008b; 2007c)	Mouse	Variation in molar morphology and shape, decreased mandible shape and size in males and females	Altered tooth morphology	–	1.00E+01	–	9.88E-03

[a] HED for rat and mouse studies based on Emond rodent and human PBPK models described in Section 3.3.6.

Table D-7. Cross-species concordance of immune system effects

Study	Species	Specific endpoint	Endpoint category	Administered dose (ng/kg-day)		Human-equivalent dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(1) Chu et al. (2001)	Rat	Decreased relative thymus weight in females	Organ weight changes	2.50E+02	1.00E+03	7.03E+00	2.96E+01
(2) Chu et al. (2007)	Rat	Reduced thymic cortex and increased medullar volume in females	Histopathological lesions	2.50E+01	2.50E+02	5.63E-01	7.03E+00
		Decreased thymus weight in females	Organ weight changes	2.50E+02	1.00E+03	7.03E+00	2.96E+01
(3) DeCaprio et al. (1986)	Guinea pig	Decreased relative thymus weight in males	Organ weight changes	6.10E-01	4.90E+00	4.11E-03 [b]	3.30E-02 [b]
(4) Franc et al. (2001)	Rat	Decreased relative thymus weight in females	Organ weight changes	1.00E+01	3.00E+01	4.49E-01	1.41E+00
(5) Kociba et al. (1976)	Rat	Increased relative spleen and thymus weights in males and females	Organ weight changes	7.14E+01	7.14E+02	3.03E+00	3.19E+01
(6) Kociba et al. (1978)	Rat	Decreased relative thymus weight	Organ weight changes	1.00E+01	1.00E+02	6.34E-01	6.35E+00
		Thymic and splenic atrophy in females	Organ weight changes	1.00E+01	1.00E+02	6.34E-01	6.35E+00
(7) Simanainen et al. (2002)	Rat	Decreased relative thymus weight in females	Organ weight changes	3.00E+02	1.00E+03	1.67E+00	6.80E+00
(8) Simanainen et al. (2003)	Rat	Decreased relative thymus weight	Organ weight changes	1.00E+02	3.00E+02	4.26E-01	1.67E+00
(9) Smialowicz et al. (2004)	Mouse	Decreased antibody response to SRBCs in females	Immunosuppressive effects	3.00E+02	1.00E+03	7.23E-01	3.28E+00
(9) Smialowicz et al. (2004)	Mouse	Decreased thymus weight in females	Organ weight changes	3.00E+03	1.00E+04	1.18E+01	4.35E+01
(10) Smialowicz et al. (2008)	Mouse	Decreased antibody response to SRBCs in females	Immunosuppressive effects	–	1.07E+00	–	6.26E-03
		Decreased relative spleen weight in females	Organ weight changes	1.07E+01	1.07E+02	9.96E-02	1.27E+00
(11) VanBirgelen et al. (1995a)	Rat	Decreased absolute and relative thymus weight in females	Organ weight changes	–	1.35E+01	–	5.14E-01

Table D-7. Cross-species concordance of immune system effects (continued)

Study	Species	Specific endpoint	Endpoint category	Administered dose (ng/kg-day)		Human-equivalent dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(12) Vos et al. (1973)7	Guinea pig	Decreased delayed-type hypersensitivity response to tuberculin	Immunosuppressive effects	1.14E+00	5.71E+00	6.43E-03	3.22E-02
		Decreased relative thymus weight, relative cervical lymph node weight	Organ weight changes	5.71E+00	2.86E+01	3.22E-02	1.61E-01
		Cortical atrophy of the thymus, lymphopenia and thymic degeneration	Histopathological lesions	5.71E+00	2.86E+01	3.22E-02	1.61E-01
(13) White et al. (1986)	Mouse	Decreased serum complement activity in females	Altered immune system components	–	1.00E+01	–	2.77E-02 [b]
		Decreased component hemolytic activity and C3 levels in females	Altered immune system components	1.00E+02	5.00E+02	5.07E-01 [b]	3.27E+00 [b]

[a] HED for rat and mouse studies based on Emond rodent and human PBPK models described in Section 3.3.6.
[b] HED based on 1st order body burden model described in Section 3.3.4.2.

Table D-8. Cross-species concordance of neurological effects

Study	Species	Specific endpoint	Endpoint category	Administered dose (ng/kg-day)		Human-equivalent dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(1) Schantz et al. (1992)	Monkey	Altered social behavior	Neurobehavioral effects	–	1.20E-01	–	8.22E-03 [b]
(2) Hojo et al. (2002)	Rat	Food-reinforced operant behavior in pups	Neurobehavioral effects	–	2.00E+01	–	5.51E-02
(3) Kuchiiwa et al. (2002)	Mouse	Decreased number of serotonin-immunoreactive neurons in the raphe nuclei of males	Histopathological lesions	–	7.00E-01	–	2.75E-03
(4) Markowski et al. (2001)	Rat	Neurobehavioral effects in pups (running, lever press, wheel spinning)	Neurobehavioral effects	–	2.00E+01	–	5.15E-02
(5) Schantz et al. (1996)	Rat	Maze errors	Neurobehavioral effects	–	2.50E+01	–	1.71E-01
(6) Zareba et al. (2002)	Rat	Reduced cortical thickness and altered brain morphometry in males and females	Brain structural alterations	6.00E+01	1.80E+02	2.35E-01	9.54E-01

[a] HED for rat and mouse studies based on Emond rodent and human PBPK models described in Section 3.3.6.
[b] HED based on 1st order body burden model described in Section 3.3.4.2.

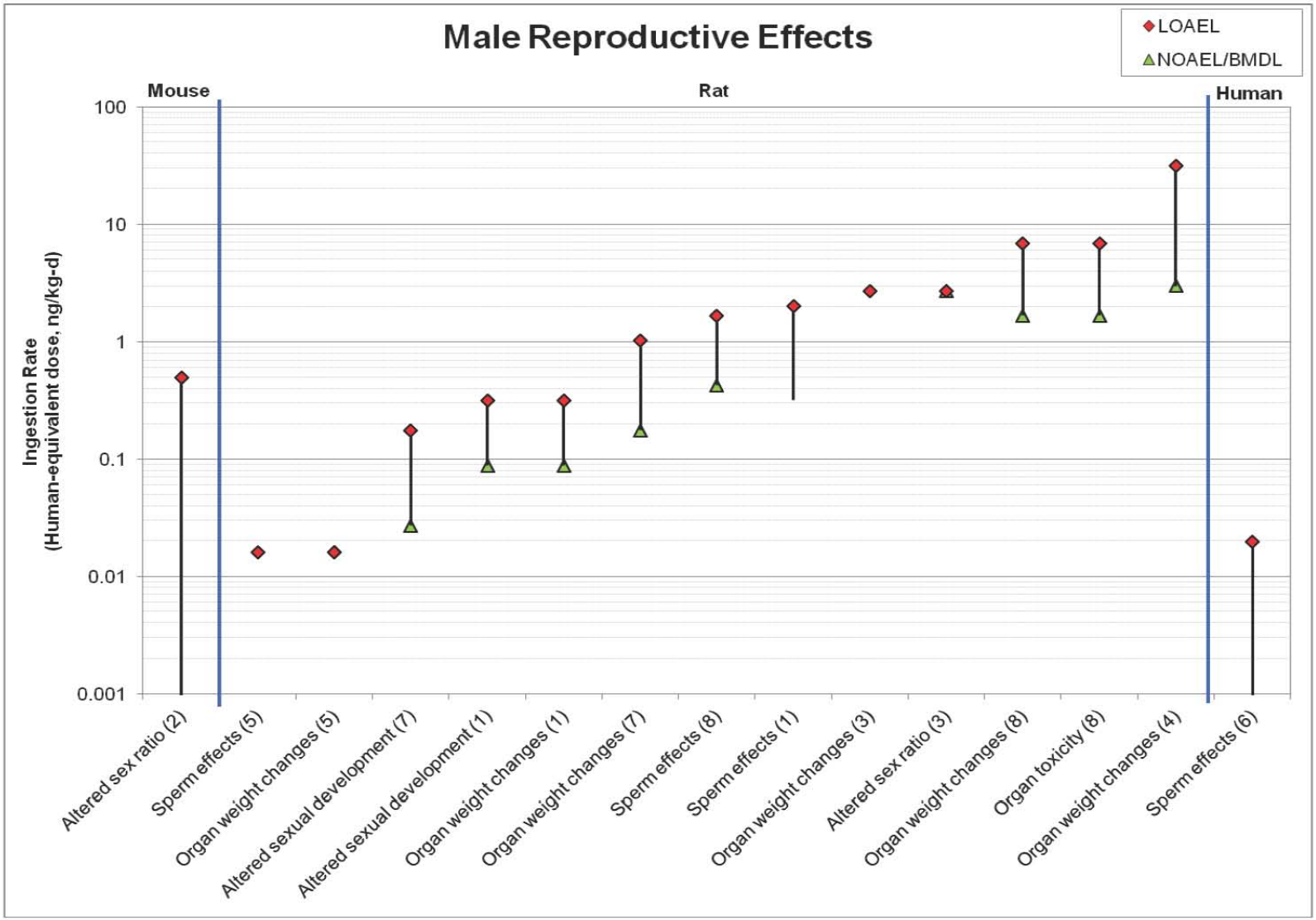

Figure D-1. Male reproductive effects across species.
The corresponding data are in Table D-3. The numbers following the effect designations indicate the corresponding study in Table D-3. Vertical solid black lines indicate the range of exposures tested below the LOAEL.

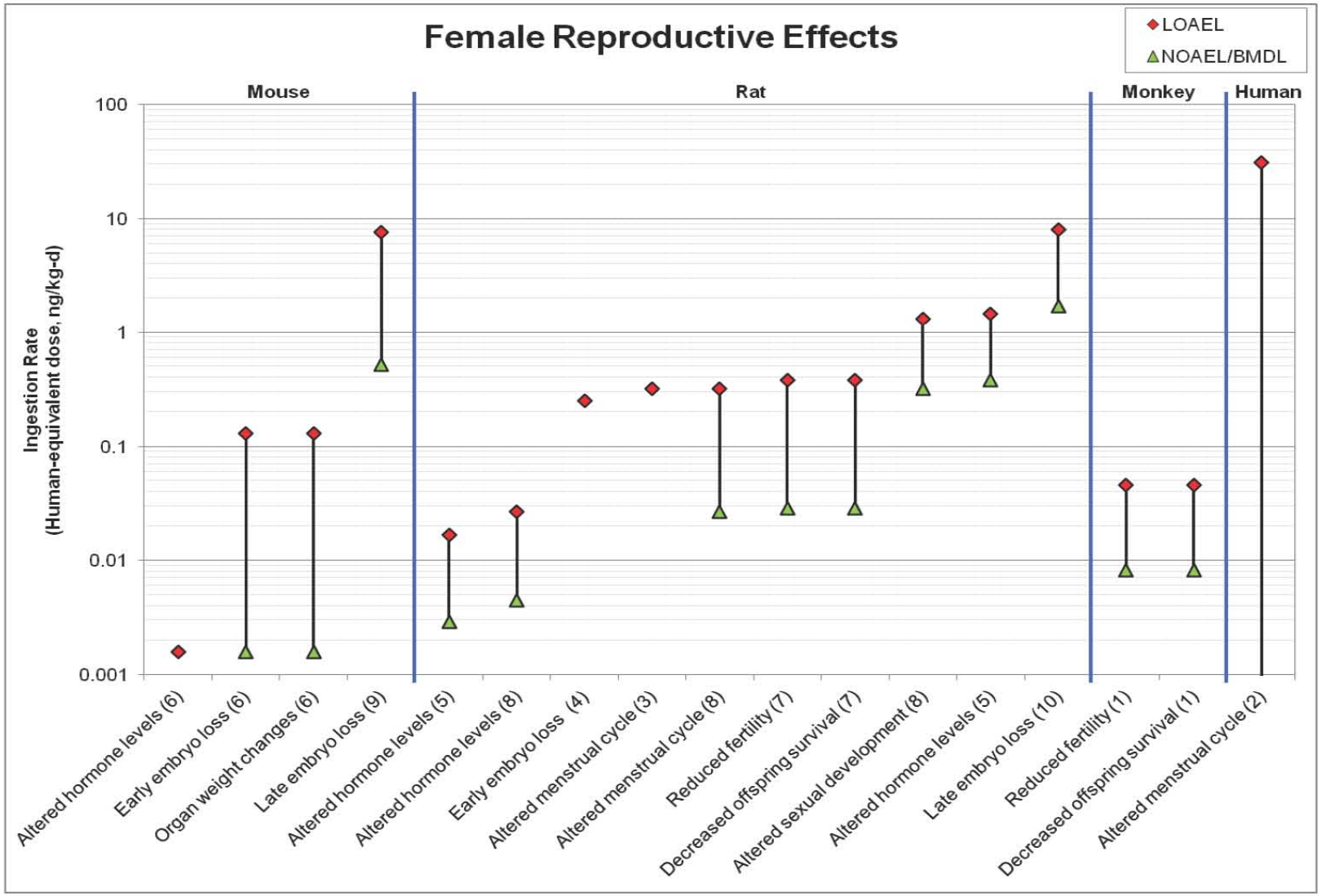

Figure D-2. Female reproductive effects across species.
The corresponding data are in Table D-4. The numbers following the effect designations indicate the corresponding study in Table D-4. Vertical solid black lines indicate the range of exposures tested below the LOAEL.

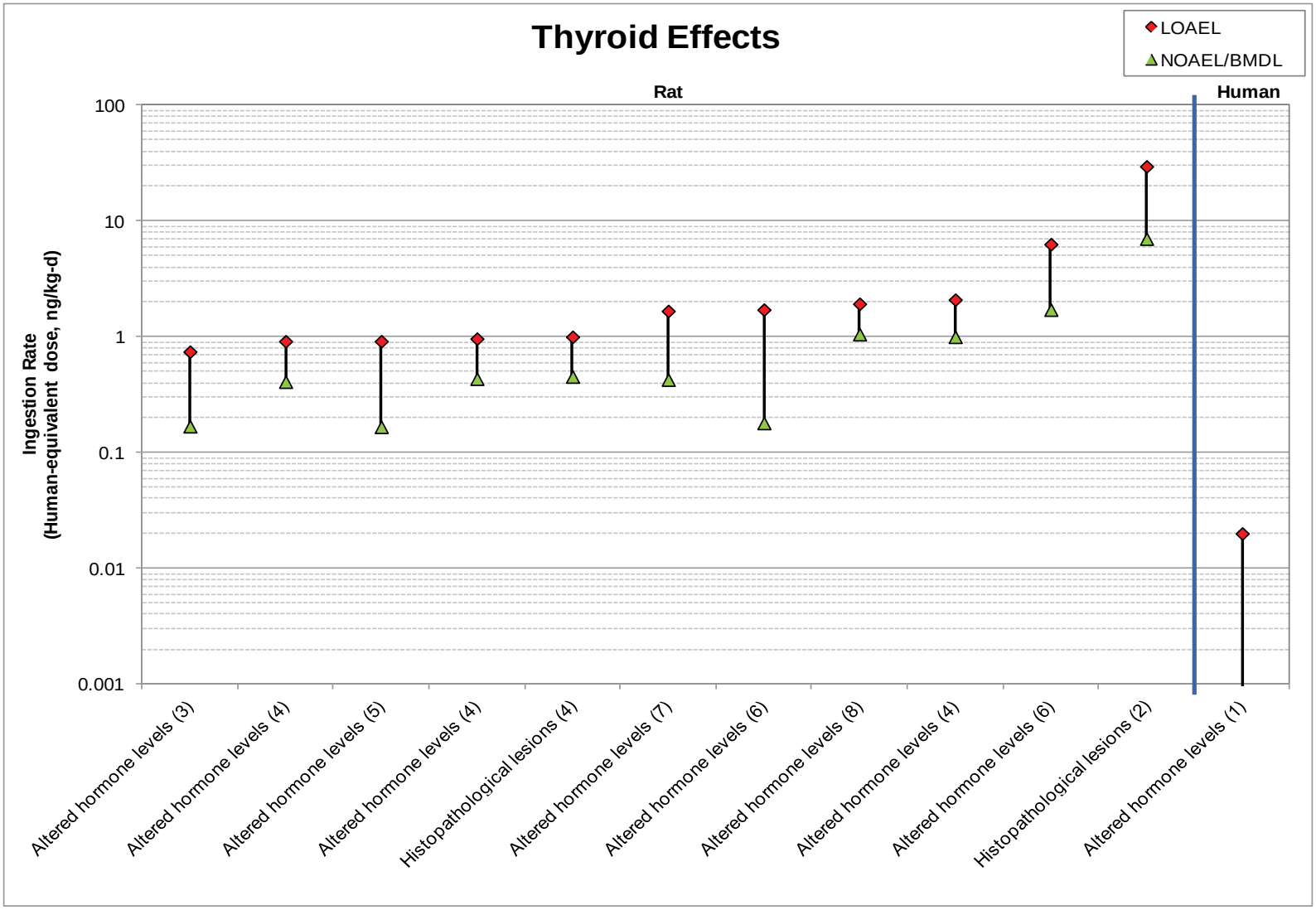

Figure D-3. Thyroid effects across species.
The corresponding data are in Table D-5. The numbers following the effect designations indicate the corresponding study in Table D-5. Vertical solid black lines indicate the range of exposures tested below the LOAEL.

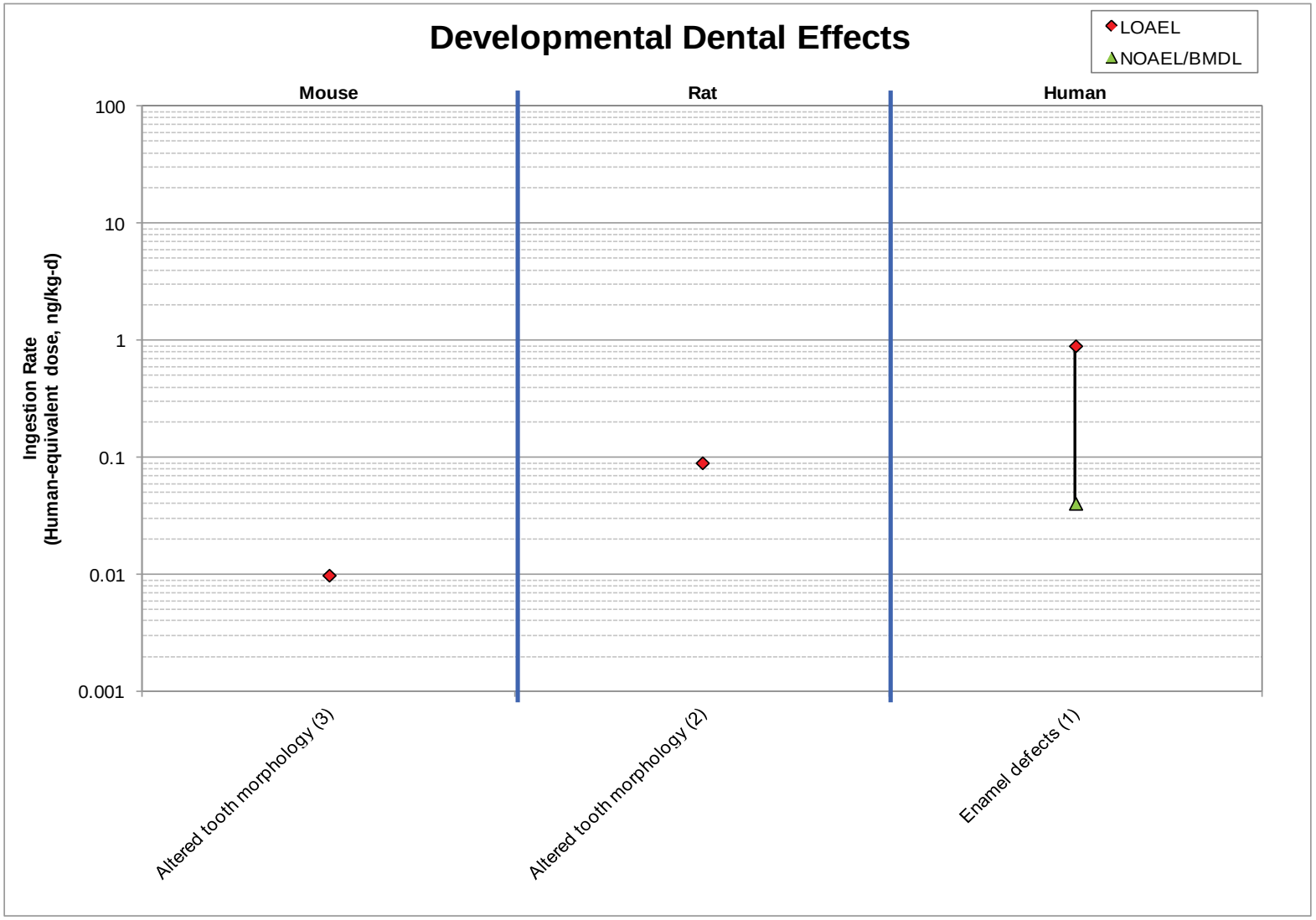

Figure D-4. Developmental dental effects across species.
The corresponding data are in Table D-6. The numbers following the effect designations indicate the corresponding study in Table D-6. Vertical solid black lines indicate the range of exposures tested below the LOAEL.

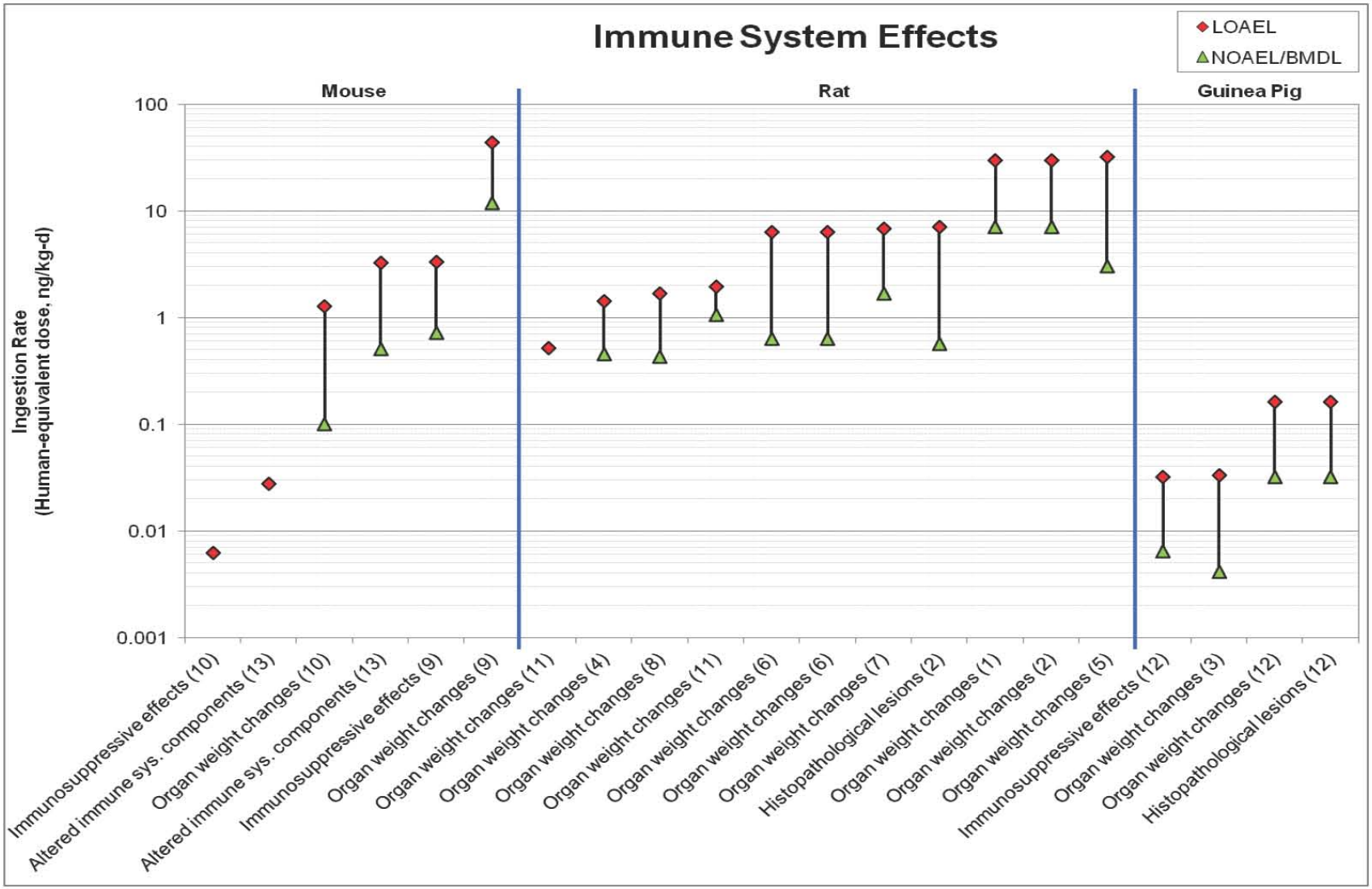

Figure D-5. Immune system effects across species.
The corresponding data are in Table D-7. The numbers following the effect designations indicate the corresponding study in Table D-7. Vertical solid black lines indicate the range of exposures tested below the LOAEL.

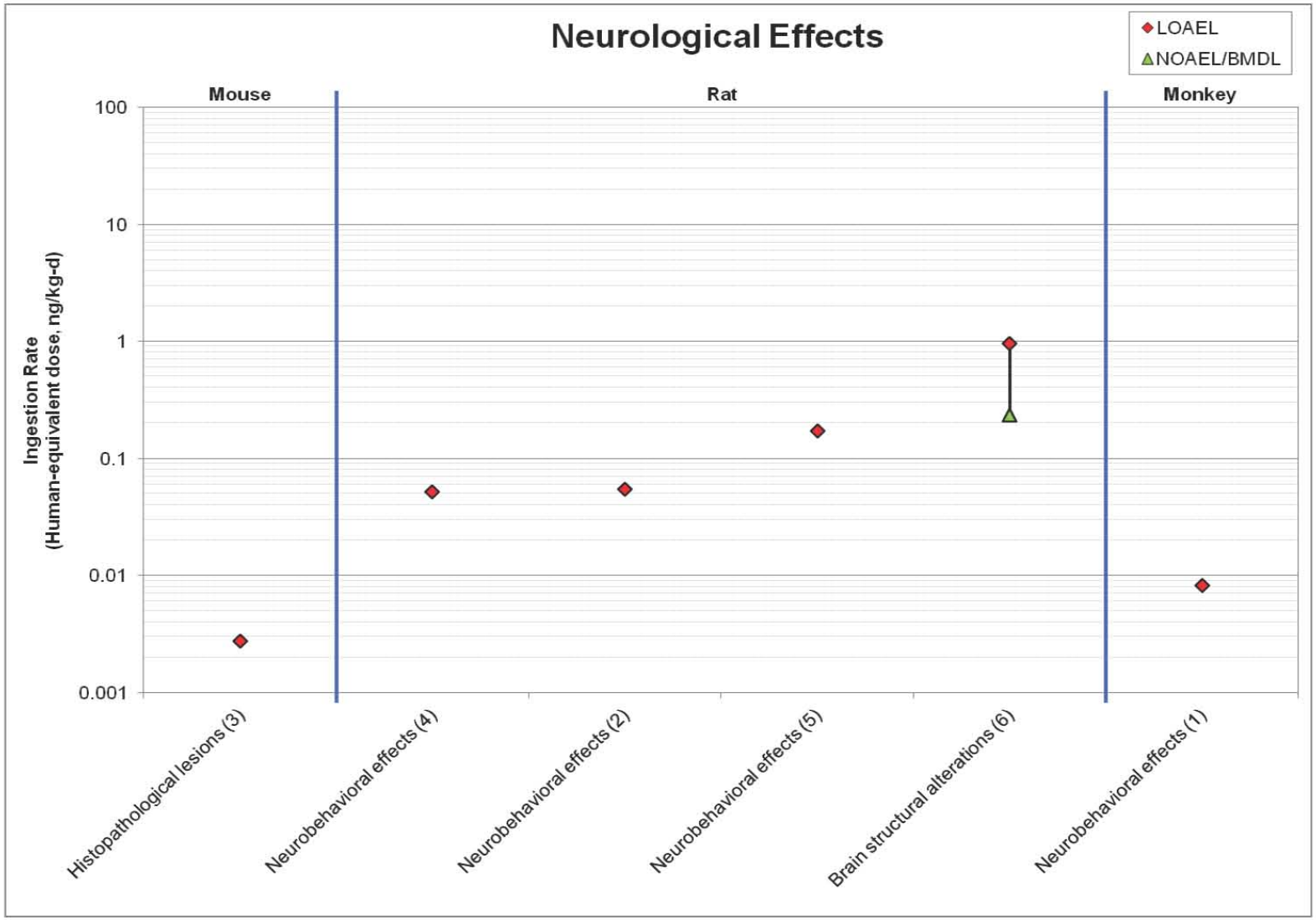

Figure D-6. Neurological effects across species.
The corresponding data are in Table D-8. The numbers following the effect designations indicate the corresponding study in Table D-8. Vertical solid black lines indicate the range of exposures tested below the LOAEL.

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APPENDIX E

Rodent Bioassay Kinetic Modeling

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National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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APPENDIX E. RODENT BIOASSAY KINETIC MODELING

E.1. LITERATURE SEARCH STRATEGY AND RESULTS—IDENTIFYING RECENT PUBLICATIONS FOR UPDATING 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD) TOXICOKINETIC MODEL INPUT PARAMETERS

The purpose of this literature search was to identify recent publications that address the input parameters for the physiologically based pharmacokinetic (PBPK) models Aylward and colleagues (described in articles published in 2005 and 2009) and Emond and colleagues (described in articles published in 2004, 2005, and 2006). This literature search was part of the U.S. Environmental Protection Agency (EPA)'s preparation of a response to the National Academy of Sciences' review (*Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment*, (NAS, 2006) of EPA *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (U.S. EPA, 2003), herein called the "2003 Reassessment." English-only references from 2003 to May 2009 were searched using bibliographic data bases relevant to health effects and toxicology of TCDD. The search focused on toxicokinetic data that could be used to update the dynamic disposition of 2,3,7,8-TCDD in mice, rats, guinea pigs, monkeys, and humans.

In the primary search, EPA identified 775 distinct citations based on the literature search criteria described below. EPA also performed an independent supplemental search to avoid missing key studies. EPA identified 28 papers for further analysis that appeared on first review to report data to update the input parameters of the Aylward and Emond PBPK models; considerations for selection are described in Section E.1.3.

E.1.1. Data Bases Searched

EPA used the following DIALOG bibliographic data bases in the primary search. Brief descriptions of the DIALOG data bases searched are provided in Section E.1.5.

1. File 6: NTIS
2. File 41: Pollution Abstracts
3. File 55: Biosis
4. File 153: IPA Toxicology
5. File 155: MEDLINE
6. File 156: ToxFile

7. File 157: Biosis Toxicology
8. File 159: CancerLit
9. File 336: RTECS

NTIS = National Technical Information Service; IPA = International Pharmaceutical Abstracts; RTECS = Registry of Toxic Effects of Chemical Substances.

The PubMed data base was used for the supplemental search.

E.1.2. Literature Search Strategy and Approach

The primary search used a tiered key-word approach, as documented below. The principal search term was the Chemical Abstract Service Registry Number (CASRN) or specific chemical name, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin or 2,3,7,8-TCDD. The next tier of search terms was species, and finally toxicokinetic keywords, as listed below. The period of the search was 2003 through May 2009, and articles were limited to English language.

The supplemental PubMed search was limited to the most recent five years (2004 to present) and used four combinations of key words:

- TCDD + pharmacokinetic + humans,
- TCDD + toxicokinetic + humans,
- TCDD + pharmacokinetic + animals, and
- TCDD + toxicokinetic + animals.

E.1.2.1. *Chemical Search Terms—DIALOG Search*

- CASRN: 1746-01-6
- 2,3,7,8-tetrachlorodibenzo-*p*-dioxin
- 2,3,7,8-TCDD

E.1.2.2. *Primary Search Terms (Species)—DIALOG Search*

- Guinea pig(s)
- Human(s)
- Monkey(s)
- Mouse
- Mice
- Rodent(s)

- Rat(s)

E.1.2.3. *Secondary Search Terms (Toxicology)—DIALOG Search*

1. Absor*
2. ADME
3. Aryl hydrocarbon receptor
4. AhR
5. Bioavail*
6. Biliar*
7. Biotransform*
8. Cytochrome
9. CYP*
10. CYP1A1
11. CYP1A2
12. Diet, dietary, diets
13. Disposit*
14. Distrib*
15. Drink*
16. Elimin*
17. Excret*
18. Epidemiolog*
19. Feces
20. Feed*
21. First order kinetics
22. Food*
23. Gastro*
24. Gavage*
25. Half-life
26. Induct*
27. Ingest*
28. In silico
29. Kinetic*
30. Liver
31. Lymph*
32. Mechanism (1w) action
33. Metabo*
34. Oral*
35. P450
36. Partition coefficient
37. PBPK
38. Pharmacodynamic*
39. Pharmacokinetic*
40. Physiologically based
41. Pharmacokinetic
42. Protein bind*
43. Toxicokinetic*
44. Uri

* = truncated.
1w = terms are within one word of each other and in the order specified (see search term 32).

ADME = absorption, distribution, metabolism, elimination; AhR = aryl hydrocarbon receptor; CYP = cytochrome P450.

E.1.3. Citation Screening Procedures and Results

Initial DIALOG searches resulted in a very large number of citation hits. Therefore, some title and key word restrictions were applied iteratively to screen out less relevant citations (e.g., requiring some search terms in title, requiring 2,3,7,8-TCDD rather than just TCDD). Then, using reference management software, pooled information obtained from the various DIALOG data bases was screened to remove duplicates. Citations then were numbered sequentially (as a unique identifier). Information retrieved included the following (when available): author(s), publication year, title, source document name, volume, and page numbers.

The DIALOG search and duplicate removal procedure produced 775 unique citations. In the next step, all 775 citations were screened for potential applicability to updating parameters in the Aylward and Emond PBPK models. Of these 775 citations, 26 were selected for more

detailed review to determine their potential applicability, and full publications were retrieved. Two citations were added from the supplemental search, giving a total of 28 articles identified for further review.

Bibliographic information for the 28 articles selected for full review is provided in the reference list at the end of this section. Table E-1 summarizes the model input parameters potentially addressed by the selected articles.

During 2003 to May 2009, the authors of the two kinetic models under consideration published several articles. For the Emond model, which was first published in 2004 (Emond et al., 2004), two subsequent papers have been published (Emond et al., 2006; 2005). The Aylward model, which originated from the 1995 papers by Carrier et al. (1995a, b), was later updated by the same group (Aylward et al., 2005a; 2005b). The major change implemented in the last two papers was the description of a desorption process in the digestive tract. The transfer rate described is slow, but for a low body burden of TCDD, this process remains significant. This concept was reported in 2002 by Moser and McLachlan (2002). The major modifications expected to update the Emond model are (1) consideration of the desorption process in the gastrointestinal tract and (2) rearrangement of the elimination constant, which will have a negligible impact on the simulation. These changes are motivated by plausible observations reported in the literature.

Because of the body burden found in humans and the importance of selecting an appropriate dose metric in human risk assessment, the physiological model is an important tool for assessing the kinetics following exposure to TCDD (Kim et al., 2003). Based on the literature identified in this search, the major contributions that should be reviewed with respect to the Aylward and Emond kinetic models are not modes of action or pharmacokinetic mechanisms, but rather information for verifying or improving the accuracy of some model parameters.

Pharmacokinetics typically refers to four distinct steps including absorption, distribution, metabolism, and excretion. Physiologically based models consider each step. In the model each step is parameterized to reflect better predictions of the real observations. Occasionally, reviewing these models is essential to determine if any key processes or parameters might be described with better accuracy. This perspective underlies the review of the literature described here. The review indicates TCDD disposition has become recognized as relatively significant since the publication of the Emond and Aylward models. The literature that provides

information related to improving these models, however, is limited. For the benefit of this exercise, EPA selected the literature that would likely contribute significantly to model response, or to clarify or confirm different key issues driving the model results. Regarding the two TCDD models, the two major issues that should be evaluated with respect to the recent literature identified are the elimination profile and the induction of CYP1A2.

Reviewing the elimination variation in different species and testing variable elimination with a data set appears to be appropriate. The literature reports that various factors might influence elimination rate. Recent publications report the influence of diverse predictors such age, body fat, or smoking habit on the elimination half-life (Milbrath et al., 2009; Kerger et al., 2007; 2006). Determining whether using the Milbrath et al. information would help account for intraspecies variability in elimination rate in the Emond and Aylward kinetic models would be useful. In 2006, Emond et al. (2006) reviewed the influence of body fat mass and CYP1A2 induction on the pharmacokinetics of TCDD. These two factors appear to contribute significantly to elimination and their influences seem to be driven by TCDD body burden. Mullerova and Kopecky (2007) discussed the influence of adipose tissue and the "yo-yo" effects on various diseases that might be influenced by persistent organic pollutant distribution. One group explored the importance of variable elimination and compared these predictions to first-order elimination using the Aylward and Emond models and supported these approaches for risk assessment (Heinzl et al., 2007). Two groups of authors considered a one-compartment model to derive the elimination half-life (Aylward et al., 2009; Nadal et al., 2008). Comparing the half-life they obtained using this approach for a range of body burden to the variable elimination half-life would be interesting.

The second important mechanism driving the distribution and elimination of TCDD is the induction of CYP1A2, identified as the major ligand protein in liver (Diliberto et al., 1997). For that process, authors suggested different aspects that should be investigated, including the importance of the dose metrics in the target tissue and the inducible level of CYP1A2 (Wilkes et al., 2008; Staskal et al., 2005). Other papers address the intraspecies variability of lethal potency in mature species versus the developing fetus (Kransler et al., 2007; Korkalainen et al., 2004). Still others point out pronounced differences among species (namely, guinea pigs, hamsters, mice, and rats) (Bohonowych and Denison, 2007), as observed in studies of long-term effects of low TCDD dose in liver and in studies comparing hepatic accumulation and clearance of TCDD

(Korenaga et al., 2007; Boverhoff et al., 2005). The interspecies variation of the binding affinity constant of AhR also has been reported (Connor and Aylward, 2006; Nohara et al., 2006).

The articles identified in this literature review should be adequate to update the Aylward and Emond models, which need to be evaluated according to the same structure of compartments described in the literature by the two model authors.

E.1.4. References Selected for More Detailed Review for Updating the PBPK Models

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Aylward, LL; Brunet, RC; Starr, TB; Carrier, G; Delzell, E; Cheng, H; Beall, C. (2005b). Exposure reconstruction for the TCDD-exposed NIOSH cohort using a concentration- and age-dependent model of elimination. Risk Anal 25: 945-956. http://dx.doi.org/10.1111/j.1539-6924.2005.00645.x.

Aylward, LL; Bodner, KM; Collins, JJ; Wilken, M; McBride, D; Burns, CJ; Hays, SM; Humphry, N. (2009). TCDD exposure estimation for workers at a New Zealand 2,4,5-T manufacturing facility based on serum sampling data. J Expo Sci Environ Epidemiol TBA: 1-10. http://dx.doi.org/10.1038/jes.2009.31.

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Boverhoff, DR; Burgoon, LD; Tashiro, C; Chittim, B; Harkema, JR; Jump, DB; Zacharewski, TR. (2005). Temporal and dose-dependent hepatic gene expression patterns in mice provide new insights into TCDD-mediated hepatotoxicity. Toxicol Sci 85: 1048-1063. http://dx.doi.org/10.1093/toxsci/kfi162.

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Kerger, BD; Leung, HW; Scott, P; Paustenbach, DJ; Needham, LL; Patterson, DG, Jr; Gerthoux, PM; Mocarelli, P. (2006). Age- and concentration-dependent elimination half-life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Seveso children. Environ Health Perspect 114: 1596-1602. http://dx.doi.org/10.1289/ehp.8884.

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E.1.5. Brief Descriptions of DIALOG Bibliographic Data Bases Searched

The NTIS database comprises summaries of U.S. government-sponsored research, development, and engineering, plus analyses prepared by federal agencies, their contractors, or grantees. It is the means through which unclassified, publicly available, unlimited distribution

reports are made available for sale from 240 agencies. Additionally, some state and local government agencies contribute summaries of their reports to the database. NTIS also provides access to the results of government-sponsored research and development from countries outside the United States. Organizations that currently contribute to the NTIS database include but are not limited to the following: the Japan Ministry of International Trade and Industry; laboratories administered by the United Kingdom Department of Industry; the German Federal Ministry of Research and Technology; and the French National Center for Scientific Research.

Pollution Abstracts provides access to environmental information that combines information on scientific research and government policies in a single resource. Topics of growing concern are extensively covered from the standpoints of atmosphere, emissions, mathematical models, effects on people and animals, and environmental action in response to global pollution issues. This database also contains material from conference proceedings and hard-to-find summarized documents along with information from primary journals in the field of pollution.

BIOSIS Previews® contains citations from Biological Abstracts® (BA) and Biological Abstracts/Reports, Reviews, and Meetings® (BA/RRM) (formerly BioResearch Index®), the major publications of BIOSIS®. These publications constitute the major English-language service providing comprehensive worldwide coverage of research in the biological and biomedical sciences. Biological Abstracts includes approximately 350,000 accounts of original research yearly from nearly 5,000 primary journal and monograph titles. BA/RRM includes an additional 200,000+ citations a year from meeting abstracts, reviews, books, book chapters, notes, letters, and selected reports.

IPA Toxicology provides focused toxicology information on all phases of the development and use of drugs and on professional pharmaceutical practice. The scope of the database ranges from the clinical and practical to the theoretical aspects of toxicology literature. A unique feature of abstracts reporting clinical studies is the inclusion of the study design, number of patients, dosage, dosage forms, and dosage schedule.

Medical Literature, Analysis, and Retrieval System Online (MEDLINE), produced by the U.S. National Library of Medicine (NLM), is NLM's premier bibliographic database. It contains more than 15 million references to journal articles in life sciences with a concentration on biomedicine. The broad coverage of the database includes basic biomedical research and the

clinical sciences since 1950, including nursing, dentistry, veterinary medicine, pharmacy, allied health, and preclinical sciences. MEDLINE also covers life sciences that are vital to biomedical practitioners, researchers, and educators, including some aspects of biology, environmental science, marine biology, and plant and animal science, as well as biophysics and chemistry. MEDLINE is indexed using NLM's controlled vocabulary, Medical Subject Headings. Approximately 400,000 records are added per year, of which more than 76% are in English. MEDLINE contains AIDSLINE, HealthSTAR, Toxline, In Process (formerly known as Pre-MEDLINE), In Data Review, and POPLINE.

ToxFile covers the toxicological, pharmacological, biochemical, and physiological effects of drugs and other chemicals. Adverse drug reactions, chemically induced diseases, carcinogenesis, mutagenesis, teratogenesis, environmental pollution, waste disposal, radiation, and food contamination are typical areas of coverage. The databases Environmental Mutagen Information Center, Developmental and Reproductive Toxicology, and Toxic Substances Control Act Test Submissions are included in ToxFile. It is not clearly stated whether the Chemical Carcinogenesis Research Information System, Hazardous Substances Data Bank, or Genetic Toxicology Data Bank are included in ToxFile. Consequently, a separate, online search was conducted to ensure that these databases were searched.

BIOSIS® Toxicology contains citations from BA and BA/RRM (formerly BioResearch Index®), the major publications of BIOSIS®, that focus on toxicology and related topics. Records are drawn from journal articles, conference papers, monographs and book chapters, notes, letters, and reports, as well as original research. U.S. patent records are also included.

CANCERLIT® is produced by the International Cancer Research DataBank Branch of the U.S. National Cancer Institute. The database consists of bibliographic records referencing cancer research publications dating from 1963 to 2002. Most records contain abstracts, and all records contain citation information and additional descriptive fields such as document type and language. Beginning with the June 1983 CANCERLIT® update, records from the MEDLINE database dealing with cancer topics have been added to CANCERLIT®.

The RTECS® is a comprehensive database of basic toxicity information for over 150,000 chemical substances including prescription and nonprescription drugs, food additives, pesticides, fungicides, herbicides, solvents, diluents, chemical wastes, reaction products of chemical waste, and substances used in both industrial and household situations. Reports of the toxic effects of

each compound are cited. In addition to toxic effects and general toxicology reviews, data on skin and/or eye irritation, mutation, reproductive consequences and tumorigenicity are provided. Federal standards and regulations, National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits and information on the activities of EPA, NIOSH, National Toxicology Program (NTP), and Occupational Safety and Health Administration regarding the substance are also included. The toxic effects are linked to literature citations from both published and unpublished governmental reports, and published articles from the scientific literature. The database corresponds to the print version of the RTECS®, formerly known as the Toxic Substances List, which was started in 1971. Originally prepared by the NIOSH, the RTECS® database is now produced and distributed by Symyx Technologies, Inc.

E.2. TOXICOKINETIC MODELING CODE (Emond et al., 2005)

E.2.1. Human Standard Model

E.2.1.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model for TCDD in Human: Standard Model (Nongestation)'

```
INITIAL  !INITIALIZATION OF PARAMETERS

     !SIMULATION PARAMETERS ====
CONSTANT EXP_TIME_ON       =     0.         ! TIME AT WHICH EXPOSURE BEGINS
(HOUR)
CONSTANT EXP_TIME_OFF      =     6.132e5  ! TIME AT WHICH EXPOSURE ENDS
(HOUR)
CONSTANT DAY_CYCLE         =     24.0     ! NUMBER OF HOURS BETWEEN DOSES
(HOUR)
CONSTANT BCK_TIME_ON       =     6.132e5     ! TIME AT WHICH BACKGROUND
EXPOSURE BEGINS (HOUR)
CONSTANT BCK_TIME_OFF      =     6.132e5     ! TIME AT WHICH BACKGROUND
EXPOSURE ENDS (HOUR)

     !EXPOSURE DOSES
CONSTANT  MSTOTBCKGR       =     0.0   ! ORAL BACKGROUND EXPOSURE DOSE
(NG/KG)
CONSTANT  MSTOT            =     1.0E-7      ! ORAL EXPOSURE DOSE (NG/KG)
CONSTANT  DOSEIV           =     0.0           ! INJECTED DOSE (NG/KG)
CONSTANT  MW             =     322.0       ! MOLECULAR WEIGHT (G/MOL)
 MSTOT_NM = MSTOT/MW                       ! CONVERTS THE DOSE TO NMOL/KG
 MSTOT_NMBCKGR = MSTOTBCKGR/MW  !CONVERTS THE BACKGROUND DOSE TO NMOL/KG
  DOSEIV_NM = DOSEIV/MW                    ! CONVERTS THE INJECTED DOSE TO
NMOL/KG

     !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW) ====
```

```
CONSTANT CFLLI0        =    0.0                  ! LIVER  (NMOL/L)

     !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) ===
CONSTANT LIBMAX        =    0.35            ! LIVER  (NMOL/L)

     ! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
===
CONSTANT KDLI          =       0.1              ! LIVER (AhR) (NMOL/L) WANG
ET AL.. 1997
CONSTANT KDLI2         =       40.0           ! LIVER (1A2) (NMOL/L) EMOND ET
AL. 2004

     !EXCRETION AND ABSORPTION CONSTANTS
CONSTANT KST           =       0.01             ! GASTRIC RATE CONSTANT (HR-
1), EMOND ET AL., 2005
CONSTANT KABS          =       0.06         ! INTESTINAL ABSORPTION CONSTANT
(HR-1), EMOND ET AL. 2005

     !ELIMINATION CONSTANTS
CONSTANT CLURI         =      4.17D-8       ! URINARY CLEARANCE (L/HR), EMOND
ET AL., 2005
CONSTANT KELV          =     1.1e-3            ! INTERSPECIES VARIABLE
ELIMINATION CONSTANT (1/HOUR)

     !CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A             =       0.7                     ! LYMPHATIC FRACTION,
WANG ET AL. (1997)

    !PARTITION COEFFICIENTS
CONSTANT PF            =       1.0e2                ! ADIPOSE TISSUE/BLOOD,
WANG ET AL. 1997
CONSTANT PRE           =       1.5                  ! REST OF THE BODY/BLOOD,
WANG ET AL. 1997
CONSTANT PLI           =       6.0                    ! LIVER/BLOOD, WANG ET
AL. 1997

     !PARAMETERS FOR INDUCTION OF CYP1A2
CONSTANT IND_ACTIVE     =       1.0           ! INCLUDE INDUCTION? (1 = YES,
0 = NO)
CONSTANT CYP1A2_1OUTZ  =   1.6e3       ! DEGRADATION CONCENTRATION CONSTANT
OF 1A2 (NMOL/L)
CONSTANT CYP1A2_1A1    =       1.6e3       ! BASAL CONCENTRATION OF 1A1
(NMOL/L)
CONSTANT CYP1A2_1EC50  =       1.3e2     ! DISSOCIATION CONSTANT TCDD-CYP1A2
(NMOL/L)
CONSTANT CYP1A2_1A2    =       1.6e3       ! BASAL CONCENTRATION OF 1A2
(NMOL/L)
CONSTANT CYP1A2_1KOUT  =       0.1       ! FIRST ORDER RATE OF DEGRADATION
(H-1)
CONSTANT CYP1A2_1TAU   =       0.25       ! HOLDING TIME (H)
CONSTANT CYP1A2_1EMAX  =       9.3e3   ! MAXIMUM INDUCTION OVER BASAL EFFECT
(UNITLESS)
CONSTANT HILL          =       0.6      !HILL CONSTANT; COOPERATIVE LIGAND
BINDING EFFECT CONSTANT (UNITLESS)
     ! DIFFUSIONAL PERMEABILITY FRACTION
CONSTANT PAFF          =      0.12                   ! ADIPOSE (UNITLESS)
```

```
CONSTANT PAREF         =      0.03                 ! REST OF BODY (UNITLESS)
CONSTANT PALIF         =      0.35                   ! LIVER (UNITLESS)

     !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT  =========
CONSTANT QFF           =       0.05      ! ADIPOSE TISSUE BLOOD FLOW FRACTION
(UNITLESS), KRISHNAN 2008
CONSTANT QLIF          =       0.26      ! LIVER (UNITLESS), KRISHNAN 2008

     !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL
COMPARTMENT VOLUME =========
CONSTANT WFB0          =       0.050    ! ADIPOSE TISSUE, WANG ET AL. 1997
CONSTANT WREB0       =       0.030    ! REST OF THE BODY, WANG ET AL. 1997
CONSTANT WLIB0         =       0.266    ! LIVER, WANG ET AL. 1997

     !EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
     !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG     =       0.0          ! TIME ELAPSED BEFORE EXPOSURE
BEGINS (WEEK)
CONSTANT WEEK_PERIOD   =       168.0     ! NUMBER OF HOURS IN THE WEEK
(HOURS)
CONSTANT WEEK_FINISH   =       168.0      ! TIME EXPOSURE ENDS (HOURS)
    !NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LAG    =       0.0        ! TIME ELAPSED BEFORE EXPOSURE
BEGINS (MONTH)

     !SET FOR BACKGROUND EXPOSURE===========
     !TIME CONSTANT FOR BACKGROUND EXPOSURE===========
CONSTANT Day_LAG_BG      =    0.0          ! TIME ELAPSED BEFORE EXPOSURE
BEGINS (HOUR)
CONSTANT Day_PERIOD_BG    =    24.0       ! LENGTH OF EXPOSURE (HOUR)

     !TIME CONSTANT FOR WEEKLY EXPOSURE
CONSTANT WEEK_LAG_BG     =    0.0       ! TIME ELAPSED BEFORE BACKGROUND
EXPOSURE BEGINS (WEEK)
CONSTANT WEEK_PERIOD_BG   =    168.0     !  NUMBER OF HOURS IN THE WEEK
(HOURS)
CONSTANT WEEK_FINISH_BG   =    168.0       ! TIME EXPOSURE ENDS (HOURS)

     ! CONSTANT USED IN CARDIAC OUTPUT EQUATION
CONSTANT QCC            =    15.36                  ! (L/KG-H),  EMOND ET AL.
2004

     ! COMPARTMENT TOTAL LIPID FRACTION
     !Data from Emonds Thesis 2001
CONSTANT F_TOTLIP         =    0.8000               ! ADIPOSE TISSUE
(UNITLESS)
CONSTANT B_TOTLIP         =    0.0057              ! BLOOD (UNITLESS)
CONSTANT RE_TOTLIP        =    0.0190             ! REST OF THE BODY
(UNITLESS)
CONSTANT LI_TOTLIP        =    0.0670               ! LIVER (UNITLESS)
CONSTANT MEANLIPID        =    974.0

END  ! END OF THE INITIAL SECTION


DYNAMIC ! DYNAMIC SIMULATION SECTION
   !
```

```
ALGORITHM  IALG          =      2        ! GEAR METHOD
CINTERVAL  CINT          =      10.0       ! COMMUNICATION INTERVAL
MAXTERVAL  MAXT          =    1.0e+10    !MAXIMUM INTERVAL CALCULATION
MINTERVAL  MINT          =    1.0E-10    !MINIMUM INTERVAL CALCULATION
VARIABLE   T             =      0.0
CONSTANT   TIMELIMIT     =     1.752e5  !SIMULATION LIMIT TIME (HOUR)
CONSTANT      Y0           =       0.0      ! AGE (YEARS) AT BEGINNING OF
SIMULATION
CONSTANT   GROWON        =        1.0    ! INCLUDE BODY WEIGHT AND HEIGHT
GROWTH? (1 = YES, 0 = NO)
  CINTXY  = CINT
  PFUNC   = CINT

  DAY=T/24.0                                   ! TIME IN DAYS
  WEEK =T/168.0                              ! TIME IN WEEKS
  MONTH =T/730.0                           ! TIME IN MONTHS
  YEAR=Y0+T/8760.0                      ! TIME IN YEARS
  GYR =Y0 + growon*T/8760.0       ! TIME FOR USE IN GROWTH EQUATION (YEARS)

DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

     ! CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
     ! NUMBER OF EXPOSURES PER DAY
 DAY_LAG     = EXP_TIME_ON       ! TIME ELAPSED BEFORE EXPOSURE BEGINS
(HOURS)
 DAY_PERIOD   = DAY_CYCLE         ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH   = CINTXY            ! LENGTH OF EXPOSURE (HOURS)
 MONTH_PERIOD = TIMELIMIT         ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH = EXP_TIME_OFF      ! LENGTH OF EXPOSURE (MONTHS)


     ! NUMBER OF EXPOSURES PER DAY AND MONTH
 DAY_FINISH_BG   = CINTXY
 MONTH_LAG_BG   = BCK_TIME_ON    !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
BEGINS (MONTHS)
 MONTH_PERIOD_BG = TIMELIMIT      ! BACKGROUND EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH_BG = BCK_TIME_OFF   ! LENGTH OF BACKGROUND EXPOSURE (MONTHS)

 B = 1.0-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER

     !HUMAN BODY WEIGHT GROWTH EQUATION========
      ! POLYNOMIAL REGRESSION EXPRESSION WRITTEN
!APRIL 10 2008, OPTIMIZED WITH DATA OF PELEKIS ET AL. 2001
! POLYNOMIAL REGRESSION EXPRESSION WRITTEN WITH
!HUH AND BOLCH 2003 FOR BMI CALCULATION

  ! BODY WEIGHT CALCULATION
  WT0 = (0.0006*GYR**3 - 0.0912*GYR**2 + 4.32*GYR + 3.652)! BODY WEIGHT IN KG

   ! BODY MASS INDEX CALCULATION
     BH =  -2D-5*GYR**4+4.2D-3*GYR**3.0-0.315*GYR**2.0+9.7465*GYR+72.098

   !HEIGHT EQUATION FORMULATED FOR USE FROM 0 TO 70 YEARS
     BHM= (BH/100.0)               !HUMAN HEIGHT IN METERS (BHM)
     HBMI= WT0/(BHM**2.0) ! HUMAN BODY MASS INDEX (BMI)

    ! ADIPOSE TISSUE FRACTION
```

```
    WT0GR= WT0*1.0e3    ! BODY WEIGHT IN GRAMS
    WF0= -6.36D-20*WT0GR**4.0 +1.12D-14*WT0GR**3.0 -5.8D-10*WT0GR**2.0 +1.2D-
5*WT0GR+5.91D-2

    ! LIVER,VOLUME FRACTION
    ! APPROACH BASED ON LUECKE (2007)
    WLI0= (3.59D-2 -(4.76D-7*WT0GR)+(8.50D-12*WT0GR**2.0)-(5.45D-
17*WT0GR**3.0))

 WRE0 = (0.91 -(WLIB0*WLI0+WFB0*WF0+WLI0+WF0))/(1.0+WREB0)
                                   !REST OF THE BODY FRACTION; UPDATED FOR
EPA ASSESSMENT
 QREF = 1.0-(QFF+QLIF)                !REST OF BODY BLOOD FLOW
 QTTQF = QFF+QREF+QLIF              ! SUM MUST EQUAL 1

   !COMPARTMENT VOLUME (L OR KG) =========
 WF  =  WF0  * WT0                  ! ADIPOSE
 WRE =  WRE0 * WT0                  ! REST OF THE BODY
 WLI =  WLI0 * WT0                  ! LIVER
 WB=0.075*WT0                         ! BLOOD

   !COMPARTMENT TISSUE BLOOD (L OR KG) =========
 WFB  =  WFB0  * WF                  ! ADIPOSE
 WREB =  WREB0 * WRE                 ! REST OF THE BODY
 WLIB =  WLIB0 * WLI                 ! LIVER
   !CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
QC= QCC*(WT0**0.75)                    ! [L BLOOD/HOUR]

QF  = QFF*QC                           ! ADIPOSE TISSUE BLOOD FLOW RATE
[L/HR]
QLI = QLIF*QC                          ! LIVER TISSUE BLOOD FLOW RATE [L/HR]
QRE = QREF*QC                      !REST OF THE BODY BLOOD FLOW RATE [L/HR]

QTTQ = QF+QRE+QLI                ! TOTAL FLOW RATE [L/HR]

   !PERMEABILITY ORGAN FLOW [L/HR]=======
PAF  = PAFF*QF                          ! ADIPOSE
PARE = PAREF*QRE                        ! REST OF THE BODY
PALI = PALIF*QLI                        ! LIVER TISSUE

   ! ABSORPTION SECTION
   ! INTRAVENOUS
 IV        =    DOSEIV_NM * WT0          !AMOUNT IN NMOL
 MSTTBCKGR =    MSTOT_NMBCKGR *WT0       !AMOUNT IN NMOL
 MSTT      =    MSTOT_NM * WT0           !AMOUNT IN NMOL

     !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIOS
DAY_EXPOSURE_BG   = PULSE(DAY_LAG_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
WEEK_EXPOSURE_BG  = PULSE(WEEK_LAG_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG = PULSE(MONTH_LAG_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
MSTTFR_BG = MSTTBCKGR/CINT

CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG
```

```
    ! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
    ABSMSTT_GB= MSTTFR_BG
ELSE
    ABSMSTT_GB = 0.0
END IF


    !REPETITIVE ORAL MAIN EXPOSURE SCENARIO
DAY_EXPOSURE   = PULSE(DAY_LAG,DAY_PERIOD,DAY_FINISH)
WEEK_EXPOSURE  = PULSE(WEEK_LAG,WEEK_PERIOD,WEEK_FINISH)
MONTH_EXPOSURE = PULSE(MONTH_LAG,MONTH_PERIOD,MONTH_FINISH)

MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
MSTTFR=MSTT/CINT

    !CONDITIONAL ORAL EXPOSURE
IF (MSTTCH.EQ.MSTT) THEN
   ABSMSTT= MSTTFR
ELSE
   ABSMSTT = 0.
END IF

 CYCLETOT=INTEG(CYCLE,0.0)

      ! MASS Balance CHANGE IN THE LUMEN
RMSTT= -(KST+KABS)*MST+ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
 MST = INTEG(RMSTT,0.)                      !AMOUNT REMAINING IN GI TRACT
(NMOL)

      ! ABSORPTION IN LYMPH CIRCULATION
LYRMLUM = KABS*MST*A
 LYMLUM = INTEG(LYRMLUM,0.0)

      ! ABSORPTION IN PORTAL CIRCULATION
LIRMLUM = KABS*MST*B
  LIMLUM = INTEG(LIRMLUM,0.0)


      !IV ABSORTPION SCENARIO ---------
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1.0-STEP(PFUNC))
 IVDOSE = integ(EXPIV,0.0)

      !SYSTEMIC BLOOD COMPARTMENT
      ! MODIFICATION OCT 8 2009
CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM)/(QC+CLURI) !
 CA = CB                                  !CONCENTRATION (NMOL/L)

    !CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM-RAURI)/QC !
    ! CA = CB                             ! CONCENTRATION (NMOL/L)

       !URINARY EXCRETION BY KIDNEY
       ! MODIFICATION OCT 8 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)
```

```
       !CONCENTRATION UNIT

  CBSNGKGLIADJ = CB*MW/(0.55*B_TOTLIP) !serum concentration in lipid adjust
(PG/G LIPID=PPT)
      CBPPT = CBSNGKGLIADJ
  CBNGKG = CB*MW

CBpptRH = CB*MW*10000/(0.55*MEANLIPID) !SERUM CONCENTRATION IN LIPID ADJUST
(PG/G LIPID=PPT)

    AUC_CBSNGKGLIADJ=INTEG(CBSNGKGLIADJ,0.0)

      !ADIPOSE TISSUE COMPARTMENT
RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)        !(NMOL/HR)
 AFB = INTEG(RAFB,0.0)                    !(NMOL)
 CFB = AFB/WFB                           !(NMOL/KG)
      !TISSUE SUBCOMPARTMENT
RAF = PAF*(CFB-CF/PF)                    !(NMOL/HR)
 AF = INTEG(RAF,0.0)                      !(NMOL)
 CF  = AF/WF                             !(NMOL/KG)

      !POST SIMULATION UNIT CONVERSION
CFTOTAL = (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION NMOL/L
CFNGKG =CFTOTAL*MW

      !REST OF THE BODY COMPARTMENT========
RAREB= QRE*(CA-CREB)-PARE*(CREB-CRE/PRE) !(NMOL/HR)
 AREB = INTEG(RAREB,0.0)                 !(NMOL)
 CREB = AREB/WREB                        !(NMOL/KG)
      !TISSUE SUBCOMPARTMENT
RARE = PARE*(CREB-CRE/PRE)               !(NMOL/HR)
 ARE = INTEG(RARE,0.0)                  !(NMOL)
 CRE  = ARE/WRE                           !(NMOL/KG)

      !POST SIMULATION UNIT CONVERSION
CRETOTAL = (ARE + AREB)/(WRE + WREB) ! TOTAL CONCENTRATION IN NMOL/L

      !LIVER COMPARTMENT
      !TISSUE BLOOD SUBCOMPARTMENT
RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM          !(NMOL/HR)
  ALIB = INTEG(RALIB,0.0)                                  !(NMOL)
 CLIB = ALIB/WLIB
      !TISSUE SUBCOMPARTMENT
 RALI =  PALI*(CLIB-CFLLIR)-REXCLI                        !(NMOL/HR)
  ALI = INTEG(RALI,0.0)                !(NMOL)
  CLI  = ALI/WLI                 !(NMOL/KG)


      !FREE TCDD IN LIVER
      ! MODIFICATION OCTOBER 8 2009
CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR)) &
        +((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR)*IND_ACTIVE)))-CFLLI,CFLLI0) !
CONCENTRATION OF FREE TCDD IN LIVER
    CFLLIR=DIM(CFLLI,0.0)
```

```
!MODIFIED FROM:
     !PARAMETER (LIVER_1RMN = 1.0E-30)
     ! CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &       !
+LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR &
     !        +LIVER_1RMN)*IND_ACTIVE)))-CFLLI,CFLLI0)
     !    CFLLIR=DIM(CFLLI,0.0)


CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR) !CONC OF TCDD BOUDN TO AhR

!CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !CONC BIND

      !POST SIMULATION UNIT CONVERSION
CLITOTAL = (ALI + ALIB)/(WLI + WLIB)       ! TOTAL CONCENTRATION IN NMOL/L
rec_occ_AHR= 100.0*CFLLIR/(KDLI+CFLLIR+1.0)  ! PERCENT  BOUND TO AhR
OCCUPANCY
PROT_occ_1A2= 100.0*CFLLIR/(KDLI2+CFLLIR)    ! PERCENT  BOUND TO 1A2
OCCUPANCY
CLINGKG= CLITOTAL*MW                        ![NG TCDD/KG]
CBNDLINGKG = CBNDLI*MW

    !FRACTION INCREASE OF INDUCTION OF CYP1A2
fold_ind=CYP1A2_1OUT/CYP1A2_1A2
VARIATIONOFAC =(CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2

    !VARIABLE ELIMINATION BASED ON THE CYP1A2
KBILE_LI_T = Kelv*VARIATIONOFAC!

 REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT RATE OF BILLIARY EXCRETION
OF DIOXIN
    EXCLI = INTEG(REXCLI,0.0)  !TOTAL AMOUNT OF DIOXIN EXCRETED

    !CHEMICAL IN CYP450 (1A2) COMPARTMENT
    !PARAMETER FOR INDUCTION OF CYP1A2

CYP1A2_1KINP = CYP1A2_1KOUT*CYP1A2_1OUTZ ! BASAL RATE OF CYP1A2 PRODUCTION
SET EQUAL TO BASAL RATE OF DEGRDATION AT STEADY STATE

    ! MODIFICATION OCTOBER 8 2009
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
&
     /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
      - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ) ! LEVELS OF CYP1A2
! MODEIFIED FROM:
!PARAMETER (CYP1A2_1RMN = 1e-30)
!CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1 + CYP1A2_1EMAX *(CBNDLI &
!     +CYP1A2_1RMN)**HILL/(CYP1A2_1EC50 + (CBNDLI + CYP1A2_1RMN)**HILL) &
!     +CYP1A2_1RMN) - CYP1A2_1KOUT*CYP1A2_1&
!     OUT, CYP1A2_1OUTZ)

! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)
CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
    CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)
 CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
    CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)
```

```
     !CHECK MASS BALANCE
  BDOSE= LYMLUM+LIMLUM+IVDOSE
  BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI
      BDIFF = BDOSE-BMASSE
     ! BODY BURDEN IN TERMS OF CONCENTRATION (NG/KG)
  BBNGKG = (AFB+AF+AREB+ARE+ALIB+ALI)*MW/WT0       !

     !COMMAND END OF THE SIMULATION
TERMT (T.GE. TIMELIMIT, 'Time limit has been reached.')

END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYTNAMIC SECTION
END   ! END OF THE PROGRAM
```

E.2.1.2. *Input File*

```
output @clear
prepare @clear year T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG  CBNDLINGKG CBNGKG
% PARAMETERS FOR SIMULATION
CINT = 1 %0.5
EXP_TIME_ON  =   0.       % TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF = 613200     %324120     % HOUR/YEAR !TIME AT WHICH EXPOSURE
ENDS (HOUR)
DAY_CYCLE    = 24         % NUMBER OF HOURS BETWEEN DOSES (HOUR)
BCK_TIME_ON  = 613200     %324120     % TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOUR)
BCK_TIME_OFF = 613200     %324120     % TIME AT WHICH BACKGROUND EXPOSURE
ENDS (HOUR)
TIMELIMIT    = 613200     %324120       %324120     % SIMULATION TIME LIMIT
(HOUR)
MSTOTBCKGR   =   0.       % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 9.97339283634997E-07       % ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV       =   0          %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 730        %
IND_ACTIVE= 1          % INDUCTION INCLUDED? (1=YES, 0=NO)
```

E.2.2. Human Gestational Model

E.2.2.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model for TCDD in Human (Gestation)'

```
INITIAL  !

     !SIMULATION PARAMETERS
CONSTANT PARA_ZERO          = 1e-30
CONSTANT EXP_TIME_ON     = 0.0       !TIME AT WHICH EXPOSURE BEGINS (HOURS)
CONSTANT EXP_TIME_OFF    = 530.0      !TIME AT WHICH EXPOSURE ENDS (HOURS)
CONSTANT DAY_CYCLE       =  24.0     !NUMBER OF HOURS BETWEEN DOSES (HOURS)
CONSTANT BCK_TIME_ON     = 0.0       !TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOURS)
```

```
CONSTANT BCK_TIME_OFF    = 0.0       !TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOURS)
CONSTANT TRANSTIME_ON    = 0.0       !CONTROL TRANSFER FROM MOTHER TO FETUS
AT 9 WEEKS OR 1512 HOURS OF GESTATION

     ! INTRAVENOUS SEQUENCY
CONSTANT IV_LAG         = 0.0
CONSTANT IV_PERIOD       = 0.0

     !PREGNANCY PARAMETER
CONSTANT CONCEPTION_T         = 0.0       !TIME OF CONCEPTION  (HOUR)
CONSTANT PFETUS          = 4.0       !PARTITION COEFFICIENT
CONSTANT CLPLA_FET       = 1.0e-3    !CLEARANCE TRANSFER FOR MOTHER TO FETUS
(L/HR)

     !CONSTANT EXPOSURE CONTROL
     !ACUTE, SUBCHRONIC, CHRONIC EXPOSURE =====
     !OR BACKGROUND EXPOSURE (IN THIS CASE 3 TIMES A DAY)===
CONSTANT MSTOTBCKGR      = 0.0       ! ORAL BACKGROUND EXPOSURE DOSE (NG/KG)
CONSTANT MSTOT           = 0.0       ! ORAL EXPOSURE DOSE (NG/KG)

     !ORAL ABSORPTION
     ! MSTT= MSTOT/1000 *WT0 *1/322*1000 !AMOUNT IN NMOL
  MSTOT_NM = MSTOT/MW              !CONVERTS THE DOSE TO NMOL/KG

     !INTRAVENOUS ABSORPTION
CONSTANT  DOSEIV         = 0.0       ! INJECTED DOSE (NG/KG)
  DOSEIV_NM = DOSEIV/MW            ! CONVERTS THE INJECTED DOSE TO NMOL/KG
CONSTANT DOSEIVLATE = 0.0            !INJECTED DOSE LATE (NG/KG)
  DOSEIVNMlate = DOSEIVLATE/MW     !AMOUNT IN NMOL/G

     !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW)====
CONSTANT CFLLI0          =  0.0      !LIVER    (NMOL/L)
CONSTANT CFLPLA0         =  0.0      !PLACENTA (NMOL/L)

     !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) (NMOL/L) ===
CONSTANT LIBMAX          = 0.35     ! LIVER  (NMOL/L)
CONSTANT PLABMAX         = 0.2      !TEMPORARY PARAMETER

     !PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
(NMOL/ML)===
CONSTANT KDLI            = 0.1      !LIVER (AhR) (NMOL/L), WANG ET AL. 1997
CONSTANT KDLI2           = 40.0       !LIVER (1A2) (NMOL/L), EMOND ET AL.
2004
CONSTANT KDPLA           = 0.1      !ASSUME IDENTICAL TO KDLI (AhR)

     !EXCRETION AND ABSORPTION CONSTANT
CONSTANT KST             = 0.01     ! GASTRIC RATE CONSTANT (HR-1), EMOND ET
AL. 2005
CONSTANT KABS            = 0.06     ! INTESTINAL ABSORPTION CONSTANT (HR-1),
EMOND ET AL. (2005)

     !INTERSPECIES ELIMINATION CONSTANT
     !TEST ELIMINATION VARIABLE, EMOND ET AL. 2005
```

```
CONSTANT KELV          =     1.1e-3 !4.0D-3          ! INTERSPECIES VARIABLE
ELIMINATION CONSTANT (1/HOUR)

     ! ELIMINATION CONSTANTS
CONSTANT CLURI           =  4.17e-8 ! URINARY CLEARANCE (L/HR), EMOND ET AL.
2005

     ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A               = 0.7        ! LYMPHATIC FRACTION, WANG ET AL. 1997

     !PARTITION COEFFICIENTS
CONSTANT PF              = 1.0e2     ! ADIPOSE TISSUE/BLOOD, WANG ET AL. 1997
CONSTANT PRE             = 1.5      ! REST OF THE BODY/BLOOD, WANG ET AL.
1997
CONSTANT PLI             = 6.0       ! LIVER/BLOOD, WANG ET AL. 1997
CONSTANT PPLA            = 1.5      ! TEMPORARY PARAMETER NOT CONFIGURED,
WANG ET AL. 1997

    !PARAMETER FOR INDUCTION OF CYP 1A2, WANG ET AL. 1997
CONSTANT IND_ACTIVE       = 1.0        ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
CONSTANT CYP1A2_1OUTZ    = 1.6e3     ! DEGRADATION CONCENTRATION CONSTANT OF
1A2 (NMOL/L)
CONSTANT CYP1A2_1A1      = 1.6e3     ! BASAL CONCENTRATION OF 1A1 (NMOL/L)
CONSTANT CYP1A2_1EC50    = 1.3e2    ! DISSOCIATION CONSTANT TCDD-CYP1A2
(NMOL/L)
CONSTANT CYP1A2_1A2      = 1.6e3     !BASAL CONCENTRATION OF 1A2 (NMOL/L)
CONSTANT CYP1A2_1KOUT    = 0.1      ! FIRST ORDER RATE OF DEGRADATION (H-1)
CONSTANT CYP1A2_1TAU     = 0.25     !HOLDING TIME (H)
CONSTANT CYP1A2_1EMAX    = 9.3e3     ! MAXIMUM INDUCTION OVER BASAL EFFECT
(UNITLESS)
CONSTANT HILL            = 0.6      !HILL CONSTANT; COOPERATIVE LIGAND
BINDING EFFECT CONSTANT (UNITLESS)

   !DIFFUSIONAL PERMEABILITY FRACTION, WANG ET AL (1997)
CONSTANT PAFF            = 0.12     ! ADIPOSE (UNITLESS)
CONSTANT PAREF           = 0.03     ! REST OF THE BODY (UNITLESS)
CONSTANT PALIF           = 0.35     ! LIVER (UNITLESS)
CONSTANT PAPLAF          = 0.3      ! OPTIMIZED PARAMETER

!TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT, KRISHNAN 2007
CONSTANT QFF             = 0.05     ! ADIPOSE TISSUE BLOOD FLOW FRACTION
(UNITLESS), KRISHNAN 2008
CONSTANT QLIF            = 0.26     ! LIVER (UNITLESS), KRISHNAN 2008

!===FRACTION OF TISSUE BLOOD WEIGHT Wang et al . (1997)
CONSTANT WFB0            = 0.050    !ADIPOSE TISSUE, WANG ET AL. 1997
CONSTANT WREB0           = 0.030    !REST OF THE BODY, WANG ET AL. 1997
CONSTANT WLIB0           = 0.266    !LIVER, WANG ET AL. 1997
CONSTANT WPLAB0          = 0.500    !ASSUME HIGHLY VASCULARIZED

! EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG       = 0.0       !TIME ELAPSED BEFORE EXPOSURE BEGINS
(WEEK)
CONSTANT WEEK_PERIOD     = 168.0      ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH     = 168.0      ! TIME EXPOSURE ENDS (HOURS)
```

```
! NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LAG      = 0.0       !TIME ELAPSED BEFORE EXPOSURE BEGINS
(MONTHS)

!======= CONSTANT FOR BACKGROUND EXPOSURE===========
CONSTANT Day_LAG_BG     = 0.0       ! TIME ELAPSED BEFORE EXPOSURE BEGINS
(HOURS)
CONSTANT Day_PERIOD_BG   = 24.0       !LENGTH OF EXPOSURE (HOURS)

! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG_BG    = 0.0      !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
BEGINS (WEEK)
CONSTANT WEEK_PERIOD_BG  = 168.0      ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH_BG  = 168.0      !TIME EXPOSURE ENDS (HOURS)


! CONSTANT USED IN CARDIAC OUTPUT EQUATION
CONSTANT QCC            =  15.36    ![L/KG-H], EMOND ET AL. 2004

! COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID
!Data from Emonds Thesis 2001
CONSTANT F_TOTLIP         =    0.8000       ! ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP         =    0.0057       ! BLOOD (UNITLESS)
CONSTANT RE_TOTLIP        =    0.0190       ! REST OF THE BODY (UNITLESS)
CONSTANT LI_TOTLIP        =    0.0670       ! LIVER (UNITLESS)
CONSTANT PLA_TOTLIP       =    0.019       ! PLACENTA (UNITLESS)
CONSTANT FETUS_TOTLIP     =    0.019     ! FETUS (UNITLESS)

CONSTANT MEANLIPID        =    974

END  ! END OF THE INITIAL SECTION

DYNAMIC ! DYNAMIC SIMULATION SECTION

ALGORITHM  IALG          =           2        ! GEAR METHOD
CINTERVAL  CINT          =          0.1       ! COMMUNICATION INTERVAL
MAXTERVAL  MAXT          =        1.0e+10     ! MAXIMUM CALCULATION INTERVAL
MINTERVAL  MINT          =        1.0E-10     ! MINIMUM CALCULATION INTERVAL
VARIABLE   T             =          0.0
CONSTANT   TIMELIMIT     =          100       !SIMULATION LIMIT TIME (HOUR)
CONSTANT      Y0           =          0.0      ! AGE (YEARS) AT BEGINNING OF
SIMULATION
CONSTANT   GROWON        =          1.0      ! INCLUDE BODY WEIGHT AND HEIGHT
GROWTH? (1=YES, 0=NO)

 CINTXY  = CINT
 PFUNC   = CINT

   !TIME TRANSFORMATION
 DAY= T/24.0
 WEEK  =T/168.0
 YEAR=Y0+T/8760.0                              ! TIME IN YEARS
  GYR =Y0 + growon*T/8760.0                    ! TIME FOR USE IN GROWTH
EQUATION

DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS
```

```
!====== CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
! NUMBER OF EXPOSURES PER DAY

 DAY_LAG         = EXP_TIME_ON    ! TIME ELAPSED BEFORE EXPOSURE BEGINS
(HOURS)
 DAY_PERIOD       = DAY_CYCLE      ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH       = CINTXY         ! LENGTH OF EXPOSURE (HOURS)
 MONTH_PERIOD     = TIMELIMIT      ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH     = EXP_TIME_OFF   ! LENGTH OF EXPOSURE (MONTHS)


! NUMBER OF EXPOSURES PER DAY AND MONTH
 DAY_FINISH_BG    = CINTXY
 MONTH_LAG_BG    = BCK_TIME_ON    !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
BEGINS (MONTHS)
 MONTH_PERIOD_BG  = TIMELIMIT      !BACKGROUND EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH_BG  = BCK_TIME_OFF   !LENGTH OF BACKGROUND EXPOSURE (MONTHS)

! INTRAVENOUS LATE
 IV_FINISH = CINTXY
 B = 1-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER

! MOTHER BODY WEIGHT GROWTH EQUATION
! MODIFICATION TO ADAPT THIS MODEL AT HUMAN MODEL
! BECAUSE LINEAR DESCRIPTION IS NOT GOOD ENOUGH FOR MOTHER GROWTH
! MOTHER BODY WEIGHT GROWTH
! HUMAN BODY WEIGHT (0 TO 45 YEARS)
! POLYNOMIAL REGRESSION EXPRESSION WRITTEN
!APRIL 10 2008, OPTIMIZED WITH DATA OF PELEKIS ET AL. 2001
! POLYNOMIAL REGRESSION EXPRESSION WRITTEN WITH
!HUH AND BOLCH 2003 FOR BMI CALCULATION

! BODY WEIGHT CALCULATION.  UNIT IN KG FOR GESTATIONAL PORTION

     WT0 = (0.0006*GYR**3 - 0.0912*GYR**2 + 4.32*GYR + 3.652)

 !BODY MASS INDEX CALCULATION

     BH =  -2D-5*GYR**4+4.2D-3*GYR**3.0-0.315*GYR**2.0+9.7465*GYR+72.098
!HEIGHT EQUATION FORMULATED FOR USE FROM 0 TO 70 YEARS
     BHM= (BH/100.0)!HUMAN HEIGHT IN METER (BHM)
     HBMI= WT0/(BHM**2.0) ! HUMAN BODY MASS INDEX (BMI)


!MODIFICATION IN KG
RTESTGEST= T-CONCEPTION_T ! TIME FOR FETAL GROWTH
TESTGEST=DIM(RTESTGEST,0.0)
! GROWTH OF FETAL TISSUE
GESTATTION_FE=((4d-15*TESTGEST**4 -3d-11*TESTGEST**3 +1d-7*TESTGEST**2 -8d-
5*TESTGEST +0.0608))
   WTFER= DIM(GESTATTION_FE,0.0) ! FETAL COMPARTMENT WEIGHT
 WTFE= WTFER

!//////////////////////////////////////////////////////////////////////
! FAT GROWTH EXPRESSION LINEAR DURING PREGNANCY
! FROM O'FLAHERTY_1992
!//////////////////////////////////////////////////////////////////////
```

```
WT0GR= WT0*1.0e3    ! MOTHER BODY WEIGHT IN G

WF0 =(-6.36D-20*WT0GR**4.0 +1.12D-14*WT0GR**3.0 &
           -5.8D-10*WT0GR**2.0+1.2D-5*WT0GR+5.91D-2) ! MOTHER FAT COMPARTMENT
GROWTH

!//////////////////////////////////////////////////////////////////////
! WPLA PLACENTA GROWTH EXPRESSION, SINGLE EXPONENTIAL WITH OFFSET
! FROM O'FLAHERTY_1992  ! FOR EACH PUP
!//////////////////////////////////////////////////////////////////////
!SAME EQUATION THEN THE FORST MODEL. BODY WEIGHT KEPT IN G
!A CORRECTION FOR THE BODY WEIGHT (WTO(KG)*1000 = WTOGR)

WPLA0N_HUMAN= (850*exp(-9.434*(exp(-5.23d-4*(TESTGEST)))))
 WPLA0R = WPLA0N_HUMAN/WT0GR
 WPLA0W = DIM(WPLA0R,0.0) ! PLACENTA WEIGHT
  WPLA0=WPLA0W

!//////////////////////////////////////////////////////////////////////
! QPLA PLACENTA GROWTH EXPRESSION, DOUBLE EXPONENTIAL WITH OFFSET
! FROM O'FLAHERTY_1992
!//////////////////////////////////////////////////////////////////////

QPLAF_HUMAN= SWITCH_trans*((1d-10*TESTGEST**3.0 -5D-7*TESTGEST**2.0
+0.0017*TESTGEST+1.1937)/QC)
  GEST_QPLAF=DIM(QPLAF_HUMAN,0.0) ! PLACENTA BLOOD FLOW RATE
  QPLAF =GEST_QPLAF

! LIVER,VOLUME FRACTION  (HUMAN 0 TO 70 YEARS)
! APPROACH BASED ON LUECKE (2007)
 WLI0= (3.59D-2 -(4.76D-7*WT0GR)+(8.50D-12*WT0GR**2.0)-(5.45D-17*WT0GR**3.0))
! LIVER VOLUME IN GROWING HUMAN

! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGAN
 WRE0 = (0.91-(WLIB0*WLI0+WFB0*WF0+ WPLAB0*WPLA0 + WLI0 + WF0 +
WPLA0))/(1+WREB0)
 QREF = 1-(QFF+QLIF+QPLAF)            !REST BODY BLOOD FLOW (ML/HR)
 QTTQF = QFF+QREF+QLIF+QPLAF          ! SUM MUST EQUAL 1

! COMPARTMENT TISSUE BLOOD VOLUME (L) =========
 WF  =  WF0  * WT0                    ! ADIPOSE TISSUE
 WRE =  WRE0 * WT0                    ! REST OF THE BODY
 WLI =  WLI0 * WT0                    ! LIVER
 WPLA=  WPLA0* WT0                    ! PLACENTA

! COMPARTMENT TISSUE VOLUME (L) =========
 WFB  =  WFB0  * WF                   ! ADIPOSE TISSUE
 WREB =  WREB0 * WRE                  ! REST OF THE BODY
 WLIB =  WLIB0 * WLI                  ! LIVER
 WPLAB = WPLAB0* WPLA                 ! PLACANTA

! TOTAL VOLUME OF COMPARTMENT (L)======
WFT =   WF                            ! TOTAL ADIPOSE TISSUE
WRET =  WRE                           ! TOTAL REST OF THE BODY
WLIT =  WLI                           ! TOTAL LIVER TISSUE
WPLAT=  WPLAB                         ! TOTAL PLACENTA TISSUE
```

```
! CONSTANT USED IN CARDIAC OUTPUT EQUATION

! UNIT CHANGED ON JULY 14 2009  (L/HR)
QC= QCC*(WT0)**0.75

QF  = QFF*QC                          ! ADIPOSE TISSUE BLOOD FLOW RATE (L/HR)
QLI = QLIF*QC                         ! LIVER TISSUE BLOOD FLOW RATE (L/HR)
QRE = QREF*QC                         !REST OF THE BODY BLOOD FLOW RATE (L/HR)
QPLA = QPLAF*QC                       !PLACENTA TISSUE BLOOD FLOW RATE (L/HR)
QTTQ = QF+QRE+QLI+QPLA     !TOTAL FLOW RATE (L/HR)

! ========= DIFFUSIONAL PERMEABILITY FACTORS FRACTION ORGAN FLOW =========
PAF  = PAFF*QF                        ! ADIPOSE TISSUE BLOOD FLOW RATE (L/HR)
PARE = PAREF*QRE                      ! REST OF THE BODY BLOOD FLOW RATE
(L/HR)
PALI = PALIF*QLI                      ! LIVER TISSUE BLOOD FLOW RATE (L/HR)
PAPLA = PAPLAF*QPLA                   ! PLACENTA TISSUE BLOOD FLOW RATE (L/HR)

!*************************************
! ABSORPTION SECTION
! ORAL
! INTRAPERITONEAL
! SUBCUTANEOUS
! INTRAVENOUS
!*************************************

!BACKGROUND EXPOSURE
!EXPOSURE FOR STEADY STATE CONSIDERATION
!REPETITIVE EXPOSURE SCENARIO

MSTOT_NMBCKGR = MSTOTBCKGR/322       !AMOUNT IN NMOL/G
MSTTBCKGR =MSTOT_NMBCKGR *WT0

DAY_EXPOSURE_BG   = PULSE(DAY_LAG_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
WEEK_EXPOSURE_BG  = PULSE(WEEK_LAG_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG = PULSE(MONTH_LAG_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
MSTTFR_BG = MSTTBCKGR/CINT

CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG

! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)

IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
    ABSMSTT_GB= MSTTFR_BG
ELSE
    ABSMSTT_GB = 0.0
END IF

CYCLETOTBG=INTEG(CYCLE_BG,0.0)

!*************************************
!MULTIROUTE  EXPOSURE
!REPETITIVE EXPOSURE SCENARIO
!*************************************
```

```
MSTT= MSTOT_NM * WT0                  !AMOUNT IN NMOL
DAY_EXPOSURE   = PULSE(DAY_LAG,DAY_PERIOD,DAY_FINISH)
WEEK_EXPOSURE  = PULSE(WEEK_LAG,WEEK_PERIOD,WEEK_FINISH)
MONTH_EXPOSURE = PULSE(MONTH_LAG,MONTH_PERIOD,MONTH_FINISH)

MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT

MSTTFR = MSTT/CINT

CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE

SUMEXPEVENT= INTEG (CYCLE,0.0) !NUMBER OF CYCLES GENERATED DURING SIMULATION

! CONDITIONAL ORAL EXPOSURE
IF (MSTTCH.EQ.MSTT) THEN
   ABSMSTT= MSTTFR
ELSE
   ABSMSTT = 0.0
END IF


 CYCLETOT=INTEG(CYCLE,0.0)

! MASS CHANGE IN THE LUMEN
 RMSTT= -(KST+KABS)*MST +ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
  MST = INTEG(RMSTT,0.0)                      !AMOUNT REMAINING IN DUODENUM
(NMOL)

! ABSORPTION IN LYMPH CIRCULATION
 LYRMLUM = KABS*MST*A
  LYMLUM = INTEG(LYRMLUM,0.0)

! ABSORPTION IN PORTAL CIRCULATION
 LIRMLUM = KABS*MST*B
  LIMLUM = INTEG(LIRMLUM,0.0)


    !IV ABSORPTION SCENARIO---------
 IV= DOSEIV_NM * WT0 !AMOUNT IN NMOL
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1-STEP(PFUNC))
 IVDOSE = integ(EXPIV,0.0)

   !IV LATE IN THE CYCLE
   !MODIFICATION JANUARY 13 2004
 IV_RlateR = DOSEIVNMlate*WT0
 IV_EXPOSURE=PULSE(IV_LAG,IV_PERIOD,IV_FINISH)

 IV_lateT = IV_EXPOSURE *IV_RlateR
 IV_late = IV_lateT/CINT

SUMEXPEVENTIV= integ(IV_EXPOSURE,0.0) !NUMBER OF CYCLES GENERATED DURING
SIMULATION

      !SYSTEMIC BLOOD COMPARTMENT
      ! MODIFICATION OCT 8 2009
CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late)/(QC+CLURI) !
```

```
 CA = CB                                    ! CONCENTRATION (NMOL/L)

     !CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late-RAURI)/QC
!(NMOL/L)

    !URINARY EXCRETION BY KIDNEY
    ! MODIFICATION OCT 8 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)

    !RAURI = CLURI * CRE
    !AURI = INTEG(RAURI,0.0)

    !UNIT CONVERSION POST SIMULATION
CONSTANT MW=322 !MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1.0e3

 CBSNGKGLIADJ = CB*MW/(0.55*B_TOTLIP) !NG SERUM LIPID ADJUSTED/KG
   AUCBS_NGKGLIADJ=integ(CBSNGKGLIADJ,0.)
CBNGKG= CB*MW   !NG/KG


    !ADIPOSE COMPARMTENT
    !TISSUE BLOOD SUBCOMPARTMENT
RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)    !(NMOL/H)
 AFB = INTEG(RAFB,0.0)                !(NMOL)
 CFB = AFB/WFB                       !(NMOL/L)
    !TISSUE SUBCOMPARTMENT
RAF = PAF*(CFB-CF/PF)                !(NMOL/H)
 AF = INTEG(RAF,0.0)                 !(NMOL)
 CF  = AF/WF                         !(NMOL/L)

    !UNIT CONVERSION POST SIMULATION
CFTOTAL= (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN NMOL/ML
CFNGKG=CFTOTAL*MW ! FAT CONCENTRATION IN NG/KG
AUCF_NGKGH=integ(CFNGKG,0.)


    !REST OF THE BODY COMPARTMENT
    !TISSUE BLOOD SUBCOMPARTMENT
RAREB= QRE *(CA-CREB)-PARE*(CREB-CRE/PRE)      !(NMOL/H)
 AREB = INTEG(RAREB,0.0)                        !(NMOL)
 CREB = AREB/WREB                              !(NMOL/L)
    !TISSUE SUBCOMPARTMENT
RARE = PARE*(CREB - CRE/PRE)                   !(NMOL/H)
 ARE = INTEG(RARE,0.0)                         !(NMOL)
 CRE  = ARE/WRE                                 !(NMOL/L)
ARETOT = ARE +AREB

    !POST SIMULATION UNIT CONVERSION
CRETOTAL= (ARE + AREB)/(WRE + WREB)            ! TOTAL CONCENTRATION (NMOL/L)
CRENGKG=CRETOTAL*MW                            ! REST OF THE BODY
CONCENTRATION (NG/KG)


    !LIVER COMPARTMENT
```

```
    !TISSUE BLOOD SUBCOMPARTMENT
 RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM ! (NMOL/HR)
  ALIB = INTEG(RALIB,0.0)                        !(NMOL)
 CLIB = ALIB/WLIB                               !(NMOL/L)
    !TISSUE SUBCOMPARMTENT
 RALI = PALI*(CLIB - CFLLIR)-REXCLI             ! (NMOL/HR)
  ALI = INTEG(RALI,0.0)                              !(NMOL)
 CLI  = ALI/WLI                                 !(NMOL/L)

    !FREE TCDD CONCENTRATION IN LIVER
      ! MODIFICATION OCTOBER 8 2009
 CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR)) &
        +((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR)*IND_ACTIVE)))-CFLLI,CFLLI0)
    CFLLIR=DIM(CFLLI,0.0) ! FREE TCDD CONCENTRATION IN LIVER
!MODIFIED FROM:
!PARAMETER (LIVER_1RMN = 1.0E-30)
! CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
!+LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2 + CFLLIR &
!+LIVER_1RMN)*IND_ACTIVE)))-CFLLI,CFLLI0)
!CFLLIR=DIM(CFLLI,0.0)

! MODIFICATION OCTOBER 8 2009
CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR) !BOUND CONCENTRATION (NMOL/L)

    !POST SIMULATION UNIT CONVERSION
CLITOTAL= (ALI + ALIB)/(WLI + WLIB) ! TOTAL CONCENTRATION (NMOL/L)
Rec_occ= CFLLIR/(KDLI+CFLLIR)
CLINGKG=CLITOTAL*MW ! LIVER CONCENTRATION IN NG/KG
  AUCLI_NGKGH=integ(CLINGKG,0.0)
CBNDLINGKG = CBNDLI*MW ! BOUND CONCENTRATION IN NG/KG
  AUCBNDLI_NGKGH =INTEG(CBNDLINGKG,0.0)

    !FRACTION INCREASE OF INDUCTION OF CYP1A2
fold_ind=CYP1A2_1OUT/CYP1A2_1A2
VARIATIONOFAC =(CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2

!VARIABLE ELIMINATION BASED ON THE CYP1A2
! MODIFICATION OCTOBER 8 2009
KBILE_LI_T = Kelv*VARIATIONOFAC! ! DOSE-DEPENDENT EXCRETION RATE CONSTANT

 REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT BILLIARY EXCRETION RATE
    EXCLI = INTEG(REXCLI,0.0)

!KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv !


!CHEMICAL IN CYP450 (1A2) COMPARTMENT

CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ ! BASAL PRODCUTION RATE OF CYP1A2
SET EQUAL TO BASAL DEGREDATION RATE

    ! MODIFICATION OCTOBER 8 2009
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
&
     /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
      - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)
!MODIFIED FROM:
```

```
!PARAMETER (CYP1A2_1RMN = 1E-30)
!CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1 + CYP1A2_1EMAX *(CBND&
!LI +CYP1A2_1RMN)**HILL/(CYP1A2_1EC50 + (CBNDLI + CYP1A2_1&
!RMN)**HILL) +CYP1A2_1RMN) - CYP1A2_1KOUT*CYP1A2_1&
!OUT, CYP1A2_1OUTZ)

! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)
CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
  CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)

CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
  CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)

    !PLACENTA COMPARTMENT
    !TISSUE BLOOD SUBCOMPARTMENT
RAPLAB= QPLA*(CA - CPLAB)-PAPLA*(CPLAB -CFLPLAR)   ! NMOL/HR)
 APLAB = INTEG(RAPLAB,0.0)                          ! (NMOL)
 CPLAB = APLAB/(WPLAB+1E-30)                       ! (NMOL/ML)
    !TISSUE SUBCOMPARTMENT
RAPLA = PAPLA*(CPLAB-CFLPLAR)-RAMPF + RAFPM        ! (NMOL/HR)
 APLA = INTEG(RAPLA,0.0)                            ! (NMOL)
 CPLA  = APLA/(WPLA+1e-30)                         ! (NMOL/ML)

    ! NEW EQUATION AUGUST 28  2009
PARAMETER (PARA_ZERO = 1.0E-30)
CFLPLA= IMPLC(CPLA-(CFLPLAR*PPLA +(PLABMAX*CFLPLAR/(KDPLA&
    +CFLPLAR+PARA_ZERO)))-CFLPLA,CFLPLA0)
CFLPLAR=DIM(CFLPLA,0.0)

    !POST SIMULATION UNIT CONVERSION
CPLATOTAL = ((APLAB+APLA)/(WPLAB+WPLA))

    !FETUS COMPARTMENT
RAFETUS= RAMPF-RAFPM
 AFETUS=INTEG(RAFETUS,0.0)
CFETUS=AFETUS/(WTFE+1.0e-30)
CFETOTAL= CFETUS
CFETUS_v = CFETUS/PFETUS

    !POST SIMULATION UNIT CONVERSION
 CFETUSNGKG = CFETUS*MW                    !(NG/KG)


    !TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
    !FETAL EXPOSURE ONLY DURING EXPOSURE

IF (T.LT.TRANSTIME_ON) THEN
 SWITCH_trans = 0.0
ELSE
 SWITCH_trans = 1
END IF

    !TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
    ! MODIFICATION 26 SEPTEMBER 2003

RAMPF = (CLPLA_FET*CPLA)*SWITCH_trans
```

```
  AMPF=INTEG(RAMPF,0.0)

    !TRANSFER OF DIOXIN FROM FETUS TO PLACENTA
RAFPM = (CLPLA_FET*CFETUS_v)*SWITCH_trans!
 AFPM = INTEG(RAFPM,0.0)

    !CHECK MASS BALANCE ----------
BDOSE= IVDOSE +LYMLUM+LIMLUM
BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB+AFETUS !
BDIFF = BDOSE-BMASSE

    !BODY BURDEN (NMOL)
BODY_BURDEN = AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB

    !BODY BURDEN CONCENTRATION (NG/KG)
 BBNGKG =(AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB)*MW/WT0

! END SIMULATION COMMAND

TERMT (T.GE. TimeLimit, 'Time limit has been reached.')

END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYNAMIC SECTION
END   ! END OF THE PROGRAM
```

E.2.2.2. *Input File*

```
output @clear
prepare @clear T  year CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG  CBNDLINGKG CBNGKG

CINT = 1
   %EXPOSURE SCENARIO
EXP_TIME_ON       = 0          %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 401190     %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE         = 24         %HOURS BETWEEN DOSES (HOUR)
BCK_TIME_ON       = 401190     %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF      = 401190     %TIME BACKGROUND EXPOSURE ENDS (HOUR)
IV_LAG            = 401190
IV_PERIOD         = 401190
    %GESTATION CONTROL
CONCEPTION_T      = 393120     %TIME OF CONCEPTION AT 45 YEARS OLD
TIMELIMIT         = 399840     %SIMULATION DURATION (HOUR)
TRANSTIME_ON      = 394632     %TRANSFER FROM MOTHER TO FETUS AT 1512 HOURS
GESTATION
    %EXPOSURE DOSE
MSTOT             = 9.977E-07  %NG OF TCDD PER KG OF BW
MSTOTBCKGR        = 0.         %ORAL BACKGROUND EXPOSURE DOSE (NG/KG)
DOSEIV            = 0.
DOSEIVLATE        = 0.

     % TRANFER MOTHER TO FETUS CLEARANCE
CLPLA_FET         = 0.001      %MOTHER TO FETUS TRANFER CLEARANCE (L/HR)
```

E.2.3. Rat Standard Model

E.2.3.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model in Rat: Standard Model (Nongestation)'

```
INITIAL  ! INITIALIZATION OF PARAMETERS

     !SIMULATION PARAMETERS
CONSTANT PARA_ZERO       =      1d-30
CONSTANT EXP_TIME_ON     =      0.0           ! TIME AT WHICH EXPOSURE BEGINS
(HOURS)
CONSTANT EXP_TIME_OFF    =     900.0           ! TIME AT WHICH EXPOSURE ENDS
(HOURS)
CONSTANT DAY_CYCLE       =     900.0            ! NUMBER OF HOURS BETWEEN
DOSES (HOURS)
CONSTANT BCK_TIME_ON     =      0.0           ! TIME AT WHICH BACKGROUND
EXPOSURE BEGINS (HOURS)
CONSTANT BCK_TIME_OFF    =      0.0           ! TIME AT WHICH BACKGROUND
EXPOSURE ENDS (HOURS)

CONSTANT MW=322 !MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1000


     !EXPOSURE DOSES
CONSTANT MSTOTBCKGR      =      0.0           !ORAL BACKGROUND EXPOSURE DOSE
(UG/KG)
CONSTANT MSTOT           =      10       !ORAL EXPOSURE DOSE (UG/KG)
CONSTANT MSTOTsc         =      0.0           !SUBCUTANEOUS EXPOSURE DOSE
(UG/KG)
CONSTANT DOSEIV          =      0.0           ! INJECTED DOSE (UG/KG)

     !ORAL DOSE
  MSTOT_NM               =   MSTOT/MW       !AMOUNT IN NMOL/G
  MSTOT_NMBCKGR          =   MSTOTBCKGR/MW  !AMOUNT IN NMOL/G

     !INTRAVENOUS DOSE
  DOSEIV_NM              =   DOSEIV/MW      !AMOUNT IN NMOL/G

     !INITIAL GUESS OF THE FREE CONCENTRATION  IN THE LIGAND (COMPARTMENT
INDICATED BELOW)====
CONSTANT CFLLI0          =     0.0            !LIVER (NMOL/ML)

     !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) (NMOL/ML) ===
CONSTANT LIBMAX          =    3.5e-4          ! LIVER (NMOL/ML), WANG ET AL.
1997

     ! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
(NMOL/ML)===
CONSTANT KDLI            =    1.0e-4          ! LIVER (AhR) (NMOL/ML), WANG
ET AL. 1997
```

```
CONSTANT KDLI2           =    4.0e-2          !LIVER (1A2) (NMOL/ML), EMOND
ET AL. 2004

     !EXCRETION AND ABSORPTION CONSTANT [RAT]
CONSTANT KST             =    0.36            ! GASTRIC RATE CONSTANT (HR-1),
WANG ET AL. (1997)
CONSTANT KABS            =    0.48            !INTESTINAL ABSORPTION CONSTANT
(HR-1), WANG ET AL. 1997

     !URINARY ELIMINATION CLEARANCE (ML/HR)
CONSTANT CLURI           =     0.01           !URINARY CLEARANCE (ML/HR),
EMOND ET AL. 2004

     !INTERSPECIES VARIABLE ELIMINATION
CONSTANT KELV            =     0.15           ! INTERSPECIES VARIABLE
ELIMINATION CONSTANT (1/HOUR) (OPTIMIZED), EMOND ET AL. 2004

     ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A               =     0.7            ! LYMPHATIC FRACTION, WANG ET
AL. 1997

     !PARTITION COEFFICIENTS
CONSTANT PF              =     100            ! ADIPOSE TISSUE/BLOOD, WANG ET
AL. 1997
CONSTANT PRE             =     1.5            ! REST OF THE BODY/BLOOD, WANG
ET AL. 1997
CONSTANT PLI             =     6.0              ! LIVER/BLOOD, WANG ET AL.
1997

     !PARAMETER FOR INDUCTION OF CYP 1A2 [MOUSE] ===
CONSTANT IND_ACTIVE       =     1.0            ! INCLUDE INDUCTION? (1 = YES,
0 = NO)
CONSTANT CYP1A2_1OUTZ    =     1.6            ! DEGRADATION CONCENTRATION
CONSTANT OF 1A2 (NMOL/ML), WANG ET AL. 1997
CONSTANT CYP1A2_1A1      =     1.6            ! BASAL CONCENTRATION OF 1A1
(NMOL/ML), WANG ET AL. 1997
CONSTANT CYP1A2_1EC50    =     0.13           ! DISSOCIATION CONSTANT TCDD-
CYP1A2 (NMOL/ML) , WANG ET AL. 1997
CONSTANT CYP1A2_1A2      =     1.6            ! BASAL CONCENTRATION OF 1A2
(NMOL/ML) Wang et al (1997)
CONSTANT CYP1A2_1KOUT    =     0.1            ! FIRST ORDER RATE OF
DEGRADATION (H-1), WANG ET AL. 1997
CONSTANT CYP1A2_1TAU     =     0.25           ! HOLDING TIME (H), WANG ET AL.
1997
CONSTANT CYP1A2_1EMAX    =     600            ! MAXIMUM INDUCTION OVER BASAL
EFFECT (UNITLESS), WANG ET AL. 1997
CONSTANT HILL            =     0.6      !HILL CONSTANT; COOPERATIVE LIGAND
BINDING EFFECT CONSTANT (UNITLESS)

   !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT
CONSTANT QFF  = 0.069                          ! ADIPOSE TISSUE BLOOD FLOW
FRACTION (UNITLESS), WANG ET AL. 1997
CONSTANT QLIF = 0.183                          ! LIVER (UNITLESS), WANG ET AL.
1997

     !DIFFUSIONAL PERMEABILITY FRACTION
```

```
CONSTANT PAFF            = 0.0910             ! ADIPOSE (UNITLESS), WANG ET
AL. 1997
CONSTANT PAREF           = 0.0298             ! REST OF THE BODY (UNITLESS),
WANG ET AL. 1997
CONSTANT PALIF           = 0.35               ! LIVER (UNITLESS), WANG ET AL.
1997

     !FRACTION OF TISSUE VOLUME (UNITLESS)
CONSTANT WLI0            =  0.0360            ! LIVER, WANG ET AL. 1997
CONSTANT WF0             =  0.069             ! BLOOD, WANG ET AL. 1997

     !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL
COMPARTMENT VOLUME =========
CONSTANT WFB0            =  0.050             ! ADIPOSE TISSUE, WANG ET AL.
1997
CONSTANT WREB0           =  0.030             ! REST OF THE BODY, WANG ET AL.
1997
CONSTANT WLIB0           =  0.266             ! LIVER , WANG ET AL. 1997

     !EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
     ! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG       = 0.0                 ! TIME ELAPSED BEFORE EXPOSURE
BEGINS (WEEK)
CONSTANT WEEK_PERIOD     = 168.0                ! NUMBER OF HOURS IN THE WEEK
(HOURS)
CONSTANT WEEK_FINISH     = 168.0                ! TIME EXPOSURE ENDS (HOURS)

     !NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LAG      = 0.0                 ! TIME ELAPSED BEFORE EXPOSURE
BEGINS (MONTH)

     !SET FOR BACKGROUND EXPOSURE===========
     !CONSTANT FOR BACKGROUND EXPOSURE===========
CONSTANT Day_LAG_BG     = 0.0                 ! TIME ELAPSED BEFORE EXPOSURE
BEGINS (HOURS)
CONSTANT Day_PERIOD_BG   = 24.0                ! LENGTH OF EXPOSURE (HOURS)

     !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG_BG    = 0.0                ! DELAY BEFORE BACKGROUND
EXPOSURE (WEEK)
CONSTANT WEEK_PERIOD_BG  = 168.0                !NUMBER OF HOURS IN THE WEEK
(HOURS)
CONSTANT WEEK_FINISH_BG  = 168.0                ! TIME EXPOSURE ENDS (HOURS)

     !GROWTH CONSTANT FOR RAT
     !CONSTANT FOR MOTHER BODY WEIGHT GROWTH ======
CONSTANT BW_T0 = 250.0                          !(IN G) CHANGED FOR
SIMULATION

     ! CONSTANT USED IN CARDIAC OUTPUT EQUATION
CONSTANT QCCAR =311.4                          !CONSTANT (ML/MIN/KG), WANG ET
AL.

     ! COMPARTMENT TOTAL LIPID FRACTION
CONSTANT F_TOTLIP        = 0.855              !ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP        = 0.0033             !BLOOD (UNITLESS)
CONSTANT RE_TOTLIP       = 0.019              !REST OF THE BODY (UNITLESS)
```

```
CONSTANT LI_TOTLIP       = 0.06               !LIVER (UNITLESS)

END      !END OF THE INITIAL SECTION

DYNAMIC  !DYNAMIC SIMULATION SECTION

ALGORITHM  IALG          =           2        ! GEAR METHOD
CINTERVAL  CINT          =          0.1       ! COMMUNICATION INTERVAL
MAXTERVAL  MAXT          =        1.0e+10     ! MAXIMUM CALCULATION INTERVAL
MINTERVAL  MINT          =        1.0E-10     ! MINIMUM CALCULATION INTERVAL
VARIABLE   T             =          0.0
CONSTANT   TIMELIMIT     =          900.0       !SIMULATION TIME LIMIT
(HOURS)
 CINTXY  = CINT
 PFUNC   = CINT

         !TIME CONVERSION
  DAY=T/24.0                                     ! TIME IN DAYS
  WEEK =T/168.0                                  ! TIME IN WEEKS
  MONTH =T/730.0                                 ! TIME IN MONTHS
  YEAR=T/8760.0                                  ! TIME IN YEARS


DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

        !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
        !NUMBER OF EXPOSURES PER DAY
 DAY_LAG     = EXP_TIME_ON                  ! TIME ELAPSED BEFORE EXPOSURE
BEGINS (HOURS)
 DAY_PERIOD   = DAY_CYCLE                    ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH   = CINTXY                       ! LENGTH OF EXPOSURE (HOURS)
 MONTH_PERIOD = TIMELIMIT                    ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH = EXP_TIME_OFF                 ! LENGTH OF EXPOSURE (MONTHS)

        !NUMBER OF EXPOSURES PER DAY AND MONTH
 DAY_FINISH_BG   = CINTXY                    ! LENGTH OF EXPOSURE (HOURS)
 MONTH_LAG_BG   = BCK_TIME_ON               ! TIME ELAPSED BEFORE BACKGROUND
EXPOSURE BEGINS (MONTHS)
 MONTH_PERIOD_BG = TIMELIMIT                 ! BACKGROUND EXPOSURE PERIOD
(MONTHS)
 MONTH_FINISH_BG = BCK_TIME_OFF              ! LENGTH OF BACKGROUND EXPOSURE
(MONTHS)


  B = 1-A                                   ! FRACTION OF DIOXIN ABSORBED IN
THE PORTAL FRACTION OF THE LIVER

        ! BODY WEIGHT GROWTH EQUATION========
 PARAMETER (BW_RMN = 1.0E-30)
 WT0= (BW_T0 *(1.0+(0.41*T)/(1402.5+T+BW_RMN))) ! IN GRAMS

        !VARIABILITY OF REST OF THE BODY DEPEND OTHERS ORGAN
 WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 + WLI0 + WF0))/(1.0+WREB0) !REST OF
THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
 QREF = 1.0-(QFF+QLIF)                        !REST OF BODY BLOOD FLOW
 QTTQF = QFF+QREF+QLIF                      ! SUM MUST EQUAL 1
```

```
        !COMPARTMENT VOLUME (G OR ML) =========
 WF  =  WF0  * WT0                          ! ADIPOSE
 WRE =  WRE0 * WT0                          ! REST OF THE BODY
 WLI =  WLI0 * WT0                          ! LIVER

        !COMPARTMENT TISSUE BLOOD VOLUME (G OR ML) =========
 WFB  =  WFB0  * WF                         ! ADIPOSE
 WREB =  WREB0 * WRE                        ! REST OF THE BODY
 WLIB =  WLIB0 * WLI                        ! LIVER

        !CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
  QC= QCCAR*60.0*(WT0/UNITCORR)**0.75

        ! COMPARTMENT BLOOD FLOW (ML/HR)
  QF  = QFF*QC                              ! ADIPOSE TISSUE BLOOD FLOW RATE
  QLI = QLIF*QC                             ! LIVER TISSUE BLOOD FLOW RATE
  QRE = QREF*QC                             ! REST OF THE BODY BLOOD FLOW
RATE
  QTTQ = QF+QRE+QLI                    ! TOTAL FLOW RATE

        !PERMEABILITY ORGAN FLOW (ML/HR)
PAF  = PAFF*QF                              ! ADIPOSE
PARE = PAREF*QRE                            ! REST OF THE BODY
PALI = PALIF*QLI                            ! LIVER TISSUE

        !CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
        !EXPOSURE + !REPETITIVE EXPOSURE SCENARIO
  IV= DOSEIV_NM * WT0  !AMOUNT IN NMOL
  MSTT= MSTOT_NM * WT0 !AMOUNT IN NMOL
  MSTTBCKGR =MSTOT_NMBCKGR *WT0

        !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIOS
  DAY_EXPOSURE_BG   = PULSE(DAY_LAG_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
  WEEK_EXPOSURE_BG  = PULSE(WEEK_LAG_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
  MONTH_EXPOSURE_BG = PULSE(MONTH_LAG_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

  MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
  MSTTFR_BG = MSTTBCKGR/CINT

  CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG

IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
    ABSMSTT_GB= MSTTFR_BG
ELSE
    ABSMSTT_GB = 0.0
END IF


        !REPETITIVE ORAL MAIN EXPOSURE SCENARIO
  DAY_EXPOSURE   = PULSE(DAY_LAG,DAY_PERIOD,DAY_FINISH)
  WEEK_EXPOSURE  = PULSE(WEEK_LAG,WEEK_PERIOD,WEEK_FINISH)
  MONTH_EXPOSURE = PULSE(MONTH_LAG,MONTH_PERIOD,MONTH_FINISH)

  MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
  CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
  MSTTFR = MSTT/CINT
```

```
  SUMEXPEVENT= integ (CYCLE,0.0) !NUMBER OF CYCLES GENERATED DURING
SIMULATION


        !CONDITIONAL ORAL EXPOSURE
IF (MSTTCH.EQ.MSTT) THEN
   ABSMSTT= MSTTFR
ELSE
   ABSMSTT = 0.0
END IF

 CYCLETOT=INTEG(CYCLE,0.0)

        !MASS CHANGE IN THE LUMEN
 RMSTT  = -(KST+KABS)*MST+ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
   MST = INTEG(RMSTT,0.0)  !AMOUNT REMAINING IN DUODENUM (NMOL)

        !ABSORPTION IN LYMPH CIRCULATION
 LYRMLUM = KABS*MST*A
   LYMLUM = INTEG(LYRMLUM,0.0)

        !ABSORPTION IN PORTAL CIRCULATION
 LIRMLUM = KABS*MST*B
   LIMLUM = INTEG(LIRMLUM,0.0)

        !PERCENT OF DOSE REMAINING IN THE GI TRACT


        !ABSORPTION of Dioxin by IV route---------
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1.0-STEP(PFUNC))
   IVDOSE = integ(EXPIV,0.0)

        !SYSTEMIC BLOOD COMPARTMENT
        ! MODIFICATION ON OCTOBER 6, 2009
CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM)/(QC+CLURI) !
   CA = CB

        !URINARY EXCRETION BY KIDNEY
        ! MODIFICATION ON OCTOBER 6, 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)

        !CONVERSION EQUATION POST SIMULATION

 CBNGKG = CB*MW*UNITCORR ![NG/KG]


CBSNGKGLIADJ= (CB*MW*UNITCORR*(1.0/B_TOTLIP)*(1.0/SERBLO))![NG of TCDD
Serum/Kg OF LIPID]

       !ADIPOSE TISSUE COMPARTMENT
       !TISSUE BLOOD SUBCOMPARTMENT
 RAFB = QF*(CA-CFB)-PAF*(CFB-CF/PF)                !(NMOL/HR)
   AFB = INTEG(RAFB,0.0)                            !(NMOL)
   CFB = AFB/WFB                                   !(NMOL/ML)
       !TISSUE SUBCOMPARTMENT
```

```
 RAF  = PAF*(CFB-CF/PF)                            !(NMOL/HR)
   AF  = INTEG(RAF,0.0)                             !(NMOL)
   CF  = AF/WF                                     !(NMOL/ML)

      !CONVERSION EQUATION POST SIMULATION
   CFTOTAL    = (AF + AFB)/(WF + WFB)       !TOTAL CONCENTRATION IN NMOL/ML

   CFNGKG   = CFTOTAL*MW*UNITCORR           ! CONCENTRATION [NG/KG]

      !REST OF THE BODY COMPARTMENT
      ! TISSUE BLOOD SUBCOMPARTMENT
 RAREB= QRE*(CA-CREB)-PARE*(CREB-CRE/PRE)           !(NMOL/HR)
   AREB = INTEG(RAREB,0.0)                           !(NMOL)
   CREB = AREB/WREB                                 !(NMOL/ML)
      ! TISSUE COMPARTMENT
 RARE = PARE*(CREB - CRE/PRE)                       !(NMOL/HR)
   ARE = INTEG(RARE,0.0)                                !(NMOL)
   CRE  = ARE/WRE                                  !(NMOL/ML)

   !CONVERSION EQUATION POST SIMULATION
   CRETOTAL= (ARE + AREB)/(WRE + WREB)              ! TOTAL CONCENTRATION IN
NMOL/ML

   CTREPGG= CRETOTAL*MW*UNITCORR !(PG/ML)
    AUC_REPGG = integ(CTREPGG,0.0)

   !LIVER COMPARTMENT
   !TISSUE BLOOD COMPARTMENT
 RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM   !(NMOL/HR)
   ALIB = INTeg(RALIB,0.0)                           !(NMOL)
   CLIB = ALIB/WLIB
   !TISSUE COMPARTMENT
 RALI =  PALI*(CLIB-CFLLIR)-REXCLI                  !(NMOL/HR)
   ALI = integ(RALI,0.0)                                !(NMOL)
   CLI  = ALI/WLI                                   !(NMOL/ML)


PARAMETER (LIVER_1RMN = 1.0E-30)
CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
+LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR &
+LIVER_1RMN)*IND_ACTIVE)))-CFLLIR,CFLLI0) ! FREE TCDD CONCENTRATION IN LIVER
CFLLIR=DIM(CFLLI,0.0)

  CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND CONCENTRATION

      !CONVERSION EQUATION POST SIMULATION
  CLITOTAL= (ALI + ALIB)/(WLI + WLIB)                ! TOTAL CONCENTRATION IN
NMOL/ML

  rec_occ_AHR= (CFLLIR/(KDLI+CFLLIR+1))*100.0          ! PERCENT OF AhR
OCCUPANCY
  PROT_occ_1A2= (CFLLIR/(KDLI2+CFLLIR))*100.0          ! PERCENT OF 1A2
OCCUPANCY
  CLINGKG =(CLITOTAL*MW*UNITCORR)
  CBNDLINGKG = CBNDLI*MW*UNITCORR
    AUCLI_NGKGH=INTEG(CLINGKG,0.0)
  CLINGG=CLITOTAL*MW
```

```
       !VARIABLE ELIMINATION HALF-LIFE BASED ON THE CONCENTRATION OF CYP1A2
    KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv ! INDUCED BILIARY
EXCRETION RATE CONSTANT

 REXCLI= (KBILE_LI_T*CFLLIR*WLI) ! DOSE-DEPENDENT BILIARY EXCRETION RATE
   EXCLI = INTEG(REXCLI,0.0)

     !CHEMICAL IN CYP450 (1A2) COMPARTMENT
  !===PARAMETER FOR INDUCTION OF CYP1A2

 CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ ! BASAL RATE OF CYP1A2 PRODUCTION
SET EQUAL TO BASAL RATE OF DEGREDATION


     ! MODIFICATION ON OCTOBER 6, 2009
 CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-
30)**HILL &
     /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &-
      - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)

! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)

 CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
    CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)
 CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
    CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)

! ------------CHECK MASS BALANCE ----------
  BDOSE= LYMLUM+LIMLUM+IVDOSE
  BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI
      BDIFF = BDOSE-BMASSE

!---------------BODY BURDEN------------------------
  BBNGKG =(((AFB+AF+AREB+ARE+ALIB+ALI)*MW)/(WT0/UNITCORR)) !
! ------------ END OF THE SIMULATION COMMAND ----------

TERMT (T.GE. TimeLimit, 'Time limit has been reached.')

END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYNAMIC SIMULATION SECTION
END   ! END OF THE PROGRAM.
```

E.2.3.2. *Input Files*

E.2.3.2.1. *Cantoni et al. (1981)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

%Cantoni et al. 1981
%protocol:  oral exposure 1 dose/week for 45 weeks; female CD-COBS rats
%dose levels: 0.01, 0.1, 1  ug/kg 1 dose/week for 45 weeks
%dose levels: 10, 100, 1000 ng/kg 1 dose/week for 45 weeks
```

```
%dose levels equivalent to: 1.43, 14.3 143 ng/kg 7 days/week for 45 weeks

MAXT              = 0.01
CINT              = 0.1
EXP_TIME_ON       = 0.       %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 7560     %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE         = 168      %HOURS BETWEEN DOSES
BCK_TIME_ON       = 0.       %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF      = 0.       %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT         = 7560     %SIMULATION DURATION (HOUR)
BW_T0             = 125      %BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT          = 0.01     %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT        = 0.1       %ORAL EXPOSURE DOSE (UG/KG)
   MSTOT        = 1          %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.2. *Chu et al. (2007) and Chu et al. (2001)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Chu et al. 2007
%protocol:  oral exposure daily for 28 days
%dose levels: 0.0025, 0.025, 0.250, 1.0 ug/kg every day for 28 days
%dose levels = 2.5, 25, 250, 1000 ng/kg every day for 28 days
MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.          %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  672.        %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  24.         %HOURS BETWEEN DOSES
BCK_TIME_ON     =  0.          %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF    =  0.          %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT       =  672.        %SIMULATION DURATIOHN (HOUR)
BW_T0           =  200.        %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT         = 0.0025      %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.025       %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.250       %ORAL EXPOSURE DOSE (UG/KG)
  MSTOT         = 1.0          %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.3. *Crofton et al. (2005)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Crofton et al. 2005
%protocol:  oral exposure daily for 4 days
%dose levels: 0.0001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, and 10 ug/kg every
day for four days
```

```
%dose levels: 0.1, 3, 10, 30, 100, 300, 1000, 3000, and 10000 ng/kg every day
for four days

MAXT            =  0.001
CINT            =  0.1
EXP_TIME_ON     =  0.          %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  96.         %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  24.         %HOURS BETWEEN DOSES
BCK_TIME_ON     =  0.          %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
BCK_TIME_OFF    =  0.          %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT       =  96.         %SIMULATION DURATION (HOUR)
BW_T0           =  250         %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  MSTOT           = 0.0001     %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.003       %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.01        %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.03        %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.1         %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.3         %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 1.          %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 3.          %ORAL EXPOSURE DOSE (UG/KG)
  MSTOT         = 10.          %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.4. *Croutch et al. (2005)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Croutch et al., 2005

 MAXT            = 0.001
 CINT            = 0.1
 TIMELIMIT       = 672       %SIMULATION DURATION (HOUR)
 EXP_TIME_ON     = 72        %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 672       %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 72        %HOURS BETWEEN DOSES
 WEEK_FINISH     = 672       %LENGTH OF EXPOSURE (HOUR)
 BCK_TIME_ON     = 0.        %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
 BCK_TIME_OFF    = 0.02      %TIME BACKGROUND EXPOSURE ENDS (HOUR)
  BW_T0          = 250       %BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOTBCKGR      = 0.0125  %INITIAL LOADING DOSE [UG/KG]
   %MSTOT           = 0.00125 %EXPOSURE DOSE [UG/KG]
   %MSTOTBCKGR   = 0.05       %INITIAL LOADING DOSE [UG/KG]
   %MSTOT        = 0.005      %EXPOSURE DOSE [UG/KG]
   %MSTOTBCKGR   = 0.2        %INITIAL LOADING DOSE [UG/KG]
   %MSTOT        = 0.02       %EXPOSURE DOSE [UG/KG]
   %MSTOTBCKGR   = 0.8        %INITIAL LOADING DOSE [UG/KG]
   %MSTOT        = 0.08       %EXPOSURE DOSE [UG/KG]
   MSTOTBCKGR   = 3.2         %INITIAL LOADING DOSE [UG/KG]
```

```
   MSTOT        = 0.32        %EXPOSURE DOSE [UG/KG]
```

E.2.3.2.5. *Fattore et al. (2000)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Fattore et al. 2000
%protocol:  oral exposure in diet for 13 weeks; SD rats
%dose levels:  0.02, 0.1, 0.2, 2 ug/kg 7 days/week for 13 weeks
%dose levels equivalent to: 20, 100, 200, 2000 ng/kg 7 days/week for 13 weeks

MAXT = 0.01
CINT  = 0.1
EXP_TIME_ON       = 0.        %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 2184      %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE         = 24        %HOURS BETWEEN DOSES
BCK_TIME_ON       = 0.        %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF      = 0.        %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT         = 2184      %SIMULATION DURATION (HOUR)
BW_T0             = 150       %BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT            = 0.02     %EXPOSURE DOSE IN UG/KG
  %MSTOT          = 0.1       %EXPOSURE DOSE IN UG/KG
  %MSTOT          = 0.2       %EXPOSURE DOSE IN UG/KG
  MSTOT          = 2          %EXPOSURE DOSE IN UG/KG
```

E.2.3.2.6. *Fox et al. (1993)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Fox 1993

 MAXT             = 0.001
 CINT             = 0.1
 TIMELIMIT        = 336       %SIMULATION DURATION (HOUR)
 EXP_TIME_ON      = 96        %TIME EXPOSURE BEGINS(HOUR)
 EXP_TIME_OFF     = 336       %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE        = 96        %HOURS BETWEEN DOSES
 BCK_TIME_ON      = 0.        %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
 BCK_TIME_OFF     = 0.02      %TIME BACKGROUND EXPOSURE ENDS (HOUR)
  BW_T0            = 200      %BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
   MSTOTBCKGR      = 0.005    %INITIAL LOADING DOSE [UG/KG]
   MSTOT           = 0.0009   %EXPOSURE DOSE [UG/KG]
   %MSTOTBCKGR   = 2.5        %INITIAL LOADING DOSE [UG/KG]
   %MSTOT        = 0.6        %EXPOSURE DOSE [UG/KG]
```

```
   %MSTOTBCKGR   = 12.        %INITIAL LOADING DOSE [UG/KG]
   %MSTOT        = 3.5        %EXPOSURE DOSE [UG/KG]
```

E.2.3.2.7. *Franc et al. (2001) Sprague-Dawley rats*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Franc et al. 2001
% dose levels: 0.140, 0.420, and 1.400 ug/kg every 2 weeks for 22 weeks
% dose levels: 140, 420, and 1400 ng/kg every 2 weeks for 22 weeks
% dose levels equivalent to 10, 30, and 100 ng/kg-day

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.          %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  3696.       %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  336.
BCK_TIME_ON     =  0.           %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF    =  0.           %TIME OF BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT       =  3696.        %SIMULATION DURATION (HOUR)
BW_T0           =  200.         %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT         = 0.14        %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT         = 0.42        %ORAL EXPOSURE DOSE (UG/KG)
   MSTOT         = 1.4          %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.8. *Franc et al. (2001) Long-Evans rats*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Franc et al. 2001
% dose levels: 0.140, 0.420, and 1.400 ug/kg every 2 weeks for 22 weeks
% dose levels: 140, 420, and 1400 ng/kg every 2 weeks for 22 weeks
% dose levels equivalent to 10, 30, and 100 ng/kg-day

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.            %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  3696.         %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  336.          %HOURS BETWEEN DOSES
BCK_TIME_ON     =  0.            %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF    =  0.            %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT       =  3696.         %SIMULATION DURATION (HOUR)
BW_T0           =  190.          %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT         = 0.14         %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT         = 0.42         %ORAL EXPOSURE DOSE (UG/KG)
```

```
   MSTOT         = 1.4           %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.9. *Franc et al. (2001) Hans Wistar rats*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Franc et al. 2001
% dose levels: 0.140, 0.420, and 1.400 ug/kg every 2 weeks for 22 weeks
% dose levels: 140, 420, and 1400 ng/kg every 2 weeks for 22 weeks
% dose levels equivalent to 10, 30, and 100 ng/kg-day

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.             %TIME EXPOSURE BEGINS(HOUR)
EXP_TIME_OFF    =  3696.          %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  336.           %HOURS BETWEEN DOSES
BCK_TIME_ON     =  0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF    =  0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT       =  3696.          %SIMULATION DURATION (HOUR)
BW_T0           =  205.           %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT         = 0.14          %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT         = 0.42          %ORAL EXPOSURE DOSE (UG/KG)
   MSTOT         = 1.4            %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.10. *Hassoun et al. (2000)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Hassoun et al. 2000
%protocol:  oral exposure for 13 weeks; SD rats
%dose levels:  0.003, 0.010, 0.022, 0.046 0.1 ug/kg 5 days/week for 13 weeks
%dose levels equivalent to: 3, 10, 22, 46 100 ng/kg 5 days/week for 13 weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9 71.4 ng/kg 7 days/week for
13 weeks

MAXT            = 0.01
CINT            = 0.1
EXP_TIME_ON     = 0.            %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    = 2184.         %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       = 24.           %HOURS BETWEEN DOSES
WEEK_PERIOD     = 168.          %HOURS IN A WEEK
WEEK_FINISH     = 119.          %LAST HOUR IN WEEK WHEN DOSE OCCURS
BCK_TIME_ON     = 0.            %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF    = 0.            %TIME EXPOSURE ENDS (HOUR)
TIMELIMIT       = 2184.         %SIMULATION DURATION (HOUR)
BW_T0           = 215.          %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
```

```
%EXPOSURE DOSE SCENARIOS (UG/KG)
     %MSTOT        = 0.003       %EXPOSURE DOSE UG/KG
     %MSTOT      = 0.010         %EXPOSURE DOSE UG/KG
     %MSTOT      = 0.022         %EXPOSURE DOSE UG/KG
     %MSTOT      = 0.046         %EXPOSURE DOSE UG/KG
     MSTOT      = 0.1            %EXPOSURE DOSE UG/KG
```

E.2.3.2.11. *Hutt et al. (2008)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Hutt et al. 2008
% dose levels: 0.050 ug/kg every week for 13 weeks
% dose levels: 50 ng/kg every week for 13 weeks
% dose levels equivalent to 7.14 ng/kg-day

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.           %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  2184.        %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  168.         %HOURS BETWEEN DOSES
BCK_TIME_ON     =  0.           %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
BCK_TIME_OFF    =  0.           %TIME BACKGROUND EXPOSURE ENDS(HOUR)
TIMELIMIT       =  2184.        %SIMULATION DURATION (HOUR)
BW_T0           =  4.5          %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   MSTOT         = 0.05         %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.12. *Kitchin and Woods (1979)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Kitchen and Woods 1979
%protocol: single oral gavage
%dose levels:  0.0006, 0.002, 0.004, 0.020, 0.060, 0.200, 0.600, 2.000,
5.000, 20.000 ug/kg single oral gavage
% dose levels = 0.6, 2, 4, 20, 60, 200, 600, 2000, 5000, 20000 ng/kg single
oral gavage
MAXT            =  0.001
CINT            =  0.1
EXP_TIME_ON     =  0.           %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  24.          %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  24.          %HOURS BETWEEN DOSES
BCK_TIME_ON     =  0.           %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
BCK_TIME_OFF    =  0.           %TIME OF BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT       =  24.          %SIMULATION DURATION (HOUR)
BW_T0           =  225.         %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
```

```
%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT          = 0.0006       %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.002        %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.004        %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.020        %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.060        %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.200        %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.600        %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 2.000        %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 5.000        %ORAL EXPOSURE DOSE (UG/KG)
  MSTOT          = 20.000        %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.13. *Kociba et al. (1976) 13 weeks*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Kociba et al. 1976.
%dose levels:  0.001, 0.01, 0.1, 1 ug/kg 5 days/week for 13 weeks
%dose levels: 1, 10, 100, 1000 ng/kg 5 days/week for 13 weeks
%dose levels equivalent to: 0.714, 7.14, 71.4, 714 ng/kg-d (adj) 7 days/week
for 13 weeks

MAXT              = 0.001
CINT              = 0.1
EXP_TIME_ON       = 0.        %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 2184      %TIME EXPOSURE ENDS (HOUR)
WEEK_PERIOD       = 168       %HOURS IN A WEEK
WEEK_FINISH       = 119       %LAST HOUR IN WEEK WHEN DOSE OCCURS
DAY_CYCLE         =  24       %HOURS BETWEEN DOSES
BCK_TIME_ON       = 0.        %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
BCK_TIME_OFF      = 0.        %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT         = 2184      %SIMULATION DURATION (HOUR)
BW_T0             = 180       %BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)
%EXPOSURE DOSE SCENARIOS (UG/KG)
%MSTOT           = 0.001      %ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT          = 0.01       %ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT          = 0.1        %ORAL EXPOSURE DOSE (UG/KG)
 MSTOT          = 1           %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.14. *Kociba et al. (1978) female, 104 weeks*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Kociba et al, 1978.
%protocol:  daily dietary exposure for 104 weeks; SD rats
%dose levels:  0.001, 0.01, 0.1 ug/kg 7 days/week for 104 weeks
%dose levels: 1, 10, 100 ng/kg 7 days/week for 104 weeks

MAXT            =  0.01
CINT            =  0.1
```

```
EXP_TIME_ON     =  0.          %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  17472       %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  24          %HOURS BETWEEN DOSES
BCK_TIME_ON     =  0.          %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF    =  0.          %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT       =  17472       %SIMULATION DURATION (HOUR)
BW_T0           =  180         %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT          = 0.001       %EXPOSURE DOSE IN UG/KG
 %MSTOT         = 0.01         %EXPOSURE DOSE IN UG/KG
 MSTOT         = 0.1           %EXPOSURE DOSE IN UG/KG
```

E.2.3.2.15. *Kociba et al. (1978) male, 104 weeks*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Kociba et al, 1978.
%dose levels:  0.001, 0.01, 0.1 ug/kg 7 days/week for 104 weeks
%dose levels: 1, 10, 100 ng/kg 7 days/week for 104 weeks

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.           %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  17472        %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  24           %HOURS BETWEEN DOSES
BCK_TIME_ON     =  0.           %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF    =  0.           %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT       =  17472        %SIMULATION DURATION (HOUR)
BW_T0           =  250          %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT          = 0.001        %EXPOSURE DOSE IN UG/KG
 %MSTOT         = 0.01          %EXPOSURE DOSE IN UG/KG
 MSTOT         = 0.1            %EXPOSURE DOSE IN UG/KG
```

E.2.3.2.16. *Latchoumycandane and Mathur (2002)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Latchoumycandane and Mathur 2002.
%protocol:  1 time per day for 45 days oral gavage
%dose levels:  0.001, 0.01, 0.1 ug/kg daily for 45 days
%dose levels:  1, 10, 100 ng/kg daily for 45 days

MAXT              = 0.01
CINT              = 0.1
EXP_TIME_ON       = 0.          %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 1080        %TIME EXPOSURE ENDS (HOUR)
```

```
DAY_CYCLE          = 24          %HOURS BETWEEN DOSES
BCK_TIME_ON        = 0.          %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF       = 0.          %TIME OF BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT          = 1080        %SIMULATION DURATION (HOUR)
BW_T0              = 200         %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT            = 0.001      %EXPOSURE DOSE UG/KG
  %MSTOT           = 0.01        %EXPOSURE DOSE UG/KG
  MSTOT           = 0.1          %EXPOSURE DOSE UG/KG
```

E.2.3.2.17. *Li et al. (1997)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Li et al 1997
% dose levels: 3, 10, 30, 100, 300, 1000, 3000, 10000, 30000 nkd one dose via
gavage, sacrificed 24 hrs later

MAXT             =  0.1
CINT             =  0.1
EXP_TIME_ON      =  0.          %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     =  24.         %TIME EXPOSURE ENDS(HOUR)
DAY_CYCLE        =  24.         %HOURS BETWEEN DOSES
BCK_TIME_ON      =  0.          %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF     =  0.          %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT        =  24.         %SIMULATION DURATION (HOUR)
BW_T0            =  56.5        %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   MSTOT          = 0.003       %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT          = 0.01       %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT          = 0.03       %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT          = 0.1        %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT          = 0.3        %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT          = 1.         %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT          = 3.         %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT          = 10.        %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT          = 30.        %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.18. *Murray et al. (1979)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Murray et al 1979
%built and check in August 7 2009
%protocol:  dietary exposure for 3 generations (assume 120 day exposure for
each)
```

```
%dose levels: 0.001 0.01, 0.1 ug/kg-d
%dose levels: 1, 10, 100  ng/kg-d

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.            %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  2880          %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  24.           %HOURS BETWEEN DOSES
BCK_TIME_ON     =  0.            %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF    =  0.            %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT       =  2880          %SIMULATION DURATION (HOUR)
BW_T0           =  4.5           % BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT           = 0.001       %ORAL EXPOSURE DOSE IN UG/KG
  %MSTOT         = 0.01          %ORAL EXPOSURE DOSE IN UG/KG
  MSTOT         = 0.1            %ORAL EXPOSURE DOSE IN UG/KG
```

E.2.3.2.19. *NTP (1982) female, chronic*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

%NTP 1982
%dose levels:  0.005, 0.025, 0.25 ug/kg twice weekly for 104 weeks
%dose levels:  5, 25, 250 ng/kg twice weekly for 104 weeks
%dose levels equivalent to: 1.43, 7.14, 71.4 ng/kg-day (adj)

MAXT               = 0.01
CINT               = 0.1
EXP_TIME_ON        = 0.            %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF       = 17472         %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE          = 84            %HOURS BETWEEN DOSES
BCK_TIME_ON        = 0.            %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF       = 0.            %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT          = 17472         %SIMULATION DURATION (HOUR)
BW_T0              = 250           %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)

  %MSTOT           = 0.005         %EXPOSURE DOSE UG/KG
  %MSTOT           = 0.025         %EXPOSURE DOSE UG/KG
  MSTOT           = 0.25           %EXPOSURE DOSE UG/KG
```

E.2.3.2.20. *NTP (1982) male,chronic*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

%NTP 1982
%dose levels:  0.005, 0.025, 0.25 ug/kg twice weekly for 104 weeks
```

```
%dose levels:  5, 25, 250 ng/kg twice weekly for 104 weeks
%dose levels equivalent to: 1.43, 7.14, 71.4 ng/kg-day (adj)

MAXT                = 0.01
CINT                = 0.1
EXP_TIME_ON         = 0.            %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF        = 17472         %TIME EXPOSURE ENDS(HOUR)
DAY_CYCLE           = 84            %HOURS BETWEEN DOSES
BCK_TIME_ON         = 0.            %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF        = 0.            %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT           = 17472         %SIMULATION DURATION (HOUR)
BW_T0               = 350           %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
%EXPOSURE DOSE SCENARIOS (UG/KG)

%MSTOT            = 0.005           %EXPOSURE DOSE UG/KG
%MSTOT            = 0.025           %EXPOSURE DOSE UG/KG
MSTOT            = 0.25             %EXPOSURE DOSE UG/KG
```

E.2.3.2.21. *NTP (2006)14 weeks*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% NTP 2006
%dose levels:  0.003, 0.010, 0.022, 0.046 0.1 ug/kg 5 days/week for 14 weeks
%dose levels equivalent to: 3, 10, 22, 46 100 ng/kg 5 days/week for 14 weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9 71.4 ng/kg-day days/week

MAXT             = 0.01
CINT             = 0.1
EXP_TIME_ON      = 0.              %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 2352            %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE        =  24             %HOURS BETWEEN DOSES
WEEK_PERIOD      = 168             %HOURS IN A WEEK
WEEK_FINISH      = 119             %LAST HOUR IN WEEK WHEN DOSE OCCURS
BCK_TIME_ON      = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF     = 0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT        = 2352            %SIMULATION DURATION (HOUR)
BW_T0            = 215             %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
%EXPOSURE DOSE SCENARIOS (UG/KG)
     %MSTOT        = 0.003         %EXPOSURE DOSE UG/KG
     %MSTOT      = 0.010           %EXPOSURE DOSE UG/KG
     %MSTOT      = 0.022           %EXPOSURE DOSE UG/KG
     %MSTOT      = 0.046           %EXPOSURE DOSE UG/KG
     MSTOT      = 0.1              %EXPOSURE DOSE UG/KG
```

E.2.3.2.22. *NTP (2006) 31 weeks*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% NTP 2006
```

```
%dose levels:  0.003, 0.010, 0.022, 0.046 0.1 ug/kg 5 days/week for 31 weeks
%dose levels equivalent to: 3, 10, 22, 46 100 ng/kg 5 days/week for 31 weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9 71.4 ng/kg 7 days/week for
31 weeks

MAXT             = 0.01
CINT             = 0.1
EXP_TIME_ON      = 0.              %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 5208            %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE        =  24             %HOURS BETWEEN DOSES
WEEK_PERIOD      = 168            %HOURS IN A WEEK
WEEK_FINISH      = 119             %LAST HOUR IN WEEK WHEN DOSE OCCURS
BCK_TIME_ON      = 0.              %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
BCK_TIME_OFF     = 0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT        = 5208            %SIMULATION DURATION (HOUR)
BW_T0            = 215             %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
     %MSTOT        = 0.003         %EXPOSURE DOSE UG/KG
     %MSTOT      = 0.010           %EXPOSURE DOSE UG/KG
     %MSTOT      = 0.022           %EXPOSURE DOSE UG/KG
     %MSTOT      = 0.046           %EXPOSURE DOSE UG/KG
     MSTOT      = 0.1              %EXPOSURE DOSE UG/KG
```

E.2.3.2.23. *NTP (2006) 53 weeks*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% NTP 2006
%protocol:  oral exposure for 53 weeks; SD rats
%dose levels:  0.003, 0.010, 0.022, 0.046 0.1 ug/kg 5 days/week for 53 weeks
%dose levels equivalent to: 3, 10, 22, 46 100 ng/kg 5 days/week for 53 weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9 71.4 ng/kg 7 days/week for
53 weeks

MAXT             = 0.01
CINT             = 0.1
EXP_TIME_ON      = 0.            %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 8904          %TIME EXPOSURE ENDS(HOUR)
DAY_CYCLE        =  24           %HOURS BETWEEN DOSES
WEEK_PERIOD      = 168           %HOURS IN A WEEK
WEEK_FINISH      = 119           %LAST HOUR IN WEEK WHEN DOSE OCCURS
BCK_TIME_ON      = 0.            %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
BCK_TIME_OFF     = 0.            %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT        = 8904          %SIMULATION DURATION (HOUR)
BW_T0            = 215           %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
     %MSTOT        = 0.003       %EXPOSURE DOSE UG/KG
     %MSTOT      = 0.010         %EXPOSURE DOSE UG/KG
     %MSTOT      = 0.022         %EXPOSURE DOSE UG/KG
     %MSTOT      = 0.046         %EXPOSURE DOSE UG/KG
```

```
     MSTOT      = 0.1             %EXPOSURE DOSE UG/KG
```

E.2.3.2.24. *NTP (2006) 2 year*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% NTP 2006
%protocol:  oral exposure for 105 weeks; SD rats
%dose levels:  0.003, 0.010, 0.022, 0.046, 0.1 ug/kg 5 days/week for 105
weeks
%dose levels equivalent to: 3, 10, 22, 46, 100 ng/kg 5 days/week for 105
weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9, 71.4 ng/kg 7 days/week
for 105 weeks

MAXT             = 0.01
CINT             = 0.1
EXP_TIME_ON      = 0.             %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 17640          %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE        =  24            %HOURS BETWEEN DOSES
WEEK_PERIOD      = 168            %HOURS IN A WEEK
WEEK_FINISH      = 119            %LAST HOUR IN WEEK WHEN DOSE OCCURS
BCK_TIME_ON      = 0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF     = 0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT        = 17640          %SIMULATION DURATION (HOUR)
BW_T0            = 215            %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
     %MSTOT        = 0.003        %EXPOSURE DOSE IN UG/KG
     %MSTOT      = 0.010          %EXPOSURE DOSE IN UG/KG
     %MSTOT      = 0.022          %EXPOSURE DOSE IN UG/KG
     %MSTOT      = 0.046          %EXPOSURE DOSE IN UG/KG
     MSTOT      = 0.1             %EXPOSURE DOSE IN UG/KG
```

E.2.3.2.25. *Sewall et al. (1995) and Maronpot et al. (1993)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG
% Sewall et al. 1995
%protocol: gavage every 2 weeks for 30 weeks
%dose levels: 0.049, 0.1498, 0.49, and 1.75 ug/kg every 2 weeks
%dose levels: 3.5, 10.7, 35, and 125 ng/kg-d or 49, 149.8, 490, and 1750
ng/kg every 2 weeks

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.            %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  5040          %TIME EXPOSURE ENDS(HOUR)
DAY_CYCLE       =  336.          %HOURS BETWEEN DOSES
BCK_TIME_ON     =  0.            %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
BCK_TIME_OFF    =  0.            %TIME BACKGROUND EXPOSURE ENDS (HOUR)
```

```
TIMELIMIT       =  5040           %SIMULATION DURATION (HOUR)
BW_T0           =  250            %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT           = 0.049        %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.1498         %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.49           %ORAL EXPOSURE DOSE (UG/KG)
  MSTOT         = 1.75            %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.26. *Shi et al. (2007) adult portion*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Shi et al 2007
%protocol:  gavage once per week for 322 days
%dose levels: 0.001, 0.005, 0.05 and 0.2 ug TCDD:kg body weight by gavage
once per week
%dose levels: 1, 5, 50 and 200 ng/kg ng TCDD:kg body weight by gavage once
per week
% dose equivalent adjusted 0.143, 0.714, 7.14 and 28.6 ng/kg-d

MAXT            =  0.0001
CINT            =  0.1
EXP_TIME_ON     =  504.            %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  7728            %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  168.            %HOURS BETWEEN DOSES
BCK_TIME_ON     =  0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF    =  0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT       =  7728            %SIMULATION DURATION (HOUR)
BW_T0           =  4.5             %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT          = 0.001         %ORAL EXPOSURE DOSE IN UG/KG
   %MSTOT         = 0.005          %ORAL EXPOSURE DOSE IN UG/KG
   %MSTOT         = 0.05           %ORAL EXPOSURE DOSE IN UG/KG
   MSTOT         = 0.2             %ORAL EXPOSURE DOSE IN UG/KG
```

E.2.3.2.27. *Van Birgelen et al. (1995)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Van Birgelen et al. (1995)
%protocol:  daily dietary exposure for 13 weeks
%dose levels: 0.0135, 0.0264, 0.0469, 0.320, 1.024 ug/kg every day for 13
weeks
% dose levels = 13.5, 26.4, 46.9, 320, 1024 ng/kg every day for 13 weeks
MAXT            =  0.001
CINT            =  0.1
EXP_TIME_ON     =  0.              %TIME EXPOSURE BEGINS (HOUR)
```

```
EXP_TIME_OFF    =  2184.          %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  24.            %HOURS BETWEEN DOSES
BCK_TIME_ON     =  0.             %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    =  0.             %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       =  2184.          %SIMULATION LIMIT TIME (HOUR)
BW_T0           =  150.           %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT         = 0.0135         %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.0264         %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.0469         %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.320          %ORAL EXPOSURE DOSE (UG/KG)
  MSTOT         = 1.024           %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.28. *Simanainen et al. (2002) and Simanainen et al. (2003)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Simanainen et al., 2002 and Simanainen et al., 2003

 MAXT            = 0.01
 CINT            = 0.1
 TIMELIMIT       = 24             %SIMULATION DURATION (HOUR)
 EXP_TIME_ON     = 0              %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 24             %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 24             %HOURS BETWEEN DOSES
 BCK_TIME_ON     = 0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF    = 0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 BW_T0           = 200            %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT        = 0.1             %EXPOSURE DOSE [UG/KG]
   MSTOT        = 0.3              %EXPOSURE DOSE [UG/KG]
```

E.2.3.2.29. *Vanden Heuvel et al. (1994)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Vanden Heuvel et al. 1994.
%protocol: single gavage
%dose levels:0.00005, 0.0001, 0.001, 0.010, 0.1, 1, 10 ug/kg-d
%dose levels equivalent to: 0.05, 0.1, 1, 10, 100, 1000, 10000 ng/kg-d

MAXT              = 0.001
CINT              = 0.1
EXP_TIME_ON       = 0.            %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 24            %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE         = 24            %HOURS BETWEEN DOSES
BCK_TIME_ON       = 0.            %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
```

```
BCK_TIME_OFF       = 0.            %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT          = 24            %SIMULATION DURATION (HOUR)
BW_T0              = 250           %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)

  %MSTOT             = 0.00005     %EXPOSURE DOSE UG/KG
  %MSTOT           = 0.0001        %EXPOSURE DOSE UG/KG
  %MSTOT           = 0.001         %EXPOSURE DOSE UG/KG
  %MSTOT           = 0.01          %EXPOSURE DOSE UG/KG
  %MSTOT           = 0.1           %EXPOSURE DOSE UG/KG
  %MSTOT           = 1             %EXPOSURE DOSE UG/KG
  MSTOT           = 10             %EXPOSURE DOSE UG/KG
```

E.2.4. Rat Gestational Model

E.2.4.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model for TCDD in Rat (Gestation)'

```
INITIAL  ! INITIALIZATION OF PARAMETERS

     !SIMULATION PARAMETERS ====
CONSTANT PARA_ZERO          = 1E-30
CONSTANT EXP_TIME_ON     = 0.0       ! TIME AT WHICH EXPOSURE BEGINS (HOURS)
CONSTANT EXP_TIME_OFF    = 530       ! TIME AT WHICH EXPOSURE ENDS (HOURS)
CONSTANT DAY_CYCLE       = 24.0      ! NUMBER OF HOURS BETWEEN DOSES (HOURS)
CONSTANT BCK_TIME_ON     = 0.0       ! TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOURS)
CONSTANT BCK_TIME_OFF    = 0.0       ! TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOURS)
CONSTANT TRANSTIME_ON    = 144.0     !CONTROL TRANSFER FROM MOTHER TO FETUS
AT GESTATIONAL DAY 6

 !UNIT CONVERSION
CONSTANT MW=322 ! MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1000


    !INTRAVENOUS SEQUENCE
constant IV_LAG         = 0.0
constant IV_PERIOD       = 0.0

    !PREGNANCY PARAMETER ====
CONSTANT CONCEPTION_T         = 0.0       !TIME OF CONCEPTION(HOUR)
CONSTANT N_FETUS         = 10.0       !NUMBER OF FETUS PRESENT

    !CONSTANT EXPOSURE CONTROL ===========
    !ACUTE, SUBCHRONIC, CHRONIC EXPOSURE =====
    !OR BACKGROUND EXPOSURE (IN THIS CASE 3 TIMES A DAY)===
CONSTANT MSTOTBCKGR      = 0.0       ! ORAL BACKGROUND EXPOSURE DOSE (UG/KG)
CONSTANT MSTOT           = 0.0       ! ORAL EXPOSURE DOSE (UG/KG)
```

```
    !ORAL ABSORPTION
  MSTOT_NM = MSTOT/MW              ! CONVERTS THE DOSE TO NMOL/G

    !INTRAVENOUS ABSORPTION
CONSTANT  DOSEIV         = 0.0       ! INJECTED DOSE (UG/KG)
  DOSEIV_NM = DOSEIV/MW            ! CONVERTS THE INJECTED DOSE TO NMOL/G
CONSTANT DOSEIVLATE = 0.0            ! INJECTED DOSE LATE (UG/KG)
  DOSEIVNMlate = DOSEIVLATE/MW     !AMOUNT IN NMOL/G

    !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW)====
CONSTANT CFLLI0          = 0.0  !LIVER    (NMOL/ML)
CONSTANT CFLPLA0         = 0.0  !PLACENTA (NMOL/ML)

    !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) (NMOL/ML) ===
CONSTANT LIBMAX          = 3.5E-4   ! LIVER  (NMOL/ML), WANG ET AL. 1997
CONSTANT PLABMAX         = 2.0E-4   !TEMPORARY PARAMETER

    ! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
(NMOL/ML)===
CONSTANT KDLI            = 1.0E-4   !LIVER (AhR) (NMOL/ML), WANG ET AL. 1997
CONSTANT KDLI2           = 4.0E-2   !LIVER (1A2) (NMOL/ML), EMOND ET AL. 2004
CONSTANT KDPLA           = 1.0E-4   !TEMPORARY PARAMETER; ASSUME IDENTICAL TO
KDLI (AhR)

    !EXCRETION AND ABSORPTION CONSTANT
CONSTANT KST             = 0.36     ! GASTRIC RATE CONSTANT (HR-1), WANG ET
AL. 1997
CONSTANT KABS            = 0.48     !INTESTINAL ABSORPTION CONSTANT (HR-1) ),
WANG ET AL. 1997

    ! ELIMINATION CONSTANTS
CONSTANT CLURI           = 0.01       ! URINARY CLEARANCE (ML/HR), EMOND ET
AL. 2004

    !INTERSPECIES ELIMINATION VARIABLE
CONSTANT kelv            = 0.15     ! INTERSPECIES VARIABLE ELIMINATION
CONSTANT (1/HOUR)

    ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A               = 0.7        ! LYMPHATIC FRACTION, WANG ET AL. 1997

    !PARTITION COEFFICIENTS
CONSTANT PF              = 100     ! ADIPOSE TISSUE/BLOOD, WANG ET AL. 1997
CONSTANT PRE             = 1.5      ! REST OF THE BODY/BLOOD, WANG ET AL.
1997
CONSTANT PLI             = 6.0       ! LIVER/BLOOD, WANG ET AL. 1997
CONSTANT PPLA            = 1.5      ! TEMPORARY PARAMETER NOT CONFIGURED,
WANG ET AL. 1997

    !PARAMETER FOR INDUCTION OF CYP 1A2, WANG ET AL. 1997
CONSTANT IND_ACTIVE       = 1.0        ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
CONSTANT CYP1A2_1OUTZ    = 1.6      ! DEGRADATION CONCENTRATION CONSTANT OF
1A2 (NMOL/ML)
CONSTANT CYP1A2_1A1      = 1.6      ! BASAL CONCENTRATION OF 1A1 (NMOL/ML)
```

```
CONSTANT CYP1A2_1EC50    = 0.13      ! DISSOCIATION CONSTANT TCDD-CYP1A2
(NMOL/ML)
CONSTANT CYP1A2_1A2      = 1.6      !BASAL CONCENTRATION OF 1A2 (NMOL/ML)
CONSTANT CYP1A2_1KOUT    = 0.1      ! FIRST ORDER RATE OF DEGRADATION (H-1)
CONSTANT CYP1A2_1TAU     = 0.25     !HOLDING TIME (H)
CONSTANT CYP1A2_1EMAX    = 600      ! MAXIMUM INDUCTION OVER BASAL EFFECT
(UNITLESS)
CONSTANT HILL            = 0.6      !HILL CONSTANT; COOPERATIVE LIGAND
BINDING EFFECT CONSTANT (UNITLESS)

    !DIFFUSIONAL PERMEABILITY FRACTION
CONSTANT PAFF            = 0.0910   !ADIPOSE (UNITLESS), WANG ET AL. 1997
CONSTANT PAREF           = 0.0298   !REST OF THE BODY  (UNITLESS), WANG ET
AL. 1997
CONSTANT PALIF           = 0.3500   !LIVER (UNITLESS), WANG ET AL. 1997
CONSTANT PAPLAF          = 0.3      !TEMPORARY PARAMETER NOT CONFIGURED

   !FRACTION OF TISSUE WEIGHT =========
CONSTANT WLI0            = 0.0360   !LIVER, WANG ET AL. 1997

   !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT
CONSTANT QFF             = 0.069    ! ADIPOSE TISSUE BLOOD FLOW FRACTION
(UNITLESS), WANG ET AL. 1997
CONSTANT QLIF            = 0.183    !LIVER (UNITLESS), WANG ET AL. 1997

   !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL COMPARTMENT
VOLUME
CONSTANT WFB0            = 0.050    !ADIPOSE TISSUE, WANG ET AL. 1997
CONSTANT WREB0           = 0.030    !REST OF THE BODY, WANG ET AL. 1997
CONSTANT WLIB0           = 0.266    !LIVER, WANG ET AL. 1997
CONSTANT WPLAB0          = 0.500    !TEMPORARY PARAMETER NOT CONFIGURED

   !EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
   !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG       = 0.0       !TIME ELAPSED BEFORE EXPOSURE BEGINS
(WEEK)
CONSTANT WEEK_PERIOD     = 168      ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH     = 168      ! TIME EXPOSURE ENDS (HOURS)

   !NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LAG      = 0.0       !TIME ELAPSED BEFORE EXPOSURE BEGINS
(MONTHS)

   !CONSTANT FOR BACKGROUND EXPOSURE===========
CONSTANT Day_LAG_BG     = 0.0       !TIME ELAPSED BEFORE EXPOSURE BEGINS
(HOURS)
CONSTANT Day_PERIOD_BG   = 24       !LENGTH OF EXPOSURE (HOURS)

   !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG_BG      = 0.0      !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
BEGINS (WEEKS)
CONSTANT WEEK_PERIOD_BG    = 168      !NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH_BG    = 168      !TIME EXPOSURE ENDS (HOURS)

   !INITIAL BODY WEIGHT
CONSTANT BW_T0             = 250      ! (IN G) WANG ET AL. 1997
```

```
CONSTANT RATIO_RATF_MOUSEF = 1.0        !RATIO OF FETUS MOUSE/RAT AT
GESTATIONAL DAY 22

   ! COMPARTMENT TOTAL LIPID FRACTION , POULIN ET AL 2000
CONSTANT F_TOTLIP          = 0.855               ! ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP          = 0.0023               ! BLOOD (UNITLESS)
CONSTANT RE_TOTLIP         = 0.019               ! REST OF THE BODY
(UNITLESS)
CONSTANT LI_TOTLIP         = 0.060               ! LIVER (UNITLESS)
CONSTANT PLA_TOTLIP        = 0.019
CONSTANT FETUS_TOTLIP      = 0.019

END     ! END OF THE INITIAL SECTION

DYNAMIC ! DYNAMIC SIMULATION SECTION
ALGORITHM  IALG          =           2        ! GEAR METHOD
CINTERVAL  CINT          =          0.1       ! COMMUNICATION INTERVAL
MAXTERVAL  MAXT          =        1.0e+10     ! MAXIMUM CALCULATION INTERVAL
MINTERVAL  MINT          =        1.0E-10     ! MINIMUM CALCULATION INTERVAL
VARIABLE   T             =          0.0
CONSTANT   TIMELIMIT     =          100       !SIMULATION LIMIT TIME (HOURS)
 CINTXY  = CINT
 PFUNC   = CINT

   !TIME CONVERSION
  DAY         = T/24           ! TIME IN DAYS
  WEEK        = T/168          ! TIME IN WEEKS
  MONTH       = T/730          ! TIME IN MONTHS
  YEAR        = T/8760         ! TIME IN YEARS

DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

   !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
   !NUMBER OF EXPOSURES PER DAY
 DAY_LAG         = EXP_TIME_ON    ! TIME ELAPSED BEFORE EXPOSURE BEGINS
(HOURS)
 DAY_PERIOD       = DAY_CYCLE      ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH       = CINTXY         ! LENGTH OF EXPOSURE (HOURS)
 MONTH_PERIOD     = TIMELIMIT      ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH     = EXP_TIME_OFF   ! LENGTH OF EXPOSURE (MONTHS)

   !NUMBER OF EXPOSURES PER DAY AND MONTH
 DAY_FINISH_BG    = CINTXY
 MONTH_LAG_BG    = BCK_TIME_ON    !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
BEGINS (MONTHS)
 MONTH_PERIOD_BG  = TIMELIMIT      !BACKGROUND EXPOSURE (MONTHS)
 MONTH_FINISH_BG  = BCK_TIME_OFF   !LENGTH OF BACKGROUND EXPOSURE (MONTHS)

   !INTRAVENOUS LATE
 IV_FINISH = CINTXY
 B = 1-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER


!FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUM
E
  ! FROM OFLAHERTY_1992
```

```
RTESTGEST= T-CONCEPTION_T
TESTGEST=DIM(RTESTGEST,0.0)

WTFER_RODENT= (2.3d-3*EXP(1.49d-2*(TESTGEST))+1.3d-2)*Gest_on
WTFER = (WTFER_RODENT*RATIO_RATF_MOUSEF*N_FETUS)
WTFE = DIM(WTFER,0.0)

  !
FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME
  ! FAT GROWTH EXPRESSION LINEAR DURING PREGNANCY
  ! FROM O'FLAHERTY_1992

WF0= (((9.66d-5*(TESTGEST))*gest_on)+0.069)

  ! PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME
  ! WPLA PLACENTA GROWTH  EXPRESSION, SINGLE EXPONENTIAL WITH OFFSET
  ! FROM O'FLAHERTY_1992  ! FOR EACH PUP

WPLA0N_RODENT = (0.6/(1+(5d+3*EXP(-0.0225*(TESTGEST)))))*N_FETUS
WPLA0R = (WPLA0N_RODENT/WT0)*Gest_on
WPLA0 = DIM(WPLA0R,0.0)

  ! PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW
RATE
  ! QPLA PLACENTA GROWTH EXPRESSION, DOUBLE EXPONENTIAL WITH OFFSET
  ! FROM O'FLAHERTY_1992

 QPLARF = (1.67d-7 *exp(9.6d-3*(TESTGEST)) &
   +1.6d-3*exp(7.9d-3*(TESTGEST))+0.0)*Gest_on*SWITCH_trans
 QPLAF=DIM(QPLARF,0.0)               !FRACTION OF FLOW RATE IN PLACENTA

  ! GESTATION CONTROL
IF (T.LT.CONCEPTION_T) THEN
    Gest_off = 1.0
    Gest_on=   0.0
ELSE
    Gest_off = 0.0
    Gest_on  = 1.0
END IF

  ! MOTHER BODY WEIGHT GROWTH EQUATION========
  ! MODIFICATION TO ADAPT THIS MODEL AT HUMAN MODEL
  ! BECAUSE LINEAR DESCRIPTION IS NOT GOOD ENOUGH FOR MOTHER GROWTH
  ! MOTHER BODY WEIGHT GROWTH

  PARAMETER (BW_RMN = 1.0E-30)
  WT0= BW_T0 *(1+(0.41*T)/(1402.5+T+BW_RMN)) ! IN GRAMS

  ! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGANS
  WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 +WPLAB0*WPLA0 + WLI0 + WF0 +
WPLA0))/(1+WREB0)  ! REST OF THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
  QREF = 1-(QFF+QLIF+QPLAF)            !REST OF BODY BLOOD FLOW RATE (ML/HR)
  QTTQF = QFF+QREF+QLIF+QPLAF          ! SUM MUST EQUAL 1

  ! COMPARTMENT VOLUME (ML OR G) =========
 WF  =  WF0  * WT0                    ! ADIPOSE TISSUE
 WRE =  WRE0 * WT0                    ! REST OF THE BODY
```

```
 WLI =  WLI0 * WT0                    ! LIVER
 WPLA=  WPLA0* WT0                    ! PLACENTA

   ! COMPARTMENT TISSUE BLOOD (ML OR G) =========
 WFB  =  WFB0  * WF                   ! ADIPOSE TISSUE
 WREB =  WREB0 * WRE                  ! REST OF THE BODY
 WLIB =  WLIB0 * WLI                  ! LIVER
 WPLAB = WPLAB0* WPLA                 ! PLACANTA

   ! CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT (ML/H) =========
   !QC= QCCAR*60*(WT0/1000.0)**0.75
CONSTANT QCC=18684.0                    ! EQUIVALENT TO 311.4 * 60
QC= QCC*(WT0/UNITCORR)**0.75

   !COMPARTMENT BLOOD FLOW RATE (ML/HR)
QF  = QFF*QC                          !ADIPOSE TISSUE BLOOD FLOW RATE
QLI = QLIF*QC                         !LIVER TISSUE BLOOD FLOW RATE
QRE = QREF*QC                         !REST OF THE BODY BLOOD FLOW RATE
QPLA = QPLAF*QC                       !PLACENTA TISSUE BLOOD FLOW RATE
QTTQ = QF+QRE+QLI+QPLA   !TOTAL FLOW RATE

    !PERMEABILITY ORGAN FLOW (ML/HR)=========
PAF  = PAFF*QF                       ! ADIPOSE TISSUE
PARE = PAREF*QRE                     ! REST OF THE BODY
PALI = PALIF*QLI                     ! LIVER TISSUE
PAPLA = PAPLAF*QPLA                  ! PLACENTA

    !*************************************
    ! ABSORPTION SECTION
    ! ORAL
    ! INTRAPERITONEAL
    ! INTRAVENOUS
    !*************************************

    !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIO

MSTOT_NMBCKGR = MSTOTBCKGR/MW       ! CONVERTS THE BACKGROUND DOSE TO NMOL/G
MSTTBCKGR =MSTOT_NMBCKGR *WT0

DAY_EXPOSURE_BG   = PULSE(DAY_LAG_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
WEEK_EXPOSURE_BG  = PULSE(WEEK_LAG_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG = PULSE(MONTH_LAG_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
MSTTFR_BG = MSTTBCKGR/CINT

CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG

    ! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)

IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
    ABSMSTT_GB= MSTTFR_BG
ELSE
    ABSMSTT_GB = 0.0
END IF

CYCLETOTBG=INTEG(CYCLE_BG,0.0)
```

```
   !REPETITIVE ORAL EXPOSURE SCENARIO

MSTT= MSTOT_NM * WT0                  !AMOUNT IN NMOL

DAY_EXPOSURE   = PULSE(DAY_LAG,DAY_PERIOD,DAY_FINISH)
WEEK_EXPOSURE  = PULSE(WEEK_LAG,WEEK_PERIOD,WEEK_FINISH)
MONTH_EXPOSURE = PULSE(MONTH_LAG,MONTH_PERIOD,MONTH_FINISH)

MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
MSTTFR = MSTT/CINT

CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
SUMEXPEVENT= INTEG (CYCLE,0.0) !NUMBER OF CYCLES GENERATED DURING SIMULATION

   ! CONDITIONAL ORAL EXPOSURE
IF (MSTTCH.EQ.MSTT) THEN
   ABSMSTT= MSTTFR
ELSE
   ABSMSTT = 0.0
END IF


 CYCLETOT=INTEG(CYCLE,0.0)

   ! MASS CHANGE IN THE LUMEN
 RMSTT= -(KST+KABS)*MST +ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
  MST = INTEG(RMSTT,0.0)                      !AMOUNT REMAINING IN DUODENUM
(NMOL)

   ! ABSORPTION IN LYMPH CIRCULATION
 LYRMLUM = KABS*MST*A
  LYMLUM = INTEG(LYRMLUM,0.0)

   ! ABSORPTION IN PORTAL CIRCULATION
 LIRMLUM = KABS*MST*B
  LIMLUM = INTEG(LIRMLUM,0.0)


! -----IV EXPOSURE ---------

 IV= DOSEIV_NM * WT0 !AMOUNT IN NMOL
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1.0-STEP(PFUNC))
 IVDOSE = integ(EXPIV,0.0)

    !------IV LATE IN THE CYCLE
    ! MODIFICATION ON January 13 2004
 IV_RlateR = DOSEIVNMlate*WT0
 IV_EXPOSURE=PULSE(IV_LAG,IV_PERIOD,IV_FINISH)

 IV_lateT = IV_EXPOSURE *IV_RlateR
 IV_late = IV_lateT/CINT

SUMEXPEVENTIV= integ (IV_EXPOSURE,0.0) !NUMBER OF CYCLES GENERATED DURING
SIMULATION
```

```
    !SYSTEMIC CONCENTRATION OF TCDD

     ! MODIFICATION ON OCTOBER 6, 2009
 CB= (QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late)/(QC+CLURI) !
  CA = CB ! CONCENTRATION (NMOL/ML)


    !URINARY EXCRETION BY KIDNEY
    ! MODIFICATION ON OCTOBER 6, 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)



  !UNIT CONVERSION POST SIMULATION
 CBSNGKGLIADJ=(CB*MW*UNITCORR*(1.0/B_TOTLIP)*(1.0/SERBLO))![NG of TCDD
Serum/Kg OF LIPID]
   AUCBS_NGKGLIADJ=integ(CBSNGKGLIADJ,0.0)


  CBNGKG= CB*MW*UNITCORR


   !ADIPOSE COMPARTMENT
   !TISSUE BLOOD COMPARTMENT
RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)    !(NMOL/H)
 AFB = INTEG(RAFB,0.0)                !(NMOL)
  CFB = AFB/WFB                       !(NMOL/ML)
   !TISSUE COMPARTMENT
RAF = PAF*(CFB-CF/PF)                !(NMOL/H)
 AF = INTEG(RAF,0.0)                 !(NMOL)
  CF  = AF/WF                         !(NM/ML)

   !UNIT CONVERSION POST SIMULATION
  CFTOTAL= (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN NMOL/ML
  CFTFREE = CFB + CF !TOTAL FREE CONCENTRATION IN FAT  (NM/ML)

  CFNGKG=CFTOTAL*MW*UNITCORR ! FAT CONCENTRATION NG/KG
    AUCF_NGKGH=integ(CFNGKG,0.0)

   !REST OF THE BODY COMPARTMENT
RAREB= QRE *(CA-CREB)-PARE*(CREB-CRE/PRE)  !(NMOL/H)
 AREB = INTEG(RAREB,0.0)                    !(NMOL)
  CREB = AREB/WREB                          !(NMOL/H)
   !TISSUE COMPARTMENT
RARE = PARE*(CREB - CRE/PRE)               !(NMOL/H)
 ARE = INTEG(RARE,0.0)                     !(NMOL)
  CRE  = ARE/WRE                            !(NMOL/ML)

   !UNIT CONVERSION POST SIMULATION
  CRETOTAL= (ARE + AREB)/(WRE + WREB)           ! TOTAL CONCENTRATION IN
NMOL/ML

  CRENGKG=CRETOTAL*MW*UNITCORR ! REST OF THE BODY CONCENTRATION IN NG/KG


   !LIVER COMPARTMENT
```

```
   !TISSUE BLOOD COMPARTMENT
 RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM !
  ALIB = INTEG(RALIB,0.0)                        !(NMOL)
   CLIB = ALIB/WLIB                             !(NMOL/ML)
   !TISSUE COMPARTMENT
 RALI = PALI*(CLIB - CFLLIR)-REXCLI            !  (NMOL/HR)
  ALI = INTEG(RALI,0.0)                             !(NMOL)
   CLI  = ALI/WLI                                !(NMOL/ML)

   !FREE TCDD CONCENTRATION IN LIVER COMPARTMENT
PARAMETER (LIVER_1RMN = 1.0E-30)
 CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
        +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2 + CFLLIR &
        +LIVER_1RMN)*IND_ACTIVE)))-CFLLI,CFLLI0)
     CFLLIR=DIM(CFLLI,0.0) ! FREE CONCENTRATION IN LIVER

  CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND CONCENTRATION

  !VARIABLE ELIMINATION BASED ON THE CYP1A2
 KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv ! INDUCED BILIARY
EXCRETION RATE CONSTANT IN LIVER
  REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT BILIARY EXCRETION RATE
    EXCLI = INTEG(REXCLI,0.0)

  !UNIT CONVERSION POST SIMULATION
  CLITOTAL= (ALI + ALIB)/(WLI + WLIB) ! TOTAL CONCENTRATION IN NMOL/ML
  Rec_occ= CFLLIR/(KDLI+CFLLIR)
  CLINGKG=CLITOTAL*MW*UNITCORR ! LIVER CONCENTRATION NG/KG
     AUCLI_NGKGH=INTEG(CLINGKG,0.0)
  CBNDLINGKG = CBNDLI*MW*UNITCORR
     AUCBNDLI_NGKGH =INTEG(CBNDLINGKG,0.0)


   !CHEMICAL IN CYP450 (1A2) COMPARTMENT
CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ


    ! MODIFICATION ON OCTOBER 6, 2009
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
&
     /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
      - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)

! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)

CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
  CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)

CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
  CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)

! TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
! FETAL EXPOSURE ONLY DURING EXPOSURE

IF (T.LT.TRANSTIME_ON) THEN
 SWITCH_trans = 0.0
```

```
ELSE
 SWITCH_trans = 1.0
END IF

!TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
! MODIFICATION 26 SEPTEMBER 2003

CONSTANT PFETUS= 4.0 !
CONSTANT CLPLA_FET = 0.17 !

RAMPF = (CLPLA_FET*CPLA) *SWITCH_trans
  AMPF=INTEG(RAMPF,0.0)

!TRANSFER OF DIOXIN FROM FETUS TO PLACENTA
RAFPM = (CLPLA_FET*CFETUS_v)*SWITCH_trans !
  AFPM = INTEG(RAFPM,0.0)

! TCDD IN PLACENTA (MOTHER) COMPARTMENT
RAPLAB= QPLA*(CA - CPLAB)-PAPLA*(CPLAB -CFLPLAR)   ! NMOL/H)
 APLAB = INTEG(RAPLAB,0.0)                          ! (NMOL)
 CPLAB = APLAB/(WPLAB+1E-30)                       ! (NMOL/ML)
RAPLA = PAPLA*(CPLAB-CFLPLAR)-RAMPF + RAFPM        ! (NMOL/H)
 APLA = INTEG(RAPLA,0.0)                            ! (NMOL)
 CPLA  = APLA/(WPLA+1e-30)                         ! (NMOL/ML)


PARAMETER (PARA_ZERO = 1.0E-30)
CFLPLA= IMPLC(CPLA-(CFLPLAR*PPLA +(PLABMAX*CFLPLAR/(KDPLA&
    +CFLPLAR+PARA_ZERO)))-CFLPLA,CFLPLA0)
CFLPLAR=DIM(CFLPLA,0.0)

   !UNIT CONVERSION POST SIMULATION
  CPLATOTAL= (APLA + APLAB)/((WPLA + WPLAB)+1e-30)! TOTAL CONCENTRATION IN
NMOL/ML



   !FETUS COMPARTMENT
RAFETUS= RAMPF-RAFPM
 AFETUS=INTEG(RAFETUS,0.0)
CFETUS=AFETUS/(WTFE+1E-30)
CFETOTAL= CFETUS
CFETUS_v = CFETUS/PFETUS

  ! UNIT CONVERSION POST SIMULATION
CFETUSNGKG = CFETUS*MW*UNITCORR                     !(NG/KG)
AUC_FENGKGH = INTEG(CFETUSNGKG,0.0)


! ------------CONTROL MASS BALANCE ----------
BDOSE= IVDOSE +LYMLUM+LIMLUM
BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB+AFETUS
BDIFF = BDOSE-BMASSE

      !BODY BURDEN (NG)
BODY_BURDEN = AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB !
BBFETUSNG     = AFETUS*MW*UNITCORR    ! UNIT (NG)
```

```
      ! BODY BURDEN IN TERMS OF CONCENTRATION (NG/KG)
 BBNGKG =(((AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB)/WT0)*MW*UNITCORR) !
  AUC_BBNGKGH=INTEG(BBNGKG,0.0)


! ------------COMMAND OF THE END OF SIMULATION ----------
TERMT (T.GE. TimeLimit, 'Time limit has been reached.')
END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYNAMIC SECTION
END   ! END OF THE PROGRAM
```

E.2.4.2. *Input Files*

E.2.4.2.1. *Bell et al. (2007)*

```
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Bell et al. 2007 (rat species)
%protocol:  daily dietary dose for 12 weeks followed by a two-week mating
time and 21-day gestation period
%dose levels: 0.0024, 0.008, 0.046 ug/kg-d with 0.00003 ug/kg-d background
%dose levels: 2.4, 8, 46 ng/kg-d with 0.03 ng/kg-day background

   %EXPOSURES SCENARIOS
 MAXT             = 0.01
 CINT             = 0.1  %
 EXP_TIME_ON      = 0               %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF     = 2856            %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE        = 24              %HOURS BETWEEN DOSES
 BCK_TIME_ON      = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF     = 2856.           %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT        = 2856            %SIMULATION DURATION(HOUR)
 BW_T0            = 85              %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 CONCEPTION_T     = 2352            %HOUR OF CONCEPTION (HOUR)
 TRANSTIME_ON     = 2496            %HOUR OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS          = 10              %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)
   MSTOT           = 0.00243        %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT           = 0.008         %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT = 0.0461                  %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.4.2.2. *Hojo et al. (2002)*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH
%Hojo et al. 2002
%protocol:  single oral dose at GD8
```

```
%dose levels: 0.02 0.06, 0.18 ug/kg  at GD8
%dose levels: 20, 60, 180  ng/kg at GD8
% author provided the body weight for each group at the beginning of
gestation (g)
    %20 ng/kg BW = 271g
    %60 ng/kg BW = 275g
    %180 ng/kg BW = 262g

%EXPOSURES SCENARIOS
 MAXT= 0.001
 CINT =0.1
 EXP_TIME_ON     = 192              %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 216              %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 24               %HOURS BETWEEN DOSES
 BCK_TIME_ON     = 0.               %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
 BCK_TIME_OFF    = 0.               %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT       = 216              %SIMULATION DURATION (HOUR)
 CONCEPTION_T    = 0.               %TIME OF CONCEPTION_(HOUR)
 TRANSTIME_ON    = 144.             %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS         = 10               %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)

   %MSTOT         = 0.02            %ORAL EXPOSURE DOSE (UG/KG)
   %BW_T0         = 275             %20 ng/kg BW = 271g

   %MSTOT        = 0.06             %ORAL EXPOSURE DOSE (UG/KG)
   %BW_T0        = 262              %60 ng/kg BW = 275g

   MSTOT        = 0.18              %ORAL EXPOSURE DOSE (UG/KG)
   BW_T0        = 278               %180 ng/kg BW = 262g
```

E.2.4.2.3. *Ikeda et al. (2005)*

```
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH

%Ikeda et al. 2005
%protocol:  loading dose of 400 ng/kg followed by weekly maintenance doses of
80 ng/kg for 6 weeks,
%dose levels: 0.4 ug/kg-day followed by weekly 0.08 ug/kg-day
%dose levels: 400 ng/kg-day followed by weekly 80 ng/kg-day

   %EXPOSURES SCENARIOS
 MAXT             =.1
 CINT             = 0.1
 EXP_TIME_ON      = 0                %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF     = 1008             %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE        = 168              %HOURS IN A WEEK
 BCK_TIME_ON      = 0.               %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF     = 167.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT        = 1008             %SIMULATION DURATION (HOUR)
 BW_T0            = 250              %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 CONCEPTION_T          = 504         %TIME OF CONCEPTION (HOUR)
```

```
 TRANSTIME_ON     = 648              %TIME OF CONCEPTION + 6 DAYS (144 HOURS)
 N_FETUS          = 10               %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)
   MSTOT           = 0.08            %ORAL EXPOSURE DOSE IN UG/KG
   MSTOTBCKGR      = 0.32            %BACKGROUND EXPOSURE IN UG/KG
```

E.2.4.2.4. *Kattainen et al. (2001) and Simanainen et al. (2004)*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Kattainen et al. 2001
%protocol:  single gavage at GD15
%dose levels: 0.03 0.1, 0.3, 1 ug/kg  at GD15
%dose levels: 30, 100 300, 1000 ng/kg at GD15

 MAXT=0.001
 CINT =0.1

   %EXPOSURES SCENARIOS
 EXP_TIME_ON         = 336            %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF        = 360            %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE           = 24             %HOURS BETWEEN DOSES
 BCK_TIME_ON         = 0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF        = 0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT           = 360            %SIMULATION DURATION (HOUR)
 BW_T0               = 190            %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION
 CONCEPTION_T             = 0.        %TIME OF CONCEPTION (HOUR)
 TRANSTIME_ON        = 144.           %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS             = 10             %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT            = 0.03             %ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT            = 0.1              %ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT            = 0.3              %ORAL EXPOSURE DOSE (UG/KG)
 MSTOT             = 1                %ORAL EXPOSURE DOSE (UG/KG
```

E.2.4.2.5. *Markowski et al. (2001)*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Markowski et al. 2001
%protocol:  single gavage at GD18
%dose levels: 0.02 0.06, 0.18 ug/kg at GD18
%dose levels: 20, 60, 180 ng/kg at GD18
```

```
%EXPOSURES SCENARIOS
 MAXT=0.0001
 CINT =0.1
 EXP_TIME_ON     = 408              %TIME EXPOSURE BEGINS(HOUR)
 EXP_TIME_OFF    = 432              %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 24               %HOURS BETWEEN DOSES
 BCK_TIME_ON     = 0.               %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF    = 0.               %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT       = 432              %SIMULATION DURATION (HOUR)
 BW_T0           = 190              %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION
 CONCEPTION_T         = 0.          %TIME OF CONCEPTION (HOUR)
 TRANSTIME_ON    = 144.             %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS         = 10               %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT         = 0.02            %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT        = 0.06             %ORAL EXPOSURE DOSE (UG/KG)
   MSTOT        = 0.18              %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.4.2.6. *Miettinen et al. (2006)*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Miettinen et al. 2006
%protocol:  single oral dose at GD15
%dose levels: 0.03 0.1, 0.3, 1 ug/kg at GD15
%dose levels: 30, 100, 300, 1000 ng/kg at GD15

 MAXT=0.01
 CINT =0.1

EXP_TIME_ON   = 336                  %TIME EXPOSURE BEGINS(HOUR)
 EXP_TIME_OFF  = 360                 %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE     = 24                  %HOURS BETWEEN DOSES
 BCK_TIME_ON   = 0.                  %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF  = 0.                  %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT     = 360                 %SIMULATION DURATION (HOUR)
 BW_T0         = 180                 %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 CONCEPTION_T       = 0.            %TIME OF CONCEPTION (HOUR)
 TRANSTIME_ON  = 144.                %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS       = 10                  %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT        = 0.03              %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT      = 0.1                 %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT      = 0.3                 %ORAL EXPOSURE DOSE (UG/KG)
   MSTOT      = 1                    %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.4.2.7. *Nohara et al. (2000)*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Nohara et al. 2000
%protocol:  single gavage at GD15
%dose levels: 0.0125, 0.050, 0.2, or 0.8 ug TCDD:kg body weight by gavage on
GD15.
%dose levels: 12.5, 50, 200, or 800 ng TCDD:kg body weight by gavage on GD15.

 MAXT=0.01
 CINT =0.1
 EXP_TIME_ON   = 336                  %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF  = 360                  %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE     = 24                   %HOURS BETWEEN DOSES
 BCK_TIME_ON   = 0.                   %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF  = 0.                   %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT     = 360                  %SIMULATION DURATION (HOUR)
 BW_T0         = 180                  %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 CONCEPTION_T  = 0.                   %TIME OF CONCEPTION (HOUR)
 TRANSTIME_ON  = 144.                 %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS       = 10                   %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT         = 0.0125             %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.050              %ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.2                %ORAL EXPOSURE DOSE (UG/KG)
  MSTOT         = 0.8                 %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.4.2.8. *Ohsako et al. (2001)*

```
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Ohsako et al. 2001
%protocol:  single oral dose at GD15
%dose levels: 0.0125, 0.05, 0.2, 0.8 ug/kg at GD15
%dose levels: 12.5, 50, 200, 800 ng/kg at GD15

 MAXT=0.01
 CINT =0.1
 EXP_TIME_ON     = 360                %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 384                %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 24                 %HOURS BETWEEN DOSES
 BCK_TIME_ON     = 0.                 %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF    = 0.                 %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT       = 384                %SIMULATION DURATION (HOUR)
 BW_T0           = 200                %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
```

```
 CONCEPTION_T         = 0.            %TIME OF CONCEPTION_(HOUR)
 TRANSTIME_ON    = 144.               %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS         = 10                 %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)

 %MSTOT        = 0.0125               %ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT        = 0.05                 %ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT        = 0.20                 %ORAL EXPOSURE DOSE (UG/KG)
 MSTOT           = 0.80               %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.4.2.9. *Schantz et al. (1996) and Amin et al. (2000)*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Amin et al. 2000 (rat species) and Schantz et al. 1996
%protocol:  daily doses on GDs 10 to 16
%dose levels: 25 and 100 ng/kg-day
%dose levels: 0.025 and 0.100 ug/kg-day

 MAXT            = 0.001
 CINT            = 0.1
 EXP_TIME_ON     = 240.              %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 384.              %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 24                %HOURS BETWEEN DOSES
 BCK_TIME_ON     = 1000.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF    = 1000.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT       = 384.              %SIMULATION DURATION (HOUR)
 BW_T0           = 250.              %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 CONCEPTION_T          = 0           %TIME OF CONCEPTION_ (HOUR)
 TRANSTIME_ON    = 144.              %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS         = 10                %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT           = .025           %ORAL EXPOSURE DOSE (UG/KG)
   MSTOT           = .100            %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.4.2.10. *Seo et al. (1995)*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Seo et al. 1995
%protocol:  daily doses on GDs 10-16
%dose levels: 0.025 and 0.1 ug/kg on GDs 10-16
%dose levels: 25 and 100 ng/kg on GDs 10-16
```

```
 MAXT = 0.01
 CINT = 0.1

 EXP_TIME_ON         = 240            %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF        = 384            %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE           = 24
 BCK_TIME_ON         = 0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF        = 0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT           = 384            %SIMULATION DURATION (HOUR)
 BW_T0               = 190            %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 CONCEPTION_T             = 0.        %TIME OF CONCEPTION (HOUR)
 TRANSTIME_ON        = 144.           %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS             = 10             %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT            = 0.025            %ORAL EXPOSURE DOSE (UG/KG)
 MSTOT            = 0.1               %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.4.2.11. *Sparschu et al. (1971)*

```
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%protocol:  daily oral dose from GD6 to GD15

%EXPOSURES SCENARIOS
 MAXT=0.01
 CINT =0.1
 EXP_TIME_ON     = 120.              %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 337.              %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 24                %HOURS BETWEEN DOSES
 BCK_TIME_ON     = 0.                %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF    = 0.                %TIME BACKGROUND EXPOSURE ENDS (HOUR)

 TIMELIMIT       = 360.              %SIMULATION DURATION (HOUR)
 BW_T0           = 295               %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 T_CONCEPTION         = 0.           %TIME OF CONCEPTION (HOUR)
 TRANSTIME_ON    = 144.              %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS         = 10                %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)

   %MSTOT         = 0.03             %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT        = 0.125             %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT        = 0.5               %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT        = 2.                %ORAL EXPOSURE DOSE (UG/KG)
   MSTOT        = 8.                 %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.5. Mouse Standard Model

E.2.5.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model for TCDD in Mice: Standard Model (Nongestation)'

```
!****************************************************

INITIAL  ! INITIALIZATION OF PARAMETERS

    !SIMULATION PARAMETERS ====
CONSTANT PARA_ZERO       =    1D-30
CONSTANT EXP_TIME_ON     =     0.0        ! TIME AT WHICH EXPOSURE BEGINS
(HOURS)
CONSTANT EXP_TIME_OFF    =    2832        ! TIME AT WHICH EXPOSURE ENDS
(HOURS)
CONSTANT DAY_CYCLE       =     24         ! NUMBER OF HOURS BETWEEN DOSES
(HOURS)
CONSTANT BCK_TIME_ON     =      0.0       ! TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOURS)
CONSTANT BCK_TIME_OFF    =      0.0       ! TIME AT WHICH BACKGROUND EXPOSURE
ENDS (HOURS)

CONSTANT MW=322 ! MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1000

    !CONSTANT EXPOSURE CONTROL ===========
    !ACUTE, SUBCHRONIC, CHRONIC EXPOSURE =====
    !OR BACKGROUND EXPOSURE (IN THIS CASE 3 TIMES A DAY)===
CONSTANT MSTOTBCKGR     =       0.0       !ORAL BACKGROUND EXPOSURE DOSE
(UG/KG)
CONSTANT MSTOT          =       0.15     !ORAL EXPOSURE DOSE (UG/KG)
CONSTANT MSTOTsc        =       0.0       ! SUBCUTANEOUS EXPOSURE DOSE
(UG/KG)

    !ORAL ABSORPTION
  MSTOT_NM              =   MSTOT/MW    !AMOUNT IN NMOL/G

    ! INTRAVENOUS ABSORPTION
CONSTANT  DOSEIV   = 0.0                  !INJECTED DOSE (UG/KG)
  DOSEIV_NM = DOSEIV/MW   ! CONVERTS THE INJECTED DOSE TO NMOL/G

  !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW)====
CONSTANT CFLLI0          =       0.0       !LIVER (NMOL/ML)

  !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) (NMOL/ML)
CONSTANT LIBMAX          =     3.5e-4     ! LIVER  (NMOL/ML), WANG ET AL.
1997

! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
(NMOL/ML)===
```

```
CONSTANT KDLI            =     1.0e-4     !LIVER (AhR)(NMOL/ML), WANG ET AL.
1997
CONSTANT KDLI2           =     2.0e-2     !LIVER (1A2)(NMOL/ML), EMOND ET AL.
2004

!===EXCRETION AND ABSORPTION CONSTANT (OPTIMIZED)
CONSTANT KST             =    0.3   ! GASTRIC RATE CONSTANT (HR-1),
CONSTANT KABS            =    0.48  !INTESTINAL ABSORPTION CONSTANT (HR-1) ),
WANG ET AL. 1997

! ELIMINATION CONSTANTS
CONSTANT CLURI           =      0.09 ! URINARY CLEARANCE (ML/HR)

! ==test elimination variable
constant kelv            =     0.4        ! INTERSPECIES VARIABLE ELIMINATION
CONSTANT (1/HOUR)

! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A               =      0.7       ! LYMPHATIC FRACTION, WANG ET AL.
1997

!PARTITION COEFFICIENTS OPTIMIZED
CONSTANT PF              =   400         ! ADIPOSE TISSUE/BLOOD
CONSTANT PRE             =    3          ! REST OF THE BODY/BLOOD, WANG ET
AL. 2000
CONSTANT PLI             =    6          ! LIVER/BLOOD, WANG ET AL. 1997

!===PARAMETER FOR INDUCTION OF CYP 1A2
CONSTANT IND_ACTIVE=     1.0     ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
CONSTANT CYP1A2_1OUTZ = 1.6   ! DEGRADATION CONCENTRATION CONSTANT OF 1A2
(NMOL/ML)
CONSTANT CYP1A2_1A1 =   1.5   ! BASAL CONCENTRATION OF 1A1 (NMOL/ML)
CONSTANT CYP1A2_1EC50 = 0.13   ! DISSOCIATION CONSTANT TCDD-CYP1A2 (NMOL/ML)
CONSTANT CYP1A2_1A2 =   1.5   ! BASAL CONCENTRATION OF 1A2 (NMOL/ML)
CONSTANT CYP1A2_1KOUT = 0.1   ! FIRST ORDER RATE OF DEGRADATION (H-1)
CONSTANT CYP1A2_1TAU  = 1.5  ! HOLDING TIME (H)
CONSTANT CYP1A2_1EMAX = 600   ! MAXIMUM INDUCTION OVER BASAL EFFECT
(UNITLESS)
CONSTANT HILL         = 0.6      !HILL CONSTANT; COOPERATIVE LIGAND BINDING
EFFECT CONSTANT (UNITLESS)
    !DIFFUSIONAL PERMEABILITY FRACTION
CONSTANT PAFF     = 0.12      ! ADIPOSE (UNITLESS), WANG ET AL. 2000
CONSTANT PAREF    = 0.03      ! REST OF THE BODY (UNITLESS)
CONSTANT PALIF    = 0.35      ! LIVER (UNITLESS)

    !COMPARTMENT TISSUE BLOOD VOLUME  =========
CONSTANT WLI0     =  0.0549   ! LIVER, ILSI 1994
CONSTANT WF0      =  0.069    ! ADIPOSE

    !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT
CONSTANT QFF  = 0.070         ! ADIPOSE TISSUE BLOOD FLOW FRACTION
(UNITLESS), LEUNG ET AL. 1990
CONSTANT QLIF = 0.161         ! LIVER (UNITLESS)  ILSI ET AL. 1994

    !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL
COMPARTMENT VOLUME
CONSTANT WFB0 =    0.050      ! ADIPOSE TISSUE, WANG ET AL. 1997
```

```
CONSTANT WREB0 =   0.030      ! REST OF THE BODY, WANG ET AL. 1997
CONSTANT WLIB0 =   0.266      ! LIVER, WANG ET AL. 1997

    ! EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
    ! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG   = 0.0     ! TIME ELAPSED BEFORE EXPOSURE BEGINS (WEEK)
CONSTANT WEEK_PERIOD = 168    ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH = 120    ! TIME EXPOSURE ENDS (HOURS)

    ! NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LAG   = 0.0    ! DELAY BEFORE EXPOSURE (MONTH)

    !SET FOR BACKGROUND EXPOSURE===========
    !CONSTANT FOR BACKGROUND EXPOSURE===========
CONSTANT Day_LAG_BG = 0.0     ! TIME ELAPSED BEFORE EXPOSURE BEGINS (HOURS)
CONSTANT Day_PERIOD_BG = 24   ! LENGTH OF EXPOSURE (HOURS)

    ! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG_BG   = 0.0 ! TIME ELAPSED BEFORE BACKGROUND EXPOSURE (WEEK)
CONSTANT WEEK_PERIOD_BG = 168 !NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH_BG = 168 ! TIME EXPOSURE ENDS (HOURS)

    !GROWTH CONSTANT FOR RAT AND MOUSE
    !CONSTANT FOR MOTHER BODY WEIGHT GROWTH ======
CONSTANT BW_T0 = 20          !CHANGED FOR SIMULATION (IN G)

    !CONSTANT USED IN CARDIAC OUTPUT EQUATION, HADDAD 2001
CONSTANT QCCAR =275         !CONSTANT (ML/MIN/KG)

    ! COMPARTMENT TOTAL LIPID FRACTION
CONSTANT F_TOTLIP =  0.855    !ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP =  0.0033   !BLOOD (UNITLESS)
CONSTANT RE_TOTLIP = 0.019    !REST OF THE BODY (UNITLESS)
CONSTANT LI_TOTLIP = 0.06     !LIVER (UNITLESS)

END  ! END OF THE INITIAL SECTION

DYNAMIC ! DYNAMIC SIMULATION SECTION

ALGORITHM  IALG          =           2        !GEAR METHOD
CINTERVAL  CINT          =          1.0       !COMMUNICATION INTERVAL
MAXTERVAL  MAXT          =        1.0e+10     !MAXIMUM CALCULATION INTERVAL
MINTERVAL  MINT          =        1.0E-10     !MINIMUM CALCULATION INTERVAL
VARIABLE   T             =          0.0       !HOUR
CONSTANT   TIMELIMIT     =          2904.0       !SIMULATION TIME LIMIT
(HOURS)
 CINTXY  = CINT
 PFUNC   = CINT

     !TIME CONVERSION
  DAY         = T/24.0           ! TIME IN DAYS
  WEEK        = T/168.0          ! TIME IN WEEKS
  MONTH       = T/730.0          ! TIME IN MONTHS
  YEAR        = T/8760.0         ! TIME IN YEARS

     !NMAX =MAX(T,CTFNGKG)
nmax =max(T,CFNGKG)
```

```
DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

     !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
     !NUMBER OF EXPOSURES PER DAY
 DAY_LAG     = EXP_TIME_ON       ! TIME ELAPSED BEFORE EXPOSURE BEGINS
(HOURS)
 DAY_PERIOD   = DAY_CYCLE         ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH   = CINTXY            ! LENGTH OF EXPOSURE (HOURS)
 MONTH_PERIOD = TIMELIMIT         ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH = EXP_TIME_OFF      ! LENGTH OF EXPOSURE (MONTHS)

     !NUMBER OF EXPOSURES PER DAY AND MONTH
 DAY_FINISH_BG   = CINTXY
 MONTH_LAG_BG   = BCK_TIME_ON    ! TIME ELAPSED BEFORE BACKGROUND EXPOSURE
BEGINS (MONTHS)
 MONTH_PERIOD_BG = TIMELIMIT      ! BACKGROUND EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH_BG = BCK_TIME_OFF   ! LENGTH OF BACKGROUND EXPOSURE (MONTHS)

     ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER
 B = 1.0-A


     !GROWTH UP EQUATION (G)

PARAMETER (BW_RMN = 1.0E-30)
WT0= (BW_T0 *(1.0+(0.41*T)/(1402.5+T+BW_RMN))) ! IN GRAMS

     ! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGANS
     !REST OF THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
 WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 + WLI0 + WF0))/(1+WREB0)

     ! REST OF THE BODY BLOOD FLOW FRACTION
 QREF = 1.0-(QFF+QLIF)            !REST OF BODY BLOOD FLOW (ML/HR)
     !SUMMATION OF BLOOD FLOW FRACTION (SHOULD BE EQUAL TO 1)
 QTTQF = QFF+QREF+QLIF          ! SUM MUST EQUAL 1

     !COMPARTMENT VOLUME (ML OR G)
 WF  =  WF0  * WT0              ! ADIPOSE
 WRE =  WRE0 * WT0              ! REST OF THE BODY
 WLI =  WLI0 * WT0              ! LIVER

     !COMPARTMENT TISSUE BLOOD (NL OR G )
 WFB  =  WFB0  * WF             ! ADIPOSE
 WREB =  WREB0 * WRE            ! REST OF THE BODY
 WLIB =  WLIB0 * WLI            ! LIVER

     !CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
  QC= QCCAR*60*(WT0/1000.0)**0.75

QF  = QFF*QC         ! ADIPOSE TISSUE BLOOD FLOW RATE (ML/HR)
QLI = QLIF*QC        ! LIVER TISSUE BLOOD FLOW RATE (ML/HR)
QRE = QREF*QC        ! REST OF THE BODY BLOOD FLOW RATE (ML/HR)

QTTQ = QF+QRE+QLI   !TOTAL FLOW RATE (ML/HR)

     !PERMEABILITY ORGAN FLOW (ML/HR) =======
```

```
PAF  = PAFF*QF       ! ADIPOSE TISSUE
PARE = PAREF*QRE     ! REST OF THE BODY
PALI = PALIF*QLI     ! LIVER TISSUE

     !ABSORPTION SECTION
     !ORAL
     !BACKGROUND EXPOSURE
     !EXPOSURE FOR STEADY STATE CONSIDERATION
     !REPETITIVE EXPOSURE SCENARIO

MSTOT_NMBCKGR = MSTOTBCKGR/322 !AMOUNT IN NMOL/G
MSTTBCKGR =MSTOT_NMBCKGR *WT0

     !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIOS
DAY_EXPOSURE_BG   = PULSE(DAY_LAG_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
WEEK_EXPOSURE_BG  = PULSE(WEEK_LAG_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG = PULSE(MONTH_LAG_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
MSTTFR_BG = MSTTBCKGR/CINT

totalBG= integ (MSTTCH_BG,0.0)
CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG


     !CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
    ABSMSTT_GB= MSTTFR_BG
ELSE
    ABSMSTT_GB = 0.0
END IF

     !EXPOSURE + !REPETITIVE EXPOSURE SCENARIO
IV= DOSEIV_NM * WT0  !AMOUNT IN NMOL
MSTT= MSTOT_NM * WT0 !AMOUNT IN NMOL

DAY_EXPOSURE   = PULSE(DAY_LAG,DAY_PERIOD,DAY_FINISH)
WEEK_EXPOSURE  = PULSE(WEEK_LAG,WEEK_PERIOD,WEEK_FINISH)
MONTH_EXPOSURE = PULSE(MONTH_LAG,MONTH_PERIOD,MONTH_FINISH)

MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE

SUMEXPEVENT= integ (CYCLE,0.0)*cint !NUMBER OF CYCLES GENERATED DURING
SIMULATION

MSTTFR = MSTT/CINT

    ! CONDITIONAL ORAL EXPOSURE
IF (MSTTCH.EQ.MSTT) THEN
   ABSMSTT= MSTTFR
ELSE
   ABSMSTT = 0.0
END IF

 CYCLETOT=INTEG(CYCLE,0.0)
```

```
    !MASS CHANGE IN THE LUMEN
RMSTT= -(KST+KABS)*MST+ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
 MST = INTEG(RMSTT,0.0)  !AMOUNT REMAINING IN DUODENUM (NMOL)

    !ABSORPTION IN LYMPH CIRCULATION
LYRMLUM = KABS*MST*A
 LYMLUM = INTEG(LYRMLUM,0.0)

    !ABSORPTION IN PORTAL CIRCULATION
LIRMLUM = KABS*MST*B
  LIMLUM = INTEG(LIRMLUM,0.0)

    !PERCENT OF DOSE REMAINING IN THE GI TRACT
RFECES = KST*MST + REXCLI
  FECES = INTEG(RFECES,0.0)
prctFECES = (FECES/(BDOSE_TOTAL+1E-30))*100


    !ABSORPTION OF DIOXIN BY IV ROUTE---------
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1.0-STEP(PFUNC))
 IVDOSE = integ(EXPIV,0.0)

    !SYSTEMIC BLOOD CONCENTRATION (NMOL/ML)
    ! MODIFICATION ON OCTOBER 6, 2009
CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM)/(QC+CLURI) !
 CA = CB

    !URINARY EXCRETION BY KIDNEY
    ! MODIFICATION ON OCTOBER 6, 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)

prctAURI = (AURI/(BDOSE_TOTAL+1E-30))*100


    !UNIT CONVERSION POST SIMULATION
CBNGKG=CB*MW*UNITCORR
CBSNGKGLIADJ= (CB*MW*UNITCORR*(1.0/B_TOTLIP)*(1.0/SERBLO))![NG of TCDD
Serum/Kg OF LIPID]
CBPMOL_KG= CB*UNITCORR*UNITCORR       !CONCENTRATION IN PMOL/KG
CBNGG = CB*MW
    !ADIPOSE TISSUE COMPARTMENT
    !TISSUE BLOOD SUBCOMPARTMENT
RAFB = QF*(CA-CFB)-PAF*(CFB-CF/PF)       !(NMOL/HR)
 AFB = INTEG(RAFB,0.0)                    !(NMOL)
 CFB = AFB/WFB                           !(NMOL/ML)
    !TISSUE SUBCOMPARTMENT
RAF  = PAF*(CFB-CF/PF)                   !(NMOL/HR)
 AF  = INTEG(RAF,0.0)                     !(NMOL)
 CF  = AF/WF                             !(NMOL/ML)

    !POST SIMULATION UNIT CONVERSION
CFTOTAL    = (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN FAT(NM/ML)
CFNGKG  = CFTOTAL*MW*UNITCORR
CFUGG=(CFTOTAL*MW)/UNITCORR
```

```
CFPMOL_KG= CFTOTAL*UNITCORR*UNITCORR       !CONCENTRATION IN PMOL/KG
CFNGG = CFTOTAL*MW

    !REST OF THE BODY COMPARTMENT
    !TISSUE BLOOD SUBCOMPARTMENT
RAREB= QRE*(CA-CREB)-PARE*(CREB-CRE/PRE)         !(NMOL/HR)
 AREB = INTEG(RAREB,0.0)                          !(NMOL)
 CREB = AREB/WREB                                !(NMOL/ML)
    !TISSUE SUBCOMPARTMENT
RARE = PARE*(CREB - CRE/PRE)                     !(NMOL/HR)
 ARE = INTEG(RARE,0.0)                           !(NMOL)
 CRE  = ARE/WRE                                   !(NMOL/ML)

    !POST SIMULATION UNIT CONVERSION
CRETOTAL= (ARE + AREB)/(WRE + WREB)              ! CONCENTRATION AT STEADY
STATE


    !LIVER COMPARTMENT
    !TISSUE BLOOD SUBCOMPARTMENT
RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM   !(NMOL/HR)
  ALIB = INTeg(RALIB,0.0)                           !(NMOL)
 CLIB = ALIB/WLIB
    !TISSUE SUBCOMPARTMENT
 RALI =  PALI*(CLIB-CFLLIR)-REXCLI                 !(NMOL/HR)
  ALI = integ(RALI,0.0)                                   !(NMOL)
  CLI  = ALI/WLI                                    !(NMOL/ML)

    !FREE TCCD CONCENTRATION IN LIVER (NMOL/ML)
PARAMETER (LIVER_1RMN = 1.0E-30)
 CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLI &
       +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR &
       +LIVER_1RMN)*IND_ACTIVE)))-CFLLI,CFLLI0)
     CFLLIR=DIM(CFLLI,0.0) ! FREE CONCENTRATION IN LIVER

CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND CONCENTRATION

   !POST SIMULATION UNIT CONVERSION
CLITOTAL= (ALI + ALIB)/(WLI + WLIB)!
rec_occ_AHR= (CFLLIR/(KDLI+CFLLIR+1E-30))*100.0  ! PERCENT OF AhR OCCUPANCY
PROT_occ_1A2= (CFLLIR/(KDLI2+CFLLIR))*100.0  ! PERCENT OF 1A2 OCCUPANCY
CLINGKG =(CLITOTAL*MW*UNITCORR)
CBNDLINGKG = CBNDLI*MW*UNITCORR
CLIUGG=(CLITOTAL*MW)/UNITCORR
CLIPMOL_KG= CLITOTAL*UNITCORR*UNITCORR       !CONCENTRATION IN PMOL/KG
CLINGG = CLITOTAL*MW

   !Fraction increase of induction of CYP1A2
fold_ind=(CYP1A2_1OUT/CYP1A2_1A2)
VARIATIONOfAC =(CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2

   !VARIABLE ELIMINATION BASED ON THE CYP1A2
KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv !INDUCED BILIARY
EXCRETION RATE CONSTANT

REXCLI= (KBILE_LI_T*CFLLIR*WLI) !DOSE-DEPENDENT EXCRETION RATE
 EXCLI = INTEG(REXCLI,0.0)
```

```
   !CHEMICAL IN CYP450 (1A2) COMPARTMENT
   !EQUATION FOR INDUCTION OF CYP1A2

CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ

   ! MODIFICATION ON OCTOBER 6, 2009
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
&
     /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
      - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)
! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)

CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
  CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)
CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
  CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)

      ! MASS BALANCE CONTROL
 BDOSE= LYMLUM+LIMLUM+IVDOSE
 BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI
 BDIFF = BDOSE-BMASSE
      ! AMOUNT TOTAL PRESENT IN THE GI TRACT
BDOSE_TOTAL =LYMLUM+LIMLUM+FECES

      !BODY BURDEN IN NG
 Body_burden =(AFB+AF+AREB+ARE+ALIB+ALI)*MW

      !BODY BURDEN CONCENTRATION (NG/KG)
 BBNGKG =(((AFB+AF+AREB+ARE+ALIB+ALI)*MW)/(WT0/UNITCORR)) !

      !COMMAND FOR END OF SIMULATION
TERMT (T.GE. TimeLimit, 'Time limit has been reached.')

END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYNAMIC SECTION
END   ! END OF PROGRAM
```

E.2.5.2. *Input Files*

E.2.5.2.1. *Della Porta (1987) female*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Della Porta 1987 for female mice.
%dose levels:  2.5 and 5 ug/kg/week for 52 weeks
%dose levels:  2500 and 5000 ng/kg/week for 52 weeks
%dose levels equivalent to: 357 and 714 ng/kg-d

MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON       = 0.             %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 8736           %TIME EXPOSURE ENDS (HOUR)
```

```
DAY_CYCLE          = 168            %HOURS BETWEEN DOSES
BCK_TIME_ON        = 0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF       = 0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT          = 8736           %SIMULATION DURATION (HOUR)
BW_T0              = 20             %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT           = 2.5          %EXPOSURE DOSE UG/KG
    MSTOT          = 5.0            %EXPOSURE DOSE UG/KG
```

E.2.5.2.2. *Della Porta (1987) male*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Della Porta 1987 for male mice.
%dose levels:  2.5 and 5 ug/kg/week for 52 weeks
%dose levels:  2500 and 5000 ng/kg/week for 52 weeks
%dose levels equivalent to: 357 and 714 ng/kg-d

MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON        = 0.             %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF       = 8736           %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE          = 168            %HOURS BETWEEN DOSES
BCK_TIME_ON        = 0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF       = 0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT          = 8736           %SIMULATION DURATION (HOUR)
BW_T0              = 26             %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT           = 2.5          %EXPOSURE DOSE UG/KG
    MSTOT          = 5.0            %EXPOSURE DOSE UG/KG
```

E.2.5.2.3. *Ishihara et al. (2007)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Ishihara 2007
%dose levels:  1) 2 ng/kg loading; 0.4 ng/kg weekly
              %2) 2,000 ng/kg loading; 400 ng/kg weekly

 MAXT              = 0.01
 CINT              = 0.1
 TIMELIMIT         = 840             %SIMULATION DURATION (HOUR)
 EXP_TIME_ON       = 168             %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF      = 840             %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE         = 168             %HOURS BETWEEN DOSES
```

```
 BCK_TIME_ON      = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF     = 0.02            %TIME BACKGROUND EXPOSURE ENDS (HOUR)
  BW_T0            = 23             %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOTBCKGR      = 0.002         %INITIAL LOADING EXPOSURE DOSE [UG/KG]
   %MSTOT           = 0.0004        %EXPOSURE DOSE [UG/KG]
   MSTOTBCKGR   = 2                 %INITIAL LOADING EXPOSURE DOSE [UG/KG]
   MSTOT        = 0.4               %EXPOSURE DOSE [UG/KG]
```

E.2.5.2.4. *Kuchiiwa et al. (2002)*

```
% Kuchiiwa 2002
%protocol:  oral exposure once weekly for 8 weeks
%dose levels:  0.0049, 0.490  ug/kg once weekly for 8 weeks

 MAXT = 0.01
 CINT  = 0.1
 TIMELIMIT       = 1344            %SIMULATION DURATION (HOUR)
 EXP_TIME_ON     = 0.              %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 1344            %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 168             %HOURS BETWEEN DOSES
 BCK_TIME_ON     = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF    = 0.0             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 BW_T0           = 25              %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT          = 0.0049         %EXPOSURE DOSE [UG/KG]
MSTOT       = 0.490                %EXPOSURE DOSE [UG/KG]
```

E.2.5.2.5. *NTP (1982) female, chronic*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% NTP 1982.
%protocol: twice weekly gavage for 104 weeks
%dose levels:  0.02, 0.1, 1 ug/kg twice weekly for 104 weeks
%dose levels:  20, 100, 1000 ng/kg twice weekly for 104 weeks
%dose levels equivalent to: 5.71, 28.57, 285.1 ng/kg-d

MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON       = 0.              %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 17472           %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE         = 84              %HOURS BETWEEN DOSES
BCK_TIME_ON       = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF      = 0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT         = 17472           %SIMULATION DURATION (HOUR)
BW_T0             = 23              %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
```

```
    %MSTOT          = 0.02          %EXPOSURE DOSE UG/KG
    %MSTOT         = 0.1            %EXPOSURE DOSE UG/KG
    MSTOT         = 1.0             %EXPOSURE DOSE UG/KG
```

E.2.5.2.6. *NTP (1982) male, chronic*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% NTP 1982.
%protocol: twice weekly gavage for 104 weeks
%dose levels:  0.005, 0.025, 0.25 ug/kg twice weekly for 104 weeks
%dose levels:  5, 25, 250 ng/kg twice weekly for 104 weeks
%dose levels equivalent to: 1.4, 7.1, 71 ng/kg-d

MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON       = 0.              %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 17472           %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE         = 84              %HOURS BETWEEN DOSES
BCK_TIME_ON       = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF      = 0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT         = 17472           %SIMULATION DURATION (HOUR)
BW_T0             = 25              %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT          = 0.005         %EXPOSURE DOSE UG/KG
    %MSTOT         = 0.025          %EXPOSURE DOSE UG/KG
    MSTOT         = 0.25            %EXPOSURE DOSE UG/KG
```

E.2.5.2.7. *Nohara et al. (2002)*

```
%Nohara 2002
%protocol:  single oral exposure dose
%dose levels:  0.005, 0.020, 0.100 and 0.500 ug/kg single dose
%dose levels equivalent 5, 20, 100 and 500 ng/kg single dose

MAXT = 0.01
CINT  = 0.1
TIMELIMIT        = 24             %SIMULATION DURATION (HOUR)
EXP_TIME_ON      = 0.             %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 24             %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE        = 24             %HOURS BETWEEN DOSES
WEEK_FINISH      = 193            %LAST HOUR WHEN DOSE OCCURS (HOUR)
BCK_TIME_ON      = 0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF     = 0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
BW_T0            = 23             %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
      %MSTOT        = 0.005        %EXPOSURE DOSE UG/KG
      %MSTOT      = 0.020          %EXPOSURE DOSE UG/KG
```

```
      %MSTOT      = 0.100            %EXPOSURE DOSE UG/KG
      MSTOT      = 0.500             %EXPOSURE DOSE UG/KG
```

E.2.5.2.8. *Smialowicz et al. (2004)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Smialowicz et al. 2004.

MAXT          = 0.01
CINT          = 0.1
TIMELIMIT     = 24.                  %SIMULATION DURATION (HOUR)
EXP_TIME_ON   = 0.                   %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF  = 24.                  %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE     =  24.                 %HOURS BETWEEN DOSES
BCK_TIME_ON   = 0.                   %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF  = 0.                   %TIME BACKGROUND EXPOSURE ENDS (HOUR)
BW_T0         = 25                   %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT      = 0.03                %EXPOSURE DOSE (UG/KG)
   %MSTOT   = 0.1                    %EXPOSURE DOSE (UG/KG)
   %MSTOT   = 0.3                    %EXPOSURE DOSE (UG/KG)
   %MSTOT   = 1.0                    %EXPOSURE DOSE (UG/KG)
   %MSTOT   = 3.0                    %EXPOSURE DOSE (UG/KG)
   MSTOT   = 10.0                    %EXPOSURE DOSE (UG/KG)
```

E.2.5.2.9. *Smialowicz et al. (2008)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Smialowicz et al. 2008.
%protocol:  oral gavage 5 days/week for 13 weeks
%dose levels:  0, 0.0015, 0.015, 0.15, 0.45 ug/kg
%dose levels:  0, 1.5, 15, 150, 450 nkd (0, 1.07, 10.7, 107, 321 nkd adj)

MAXT          = 0.01
CINT          = 0.1
TIMELIMIT     = 2184                 %SIMULATION DURATION (HOUR)
EXP_TIME_ON   = 0.                   %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF  = 2184                 %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE     =  24                  %HOURS BETWEEN DOSES
WEEK_PERIOD   = 168                  %HOURS IN A WEEK
WEEK_FINISH   = 119                  %LAST HOUR IN WEEK WHERE DOSE OCCURS
BCK_TIME_ON   = 0.                   %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF  = 0.                   %TIME BACKGROUND EXPOSURE ENDS (HOUR)
BW_T0         = 28                   %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT      = 0.0015              %EXPOSURE DOSE (UG/KG)
```

```
   %MSTOT   = 0.015                  %EXPOSURE DOSE (UG/KG)
   %MSTOT   = 0.150                  %EXPOSURE DOSE (UG/KG)
   MSTOT   = 0.450                   %EXPOSURE DOSE (UG/KG)
```

E.2.5.2.10. *Toth et al. (1979) 1 year*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Toth et al. 1979
%protocol:  weekly gavage for 1 year
%dose levels:  7, 700, 7000 ng/kg once weekly for 52 weeks (1 year)
%dose levels:  0.007, 0.7, 7 ug/kg once weekly for 52 weeks (1 year)
%dose equivalent: 1, 100, 1000 ng/kg-day

MAXT         = 0.01
CINT         = 0.1
TIMELIMIT    = 8760                  %SIMULATION DURATION (HOUR)
EXP_TIME_ON  = 0.                    %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF = 8760                  %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE    =  168                  %HOURS BETWEEN DOSES
BCK_TIME_ON  = 0.                    %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
BCK_TIME_OFF = 0.                    %TIME BACKGROUND EXPOSURE ENDS (HOUR)
BW_T0        = 27                    %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT    = 0.007                %EXPOSURE DOSE (UG/KG)
    %MSTOT = 0.7                     %EXPOSURE DOSE (UG/KG)
    MSTOT = 7                        %EXPOSURE DOSE (UG/KG)
```

E.2.5.2.11. *Weber et al. (1995)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

%Weber et al. 1995 C57 strain
%protocol:  single oral exposure dose

MAXT = 0.01
CINT  = 0.1
TIMELIMIT        = 24                %SIMULATION DURATION (HOUR)
EXP_TIME_ON      = 0.                %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 24                %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE        = 24                %HOURS BETWEEN DOSES
BCK_TIME_ON      = 0.                %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF     = 0.                %TIME BACKGROUND EXPOSURE ENDS (HOUR)
BW_T0            = 24.1              %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
      %MSTOT       = 0.03            %EXPOSURE DOSE UG/KG
```

```
      %MSTOT      = 0.1              %EXPOSURE DOSE UG/KG
      %MSTOT      = 0.3              %EXPOSURE DOSE UG/KG
      %MSTOT      = 1.0              %EXPOSURE DOSE UG/KG
      %MSTOT      = 3.0              %EXPOSURE DOSE UG/KG
      %MSTOT      = 9.4              %EXPOSURE DOSE UG/KG
      %MSTOT      = 37.5             %EXPOSURE DOSE UG/KG
      %MSTOT      = 75.0             %EXPOSURE DOSE UG/KG
      %MSTOT      = 100.0            %EXPOSURE DOSE UG/KG
      %MSTOT      = 133.0            %EXPOSURE DOSE UG/KG
      %MSTOT      = 150.0            %EXPOSURE DOSE UG/KG
      MSTOT      = 235.0             %EXPOSURE DOSE UG/KG
```

E.2.5.2.12. *White et al. (1986)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% White et al 1986
%protocol:  oral exposure single dose
%dose levels: 10, 50, 100, 500, 1000, 2000 ng /kg-d ug/kg 1/day for 14
consecutive days
%dose levels: 0.010, 0.050, 0.100, 0.500, 1.0, 2.0 ug /kg-d ug/kg 1/day for
14 consecutive days

MAXT         = 0.01
CINT         = 0.1
TIMELIMIT    = 336                  %SIMULATION DURATION (HOUR)
EXP_TIME_ON  = 0.                   %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF = 336                  %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE    =  24                  %HOURS BETWEEN DOSES
BCK_TIME_ON  = 0.                   %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF = 0.                   %TIME BACKGROUND EXPOSURE ENDS (HOUR)
BW_T0        = 23                   %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT = 0.010                   %EXPOSURE DOSE IN UG/KG
   %MSTOT = 0.050                   %EXPOSURE DOSE IN UG/KG
   %MSTOT = 0.100                   %EXPOSURE DOSE IN UG/KG
   %MSTOT = 0.500                   %EXPOSURE DOSE IN UG/KG
   %MSTOT =  1                      %EXPOSURE DOSE IN UG/KG
   MSTOT =  2                       %EXPOSURE DOSE IN UG/KG
```

E.2.6. Mouse Gestational Model

E.2.6.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model for TCDD in Mice (Gestation)'

```
INITIAL  !

     !SIMULATION PARAMETERS ====
CONSTANT PARA_ZERO          = 1E-30
CONSTANT EXP_TIME_ON     = 288.       ! TIME AT WHICH EXPOSURE BEGINS (HOURS)
```

```
CONSTANT EXP_TIME_OFF    = 504      ! TIME AT WHICH EXPOSURE ENDS (HOURS)
CONSTANT DAY_CYCLE       =  504.     ! NUMBER OF HOURS BETWEEN DOSES (HOURS)
CONSTANT BCK_TIME_ON     = 0.0       ! TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOURS)
CONSTANT BCK_TIME_OFF    = 0.0       ! TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOURS)
CONSTANT TRANSTIME_ON    = 144       !CONTROL TRANSFER FROM MOTHER TO FETUS
AT GESTATIONAL DAY 6

    !UNIT CONVERSION
CONSTANT MW=322 ! MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1000

    !INTRAVENOUS SEQUENCY
constant IV_LAG         = 0.0
constant IV_PERIOD       = 0.0

    !PREGNANCY PARAMETER ====
CONSTANT CONCEPTION_T         = 0.0       !TIME OF CONCEPTION (HOUR)
CONSTANT N_FETUS         = 10       !NUMBER OF FETUS PRESENT

    !CONSTANT EXPOSURE CONTROL ===========
    !ACUTE, SUBCHRONIC, CHRONIC EXPOSURE =====
    !OR BACKGROUND EXPOSURE (IN THIS CASE 3 TIMES A DAY)===
CONSTANT MSTOTBCKGR      = 0.0       ! ORAL BACKGROUND EXPOSURE DOSE (UG/KG)
CONSTANT MSTOT           = 0.0       ! ORAL EXPOSURE DOSE (UG/KG)

    !ORAL ABSORPTION
  MSTOT_NM = MSTOT/MW              !CONVERTS THE DOSE TO NMOL/G

    ! INTRAVENOUS ABSORPTION
CONSTANT  DOSEIV         = 0.0       ! INJECTED DOSE (UG/KG)
  DOSEIV_NM = DOSEIV/MW            ! CONVERTS THE INJECTED DOSE TO NMOL/G
CONSTANT DOSEIVLATE = 0.0            ! INJECTED DOSE LATE (UG/KG)
  DOSEIVNMlate = DOSEIVLATE/MW     !AMOUNT IN NMOL/G

    !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW)====
CONSTANT CFLLI0          = 0.0  !LIVER    (NMOL/ML)
CONSTANT CFLPLA0         = 0.0  !PLACENTA (NMOL/ML)

    !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) (NMOL/ML) ===
CONSTANT LIBMAX          = 3.5E-4   ! LIVER  (NMOL/ML), WANG ET AL. 1997
CONSTANT PLABMAX         = 2.0E-4   !TEMPORARY PARAMETER

    ! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
(NMOL/ML)===
CONSTANT KDLI            = 1.0E-4   !LIVER (AhR) (NMOL/ML), WANG ET AL. 1997
CONSTANT KDLI2           = 4.0E-2   !LIVER (1A2) (NMOL/ML), EMOND ET AL. 2004
CONSTANT KDPLA           = 1.0E-4   !TEMPORARY PARAMETER (AhR)

    !EXCRETION AND ABSORPTION CONSTANT
CONSTANT KST             =    0.3   ! GASTRIC RATE CONSTANT (HR-1)
CONSTANT KABS            =    0.48  !INTESTINAL ABSORPTION CONSTANT (HR-1) ),
WANG ET AL. 1997
```

```
! ELIMINATION CONSTANTS
CONSTANT CLURI           =      0.09 ! URINARY CLEARANCE (ML/HR)

   !TEST ELIMINATION VARIABLE
constant kelv            =     0.4        ! INTERSPECIES VARIABLE ELIMINATION
CONSTANT (1/HOUR)

    ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A               = 0.7        ! LYMPHATIC FRACTION, WANG ET AL. 1997

    !PARTITION COEFFICIENTS
CONSTANT PF              = 400    ! ADIPOSE TISSUE/BLOOD
CONSTANT PRE             = 3      ! REST OF THE BODY/BLOOD, WANG ET AL. 2000
CONSTANT PLI             = 6     ! LIVER/BLOOD, WANG ET AL. 1997
CONSTANT PPLA            = 3      ! TEMPORARY PARAMETER NOT CONFIGURED

    !PARAMETER FOR INDUCTION OF CYP 1A2, WANG ET AL. 1997 OR OPTIMIZED
CONSTANT IND_ACTIVE       = 1        ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
CONSTANT CYP1A2_1OUTZ    = 1.6      ! DEGRADATION CONCENTRATION CONSTANT OF
1A2 (NMOL/ML) (OPTIMIZED)
CONSTANT CYP1A2_1A1      = 1.5      ! BASAL CONCENTRATION OF 1A1 (NMOL/ML),
WANG ET AL . (2000)
CONSTANT CYP1A2_1EC50    = 0.13      ! DISSOCIATION CONSTANT TCDD-CYP1A2
(NMOL/ML)
CONSTANT CYP1A2_1A2      = 1.5      !BASAL CONCENTRATION OF 1A2
(NMOL/ML),WANG ET AL. (2000)
CONSTANT CYP1A2_1KOUT    = 0.1      ! FIRST ORDER RATE OF DEGRADATION (H-1)
CONSTANT CYP1A2_1TAU     = 1.5      !HOLDING TIME (H) (OPTIMIZED), WANG ET AL
. (2000)
CONSTANT CYP1A2_1EMAX    = 600      ! MAXIMUM INDUCTION OVER BASAL EFFECT
(UNITLESS)
CONSTANT HILL            = 0.6      !HILL CONSTANT; COOPERATIVELY LIGAND
BINDING EFFECT CONSTANT (UNITLESS)

    !DIFFUSIONAL PERMEABILITY FRACTION, WANG ET AL. 1997
CONSTANT PAFF            = 0.12   !ADIPOSE (UNITLESS) OPTIMIZED, WANG ET AL.
2000
CONSTANT PAREF           = 0.03   !REST OF THE BODY (UNITLESS)
CONSTANT PALIF           = 0.35   !LIVER (UNITLESS)
CONSTANT PAPLAF          = 0.03   !TEMPORARY PARAMETER NOT CONFIGURED

   !FRACTION OF TISSUE WEIGHT =========
CONSTANT WLI0            = 0.0549   !LIVER  ILSI (1994)

   !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT CONSTANT QFF
= 0.070    ! ADIPOSE TISSUE BLOOD FLOW FRACTION (UNITLESS), LEUNG ET AL. 1990
CONSTANT QLIF            = 0.161    !LIVER (UNITLESS), ILSI 1994

   !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL COMPARTMENT
VOLUME
CONSTANT WFB0            = 0.050    !ADIPOSE TISSUE, WANG ET AL. 1997
CONSTANT WREB0           = 0.030    !REST OF THE BODY, WANG ET AL. 1997
CONSTANT WLIB0           = 0.266    !LIVER, WANG ET AL. 1997
CONSTANT WPLAB0          = 0.500    !TEMPORARY PARAMETER NOT CONFIGURED

   !EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
```

```
   !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG       = 0.0       !TIME ELAPSED BEFORE EXPOSURE BEGINS
(WEEK)
CONSTANT WEEK_PERIOD     = 168      ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH     = 168      ! TIME EXPOSURE ENDS (HOURS)

   !NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LAG      = 0.0       !TIME ELAPSED BEFORE EXPOSURE BEGINS
(MONTH)

   !CONSTANT FOR BACKGROUND EXPOSURE===========
CONSTANT Day_LAG_BG     = 0.0       ! TIME ELAPSED BEFORE EXPOSURE BEGINS
(HOUR)
CONSTANT Day_PERIOD_BG   = 24       !LENGTH OF EXPOSURE (HOUR)

   !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG_BG      = 0.0      !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
(WEEK)
CONSTANT WEEK_PERIOD_BG    = 168      ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH_BG    = 168      !TIME EXPOSURE ENDS (HOURS)

   !INITIAL BODY WEIGHT
CONSTANT BW_T0             = 30      ! WANG ET AL. 1997 (IN G)
CONSTANT RATIO_RATF_MOUSEF = 0.2        !RATIO OF FETUS MOUSE/RAT AT
GESTATIONAL DAY 22
                                        ! FOR RAT (1) AND FOR MOUSE (0.2)

   !COMPARTMENT TOTAL LIPID FRACTION , POULIN ET AL. 2000
CONSTANT F_TOTLIP          = 0.855               ! ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP          = 0.0033               ! BLOOD (UNITLESS)
CONSTANT RE_TOTLIP         = 0.019               ! REST OF THE BODY
(UNITLESS)
CONSTANT LI_TOTLIP         = 0.060               ! LIVER (UNITLESS)
CONSTANT PLA_TOTLIP        = 0.019               ! PLACENTA (UNITLESS)
CONSTANT FETUS_TOTLIP      = 0.019            ! FETUS (UNITLESS)

END     ! END OF THE INITIAL SECTION

DYNAMIC ! DYNAMIC SIMULATION SECTION
ALGORITHM  IALG          =           2        ! GEAR METHOD
CINTERVAL  CINT          =          0.1       ! COMMUNICATION INTERVAL
MAXTERVAL  MAXT          =        1.0e+10     ! MAXIMUM CALCULATION INTERVAL
MINTERVAL  MINT          =        1.0E-10     ! MINIMUM CALCULATION INTERVAL
VARIABLE   T             =          0.0
CONSTANT   TIMELIMIT     =          313       !SIMULATION LIMIT TIME (HOUR)
 CINTXY  = CINT
 PFUNC   = CINT

   !TIME CONVERSION
  DAY         = T/24           ! TIME IN DAYS
  WEEK        = T/168          ! TIME IN WEEKS
  MONTH       = T/730          ! TIME IN MONTHS
  YEAR        = T/8760         ! TIME IN YEARS

DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

   !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
```

```
   !NUMBER OF EXPOSURES PER DAY
 DAY_LAG         = EXP_TIME_ON    ! TIME ELAPSED BEFORE EXPOSURE BEGINS
(HOURS)
 DAY_PERIOD       = DAY_CYCLE      ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH       = CINTXY         ! LENGTH OF EXPOSURE (HOURS)
 MONTH_PERIOD     = TIMELIMIT      ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH     = EXP_TIME_OFF   ! LENGTH OF EXPOSURE (MONTHS)

   !NUMBER OF EXPOSURES PER DAY AND MONTH
 DAY_FINISH_BG    = CINTXY
 MONTH_LAG_BG    = BCK_TIME_ON    !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
BEGINS (MONTHS)
 MONTH_PERIOD_BG  = TIMELIMIT      !BACKGROUND EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH_BG  = BCK_TIME_OFF   !LENGTH OF BACKGROUND EXPOSURE (MONTHS)

   !INTRAVENOUS LATE
 IV_FINISH = CINTXY
 B = 1-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER


!FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUM
E
  ! FROM OFLAHERTY_1992

RTESTGEST= T-CONCEPTION_T
TESTGEST=DIM(RTESTGEST,0.0)

WTFER_RODENT= (2.3d-3*EXP(1.49d-2*(TESTGEST))+1.3d-2)*Gest_on
WTFER = (WTFER_RODENT*RATIO_RATF_MOUSEF*N_FETUS)
WTFE = DIM(WTFER,0.0)

  !
FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME
  ! FAT GROWTH EXPRESSION LINEAR DURING PREGNANCY
  ! FROM O'FLAHERTY_1992

WF0= (((9.66d-5*(TESTGEST))*gest_on)+0.069)

  ! PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME
  ! WPLA PLACENTA GROWTH EXPRESSION, SINGLE EXPONENTIAL WITH OFFSET
  ! FROM O'FLAHERTY_1992  ! FOR EACH PUP

WPLA0N_RODENT = (0.6/(1+(5d+3*EXP(-0.0225*(TESTGEST)))))*N_FETUS
WPLA0R = (WPLA0N_RODENT/WT0)*Gest_on
WPLA0 = DIM(WPLA0R,0.0)

  ! PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW
RATE
  ! QPLA PLACENTA GROWTH EXPRESSION, DOUBLE EXPONENTIAL WITH OFFSET
  ! FROM O'FLAHERTY_1992

 QPLARF = (1.67d-7 *exp(9.6d-3*(TESTGEST)) &
   +1.6d-3*exp(7.9d-3*(TESTGEST))+0.0)*Gest_on*SWITCH_trans
 QPLAF=DIM(QPLARF,0.0)               !FRACTION OF FLOW RATE IN PLACENTA

  ! GESTATION CONTROL
IF (T.LT.CONCEPTION_T) THEN
```

```
    Gest_off = 1
    Gest_on=   0.0
ELSE
    Gest_off = 0.0
    Gest_on  = 1
END IF

  ! MOTHER BODY WEIGHT GROWTH EQUATION========
  ! MODIFICATION TO ADAPT THIS MODEL AT HUMAN MODEL
  ! BECAUSE LINEAR DESCRIPTION IS NOT GOOD ENOUGH FOR MOTHER GROWTH
  ! MOTHER BODY WEIGHT GROWTH

  PARAMETER (BW_RMN = 1.0E-30)
  WT0= BW_T0 *(1.0+(0.41*T)/(1402.5+T+BW_RMN)) ! IN GRAMS

  ! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGANS
  WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 +WPLAB0*WPLA0 + WLI0 + WF0 +
WPLA0))/(1.0+WREB0)  ! REST OF THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
  QREF = 1.0-(QFF+QLIF+QPLAF)            !REST OF BODY BLOOD FLOW RATE
FRACTION
  QTTQF = QFF+QREF+QLIF+QPLAF          ! SUM MUST EQUAL 1

  ! COMPARTMENT VOLUME (ML OR G) =========
 WF  =  WF0  * WT0                    ! ADIPOSE TISSUE
 WRE =  WRE0 * WT0                    ! REST OF THE BODY
 WLI =  WLI0 * WT0                    ! LIVER
 WPLA=  WPLA0* WT0                    ! PLACENTA

   ! COMPARTMENT TISSUE BLOOD (ML OR G) =========
 WFB  =  WFB0  * WF                   ! ADIPOSE TISSUE
 WREB =  WREB0 * WRE                  ! REST OF THE BODY
 WLIB =  WLIB0 * WLI                  ! LIVER
 WPLAB = WPLAB0* WPLA                 ! PLACANTA

   ! CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
   !QC= QCCAR*60*(WT0/1000.0)**0.75
CONSTANT QCC=16500                    ! EQUIVALENT TO 275 * 60
QC= QCC*(WT0/UNITCORR)**0.75

   !COMPARTMENT BLOOD FLOW RATE (ML/HR)
QF  = QFF*QC                          !ADIPOSE TISSUE BLOOD FLOW RATE
QLI = QLIF*QC                         !LIVER TISSUE BLOOD FLOW RATE
QRE = QREF*QC                         !REST OF THE BODY BLOOD FLOW RATE
QPLA = QPLAF*QC                       !PLACENTA TISSUE BLOOD FLOW RATE
QTTQ = QF+QRE+QLI+QPLA   !TOTAL FLOW RATE

    !PERMEABILITY ORGAN FLOW (ML/HR)=========
PAF  = PAFF*QF                       ! ADIPOSE TISSUE
PARE = PAREF*QRE                     ! REST OF THE BODY
PALI = PALIF*QLI                     ! LIVER TISSUE
PAPLA = PAPLAF*QPLA                  ! PLACENTA

    !*************************************
    ! ABSORPTION SECTION
    ! ORAL,
    ! INTRAPERITONEAL,
    ! INTRAVENOUS
```

```
    !*************************************

    !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIO

MSTOT_NMBCKGR = MSTOTBCKGR/322       !AMOUNT IN NMOL/G
MSTTBCKGR =MSTOT_NMBCKGR *WT0

DAY_EXPOSURE_BG   = PULSE(DAY_LAG_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
WEEK_EXPOSURE_BG  = PULSE(WEEK_LAG_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG = PULSE(MONTH_LAG_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
MSTTFR_BG = MSTTBCKGR/CINT

CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG

    ! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)

IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
    ABSMSTT_GB= MSTTFR_BG
ELSE
    ABSMSTT_GB = 0.0
END IF

CYCLETOTBG=INTEG(CYCLE_BG,0.0)

   !REPETITIVE ORAL EXPOSURE SCENARIO

MSTT= MSTOT_NM * WT0                  !AMOUNT IN NMOL

DAY_EXPOSURE   = PULSE(DAY_LAG,DAY_PERIOD,DAY_FINISH)
WEEK_EXPOSURE  = PULSE(WEEK_LAG,WEEK_PERIOD,WEEK_FINISH)
MONTH_EXPOSURE = PULSE(MONTH_LAG,MONTH_PERIOD,MONTH_FINISH)

MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
MSTTFR = MSTT/CINT

CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
SUMEXPEVENT= INTEG (CYCLE,0.0)/cint !NUMBER OF CYCLES GENERATED DURING
SIMULATION

   ! CONDITIONAL ORAL EXPOSURE
IF (MSTTCH.EQ.MSTT) THEN
   ABSMSTT= MSTTFR
ELSE
   ABSMSTT = 0.0
END IF


 CYCLETOT=INTEG(CYCLE,0.0)

   ! MASS CHANGE IN THE LUMEN
 RMSTT= -(KST+KABS)*MST +ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
  MST = INTEG(RMSTT,0.0)                      !AMOUNT REMAINING IN DUODENUM
(NMOL)

   ! ABSORPTION IN LYMPH CIRCULATION
```

```
 LYRMLUM = KABS*MST*A
  LYMLUM = INTEG(LYRMLUM,0.0)

   ! ABSORPTION IN PORTAL CIRCULATION
 LIRMLUM = KABS*MST*B
  LIMLUM = INTEG(LIRMLUM,0.0)


! -----IV EXPOSURE ---------

 IV= DOSEIV_NM * WT0 !AMOUNT IN NMOL
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1.0-STEP(PFUNC))
 IVDOSE = integ(EXPIV,0.0)

    !------IV late in the cycle
    ! MODIFICATION ON January 13 2004
 IV_RlateR = DOSEIVNMlate*WT0
 IV_EXPOSURE=PULSE(IV_LAG,IV_PERIOD,IV_FINISH)

 IV_lateT = IV_EXPOSURE *IV_RlateR
 IV_late = IV_lateT/CINT

SUMEXPEVENTIV= integ (IV_EXPOSURE,0.0) !NUMBER OF CYCLES GENERATED DURING
SIMULATION

    !SYSTEMIC CONCENTRATION OF TCDD
    ! MODIFICATION ON OCTOBER 6, 2009
 CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late)/(QC+CLURI) !
 CA = CB ! CONCENTRATION (NMOL/ML)

    !URINARY EXCRETION BY KIDNEY
    !MODIFICATION ON OCTOBER 6, 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)

  !UNIT CONVERSION POST SIMULATION
 CBSNGKGLIADJ=(CB*MW*UNITCORR*(1/B_TOTLIP)*(1/SERBLO))![NG of TCDD Serum/Kg
OF LIPID]
   AUCBS_NGKGLIADJ=integ(CBSNGKGLIADJ,0.0)


  CBNGKG= CB*MW*UNITCORR
  CBNGG = CB*MW

   !ADIPOSE COMPARTMENT
   !TISSUE BLOOD COMPARTMENT
RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)    !(NMOL/H)
 AFB = INTEG(RAFB,0.0)                !(NMOL)
  CFB = AFB/WFB                       !(NMOL/ML)
   !TISSUE COMPARTMENT
RAF = PAF*(CFB-CF/PF)                !(NMOL/H)
 AF = INTEG(RAF,0.0)                 !(NMOL)
  CF  = AF/WF                         !(NMOL/ML)

   !UNIT CONVERSION POST SIMULATION
  CFTOTAL= (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN NMOL/ML
```

```
  CFTFREE = CFB + CF !TOTAL FREE CONCENTRATION IN FAT  (NM/ML)

  CFNGKG=CFTOTAL*MW*UNITCORR ! FAT CONCENTRATION IN NG/KG
    AUCF_NGKGH=integ(CFNGKG,0.0)
  CFNGG = CFTOTAL*MW

   !REST OF THE BODY COMPARTMENT
RAREB= QRE *(CA-CREB)-PARE*(CREB-CRE/PRE)  !(NMOL/H)
 AREB = INTEG(RAREB,0.0)                    !(NMOL)
  CREB = AREB/WREB                          !(NMOL/H)
   !TISSUE COMPARTMENT
RARE = PARE*(CREB - CRE/PRE)               !(NMOL/H)
 ARE = INTEG(RARE,0.0)                     !(NMOL)
  CRE  = ARE/WRE                            !(NMOL/ML)

   !UNIT CONVERSION POST SIMULATION
  CRETOTAL= (ARE + AREB)/(WRE + WREB)           ! TOTAL CONCENTRATION IN
NMOL/ML
      CRENGKG=CRETOTAL*MW*UNITCORR ! REST OF THE BODY CONCENTRATION IN NG/KG


   !LIVER COMPARTMENT
   !TISSUE BLOOD COMPARTMENT
 RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM !
  ALIB = INTEG(RALIB,0.0)                       !(NMOL)
   CLIB = ALIB/WLIB                            !(NMOL/ML)
   !TISSUE COMPARTMENT
 RALI = PALI*(CLIB - CFLLIR)-REXCLI            !  (NMOL/HR)
  ALI = INTEG(RALI,0.0)                             !(NMOL)
   CLI  = ALI/WLI                                !(NMOL/ML)

   !FREE TCDD IN LIVER COMPARTMENT
PARAMETER (LIVER_1RMN = 1.0E-30)
 CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
        +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2 + CFLLIR &
        +LIVER_1RMN)*IND_ACTIVE)))-CFLLI,CFLLI0)
     CFLLIR=DIM(CFLLI,0.0) ! FREE CONCENTRATION IN LIVER

  CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND CONCENTRATION

  !VARIABLE ELIMINATION BASED ON THE CYP1A2
 KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv ! INDUCED BILIARY
EXCRETION RATE CONSTANT
  REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT EXCRETION RATE
    EXCLI = INTEG(REXCLI,0.0)

  !UNIT CONVERSION POST SIMULATION
  CLITOTAL= (ALI + ALIB)/(WLI + WLIB) ! TOTAL CONCENTRATION IN NMOL/ML

  Rec_occ= CFLLIR/(KDLI+CFLLIR)
  CLINGKG=CLITOTAL*MW*UNITCORR ! LIVER CONCENTRATION IN NG/KG
     AUCLI_NGKGH=INTEG(CLINGKG,0.0)
  CBNDLINGKG = CBNDLI*MW*UNITCORR
     AUCBNDLI_NGKGH =INTEG(CBNDLINGKG,0.0)
  CLINGG = CLITOTAL*MW

   !CHEMICAL IN CYP450 (1A2) COMPARTMENT
```

```
CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ ! BASAL RATE OF CYP1A2 PRODUCTION
SET EQUAL TO BASAL RATE OF DEGREDATION

   ! MODIFICATION ON OCTOBER 6, 2009
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
&
     /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
      - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)

! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)

      CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
  CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)

CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
  CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)

! TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
! FETAL EXPOSURE ONLY DURING EXPOSURE

IF (T.LT.TRANSTIME_ON) THEN
 SWITCH_trans = 0.0
ELSE
 SWITCH_trans = 1
END IF

!TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
! MODIFICATION 26 SEPTEMBER 2003

CONSTANT PFETUS= 4 !
CONSTANT CLPLA_FET = 0.17 !

RAMPF = (CLPLA_FET*CPLA) *SWITCH_trans
  AMPF=INTEG(RAMPF,0.0)

!TRANSFER OF DIOXIN FROM FETUS TO PLACENTA
RAFPM = (CLPLA_FET*CFETUS_v)*SWITCH_trans !
  AFPM = INTEG(RAFPM,0.0)

! TCDD IN PLACENTA MOTHER COMPARTMENT
RAPLAB= QPLA*(CA - CPLAB)-PAPLA*(CPLAB -CFLPLAR)   ! NMOL/H)
 APLAB = INTEG(RAPLAB,0.0)                          ! (NMOL)
 CPLAB = APLAB/(WPLAB+1E-30)                       ! (NMOL/ML)
RAPLA = PAPLA*(CPLAB-CFLPLAR)-RAMPF + RAFPM        ! (NMOL/H)
 APLA = INTEG(RAPLA,0.0)                            ! (NMOL)
 CPLA  = APLA/(WPLA+1e-30)                         ! (NMOL/ML)

PARAMETER (PARA_ZERO = 1.0E-30)
CFLPLA= IMPLC(CPLA-(CFLPLAR*PPLA +(PLABMAX*CFLPLAR/(KDPLA&
    +CFLPLAR+PARA_ZERO)))-CFLPLA,CFLPLA0)
CFLPLAR=DIM(CFLPLA,0.0)

   !UNIT CONVERSION POST SIMULATION
  CPLATOTAL= (APLA + APLAB)/((WPLA + WPLAB)+1e-30)! TOTAL CONCENTRATION IN
NMOL/ML
```

```
  CPLANGG = CPLATOTAL*MW

   !FETUS COMPARTMENT
RAFETUS= RAMPF-RAFPM
 AFETUS=INTEG(RAFETUS,0.0)
CFETUS=AFETUS/(WTFE+1E-30)
CFETOTAL= CFETUS
CFETUS_v = CFETUS/PFETUS

  ! UNIT CONVERSION POST SIMULATION
CFETUSNGKG = CFETUS*MW*UNITCORR                    !(NG/KG)
AUC_FENGKGH = INTEG(CFETUSNGKG,0.0)
CFETUSNGG = CFETOTAL*MW

! ------------CONTROL MASS BALANCE ----------
BDOSE= IVDOSE +LYMLUM+LIMLUM
BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB+AFETUS
BDIFF = BDOSE-BMASSE

      !BODY BURDEN (NG)
BODY_BURDEN = AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB !
BBFETUSNG     = AFETUS*MW*UNITCORR    ! NG
      ! BODY BURDEN IN TERMS OF CONCENTRATION (NG/KG)
 BBNGKG =(((AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB)/WT0)*MW*UNITCORR) !
  AUC_BBNGKGH=INTEG(BBNGKG,0.0)


! ------------COMMAND OF THE END OF SIMULATION ----------
TERMT (T.GE. TimeLimit, 'Time limit has been reached.')
END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYNAMIC SECTION
END   ! END OF THE PROGRAM
```

E.2.6.2. *Input Files*

E.2.6.2.1. *Keller et al. (2007)*

```
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Keller et al. 2007
%protocol:  single oral dose at GD13
%dose levels: 0.01, 0.100 1 ug/kg at GD13
%dose levels:   10, 100 1000 ng/kg at GD13

 MAXT=0.01
 CINT =0.1
 EXP_TIME_ON     = 312.              %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 336               %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 24                %HOURS BETWEEN DOSES
 BCK_TIME_ON     = 0.                %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF    = 0.                %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT       = 336               %SIMULATION DURATION (HOUR)
```

```
 BW_T0           = 24                %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 CONCEPTION_T         = 0.           %TIME OF CONCEPTION (HOUR)
 TRANSTIME_ON    = 144.              %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS         = 10                %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)

   %MSTOT         = 0.01             %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT        = 0.1               %ORAL EXPOSURE DOSE (UG/KG)
   MSTOT        = 1                  %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.6.2.2. *Li et al. (2006)*

```
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH
%Li et al.2006
%protocol:  daily oral dose from GD1 to GD3
%dose levels: 0.002, 0.050, 0.10 ug/kg-day at GD1 to GD3
%dose levels: 2, 50, 100 ng/kg-day from GD1 to GD3

 MAXT=0.001
 CINT =0.1
 EXP_TIME_ON     = 0.                %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 72                %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 24                %HOURS BETWEEN DOSES
 BCK_TIME_ON     = 0.                %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF    = 0.                %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT       = 72.               %SIMULATION DURATION (HOUR)
 BW_T0           = 27                %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 CONCEPTION_T         = 0.           %TIME OF CONCEPTION (HOUR)
 TRANSTIME_ON    = 144.              %TIME OF CONCEPATION + 6 DAYS(144 HOURS)
 N_FETUS         = 10                %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)

   %MSTOT         = 0.002            %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT        = 0.05              %ORAL EXPOSURE DOSE (UG/KG)
   MSTOT        = 0.10               %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.6.2.3. *Smith et al. (1976)*

```
      output @clear
      prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG
AUCLI_NGKGH AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG
AUCBNDLI_NGKGH CBNGKG AUC_CBNGKGH

 %protocol:  daily oral dose from GD6 to GD15

 %EXPOSURES SCENARIOS
  MAXT=0.01
  CINT =0.1
```

```
  EXP_TIME_ON     = 120.            %TIME EXPOSURE BEGINS (HOUR)
  EXP_TIME_OFF    = 337.            %TIME EXPOSURE ENDS (HOUR)
  DAY_CYCLE       = 24              %HOURS BETWEEN DOSES
  BCK_TIME_ON     = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
  BCK_TIME_OFF    = 0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
  TIMELIMIT       = 360.            %SIMULATION DURATION (HOUR)
  BW_T0           = 28.5            %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
  CONCEPTION_T    = 0.              %TIME OF CONCEPTION (HOUR)
  TRANSTIME_ON    = 144.            %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
  N_FETUS         = 10              %NUMBER OF FETUSES

 %EXPOSURE DOSE SCENARIOS (UG/KG)

    %MSTOT         = 0.001          %ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT        = 0.01            %ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT        = 0.10            %ORAL EXPOSURE DOSE (UG/KG)
```

E.3. TOXICOKINETIC MODELING RESULTS FOR KEY ANIMAL BIOASSAY STUDIES

The simulated TCDD serum-adjusted lipid concentrations reported in this appendix for the rodent bioassays were converted to TCDD concentrations in rodent whole blood. Initially, EPA multiplied the serum-adjusted lipid concentrations by 0.0033, the ratio of lipid content to total serum volume, then by 0.55, the value of the hematocrit. This product yields the TCDD concentration in whole rodent blood as predicted by the PBPK model. EPA assumed that the same whole blood TCDD concentration would result in the same effects in humans and rodents.

This conversion accomplishes the following:

1. Allows the human equivalent dose to be based on equivalent blood concentration (that represents serum plus erythrocyte TCDD), which is proportional to tissue exposure;
2. Avoids criticism that the total blood concentration is normalized to serum lipid alone in an unbalanced way (thus EPA does not contradict Centers for Disease Control and Prevention data or methods);
3. Factors out any impact of the lipid content used in the PBPK model; and
4. TCDD concentration in whole blood is encouraged for use in the assessments by the National Academy of Sciences (2006, p. 43); see additional information in Section 3.3.

E.3.1. Nongestational Studies

E.3.1.1. *Cantoni et al. (1981)*

Type:	Rat	**Dose:**	10, 100, and 1,000 ng/kg-week
Strain:	CD-COBS rats	**Route:**	Oral gavage exposure
Body weight:	BW = 125 g	**Regime:**	1 dose/week for 45 weeks
Sex:	Female	**Simulation time:**	7,560 hours (45 weeks)

BW = body weight.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
1.43	Emond	1.85	3.70 (@ 7,392 hours)	1.82
	CADM	-	-	-
14.29	Emond	8.84	26.6 (@ 7,392 hours)	7.97
	CADM	-	-	-
142.86	Emond	50.0	227 (@ 7,392 hours)	41.9
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
1.43	Emond		328 (@ 7,398 hours)	
	CADM	382	431	431
14.29	Emond	2,176	2,860 (@ 7,231 hours)	1,928
	CADM	3,973	4,330	4,330
142.86	Emond	20,500	26,978 (@ 7,399 hours)	17,255
	CADM	39,955	43,329	43,329
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
1.43	Emond	175	200 (@ 7,431 hours)	181
	CADM	256	280	244
14.29	Emond	837	937 (@ 7,427 hours)	807
	CADM	1,237	1,352	1,167
142.86	Emond	4,741	5,374 (@ 7,424 hours)	4,349
	CADM	10,278	11,224	9,734
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
1.43	Emond	26.1	31.7 (@ 7,398 hours)	26.3
	CADM	32.4	35.0	35.0
14.29	Emond	170	210 (@ 7,230 hours)	156
	CADM	230	243	243
142.86	Emond	1,337	1,695 (@ 7,398 hours)	1,151
	CADM	2,154	2,266	2,266

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
1.43	Emond	6.04	7.76 (@ 7,396 hours)	6.01
	CADM	-	-	-
14.29	Emond	23.7	29.1 (@ 7,228 hours)	22.2
	CADM	-	-	-
142.86	Emond	66.8	80.0 (@ 1 hours)	63.4
	CADM	-	-	-

Max = maximum; CADM = concentration- and age-dependent elimination model.

E.3.1.2. *Chu et al.(2007; 2001)*

Type:	Rat	**Dose:**	2.5, 25, 250, and 1,000 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral exposure
Body weight:	200 g	**Regime:**	1 dose per day for 28 days
Sex:	Female	**Simulation time:**	672 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
2.5	Emond	1.26	2.35 (@ 648 hours)	1.88
	CADM			
25	Emond	7.66	15.3 (@ 648 hours)	10.4
	CADM			
250	Emond	48.8	113 (@ 648 hours)	63.7
	CADM	-	-	-
1,000	Emond	169	418 (@ 648 hours)	222
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
2.5	Emond	148	268 (@ 652 hours)	255
	CADM	337	505	505
25	Emond	1,777	2,953 (@ 653 hours)	2,806
	CADM	4,422	5,786	5,786
250	Emond	19,232	30,262 (@ 653 hours)	28,668
	CADM	45,872	58,681	58,681
1,000	Emond	77,819	120,400 (@ 653 hours)	113,890
	CADM	184,076	234,992	234,992
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
2.5	Emond	108	180 (@ 668 hours)	180
	CADM	295	362	362
25	Emond	660	1,020 (@ 659 hours)	1,015
	CADM	1,703	2,057	2,057

250	Emond	4,210	6,433 (@ 655 hours)	6,354
	CADM	14,899	18,210	18,210
1,000	Emond	14,576	22,610 (@ 655 hours)	22,280
	CADM	58,824	72,002	72,002
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
2.5	Emond	16.1	27.5 (@ 652 hours)	26.9
	CADM	30.0	40.9	40.9
25	Emond	138	222 (@ 652 hours)	214
	CADM	261	336	336
250	Emond	1,239	1,935 (@ 652 hours)	1,842
	CADM	2,544	3,243	3,243
1,000	Emond	4,801	7,444 (@ 652 hours)	7,067
	CADM	10,150	12,930	12,930
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
2.5	Emond	4.15	6.51 (@ 652 hours)	6.21
	CADM	-	-	-
25	Emond	20.5	28.5 (@ 652 hours)	27.4
	CADM	-	-	-
250	Emond	63.3	76.0 (@ 652 hours)	74.7
	CADM	-	-	-
1,000	Emond	90.2	99.0 (@ 653 hours)	98.3
	CADM	-	-	-

E.3.1.3. *Crofton et al. (2005)*

Type:	Rats	**Dose:**	0, 0.1, 3, 10, 30, 100, 300, 1,000, 3,000, and 10,000 ng/kg-day
Strain:	Long Evans	**Route:**	Oral exposure
Body weight:	BW = 190 g (4 weeks old)	**Regime:**	One dose per day for 4 days
Sex:	Female	**Simulation time:**	96 hours

The CADM model was not run because the dosing duration is lower than the resolution of the model (1 week).

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.1	Emond	0.0202	0.041 (@ 72 hours)	0.0244
	CADM	-	-	-
3	Emond	0.488	1.10 (@ 72 hours)	0.582
	CADM	-	-	-
10	Emond	1.38	3.40 (@ 72 hours)	1.62
	CADM	-	-	-
30	Emond	3.46	9.44 (@ 72 hours)	3.93
	CADM	-	-	-

100	Emond	9.26	29.0 (@ 72 hours)	10.2
	CADM	-	-	-
300	Emond	23.1	81.8 (@ 72 hours)	24.5
	CADM	-	-	-
1,000	Emond	65.7	260 (@ 72 hours)	68.2
	CADM	-	-	-
3,000	Emond	181	764 (@ 72 hours)	187
	CADM	-	-	-
10,000	Emond	583	2,527 (@ 72 hours)	607
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.1	Emond	0.919	1.55 (@ 75 hours)	1.18
	CADM	-	-	-
3	Emond	37.4	62.6 (@ 76 hours)	53.3
	CADM	-	-	-
10	Emond	145	242 (@ 77 hours)	214
	CADM	-	-	-
30	Emond	494	818 (@ 78 hours)	742
	CADM	-	-	-
100	Emond	1,839	3,025 (@ 78 hours)	2,793
	CADM	-	-	-
300	Emond	5,925	9,692 (@ 78 hours)	9,028
	CADM	-	-	-
1,000	Emond	20,717	33,738 (@ 79 hours)	31,564
	CADM	-	-	-
3,000	Emond	63,511	103,140 (@ 79 hours)	96,545
	CADM	-	-	-
10,000	Emond	212,890	344,910 (@ 79 hours)	321,960
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.1	Emond	1.00	1.93 (@ 96 hours)	1.93
	CADM	-	-	-
3	Emond	24.6	45.9 (@ 96 hours)	45.9
	CADM	-	-	-
10	Emond	70.3	129 (@ 96 hours)	129
	CADM	-	-	-
30	Emond	177	317 (@ 96 hours)	317
	CADM	-	-	-
100	Emond	480	838 (@ 96 hours)	838
	CADM	-	-	-
300	Emond	1,206	2,065 (@ 96 hours)	2,065
	CADM	-	-	-
1,000	Emond	3,452	5,836 (@ 96 hours)	5,836
	CADM	-	-	-
3,000	Emond	9,522	16,050 (@ 96 hours)	16,050
	CADM	-	-	-
10,000	Emond	30,657	51,918 (@ 96 hours)	51,918
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.1	Emond	0.138	0.224 (@ 79 hours)	0.223
	CADM	-	-	-
3	Emond	4.04	6.56 (@ 78 hours)	6.44
	CADM	-	-	-
10	Emond	13.3	21.5 (@ 78 hours)	21.0
	CADM	-	-	-
30	Emond	39.3	63.5 (@ 78 hours)	61.5
	CADM	-	-	-
100	Emond	129	208 (@ 78 hours)	200
	CADM	-	-	-
300	Emond	384	618 (@ 77 hours)	590
	CADM	-	-	-
1,000	Emond	1,270	2,041 (@ 77 hours)	1,942
	CADM	-	-	-
3,000	Emond	3,793	6,094 (@ 77 hours)	5,784
	CADM	-	-	-
10,000	Emond	12,595	20,226 (@ 77 hours)	19,154
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.1	Emond	0	0.115 (@ 75 hours)	0
	CADM	-	-	-
3	Emond	2	2.47 (@ 76 hours)	2
	CADM	-	-	-
10	Emond	4	6.42 (@ 76 hours)	5
	CADM	-	-	-
30	Emond	10	14.1 (@ 76 hours)	12
	CADM	-	-	-
100	Emond	22	29.9 (@ 76 hours)	27
	CADM	-	-	-
300	Emond	41	51.9 (@ 77 hours)	49
	CADM	-	-	-
1,000	Emond	68	80.2 (@ 1 hours)	77
	CADM	-	-	-
3,000	Emond	90	98.6 (@ 1 hours)	96
	CADM	-	-	-
10,000	Emond	104	108 (@ 1 hours)	107
	CADM	-	-	-

E.3.1.4. *Croutch et al. (2005)*

Type:	Rat	**Dose:**	12.5, 50, 200, 800, and 3,200 ng/kg initial and 1.25, 5, 20, 80, and 320 ng/kg maintenance doses every 4 days (equivalent to 0.85, 3.4, 13.6, 54.3, and 217 ng/kg-day)
Strain:	Sprague-Dawley	**Route:**	Gavage
Body weight:	250 g	**Regime:**	One initial dose and maintenance doses every 3 days for 28 days
Sex:	Female	**Simulation time:**	672 hours

The CADM model was not run because the dosing protocol includes both initial and maintenance doses, which is not supported in the model.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.85	Emond	0.340	0.723 (@ 648 hours)	0.513
	CADM	-	-	-
3.4	Emond	1.10	2.44 (@ 648 hours)	1.55
	CADM	-	-	-
13.6	Emond	3.29	8.69 (@ 0 hours)	4.36
	CADM	-	-	-
54.3	Emond	9.58	34.8 (@ 0 hours)	12.1
	CADM	-	-	-
217	Emond	28.7	139 (@ 0 hours)	35.0
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.85	Emond	25.6	46.8 (@ 653 hours)	43.9
	CADM	-	-	-
3.4	Emond	119	206 (@ 654 hours)	195
	CADM	-	-	-
13.6	Emond	538	877 (@ 654 hours)	834
	CADM	-	-	-
54.3	Emond	2,339	3,617 (@ 655 hours)	3,444
	CADM	-	-	-
217	Emond	9,824	14,634 (@ 655 hours)	13,931
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.85	Emond	29.0	46.9 (@ 672 hours)	46.9
	CADM	-	-	-

3.4	Emond	94.1	143 (@ 672 hours)	143
	CADM	-	-	-
13.6	Emond	284	409 (@ 672 hours)	409
	CADM	-	-	-
54.3	Emond	828	1,149 (@ 670 hours)	1,149
	CADM	-	-	-
217	Emond	2,480	3,389 (@ 666 hours)	3,384
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.85	Emond	3.67	6.09 (@ 654 hours)	6.00
	CADM	-	-	-
3.4	Emond	13.5	21.6 (@ 653 hours)	21.1
	CADM	-	-	-
13.6	Emond	48.9	75.0 (@ 653 hours)	72.8
	CADM	-	-	-
54.3	Emond	178	264 (@ 653 hours)	254
	CADM	-	-	-
217	Emond	661	963 (@ 653 hours)	922
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.85	Emond	1.17	1.93 (@ 652 hours)	1.77
	CADM	-	-	-
3.4	Emond	3.65	5.59 (@ 652 hours)	5.18
	CADM	-	-	-
13.6	Emond	10.1	14.4 (@ 652 hours)	13.4
	CADM	-	-	-
54.3	Emond	24.7	35.8 (@ 1 hour)	30.6
	CADM	-	-	-
217	Emond	50.5	69.9 (@ 1 hour)	58.6
	CADM	-	-	-

E.3.1.5. *Della Porta et al. (1987) Female*

Type:	Mouse	**Dose:**	2,500 and 5,000 ng/kg-week (equivalent to 357 and 714 ng/kg-day)
Strain:	B6C3	**Route:**	Gavage
Body weight:	BW = 20 g (6 weeks old)	**Regime:**	Once a week for 52 weeks
Sex:	Female	**Simulation time:**	8,736 hours

The CADM model was not run because the study duration is longer than the allowed model duration.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	67.0	741 (@ 8,568 hours)	46.8
	CADM	-	-	-
714	Emond	37.6	374 (@ 8,568 hours)	27.2
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	50,269	70,070 (@ 8,577 hours)	37,389
	CADM	-	-	-
714	Emond	25,422	35,352 (@ 8,577 hours)	19,105
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	25,235	28,559 (@ 8,589 hours)	22,498
	CADM	-	-	-
714	Emond	14,162	15,914 (@ 8,590 hours)	12,810
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	5,473	7,247 (@ 8,574 hours)	4,335
	CADM	-	-	-
714	Emond	2,878	3,774 (@ 8,574 hours)	2,318
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	71.5	99.1 (@ 2 hours)	65.4
	CADM	-	-	-
714	Emond	56.4	88.6 (@ 2 hours)	50.4
	CADM	-	-	-

E.3.1.6. *Della Porta et al. (1987) Male*

Type:	Mouse	**Dose:**	2,500 and 5,000 ng/kg-week (equivalent to 357 and 714 ng/kg-day)
Strain:	B6C3	**Route:**	Gavage
Body weight:	26 g (6 weeks old)	**Regime:**	Once a week for 52 weeks
Sex:	Male	**Simulation time:**	8,736 hours

The CADM model was not run because the study duration is longer than the allowed model duration.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	67.8	787 (@ 8,568 hours)	47.0
	CADM	-	-	-
714	Emond	38.0	398 (@ 8,568 hours)	27.3
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	50,397	70,052 (@ 8,577 hours)	37,483
	CADM	-	-	-
714	Emond	25,493	35,347 (@ 8,577 hours)	19,155
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	25,516	28,851 (@ 8,589 hours)	22,861
	CADM	-	-	-
714	Emond	14,306	16,061 (@ 8,590 hours)	12,999
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	5,504	7,282 (@ 8,574 hours)	4,368
	CADM	-	-	-
714	Emond	2,894	3,791 (@ 8,574 hours)	2,335
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	71.6	99.2 (@ 2 hours)	65.4
	CADM	-	-	-
714	Emond	56.4	88.6 (@ 2 hours)	50.4
	CADM	-	-	-

E.3.1.7. *Fattore et al. (2000)*

Type:	Rat	**Dose:**	20, 200, 2,000 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Dietary exposure
Body weight:	BW 150 g (7 weeks old)	**Regime:**	Every day for 13 weeks
Sex:	Female and male	**Simulation time:**	2,184 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
20	Emond	9.59	15.0 (@ 2,160 hours)	11.1
	CADM	-	-	-
200	Emond	57.6	102 (@ 2,160 hours)	63.9
	CADM	-	-	-
2,000	Emond	476	903 (@ 2,160 hours)	522
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
20	Emond	2,448	3,228 (@ 2,164 hours)	3,078
	CADM	4,815	5,639	5,639
200	Emond	24,136	30,245 (@ 2,164 hours)	28,709
	CADM	48,824	56,499	56,499
2,000	Emond	234,170	288,020 (@ 2,164 hours)	272,590
	CADM	488,957	565,103	565,103
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
20	Emond	890	1,113 (@ 2,166 hours)	1,101
	CADM	1,663	1,796	1,756
200	Emond	5,355	6,542 (@ 2,165 hours)	6,430
	CADM	14,378	15,604	15,292
2,000	Emond	44,176	54,246 (@ 2,165 hours)	53,140
	CADM	141,356	153,534	150,516
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
20	Emond	187	242 (@ 2,164 hours)	233
	CADM	281	324	324
200	Emond	1,556	1,940 (@ 2,164 hours)	1,850
	CADM	2,688	3,084	3,084
2,000	Emond	14,432	17,797 (@ 2,164 hours)	16,891
	CADM	26,746	30,674	30,674
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
20	Emond	24.9	29.8 (@ 2,164 hours)	28.8
	CADM	-	-	-
200	Emond	69.4	76.0 (@ 2,164 hours)	74.7
	CADM	-	-	-
2,000	Emond	104	106 (@ 2,164 hours)	106
	CADM	-	-	-

E.3.1.8. *Fox et al. (1993)*

Type:	Rat	**Dose:**	5, 2,500, and 12,000 ng/kg initial and 0.9, 600, or 3,500 ng/kg maintenance doses every 4 days (equivalent to 0.55, 307, and 1,607 ng/kg-day)
Strain:	Sprague-Dawley	**Route:**	Gavage
Body weight:	200 g (12 weeks old)	**Regime:**	One initial dose and maintenance doses every 4 days for 14 days
Sex:	Male and Female	**Simulation time:**	336 hours

The CADM model was not run because the dosing protocol includes both initial and maintenance doses, which is not supported in the model.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.55	Emond	0.119	0.314 (@ 288 hours)	0.173
	CADM	-	-	-
307	Emond	25.4	143 (@ 288 hours)	32.8
	CADM	-	-	-
1,607	Emond	112	797 (@ 288 hours)	150
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.55	Emond	6.95	14.3 (@ 292 hours)	11.1
	CADM	-	-	-
307	Emond	8,138	14,826 (@ 296 hours)	12,897
	CADM	-	-	-
1,607	Emond	46,701	86,754 (@ 296 hours)	75,253
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.55	Emond	9.14	16.1 (@ 336 hours)	16.1
	CADM	-	-	-
307	Emond	1,997	3,197 (@ 324 hours)	3,186
	CADM	-	-	-
1,607	Emond	8,710	14,716 (@ 323 hours)	14,638
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.55	Emond	1.12	1.92 (@ 295 hours)	1.88
	CADM	-	-	-
307	Emond	545	952 (@ 294 hours)	857
	CADM	-	-	-

1,607	Emond	2,890	5,239 (@ 294 hours)	4,667
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.55	Emond	0.409	0.803 (@ 292 hours)	0.604
	CADM	-	-	-
307	Emond	45.9	63.7 (@ 1 hour)	56.8
	CADM	-	-	-
1,607	Emond	82.1	95.8 (@ 1 hour)	92.7
	CADM	-	-	-

E.3.1.9. *Franc et al. (2001) Sprague-Dawley Rats*

Type:	Rats	**Dose:**	140, 420, and 1,400 ng/kg every 2 weeks (equivalent to 10, 30, and 100 ng/kg-day)
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	200 g (10 weeks old)	**Regime:**	Once every 2 weeks for 22 weeks
Sex:	Female	**Simulation time:**	3,696 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	6.59	34.6 (@ 3,360 hours)	5.52
	CADM	-	-	-
30	Emond	14.5	98.1 (@ 3,360 hours)	11.3
	CADM	-	-	-
WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
100	Emond	36.4	315 (@ 3,360 hours)	26.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	1,447	2,458 (@ 3,368 hours)	1,150
	CADM	2,616	3,620	2,174
30	Emond	4,228	7,161 (@ 3,368 hours)	3,120
	CADM	7,936	10,899	6,510
100	Emond	13,821	23,417 (@ 3,368 hours)	9,658
	CADM	26,564	36,361	21,703
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	619	787 (@ 3,417 hours)	560
	CADM	966	1,230	759
30	Emond	1,362	1,741 (@ 3,415 hours)	1,161
	CADM	2,448	3,203	1,849

100	Emond	3,430	4,464 (@ 3,412 hours)	2,755
	CADM	7,573	10,052	5,606
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	119	177 (@ 3,366 hours)	99.5
	CADM	159	212	133
30	Emond	308	472 (@ 3,366 hours)	240
	CADM	450	603	367
100	Emond	921	1,445 (@ 3,366 hours)	671
	CADM	1,462	1,969	1,181
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	18.6	32.9 (@ 1 hour)	16.4
	CADM	-	-	-
30	Emond	33.7	59.2 (@ 1 hour)	29.0
	CADM	-	-	-
100	Emond	57.5	86.9 (@ 1 hour)	50.4
	CADM	-	-	-

E.3.1.10. *Franc et al. (2001) Long-Evans Rats*

Type:	Rats	**Dose:**	140, 420, and 1,400 ng/kg every 2 weeks (equivalent to 10, 30, and 100 ng/kg-day)
Strain:	Long-Evans	**Route:**	Oral gavage
Body weight:	190 g (10 weeks old)	**Regime:**	Once every 2 weeks for 22 weeks
Sex:	Female	**Simulation time:**	3,696 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	6.58	34.2 (@ 3,360 hours)	5.52
	CADM	-	-	-
30	Emond	14.5	97.0 (@ 3,360 hours)	11.3
	CADM	-	-	-
100	Emond	36.4	312 (@ 3,360 hours)	26.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	1,447	2,458 (@ 3,368 hours)	1,150
	CADM	2,616	3,620	2,174
30	Emond	4,228	7,161 (@ 3,368 hours)	3,121
	CADM	7,936	10,899	6,510
100	Emond	13,821	23,421 (@ 3,368 hours)	9,659
	CADM	26,564	36,361	21,703

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	619	788 (@ 3,417 hours)	560
	CADM	966	1,230	759
30	Emond	1,362	1,742 (@ 3,414 hours)	1,160
	CADM	2,448	3,203	1,849
100	Emond	3,429	4,466 (@ 3,412 hours)	2,752
	CADM	7,573	10,052	5,606
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	119	177 (@ 3,366 hours)	99.5
	CADM	159	212	133
30	Emond	308	472 (@ 3,366 hours)	240
	CADM	450	603	367
100	Emond	921	1,445 (@ 3,366 hours)	671
	CADM	1,462	1,969	1,181
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	18.6	32.9 (@ 1 hour)	16.4
	CADM	-	-	-
30	Emond	33.7	59.2 (@ 1 hour)	29.0
	CADM	-	-	-
100	Emond	57.5	86.9 (@ 1 hour)	50.4
	CADM	-	-	-

E.3.1.11. *Franc et al. (2001) Hans Wistar Rats*

Type:	Rats	**Dose:**	140, 420, and 1,400 ng/kg every 2 weeks (equivalent to 10, 30, and 100 ng/kg-day)
Strain:	Hans Wistar	**Route:**	Oral gavage
Body weight:	205 g (10 weeks old)	**Regime:**	Once every 2 weeks for 22 weeks
Sex:	Female	**Simulation time:**	3,696 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	6.59	34.7 (@ 3,360 hours)	5.52
	CADM	-	-	-
30	Emond	14.5	98.7 (@ 3,360 hours)	11.3
	CADM	-	-	-
100	Emond	36.4	317 (@ 3,360 hours)	26.4
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	1,447	2,458 (@ 3,368 hours)	1,150
	CADM	2,616	3,620	2,174
30	Emond	4,228	7,160 (@ 3,368 hours)	3,120
	CADM	7,936	10,899	6,510
100	Emond	13,821	23,416 (@ 3,368 hours)	9,658
	CADM	26,564	36,361	21,703
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	619	787 (@ 3,418 hours)	560
	CADM	966	1,230	759
30	Emond	1,363	1,741 (@ 3,415 hours)	1,162
	CADM	2,448	3,203	1,849
100	Emond	3,431	4,463 (@ 3,412 hours)	2,757
	CADM	7,573	10,052	5,606
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	119	177 (@ 3,366 hours)	99.5
	CADM	159	212	133
30	Emond	308	472 (@ 3,366 hours)	240
	CADM	450	603	367
100	Emond	921	1,446 (@ 3,366 hours)	671
	CADM	1,462	1,969	1,181
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
10	Emond	18.6	32.9 (@ 1 hour)	16.4
	CADM	-	-	-
30	Emond	33.7	59.2 (@ 1 hour)	29.0
	CADM	-	-	-
100	Emond	57.5	86.9 (@ 1 hour)	50.4
	CADM	-	-	-

E.3.1.12. *Hassoun et al. (2000)*

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day (2.14, 7.14, 15.7, 32.9, and 71.4 ng/kg-day adjusted doses)
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	BW = 215 g (8 weeks old)	**Regime:**	5 days/week for 13 weeks
Sex:	Female	**Simulation time:**	2,184 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
2.14	Emond	1.94	3.12 (@ 2,112 hours)	1,303.17
	CADM	-	-	-
7.14	Emond	4.6136	7.71 (@ 2,112 hours)	2,901.26
	CADM	-	-	-
15.7	Emond	8.147	14.2 (@ 2,112 hours)	4,947.3
	CADM	-	-	-
32.9	Emond	14.009	25.8 (@ 2,112 hours)	8,277
	CADM	-	-	-
71.4	Emond	25.34	49.7 (@ 2,112 hours)	14,637
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
2.14	Emond	266.8	399 (@ 2,116 hours)	349
	CADM	470	595	595
7.14	Emond	888	1,259 (@ 2,117 hours)	1,079
	CADM	1,678	2,001	2,001
15.7	Emond	1,948.499	2,689 (@ 2,117 hours)	2,278.182
	CADM	1,768	4,428	4,428
32.9	Emond	4,055.031	5,484 (@ 2,117 hours)	4,607.265
	CADM	7,957	9,272	9,272
71.4	Emond	8,774.97	11,692 (@ 2,117 hours)	9,754.31
	CADM	17,387	20,170	20,170
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
2.14	Emond	179.2	243 (@ 2,126 hours)	234.9
	CADM	325	355	349
7.14	Emond	427	553 (@ 2,124 hours)	528
	CADM	730	787	769
15.7	Emond	755	958 (@ 2,123 hours)	908
	CADM	1,356	1,463	1,430
32.9	Emond	1,299	1,627 (@ 2,122 hours)	1,529
	CADM	2,577	2,787	2,727
71.4	Emond	2,349.892	2,928 (@ 2,121 hours)	2,727.240
	CADM	5,304	5,748	5,630
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
2.14	Emond	27.425	38.9 (@ 2,116 hours)	35.720
	CADM	38.2	45.9	45.9
7.14	Emond	76.87	105 (@ 2,116 hours)	93.67
	CADM	108	126	126
15.7	Emond	153.1	205 (@ 2,116 hours)	180.2
	CADM	224	258	258
32.9	Emond	295	390 (@ 2,116 hours)	339
	CADM	453	522	522
71.4	Emond	600	785 (@ 2,116 hours)	674
	CADM	970	1,113	1,113

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
2.14	Emond	6	8.48 (@ 2,116 hours)	8
	CADM	-	-	-
7.14	Emond	13.7242	17.5 (@ 2,116 hours)	15.7348
	CADM	-	-	-
15.7	Emond	21.9703	27.1 (@ 2,116 hours)	24.4047
	CADM	-	-	-
32.9	Emond	32.817	39.2 (@ 2,116 hours)	35.608
	CADM	-	-	-
71.4	Emond	47.54	55.0 (@ 2,116 hours)	50.63
	CADM	-	-	-

E.3.1.13. *Hutt et al. (2008)*

Type:	Rat	**Dose:**	50 ng/kg-week (equivalent to 7.14 ng/kg-day)
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	4.5 g (weight at birth)	**Regime:**	1 per week for 13 weeks
Sex:	Female	**Simulation time:**	2,184 hours (weekly exposure)

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
7.14	Emond	4.49	8.86 (@ 2,016 hours)	4.71
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
7.14	Emond	867.4	1,363 (@ 2,021 hours)	928.1
	CADM	1,678	2,007	2,007
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
7.14	Emond	423.6	555 (@ 2,040 hours)	459.9
	CADM	730	787.1	769
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
7.14	Emond	76	108 (@ 2,022 hours)	81
	CADM	108	126	126
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
7.14	Emond	14	19.4 (@ 2,020 hours)	14
	CADM	-	-	-

E.3.1.14. *Ishihara et al. (2007)*

Type:	Mouse	**Dose:**	2 and 2,000 ng/kg-week initial and 0.4 or 400 ng/kg-week maintenance (equivalent to 0.024 and 2.4 ng/kg-day)
Strain:	ICR	**Route:**	Gavage
Body weight:	23 g (7 weeks old)	**Regime:**	One initial dose and weekly maintenance doses for 5 weeks
Sex:	Male and Female	**Simulation time:**	840 hours

The CADM model was not run because the dosing protocol includes both initial and maintenance doses, which is not supported in the model.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.024	Emond	0.0172	0.076 (@ 672 hours)	0.0247
	CADM	-	-	-
2.4	Emond	7.04	61.2 (@ 672 hours)	6.47
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.024	Emond	1.45	3.65 (@ 677 hours)	2.13
	CADM	-	-	-
2.4	Emond	2,805	5,059 (@ 680 hours)	2,758
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.024	Emond	5.48	9.88 (@ 749 hours)	9.63
	CADM	-	-	-
2.4	Emond	2,352	3,284 (@ 712 hours)	2,856
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.024	Emond	0.537	0.964 (@ 680 hours)	0.902
	CADM	-	-	-
2.4	Emond	381	617 (@ 678 hours)	413
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.024	Emond	0.0599	0.150 (@ 676 hours)	0.0861
	CADM	-	-	-
2.4	Emond	18.6	43.6 (@ 2 hours)	18.4
	CADM	-	-	-

E.3.1.15. *Kitchin and Woods (1979)*

Type:	Rats	**Dose:**	0, 0.6, 2, 4, 20, 60, 200, 600, 2,000, 5,000, 20,000 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral exposure
Body weight:	BW = 225 g (200 to 250 g)	**Regime:**	Single dose
Sex:	Female	**Simulation time:**	24 hours

1 week is the minimum that can be simulated with the CADM model, so the CADM model was not used.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.6	Emond	0.0645	0.126 (@ 0 hours)	0.0441
	CADM	-	-	-
2	Emond	0.202	0.421 (@ 0 hours)	0.137
	CADM	-	-	-
4	Emond	0.384	0.841 (@ 0 hours)	0.258
	CADM	-	-	-
20	Emond	1.61	4.21 (@ 0 hours)	1.04
	CADM	-	-	-
60	Emond	4.15	12.6 (@ 0 hours)	2.55
	CADM	-	-	-
200	Emond	11.6	42.1 (@ 0 hours)	6.61
	CADM	-	-	-
600	Emond	30.3	126 (@ 0 hours)	15.8
	CADM	-	-	-
2,000	Emond	90.9	422 (@ 0 hours)	42.8
	CADM	-	-	-
5,000	Emond	218	1,056 (@ 0 hours)	96.9
	CADM	-	-	-
20,000	Emond	863	4,233 (@ 0 hours)	365
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.6	Emond	2.95	3.81 (@ 4 hours)	2.31
	CADM	-	-	-
2	Emond	10.5	12.9 (@ 4 hours)	8.69
	CADM	-	-	-
4	Emond	22.2	26.3 (@ 4 hours)	18.9
	CADM	-	-	-
20	Emond	128	143 (@ 6 hours)	118
	CADM	-	-	-
60	Emond	420	463 (@ 8 hours)	406
	CADM	-	-	-
200	Emond	1,523	1,666 (@ 9 hours)	1,526
	CADM	-	-	-

600	Emond	4,821	5,258 (@ 10 hours)	4,932
	CADM	-	-	-
2,000	Emond	16,603	18,080 (@ 11 hours)	17,226
	CADM	-	-	-
5,000	Emond	41,971	45,674 (@ 11 hours)	43,803
	CADM	-	-	-
20,000	Emond	167,820	182,580 (@ 11 hours)	175,890
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.6	Emond	1.60	2.47 (@ 24 hours)	2.47
	CADM	-	-	-
2	Emond	5.07	7.71 (@ 24 hours)	7.71
	CADM	-	-	-
4	Emond	9.68	14.6 (@ 24 hours)	14.6
	CADM	-	-	-
20	Emond	41.7	60.7 (@ 24 hours)	60.7
	CADM	-	-	-
60	Emond	110	155 (@ 24 hours)	155
	CADM	-	-	-
200	Emond	317	427 (@ 24 hours)	427
	CADM	-	-	-
600	Emond	851	1,102 (@ 24 hours)	1,102
	CADM	-	-	-
2,000	Emond	2,620	3,276 (@ 24 hours)	3,276
	CADM	-	-	-
5,000	Emond	6,361	7,816 (@ 24 hours)	7,816
	CADM	-	-	-
20,000	Emond	25,401	30,827 (@ 24 hours)	30,827
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.6	Emond	0.322	0.341 (@ 9 hours)	0.338
	CADM	-	-	-
2	Emond	1.07	1.14 (@ 8 hours)	1.12
	CADM	-	-	-
4	Emond	2.14	2.27 (@ 8 hours)	2.23
	CADM	-	-	-
20	Emond	10.6	11.3 (@ 8 hours)	11.0
	CADM	-	-	-
60	Emond	31.7	33.8 (@ 7 hours)	32.8
	CADM	-	-	-
200	Emond	105	112 (@ 7 hours)	108
	CADM	-	-	-
600	Emond	315	337 (@ 7 hours)	324
	CADM	-	-	-
2,000	Emond	1,049	1,123 (@ 7 hours)	1,074
	CADM	-	-	-
5,000	Emond	2,621	2,806 (@ 7 hours)	2,680
	CADM	-	-	-

20,000	Emond	10,468	11,215 (@ 7 hours)	10,693
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.6	Emond	0.216	0.309 (@ 3 hours)	0.159
	CADM	-	-	-
2	Emond	0.668	0.975 (@ 3 hours)	0.494
	CADM	-	-	-
4	Emond	1.25	1.86 (@ 3 hours)	0.927
	CADM	-	-	-
20	Emond	4.87	7.67 (@ 2 hours)	3.66
	CADM	-	-	-
60	Emond	11.2	18.3 (@ 2 hours)	8.55
	CADM	-	-	-
200	Emond	25.1	40.8 (@ 1 hours)	19.7
	CADM	-	-	-
600	Emond	45.8	68.2 (@ 1 hours)	37.6
	CADM	-	-	-
2,000	Emond	73.3	93.1 (@ 1 hour)	64.7
	CADM	-	-	-
5,000	Emond	90.9	104 (@ 1 hour)	84.7
	CADM	-	-	-
20,000	Emond	106	110 (@ 1 hour)	104
	CADM	-	-	-

E.3.1.16. *Kociba et al. (1976)*

Type:	Rats	**Dose:**	1, 10, 100, and 1,000 ng/kg-day
Strain:	Sprague-Dawley (Spartan)	**Route:**	Dietary exposure
Body weight:	BW = 180 g (170–190 g)	**Regime:**	5 days/week for 13 weeks
Sex:	Female	**Simulation time:**	2,184 hours (13 weeks exposed)

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.714	Emond	0.859	1.38 (@ 2,112 hours)	1.13
	CADM	-	-	-
7.143	Emond	4.61	7.62 (@ 2,112 hours)	5.27
	CADM	-	-	-
71.43	Emond	25.3	48.8 (@ 2,112 hours)	26.6
	CADM	-	-	-
714.3	Emond	181	403 (@ 2,112 hours)	184
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.714	Emond	88.3	140 (@ 2,116 hours)	126
	CADM	136	192	192
7.143	Emond	888	1,259 (@ 2,117 hours)	1,079
	CADM	1,678	2,007	2,007
71.43	Emond	8,776	11,693 (@ 2,117 hours)	9,756
	CADM	17,387	20,170	20,170
714.3	Emond	86,329	112,580 (@ 2,117 hours)	92,835
	CADM	174,576	201,814	201,814
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.714	Emond	79.4	114 (@ 2,129 hours)	111
	CADM	165	190	189
7.143	Emond	427	553 (@ 2,124 hours)	528
	CADM	730	787	769
71.43	Emond	2,348	2,925 (@ 2,121 hours)	2,720
	CADM	5,305	5,748	5,630
714.3	Emond	16,815	21,126 (@ 2,120 hours)	19,233
	CADM	50,658	55,013	53,928
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.714	Emond	10.8	16.1 (@ 2,116 hours)	15.1
	CADM	15.9	20.0	20.0
7.143	Emond	76.9	105 (@ 2,116 hours)	93.6
	CADM	108	126	126
71.43	Emond	600	785 (@ 2,116 hours)	673
	CADM	969	1,113	1,113
714.3	Emond	5,366	6,960 (@ 2,116 hours)	5,842
	CADM	9,562	10,967	10,967
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.714	Emond	2.89	4.17 (@ 2,116 hours)	3.81
	CADM	-	-	-
7.143	Emond	13.7	17.5 (@ 2,116 hours)	15.7
	CADM	-	-	-
71.43	Emond	47.5	55.0 (@ 2,116 hours)	50.6
	CADM	-	-	-
714.3	Emond	93.4	98.2 (@ 2,117 hours)	95.7
	CADM	-	-	-

E.3.1.17. *Kociba et al. (1978) Female*

Type:	Rats	**Dose:**	0, 1, 10, and 100 ng/kg-day
Strain:	Sprague-Dawley (Spartan)	**Route:**	Dietary exposure
Body weight:	BW = 180 g (170−190 g)	**Regime:**	7 days/week for 104 weeks
Sex:	Female	**Simulation time:**	17,472 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	1.55	1.92 (@ 17,448 hours)	1.69
	CADM	-	-	-
10	Emond	7.15	9.25 (@ 17,448 hours)	7.16
	CADM	-	-	-
100	Emond	38.6	57.5 (@ 17,448 hours)	37.1
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	192	226 (@ 17,452 hours)	218
	CADM	295	334	334
10	Emond	1,618	1,742 (@ 17,452 hours)	1,665
	CADM	3,013	3,348	3,348
100	Emond	14,892	15,673 (@ 17,452 hours)	14,907
	CADM	30.239	33.488	33.488
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	147	165 (@ 17,457 hours)	164
	CADM	198	229	181
10	Emond	680	713 (@ 17,454 hours)	706
	CADM	869	1,015	788
100	Emond	3,663	3,788 (@ 17,454 hours)	3,731
	CADM	6.816	7,939	6.195
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	21.2	24.3 (@ 17,452 hours)	23.8
	CADM	26.1	27.0	27.0
10	Emond	131	140 (@ 17,452 hours)	136
	CADM	171	176	176
100	Emond	989	1,039 (@ 17,452 hours)	994
	CADM	1,562	1,601	1,601

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	5.11	5.77 (@ 17,452 hours)	5.59
	CADM	-	-	-
10	Emond	20.0	21.1 (@ 17,452 hours)	20.4
	CADM	-	-	-
100	Emond	59.9	61.5 (@ 17,452 hours)	60.1
	CADM	-	-	-

E.3.1.18. *Kociba et al. (1978) Male*

Type:	Rats	**Dose:**	0, 1, 10, and 100 ng/kg-day
Strain:	Sprague-Dawley (Spartan)	**Route:**	Dietary exposure
Body weight:	BW approximated to be 250 g	**Regime:**	7 days/week for 104 weeks
Sex:	Male	**Simulation time:**	17,472 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	1.56	1.96 (@ 17,448 hours)	1.70
	CADM	-	-	-
10	Emond	7.16	9.35 (@ 17,448 hours)	7.11
	CADM	-	-	-
100	Emond	38.7	59.3 (@ 17,448 hours)	37.1
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	194	229 (@ 17,452 hours)	221
	CADM	295	334	334
10	Emond	1,616	1,723 (@ 17,452 hours)	1,649
	CADM	3,013	3,348	3,348
100	Emond	14,898	15,671 (@ 17,452 hours)	14,912
	CADM	30.239	33.488	33.488
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	148	167 (@ 17,456 hours)	166
	CADM	198	229	181
10	Emond	680	709 (@ 17,454 hours)	703
	CADM	869	1,015	788
100	Emond	3,677	3,803 (@ 17,453 hours)	3,747
	CADM	6.816	7,939	6.195

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	21.4	24.6 (@ 17,452 hours	24.1
	CADM	26.1	27.0	27.0
10	Emond	131	139 (@ 17,452 hours)	134
	CADM	171	176	176
100	Emond	991	1,041 (@ 17,452 hours)	995
	CADM	1,562	1,601	1,601
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	5.15	5.83 (@ 17,452 hours)	5.64
	CADM	-	-	-
10	Emond	20.0	21.0 (@ 17,452 hours)	20.3
	CADM	-	-	-
100	Emond	60.0	61.5 (@ 17,452 hours)	60.1
	CADM	-	-	-

E.3.1.19. *Kuchiiwa et al. (2002)*

Type:	Mouse	**Dose:**	4.9 and 490 ng/kg-week (equivalent to 0.7 and 70 ng/kg-day)
Strain:	ddy	**Route:**	Gavage
Body weight:	25 g	**Regime:**	Once a week for 8 weeks
Sex:	Female	**Simulation time:**	1,344 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.7	Emond	0.257	1.01 (@ 1,176 hours)	0.323
	CADM	-	-	-
70	Emond	9.12	77.7 (@ 1,176 hours)	8.10
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.7	Emond	33.7	68.0 (@ 1,182 hours)	44.7
	CADM	28.4	51.1	41.7
70	Emond	4,033	6,796 (@ 1,185 hours)	3,769
	CADM	5,306	8,597	3,914
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.7	Emond	88.3	138 (@ 1,236 hours)	131
	CADM	92.1	144	125

70	Emond	3,199	4,252 (@ 1,207 hours)	3,633
	CADM	2,072	2,848	1,739
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.7	Emond	9.32	15.3 (@ 1,182 hours)	13.3
	CADM	12.3	19.5	16.9
70	Emond	533	818 (@ 1,182 hours)	544
	CADM	499	749	748
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.7	Emond	0.877	1.67 (@ 1,181 hours)	1.11
	CADM	-	-	-
70	Emond	22.8	48.9 (@ 2 hours)	22.1
	CADM	-	-	-

E.3.1.20. *Latchoumycandane and Mathur (2002)*

Type:	Rat	**Dose:**	0, 1, 10, and 100 ng/kg-day
Strain:	Wistar	**Route:**	Oral gavage
Body weight:	BW = 200 g (45 days old)	**Regime:**	1 per day for 45 days
Sex:	Male	**Simulation time:**	1,080 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	0.785	1.37 (@ 1,056 hours)	1.18
	CADM	-	-	-
10	Emond	4.65	8.18 (@ 1,056 hours)	6.18
	CADM	-	-	-
100	Emond	27.3	53.9 (@ 1,056 hours)	33.8
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	78.5	138 (@ 1,060 hours)	133
	CADM	142	217	182
10	Emond	902	1,423 (@ 1,060 hours)	1,358
	CADM	1,952	2,550	1,980
100	Emond	9,579	14,015 (@ 1,061 hours)	13,306
	CADM	20,541	25,915	20,018

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	69.8	113 (@ 1,072 hours)	113
	CADM	179	220	198
10	Emond	416	608 (@ 1,065 hours)	604
	CADM	861	1,009	821
100	Emond	2,448	3,425 (@ 1,062 hours)	3,380
	CADM	6,581	7,866	6,035
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	9.56	15.9 (@ 1,060 hours)	15.6
	CADM	16.4	22.2	19.7
10	Emond	76.7	117 (@ 1,060 hours)	113
	CADM	124	157	125.2
100	Emond	646	933 (@ 1,060 hours)	891
	CADM	1,147	1,439	1,114
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	2.64	4.12 (@ 1,060 hours)	3.96
	CADM	-	-	-
10	Emond	13.7	18.8 (@ 1,060 hours)	18.1
	CADM	-	-	-
100	Emond	48.6	59.0 (@ 1,060 hours)	57.5
	CADM	-	-	-

E.3.1.21. *Li et al. (1997)*

Type:	Rats	**Dose:**	0, 3, 10, 30, 100, 300, 1,000, 3,000, 10,000, and 30,000 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Gastric intubation
Body weight:	BW = 56.5 g (22 days old, 55 to 58 g)	**Regime:**	One dose for one day
Sex:	Female	**Simulation time:**	24 hours

The CADM model was not run because the dosing duration is lower than the resolution of the model (1 week)

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
3	Emond	0.266	0.470 (@ 1 hour)	0.180
	CADM	-	-	-

10	Emond	0.799	1.57 (@ 1 hour)	0.535
	CADM	-	-	-
30	Emond	2.10	4.68 (@ 1 hour)	1.37
	CADM	-	-	-
100	Emond	5.87	15.6 (@ 1 hour)	3.68
	CADM	-	-	-
300	Emond	15.0	46.8 (@ 0 hours)	8.83
	CADM	-	-	-
1,000	Emond	43.3	156 (@ 0 hours)	23.4
	CADM	-	-	-
3,000	Emond	120	469 (@ 0 hours)	59.9
	CADM	-	-	-
10,000	Emond	386	1,570 (@ 0 hours)	182
	CADM	-	-	-
30,000	Emond	1,172	4,762 (@ 0 hours)	535
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
3	Emond	14.7	18.6 (@ 4 hours)	11.9
	CADM	-	-	-
10	Emond	55.0	65.2 (@ 5 hours)	47.6
	CADM	-	-	-
30	Emond	185	210 (@ 6 hours)	170
	CADM	-	-	-
100	Emond	690	768 (@ 7 hours)	666
	CADM	-	-	-
300	Emond	2,248	2,473 (@ 8 hours)	2,240
	CADM	-	-	-
1,000	Emond	7,938	8,671 (@ 9 hours)	8,094
	CADM	-	-	-
3,000	Emond	24,474	26,639 (@ 9 hours)	25,267
	CADM	-	-	-
10,000	Emond	82,349	89,464 (@ 9 hours)	85,597
	CADM	-	-	-
30,000	Emond	245,610	265,670 (@ 10 hours)	255,390
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
3	Emond	8.75	12.7 (@ 24 hours)	12.7
	CADM	-	-	-
10	Emond	26.6	38.0 (@ 24 hours)	38.0
	CADM	-	-	-
30	Emond	70.8	98.9 (@ 24 hours)	98.9
	CADM	-	-	-
100	Emond	202	273 (@ 24 hours)	273
	CADM	-	-	-
300	Emond	530	689 (@ 24 hours)	689
	CADM	-	-	-

1,000	Emond	1,573	1,958 (@ 24 hours)	1,958
	CADM	-	-	-
3,000	Emond	4,433	5,358 (@ 24 hours)	5,358
	CADM	-	-	-
10,000	Emond	14,428	17,119 (@ 24 hours)	17,119
	CADM	-	-	-
30,000	Emond	44,361	51,948 (@ 22 hours)	51,898
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
3	Emond	1.60	1.70 (@ 8 hours)	1.68
	CADM	-	-	-
10	Emond	5.33	5.66 (@ 8 hours)	5.56
	CADM	-	-	-
30	Emond	15.9	16.9 (@ 8 hours)	16.5
	CADM	-	-	-
100	Emond	52.8	56.2 (@ 7 hours)	54.5
	CADM	-	-	-
300	Emond	158	169 (@ 7 hours)	163
	CADM	-	-	-
1,000	Emond	525	561 (@ 7 hours)	539
	CADM	-	-	-
3,000	Emond	1,574	1,684 (@ 7 hours)	1,611
	CADM	-	-	-
10,000	Emond	5,240	5,610 (@ 7 hours)	5,360
	CADM	-	-	-
30,000	Emond	15,758	16,815 (@ 7 hours)	16,041
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
3	Emond	0.89	1.37 (@ 3 hours)	0.64
	CADM	-	-	-
10	Emond	2.58	4.10 (@ 2 hours)	1.88
	CADM	-	-	-
30	Emond	6.37	10.5 (@ 2 hours)	4.71
	CADM	-	-	-
100	Emond	15.54	25.9 (@ 2 hours)	11.77
	CADM	-	-	-
300	Emond	31.25	50.1 (@ 1 hour)	24.57
	CADM	-	-	-
1,000	Emond	56.75	79.8 (@ 1 hour)	47.62
	CADM	-	-	-
3,000	Emond	81.28	98.4 (@ 1 hour)	73.32
	CADM	-	-	-
10,000	Emond	99.77	108 (@ 1 hour)	95.68
	CADM	-	-	-
30,000	Emond	107.69	111 (@ 1 hour)	106.24
	CADM	-	-	-

E.3.1.22. *Murray et al. (1979) Adult Portion*

Type:	Rat	**Dose:**	1, 10, and 100 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Dietary exposure
Body weight:	BW = 4.5 g	**Regime:**	Once per day for 120 days
Sex:	Female	**Simulation time:**	2,880 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	1.12	1.51 (@ 2,856 hours)	1.42
	CADM	-	-	-
10	Emond	5.88	7.59 (@ 2,856 hours)	6.75
	CADM	-	-	-
100	Emond	32.7	44.3 (@ 2,856 hours)	36.0
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	128	180 (@ 2,859 hours)	173
	CADM	232	312	312
10	Emond	1,273	1,618 (@ 2,860 hours)	1,540
	CADM	2,613	3,179	3,179
100	Emond	12,601	15,281 (@ 2,860 hours)	14,460
	CADM	26,609	31,868	31,868
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	106	139 (@ 2,865 hours)	138
	CADM	209	243	236
10	Emond	556	665 (@ 2,864 hours)	657
	CADM	975	1,103	1,053
100	Emond	3,095	3,604 (@ 2,862 hours)	3,534
	CADM	7,742	8,790	8,427
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	14.8	20.0 (@ 2,860 hours)	19.6
	CADM	22.5	28.3	28.3
10	Emond	105	130 (@ 2,860 hours)	126
	CADM	159	189	189
100	Emond	837	1,003 (@ 2,860 hours)	957
	CADM	1,468	1,738	1,738

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	3.77	4.95 (@ 2,859 hours)	4.77
	CADM	-	-	-
10	Emond	17.1	20.3 (@ 2,859 hours)	19.5
	CADM	-	-	-
100	Emond	55.3	60.9 (@ 2,860 hours)	59.4
	CADM	-	-	-

E.3.1.23. *NTP (1982) Female Rats, Chronic*

Type:	Rat	**Dose:**	10, 50, and 500 ng/kg-week, 2 doses/week
Strain:	Osborne-Mendel	**Route:**	Oral exposure
Body weight	BW = 250 g (6 weeks old)	**Regime:**	2 doses/week
Sex:	Female	**Simulation time**	17,472 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	1.96	3.11 (@ 17,220 hours)	1.94
	CADM	-	-	-
7.1	Emond	5.69	11.0 (@ 17,388 hours)	5.40
	CADM	-	-	-
71	Emond	29.8	82.2 (@ 17,388 hours)	26.9
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	265	308 (@ 17,226 hours)	265
	CADM	424	477	477
7.1	Emond	1,175	1,338 (@ 17,394 hours)	1,117
	CADM	2,150	2,391	2,391
71	Emond	10,734	12,182 (@ 17,395 hours)	9,882
	CADM	21,596	23,920	23,920
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	186	200 (@ 17,328 hours)	193
	CADM	241	280	220

7.1	Emond	541	569 (@ 17,409 hours)	544
	CADM	673	787	610
71	Emond	2,826	2,973 (@ 17,404 hours)	2,769
	CADM	4,934	5,748	4,483
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	27.9	31.1 (@ 17,225 hours)	
	CADM	33.9	35.0	35.0
7.1	Emond	99.4	110 (@ 17,393 hours)	96.7
	CADM	126.4	129.8	129.8
71	Emond	729	814 (@ 17,393 hours)	683
	CADM	1,121	1,149	1,149
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	6.37	7.26 (@ 17,224 hours)	6.38
	CADM	-	-	-
7.1	Emond	16.6	18.5 (@ 17,392 hours)	16.1
	CADM	-	-	-
71	Emond	52.7	56.4 (@ 17,393 hours)	50.9
	CADM	-	-	-

E.3.1.24. *NTP (1982) Male Rats, Chronic*

Type:	Rat	**Dose:**	10, 50, and 500 ng/kg-week, 2 doses/week
Strain:	Osborne-Mendel	**Route:**	Oral exposure
Body weight	BW = 350 g (6 weeks old)	**Regime:**	2 doses/week
Sex:	Male	**Simulation time**	17,472 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	1.96	3.18 (@ 17,388 hours)	1.93
	CADM	-	-	-
7.1	Emond	5.70	11.4 (@ 17,388 hours)	5.39
	CADM	-	-	-
71	Emond	29.9	87.0 (@ 17,388 hours)	26.9
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	265	306 (@ 17,394 hours)	263
	CADM	424	477	477
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
7.1	Emond	1,174	1,334 (@ 17,394 hours)	1,114
	CADM	2,150	2,391	2,391
71	Emond	10,736	12,170 (@ 17,395 hours)	9,881
	CADM	21,596	23,920	23,920
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	186	199 (@ 17,412 hours)	193
	CADM	241	280	220
7.1	Emond	541	569 (@ 17,409 hours)	544
	CADM	673	787	610
71	Emond	2,836	2,983 (@ 17,404 hours)	2,784
	CADM	4,934	5,748	4,483
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	27.8	30.9 (@ 17,393 hours)	28.2
	CADM	33.9	35.0	35.0
7.1	Emond	99.5	110 (@ 17,393 hours)	96.6
	CADM	126.4	129.8	129.8
71	Emond	730	816 (@ 17,393 hours)	684
	CADM	1,121	1,149	1,149
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	6.36	7.22 (@ 17,392 hours)	6.35
	CADM	-	-	-
7.1	Emond	16.6	18.4 (@ 17,392 hours)	16.0
	CADM	-	-	-
71	Emond	52.7	56.3 (@ 17,393 hours)	50.9
	CADM	-	-	-

E.3.1.25. *NTP (1982) Female Mice, Chronic*

Type:	Mice	**Dose:**	40, 200, and 2,000 ng/kg-week, 2 doses/week
Strain:	$B6C3F_1$	**Route:**	Oral exposure
Body weight	BW = 23 g (6 weeks old)	**Regime:**	2 doses/week
Sex:	Female	**Simulation time**	17,472 hours

The CADM model was not run because the study duration is longer than the allowed model duration.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
5.7	Emond	1.95	4.86 (@ 16,800 hours)	1.82
	CADM	-	-	-
28.6	Emond	5.84	19.8 (@ 17,388 hours)	5.17
	CADM	-	-	-
286	Emond	32.1	171 (@ 16,884 hours)	26.0
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
5.7	Emond	490	582 (@ 16,807 hours)	463
	CADM	-	-	-
28.6	Emond	2,236	2,629 (@ 17,395 hours)	2,025
	CADM	-	-	-
286	Emond	20,841	24,353 (@ 17,396 hours)	18,182
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
5.7	Emond	737	785 (@ 17,408 hours)	757
	CADM	-	-	-
28.6	Emond	2,213	2,337 (@ 17,404 hours)	2,216
	CADM	-	-	-
286	Emond	12,138	12,861 (@ 17,400 hours)	11,775
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
5.7	Emond	91.9	103 (@ 17,393 hours)	91.2
	CADM	-	-	-
28.6	Emond	329	370 (@ 17,393 hours)	313
	CADM	-	-	-

286	Emond	2,400	2,740 (@ 17,393 hours)	2,176
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
5.7	Emond	6.18	7.29 (@ 16,805 hours)	5.93
	CADM	-	-	-
28.6	Emond	16.3	18.9 (@ 17,393 hours)	15.3
	CADM	-	-	-
286	Emond	52.3	67.8 (@ 2 hours)	49.3
	CADM	-	-	-

E.3.1.26. *NTP (1982) Male Mice, Chronic*

Type:	Mice	**Dose:**	10, 50, and 500 ng/kg-week, 2 doses during the week
Strain:	$B6C3F_1$	**Route:**	Oral exposure
Body weight	BW = 25 g (6 weeks old)	**Regime:**	2 doses/week
Sex:	Male	**Simulation time**	17,472 hours (104 week of exposure)

The CADM model was not run because the study duration is longer than the allowed model duration.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	0.767	1.53 (@ 17,304 hours)	0.749
	CADM	-	-	-
7.1	Emond	2.27	5.99 (@ 17,052 hours)	2.11
	CADM	-	-	-
71	Emond	11.2	46.7 (@ 17,388 hours)	9.59
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	138	165 (@ 17,310 hours)	136
	CADM	-	-	-
7.1	Emond	606	722 (@ 17,059 hours)	571
	CADM	-	-	-
71	Emond	5,409	6,328 (@ 17,395 hours)	4,805
	CADM	-	-	-

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	290	314 (@ 17,411 hours)	306
	CADM	-	-	-
7.1	Emond	860	918 (@ 17,155 hours)	883
	CADM	-	-	-
71	Emond	4,257	4,490 (@ 17,402 hours)	4,204
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	32.3	36.2 (@ 17,309 hours)	33.3
	CADM	-	-	-
7.1	Emond	110	123 (@ 17,057 hours)	108
	CADM	-	-	-
71	Emond	710	802 (@ 17,393 hours)	660
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	2.56	3.03 (@ 17,309 hours)	2.53
	CADM	-	-	-
7.1	Emond	7.12	8.40 (@ 17,057 hours)	6.82
	CADM	-	-	-
71	Emond	27.1	32.4 (@ 2 hours)	25.3
	CADM	-	-	-

E.3.1.27. *NTP (2006) 14 Weeks*

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, and 100 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	BW = 215 g (8 weeks old)	**Regime:**	5 days/week for 14 weeks
Sex:	Female and male	**Simulation time:**	2,352 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	1.98	3.15 (@ 2,280 hours)	2.39
	CADM	-	-	-
7.14	Emond	4.69	7.75 (@ 2,280 hours)	5.30
	CADM	-	-	-

15.7	Emond	8.27	14.3 (@ 2,280 hours)	9.02
	CADM	-	-	-
32.9	Emond	14.2	25.9 (@ 2,280 hours)	15.1
	CADM	-	-	-
71.4	Emond	25.7	49.8 (@ 2,280 hours)	26.6
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	275	404 (@ 2,284 hours)	354
	CADM	479	599	599
7.14	Emond	909	1,270 (@ 2,285 hours)	1,089
	CADM	1,702	2,017	2,017
15.7	Emond	1,988	2,703 (@ 2,285 hours)	2,291
	CADM	3,817	4,449	4,449
32.9	Emond	4,129	5,508 (@ 2,285 hours)	4,628
	CADM	8,054	9,314	9,314
71.4	Emond	8,921	11,734 (@ 2,285 hours)	9,792
	CADM	17,592	20,262	20,262
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	184	246 (@ 2,294 hours)	237
	CADM	326	355	347
7.14	Emond	436	557 (@ 2,292 hours)	532
	CADM	733	787	765
15.7	Emond	768	962 (@ 2,291 hours)	912
	CADM	1,361	1,463	1,422
32.9	Emond	1,319	1,633 (@ 2,289 hours)	1,535
	CADM	2,587	2,787	2,712
71.4	Emond	2,385	2,938 (@ 2,289 hours)	2,736
	CADM	5,326	5,748	5,599
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	28.2	39.4 (@ 2,284 hours)	36.1
	CADM	38.8	46.1	46.1
7.14	Emond	78.5	106 (@ 2,284 hours)	94.4
	CADM	109	126	126
15.7	Emond	156	206 (@ 2,284 hours)	181
	CADM	226	259	259
32.9	Emond	300	391 (@ 2,284 hours)	340
	CADM	459	523	523
71.4	Emond	610	788 (@ 2,284 hours)	676
	CADM	980	1,117	1,117

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	6.41	8.55 (@ 2,284 hours)	7.74
	CADM	-	-	-
7.14	Emond	13.9	17.6 (@ 2,284 hours)	15.8
	CADM	-	-	-
15.7	Emond	22.2	27.2 (@ 2,284 hours)	24.5
	CADM	-	-	-
32.9	Emond	33.2	39.3 (@ 2,284 hours)	35.7
	CADM	-	-	-
71.4	Emond	47.9	55.1 (@ 2,284 hours)	50.7
	CADM	-	-	-

E.3.1.28. *NTP (2006) 31 Weeks*

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	BW = 215 g (8 weeks old)	**Regime:**	5 days/week for 31 weeks
Sex:	Female and male	**Simulation time:**	5,208 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	2.33	3.25 (@ 3,960 hours)	2.48
	CADM	-	-	-
7.14	Emond	5.32	7.89 (@ 3,960 hours)	5.40
	CADM	-	-	-
15.7	Emond	9.21	14.5 (@ 3,960 hours)	9.15
	CADM	-	-	-
32.9	Emond	15.7	26.2 (@ 5,136 hours)	15.3
	CADM	-	-	-
71.4	Emond	28.1	50.4 (@ 5,136 hours)	27.0
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	341	425 (@ 5,140 hours)	373
	CADM	555	631	631
7.14	Emond	1,075	1,308 (@ 3,965 hours)	1,117
	CADM	1,906	2,112	2,112
15.7	Emond	2,296	2,756 (@ 3,965 hours)	2,336
	CADM	4,229	4,652	4,652
32.9	Emond	4,696	5,597 (@ 5,141 hours)	4,712
	CADM	8,880	9,732	9,732

71.4	Emond	10,033	11,905 (@ 5,141 hours)	9,953
	CADM	19,347	21,163	21,163
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	220	256 (@ 5,149 hours)	246
	CADM	329	355	320
7.14	Emond	501	570 (@ 4,139 hours)	542
	CADM	732	787	706
15.7	Emond	868	978 (@ 4,138 hours)	926
	CADM	1,361	1,463	1,315
32.9	Emond	1,476	1,657 (@ 5,145 hours)	1,558
	CADM	2,591	2,787	2,509
71.4	Emond	2,652	2,978 (@ 5,144 hours)	2,775
	CADM	5,344	5,748	5,183
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	34.2	41.2 (@ 5,140 hours)	37.8
	CADM	43.2	47.1	47.1
7.14	Emond	91.6	108 (@ 3,964 hours)	96.6
	CADM	119	129	129
15.7	Emond	178	209 (@ 3,964 hours)	184
	CADM	246	264	264
32.9	Emond	339	398 (@ 5,140 hours)	346
	CADM	498	533	533
71.4	Emond	682	799 (@ 5,140 hours)	687
	CADM	1,063	1,138	1,138
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	7.48	8.83 (@ 5,140 hours)	8.01
	CADM	-	-	-
7.14	Emond	15.6	17.9 (@ 3,964 hours)	16.1
	CADM	-	-	-
15.7	Emond	24.3	27.4 (@ 3,964 hours)	24.8
	CADM	-	-	-
32.9	Emond	35.7	39.6 (@ 5,140 hours)	36.0
	CADM	-	-	-
71.4	Emond	50.9	55.4 (@ 5,140 hours)	51.1
	CADM	-	-	-

E.3.1.29. *NTP (2006) 53 Weeks*

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	BW = 215 g (8 weeks old)	**Regime:**	5 days/week for 53 weeks
Sex:	Female and male	**Simulation time:**	8,904 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	2.46	3.25 (@ 6,312 hours)	2.48
	CADM	-	-	-
7.14	Emond	5.53	7.89 (@ 3,960 hours)	5.41
	CADM	-	-	-
15.7	Emond	9.54	14.5 (@ 8,832 hours)	9.17
	CADM	-	-	-
32.9	Emond	16.2	26.3 (@ 8,832 hours)	15.3
	CADM	-	-	-
71.4	Emond	29.0	50.6 (@ 8,832 hours)	27.1
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	366	426 (@ 6,316 hours)	373
	CADM	593	656	656
7.14	Emond	1,134	1,308 (@ 3,965 hours)	1,121
	CADM	2,010	2,197	2,197
15.7	Emond	2,406	2,759 (@ 8,837 hours)	2,345
	CADM	4,446	4,836	4,836
32.9	Emond	4,902	5,612 (@ 8,837 hours)	4,727
	CADM	9,318	10,115	10,115
71.4	Emond	10,439	11,938 (@ 8,837 hours)	9,985
	CADM	20,284	21,993	21,993
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	233	256 (@ 6,325 hours)	247
	CADM	321	355	301
7.14	Emond	524	570 (@ 4,139 hours)	544
	CADM	711	787	663
15.7	Emond	904	980 (@ 8,842 hours)	929
	CADM	1,323	1,463	1,236
32.9	Emond	1,533	1,661 (@ 8,841 hours)	1,562
	CADM	2,522	2,787	2,359
71.4	Emond	2,749	2,986 (@ 8,840 hours)	2,784
	CADM	5,205	5,748	4,873

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	36.4	41.2 (@ 6,316 hours)	37.8
	CADM	44.9	47.4	47.4
7.14	Emond	96.1	108 (@ 3,964 hours)	96.9
	CADM	123	129	129
15.7	Emond	186	210 (@ 8,836 hours)	185
	CADM	254	266	266
32.9	Emond	353	399 (@ 8,836 hours)	347
	CADM	513	536	536
71.4	Emond	709	801 (@ 8,836 hours)	689
	CADM	1,096	1,144	1,144
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	7.87	8.84 (@ 6,316 hours)	8.01
	CADM	-	-	-
7.14	Emond	16.2	17.9 (@ 3,964 hours)	16.1
	CADM	-	-	-
15.7	Emond	25.1	27.5 (@ 8,836 hours)	24.8
	CADM	-	-	-
32.9	Emond	36.6	39.7 (@ 8,836 hours)	36.1
	CADM	-	-	-
71.4	Emond	51.9	55.4 (@ 8,836 hours)	51.1
	CADM	-	-	-

E.3.1.30. *NTP (2006) 2 Years*

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	BW = 215 g (8 weeks old)	**Regime:**	5 days/week for 105 weeks
Sex:	Female and male	**Simulation time:**	17,640 hours

The CADM model simulates for 104 weeks only (17,472 hours). As a result, the terminal values from the CADM model may be underestimated compared to the Emond model, which considers the full 105 weeks of exposure.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	2.56	3.47 (@ 17,568 hours)	2.62
	CADM	-	-	-
7.14	Emond	5.69	7.97 (@ 17,568 hours)	5.46
	CADM	-	-	-

15.7	Emond	9.79	14.6 (@ 17,568 hours)	9.22
	CADM	-	-	-
32.9	Emond	16.6	26.4 (@ 17,568 hours)	15.4
	CADM	-	-	-
71.4	Emond	29.7	50.8 (@ 17,568 hours)	27.1
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	385	460 (@ 17,572 hours)	403
	CADM	639	717	717
7.14	Emond	1,177	1,320 (@ 17,573 hours)	1,135
	CADM	2,150	2,391	2,391
15.7	Emond	2,487	2,779 (@ 17,573 hours)	2,361
	CADM	4,742	5,261	5,261
32.9	Emond	5,051	5,637 (@ 17,573 hours)	4,749
	CADM	9,927	11,002	11,002
71.4	Emond	10,734	11,976 (@ 17,573hr)	10,018
	CADM	21,596	23,920	23,920
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	243	271 (@ 17,581 hours)	261
	CADM	304	355	277
7.14	Emond	541	575 (@ 17,579 hours)	549
	CADM	673	787	610
15.7	Emond	930	985 (@ 17,578 hours)	934
	CADM	1,253	1,463	1,137
32.9	Emond	1,574	1,667 (@ 17,577 hours)	1,568
	CADM	2,390	2,787	2,170
71.4	Emond	2,821	2,995 (@ 17,576 hours)	2,792
	CADM	4,934	5,748	4,934
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	38.1	44.0 (@ 17,572 hours)	40.4
	CADM	46.2	47.6	47.6
7.14	Emond	99.5	109 (@ 17,572 hours)	97.9
	CADM	126	130	130
15.7	Emond	192	211 (@ 17,572 hours)	186
	CADM	260	267	267
32.9	Emond	364	400 (@ 17,572 hours)	348
	CADM	525	538	538
71.4	Emond	729	804 (@ 17,572 hours)	691
	CADM	1,121	1,149	1,149

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
2.14	Emond	8.17	9.30 (@ 17,572 hours)	8.43
	CADM	-	-	-
7.14	Emond	16.6	18.0 (@ 17,572 hours)	16.2
	CADM	-	-	-
15.7	Emond	25.6	27.6 (@ 17,572 hours)	24.9
	CADM	-	-	-
32.9	Emond	37.3	39.7 (@ 17,572 hours)	36.2
	CADM	-	-	-
71.4	Emond	52.7	55.5 (@ 17,572 hours)	51.2
	CADM	-	-	-

E.3.1.31. *Nohara et al. (2002)*

Type:	Mice	**Dose:**	5, 20, 100, and 500 ng/kg
Strain:	Four strains	**Route:**	Gavage
Body weight:	BW = 23 g (8 weeks old)	**Regime:**	Single dose
Sex:	Female	**Simulation time:**	24 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
5	Emond	0.229	0.686 (@ 0 hours)	0.135
	CADM	-	-	-
20	Emond	0.817	2.74 (@ 0 hours)	0.448
	CADM	-	-	-
100	Emond	3.41	13.7 (@ 0 hours)	1.65
	CADM	-	-	-
500	Emond	14.2	68.6 (@ 0 hours)	5.70
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
5	Emond	19.8	23.6 (@ 5 hours)	16.8
	CADM	6.80	6.80	6.80
20	Emond	85.7	96.3 (@ 6 hours)	77.8
	CADM	38.7	38.7	38.7
100	Emond	472	517 (@ 10 hours)	458
	CADM	416	416	416
500	Emond	2,541	2,785 (@ 11 hours)	2,578
	CADM	3,998	3,998	3,998

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
5	Emond	13.5	20.4 (@ 24 hours)	20.4
	CADM	31.1	31.1	31.1
20	Emond	49.6	72.3 (@ 24 hours)	72.3
	CADM	119	119	119
100	Emond	217	299 (@ 24 hours)	299
	CADM	506	506	506
500	Emond	952	1,231 (@ 24 hours)	1,231
	CADM	1,761	1,761	1,761
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
5	Emond	2.84	3.03 (@ 8 hours)	2.96
	CADM	4.00	4.00	4.00
20	Emond	11.3	12.1 (@ 8 hours)	11.7
	CADM	16.0	16.0	16.0
100	Emond	55.9	60.0 (@ 7 hours)	57.4
	CADM	80.0	80.0	80.0
500	Emond	276	298 (@ 7 hours)	282
	CADM	400	400	400
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
5	Emond	0.715	1.07 (@ 3 hours)	0.507
	CADM	-	-	-
20	Emond	2.40	3.99 (@ 3 hours)	1.67
	CADM	-	-	-
100	Emond	8.61	16.4 (@ 2 hours)	5.88
	CADM	-	-	-
500	Emond	25.5	49.4 (@ 2 hours)	17.8
	CADM	-	-	-

E.3.1.32. *Sewall et al. (1995) and Maronpot et al. (1993)*

Type:	Rat	**Dose:**	49, 149.8, 490, and 1,750 ng/kg every 2 weeks (equivalent to 3.5, 10.7, 35, and 125 ng/kg-day)
Strain:	Sprauge-Dawley	**Route:**	Oral gavage
Body weight:	BW = 250 g (12 weeks old)	**Regime:**	Once every 2 weeks for 30 weeks
Sex:	Female	**Simulation time:**	5,040 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
3.5	Emond	3.29	13.7 (@ 4,704 hours)	2.88
	CADM	-	-	-
10.7	Emond	7.11	38.7 (@ 4,704 hours)	5.79
	CADM	-	-	-
35	Emond	16.6	120 (@ 4,704 hours)	12.6
	CADM	-	-	-
125	Emond	44.7	414 (@ 4,704 hours)	31.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
3.5	Emond	550	901 (@ 4,711 hours)	459
	CADM	928	1,273	786
10.7	Emond	1,605	2,632 (@ 4,712 hours)	1,229
	CADM	2,891	3,940	2,373
35	Emond	5,072	8,350 (@ 4,712 hours)	3,618
	CADM	9,534	12,926	7,744
125	Emond	17,683	29,256 (@ 4,713 hours)	12,011
	CADM	34,145	46,190	27,659
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
3.5	Emond	310	383 (@ 4,765 hours)	290
	CADM	451	560	367
10.7	Emond	670	827 (@ 4,763 hours)	590
	CADM	1,008	1,300	774
35	Emond	1,569	1,957 (@ 4,760 hours)	1,304
	CADM	2,786	3,693	2,054
125	Emond	4,217	5,376 (@ 4,757 hours)	3,303
	CADM	9,308	12,496	6,738
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
3.5	Emond	51.4	72.5 (@ 4,710 hours)	45.3
	CADM	64.8	83.25	56.0
10.7	Emond	130	189 (@ 4,710 hours)	106
	CADM	173	227	143
35	Emond	364	546 (@ 4,710 hours)	274
	CADM	534	704	429
125	Emond	1,164	1,793 (@ 4,710 hours)	824
	CADM	1,863	2,468	−1,483

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
3.5	Emond	10.2	15.8 (@ 2 hours)	9.18
	CADM	-	-	-
10.7	Emond	19.8	34.4 (@ 1 hours)	17.0
	CADM	-	-	-
35	Emond	37.0	63.2 (@ 1 hours)	31.4
	CADM	-	-	-
125	Emond	63.1	90.9 (@ 1 hours)	55.2
	CADM	-	-	-

E.3.1.33. *Shi et al. (2007) Adult Portion*

Type:	Rat	**Dose:**	1, 5, 50, and 200 ng/kg-week (equivalent to 0.143, 0.714, 7.14, and 28.6 ng/kg-day)
Strain:	Sprague-Dawley	**Route:**	Oral exposure
Body weight:	BW = 4.5 g	**Regime:**	Weekly doses for 11 months
Sex:	Female	**Simulation time:**	8,040 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.143	Emond	0.342	0.475 (@ 7,561 hours)	0.380
	CADM	-	-	-
0.714	Emond	1.07	1.53 (@ 7,560 hours)	1.09
	CADM	-	-	-
7.14	Emond	5.23	9.12 (@ 7,560 hours)	4.86
	CADM	-	-	-
28.6	Emond	13.9	29.2 (@ 7,560 hours)	12.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.143	Emond	26.1	36.5 (@ 7,564 hours)	29.6
	CADM	33.6	42.6	42.6
0.714	Emond	118	159 (@ 7,564 hours)	120
	CADM	189	216	216
7.14	Emond	1,068	1,415 (@ 7,565 hours)	970
	CADM	1,992	2,178	2,178
28.6	Emond	4,119	5,450 (@ 7,565 hours)	3,574
	CADM	8,031	8,722	8,722

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.143	Emond	32.5	40.0 (@ 7,583 hours)	36.7
	CADM	71.0	78.6	73.8
0.714	Emond	102	120 (@ 7,584 hours)	106
	CADM	173	190	167
7.14	Emond	497	571 (@ 7,584 hours)	475
	CADM	716	787	671
28.6	Emond	1,322	1,527 (@ 7,584 hours)	1,217
	CADM	2,237	2,457	2,104
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.143	Emond	3.94	4.99 (@ 7,566 hours)	4.45
	CADM	6.6	7.6	7.6
0.714	Emond	14.0	17.2 (@ 7,566 hours)	14.5
	CADM	19.6	21.2	21.2
7.14	Emond	90.8	112 (@ 7,566 hours)	84.4
	CADM	123	129	129
28.6	Emond	300	374 (@ 7,566 hours)	266
	CADM	446	468	468
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.143	Emond	1.18	1.60 (@ 7,563 hours)	1.31
	CADM	-	-	-
0.714	Emond	3.62	4.75 (@ 7,563 hours)	3.70
	CADM	-	-	-
7.14	Emond	15.6	19.7 (@ 7,564 hours)	14.7
	CADM	-	-	-
28.6	Emond	33.5	40.7 (@ 7,564 hours)	31.2
	CADM	-	-	-

E.3.1.34. *Simanainen et al. (2002) and Simanainen et al. (2003)*

Type:	Rats	**Dose:**	100 and 300 ng/kg
Strain:	Hans/Wistar and Long-Evans	**Route:**	Oral gavage
Body weight:	BW = 200 g	**Regime:**	Single dose
Sex:	Female	**Simulation time:**	24 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
100	Emond	6.36	20.5 (@ 0 hours)	3.82
	CADM	-	-	-
300	Emond	16.3	61.5 (@ 0 hours)	9.07
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
100	Emond	725	796 (@ 8 hours)	711
	CADM	-	-	-
300	Emond	2,331	2,547 (@ 9 hours)	2,352
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
100	Emond	174	241 (@ 24 hours)	241
	CADM	-	-	-
300	Emond	461	611 (@ 24 hours)	611
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
100	Emond	52.8	56.3 (@ 7 hours)	54.5
	CADM	-	-	-
300	Emond	158	169 (@ 7 hours)	162
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
100	Emond	16.0	26.4 (@ 2 hours)	12.3
	CADM	-	-	-
300	Emond	31.8	50.6 (@ 1 hour)	25.3
	CADM	-	-	-

E.3.1.35. *Smialowicz et al. (2004)*

Type:	Mice	**Dose:**	30, 100, 300, 1,000, 3,000, and 10,000 ng/kg
Strain:	C57BL/6N	**Route:**	Oral gavage
Body weight:	BW = 25 g (Age not specified)	**Regime:**	Single dose
Sex:	Female	**Simulation time:**	24 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
30	Emond	1.19	4.19 (@ 0 hours)	0.632
	CADM	-	-	-
100	Emond	3.44	14.0 (@ 0 hours)	1.65
	CADM	-	-	-
300	Emond	9.08	42.0 (@ 0 hours)	3.87
	CADM	-	-	-
1,000	Emond	26.9	140 (@ 0 hours)	9.76
	CADM	-	-	-
3,000	Emond	75.1	420 (@ 0 hours)	23.5
	CADM	-	-	-
10,000	Emond	242	1,403 (@ 0 hours)	66.7
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
30	Emond	132	147 (@ 7 hours)	123
	CADM	68.6	68.6	68.6
100	Emond	473	518 (@ 10 hours)	461
	CADM	416	416	416
300	Emond	1,498	1,641 (@ 11 hours)	1,506
	CADM	2,039	2,039	2,039
1,000	Emond	5,199	5,700 (@ 12 hours)	5,345
	CADM	9,294	9,294	9,294
3,000	Emond	15,934	17,473 (@ 12 hours)	16,586
	CADM	31,419	31,419	31,419
10,000	Emond	53,457	58,629 (@ 13 hours)	56,056
	CADM	109,703	109,703	109,703
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
30	Emond	71.4	103 (@ 24 hours)	103
	CADM	174	174	174
100	Emond	215	296 (@ 24 hours)	296
	CADM	506	506	506
300	Emond	588	776 (@ 24 hours)	776
	CADM	1,201	1,201	1,201
1,000	Emond	1,804	2,278 (@ 24 hours)	2,278
	CADM	3,002	3,002	3,002
3,000	Emond	5,165	6,333 (@ 24 hours)	6,333
	CADM	7,593	7,593	7,593
10,000	Emond	16,888	20,306 (@ 24 hours)	20,306
	CADM	23,319	23,319	23,319

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
30	Emond	16.9	18.1 (@ 7 hours)	17.5
	CADM	24.0	24.0	24.0
100	Emond	55.9	60.0 (@ 7 hours)	57.4
	CADM	80.0	80.0	80.0
300	Emond	166	179 (@ 7 hours)	170
	CADM	240	240	240
1,000	Emond	550	594 (@ 7 hours)	560
	CADM	800	800	800
3,000	Emond	1,646	1,778 (@ 7 hours)	1,668
	CADM	2,400	2,400	2,400
10,000	Emond	5,469	5,916 (@ 7 hours)	5,528
	CADM	8,000	8,000	8,000
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
30	Emond	3.37	5.79 (@ 3 hours)	2.34
	CADM	-	-	-
100	Emond	8.63	16.4 (@ 2 hours)	5.90
	CADM	-	-	-
300	Emond	18.6	36.6 (@ 2 hours)	12.8
	CADM	-	-	-
1,000	Emond	37.6	67.8 (@ 2 hours)	27.2
	CADM	-	-	-
3,000	Emond	61.3	91.8 (@ 2 hours)	48.3
	CADM	-	-	-
10,000	Emond	86.5	106 (@ 2 hours)	76.1
	CADM	-	-	-

E.3.1.36. *Smialowicz et al. (2008)*

Type:	Mice	**Dose:**	0, 1.5, 15, 150, and 450 ng/kg-day
Strain:	$B6C3F_1$	**Route:**	Oral gavage
Body weight:	BW = 28 g (13 weeks old)	**Regime:**	5 days/week for 13 weeks
Sex:	Female	**Simulation time:**	2,184 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.07	Emond	0.438	0.815 (@ 2,112 hours)	0.557
	CADM	-	-	-
10.7	Emond	2.46	5.12 (@ 2,112 hours)	2.65
	CADM	-	-	-

107	Emond	13.4	36.4 (@ 2,112 hours)	12.7
	CADM	-	-	-
321	Emond	31.6	98.6 (@ 2,112 hours)	28.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.07	Emond	67.1	107 (@ 2,116 hours)	91.5
	CADM	59.8	91.9	84.2
10.7	Emond	683	971 (@ 2,117 hours)	787
	CADM	776	1,000	825
107	Emond	6,784	9,010 (@ 2,117 hours)	7,043
	CADM	8,441	10,306	7,863
321	Emond	20,218	26,379 (@ 2,117 hours)	20,405
	CADM	25.626	31,006	23.460
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.07	Emond	156	229 (@ 2,130 hours)	225
	CADM	153	210	199
10.7	Emond	885	1,155 (@ 2,124 hours)	1,111
	CADM	697	815	735
107	Emond	4,831	5,979 (@ 2,120 hours)	5,591
	CADM	2,802	3,224	2,684
321	Emond	11,420	14,037 (@ 2,119 hours)	12,920
	CADM	6,408	7,509	5.972
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.07	Emond	17.0	25.5 (@ 2,116 hours)	23.9
	CADM	21.1	29.3	27.7
10.7	Emond	117	159 (@ 2,116 hours)	141
	CADM	120	145	127
107	Emond	852	1,103 (@ 2,116 hours)	923
	CADM	736	875	694
321	Emond	2,304	2,958 (@ 2,116 hours)	2,419
	CADM	1.983	2,370	1.828
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.07	Emond	1.48	2.17 (@ 2,116 hours)	1.90
	CADM	-	-	-
10.7	Emond	7.60	9.86 (@ 2,116 hours)	8.42
	CADM	-	-	-
107	Emond	30.3	36.0 (@ 2,117 hours)	31.1
	CADM	-	-	-
321	Emond	51.1	58.1 (@ 2,117 hours)	51.8
	CADM	-	-	-

E.3.1.37. *Toth et al. (1979) 1 Year*

Type:	Mice	**Dose:**	7, 700, and 7,000 ng/kg-week
Strain:	Swiss/H/Riop	**Route:**	Oral gavage In gastric tube
Body weight:	BW = 27 g (10 weeks old)	**Regime:**	Once per week for 1 year (365 days)
Sex:	Female and male	**Simulation time:**	8,760 hours

The CADM model was not run because the study duration is longer than the allowed model duration.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	0.573	1.61 (@ 8,736 hours)	0.682
	CADM	-	-	-
100	Emond	14.2	116 (@ 8,736 hours)	15.7
	CADM	-	-	-
1,000	Emond	91.2	1,108 (@ 8,736 hours)	99.3
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	94.2	131 (@ 8,743 hours)	123
	CADM	-	-	-
100	Emond	7,343	10,134 (@ 8,745 hours)	9,604
	CADM	-	-	-
1,000	Emond	70,243	97,658 (@ 8,745 hours)	92,506
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	215	247 (@ 8,613 hours)	245
	CADM	-	-	-
100	Emond	5,339	5,914 (@ 8,760 hours)	5,914
	CADM	-	-	-
1,000	Emond	34,249	38,828 (@ 8,756 hours)	38,807
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	23.4	28.4 (@ 8,742 hours)	27.9
	CADM	-	-	-
100	Emond	929	1,189 (@ 8,742 hours)	1,132
	CADM	-	-	-

1,000	Emond	7,569	10,045 (@ 8,742 hours)	9,471
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	1.93	2.65 (@ 8,741 hours)	2.35
	CADM	-	-	-
100	Emond	31.8	58.4 (@ 2 hours)	36.7
	CADM	-	-	-
1,000	Emond	78.6	103 (@ 2 hours)	84.8
	CADM	-	-	-

E.3.1.38. *Van Birgelen et al. (1995)*

Type:	Rat	**Dose:**	0, 13.5, 26.4, 46.9, 320, and 1,024 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	BW = 150 g	**Regime:**	Once per day for 13 weeks
Sex:	Female	**Simulation time:**	2,184 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
13.5	Emond	7.20	11.1 (@ 2,160 hours)	8.47
	CADM	-	-	-
26.4	Emond	11.8	18.6 (@ 2,160 hours)	13.5
	CADM	-	-	-
46.9	Emond	18.1	29.6 (@ 2,160 hours)	20.5
	CADM	-	-	-
320	Emond	86.4	156 (@ 2,160 hours)	95.4
	CADM	-	-	-
1,024	Emond	250	470 (@ 2,160 hours)	275
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
13.5	Emond	1,655	2,208 (@ 2,164 hours)	2,107
	CADM	3,228	3,802	3,802
26.4	Emond	3,228	4,216 (@ 2,164 hours)	4,017
	CADM	6,379	7,447	7,447
46.9	Emond	5,719	7,366 (@ 2,164 hours)	7,008
	CADM	11,390	13,240	13,240
320	Emond	38,484	47,999 (@ 2,164 hours)	45,537
	CADM	78,166	90,406	90,406

1,024	Emond	121,640	150,410 (@ 2,164 hours)	142,510
	CADM	250,307	289,326	289,326
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
13.5	Emond	669	843 (@ 2,167 hours)	835
	CADM	1,197	1,291	1,261
26.4	Emond	1,092	1,357 (@ 2,166 hours)	1,342
	CADM	2,119	2,290	2,240
46.9	Emond	1,680	2,071 (@ 2,166 hours)	2,045
	CADM	3,572	3,866	3,785
320	Emond	8,027	9,816 (@ 2,165 hours)	9,639
	CADM	22,844	24,800	24,308
1,024	Emond	23,234	28,519 (@ 2,165 hours)	27,954
	CADM	72,506	78,746	77,195
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
13.5	Emond	132	173 (@ 2,164 hours)	167
	CADM	194	224	224
26.4	Emond	240	308 (@ 2,164 hours)	296
	CADM	367	423	423
46.9	Emond	404	513 (@ 2,164 hours)	492
	CADM	641	737	737
320	Emond	2,437	3,031 (@ 2,164 hours)	2,887
	CADM	4,292	4,294	4,294
1,024	Emond	7,521	9,310 (@ 2,164 hours)	8,846
	CADM	13,702	15,714	15,714
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
13.5	Emond	19.9	24.2 (@ 2,164 hours)	23.4
	CADM	-	-	-
26.4	Emond	29.0	34.3 (@ 2,164 hours)	33.2
	CADM	-	-	-
46.9	Emond	38.8	45.0 (@ 2,164 hours)	43.7
	CADM	-	-	-
320	Emond	79.1	85.2 (@ 2,164 hours)	84.1
	CADM	-	-	-
1,024	Emond	97.5	101 (@ 2,164 hours)	101
	CADM	-	-	-

E.3.1.39. *Vanden Heuvel et al. (1994)*

Type:	Rat	**Dose:**	0.05, 0.1, 1, 10, 100, 1,000, 10,000 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	BW = 250 g (10 weeks old; BW 225 to 275 g)	**Regime:**	Single dose
Sex:	Female	**Simulation time:**	24 hours

The CADM model was not run because the study duration is longer than the allowed model duration.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.05	Emond	0.01	0.011 (@ 0 hours)	0.0039
	CADM	-	-	-
0.1	Emond	0.0113	0.022 (@ 0 hours)	0.008
	CADM	-	-	-
1	Emond	0.106	0.215 (@ 0 hours)	0.0723
	CADM	-	-	-
10	Emond	0.883	2.15 (@ 0 hours)	0.583
	CADM	-	-	-
100	Emond	6.45	21.5 (@ 0 hours)	3.85
	CADM	-	-	-
1,000	Emond	48.3	216 (@ 0 hours)	23.9
	CADM	-	-	-
10,000	Emond	435	2,166 (@ 0 hours)	186
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.05	Emond	0.232	0.315 (@ 3 hours)	0.173
	CADM	-	-	0.0140
0.1	Emond	0.469	0.631 (@ 3 hours)	0.353
	CADM	-	-	0.0320
1	Emond	5.08	6.42 (@ 4 hours)	4.08
	CADM	-	-	0.950
10	Emond	60.2	68.7 (@ 5 hours)	54.1
	CADM	-	-	52.7
100	Emond	730	800 (@ 9 hours)	719
	CADM	-	-	1,342
1,000	Emond	8,186	8,919 (@ 11 hours)	8,442
	CADM	-	-	15,967
10,000	Emond	84,254	91,675 (@ 11 hours)	88,230
	CADM	-	-	162,773

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.05	Emond	0.138	0.215 (@ 24 hours)	0.215
	CADM	-	-	0.780
0.1	Emond	0.274	0.427 (@ 24 hours)	0.427
	CADM	-	-	1.57
1	Emond	2.58	3.97 (@ 24 hours)	3.97
	CADM	-	-	15.3
10	Emond	22.1	32.8 (@ 24 hours)	32.8
	CADM	-	-	125
100	Emond	170	235 (@ 24 hours)	235
	CADM	-	-	739
1,000	Emond	1,348	1,720 (@ 24 hours)	1,720
	CADM	-	-	5,779
10,000	Emond	12,500	15,265 (@ 24 hours)	15,265
	CADM	-	-	55,825
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.05	Emond	0.0269	0.028 (@ 9 hours)	0.0283
	CADM	-	-	0.0450
0.1	Emond	0.0538	0.057 (@ 9 hours)	0.0565
	CADM	-	-	0.0900
1	Emond	0.536	0.568 (@ 9 hours)	0.562
	CADM	-	-	0.900
10	Emond	5.32	5.65 (@ 8 hours)	5.55
	CADM	-	-	9.00
100	Emond	52.8	56.3 (@ 7 hours)	54.4
	CADM	-	-	90.0
1,000	Emond	525	562 (@ 7 hours)	538
	CADM	-	-	900
10,000	Emond	5,238	5,610 (@ 7 hours)	5,353
	CADM	-	-	9,000
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.05	Emond	0.0194	0.027 (@ 3 hours)	0.0142
	CADM	-	-	-
0.1	Emond	0.0383	0.054 (@ 3 hours)	0.0281
	CADM	-	-	-
1	Emond	0.353	0.506 (@ 3 hours)	0.261
	CADM	-	-	-
10	Emond	2.77	4.24 (@ 2 hours)	2.08
	CADM	-	-	-
100	Emond	16.1	26.4 (@ 2 hours)	12.4
	CADM	-	-	-

1,000	Emond	57.4	80.2 (@ 1 hour)	48.5
	CADM	-	-	-
10,000	Emond	100	108 (@ 1 hour)	96.1
	CADM	-	-	-

E.3.1.40. *Weber et al. (1995) C57 Mice*

Type:	Mouse	**Dose:**	30, 100, 300, 1,000, 3,000, 9,400, 37,500, 75,000, 100,000, 133,000, 150,000, and 235,000 ng/kg
Strains:	C57BL/6J (C57)	**Route:**	Gavage
Body weight:	24.1 g (7−8 weeks old)	**Regime:**	Single dose
Sex:	Male	**Simulation time:**	24 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
30	Emond	1.18	4.16 (@ 0 hours)	0.630
	CADM	-	-	-
100	Emond	3.43	13.9 (@ 0 hours)	1.65
	CADM	-	-	-
300	Emond	9.05	41.6 (@ 0 hours)	3.86
	CADM	-	-	-
1,000	Emond	26.8	139 (@ 0 hours)	9.74
	CADM	-	-	-
3,000	Emond	74.8	417 (@ 0 hours)	23.5
	CADM	-	-	-
9,400	Emond	226	1,307 (@ 0 hours)	63.0
	CADM	-	-	-
37,500	Emond	917	5,223 (@ 0 hours)	231
	CADM	-	-	-
75,000	Emond	1,929	10,464 (@ 0 hours)	459
	CADM	-	-	-
100,000	Emond	2,668	13,967 (@ 0 hours)	612
	CADM	-	-	-
133,000	Emond	3,725	18,603 (@ 0 hours)	815
	CADM	-	-	-
150,000	Emond	4,301	21,287 (@ 1 hours)	920
	CADM	-	-	-
235,000	Emond	7,426	39,404 (@ 1 hours)	1,456
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
30	Emond	132	146 (@ 7 hours)	122
	CADM	68.6	68.6	68.6
100	Emond	473	517 (@ 10 hours)	460
	CADM	416	416	416
300	Emond	1,497	1,639 (@ 11 hours)	1,503
	CADM	2,039	2,039	2,039
1,000	Emond	5,194	5,695 (@ 12 hours)	5,337
	CADM	9,294	9,294	9,294
3,000	Emond	15,923	17,461 (@ 12 hours)	16,565
	CADM	31,419	31,419	31,419
9,400	Emond	50,222	55,080 (@ 13 hours)	52,624
	CADM	102,986	102,986	102,986
37,500	Emond	196,690	216,050 (@ 13 hours)	207,410
	CADM	417,663	417,663	417,663
75,000	Emond	379,350	418,260 (@ 13 hours)	402,930
	CADM	837,656	837,656	837,656
100,000	Emond	491,890	544,360 (@ 14 hours)	525,670
	CADM	1,117,654	1,117,654	1,117,654
133,000	Emond	629,230	700,560 (@ 14 hours)	678,650
	CADM	1,487,253	1,487,253	1,487,253
150,000	Emond	695,520	777,030 (@ 15 hours)	753,880
	CADM	1,677,652	1,677,652	1,677,652
235,000	Emond	993,260	1,128,600 (@ 16 hours)	1,101,800
	CADM	2,629,651	2,629,651	2,629,651
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
30	Emond	71.8	103 (@ 24 hours)	103
	CADM	174	174	174
100	Emond	216	297 (@ 24 hours)	297
	CADM	506	506	506
300	Emond	591	779 (@ 24 hours)	779
	CADM	1,201	1,201	1,201
1,000	Emond	1,810	2,286 (@ 24 hours)	2,286
	CADM	3,002	3,002	3,002
3,000	Emond	5,183	6,354 (@ 24 hours)	6,354
	CADM	7,593	7,593	7,593
9,400	Emond	15,932	19,164 (@ 24 hours)	19,164
	CADM	21,974	21,974	21,974
37,500	Emond	65,208	77,479 (@ 24 hours)	77,479
	CADM	84,935	84,935	84,935
75,000	Emond	137,960	162,720 (@ 24 hours)	162,720
	CADM	168,938	168,938	168,938
100,000	Emond	191,630	224,920 (@ 24 hours)	224,920
	CADM	224,938	224,938	224,938
133,000	Emond	268,900	313,670 (@ 23 hours)	313,580
	CADM	298,859	298,859	298,859

150,000	Emond	311,290	362,150 (@ 22 hours)	361,880
	CADM	336,939	336,939	336,939
235,000	Emond	542,350	625,850 (@ 19 hours)	623,390
	CADM	527,340	527,340	527,340
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
30	Emond	16.9	18.1 (@ 7 hours)	17.5
	CADM	24.0	24.0	24.0
100	Emond	55.9	60.0 (@ 7 hours)	57.4
	CADM	80.0	80.0	80.0
300	Emond	166	179 (@ 7 hours)	170
	CADM	240	240	240
1,000	Emond	550	594 (@ 7 hours)	560
	CADM	800	800	800
3,000	Emond	1,646	1,778 (@ 7 hours)	1,668
	CADM	2,400	2,400	2,400
9,400	Emond	5,141	5,561 (@ 7 hours)	5,197
	CADM	7,520	7,520	7,520
37,500	Emond	20,411	22,102 (@ 7 hours)	20,591
	CADM	30,000	30,000	30,000
75,000	Emond	40,607	43,991 (@ 6 hours)	40,914
	CADM	60,000	60,000	60,000
100,000	Emond	53,951	58,459 (@ 6 hours)	54,329
	CADM	80,000	80,000	80,000
133,000	Emond	71,431	77,411 (@ 6 hours)	71,888
	CADM	106,400	106,400	106,400
150,000	Emond	80,385	87,121 (@ 6 hours)	80,879
	CADM	120,000	120,000	120,000
235,000	Emond	124,740	135,260 (@ 6 hours)	125,340
	CADM	188,000	188,000	188,000
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
30	Emond	3.37	5.79 (@ 3 hours)	2.33
	CADM	-	-	-
100	Emond	8.62	16.4 (@ 2 hours)	5.89
	CADM	-	-	-
300	Emond	18.6	36.6 (@ 2 hours)	12.8
	CADM	-	-	-
1,000	Emond	37.6	67.8 (@ 2 hours)	27.1
	CADM	-	-	-
3,000	Emond	61.3	91.8 (@ 2 hours)	48.3
	CADM	-	-	-
9,400	Emond	85.4	105 (@ 2 hours)	74.7
	CADM	-	-	-
37,500	Emond	103.3	111 (@ 2 hours)	98.7
	CADM	-	-	-
75,000	Emond	107.6	112 (@ 2 hours)	105.1
	CADM	-	-	-

100,000	Emond	108.7	112 (@ 2 hours)	106.9
	CADM	-	-	-
133,000	Emond	109.6	112 (@ 1 hour)	108.2
	CADM	-	-	-
150,000	Emond	109.9	112 (@ 1 hour)	108.7
	CADM	-	-	-
235,000	Emond	110.7	113 (@ 1 hour)	110.1
	CADM	-	-	-

E.3.1.41. *White et al. (1986)*

Type:	Mice	**Dose:**	10, 50, 100, 500, 1,000, 2,000 ng/kg-day
Strain:	$B6C3F_1$	**Route:**	Oral gavage
Body weight:	BW = 23 g (7 weeks old)	**Regime:**	Once per day for 14 days
Sex:	Female	**Simulation time:**	336 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
10	Emond	1.09	2.73 (@ 312 hours)	1.42
	CADM	-	-	-
50	Emond	4.08	11.6 (@ 312 hours)	4.98
	CADM	-	-	-
100	Emond	7.14	21.7 (@ 312 hours)	8.44
	CADM	-	-	-
500	Emond	26.8	96.5 (@ 312 hours)	29.8
	CADM	-	-	-
1,000	Emond	48.7	187 (@ 312 hours)	53.1
	CADM	-	-	-
2,000	Emond	90.6	365 (@ 312 hours)	97.5
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
10	Emond	216	375 (@ 317 hours)	343
	CADM	232	463	463
50	Emond	1,279	2,164 (@ 317 hours)	1,997
	CADM	1,902	3,261	3,261
100	Emond	2,707	4,525 (@ 317 hours)	4,184
	CADM	4,285	6,923	6,923
500	Emond	14,802	24,165 (@ 317 hours)	22,383
	CADM	24,327	36,362	36,362
1,000	Emond	30,278	49,034 (@ 317 hours)	45,414
	CADM	49,617	73,145	73,145

2,000	Emond	61,381	98,703 (@ 317 hours)	91,363
	CADM	100,261	146,695	146,695
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
10	Emond	279	507 (@ 336 hours)	507
	CADM	338	537	537
50	Emond	1,056	1,846 (@ 336 hours)	1,846
	CADM	1,103	1,564	1,564
100	Emond	1,854	3,195 (@ 333 hours)	3,195
	CADM	1,781	2,470	2,470
500	Emond	7,008	11,868 (@ 324 hours)	11,816
	CADM	6,119	8,594	8,594
1,000	Emond	12,746	21,566 (@ 323 hours)	21,424
	CADM	11,248	15,993	15,993
2,000	Emond	23,691	40,177 (@ 322 hours)	39,843
	CADM	21,417	30,726	30,726
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
10	Emond	37.7	65.9 (@ 317 hours)	63.8
	CADM	51.3	85.9	85.9
50	Emond	175	297 (@ 317 hours)	284
	CADM	222	342	342
100	Emond	338	570 (@ 316 hours)	542
	CADM	416	624	624
500	Emond	1,597	2,637 (@ 316 hours)	2,480
	CADM	1,887	2,754	2,754
1,000	Emond	3,137	5,153 (@ 316 hours)	4,830
	CADM	3,702	5,387	5,387
2,000	Emond	6,186	10,118 (@ 316 hours)	9,459
	CADM	7,324	10,643	10,643
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
10	Emond	3.49	5.32 (@ 316 hours)	4.82
	CADM	-	-	-
50	Emond	11.4	16.4 (@ 317 hours)	15.1
	CADM	-	-	-
100	Emond	18.1	25.1 (@ 317 hours)	23.4
	CADM	-	-	-
500	Emond	44.2	56.2 (@ 317 hours)	53.8
	CADM	-	-	-
1,000	Emond	59.3	71.9 (@ 317 hours)	69.7
	CADM	-	-	-
2,000	Emond	74.4	86.1 (@ 317 hours)	84.3
	CADM	-	-	-

E.3.2. Gestational Studies

E.3.2.1. *Bell et al. (2007)*

Type:	Rat	**Dose:**	2.4, 8, and 46 ng/kg-day with a 0.03 ng/kg-day background
Strain:	Han/Wistar	**Route:**	Dietary exposure
Body weight:	BW = 85 g (6 weeks old)	**Regime:**	Once per day for 12 weeks prior to mating, during the 2 week mating period, and during gestation
Sex:	Female	**Simulation time:**	2,352 hours (98 days) prior to gestation + 504 hours (21 days) during gestation for a total simulation of 2,856 hours

Time averages are computed during the gestation period only.

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2.43	2.20	6,295	3.10 (@ 2,352 hours)	2.20
8.03	5.14	14,674	7.31 (@ 2,352 hours)	5.08
46.03	18.4	52,584	28.1 (@ 2,352 hours)	18.1
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2.43	320	914,290	437 (@ 2,356 hours)	321
8.03	1,040	2,969,800	1,349 (@ 2,356 hours)	1,042
46.03	5,892	16,829,000	7,289 (@ 2,356 hours)	6,007
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2.43	205	585,530	263 (@ 2,336 hours)	211
8.03	478	1,365,100	589 (@ 2,335 hours)	486
46.03	1,713	4,891,500	2,045 (@ 2,334 hours)	1,745
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2.43	33.0	94,390	44.4 (@ 2,836 hours)	43.4
8.03	90.4	258,110	117 (@ 2,836 hours)	114
46.03	422	1,206,500	531 (@ 2,836 hours)	511
FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2.43	3.03	8,648	39.6 (@ 2,530 hours)	6.48
8.03	6.65	18,999	86.7 (@ 2,529 hours)	14.4

46.03	20.9	59,794	272 (@ 2,527 hours)	46.0
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2.43	7.10	20,289	8.98 (@ 2,356 hours)	7.23
8.03	15.1	43,242	18.2 (@ 2,356 hours)	15.4
46.03	39.6	113,070	44.8 (@ 2,356 hours)	40.6

E.3.2.2. *Hojo et al. (2002)*

Type:	Rat	**Dose:**	20, 60, and 180 ng/kg
Strain:	Sprague-Dawley	**Route:**	Oral exposure
Body weight	20 ng/kg BW = 271 g 60 ng/kg BW = 275 g 180 ng/kg BW = 262 g	**Regime:**	Single dose on GD 8
Sex:	Female	**Simulation time**	216 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
20	1.62	39.1	4.47 (@ 192 hours)	1.02
60	4.17	100	13.3 (@ 192 hours)	2.50
180	10.7	258	40.3 (@ 192 hours)	5.96
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
20	128	20,554	144 (@ 198 hours)	43.2
60	420	72,340	465 (@ 200 hours)	147
180	1,364	250,820	1,497 (@ 201 hours)	497
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
20	32.5	17,253	63.0 (@ 281 hours)	49.4
60	86.4	44,093	161 (@ 284 hours)	124
180	226	108,730	398 (@ 286 hours)	301
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
20	10.6	3,054	11.3 (@ 200 hours)	8.67
60	31.8	8,702	33.8 (@ 199 hours)	23.6
180	95.0	24,747	101 (@ 199 hours)	63.4

FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
20	15.9	2,334	18.4 (@ 206 hours)	1.64
60	39.8	5,829	45.7 (@ 205 hours)	4.10
180	96.3	13,866	110 (@ 203 hours)	9.72
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
20	4.88	759	7.74 (@ 194 hours)	1.75
60	11.2	1,848	18.5 (@ 194 hours)	4.26
180	23.6	4,157	38.5 (@ 193 hours)	9.65

E.3.2.3. *Ikeda et al. (2005)*

Type:	Rat	**Dose:**	400 ng/kg single dose and 80 ng/kg weekly maintenance dose
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	BW = 250 g (10 weeks old)	**Regime:**	400 ng/kg single dose, two weekly maintenance doses prior to gestation and weekly maintenance doses during gestation
Sex:	Female	**Simulation time:**	504 hours (21 days) prior to gestation + 504 hours (21 days) during gestation for a total simulation of 1,008 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
16.5	22.9	23,086	101 (@ 144 hours)	10.1
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
16.5	7,755	7,817,300	17,016 (@ 150 hours)	2,698
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
16.5	2,087	2,103,900	3,663 (@ 184 hours)	1,028

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
16.5	548	552,590	1,085 (@ 149 hours)	262
FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
16.5	45.9	46,290	245 (@ 679 hours)	30.2
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
16.5	44.0	44,361	63.8 (@ 149 hours)	26.8

E.3.2.4. *Kattainen et al. (2001) and Simanainen et al. (2004)*

Type:	Rat	**Dose:**	30, 100, 300, and 1,000 ng/kg
Strain:	Han/Wistar (Kuopio) and Long/Evans (Turku/AB) crossing.	**Route:**	Oral exposure
Body weight:	BW = 190 g (BW not specified)*	**Regime:**	Single dose on GD 15
Sex:	Female	**Simulation time:**	360 hours

*Derelanko and Hollinger (1995).

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	2.23	53.7	5.95 (@ 336 hours)	1.36
100	6.25	150	19.8 (@ 336 hours)	3.62
300	16.1	387	59.8 (@ 336 hours)	8.62
1,000	46.9	1,128	200 (@ 336 hours)	22.7
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	193	4,648	219 (@ 342 hours)	175
100	713	17,141	793 (@ 344 hours)	680
300	2,298	55,266	2,533 (@ 345 hours)	2,267
1,000	8,055	193,720	8,831 (@ 345 hours)	8,134

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	42.8	1,027	62.8 (@ 360 hours)	62.8
100	123	2,964	175 (@ 360 hours)	175
300	327	7,853	446 (@ 360 hours)	446
1,000	981	23,588	1,289 (@ 360 hours)	1,289
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	15.9	382	16.9 (@ 343 hours)	16.4
100	52.7	1,266	56.2 (@ 343 hours)	54.3
300	158	3,791	168 (@ 343 hours)	162
1,000	524	12,612	561 (@ 343 hours)	538
FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	4.86	117	6.66 (@ 360 hours)	6.66
100	13.2	317	17.6 (@ 360 hours)	17.6
300	31.5	758	41.2 (@ 360 hours)	41.2
1,000	82.2	1,975	104 (@ 360 hours)	104
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	6.57	158	10.7 (@ 338 hours)	4.80
100	15.8	381	26.3 (@ 338 hours)	11.9
300	31.6	760	50.6 (@ 337 hours)	24.7
1,000	57.1	1,373	80.1 (@ 337 hours)	47.7

E.3.2.5. *Keller et al. (2007)*

Type:	Mouse	**Dose:**	10, 100, and 1,000 ng/kg
Strain:	CBA/J and C3H/HeJ	**Route:**	Oral
Body weight:	BW = 24 g (BW not specified)	**Regime:**	Single dose on GD 13
Sex:	Female	**Simulation time:**	336 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
10	0.537	12.9	1.43 (@ 312 hours)	0.269
100	4.29	103	14.3 (@ 312 hours)	1.95
1,000	34.1	820	143 (@ 312 hours)	12.3

LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
10	30.6	737	39.8 (@ 316 hours)	22.2
100	371	8,922	421 (@ 319 hours)	317
1,000	4,214	101,360	4,697 (@ 321 hours)	3,940
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
10	22.4	538	33.3 (@ 336 hours)	33.3
100	188	4,523	264 (@ 336 hours)	264
1,000	1,591	38,233	2,080 (@ 336 hours)	2,080
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
10	5.57	134	5.99 (@ 319 hours)	5.72
100	54.3	1,306	59.0 (@ 318 hours)	54.7
1,000	530	12,747	581 (@ 318 hours)	524
FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
10	2.57	61.7	3.80 (@ 336 hours)	3.80
100	21.7	522	30.0 (@ 334 hours)	29.9
1,000	179	4,312	233 (@ 329 hours)	225
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
10	1.74	41.8	3.14 (@ 315 hours)	1.01
100	11.5	276	23.5 (@ 314 hours)	6.99
1,000	46.7	1,123	79.8 (@ 314 hours)	32.9

E.3.2.6. *Li et al. (2006) 3 Day*

Type:	Mouse	**Dose:**	2, 50, and 100 ng/kg-day
Strain:	NIH	**Route:**	Oral
Body weight:	BW = 27 g (25−28 g)	**Regime:**	Daily exposure from GD 1 to GD 3
Sex:	Female	**Simulation time:**	72 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ([ng/kg] • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2	0.159	11.4	0.392 (@ 48 hours)	0.136

50	2.84	205	8.90 (@ 48 hours)	2.38
100	5.12	369	17.3 (@ 48 hours)	4.20
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2	8.98	647	15.1 (@ 52 hours)	9.10
50	333	23,971	539 (@ 53 hours)	402
100	718	51,738	1,156 (@ 53 hours)	888
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2	17.0	1,227	31.1 (@ 72 hours)	31.1
50	315	22,704	548 (@ 72 hours)	548
100	576	41,460	984 (@ 72 hours)	984
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2	2.29	165	3.51 (@ 55 hours)	3.43
50	53.6	3,863	82.2 (@ 54 hours)	77.1
100	105	7,598	162 (@ 53 hours)	150
FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2	0.0	0	0.000 (@ 72 hours)	0.00
50	0.0	0	0.000 (@ 72 hours)	0.00
100	0.0	0	0.000 (@ 72 hours)	0.00
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2	0.538	38.8	0.864 (@ 51 hours)	0.498
50	8.24	594	13.5 (@ 2 hours)	8.16
100	13.6	981	23.7 (@ 2 hours)	13.6

E.3.2.7. *Markowski et al. (2001)*

Type:	Rat	**Dose:**	20, 60, and 180 ng/kg
Strain:	Holtzman rats	**Route:**	Oral exposure
Body weight:	BW = 190 g (BW not specified)*	**Regime:**	Single dose on GD 18
Sex:	Female	**Simulation time:**	432 hours

*Derelanko and Hollinger (1995).

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
20	1.56	37.5	3.82 (@ 408 hours)	0.958
60	4.03	97.0	11.5 (@ 408 hours)	2.38
180	10.3	248	34.8 (@ 408 hours)	5.72
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
20	123	2,959	141 (@ 414 hours)	109
60	409	9,843	459 (@ 415 hours)	382
180	1,334	32,086	1,479 (@ 416 hours)	1,295
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
20	27.9	670	41.6 (@ 432 hours)	41.6
60	74.0	1,778	107 (@ 432 hours)	107
180	195	4,685	273 (@ 432 hours)	273
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
20	10.6	254	11.2 (@ 415 hours)	10.9
60	31.7	762	33.8 (@ 415 hours)	32.7
180	94.7	2,278	101 (@ 415 hours)	97.5
FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
20	1.26	30.2	1.80 (@ 432 hours)	1.80
60	3.21	77.2	4.49 (@ 432 hours)	4.49
180	7.81	188	10.7 (@ 432 hours)	10.7
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
20	4.74	114	7.59 (@ 410 hours)	3.43
60	11.0	265	18.2 (@ 410 hours)	8.16
180	23.2	559	38.1 (@ 409 hours)	17.7

E.3.2.8. *Mietinnen et al. (2006)*

Type:	Rat	**Dose:**	30, 100, 300, and 1,000 ng/kg
Strain:	Cross-breeding of Han/Wistar and Long-Evans rats	**Route:**	Oral exposure
Body weight:	BW = 180 g (11 weeks old)	**Regime:**	Single dose on GD 15
Sex:	Female	**Simulation time:**	360 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	2.22	53.4	5.87 (@ 336 hours)	1.36
100	6.23	150	19.6 (@ 336 hours)	3.61
300	16.0	386	59.0 (@ 336 hours)	8.61
1,000	46.6	1,123	198 (@ 336 hours)	22.7
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	193	4,631	219 (@ 342 hours)	174
100	711	17,096	791 (@ 344 hours)	677
300	2,294	55,166	2,530 (@ 345 hours)	2,260
1,000	8,042	193,410	8,820 (@ 345 hours)	8,114
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	43.0	1,034	63.2 (@ 360 hours)	63.2
100	124	2,984	176 (@ 360 hours)	176
300	329	7,905	449 (@ 360 hours)	449
1,000	987	23,729	1,296 (@ 360 hours)	1,296
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	15.9	381	16.9 (@ 343 hours)	16.4
100	52.6	1,266	56.1 (@ 343 hours)	54.3
300	158	3,791	168 (@ 343 hours)	162
1,000	524	12,609	561 (@ 343 hours)	538
FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	4.83	116	6.62 (@ 360 hours)	6.62
100	13.1	315	17.5 (@ 360 hours)	17.5
300	31.3	753	41.0 (@ 360 hours)	41.0

1,000	81.7	1,963	104 (@ 360 hours)	104
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	6.56	158	10.7 (@ 338 hours)	4.78
100	15.8	381	26.3 (@ 338 hours)	11.9
300	31.6	760	50.5 (@ 337 hours)	24.6
1,000	57.0	1,372	80.1 (@ 337 hours)	47.6

E.3.2.9. *Nohara et al. (2000)*

Type:	Rat	**Dose:**	12.5, 50, 200, or 800 ng TCDD/kg
Strain:	Holtzman rats	**Route:**	Oral exposure
Body weight:	BW = 190 g (BW not specified)[a]	**Regime:**	Single dose on GD 15
Sex:	Female	**Simulation time:**	360 hours

[a]Derelanko and Hollinger (1995).

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	1.03	24.8	2.44 (@ 336 hours)	0.645
50	3.45	82.9	9.78 (@ 336 hours)	2.07
200	11.3	271	39.2 (@ 336 hours)	6.25
800	38.1	918	158 (@ 336 hours)	18.9
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	73.8	1,776	86.1 (@ 341 hours)	63.6
50	336	8,084	378 (@ 343 hours)	311
200	1,492	35,890	1,651 (@ 344 hours)	1,454
800	6,389	153,640	7,012 (@ 345 hours)	6,423
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	19.7	473	29.5 (@ 360 hours)	29.5
50	67.6	1,624	97.8 (@ 360 hours)	97.8
200	229	5,504	317 (@ 360 hours)	317
800	803	19,292	1,061 (@ 360 hours)	1,061

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	6.62	159	7.04 (@ 343 hours)	6.88
50	26.4	635	28.1 (@ 343 hours)	27.3
200	105	2,528	112 (@ 343 hours)	108
800	420	10,092	449 (@ 343 hours)	430
FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	2.25	54.0	3.14 (@ 360 hours)	3.14
50	7.43	179	10.1 (@ 360 hours)	10.1
200	22.8	548	30.1 (@ 360 hours)	30.1
800	68.1	1,638	87.0 (@ 360 hours)	87.0
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	3.24	77.9	5.12 (@ 338 hours)	2.32
50	9.66	232	16.0 (@ 338 hours)	7.12
200	24.8	597	40.7 (@ 337 hours)	19.0
800	51.9	1,248	75.0 (@ 337 hours)	42.7

E.3.2.10. *Ohsako et al. (2001)*

Type:	Rat	**Dose:**	12.5, 50, 200, and 800 ng/kg-day
Strain:	Holtzmann	**Route:**	Oral exposure
Body weight	10 weeks old (200 g)	**Regime:**	Single dose on GD 15
Sex:	Female	**Simulation time**	384 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	1.04	25.0	2.48 (@ 360 hours)	0.649
50	3.47	83.6	9.93 (@ 360 hours)	2.07
200	11.4	273	39.9 (@ 360 hours)	6.26
800	38.4	925	161 (@ 360 hours)	18.9
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	74.3	1,788	86.5 (@ 365 hours)	64.2
50	338	8,126	379 (@ 367 hours)	314
200	1,497	36,006	1,655 (@ 368 hours)	1,461
800	6,402	153,960	7,025 (@ 369 hours)	6,443

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	19.0	457	28.6 (@ 384 hours)	28.6
50	65.3	1,569	94.7 (@ 384 hours)	94.7
200	221	5,321	307 (@ 384 hours)	307
800	777	18,671	1,029 (@ 384 hours)	1,029
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	6.63	159	7.05 (@ 367 hours)	6.89
50	26.4	635	28.2 (@ 367 hours)	27.3
200	105	2,529	112 (@ 367 hours)	108
800	420	10,093	449 (@ 367 hours)	430
FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	1.65	39.5	2.33 (@ 384 hours)	2.33
50	5.44	131	7.48 (@ 384 hours)	7.48
200	16.7	401	22.3 (@ 384 hours)	22.3
800	49.9	1,200	64.6 (@ 384 hours)	64.6
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	3.25	78.3	5.13 (@ 362 hours)	2.34
50	9.69	233	16.0 (@ 362 hours)	7.16
200	24.9	598	40.7 (@ 361 hours)	19.1
800	51.9	1,249	75.0 (@ 361 hours)	42.8

E.3.2.11. *Schantz et al. (1996) and Amin et al. (2000)*

Type:	Rat	**Dose:**	25 and 100 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral exposure
Body weight:	BW = 250 g (BW not specified)	**Regime:**	Daily doses from GD 10−16
Sex:	Female	**Simulation time:**	384 hours; time averages are calculated from the beginning of the dosing

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	3.38	487	8.63 (@ 360 hours)	4.03
100	10.6	1,522	31.1 (@ 360 hours)	12.3

LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	512	73,686	871 (@ 365 hours)	778
100	2,374	341,960	4,012 (@ 366 hours)	3,665
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	169	24,323	306 (@ 384 hours)	306
100	532	76,675	950 (@ 384 hours)	950
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	45.1	6,490	76.6 (@ 365 hours)	74.3
100	177	25,438	298 (@ 365 hours)	287
FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	25.2	3,627	30.4 (@ 343 hours)	27.3
100	74.1	10,672	88.1 (@ 342 hours)	77.9
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	9.99	1,439	14.4 (@ 364 hours)	12.8
100	25.2	3,632	34.2 (@ 364 hours)	31.6

E.3.2.12. *Seo et al. (1995)*

Type:	Rat	**Dose:**	25 and 100 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral exposure
Body weight:	BW = 190 g (BW not specified)	**Regime:**	Daily doses from GD 10−16
Sex:	Female	**Simulation time:**	384 hours; time averages are calculated from the beginning of the dosing

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	3.33	479	8.25 (@ 360 hours)	4.00
100	10.4	1,498	29.6 (@ 360 hours)	12.2

LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	504	72,592	861 (@ 365 hours)	767
100	2,347	337,970	3,978 (@ 365 hours)	3,627
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	172	24,807	310 (@ 384 hours)	310
100	542	78,097	962 (@ 384 hours)	962
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	45.0	6,486	76.5 (@ 365 hours)	74.2
100	176	25,387	298 (@ 365 hours)	287
FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	24.7	3,551	29.8 (@ 343 hours)	26.8
100	72.6	10,456	86.6 (@ 342 hours)	76.8
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	9.90	1,426	14.3 (@ 364 hours)	12.7
100	25.0	3,607	34.1 (@ 364 hours)	31.4

E.3.2.13. *Smith et al. (1976)*

Type:	Mouse	**Dose:**	1, 10, 100, 1,000, and 3,000 ng/kg-day
Strain:	CF-1	**Route:**	Gavage
Body weight:	Mean 28–29 g (GD 6)	**Regime:**	Daily doses from GD 6−15
Sex:	Female	**Simulation time:**	360 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
1	0.124	29.8	0.274 (@ 336 hours)	0.136
10	1.01	243	2.47 (@ 336 hours)	1.08
100	7.11	1,707	21.1 (@ 336 hours)	7.16
1,000	50.6	12,145	188 (@ 336 hours)	47.4

3,000	138	33,142	554 (@ 336 hours)	127
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
1	7.23	1,735	12.3 (@ 339 hours)	8.71
10	101	24,194	167 (@ 340 hours)	128
100	1,381	331,570	2,196 (@ 341 hours)	1,788
1,000	16,329	3,919,700	25,189 (@ 341 hours)	20,932
3,000	50,491	12,120,000	77,170 (@ 341 hours)	64,246
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
1	22.8	5,477	41.1 (@ 360 hours)	41.1
10	188	45,189	331 (@ 360 hours)	331
100	1,344	322,580	2,289 (@ 360 hours)	2,289
1,000	9,659	2,318,300	16,123 (@ 357 hours)	16,117
3,000	26,368	6,328,900	44,004 (@ 355 hours)	43,959
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
1	3.07	736	5.48 (@ 342 hours)	5.40
10	28.1	6,745	49.1 (@ 341 hours)	47.5
100	246	59,076	415 (@ 340 hours)	390
1,000	2,211	530,720	3,626 (@ 340 hours)	3,316
3,000	6,446	1,547,200	10,500 (@ 340 hours)	9,535
FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
1	1.90	456	2.45 (@ 274 hours)	2.15
10	15.4	3,703	19.9 (@ 249 hours)	16.9
100	105	25,190	137 (@ 247 hours)	111
1,000	659	158,110	880 (@ 246 hours)	686
3,000	1,663	399,230	2,254 (@ 246 hours)	1,744
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
1	0.428	103	0.694 (@ 339 hours)	0.485
10	3.30	791	4.93 (@ 340 hours)	3.77
100	18.5	4,435	24.9 (@ 340 hours)	20.9
1,000	61.9	14,855	79.8 (@ 122 hours)	67.4
3,000	85.2	20,450	98.9 (@ 122 hours)	90.1

E.3.2.14. *Sparschu et al. (1971)*

Type:	Rat	**Dose:**	30, 125, 500, 2,000, and 8,000 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Gavage
Body weight:	BW = 295 g (290−300 g)	**Regime:**	Daily doses from GD 6−15
Sex:	Female	**Simulation time:**	360 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	5.09	1,222	12.4 (@ 336 hours)	6.52
125	16.3	3,908	45.5 (@ 336 hours)	20.4
500	52.9	12,690	168 (@ 336 hours)	65.6
2,000	188	45,188	646 (@ 336 hours)	235
8,000	732	175,750	2,572 (@ 336 hours)	928
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	946	227,090	1,636 (@ 341 hours)	1,507
125	4,480	1,075,300	7,644 (@ 341 hours)	7,105
500	19,233	4,616,400	32,428 (@ 341 hours)	30,252
2,000	79,288	19,031,000	132,390 (@ 341 hours)	123,500
8,000	316,550	75,979,000	522,920 (@ 341 hours)	485,720
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	317	75,978	547 (@ 360 hours)	547
125	1,016	243,930	1,739 (@ 360 hours)	1,739
500	3,295	790,910	5,663 (@ 360 hours)	5,663
2,000	11,671	2,801,200	20,374 (@ 360 hours)	20,374
8,000	45,125	10,831,000	80,136 (@ 360 hours)	80,136
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	80.6	19,348	140 (@ 341 hours)	136
125	324	77,864	559 (@ 341 hours)	537
500	1,266	303,960	2,169 (@ 341 hours)	2,071
2,000	4,996	1,199,100	8,527 (@ 341 hours)	8,117
8,000	19,780	4,747,500	33,634 (@ 340 hours)	31,926
FETUS (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	53.8	12,906	69.5 (@ 247 hours)	54.1

125	156	37,342	202 (@ 246 hours)	153
500	430	103,180	560 (@ 245 hours)	424
2,000	1,311	314,680	1,721 (@ 269 hours)	1,334
8,000	4,694	1,126,700	6,255 (@ 269 hours)	4,943
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hours)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	14.4	3,452	20.7 (@ 340 hours)	19.2
125	34.5	8,279	46.2 (@ 340 hours)	43.9
500	64.0	15,367	77.7 (@ 341 hours)	75.8
2,000	91.2	21,890	100 (@ 341 hours)	99.2
8,000	106	25,389	109 (@ 341 hours)	109

Table E-1. Model input parameters potentially addressed by selected articles

Articles	Model input parameters potentially addressed										
	Absorption	Desorption	Distribution	Elimination	Kinetics	Induction CYP1A1	Interspecies differences	Age Differences	Aryl hydrocarbon	Mode of action	Partition coefficient
Aylward et al. (2005a)	●	●	●	●	●						
Aylward et al. (2005b)	●	●	●	●	●						
Aylward et al. (2009)				●							
Bohonowych and Denison (2007)						●	●		●		
Boverhof et al. (2005)						●	●				
Connor and Aylward (2006)							●	●	●		
Heinzl et al. (2007)			●						●		
Irigaray et al. (2005)			●				●				
Kerger et al. (2006)			●		●			●			
Kerger et al. (2007)								●			
Kim et al. (2003)			●								
Korenaga et al. (2007)						●	●				
Korkalainen et al. (2004)							●	●			
Kransler et al. (2007)							●	●			
Maruyama et al. (2002)	●		●	●							
Maruyama et al. (2003)	●		●	●							
Maruyama and Aoki (2006)	●		●	●							
Milbrath et al. (2009)			●	●	●		●				
Moser and McLachlan (2002)		●		●							
Mullerova and Kopecky(2007)			●								
Nadal et al. (2009)				●	●						
Nohara et al. (2006)							●		●		
Olsman et al. (2007)									●		
Saghir et al. (2005)			●	●	●						
Schecter et al. (2003)				●				●			
Staskal et al. (2005)						●			●		
Toyoshiba et al. (2004)			●			●			●		
Wilkes et al. (2008)						●					

Partition coefficient estimates and CYP parameter value estimates were derived from Wang et al., (2000; 1997) and Santostefano et al. (1998).

E.4. RESPONSE SURFACE TABLES

In order to calculate human equivalent doses, the human model must be run with a daily intake which gives average blood concentrations which match the average concentrations in the rodent models. However, such calculation can require numerous human model runs with repeated intake adjustments in order to reach the target blood concentrations. To facilitate this process, a response surface was created for the human model. In the response surface, numerous intakes were run and the blood, fat, and body burden average concentrations were recorded. These tables can then be used to estimate the intake which would give a target blood concentration. The two closest intakes are found and the intake is estimated by linearly interpolating between the two doses. Then, this intake is run through the human model to confirm that the average blood concentration is within a specified tolerance of the target blood concentration.

For the current analysis, three different response surfaces were created: nongestational lifetime to be used with long-term animal bioassays, nongestational 5 year average runs to be used with shorter term animal bioassays, and gestational to be used with gestational animal bioassays. All three response surfaces are shown in the following tables.

E.4.1. Nongestational Lifetime

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
1.03E-09	2.78E-05	8.69E-06	2.93E-07
1.09E-09	2.95E-05	9.21E-06	3.11E-07
1.16E-09	3.13E-05	9.77E-06	3.30E-07
1.23E-09	3.32E-05	1.04E-05	3.49E-07
1.30E-09	3.52E-05	1.10E-05	3.70E-07
1.38E-09	3.73E-05	1.16E-05	3.93E-07
1.46E-09	3.95E-05	1.23E-05	4.16E-07
1.55E-09	4.19E-05	1.31E-05	4.41E-07
1.64E-09	4.44E-05	1.38E-05	4.68E-07
1.74E-09	4.70E-05	1.47E-05	4.96E-07
1.84E-09	4.99E-05	1.56E-05	5.25E-07
1.95E-09	5.28E-05	1.65E-05	5.57E-07
2.07E-09	5.60E-05	1.75E-05	5.90E-07
2.20E-09	5.94E-05	1.85E-05	6.26E-07
2.33E-09	6.29E-05	1.96E-05	6.63E-07
2.47E-09	6.67E-05	2.08E-05	7.03E-07
2.62E-09	7.07E-05	2.21E-05	7.45E-07
2.77E-09	7.49E-05	2.34E-05	7.90E-07
2.94E-09	7.94E-05	2.48E-05	8.37E-07
3.12E-09	8.42E-05	2.63E-05	8.87E-07
3.30E-09	8.92E-05	2.79E-05	9.40E-07
3.50E-09	9.46E-05	2.95E-05	9.97E-07
3.71E-09	1.00E-04	3.13E-05	1.06E-06
3.93E-09	1.06E-04	3.32E-05	1.12E-06
4.17E-09	1.13E-04	3.52E-05	1.19E-06
4.42E-09	1.19E-04	3.73E-05	1.26E-06
4.68E-09	1.27E-04	3.95E-05	1.33E-06
4.97E-09	1.34E-04	4.19E-05	1.41E-06
5.26E-09	1.42E-04	4.44E-05	1.50E-06
5.58E-09	1.51E-04	4.70E-05	1.59E-06
5.91E-09	1.60E-04	4.99E-05	1.68E-06
6.27E-09	1.69E-04	5.28E-05	1.78E-06
6.65E-09	1.79E-04	5.60E-05	1.89E-06
7.04E-09	1.90E-04	5.94E-05	2.00E-06
7.47E-09	2.02E-04	6.29E-05	2.12E-06

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
7.92E-09	2.14E-04	6.67E-05	2.25E-06
8.39E-09	2.26E-04	7.07E-05	2.39E-06
8.89E-09	2.40E-04	7.49E-05	2.53E-06
9.43E-09	2.54E-04	7.94E-05	2.68E-06
9.99E-09	2.70E-04	8.42E-05	2.84E-06
1.06E-08	2.86E-04	8.92E-05	3.01E-06
1.12E-08	3.03E-04	9.46E-05	3.19E-06
1.19E-08	3.21E-04	1.00E-04	3.38E-06
1.26E-08	3.40E-04	1.06E-04	3.58E-06
1.34E-08	3.61E-04	1.13E-04	3.80E-06
1.42E-08	3.82E-04	1.19E-04	4.03E-06
1.50E-08	4.05E-04	1.26E-04	4.27E-06
1.59E-08	4.29E-04	1.34E-04	4.52E-06
1.69E-08	4.55E-04	1.42E-04	4.79E-06
1.79E-08	4.82E-04	1.51E-04	5.08E-06
1.90E-08	5.11E-04	1.60E-04	5.38E-06
2.01E-08	5.42E-04	1.69E-04	5.71E-06
2.13E-08	5.74E-04	1.79E-04	6.05E-06
2.26E-08	6.08E-04	1.90E-04	6.41E-06
2.39E-08	6.45E-04	2.01E-04	6.79E-06
2.54E-08	6.83E-04	2.13E-04	7.20E-06
2.69E-08	7.24E-04	2.26E-04	7.63E-06
2.85E-08	7.67E-04	2.40E-04	8.08E-06
3.02E-08	8.13E-04	2.54E-04	8.57E-06
3.20E-08	8.62E-04	2.69E-04	9.08E-06
3.40E-08	9.13E-04	2.85E-04	9.62E-06
3.60E-08	9.68E-04	3.02E-04	1.02E-05
3.82E-08	1.03E-03	3.21E-04	1.08E-05
4.05E-08	1.09E-03	3.40E-04	1.15E-05
4.29E-08	1.15E-03	3.60E-04	1.21E-05
4.55E-08	1.22E-03	3.81E-04	1.29E-05
4.82E-08	1.29E-03	4.04E-04	1.36E-05
5.11E-08	1.37E-03	4.28E-04	1.44E-05
5.41E-08	1.45E-03	4.54E-04	1.53E-05
5.74E-08	1.54E-03	4.81E-04	1.62E-05
6.08E-08	1.63E-03	5.10E-04	1.72E-05
6.45E-08	1.73E-03	5.40E-04	1.82E-05

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
6.84E-08	1.83E-03	5.73E-04	1.93E-05
7.25E-08	1.94E-03	6.07E-04	2.04E-05
7.68E-08	2.06E-03	6.43E-04	2.17E-05
8.14E-08	2.18E-03	6.81E-04	2.30E-05
8.63E-08	2.31E-03	7.22E-04	2.43E-05
9.15E-08	2.45E-03	7.65E-04	2.58E-05
9.70E-08	2.59E-03	8.11E-04	2.73E-05
1.03E-07	2.75E-03	8.59E-04	2.89E-05
1.09E-07	2.91E-03	9.10E-04	3.06E-05
1.15E-07	3.08E-03	9.64E-04	3.25E-05
1.22E-07	3.27E-03	1.02E-03	3.44E-05
1.30E-07	3.46E-03	1.08E-03	3.64E-05
1.38E-07	3.67E-03	1.15E-03	3.86E-05
1.46E-07	3.88E-03	1.22E-03	4.09E-05
1.55E-07	4.11E-03	1.29E-03	4.33E-05
1.64E-07	4.36E-03	1.36E-03	4.59E-05
1.74E-07	4.62E-03	1.45E-03	4.86E-05
1.84E-07	4.89E-03	1.53E-03	5.15E-05
1.95E-07	5.18E-03	1.62E-03	5.46E-05
2.07E-07	5.49E-03	1.72E-03	5.78E-05
2.19E-07	5.81E-03	1.82E-03	6.12E-05
2.32E-07	6.16E-03	1.93E-03	6.49E-05
2.46E-07	6.52E-03	2.04E-03	6.87E-05
2.61E-07	6.91E-03	2.17E-03	7.28E-05
2.77E-07	7.32E-03	2.29E-03	7.71E-05
2.93E-07	7.75E-03	2.43E-03	8.16E-05
3.11E-07	8.21E-03	2.57E-03	8.65E-05
3.30E-07	8.69E-03	2.73E-03	9.16E-05
3.49E-07	9.21E-03	2.89E-03	9.70E-05
3.70E-07	9.75E-03	3.06E-03	1.03E-04
3.93E-07	1.03E-02	3.24E-03	1.09E-04
4.16E-07	1.09E-02	3.43E-03	1.15E-04
4.41E-07	1.16E-02	3.63E-03	1.22E-04
4.68E-07	1.23E-02	3.85E-03	1.29E-04
4.96E-07	1.30E-02	4.08E-03	1.37E-04
5.25E-07	1.37E-02	4.32E-03	1.45E-04
5.57E-07	1.46E-02	4.57E-03	1.53E-04

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
5.90E-07	1.54E-02	4.84E-03	1.62E-04
6.26E-07	1.63E-02	5.13E-03	1.72E-04
6.63E-07	1.73E-02	5.43E-03	1.82E-04
7.03E-07	1.83E-02	5.75E-03	1.93E-04
7.45E-07	1.93E-02	6.09E-03	2.04E-04
7.90E-07	2.05E-02	6.45E-03	2.16E-04
8.37E-07	2.17E-02	6.82E-03	2.28E-04
8.88E-07	2.29E-02	7.22E-03	2.42E-04
9.41E-07	2.43E-02	7.65E-03	2.56E-04
9.97E-07	2.57E-02	8.10E-03	2.71E-04
1.01E-06	2.61E-02	8.21E-03	2.75E-04
1.03E-06	2.64E-02	8.33E-03	2.79E-04
1.04E-06	2.68E-02	8.45E-03	2.83E-04
1.06E-06	2.72E-02	8.58E-03	2.87E-04
1.07E-06	2.76E-02	8.70E-03	2.91E-04
1.09E-06	2.80E-02	8.83E-03	2.95E-04
1.11E-06	2.84E-02	8.96E-03	2.99E-04
1.12E-06	2.88E-02	9.09E-03	3.04E-04
1.14E-06	2.92E-02	9.22E-03	3.08E-04
1.16E-06	2.97E-02	9.35E-03	3.12E-04
1.17E-06	3.01E-02	9.49E-03	3.17E-04
1.19E-06	3.05E-02	9.63E-03	3.21E-04
1.21E-06	3.10E-02	9.77E-03	3.26E-04
1.23E-06	3.14E-02	9.91E-03	3.31E-04
1.24E-06	3.19E-02	1.01E-02	3.36E-04
1.26E-06	3.23E-02	1.02E-02	3.40E-04
1.28E-06	3.28E-02	1.03E-02	3.45E-04
1.30E-06	3.33E-02	1.05E-02	3.50E-04
1.32E-06	3.37E-02	1.06E-02	3.55E-04
1.34E-06	3.42E-02	1.08E-02	3.60E-04
1.36E-06	3.47E-02	1.10E-02	3.66E-04
1.38E-06	3.52E-02	1.11E-02	3.71E-04
1.40E-06	3.57E-02	1.13E-02	3.76E-04
1.42E-06	3.62E-02	1.14E-02	3.82E-04
1.44E-06	3.67E-02	1.16E-02	3.87E-04
1.46E-06	3.73E-02	1.18E-02	3.93E-04
1.49E-06	3.78E-02	1.19E-02	3.98E-04

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
1.53E-06	3.89E-02	1.23E-02	4.10E-04
1.58E-06	4.00E-02	1.27E-02	4.22E-04
1.62E-06	4.12E-02	1.30E-02	4.34E-04
1.67E-06	4.24E-02	1.34E-02	4.46E-04
1.72E-06	4.36E-02	1.38E-02	4.59E-04
1.77E-06	4.49E-02	1.42E-02	4.72E-04
1.83E-06	4.61E-02	1.46E-02	4.86E-04
1.88E-06	4.75E-02	1.50E-02	5.00E-04
1.94E-06	4.88E-02	1.55E-02	5.14E-04
2.00E-06	5.02E-02	1.59E-02	5.29E-04
2.06E-06	5.17E-02	1.64E-02	5.44E-04
2.12E-06	5.32E-02	1.68E-02	5.60E-04
2.18E-06	5.47E-02	1.73E-02	5.76E-04
2.25E-06	5.63E-02	1.78E-02	5.93E-04
2.32E-06	5.79E-02	1.84E-02	6.10E-04
2.39E-06	5.95E-02	1.89E-02	6.27E-04
2.46E-06	6.12E-02	1.94E-02	6.45E-04
2.53E-06	6.30E-02	2.00E-02	6.64E-04
2.61E-06	6.48E-02	2.06E-02	6.83E-04
2.68E-06	6.66E-02	2.12E-02	7.02E-04
2.76E-06	6.85E-02	2.18E-02	7.22E-04
2.85E-06	7.05E-02	2.24E-02	7.43E-04
2.93E-06	7.25E-02	2.30E-02	7.64E-04
3.02E-06	7.46E-02	2.37E-02	7.86E-04
3.11E-06	7.67E-02	2.44E-02	8.08E-04
3.21E-06	7.89E-02	2.51E-02	8.31E-04
3.30E-06	8.11E-02	2.58E-02	8.54E-04
3.40E-06	8.34E-02	2.65E-02	8.79E-04
3.50E-06	8.58E-02	2.73E-02	9.04E-04
3.61E-06	8.82E-02	2.81E-02	9.29E-04
3.72E-06	9.07E-02	2.89E-02	9.55E-04
3.83E-06	9.33E-02	2.97E-02	9.82E-04
3.94E-06	9.59E-02	3.06E-02	1.01E-03
4.06E-06	9.86E-02	3.14E-02	1.04E-03
4.18E-06	1.01E-01	3.23E-02	1.07E-03
4.31E-06	1.04E-01	3.33E-02	1.10E-03
4.44E-06	1.07E-01	3.42E-02	1.13E-03

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
4.57E-06	1.10E-01	3.52E-02	1.16E-03
4.71E-06	1.13E-01	3.62E-02	1.19E-03
4.85E-06	1.16E-01	3.72E-02	1.23E-03
4.99E-06	1.20E-01	3.83E-02	1.26E-03
5.14E-06	1.23E-01	3.94E-02	1.30E-03
5.30E-06	1.27E-01	4.05E-02	1.33E-03
5.46E-06	1.30E-01	4.16E-02	1.37E-03
5.62E-06	1.34E-01	4.28E-02	1.41E-03
5.79E-06	1.37E-01	4.40E-02	1.45E-03
5.96E-06	1.41E-01	4.53E-02	1.49E-03
6.14E-06	1.45E-01	4.65E-02	1.53E-03
6.33E-06	1.49E-01	4.78E-02	1.57E-03
6.52E-06	1.53E-01	4.92E-02	1.62E-03
6.71E-06	1.58E-01	5.06E-02	1.66E-03
6.91E-06	1.62E-01	5.20E-02	1.71E-03
7.12E-06	1.66E-01	5.35E-02	1.75E-03
7.33E-06	1.71E-01	5.50E-02	1.80E-03
7.55E-06	1.76E-01	5.65E-02	1.85E-03
7.78E-06	1.81E-01	5.81E-02	1.90E-03
8.01E-06	1.86E-01	5.97E-02	1.95E-03
8.25E-06	1.91E-01	6.14E-02	2.01E-03
8.50E-06	1.96E-01	6.31E-02	2.06E-03
8.76E-06	2.01E-01	6.49E-02	2.12E-03
9.02E-06	2.07E-01	6.67E-02	2.18E-03
9.29E-06	2.12E-01	6.86E-02	2.24E-03
9.57E-06	2.18E-01	7.05E-02	2.30E-03
9.86E-06	2.24E-01	7.24E-02	2.36E-03
1.02E-05	2.30E-01	7.45E-02	2.43E-03
1.05E-05	2.37E-01	7.65E-02	2.49E-03
1.08E-05	2.43E-01	7.86E-02	2.56E-03
1.11E-05	2.50E-01	8.08E-02	2.63E-03
1.14E-05	2.56E-01	8.31E-02	2.70E-03
1.18E-05	2.63E-01	8.54E-02	2.77E-03
1.21E-05	2.71E-01	8.77E-02	2.85E-03
1.25E-05	2.78E-01	9.01E-02	2.93E-03
1.29E-05	2.85E-01	9.26E-02	3.01E-03
1.32E-05	2.93E-01	9.52E-02	3.09E-03

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
1.36E-05	3.01E-01	9.78E-02	3.17E-03
1.41E-05	3.09E-01	1.00E-01	3.25E-03
1.45E-05	3.17E-01	1.03E-01	3.34E-03
1.49E-05	3.26E-01	1.06E-01	3.43E-03
1.54E-05	3.34E-01	1.09E-01	3.52E-03
1.58E-05	3.43E-01	1.12E-01	3.62E-03
1.63E-05	3.53E-01	1.15E-01	3.71E-03
1.68E-05	3.62E-01	1.18E-01	3.81E-03
1.73E-05	3.72E-01	1.21E-01	3.91E-03
1.78E-05	3.81E-01	1.25E-01	4.02E-03
1.83E-05	3.92E-01	1.28E-01	4.12E-03
1.89E-05	4.02E-01	1.32E-01	4.23E-03
1.95E-05	4.13E-01	1.35E-01	4.34E-03
2.00E-05	4.23E-01	1.39E-01	4.46E-03
2.06E-05	4.35E-01	1.43E-01	4.58E-03
2.13E-05	4.46E-01	1.46E-01	4.70E-03
2.19E-05	4.58E-01	1.50E-01	4.82E-03
2.25E-05	4.70E-01	1.54E-01	4.95E-03
2.32E-05	4.82E-01	1.59E-01	5.07E-03
2.39E-05	4.94E-01	1.63E-01	5.21E-03
2.46E-05	5.07E-01	1.67E-01	5.34E-03
2.54E-05	5.21E-01	1.72E-01	5.48E-03
2.61E-05	5.34E-01	1.76E-01	5.62E-03
2.69E-05	5.48E-01	1.81E-01	5.77E-03
2.77E-05	5.62E-01	1.86E-01	5.92E-03
2.86E-05	5.77E-01	1.91E-01	6.07E-03
2.94E-05	5.92E-01	1.96E-01	6.23E-03
3.03E-05	6.07E-01	2.01E-01	6.39E-03
3.12E-05	6.22E-01	2.06E-01	6.55E-03
3.21E-05	6.38E-01	2.12E-01	6.72E-03
3.31E-05	6.55E-01	2.18E-01	6.90E-03
3.41E-05	6.72E-01	2.23E-01	7.07E-03
3.51E-05	6.89E-01	2.29E-01	7.25E-03
3.62E-05	7.06E-01	2.35E-01	7.44E-03
3.73E-05	7.25E-01	2.42E-01	7.63E-03
3.84E-05	7.43E-01	2.48E-01	7.82E-03
3.95E-05	7.62E-01	2.54E-01	8.02E-03

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
4.07E-05	7.81E-01	2.61E-01	8.22E-03
4.19E-05	8.01E-01	2.68E-01	8.43E-03
4.32E-05	8.21E-01	2.75E-01	8.64E-03
4.45E-05	8.42E-01	2.82E-01	8.86E-03
4.58E-05	8.63E-01	2.90E-01	9.08E-03
4.72E-05	8.84E-01	2.97E-01	9.31E-03
4.86E-05	9.07E-01	3.05E-01	9.55E-03
5.01E-05	9.29E-01	3.13E-01	9.78E-03
5.16E-05	9.53E-01	3.21E-01	1.00E-02
5.31E-05	9.76E-01	3.29E-01	1.03E-02
5.47E-05	1.00E+00	3.38E-01	1.05E-02
5.64E-05	1.03E+00	3.47E-01	1.08E-02
5.81E-05	1.05E+00	3.56E-01	1.11E-02
5.98E-05	1.08E+00	3.65E-01	1.13E-02
6.16E-05	1.10E+00	3.74E-01	1.16E-02
6.34E-05	1.13E+00	3.84E-01	1.19E-02
6.54E-05	1.16E+00	3.94E-01	1.22E-02
6.73E-05	1.19E+00	4.04E-01	1.25E-02
6.93E-05	1.22E+00	4.14E-01	1.28E-02
7.14E-05	1.25E+00	4.25E-01	1.31E-02
7.36E-05	1.28E+00	4.36E-01	1.34E-02
7.58E-05	1.31E+00	4.47E-01	1.38E-02
7.80E-05	1.34E+00	4.58E-01	1.41E-02
8.04E-05	1.37E+00	4.70E-01	1.44E-02
8.28E-05	1.40E+00	4.82E-01	1.48E-02
8.53E-05	1.44E+00	4.94E-01	1.51E-02
8.78E-05	1.47E+00	5.07E-01	1.55E-02
9.05E-05	1.51E+00	5.19E-01	1.59E-02
9.32E-05	1.55E+00	5.33E-01	1.63E-02
9.60E-05	1.58E+00	5.46E-01	1.67E-02
9.89E-05	1.62E+00	5.60E-01	1.71E-02
1.02E-04	1.66E+00	5.74E-01	1.75E-02
1.05E-04	1.70E+00	5.89E-01	1.79E-02
1.08E-04	1.74E+00	6.04E-01	1.83E-02
1.11E-04	1.78E+00	6.19E-01	1.88E-02
1.15E-04	1.82E+00	6.34E-01	1.92E-02
1.18E-04	1.87E+00	6.50E-01	1.96E-02

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
1.22E-04	1.91E+00	6.66E-01	2.01E-02
1.25E-04	1.96E+00	6.83E-01	2.06E-02
1.29E-04	2.00E+00	7.00E-01	2.11E-02
1.33E-04	2.05E+00	7.17E-01	2.16E-02
1.37E-04	2.10E+00	7.35E-01	2.21E-02
1.41E-04	2.15E+00	7.53E-01	2.26E-02
1.45E-04	2.20E+00	7.72E-01	2.31E-02
1.50E-04	2.25E+00	7.91E-01	2.36E-02
1.54E-04	2.30E+00	8.11E-01	2.42E-02
1.59E-04	2.35E+00	8.31E-01	2.48E-02
1.63E-04	2.41E+00	8.51E-01	2.53E-02
1.68E-04	2.46E+00	8.72E-01	2.59E-02
1.73E-04	2.52E+00	8.94E-01	2.65E-02
1.79E-04	2.58E+00	9.16E-01	2.71E-02
1.84E-04	2.64E+00	9.39E-01	2.78E-02
1.89E-04	2.70E+00	9.62E-01	2.84E-02
1.95E-04	2.76E+00	9.85E-01	2.90E-02
2.01E-04	2.82E+00	1.01E+00	2.97E-02
2.07E-04	2.89E+00	1.03E+00	3.04E-02
2.13E-04	2.96E+00	1.06E+00	3.11E-02
2.20E-04	3.02E+00	1.09E+00	3.18E-02
2.26E-04	3.09E+00	1.11E+00	3.25E-02
2.33E-04	3.16E+00	1.14E+00	3.33E-02
2.40E-04	3.23E+00	1.17E+00	3.40E-02
2.47E-04	3.31E+00	1.20E+00	3.48E-02
2.55E-04	3.38E+00	1.23E+00	3.56E-02
2.62E-04	3.46E+00	1.26E+00	3.64E-02
2.70E-04	3.54E+00	1.29E+00	3.72E-02
2.78E-04	3.62E+00	1.32E+00	3.81E-02
2.86E-04	3.70E+00	1.35E+00	3.89E-02
2.95E-04	3.78E+00	1.38E+00	3.98E-02
3.04E-04	3.86E+00	1.42E+00	4.07E-02
3.13E-04	3.95E+00	1.45E+00	4.16E-02
3.22E-04	4.04E+00	1.49E+00	4.25E-02
3.32E-04	4.13E+00	1.52E+00	4.34E-02
3.42E-04	4.22E+00	1.56E+00	4.44E-02
3.52E-04	4.31E+00	1.59E+00	4.54E-02

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
3.63E-04	4.41E+00	1.63E+00	4.64E-02
3.74E-04	4.50E+00	1.67E+00	4.74E-02
3.85E-04	4.60E+00	1.71E+00	4.85E-02
3.97E-04	4.71E+00	1.75E+00	4.95E-02
4.08E-04	4.81E+00	1.80E+00	5.06E-02
4.21E-04	4.92E+00	1.84E+00	5.17E-02
4.33E-04	5.02E+00	1.89E+00	5.29E-02
4.46E-04	5.13E+00	1.93E+00	5.40E-02
4.60E-04	5.25E+00	1.98E+00	5.52E-02
4.74E-04	5.36E+00	2.03E+00	5.64E-02
4.88E-04	5.48E+00	2.07E+00	5.77E-02
5.02E-04	5.60E+00	2.12E+00	5.89E-02
5.17E-04	5.72E+00	2.18E+00	6.02E-02
5.33E-04	5.85E+00	2.23E+00	6.15E-02
5.49E-04	5.97E+00	2.28E+00	6.29E-02
5.65E-04	6.10E+00	2.34E+00	6.42E-02
5.82E-04	6.24E+00	2.39E+00	6.56E-02
6.00E-04	6.37E+00	2.45E+00	6.71E-02
6.18E-04	6.51E+00	2.51E+00	6.85E-02
6.36E-04	6.65E+00	2.57E+00	7.00E-02
6.55E-04	6.79E+00	2.63E+00	7.15E-02
6.75E-04	6.94E+00	2.69E+00	7.30E-02
6.95E-04	7.09E+00	2.76E+00	7.46E-02
7.16E-04	7.24E+00	2.82E+00	7.62E-02
7.38E-04	7.39E+00	2.89E+00	7.78E-02
7.60E-04	7.55E+00	2.96E+00	7.94E-02
7.83E-04	7.71E+00	3.03E+00	8.11E-02
8.06E-04	7.87E+00	3.10E+00	8.29E-02
8.30E-04	8.04E+00	3.17E+00	8.46E-02
8.55E-04	8.21E+00	3.25E+00	8.64E-02
8.81E-04	8.38E+00	3.33E+00	8.82E-02
9.07E-04	8.56E+00	3.41E+00	9.01E-02
9.21E-04	8.65E+00	3.45E+00	9.11E-02
9.35E-04	8.74E+00	3.49E+00	9.20E-02
9.49E-04	8.84E+00	3.53E+00	9.30E-02
9.63E-04	8.93E+00	3.57E+00	9.40E-02
9.69E-04	8.97E+00	3.59E+00	9.44E-02

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
9.77E-04	9.02E+00	3.61E+00	9.49E-02
9.84E-04	9.07E+00	3.63E+00	9.54E-02
9.91E-04	9.12E+00	3.66E+00	9.59E-02
9.98E-04	9.16E+00	3.68E+00	9.64E-02
1.01E-03	9.21E+00	3.70E+00	9.69E-02
1.02E-03	9.31E+00	3.74E+00	9.80E-02
1.04E-03	9.41E+00	3.79E+00	9.90E-02
1.05E-03	9.50E+00	3.83E+00	1.00E-01
1.07E-03	9.60E+00	3.88E+00	1.01E-01
1.08E-03	9.70E+00	3.92E+00	1.02E-01
1.10E-03	9.81E+00	3.97E+00	1.03E-01
1.12E-03	9.91E+00	4.02E+00	1.04E-01
1.13E-03	1.00E+01	4.06E+00	1.05E-01
1.15E-03	1.01E+01	4.11E+00	1.06E-01
1.17E-03	1.02E+01	4.16E+00	1.08E-01
1.18E-03	1.03E+01	4.21E+00	1.09E-01
1.20E-03	1.04E+01	4.26E+00	1.10E-01
1.22E-03	1.05E+01	4.31E+00	1.11E-01
1.24E-03	1.07E+01	4.36E+00	1.12E-01
1.26E-03	1.08E+01	4.41E+00	1.13E-01
1.27E-03	1.09E+01	4.46E+00	1.14E-01
1.29E-03	1.10E+01	4.52E+00	1.16E-01
1.31E-03	1.11E+01	4.57E+00	1.17E-01
1.33E-03	1.12E+01	4.62E+00	1.18E-01
1.35E-03	1.13E+01	4.68E+00	1.19E-01
1.37E-03	1.14E+01	4.73E+00	1.20E-01
1.39E-03	1.16E+01	4.79E+00	1.22E-01
1.41E-03	1.17E+01	4.85E+00	1.23E-01
1.43E-03	1.18E+01	4.91E+00	1.24E-01
1.46E-03	1.19E+01	4.96E+00	1.26E-01
1.48E-03	1.21E+01	5.02E+00	1.27E-01
1.50E-03	1.22E+01	5.08E+00	1.28E-01
1.52E-03	1.23E+01	5.14E+00	1.29E-01
1.54E-03	1.24E+01	5.20E+00	1.31E-01
1.57E-03	1.26E+01	5.26E+00	1.32E-01
1.59E-03	1.28E+01	5.39E+00	1.35E-01
1.61E-03	1.31E+01	5.54E+00	1.38E-01

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
1.64E-03	1.33E+01	5.60E+00	1.39E-01
1.66E-03	1.33E+01	5.62E+00	1.40E-01
1.69E-03	1.34E+01	5.67E+00	1.41E-01
1.71E-03	1.35E+01	5.73E+00	1.42E-01
1.74E-03	1.36E+01	5.77E+00	1.43E-01
1.76E-03	1.37E+01	5.80E+00	1.44E-01
1.79E-03	1.38E+01	5.87E+00	1.45E-01
1.82E-03	1.39E+01	5.94E+00	1.47E-01
1.84E-03	1.41E+01	6.01E+00	1.48E-01
1.87E-03	1.43E+01	6.11E+00	1.50E-01
1.90E-03	1.46E+01	6.31E+00	1.54E-01
1.93E-03	1.49E+01	6.45E+00	1.57E-01
1.96E-03	1.49E+01	6.42E+00	1.57E-01
1.99E-03	1.50E+01	6.48E+00	1.58E-01
2.02E-03	1.51E+01	6.55E+00	1.59E-01
2.08E-03	1.54E+01	6.66E+00	1.62E-01
2.14E-03	1.56E+01	6.77E+00	1.64E-01
2.20E-03	1.59E+01	6.93E+00	1.68E-01
2.27E-03	1.62E+01	7.09E+00	1.71E-01
2.34E-03	1.66E+01	7.25E+00	1.74E-01
2.41E-03	1.69E+01	7.42E+00	1.78E-01
2.48E-03	1.72E+01	7.60E+00	1.81E-01
2.55E-03	1.76E+01	7.78E+00	1.85E-01
2.63E-03	1.79E+01	7.96E+00	1.89E-01
2.71E-03	1.83E+01	8.15E+00	1.93E-01
2.79E-03	1.87E+01	8.35E+00	1.97E-01
2.87E-03	1.91E+01	8.55E+00	2.00E-01
2.96E-03	1.94E+01	8.75E+00	2.05E-01
3.05E-03	1.98E+01	8.96E+00	2.09E-01
3.14E-03	2.02E+01	9.17E+00	2.13E-01
3.23E-03	2.07E+01	9.41E+00	2.18E-01
3.33E-03	2.11E+01	9.63E+00	2.22E-01
3.43E-03	2.15E+01	9.85E+00	2.26E-01
3.53E-03	2.19E+01	1.01E+01	2.31E-01
3.64E-03	2.23E+01	1.03E+01	2.35E-01
3.75E-03	2.29E+01	1.06E+01	2.41E-01
3.81E-03	2.31E+01	1.08E+01	2.43E-01

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
3.86E-03	2.32E+01	1.08E+01	2.44E-01
3.98E-03	2.36E+01	1.10E+01	2.48E-01
4.10E-03	2.40E+01	1.12E+01	2.52E-01
4.22E-03	2.44E+01	1.14E+01	2.56E-01
4.35E-03	2.48E+01	1.17E+01	2.61E-01
4.48E-03	2.53E+01	1.19E+01	2.66E-01
4.61E-03	2.58E+01	1.22E+01	2.71E-01
4.75E-03	2.63E+01	1.25E+01	2.77E-01
4.89E-03	2.68E+01	1.28E+01	2.82E-01
5.04E-03	2.75E+01	1.32E+01	2.89E-01
5.19E-03	2.82E+01	1.36E+01	2.97E-01
5.35E-03	2.89E+01	1.41E+01	3.04E-01
5.51E-03	2.96E+01	1.45E+01	3.11E-01
5.67E-03	3.04E+01	1.50E+01	3.20E-01
5.84E-03	3.10E+01	1.53E+01	3.26E-01
5.93E-03	3.13E+01	1.55E+01	3.29E-01
6.02E-03	3.16E+01	1.57E+01	3.32E-01
6.20E-03	3.22E+01	1.61E+01	3.39E-01
6.38E-03	3.29E+01	1.65E+01	3.46E-01
6.57E-03	3.34E+01	1.68E+01	3.51E-01
6.77E-03	3.40E+01	1.72E+01	3.58E-01
6.98E-03	3.45E+01	1.75E+01	3.63E-01
7.18E-03	3.54E+01	1.80E+01	3.72E-01
7.40E-03	3.61E+01	1.85E+01	3.80E-01
7.51E-03	3.64E+01	1.87E+01	3.83E-01
7.62E-03	3.68E+01	1.89E+01	3.87E-01
7.85E-03	3.75E+01	1.93E+01	3.94E-01
8.09E-03	3.82E+01	1.98E+01	4.02E-01
8.33E-03	3.89E+01	2.02E+01	4.09E-01
8.58E-03	3.96E+01	2.07E+01	4.17E-01
8.71E-03	4.00E+01	2.10E+01	4.21E-01
8.84E-03	4.04E+01	2.12E+01	4.25E-01
9.10E-03	4.12E+01	2.17E+01	4.34E-01
9.37E-03	4.20E+01	2.23E+01	4.42E-01
9.66E-03	4.29E+01	2.28E+01	4.51E-01
9.94E-03	4.37E+01	2.34E+01	4.60E-01
1.02E-02	4.46E+01	2.39E+01	4.69E-01

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
1.06E-02	4.54E+01	2.45E+01	4.78E-01
1.09E-02	4.63E+01	2.51E+01	4.87E-01
1.12E-02	4.73E+01	2.58E+01	4.98E-01
1.15E-02	4.83E+01	2.65E+01	5.08E-01
1.19E-02	4.93E+01	2.72E+01	5.19E-01
1.22E-02	5.02E+01	2.78E+01	5.28E-01
1.26E-02	5.11E+01	2.84E+01	5.38E-01
1.30E-02	5.22E+01	2.91E+01	5.49E-01
1.34E-02	5.31E+01	2.98E+01	5.59E-01
1.38E-02	5.42E+01	3.06E+01	5.70E-01
1.42E-02	5.53E+01	3.14E+01	5.82E-01
1.46E-02	5.66E+01	3.24E+01	5.95E-01
1.50E-02	5.76E+01	3.31E+01	6.07E-01
1.55E-02	5.87E+01	3.39E+01	6.18E-01
1.60E-02	5.99E+01	3.47E+01	6.30E-01
1.64E-02	6.10E+01	3.56E+01	6.42E-01
1.69E-02	6.22E+01	3.65E+01	6.55E-01
1.74E-02	6.34E+01	3.73E+01	6.67E-01
1.80E-02	6.46E+01	3.83E+01	6.80E-01
1.85E-02	6.59E+01	3.92E+01	6.93E-01
1.91E-02	6.71E+01	4.02E+01	7.06E-01
1.96E-02	6.88E+01	4.15E+01	7.24E-01
2.02E-02	7.01E+01	4.25E+01	7.38E-01
2.08E-02	7.14E+01	4.35E+01	7.52E-01
2.14E-02	7.26E+01	4.44E+01	7.64E-01
2.21E-02	7.40E+01	4.55E+01	7.79E-01
2.28E-02	7.55E+01	4.67E+01	7.94E-01
2.34E-02	7.69E+01	4.78E+01	8.10E-01
2.41E-02	7.85E+01	4.91E+01	8.26E-01
2.49E-02	8.00E+01	5.04E+01	8.42E-01
2.56E-02	8.16E+01	5.16E+01	8.59E-01
2.64E-02	8.32E+01	5.30E+01	8.76E-01
2.72E-02	8.48E+01	5.43E+01	8.93E-01
2.80E-02	8.64E+01	5.56E+01	9.09E-01
2.88E-02	8.81E+01	5.70E+01	9.27E-01
2.97E-02	8.98E+01	5.85E+01	9.45E-01
3.06E-02	9.15E+01	5.99E+01	9.63E-01

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
3.15E-02	9.33E+01	6.14E+01	9.81E-01
3.24E-02	9.51E+01	6.30E+01	1.00E+00
3.34E-02	9.69E+01	6.46E+01	1.02E+00
3.44E-02	9.88E+01	6.62E+01	1.04E+00
3.54E-02	1.01E+02	6.79E+01	1.06E+00
3.65E-02	1.03E+02	6.97E+01	1.08E+00
3.76E-02	1.05E+02	7.15E+01	1.10E+00
3.87E-02	1.07E+02	7.33E+01	1.12E+00
3.99E-02	1.09E+02	7.52E+01	1.14E+00
4.11E-02	1.11E+02	7.71E+01	1.17E+00
4.23E-02	1.13E+02	7.91E+01	1.19E+00
4.36E-02	1.15E+02	8.12E+01	1.21E+00
4.49E-02	1.18E+02	8.33E+01	1.24E+00
4.63E-02	1.20E+02	8.54E+01	1.26E+00
4.76E-02	1.22E+02	8.77E+01	1.29E+00
4.91E-02	1.25E+02	9.00E+01	1.31E+00
5.05E-02	1.27E+02	9.24E+01	1.34E+00
5.21E-02	1.30E+02	9.47E+01	1.36E+00
5.36E-02	1.32E+02	9.71E+01	1.39E+00
5.52E-02	1.34E+02	9.95E+01	1.41E+00
5.69E-02	1.37E+02	1.02E+02	1.44E+00
5.86E-02	1.40E+02	1.05E+02	1.47E+00
6.03E-02	1.43E+02	1.08E+02	1.50E+00
6.22E-02	1.45E+02	1.10E+02	1.53E+00
6.40E-02	1.48E+02	1.13E+02	1.56E+00
6.59E-02	1.51E+02	1.16E+02	1.59E+00
6.79E-02	1.54E+02	1.19E+02	1.62E+00
7.00E-02	1.57E+02	1.22E+02	1.65E+00
7.21E-02	1.60E+02	1.26E+02	1.69E+00
7.42E-02	1.63E+02	1.29E+02	1.72E+00
7.64E-02	1.66E+02	1.32E+02	1.75E+00
7.87E-02	1.70E+02	1.36E+02	1.79E+00
8.11E-02	1.73E+02	1.39E+02	1.82E+00
8.35E-02	1.76E+02	1.43E+02	1.86E+00
8.60E-02	1.80E+02	1.47E+02	1.89E+00
8.86E-02	1.84E+02	1.51E+02	1.93E+00
9.13E-02	1.87E+02	1.55E+02	1.97E+00

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
9.40E-02	1.91E+02	1.59E+02	2.01E+00
9.68E-02	1.95E+02	1.63E+02	2.05E+00
9.97E-02	1.98E+02	1.68E+02	2.09E+00
1.03E-01	2.02E+02	1.72E+02	2.13E+00
1.06E-01	2.06E+02	1.77E+02	2.17E+00
1.09E-01	2.10E+02	1.81E+02	2.21E+00
1.12E-01	2.14E+02	1.86E+02	2.26E+00
1.16E-01	2.19E+02	1.91E+02	2.30E+00
1.19E-01	2.23E+02	1.96E+02	2.35E+00
1.23E-01	2.27E+02	2.02E+02	2.39E+00
1.26E-01	2.32E+02	2.07E+02	2.44E+00
1.30E-01	2.36E+02	2.12E+02	2.48E+00
1.34E-01	2.41E+02	2.18E+02	2.53E+00
1.38E-01	2.45E+02	2.24E+02	2.58E+00
1.42E-01	2.50E+02	2.30E+02	2.63E+00
1.46E-01	2.55E+02	2.36E+02	2.69E+00
1.51E-01	2.60E+02	2.43E+02	2.74E+00
1.55E-01	2.65E+02	2.49E+02	2.79E+00
1.60E-01	2.71E+02	2.56E+02	2.85E+00
1.65E-01	2.76E+02	2.63E+02	2.90E+00
1.70E-01	2.81E+02	2.70E+02	2.96E+00
1.75E-01	2.87E+02	2.77E+02	3.02E+00
1.80E-01	2.93E+02	2.85E+02	3.08E+00
1.86E-01	2.98E+02	2.92E+02	3.14E+00
1.91E-01	3.04E+02	3.00E+02	3.20E+00
1.97E-01	3.10E+02	3.08E+02	3.26E+00
2.03E-01	3.16E+02	3.17E+02	3.33E+00
2.09E-01	3.23E+02	3.25E+02	3.39E+00
2.15E-01	3.29E+02	3.34E+02	3.46E+00
2.22E-01	3.35E+02	3.43E+02	3.53E+00
2.28E-01	3.42E+02	3.53E+02	3.60E+00
2.35E-01	3.49E+02	3.62E+02	3.67E+00
2.42E-01	3.56E+02	3.72E+02	3.74E+00
2.49E-01	3.63E+02	3.82E+02	3.82E+00
2.57E-01	3.70E+02	3.93E+02	3.89E+00
2.65E-01	3.77E+02	4.03E+02	3.97E+00
2.72E-01	3.85E+02	4.14E+02	4.05E+00

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
2.81E-01	3.93E+02	4.26E+02	4.13E+00
2.89E-01	4.00E+02	4.38E+02	4.21E+00
2.98E-01	4.08E+02	4.50E+02	4.30E+00
3.07E-01	4.16E+02	4.62E+02	4.38E+00
3.16E-01	4.25E+02	4.75E+02	4.47E+00
3.25E-01	4.33E+02	4.88E+02	4.56E+00
3.35E-01	4.42E+02	5.01E+02	4.65E+00
3.45E-01	4.51E+02	5.15E+02	4.74E+00
3.56E-01	4.60E+02	5.29E+02	4.84E+00
3.66E-01	4.69E+02	5.44E+02	4.94E+00
3.77E-01	4.78E+02	5.59E+02	5.03E+00
3.89E-01	4.88E+02	5.74E+02	5.14E+00
4.00E-01	4.98E+02	5.90E+02	5.24E+00
4.12E-01	5.08E+02	6.07E+02	5.34E+00
4.25E-01	5.18E+02	6.23E+02	5.45E+00
4.37E-01	5.28E+02	6.41E+02	5.56E+00
4.50E-01	5.39E+02	6.58E+02	5.67E+00
4.64E-01	5.50E+02	6.77E+02	5.79E+00
4.78E-01	5.61E+02	6.96E+02	5.90E+00
4.92E-01	5.72E+02	7.15E+02	6.02E+00
5.07E-01	5.84E+02	7.35E+02	6.14E+00
5.22E-01	5.96E+02	7.55E+02	6.27E+00
5.38E-01	6.08E+02	7.76E+02	6.40E+00
5.54E-01	6.20E+02	7.98E+02	6.53E+00
5.71E-01	6.33E+02	8.20E+02	6.66E+00
5.88E-01	6.46E+02	8.43E+02	6.79E+00
6.05E-01	6.59E+02	8.67E+02	6.93E+00
6.23E-01	6.72E+02	8.91E+02	7.07E+00
6.42E-01	6.86E+02	9.16E+02	7.22E+00
6.61E-01	7.00E+02	9.42E+02	7.37E+00
6.81E-01	7.14E+02	9.68E+02	7.52E+00
7.02E-01	7.29E+02	9.95E+02	7.67E+00
7.23E-01	7.44E+02	1.02E+03	7.83E+00
7.44E-01	7.59E+02	1.05E+03	7.99E+00
7.67E-01	7.75E+02	1.08E+03	8.15E+00
7.90E-01	7.91E+02	1.11E+03	8.32E+00
8.13E-01	8.07E+02	1.14E+03	8.49E+00

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
8.38E-01	8.24E+02	1.18E+03	8.67E+00
8.63E-01	8.41E+02	1.21E+03	8.85E+00
8.89E-01	8.58E+02	1.24E+03	9.03E+00
9.16E-01	8.76E+02	1.28E+03	9.22E+00
9.43E-01	8.94E+02	1.31E+03	9.41E+00
9.71E-01	9.13E+02	1.35E+03	9.60E+00
1.00E+00	9.32E+02	1.39E+03	9.80E+00
1.03E+00	9.51E+02	1.43E+03	1.00E+01
1.06E+00	9.71E+02	1.47E+03	1.02E+01
1.09E+00	9.91E+02	1.51E+03	1.04E+01
1.13E+00	1.01E+03	1.55E+03	1.06E+01
1.16E+00	1.03E+03	1.60E+03	1.09E+01
1.19E+00	1.05E+03	1.64E+03	1.11E+01
1.23E+00	1.08E+03	1.69E+03	1.13E+01
1.27E+00	1.10E+03	1.74E+03	1.16E+01
1.31E+00	1.12E+03	1.79E+03	1.18E+01
1.34E+00	1.15E+03	1.84E+03	1.21E+01
1.38E+00	1.17E+03	1.89E+03	1.23E+01
1.43E+00	1.20E+03	1.94E+03	1.26E+01
1.47E+00	1.22E+03	2.00E+03	1.29E+01
1.51E+00	1.25E+03	2.06E+03	1.31E+01
1.56E+00	1.27E+03	2.12E+03	1.34E+01
1.61E+00	1.30E+03	2.18E+03	1.37E+01
1.65E+00	1.33E+03	2.24E+03	1.40E+01
1.70E+00	1.36E+03	2.30E+03	1.43E+01
1.75E+00	1.39E+03	2.37E+03	1.46E+01
1.81E+00	1.42E+03	2.44E+03	1.49E+01
1.86E+00	1.45E+03	2.51E+03	1.52E+01
1.92E+00	1.48E+03	2.58E+03	1.56E+01
1.97E+00	1.51E+03	2.65E+03	1.59E+01
2.03E+00	1.54E+03	2.73E+03	1.62E+01
2.09E+00	1.58E+03	2.80E+03	1.66E+01
2.16E+00	1.61E+03	2.89E+03	1.70E+01
2.22E+00	1.65E+03	2.97E+03	1.73E+01
2.29E+00	1.68E+03	3.05E+03	1.77E+01
2.36E+00	1.72E+03	3.14E+03	1.81E+01
2.43E+00	1.76E+03	3.23E+03	1.85E+01

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
2.50E+00	1.80E+03	3.32E+03	1.89E+01
2.58E+00	1.84E+03	3.42E+03	1.93E+01
2.65E+00	1.88E+03	3.52E+03	1.97E+01
2.73E+00	1.92E+03	3.62E+03	2.02E+01
2.82E+00	1.96E+03	3.73E+03	2.06E+01
2.90E+00	2.00E+03	3.83E+03	2.11E+01
2.99E+00	2.05E+03	3.94E+03	2.16E+01
3.08E+00	2.09E+03	4.06E+03	2.20E+01
3.17E+00	2.14E+03	4.17E+03	2.25E+01
3.26E+00	2.19E+03	4.30E+03	2.30E+01
3.36E+00	2.24E+03	4.42E+03	2.36E+01
3.46E+00	2.29E+03	4.55E+03	2.41E+01
3.57E+00	2.34E+03	4.68E+03	2.46E+01
3.67E+00	2.39E+03	4.81E+03	2.52E+01
3.78E+00	2.45E+03	4.95E+03	2.58E+01
3.90E+00	2.51E+03	5.10E+03	2.64E+01
4.01E+00	2.56E+03	5.25E+03	2.70E+01
4.13E+00	2.62E+03	5.40E+03	2.76E+01
4.26E+00	2.68E+03	5.55E+03	2.82E+01
4.39E+00	2.74E+03	5.72E+03	2.89E+01
4.52E+00	2.81E+03	5.88E+03	2.95E+01
4.65E+00	2.87E+03	6.05E+03	3.02E+01
4.79E+00	2.94E+03	6.23E+03	3.09E+01
4.94E+00	3.01E+03	6.41E+03	3.16E+01
5.08E+00	3.08E+03	6.60E+03	3.24E+01
5.24E+00	3.15E+03	6.79E+03	3.31E+01
5.39E+00	3.22E+03	6.99E+03	3.39E+01
5.56E+00	3.30E+03	7.19E+03	3.47E+01
5.72E+00	3.38E+03	7.40E+03	3.55E+01
5.89E+00	3.46E+03	7.61E+03	3.64E+01
6.07E+00	3.54E+03	7.84E+03	3.72E+01
6.25E+00	3.62E+03	8.07E+03	3.81E+01
6.44E+00	3.71E+03	8.30E+03	3.90E+01
6.63E+00	3.80E+03	8.54E+03	3.99E+01
6.83E+00	3.89E+03	8.79E+03	4.09E+01
7.04E+00	3.98E+03	9.05E+03	4.19E+01
7.25E+00	4.08E+03	9.31E+03	4.29E+01

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
7.47E+00	4.18E+03	9.59E+03	4.39E+01
7.69E+00	4.28E+03	9.87E+03	4.50E+01
7.92E+00	4.38E+03	1.02E+04	4.61E+01
8.16E+00	4.49E+03	1.05E+04	4.72E+01
8.40E+00	4.60E+03	1.08E+04	4.84E+01
8.66E+00	4.71E+03	1.11E+04	4.95E+01
8.92E+00	4.82E+03	1.14E+04	5.08E+01
9.18E+00	4.94E+03	1.17E+04	5.20E+01
9.46E+00	5.07E+03	1.21E+04	5.33E+01
9.74E+00	5.19E+03	1.24E+04	5.46E+01
1.00E+01	5.32E+03	1.28E+04	5.60E+01
1.06E+01	5.58E+03	1.35E+04	5.88E+01
1.13E+01	5.86E+03	1.43E+04	6.17E+01
1.20E+01	6.16E+03	1.52E+04	6.48E+01
1.27E+01	6.47E+03	1.61E+04	6.81E+01
1.34E+01	6.80E+03	1.70E+04	7.15E+01
1.42E+01	7.14E+03	1.80E+04	7.52E+01
1.51E+01	7.51E+03	1.91E+04	7.90E+01
1.60E+01	7.90E+03	2.02E+04	8.31E+01
1.70E+01	8.31E+03	2.14E+04	8.74E+01
1.80E+01	8.74E+03	2.26E+04	9.20E+01
1.90E+01	9.20E+03	2.40E+04	9.68E+01
2.02E+01	9.68E+03	2.54E+04	1.02E+02
2.14E+01	1.02E+04	2.69E+04	1.07E+02
2.27E+01	1.07E+04	2.85E+04	1.13E+02
2.40E+01	1.13E+04	3.01E+04	1.19E+02
2.55E+01	1.19E+04	3.19E+04	1.25E+02
2.70E+01	1.26E+04	3.38E+04	1.32E+02
2.86E+01	1.32E+04	3.58E+04	1.39E+02
3.04E+01	1.40E+04	3.79E+04	1.47E+02
3.22E+01	1.47E+04	4.01E+04	1.55E+02
3.41E+01	1.55E+04	4.25E+04	1.63E+02
3.62E+01	1.64E+04	4.50E+04	1.72E+02
3.83E+01	1.73E+04	4.77E+04	1.82E+02
4.06E+01	1.82E+04	5.05E+04	1.92E+02
4.31E+01	1.92E+04	5.34E+04	2.02E+02
4.57E+01	2.03E+04	5.66E+04	2.14E+02

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body burden (ng/kg)	Blood (ng/kg)
4.84E+01	2.14E+04	5.99E+04	2.26E+02
5.13E+01	2.27E+04	6.34E+04	2.38E+02
5.44E+01	2.39E+04	6.71E+04	2.52E+02
5.76E+01	2.53E+04	7.11E+04	2.66E+02
6.11E+01	2.67E+04	7.52E+04	2.81E+02
6.48E+01	2.82E+04	7.97E+04	2.97E+02
6.86E+01	2.98E+04	8.43E+04	3.14E+02
7.28E+01	3.15E+04	8.93E+04	3.32E+02
7.71E+01	3.33E+04	9.45E+04	3.51E+02
8.18E+01	3.53E+04	1.00E+05	3.71E+02
8.67E+01	3.73E+04	1.06E+05	3.92E+02
9.19E+01	3.94E+04	1.12E+05	4.15E+02
9.74E+01	4.17E+04	1.19E+05	4.39E+02
1.03E+02	4.41E+04	1.25E+05	4.64E+02
1.09E+02	4.67E+04	1.33E+05	4.91E+02
1.16E+02	4.94E+04	1.40E+05	5.20E+02
1.23E+02	5.23E+04	1.48E+05	5.50E+02
1.30E+02	5.54E+04	1.57E+05	5.82E+02
1.38E+02	5.86E+04	1.66E+05	6.17E+02
1.46E+02	6.20E+04	1.76E+05	6.53E+02

E.4.2. Nongestational 5-Year Peak Average

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.03E-09	6.14E-05	1.92E-05	6.46E-07
1.09E-09	6.51E-05	2.03E-05	6.85E-07
1.16E-09	6.90E-05	2.15E-05	7.26E-07
1.23E-09	7.32E-05	2.28E-05	7.69E-07
1.30E-09	7.75E-05	2.42E-05	8.15E-07
1.38E-09	8.22E-05	2.56E-05	8.64E-07
1.46E-09	8.71E-05	2.72E-05	9.16E-07
1.55E-09	9.23E-05	2.88E-05	9.71E-07
1.64E-09	9.79E-05	3.05E-05	1.03E-06
1.74E-09	1.04E-04	3.24E-05	1.09E-06
1.84E-09	1.10E-04	3.43E-05	1.16E-06
1.95E-09	1.17E-04	3.64E-05	1.23E-06
2.07E-09	1.24E-04	3.85E-05	1.30E-06
2.20E-09	1.31E-04	4.08E-05	1.38E-06
2.33E-09	1.39E-04	4.33E-05	1.46E-06
2.47E-09	1.47E-04	4.59E-05	1.55E-06
2.62E-09	1.56E-04	4.86E-05	1.64E-06
2.77E-09	1.65E-04	5.15E-05	1.74E-06
2.94E-09	1.75E-04	5.46E-05	1.84E-06
3.12E-09	1.86E-04	5.79E-05	1.95E-06
3.30E-09	1.97E-04	6.14E-05	2.07E-06
3.50E-09	2.09E-04	6.51E-05	2.19E-06
3.71E-09	2.21E-04	6.90E-05	2.32E-06
3.93E-09	2.34E-04	7.31E-05	2.46E-06
4.17E-09	2.48E-04	7.75E-05	2.61E-06
4.42E-09	2.63E-04	8.21E-05	2.77E-06
4.68E-09	2.79E-04	8.70E-05	2.93E-06
4.97E-09	2.96E-04	9.22E-05	3.11E-06
5.26E-09	3.13E-04	9.78E-05	3.29E-06
5.58E-09	3.32E-04	1.04E-04	3.49E-06
5.91E-09	3.52E-04	1.10E-04	3.70E-06
6.27E-09	3.73E-04	1.16E-04	3.92E-06
6.65E-09	3.95E-04	1.23E-04	4.16E-06

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.04E-09	4.19E-04	1.31E-04	4.41E-06
7.47E-09	4.44E-04	1.39E-04	4.67E-06
7.92E-09	4.71E-04	1.47E-04	4.95E-06
8.39E-09	4.99E-04	1.56E-04	5.24E-06
8.89E-09	5.29E-04	1.65E-04	5.56E-06
9.43E-09	5.60E-04	1.75E-04	5.89E-06
9.99E-09	5.94E-04	1.85E-04	6.24E-06
1.06E-08	6.29E-04	1.96E-04	6.62E-06
1.12E-08	6.67E-04	2.08E-04	7.01E-06
1.19E-08	7.07E-04	2.21E-04	7.43E-06
1.26E-08	7.49E-04	2.34E-04	7.88E-06
1.34E-08	7.94E-04	2.48E-04	8.35E-06
1.42E-08	8.41E-04	2.63E-04	8.84E-06
1.50E-08	8.91E-04	2.78E-04	9.37E-06
1.59E-08	9.45E-04	2.95E-04	9.93E-06
1.69E-08	1.00E-03	3.13E-04	1.05E-05
1.79E-08	1.06E-03	3.31E-04	1.12E-05
1.90E-08	1.12E-03	3.51E-04	1.18E-05
2.01E-08	1.19E-03	3.72E-04	1.25E-05
2.13E-08	1.26E-03	3.94E-04	1.33E-05
2.26E-08	1.34E-03	4.18E-04	1.41E-05
2.39E-08	1.42E-03	4.43E-04	1.49E-05
2.54E-08	1.50E-03	4.69E-04	1.58E-05
2.69E-08	1.59E-03	4.97E-04	1.67E-05
2.85E-08	1.69E-03	5.27E-04	1.77E-05
3.02E-08	1.79E-03	5.58E-04	1.88E-05
3.20E-08	1.89E-03	5.92E-04	1.99E-05
3.40E-08	2.01E-03	6.27E-04	2.11E-05
3.60E-08	2.13E-03	6.64E-04	2.24E-05
3.82E-08	2.25E-03	7.04E-04	2.37E-05
4.05E-08	2.39E-03	7.46E-04	2.51E-05
4.29E-08	2.53E-03	7.91E-04	2.66E-05
4.55E-08	2.68E-03	8.38E-04	2.82E-05
4.82E-08	2.84E-03	8.88E-04	2.99E-05
5.11E-08	3.01E-03	9.40E-04	3.16E-05
5.41E-08	3.19E-03	9.96E-04	3.35E-05

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
5.74E-08	3.38E-03	1.06E-03	3.55E-05
6.08E-08	3.58E-03	1.12E-03	3.76E-05
6.45E-08	3.79E-03	1.19E-03	3.99E-05
6.84E-08	4.02E-03	1.26E-03	4.22E-05
7.25E-08	4.25E-03	1.33E-03	4.47E-05
7.68E-08	4.51E-03	1.41E-03	4.74E-05
8.14E-08	4.77E-03	1.49E-03	5.02E-05
8.63E-08	5.06E-03	1.58E-03	5.32E-05
9.15E-08	5.36E-03	1.68E-03	5.63E-05
9.70E-08	5.67E-03	1.78E-03	5.97E-05
1.03E-07	6.01E-03	1.88E-03	6.32E-05
1.09E-07	6.37E-03	1.99E-03	6.69E-05
1.15E-07	6.74E-03	2.11E-03	7.09E-05
1.22E-07	7.14E-03	2.24E-03	7.51E-05
1.30E-07	7.56E-03	2.37E-03	7.95E-05
1.38E-07	8.01E-03	2.51E-03	8.42E-05
1.46E-07	8.48E-03	2.66E-03	8.92E-05
1.55E-07	8.98E-03	2.82E-03	9.45E-05
1.64E-07	9.51E-03	2.98E-03	1.00E-04
1.74E-07	1.01E-02	3.16E-03	1.06E-04
1.84E-07	1.07E-02	3.34E-03	1.12E-04
1.95E-07	1.13E-02	3.54E-03	1.19E-04
2.07E-07	1.20E-02	3.75E-03	1.26E-04
2.19E-07	1.27E-02	3.97E-03	1.33E-04
2.32E-07	1.34E-02	4.21E-03	1.41E-04
2.46E-07	1.42E-02	4.46E-03	1.49E-04
2.61E-07	1.50E-02	4.72E-03	1.58E-04
2.77E-07	1.59E-02	5.00E-03	1.67E-04
2.93E-07	1.68E-02	5.29E-03	1.77E-04
3.11E-07	1.78E-02	5.60E-03	1.87E-04
3.30E-07	1.89E-02	5.93E-03	1.98E-04
3.49E-07	2.00E-02	6.28E-03	2.10E-04
3.70E-07	2.11E-02	6.65E-03	2.22E-04
3.93E-07	2.24E-02	7.04E-03	2.35E-04
4.16E-07	2.37E-02	7.45E-03	2.49E-04
4.41E-07	2.51E-02	7.89E-03	2.63E-04

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.68E-07	2.65E-02	8.35E-03	2.79E-04
4.96E-07	2.81E-02	8.83E-03	2.95E-04
5.25E-07	2.97E-02	9.35E-03	3.12E-04
5.57E-07	3.14E-02	9.90E-03	3.30E-04
5.90E-07	3.32E-02	1.05E-02	3.49E-04
6.26E-07	3.51E-02	1.11E-02	3.69E-04
6.63E-07	3.72E-02	1.17E-02	3.91E-04
7.03E-07	3.93E-02	1.24E-02	4.13E-04
7.45E-07	4.16E-02	1.31E-02	4.37E-04
7.90E-07	4.40E-02	1.39E-02	4.62E-04
8.37E-07	4.65E-02	1.47E-02	4.89E-04
8.88E-07	4.92E-02	1.55E-02	5.17E-04
9.41E-07	5.20E-02	1.64E-02	5.47E-04
9.97E-07	5.50E-02	1.74E-02	5.78E-04
1.01E-06	5.57E-02	1.76E-02	5.86E-04
1.03E-06	5.65E-02	1.79E-02	5.94E-04
1.04E-06	5.73E-02	1.82E-02	6.03E-04
1.06E-06	5.82E-02	1.84E-02	6.11E-04
1.07E-06	5.90E-02	1.87E-02	6.20E-04
1.09E-06	5.98E-02	1.89E-02	6.29E-04
1.11E-06	6.07E-02	1.92E-02	6.38E-04
1.12E-06	6.15E-02	1.95E-02	6.47E-04
1.14E-06	6.24E-02	1.98E-02	6.56E-04
1.16E-06	6.33E-02	2.00E-02	6.65E-04
1.17E-06	6.42E-02	2.03E-02	6.75E-04
1.19E-06	6.51E-02	2.06E-02	6.84E-04
1.21E-06	6.60E-02	2.09E-02	6.94E-04
1.23E-06	6.69E-02	2.12E-02	7.04E-04
1.24E-06	6.79E-02	2.15E-02	7.13E-04
1.26E-06	6.88E-02	2.18E-02	7.24E-04
1.28E-06	6.98E-02	2.21E-02	7.34E-04
1.30E-06	7.08E-02	2.25E-02	7.44E-04
1.32E-06	7.18E-02	2.28E-02	7.55E-04
1.34E-06	7.28E-02	2.31E-02	7.65E-04
1.36E-06	7.38E-02	2.34E-02	7.76E-04
1.38E-06	7.49E-02	2.38E-02	7.87E-04

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.40E-06	7.59E-02	2.41E-02	7.98E-04
1.42E-06	7.70E-02	2.44E-02	8.09E-04
1.44E-06	7.81E-02	2.48E-02	8.21E-04
1.46E-06	7.92E-02	2.51E-02	8.32E-04
1.49E-06	8.03E-02	2.55E-02	8.44E-04
1.53E-06	8.25E-02	2.62E-02	8.68E-04
1.58E-06	8.49E-02	2.70E-02	8.92E-04
1.62E-06	8.73E-02	2.77E-02	9.17E-04
1.67E-06	8.97E-02	2.85E-02	9.43E-04
1.72E-06	9.23E-02	2.93E-02	9.70E-04
1.77E-06	9.48E-02	3.02E-02	9.97E-04
1.83E-06	9.75E-02	3.10E-02	1.02E-03
1.88E-06	1.00E-01	3.19E-02	1.05E-03
1.94E-06	1.03E-01	3.28E-02	1.08E-03
2.00E-06	1.06E-01	3.38E-02	1.11E-03
2.06E-06	1.09E-01	3.47E-02	1.14E-03
2.12E-06	1.12E-01	3.57E-02	1.18E-03
2.18E-06	1.15E-01	3.67E-02	1.21E-03
2.25E-06	1.18E-01	3.77E-02	1.24E-03
2.32E-06	1.22E-01	3.88E-02	1.28E-03
2.39E-06	1.25E-01	3.99E-02	1.31E-03
2.46E-06	1.28E-01	4.10E-02	1.35E-03
2.53E-06	1.32E-01	4.22E-02	1.39E-03
2.61E-06	1.36E-01	4.34E-02	1.43E-03
2.68E-06	1.39E-01	4.46E-02	1.47E-03
2.76E-06	1.43E-01	4.58E-02	1.51E-03
2.85E-06	1.47E-01	4.71E-02	1.55E-03
2.93E-06	1.51E-01	4.84E-02	1.59E-03
3.02E-06	1.55E-01	4.98E-02	1.63E-03
3.11E-06	1.60E-01	5.12E-02	1.68E-03
3.21E-06	1.64E-01	5.26E-02	1.73E-03
3.30E-06	1.69E-01	5.41E-02	1.77E-03
3.40E-06	1.73E-01	5.56E-02	1.82E-03
3.50E-06	1.78E-01	5.71E-02	1.87E-03
3.61E-06	1.83E-01	5.87E-02	1.92E-03
3.72E-06	1.88E-01	6.04E-02	1.97E-03

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.83E-06	1.93E-01	6.20E-02	2.03E-03
3.94E-06	1.98E-01	6.38E-02	2.08E-03
4.06E-06	2.04E-01	6.55E-02	2.14E-03
4.18E-06	2.09E-01	6.73E-02	2.20E-03
4.31E-06	2.15E-01	6.92E-02	2.26E-03
4.44E-06	2.21E-01	7.11E-02	2.32E-03
4.57E-06	2.27E-01	7.31E-02	2.38E-03
4.71E-06	2.33E-01	7.51E-02	2.45E-03
4.85E-06	2.39E-01	7.71E-02	2.51E-03
4.99E-06	2.45E-01	7.92E-02	2.58E-03
5.14E-06	2.52E-01	8.14E-02	2.65E-03
5.30E-06	2.59E-01	8.36E-02	2.72E-03
5.46E-06	2.66E-01	8.59E-02	2.79E-03
5.62E-06	2.73E-01	8.83E-02	2.87E-03
5.79E-06	2.80E-01	9.07E-02	2.94E-03
5.96E-06	2.87E-01	9.31E-02	3.02E-03
6.14E-06	2.95E-01	9.57E-02	3.10E-03
6.33E-06	3.03E-01	9.83E-02	3.18E-03
6.52E-06	3.11E-01	1.01E-01	3.27E-03
6.71E-06	3.19E-01	1.04E-01	3.35E-03
6.91E-06	3.28E-01	1.06E-01	3.44E-03
7.12E-06	3.36E-01	1.09E-01	3.53E-03
7.33E-06	3.45E-01	1.12E-01	3.63E-03
7.55E-06	3.54E-01	1.15E-01	3.72E-03
7.78E-06	3.63E-01	1.18E-01	3.82E-03
8.01E-06	3.73E-01	1.22E-01	3.92E-03
8.25E-06	3.83E-01	1.25E-01	4.02E-03
8.50E-06	3.93E-01	1.28E-01	4.12E-03
8.76E-06	4.03E-01	1.32E-01	4.23E-03
9.02E-06	4.13E-01	1.35E-01	4.34E-03
9.29E-06	4.24E-01	1.39E-01	4.45E-03
9.57E-06	4.35E-01	1.42E-01	4.57E-03
9.86E-06	4.46E-01	1.46E-01	4.69E-03
1.02E-05	4.58E-01	1.50E-01	4.81E-03
1.05E-05	4.69E-01	1.54E-01	4.93E-03
1.08E-05	4.81E-01	1.58E-01	5.06E-03

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.11E-05	4.94E-01	1.62E-01	5.19E-03
1.14E-05	5.06E-01	1.67E-01	5.32E-03
1.18E-05	5.19E-01	1.71E-01	5.45E-03
1.21E-05	5.32E-01	1.75E-01	5.59E-03
1.25E-05	5.46E-01	1.80E-01	5.74E-03
1.29E-05	5.60E-01	1.85E-01	5.88E-03
1.32E-05	5.74E-01	1.90E-01	6.03E-03
1.36E-05	5.88E-01	1.94E-01	6.18E-03
1.41E-05	6.03E-01	1.99E-01	6.34E-03
1.45E-05	6.18E-01	2.05E-01	6.49E-03
1.49E-05	6.34E-01	2.10E-01	6.66E-03
1.54E-05	6.49E-01	2.15E-01	6.82E-03
1.58E-05	6.66E-01	2.21E-01	6.99E-03
1.63E-05	6.82E-01	2.27E-01	7.17E-03
1.68E-05	6.99E-01	2.32E-01	7.34E-03
1.73E-05	7.16E-01	2.38E-01	7.53E-03
1.78E-05	7.34E-01	2.45E-01	7.71E-03
1.83E-05	7.52E-01	2.51E-01	7.90E-03
1.89E-05	7.71E-01	2.57E-01	8.09E-03
1.95E-05	7.89E-01	2.64E-01	8.29E-03
2.00E-05	8.09E-01	2.70E-01	8.50E-03
2.06E-05	8.29E-01	2.77E-01	8.70E-03
2.13E-05	8.49E-01	2.84E-01	8.91E-03
2.19E-05	8.69E-01	2.91E-01	9.13E-03
2.25E-05	8.90E-01	2.99E-01	9.35E-03
2.32E-05	9.12E-01	3.06E-01	9.58E-03
2.39E-05	9.34E-01	3.14E-01	9.81E-03
2.46E-05	9.56E-01	3.22E-01	1.00E-02
2.54E-05	9.79E-01	3.30E-01	1.03E-02
2.61E-05	1.00E+00	3.38E-01	1.05E-02
2.69E-05	1.03E+00	3.47E-01	1.08E-02
2.77E-05	1.05E+00	3.55E-01	1.10E-02
2.86E-05	1.08E+00	3.64E-01	1.13E-02
2.94E-05	1.10E+00	3.73E-01	1.16E-02
3.03E-05	1.13E+00	3.82E-01	1.18E-02
3.12E-05	1.15E+00	3.92E-01	1.21E-02

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.21E-05	1.18E+00	4.02E-01	1.24E-02
3.31E-05	1.21E+00	4.11E-01	1.27E-02
3.41E-05	1.24E+00	4.22E-01	1.30E-02
3.51E-05	1.27E+00	4.32E-01	1.33E-02
3.62E-05	1.30E+00	4.43E-01	1.36E-02
3.73E-05	1.33E+00	4.54E-01	1.39E-02
3.84E-05	1.36E+00	4.65E-01	1.43E-02
3.95E-05	1.39E+00	4.76E-01	1.46E-02
4.07E-05	1.42E+00	4.87E-01	1.49E-02
4.19E-05	1.45E+00	4.99E-01	1.53E-02
4.32E-05	1.49E+00	5.11E-01	1.56E-02
4.45E-05	1.52E+00	5.24E-01	1.60E-02
4.58E-05	1.56E+00	5.36E-01	1.63E-02
4.72E-05	1.59E+00	5.49E-01	1.67E-02
4.86E-05	1.63E+00	5.62E-01	1.71E-02
5.01E-05	1.66E+00	5.76E-01	1.75E-02
5.16E-05	1.70E+00	5.89E-01	1.79E-02
5.31E-05	1.74E+00	6.04E-01	1.83E-02
5.47E-05	1.78E+00	6.18E-01	1.87E-02
5.64E-05	1.82E+00	6.33E-01	1.91E-02
5.81E-05	1.86E+00	6.48E-01	1.95E-02
5.98E-05	1.90E+00	6.63E-01	2.00E-02
6.16E-05	1.94E+00	6.79E-01	2.04E-02
6.34E-05	1.99E+00	6.95E-01	2.09E-02
6.54E-05	2.03E+00	7.11E-01	2.13E-02
6.73E-05	2.08E+00	7.28E-01	2.18E-02
6.93E-05	2.12E+00	7.45E-01	2.23E-02
7.14E-05	2.17E+00	7.62E-01	2.28E-02
7.36E-05	2.22E+00	7.80E-01	2.33E-02
7.58E-05	2.26E+00	7.98E-01	2.38E-02
7.80E-05	2.31E+00	8.17E-01	2.43E-02
8.04E-05	2.36E+00	8.36E-01	2.48E-02
8.28E-05	2.42E+00	8.55E-01	2.54E-02
8.53E-05	2.47E+00	8.75E-01	2.59E-02
8.78E-05	2.52E+00	8.95E-01	2.65E-02
9.05E-05	2.58E+00	9.16E-01	2.70E-02

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
9.32E-05	2.63E+00	9.37E-01	2.76E-02
9.60E-05	2.69E+00	9.58E-01	2.82E-02
9.89E-05	2.75E+00	9.81E-01	2.88E-02
1.02E-04	2.81E+00	1.00E+00	2.95E-02
1.05E-04	2.87E+00	1.03E+00	3.01E-02
1.08E-04	2.93E+00	1.05E+00	3.07E-02
1.11E-04	2.99E+00	1.07E+00	3.14E-02
1.15E-04	3.05E+00	1.10E+00	3.20E-02
1.18E-04	3.12E+00	1.12E+00	3.27E-02
1.22E-04	3.18E+00	1.15E+00	3.34E-02
1.25E-04	3.25E+00	1.17E+00	3.41E-02
1.29E-04	3.32E+00	1.20E+00	3.48E-02
1.33E-04	3.39E+00	1.23E+00	3.55E-02
1.37E-04	3.46E+00	1.26E+00	3.63E-02
1.41E-04	3.53E+00	1.28E+00	3.70E-02
1.45E-04	3.60E+00	1.31E+00	3.78E-02
1.50E-04	3.68E+00	1.34E+00	3.86E-02
1.54E-04	3.75E+00	1.37E+00	3.94E-02
1.59E-04	3.83E+00	1.40E+00	4.02E-02
1.63E-04	3.91E+00	1.43E+00	4.10E-02
1.68E-04	3.99E+00	1.47E+00	4.19E-02
1.73E-04	4.07E+00	1.50E+00	4.27E-02
1.79E-04	4.16E+00	1.53E+00	4.36E-02
1.84E-04	4.24E+00	1.57E+00	4.45E-02
1.89E-04	4.33E+00	1.60E+00	4.55E-02
1.95E-04	4.42E+00	1.64E+00	4.64E-02
2.01E-04	4.51E+00	1.67E+00	4.73E-02
2.07E-04	4.60E+00	1.71E+00	4.83E-02
2.13E-04	4.69E+00	1.75E+00	4.93E-02
2.20E-04	4.79E+00	1.79E+00	5.03E-02
2.26E-04	4.89E+00	1.83E+00	5.13E-02
2.33E-04	4.99E+00	1.87E+00	5.23E-02
2.40E-04	5.09E+00	1.91E+00	5.34E-02
2.47E-04	5.19E+00	1.95E+00	5.45E-02
2.55E-04	5.29E+00	2.00E+00	5.56E-02
2.62E-04	5.40E+00	2.04E+00	5.67E-02

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
2.70E-04	5.51E+00	2.09E+00	5.78E-02
2.78E-04	5.62E+00	2.13E+00	5.90E-02
2.86E-04	5.73E+00	2.18E+00	6.01E-02
2.95E-04	5.85E+00	2.23E+00	6.13E-02
3.04E-04	5.96E+00	2.28E+00	6.26E-02
3.13E-04	6.08E+00	2.33E+00	6.38E-02
3.22E-04	6.20E+00	2.38E+00	6.51E-02
3.32E-04	6.32E+00	2.43E+00	6.63E-02
3.42E-04	6.45E+00	2.48E+00	6.76E-02
3.52E-04	6.57E+00	2.54E+00	6.90E-02
3.63E-04	6.70E+00	2.59E+00	7.03E-02
3.74E-04	6.84E+00	2.65E+00	7.17E-02
3.85E-04	6.97E+00	2.71E+00	7.32E-02
3.97E-04	7.11E+00	2.77E+00	7.46E-02
4.08E-04	7.25E+00	2.83E+00	7.61E-02
4.21E-04	7.39E+00	2.89E+00	7.76E-02
4.33E-04	7.54E+00	2.96E+00	7.91E-02
4.46E-04	7.68E+00	3.02E+00	8.06E-02
4.60E-04	7.83E+00	3.09E+00	8.22E-02
4.74E-04	7.99E+00	3.16E+00	8.38E-02
4.88E-04	8.15E+00	3.23E+00	8.55E-02
5.02E-04	8.30E+00	3.30E+00	8.71E-02
5.17E-04	8.47E+00	3.37E+00	8.88E-02
5.33E-04	8.63E+00	3.45E+00	9.06E-02
5.49E-04	8.80E+00	3.52E+00	9.23E-02
5.65E-04	8.97E+00	3.60E+00	9.41E-02
5.82E-04	9.14E+00	3.68E+00	9.59E-02
6.00E-04	9.32E+00	3.76E+00	9.78E-02
6.18E-04	9.50E+00	3.85E+00	9.97E-02
6.36E-04	9.68E+00	3.93E+00	1.02E-01
6.55E-04	9.87E+00	4.02E+00	1.04E-01
6.75E-04	1.01E+01	4.11E+00	1.06E-01
6.95E-04	1.03E+01	4.20E+00	1.08E-01
7.16E-04	1.05E+01	4.29E+00	1.10E-01
7.38E-04	1.07E+01	4.38E+00	1.12E-01
7.60E-04	1.09E+01	4.48E+00	1.14E-01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.83E-04	1.11E+01	4.58E+00	1.16E-01
8.06E-04	1.13E+01	4.68E+00	1.18E-01
8.30E-04	1.15E+01	4.78E+00	1.21E-01
8.55E-04	1.17E+01	4.89E+00	1.23E-01
8.81E-04	1.19E+01	5.00E+00	1.25E-01
9.07E-04	1.22E+01	5.11E+00	1.28E-01
9.21E-04	1.23E+01	5.16E+00	1.29E-01
9.35E-04	1.24E+01	5.22E+00	1.30E-01
9.49E-04	1.25E+01	5.28E+00	1.31E-01
9.63E-04	1.26E+01	5.34E+00	1.33E-01
9.69E-04	1.27E+01	5.36E+00	1.33E-01
9.77E-04	1.28E+01	5.40E+00	1.34E-01
9.84E-04	1.28E+01	5.42E+00	1.34E-01
9.91E-04	1.29E+01	5.45E+00	1.35E-01
9.98E-04	1.29E+01	5.48E+00	1.36E-01
1.01E-03	1.30E+01	5.51E+00	1.36E-01
1.02E-03	1.31E+01	5.58E+00	1.38E-01
1.04E-03	1.32E+01	5.64E+00	1.39E-01
1.05E-03	1.34E+01	5.70E+00	1.40E-01
1.07E-03	1.35E+01	5.76E+00	1.42E-01
1.08E-03	1.36E+01	5.82E+00	1.43E-01
1.10E-03	1.38E+01	5.89E+00	1.44E-01
1.12E-03	1.39E+01	5.95E+00	1.46E-01
1.13E-03	1.40E+01	6.02E+00	1.47E-01
1.15E-03	1.41E+01	6.09E+00	1.48E-01
1.17E-03	1.43E+01	6.15E+00	1.50E-01
1.18E-03	1.44E+01	6.22E+00	1.51E-01
1.20E-03	1.45E+01	6.29E+00	1.53E-01
1.22E-03	1.47E+01	6.36E+00	1.54E-01
1.24E-03	1.48E+01	6.43E+00	1.55E-01
1.26E-03	1.50E+01	6.50E+00	1.57E-01
1.27E-03	1.51E+01	6.57E+00	1.58E-01
1.29E-03	1.52E+01	6.64E+00	1.60E-01
1.31E-03	1.54E+01	6.72E+00	1.61E-01
1.33E-03	1.55E+01	6.79E+00	1.63E-01
1.35E-03	1.57E+01	6.87E+00	1.64E-01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.37E-03	1.58E+01	6.94E+00	1.66E-01
1.39E-03	1.60E+01	7.02E+00	1.68E-01
1.41E-03	1.61E+01	7.10E+00	1.69E-01
1.43E-03	1.63E+01	7.18E+00	1.71E-01
1.46E-03	1.64E+01	7.26E+00	1.72E-01
1.48E-03	1.66E+01	7.34E+00	1.74E-01
1.50E-03	1.67E+01	7.42E+00	1.76E-01
1.52E-03	1.69E+01	7.50E+00	1.77E-01
1.54E-03	1.71E+01	7.58E+00	1.79E-01
1.57E-03	1.72E+01	7.67E+00	1.81E-01
1.59E-03	1.75E+01	7.86E+00	1.84E-01
1.61E-03	1.80E+01	8.23E+00	1.89E-01
1.64E-03	1.83E+01	8.35E+00	1.92E-01
1.66E-03	1.85E+01	8.36E+00	1.94E-01
1.69E-03	1.87E+01	8.43E+00	1.96E-01
1.71E-03	1.90E+01	8.54E+00	2.00E-01
1.74E-03	1.90E+01	8.52E+00	1.99E-01
1.76E-03	1.86E+01	8.38E+00	1.95E-01
1.79E-03	1.87E+01	8.47E+00	1.96E-01
1.82E-03	1.89E+01	8.57E+00	1.98E-01
1.84E-03	1.91E+01	8.66E+00	2.00E-01
1.87E-03	1.93E+01	8.80E+00	2.03E-01
1.90E-03	1.98E+01	9.14E+00	2.07E-01
1.93E-03	2.02E+01	9.51E+00	2.12E-01
1.96E-03	2.03E+01	9.42E+00	2.13E-01
1.99E-03	2.05E+01	9.53E+00	2.15E-01
2.02E-03	2.09E+01	9.67E+00	2.19E-01
2.08E-03	2.10E+01	9.70E+00	2.20E-01
2.14E-03	2.09E+01	9.68E+00	2.20E-01
2.20E-03	2.13E+01	9.90E+00	2.24E-01
2.27E-03	2.17E+01	1.01E+01	2.28E-01
2.34E-03	2.21E+01	1.03E+01	2.32E-01
2.41E-03	2.26E+01	1.06E+01	2.37E-01
2.48E-03	2.30E+01	1.08E+01	2.41E-01
2.55E-03	2.34E+01	1.11E+01	2.45E-01
2.63E-03	2.38E+01	1.13E+01	2.50E-01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
2.71E-03	2.43E+01	1.16E+01	2.55E-01
2.79E-03	2.47E+01	1.18E+01	2.60E-01
2.87E-03	2.52E+01	1.21E+01	2.64E-01
2.96E-03	2.57E+01	1.24E+01	2.69E-01
3.05E-03	2.62E+01	1.26E+01	2.74E-01
3.14E-03	2.66E+01	1.29E+01	2.79E-01
3.23E-03	2.72E+01	1.33E+01	2.85E-01
3.33E-03	2.78E+01	1.36E+01	2.91E-01
3.43E-03	2.82E+01	1.38E+01	2.95E-01
3.53E-03	2.87E+01	1.41E+01	3.01E-01
3.64E-03	2.92E+01	1.45E+01	3.07E-01
3.75E-03	2.99E+01	1.49E+01	3.13E-01
3.81E-03	3.02E+01	1.51E+01	3.17E-01
3.86E-03	3.04E+01	1.52E+01	3.18E-01
3.98E-03	3.09E+01	1.54E+01	3.24E-01
4.10E-03	3.11E+01	1.55E+01	3.26E-01
4.22E-03	3.15E+01	1.58E+01	3.30E-01
4.35E-03	3.20E+01	1.61E+01	3.36E-01
4.48E-03	3.26E+01	1.65E+01	3.42E-01
4.61E-03	3.32E+01	1.69E+01	3.49E-01
4.75E-03	3.39E+01	1.73E+01	3.55E-01
4.89E-03	3.45E+01	1.77E+01	3.62E-01
5.04E-03	3.53E+01	1.83E+01	3.70E-01
5.19E-03	3.63E+01	1.91E+01	3.81E-01
5.35E-03	3.75E+01	1.96E+01	3.93E-01
5.51E-03	3.82E+01	2.01E+01	4.01E-01
5.67E-03	3.93E+01	2.08E+01	4.12E-01
5.84E-03	4.01E+01	2.13E+01	4.20E-01
5.93E-03	4.04E+01	2.15E+01	4.24E-01
6.02E-03	4.08E+01	2.18E+01	4.28E-01
6.20E-03	4.15E+01	2.22E+01	4.35E-01
6.38E-03	4.23E+01	2.28E+01	4.44E-01
6.57E-03	4.29E+01	2.31E+01	4.50E-01
6.77E-03	4.35E+01	2.35E+01	4.57E-01
6.98E-03	4.39E+01	2.39E+01	4.60E-01
7.18E-03	4.50E+01	2.47E+01	4.71E-01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.40E-03	4.58E+01	2.53E+01	4.80E-01
7.51E-03	4.63E+01	2.56E+01	4.85E-01
7.62E-03	4.68E+01	2.58E+01	4.90E-01
7.85E-03	4.76E+01	2.63E+01	4.99E-01
8.09E-03	4.83E+01	2.68E+01	5.06E-01
8.33E-03	4.91E+01	2.74E+01	5.15E-01
8.58E-03	5.00E+01	2.81E+01	5.24E-01
8.71E-03	5.05E+01	2.84E+01	5.29E-01
8.84E-03	5.09E+01	2.87E+01	5.34E-01
9.10E-03	5.19E+01	2.94E+01	5.44E-01
9.37E-03	5.28E+01	3.01E+01	5.54E-01
9.66E-03	5.38E+01	3.08E+01	5.64E-01
9.94E-03	5.48E+01	3.15E+01	5.75E-01
1.02E-02	5.58E+01	3.22E+01	5.85E-01
1.06E-02	5.68E+01	3.30E+01	5.96E-01
1.09E-02	5.79E+01	3.38E+01	6.07E-01
1.12E-02	5.91E+01	3.47E+01	6.20E-01
1.15E-02	6.03E+01	3.56E+01	6.32E-01
1.19E-02	6.14E+01	3.65E+01	6.44E-01
1.22E-02	6.24E+01	3.72E+01	6.54E-01
1.26E-02	6.37E+01	3.80E+01	6.67E-01
1.30E-02	6.50E+01	3.90E+01	6.82E-01
1.34E-02	6.61E+01	3.98E+01	6.93E-01
1.38E-02	6.74E+01	4.09E+01	7.07E-01
1.42E-02	6.88E+01	4.19E+01	7.21E-01
1.46E-02	7.02E+01	4.32E+01	7.36E-01
1.50E-02	7.15E+01	4.41E+01	7.49E-01
1.55E-02	7.28E+01	4.51E+01	7.63E-01
1.60E-02	7.42E+01	4.62E+01	7.78E-01
1.64E-02	7.54E+01	4.73E+01	7.91E-01
1.69E-02	7.69E+01	4.84E+01	8.06E-01
1.74E-02	7.82E+01	4.96E+01	8.20E-01
1.80E-02	7.96E+01	5.07E+01	8.34E-01
1.85E-02	8.10E+01	5.18E+01	8.49E-01
1.91E-02	8.24E+01	5.30E+01	8.64E-01
1.96E-02	8.45E+01	5.48E+01	8.86E-01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
2.02E-02	8.61E+01	5.60E+01	9.02E-01
2.08E-02	8.76E+01	5.73E+01	9.18E-01
2.14E-02	8.88E+01	5.84E+01	9.30E-01
2.21E-02	9.05E+01	5.98E+01	9.48E-01
2.28E-02	9.22E+01	6.13E+01	9.67E-01
2.34E-02	9.39E+01	6.28E+01	9.84E-01
2.41E-02	9.57E+01	6.43E+01	1.00E+00
2.49E-02	9.76E+01	6.60E+01	1.02E+00
2.56E-02	9.94E+01	6.76E+01	1.04E+00
2.64E-02	1.01E+02	6.93E+01	1.06E+00
2.72E-02	1.03E+02	7.10E+01	1.08E+00
2.80E-02	1.05E+02	7.26E+01	1.10E+00
2.88E-02	1.07E+02	7.44E+01	1.12E+00
2.97E-02	1.09E+02	7.62E+01	1.14E+00
3.06E-02	1.11E+02	7.80E+01	1.16E+00
3.15E-02	1.13E+02	7.99E+01	1.18E+00
3.24E-02	1.15E+02	8.19E+01	1.21E+00
3.34E-02	1.17E+02	8.39E+01	1.23E+00
3.44E-02	1.19E+02	8.60E+01	1.25E+00
3.54E-02	1.22E+02	8.81E+01	1.28E+00
3.65E-02	1.24E+02	9.03E+01	1.30E+00
3.76E-02	1.26E+02	9.26E+01	1.32E+00
3.87E-02	1.29E+02	9.49E+01	1.35E+00
3.99E-02	1.31E+02	9.73E+01	1.38E+00
4.11E-02	1.34E+02	9.97E+01	1.40E+00
4.23E-02	1.36E+02	1.02E+02	1.43E+00
4.36E-02	1.39E+02	1.05E+02	1.45E+00
4.49E-02	1.41E+02	1.07E+02	1.48E+00
4.63E-02	1.44E+02	1.10E+02	1.51E+00
4.76E-02	1.47E+02	1.13E+02	1.54E+00
4.91E-02	1.50E+02	1.16E+02	1.57E+00
5.05E-02	1.53E+02	1.19E+02	1.60E+00
5.21E-02	1.55E+02	1.22E+02	1.63E+00
5.36E-02	1.58E+02	1.24E+02	1.66E+00
5.52E-02	1.61E+02	1.28E+02	1.69E+00
5.69E-02	1.64E+02	1.31E+02	1.72E+00

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
5.86E-02	1.68E+02	1.35E+02	1.76E+00
6.03E-02	1.71E+02	1.38E+02	1.79E+00
6.22E-02	1.74E+02	1.41E+02	1.82E+00
6.40E-02	1.77E+02	1.44E+02	1.85E+00
6.59E-02	1.80E+02	1.48E+02	1.89E+00
6.79E-02	1.84E+02	1.52E+02	1.92E+00
7.00E-02	1.87E+02	1.56E+02	1.96E+00
7.21E-02	1.91E+02	1.60E+02	2.00E+00
7.42E-02	1.95E+02	1.64E+02	2.04E+00
7.64E-02	1.98E+02	1.68E+02	2.08E+00
7.87E-02	2.02E+02	1.73E+02	2.12E+00
8.11E-02	2.06E+02	1.77E+02	2.16E+00
8.35E-02	2.10E+02	1.82E+02	2.20E+00
8.60E-02	2.14E+02	1.87E+02	2.24E+00
8.86E-02	2.18E+02	1.92E+02	2.29E+00
9.13E-02	2.22E+02	1.96E+02	2.33E+00
9.40E-02	2.26E+02	2.01E+02	2.37E+00
9.68E-02	2.31E+02	2.07E+02	2.42E+00
9.97E-02	2.35E+02	2.12E+02	2.47E+00
1.03E-01	2.40E+02	2.18E+02	2.51E+00
1.06E-01	2.44E+02	2.23E+02	2.56E+00
1.09E-01	2.49E+02	2.29E+02	2.61E+00
1.12E-01	2.54E+02	2.35E+02	2.66E+00
1.16E-01	2.59E+02	2.41E+02	2.71E+00
1.19E-01	2.64E+02	2.48E+02	2.76E+00
1.23E-01	2.69E+02	2.54E+02	2.82E+00
1.26E-01	2.74E+02	2.60E+02	2.87E+00
1.30E-01	2.79E+02	2.67E+02	2.92E+00
1.34E-01	2.84E+02	2.74E+02	2.98E+00
1.38E-01	2.90E+02	2.81E+02	3.04E+00
1.42E-01	2.95E+02	2.89E+02	3.09E+00
1.46E-01	3.01E+02	2.96E+02	3.15E+00
1.51E-01	3.07E+02	3.04E+02	3.21E+00
1.55E-01	3.13E+02	3.12E+02	3.28E+00
1.60E-01	3.19E+02	3.20E+02	3.34E+00
1.65E-01	3.25E+02	3.29E+02	3.40E+00

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.70E-01	3.31E+02	3.37E+02	3.47E+00
1.75E-01	3.38E+02	3.46E+02	3.54E+00
1.80E-01	3.44E+02	3.55E+02	3.61E+00
1.86E-01	3.51E+02	3.65E+02	3.68E+00
1.91E-01	3.58E+02	3.75E+02	3.75E+00
1.97E-01	3.65E+02	3.85E+02	3.82E+00
2.03E-01	3.72E+02	3.95E+02	3.90E+00
2.09E-01	3.79E+02	4.05E+02	3.97E+00
2.15E-01	3.86E+02	4.16E+02	4.05E+00
2.22E-01	3.94E+02	4.27E+02	4.13E+00
2.28E-01	4.01E+02	4.39E+02	4.21E+00
2.35E-01	4.09E+02	4.50E+02	4.29E+00
2.42E-01	4.17E+02	4.62E+02	4.37E+00
2.49E-01	4.25E+02	4.74E+02	4.46E+00
2.57E-01	4.34E+02	4.87E+02	4.54E+00
2.65E-01	4.42E+02	5.00E+02	4.63E+00
2.72E-01	4.51E+02	5.14E+02	4.73E+00
2.81E-01	4.60E+02	5.28E+02	4.82E+00
2.89E-01	4.69E+02	5.42E+02	4.91E+00
2.98E-01	4.78E+02	5.56E+02	5.01E+00
3.07E-01	4.87E+02	5.71E+02	5.11E+00
3.16E-01	4.97E+02	5.87E+02	5.21E+00
3.25E-01	5.07E+02	6.03E+02	5.31E+00
3.35E-01	5.17E+02	6.19E+02	5.42E+00
3.45E-01	5.27E+02	6.36E+02	5.52E+00
3.56E-01	5.38E+02	6.53E+02	5.63E+00
3.66E-01	5.48E+02	6.71E+02	5.75E+00
3.77E-01	5.59E+02	6.89E+02	5.86E+00
3.89E-01	5.70E+02	7.08E+02	5.98E+00
4.00E-01	5.82E+02	7.27E+02	6.09E+00
4.12E-01	5.93E+02	7.47E+02	6.22E+00
4.25E-01	6.05E+02	7.67E+02	6.34E+00
4.37E-01	6.17E+02	7.88E+02	6.47E+00
4.50E-01	6.29E+02	8.10E+02	6.60E+00
4.64E-01	6.42E+02	8.32E+02	6.73E+00
4.78E-01	6.55E+02	8.55E+02	6.86E+00

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.92E-01	6.68E+02	8.78E+02	7.00E+00
5.07E-01	6.81E+02	9.02E+02	7.14E+00
5.22E-01	6.95E+02	9.26E+02	7.28E+00
5.38E-01	7.09E+02	9.52E+02	7.43E+00
5.54E-01	7.23E+02	9.78E+02	7.58E+00
5.71E-01	7.38E+02	1.01E+03	7.73E+00
5.88E-01	7.53E+02	1.03E+03	7.89E+00
6.05E-01	7.68E+02	1.06E+03	8.05E+00
6.23E-01	7.83E+02	1.09E+03	8.21E+00
6.42E-01	7.99E+02	1.12E+03	8.38E+00
6.61E-01	8.16E+02	1.15E+03	8.55E+00
6.81E-01	8.32E+02	1.18E+03	8.72E+00
7.02E-01	8.49E+02	1.22E+03	8.90E+00
7.23E-01	8.66E+02	1.25E+03	9.08E+00
7.44E-01	8.84E+02	1.28E+03	9.27E+00
7.67E-01	9.02E+02	1.32E+03	9.46E+00
7.90E-01	9.21E+02	1.36E+03	9.65E+00
8.13E-01	9.40E+02	1.39E+03	9.85E+00
8.38E-01	9.59E+02	1.43E+03	1.00E+01
8.63E-01	9.78E+02	1.47E+03	1.03E+01
8.89E-01	9.99E+02	1.51E+03	1.05E+01
9.16E-01	1.02E+03	1.56E+03	1.07E+01
9.43E-01	1.04E+03	1.60E+03	1.09E+01
9.71E-01	1.06E+03	1.64E+03	1.11E+01
1.00E+00	1.08E+03	1.69E+03	1.14E+01
1.03E+00	1.11E+03	1.74E+03	1.16E+01
1.06E+00	1.13E+03	1.79E+03	1.18E+01
1.09E+00	1.15E+03	1.84E+03	1.21E+01
1.13E+00	1.18E+03	1.89E+03	1.23E+01
1.16E+00	1.20E+03	1.94E+03	1.26E+01
1.19E+00	1.23E+03	1.99E+03	1.29E+01
1.23E+00	1.25E+03	2.05E+03	1.31E+01
1.27E+00	1.28E+03	2.11E+03	1.34E+01
1.31E+00	1.31E+03	2.17E+03	1.37E+01
1.34E+00	1.33E+03	2.23E+03	1.40E+01
1.38E+00	1.36E+03	2.29E+03	1.43E+01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.43E+00	1.39E+03	2.36E+03	1.46E+01
1.47E+00	1.42E+03	2.42E+03	1.49E+01
1.51E+00	1.45E+03	2.49E+03	1.52E+01
1.56E+00	1.48E+03	2.56E+03	1.55E+01
1.61E+00	1.51E+03	2.63E+03	1.59E+01
1.65E+00	1.55E+03	2.71E+03	1.62E+01
1.70E+00	1.58E+03	2.79E+03	1.66E+01
1.75E+00	1.61E+03	2.86E+03	1.69E+01
1.81E+00	1.65E+03	2.95E+03	1.73E+01
1.86E+00	1.68E+03	3.03E+03	1.77E+01
1.92E+00	1.72E+03	3.11E+03	1.80E+01
1.97E+00	1.76E+03	3.20E+03	1.84E+01
2.03E+00	1.80E+03	3.29E+03	1.88E+01
2.09E+00	1.84E+03	3.39E+03	1.92E+01
2.16E+00	1.88E+03	3.48E+03	1.97E+01
2.22E+00	1.92E+03	3.58E+03	2.01E+01
2.29E+00	1.96E+03	3.69E+03	2.05E+01
2.36E+00	2.00E+03	3.79E+03	2.10E+01
2.43E+00	2.05E+03	3.90E+03	2.14E+01
2.50E+00	2.09E+03	4.01E+03	2.19E+01
2.58E+00	2.14E+03	4.12E+03	2.24E+01
2.65E+00	2.19E+03	4.24E+03	2.29E+01
2.73E+00	2.23E+03	4.36E+03	2.34E+01
2.82E+00	2.28E+03	4.49E+03	2.39E+01
2.90E+00	2.33E+03	4.62E+03	2.45E+01
2.99E+00	2.39E+03	4.75E+03	2.50E+01
3.08E+00	2.44E+03	4.89E+03	2.56E+01
3.17E+00	2.50E+03	5.03E+03	2.62E+01
3.26E+00	2.55E+03	5.17E+03	2.67E+01
3.36E+00	2.61E+03	5.32E+03	2.74E+01
3.46E+00	2.67E+03	5.47E+03	2.80E+01
3.57E+00	2.73E+03	5.63E+03	2.86E+01
3.67E+00	2.79E+03	5.79E+03	2.93E+01
3.78E+00	2.86E+03	5.96E+03	2.99E+01
3.90E+00	2.92E+03	6.13E+03	3.06E+01
4.01E+00	2.99E+03	6.30E+03	3.13E+01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.13E+00	3.06E+03	6.49E+03	3.21E+01
4.26E+00	3.13E+03	6.67E+03	3.28E+01
4.39E+00	3.20E+03	6.87E+03	3.36E+01
4.52E+00	3.28E+03	7.06E+03	3.43E+01
4.65E+00	3.35E+03	7.27E+03	3.51E+01
4.79E+00	3.43E+03	7.48E+03	3.60E+01
4.94E+00	3.51E+03	7.69E+03	3.68E+01
5.08E+00	3.59E+03	7.92E+03	3.77E+01
5.24E+00	3.68E+03	8.15E+03	3.86E+01
5.39E+00	3.77E+03	8.38E+03	3.95E+01
5.56E+00	3.85E+03	8.62E+03	4.04E+01
5.72E+00	3.95E+03	8.87E+03	4.14E+01
5.89E+00	4.04E+03	9.13E+03	4.23E+01
6.07E+00	4.14E+03	9.40E+03	4.34E+01
6.25E+00	4.24E+03	9.67E+03	4.44E+01
6.44E+00	4.34E+03	9.95E+03	4.55E+01
6.63E+00	4.44E+03	1.02E+04	4.66E+01
6.83E+00	4.55E+03	1.05E+04	4.77E+01
7.04E+00	4.66E+03	1.08E+04	4.88E+01
7.25E+00	4.77E+03	1.12E+04	5.00E+01
7.47E+00	4.89E+03	1.15E+04	5.12E+01
7.69E+00	5.01E+03	1.18E+04	5.25E+01
7.92E+00	5.13E+03	1.22E+04	5.38E+01
8.16E+00	5.26E+03	1.25E+04	5.51E+01
8.40E+00	5.39E+03	1.29E+04	5.65E+01
8.66E+00	5.52E+03	1.33E+04	5.79E+01
8.92E+00	5.66E+03	1.36E+04	5.93E+01
9.18E+00	5.80E+03	1.40E+04	6.08E+01
9.46E+00	5.94E+03	1.44E+04	6.23E+01
9.74E+00	6.09E+03	1.49E+04	6.38E+01
1.00E+01	6.24E+03	1.53E+04	6.54E+01
1.06E+01	6.56E+03	1.62E+04	6.87E+01
1.13E+01	6.89E+03	1.71E+04	7.22E+01
1.20E+01	7.24E+03	1.81E+04	7.58E+01
1.27E+01	7.61E+03	1.92E+04	7.97E+01
1.34E+01	8.00E+03	2.03E+04	8.38E+01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.42E+01	8.41E+03	2.15E+04	8.81E+01
1.51E+01	8.84E+03	2.28E+04	9.27E+01
1.60E+01	9.30E+03	2.41E+04	9.75E+01
1.70E+01	9.79E+03	2.55E+04	1.03E+02
1.80E+01	1.03E+04	2.70E+04	1.08E+02
1.90E+01	1.09E+04	2.86E+04	1.14E+02
2.02E+01	1.14E+04	3.03E+04	1.20E+02
2.14E+01	1.20E+04	3.21E+04	1.26E+02
2.27E+01	1.27E+04	3.39E+04	1.33E+02
2.40E+01	1.34E+04	3.59E+04	1.40E+02
2.55E+01	1.41E+04	3.80E+04	1.48E+02
2.70E+01	1.49E+04	4.03E+04	1.56E+02
2.86E+01	1.57E+04	4.26E+04	1.64E+02
3.04E+01	1.65E+04	4.52E+04	1.73E+02
3.22E+01	1.74E+04	4.78E+04	1.83E+02
3.41E+01	1.84E+04	5.06E+04	1.93E+02
3.62E+01	1.94E+04	5.36E+04	2.03E+02
3.83E+01	2.05E+04	5.67E+04	2.15E+02
4.06E+01	2.16E+04	6.00E+04	2.27E+02
4.31E+01	2.28E+04	6.36E+04	2.39E+02
4.57E+01	2.41E+04	6.73E+04	2.53E+02
4.84E+01	2.55E+04	7.12E+04	2.67E+02
5.13E+01	2.69E+04	7.54E+04	2.82E+02
5.44E+01	2.84E+04	7.98E+04	2.98E+02
5.76E+01	3.00E+04	8.45E+04	3.15E+02
6.11E+01	3.17E+04	8.94E+04	3.33E+02
6.48E+01	3.36E+04	9.46E+04	3.52E+02
6.86E+01	3.55E+04	1.00E+05	3.72E+02
7.28E+01	3.75E+04	1.06E+05	3.93E+02
7.71E+01	3.97E+04	1.12E+05	4.16E+02
8.18E+01	4.20E+04	1.19E+05	4.40E+02
8.67E+01	4.44E+04	1.25E+05	4.65E+02
9.19E+01	4.69E+04	1.33E+05	4.92E+02
9.74E+01	4.97E+04	1.40E+05	5.20E+02
1.03E+02	5.25E+04	1.49E+05	5.51E+02
1.09E+02	5.56E+04	1.57E+05	5.83E+02

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
1.16E+02	5.88E+04	1.66E+05	6.17E+02
1.23E+02	6.23E+04	1.76E+05	6.53E+02
1.30E+02	6.59E+04	1.86E+05	6.91E+02
1.38E+02	6.97E+04	1.96E+05	7.31E+02
1.46E+02	7.38E+04	2.07E+05	7.74E+02

E.4.3. Gestational

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.03E-09	2.89E-05	1.14E-05	3.05E-07
1.09E-09	3.07E-05	1.21E-05	3.23E-07
1.16E-09	3.25E-05	1.28E-05	3.42E-07
1.23E-09	3.45E-05	1.36E-05	3.63E-07
1.30E-09	3.65E-05	1.44E-05	3.89E-07
1.38E-09	3.87E-05	1.53E-05	4.07E-07
1.46E-09	4.11E-05	1.62E-05	4.31E-07
1.55E-09	4.35E-05	1.71E-05	4.54E-07
1.64E-09	4.61E-05	1.82E-05	4.81E-07
1.74E-09	4.88E-05	1.92E-05	5.14E-07
1.84E-09	5.18E-05	2.04E-05	5.45E-07
1.95E-09	5.49E-05	2.16E-05	5.78E-07
2.07E-09	5.82E-05	2.29E-05	6.13E-07
2.20E-09	6.17E-05	2.43E-05	6.49E-07
2.33E-09	6.53E-05	2.58E-05	6.88E-07
2.47E-09	6.93E-05	2.73E-05	7.30E-07
2.62E-09	7.34E-05	2.89E-05	7.73E-07
2.77E-09	7.79E-05	3.07E-05	8.18E-07
2.94E-09	8.25E-05	3.25E-05	8.69E-07
3.12E-09	8.74E-05	3.45E-05	9.21E-07
3.30E-09	9.27E-05	3.65E-05	9.76E-07
3.50E-09	9.83E-05	3.88E-05	1.03E-06
3.71E-09	1.04E-04	4.11E-05	1.09E-06
3.93E-09	1.10E-04	4.35E-05	1.16E-06
4.17E-09	1.17E-04	4.61E-05	1.23E-06
4.42E-09	1.24E-04	4.89E-05	1.31E-06
4.68E-09	1.31E-04	5.18E-05	1.38E-06
4.97E-09	1.39E-04	5.49E-05	1.47E-06
5.26E-09	1.48E-04	5.83E-05	1.55E-06
5.58E-09	1.57E-04	6.18E-05	1.65E-06
5.91E-09	1.66E-04	6.55E-05	1.73E-06
6.27E-09	1.76E-04	6.93E-05	1.85E-06
6.65E-09	1.86E-04	7.35E-05	1.96E-06
7.04E-09	1.98E-04	7.79E-05	2.08E-06
7.47E-09	2.09E-04	8.26E-05	2.21E-06

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.92E-09	2.22E-04	8.75E-05	2.34E-06
8.39E-09	2.35E-04	9.27E-05	2.48E-06
8.89E-09	2.49E-04	9.83E-05	2.63E-06
9.43E-09	2.64E-04	1.04E-04	2.78E-06
9.99E-09	2.80E-04	1.10E-04	2.95E-06
1.06E-08	2.97E-04	1.17E-04	3.14E-06
1.12E-08	3.15E-04	1.24E-04	3.31E-06
1.19E-08	3.34E-04	1.32E-04	3.52E-06
1.26E-08	3.54E-04	1.40E-04	3.70E-06
1.34E-08	3.75E-04	1.48E-04	3.95E-06
1.42E-08	3.97E-04	1.57E-04	4.18E-06
1.50E-08	4.21E-04	1.66E-04	4.43E-06
1.59E-08	4.47E-04	1.76E-04	4.70E-06
1.69E-08	4.73E-04	1.86E-04	4.98E-06
1.79E-08	5.01E-04	1.98E-04	5.28E-06
1.90E-08	5.31E-04	2.10E-04	5.59E-06
2.01E-08	5.63E-04	2.22E-04	5.93E-06
2.13E-08	5.97E-04	2.35E-04	6.28E-06
2.26E-08	6.33E-04	2.49E-04	6.66E-06
2.39E-08	6.71E-04	2.65E-04	7.03E-06
2.54E-08	7.11E-04	2.80E-04	7.48E-06
2.69E-08	7.53E-04	2.97E-04	7.93E-06
2.85E-08	7.98E-04	3.15E-04	8.40E-06
3.02E-08	8.46E-04	3.34E-04	8.91E-06
3.20E-08	8.97E-04	3.54E-04	9.44E-06
3.40E-08	9.50E-04	3.75E-04	1.00E-05
3.60E-08	1.01E-03	3.97E-04	1.06E-05
3.82E-08	1.07E-03	4.21E-04	1.12E-05
4.05E-08	1.13E-03	4.46E-04	1.19E-05
4.29E-08	1.20E-03	4.73E-04	1.26E-05
4.55E-08	1.27E-03	5.01E-04	1.34E-05
4.82E-08	1.35E-03	5.31E-04	1.42E-05
5.11E-08	1.43E-03	5.63E-04	1.50E-05
5.41E-08	1.51E-03	5.97E-04	1.59E-05
5.74E-08	1.60E-03	6.32E-04	1.69E-05
6.08E-08	1.70E-03	6.70E-04	1.79E-05
6.45E-08	1.80E-03	7.10E-04	1.90E-05

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
6.84E-08	1.91E-03	7.53E-04	2.01E-05
7.25E-08	2.02E-03	7.98E-04	2.13E-05
7.68E-08	2.14E-03	8.45E-04	2.26E-05
8.14E-08	2.27E-03	8.96E-04	2.39E-05
8.63E-08	2.41E-03	9.50E-04	2.53E-05
9.15E-08	2.55E-03	1.01E-03	2.68E-05
9.70E-08	2.70E-03	1.07E-03	2.85E-05
1.03E-07	2.86E-03	1.13E-03	3.01E-05
1.09E-07	3.03E-03	1.20E-03	3.19E-05
1.15E-07	3.22E-03	1.27E-03	3.39E-05
1.22E-07	3.41E-03	1.35E-03	3.59E-05
1.30E-07	3.61E-03	1.43E-03	3.80E-05
1.38E-07	3.83E-03	1.51E-03	4.03E-05
1.46E-07	4.05E-03	1.60E-03	4.27E-05
1.55E-07	4.30E-03	1.70E-03	4.52E-05
1.64E-07	4.55E-03	1.80E-03	4.79E-05
1.74E-07	4.82E-03	1.90E-03	5.08E-05
1.84E-07	5.11E-03	2.02E-03	5.38E-05
1.95E-07	5.41E-03	2.14E-03	5.70E-05
2.07E-07	5.74E-03	2.27E-03	6.04E-05
2.19E-07	6.08E-03	2.40E-03	6.40E-05
2.32E-07	6.44E-03	2.54E-03	6.78E-05
2.46E-07	6.82E-03	2.70E-03	7.18E-05
2.61E-07	7.23E-03	2.86E-03	7.61E-05
2.77E-07	7.66E-03	3.03E-03	8.06E-05
2.93E-07	8.11E-03	3.21E-03	8.54E-05
3.11E-07	8.60E-03	3.40E-03	9.05E-05
3.30E-07	9.11E-03	3.60E-03	9.58E-05
3.49E-07	9.65E-03	3.82E-03	1.02E-04
3.70E-07	1.02E-02	4.04E-03	1.08E-04
3.93E-07	1.08E-02	4.28E-03	1.14E-04
4.16E-07	1.15E-02	4.54E-03	1.21E-04
4.41E-07	1.21E-02	4.81E-03	1.28E-04
4.68E-07	1.29E-02	5.09E-03	1.35E-04
4.96E-07	1.36E-02	5.39E-03	1.43E-04
5.25E-07	1.44E-02	5.72E-03	1.52E-04
5.57E-07	1.53E-02	6.05E-03	1.61E-04

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
5.90E-07	1.62E-02	6.41E-03	1.70E-04
6.26E-07	1.72E-02	6.79E-03	1.81E-04
6.63E-07	1.82E-02	7.20E-03	1.91E-04
7.03E-07	1.92E-02	7.62E-03	2.02E-04
7.45E-07	2.04E-02	8.08E-03	2.14E-04
7.90E-07	2.16E-02	8.55E-03	2.27E-04
8.37E-07	2.29E-02	9.06E-03	2.40E-04
8.88E-07	2.42E-02	9.60E-03	2.55E-04
9.41E-07	2.56E-02	1.02E-02	2.70E-04
9.97E-07	2.71E-02	1.08E-02	2.86E-04
1.01E-06	2.75E-02	1.09E-02	2.90E-04
1.03E-06	2.79E-02	1.11E-02	2.94E-04
1.04E-06	2.83E-02	1.12E-02	2.98E-04
1.06E-06	2.88E-02	1.14E-02	3.03E-04
1.07E-06	2.92E-02	1.16E-02	3.07E-04
1.09E-06	2.96E-02	1.17E-02	3.11E-04
1.11E-06	3.00E-02	1.19E-02	3.16E-04
1.12E-06	3.05E-02	1.21E-02	3.21E-04
1.14E-06	3.09E-02	1.23E-02	3.25E-04
1.16E-06	3.14E-02	1.24E-02	3.30E-04
1.17E-06	3.18E-02	1.26E-02	3.35E-04
1.19E-06	3.23E-02	1.28E-02	3.40E-04
1.21E-06	3.27E-02	1.30E-02	3.45E-04
1.23E-06	3.32E-02	1.32E-02	3.50E-04
1.24E-06	3.37E-02	1.34E-02	3.55E-04
1.26E-06	3.42E-02	1.36E-02	3.60E-04
1.28E-06	3.47E-02	1.38E-02	3.65E-04
1.30E-06	3.52E-02	1.40E-02	3.71E-04
1.32E-06	3.57E-02	1.42E-02	3.76E-04
1.34E-06	3.62E-02	1.44E-02	3.81E-04
1.36E-06	3.68E-02	1.46E-02	3.87E-04
1.38E-06	3.73E-02	1.48E-02	3.93E-04
1.40E-06	3.78E-02	1.50E-02	3.98E-04
1.42E-06	3.84E-02	1.53E-02	4.04E-04
1.44E-06	3.89E-02	1.55E-02	4.10E-04
1.46E-06	3.95E-02	1.57E-02	4.16E-04
1.49E-06	4.01E-02	1.59E-02	4.22E-04

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.53E-06	4.13E-02	1.64E-02	4.34E-04
1.58E-06	4.25E-02	1.69E-02	4.47E-04
1.62E-06	4.37E-02	1.74E-02	4.60E-04
1.67E-06	4.50E-02	1.79E-02	4.73E-04
1.72E-06	4.63E-02	1.84E-02	4.87E-04
1.77E-06	4.77E-02	1.90E-02	5.02E-04
1.83E-06	4.91E-02	1.95E-02	5.16E-04
1.88E-06	5.05E-02	2.01E-02	5.31E-04
1.94E-06	5.20E-02	2.07E-02	5.47E-04
2.00E-06	5.35E-02	2.13E-02	5.63E-04
2.06E-06	5.50E-02	2.19E-02	5.79E-04
2.12E-06	5.66E-02	2.26E-02	5.96E-04
2.18E-06	5.83E-02	2.32E-02	6.13E-04
2.25E-06	6.00E-02	2.39E-02	6.31E-04
2.32E-06	6.17E-02	2.46E-02	6.50E-04
2.39E-06	6.35E-02	2.53E-02	6.68E-04
2.46E-06	6.54E-02	2.61E-02	6.88E-04
2.53E-06	6.73E-02	2.68E-02	7.08E-04
2.61E-06	6.92E-02	2.76E-02	7.28E-04
2.68E-06	7.12E-02	2.84E-02	7.49E-04
2.76E-06	7.33E-02	2.92E-02	7.71E-04
2.85E-06	7.54E-02	3.01E-02	7.94E-04
2.93E-06	7.76E-02	3.10E-02	8.17E-04
3.02E-06	7.98E-02	3.19E-02	8.40E-04
3.11E-06	8.22E-02	3.28E-02	8.64E-04
3.21E-06	8.45E-02	3.38E-02	8.89E-04
3.30E-06	8.70E-02	3.47E-02	9.15E-04
3.40E-06	8.95E-02	3.57E-02	9.42E-04
3.50E-06	9.21E-02	3.68E-02	9.69E-04
3.61E-06	9.47E-02	3.79E-02	9.97E-04
3.72E-06	9.74E-02	3.90E-02	1.03E-03
3.83E-06	1.00E-01	4.01E-02	1.05E-03
3.94E-06	1.03E-01	4.13E-02	1.09E-03
4.06E-06	1.06E-01	4.25E-02	1.12E-03
4.18E-06	1.09E-01	4.37E-02	1.15E-03
4.31E-06	1.12E-01	4.49E-02	1.18E-03
4.44E-06	1.15E-01	4.63E-02	1.22E-03

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.57E-06	1.19E-01	4.76E-02	1.25E-03
4.71E-06	1.22E-01	4.90E-02	1.29E-03
4.85E-06	1.26E-01	5.04E-02	1.32E-03
4.99E-06	1.29E-01	5.18E-02	1.36E-03
5.14E-06	1.33E-01	5.33E-02	1.40E-03
5.30E-06	1.37E-01	5.49E-02	1.44E-03
5.46E-06	1.41E-01	5.64E-02	1.48E-03
5.62E-06	1.45E-01	5.81E-02	1.52E-03
5.79E-06	1.49E-01	5.97E-02	1.57E-03
5.96E-06	1.53E-01	6.15E-02	1.61E-03
6.14E-06	1.57E-01	6.32E-02	1.66E-03
6.33E-06	1.62E-01	6.51E-02	1.70E-03
6.52E-06	1.66E-01	6.69E-02	1.75E-03
6.71E-06	1.71E-01	6.88E-02	1.80E-03
6.91E-06	1.76E-01	7.08E-02	1.85E-03
7.12E-06	1.81E-01	7.29E-02	1.90E-03
7.33E-06	1.86E-01	7.49E-02	1.96E-03
7.55E-06	1.91E-01	7.71E-02	2.01E-03
7.78E-06	1.97E-01	7.93E-02	2.07E-03
8.01E-06	2.02E-01	8.16E-02	2.13E-03
8.25E-06	2.08E-01	8.39E-02	2.19E-03
8.50E-06	2.14E-01	8.63E-02	2.25E-03
8.76E-06	2.20E-01	8.88E-02	2.31E-03
9.02E-06	2.26E-01	9.13E-02	2.38E-03
9.29E-06	2.33E-01	9.39E-02	2.45E-03
9.57E-06	2.39E-01	9.66E-02	2.51E-03
9.86E-06	2.46E-01	9.93E-02	2.59E-03
1.02E-05	2.53E-01	1.02E-01	2.66E-03
1.05E-05	2.60E-01	1.05E-01	2.73E-03
1.08E-05	2.67E-01	1.08E-01	2.81E-03
1.11E-05	2.74E-01	1.11E-01	2.89E-03
1.14E-05	2.82E-01	1.14E-01	2.97E-03
1.18E-05	2.90E-01	1.17E-01	3.05E-03
1.21E-05	2.98E-01	1.21E-01	3.13E-03
1.25E-05	3.06E-01	1.24E-01	3.22E-03
1.29E-05	3.15E-01	1.28E-01	3.31E-03
1.32E-05	3.23E-01	1.31E-01	3.40E-03

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.36E-05	3.32E-01	1.35E-01	3.50E-03
1.41E-05	3.42E-01	1.39E-01	3.59E-03
1.45E-05	3.51E-01	1.43E-01	3.69E-03
1.49E-05	3.61E-01	1.47E-01	3.79E-03
1.54E-05	3.71E-01	1.51E-01	3.90E-03
1.58E-05	3.81E-01	1.55E-01	4.01E-03
1.63E-05	3.91E-01	1.59E-01	4.12E-03
1.68E-05	4.02E-01	1.64E-01	4.23E-03
1.73E-05	4.13E-01	1.68E-01	4.34E-03
1.78E-05	4.24E-01	1.73E-01	4.46E-03
1.83E-05	4.36E-01	1.78E-01	4.59E-03
1.89E-05	4.48E-01	1.83E-01	4.71E-03
1.95E-05	4.60E-01	1.88E-01	4.84E-03
2.00E-05	4.73E-01	1.93E-01	4.97E-03
2.06E-05	4.85E-01	1.99E-01	5.11E-03
2.13E-05	4.99E-01	2.04E-01	5.24E-03
2.19E-05	5.12E-01	2.10E-01	5.39E-03
2.25E-05	5.26E-01	2.16E-01	5.53E-03
2.32E-05	5.40E-01	2.22E-01	5.68E-03
2.39E-05	5.55E-01	2.28E-01	5.83E-03
2.46E-05	5.70E-01	2.34E-01	5.99E-03
2.54E-05	5.85E-01	2.40E-01	6.15E-03
2.61E-05	6.01E-01	2.47E-01	6.32E-03
2.69E-05	6.17E-01	2.54E-01	6.49E-03
2.77E-05	6.33E-01	2.61E-01	6.66E-03
2.86E-05	6.50E-01	2.68E-01	6.84E-03
2.94E-05	6.68E-01	2.75E-01	7.02E-03
3.03E-05	6.85E-01	2.83E-01	7.21E-03
3.12E-05	7.04E-01	2.91E-01	7.40E-03
3.21E-05	7.22E-01	2.98E-01	7.60E-03
3.31E-05	7.41E-01	3.07E-01	7.80E-03
3.41E-05	7.61E-01	3.15E-01	8.00E-03
3.51E-05	7.81E-01	3.24E-01	8.21E-03
3.62E-05	8.02E-01	3.32E-01	8.43E-03
3.73E-05	8.24E-01	3.42E-01	8.66E-03
3.84E-05	8.46E-01	3.51E-01	8.89E-03
3.95E-05	8.68E-01	3.61E-01	9.12E-03

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.07E-05	8.91E-01	3.70E-01	9.36E-03
4.19E-05	9.14E-01	3.80E-01	9.61E-03
4.32E-05	9.38E-01	3.91E-01	9.86E-03
4.45E-05	9.62E-01	4.01E-01	1.01E-02
4.58E-05	9.87E-01	4.12E-01	1.04E-02
4.72E-05	1.01E+00	4.23E-01	1.07E-02
4.86E-05	1.04E+00	4.34E-01	1.09E-02
5.01E-05	1.07E+00	4.46E-01	1.12E-02
5.16E-05	1.09E+00	4.58E-01	1.15E-02
5.31E-05	1.12E+00	4.70E-01	1.18E-02
5.47E-05	1.15E+00	4.82E-01	1.21E-02
5.64E-05	1.18E+00	4.95E-01	1.24E-02
5.81E-05	1.21E+00	5.08E-01	1.27E-02
5.98E-05	1.24E+00	5.22E-01	1.30E-02
6.16E-05	1.27E+00	5.35E-01	1.34E-02
6.34E-05	1.30E+00	5.49E-01	1.37E-02
6.54E-05	1.34E+00	5.63E-01	1.40E-02
6.73E-05	1.37E+00	5.78E-01	1.44E-02
6.93E-05	1.40E+00	5.93E-01	1.48E-02
7.14E-05	1.44E+00	6.09E-01	1.51E-02
7.36E-05	1.48E+00	6.25E-01	1.55E-02
7.58E-05	1.51E+00	6.41E-01	1.59E-02
7.80E-05	1.55E+00	6.58E-01	1.63E-02
8.04E-05	1.59E+00	6.75E-01	1.67E-02
8.28E-05	1.63E+00	6.92E-01	1.71E-02
8.53E-05	1.67E+00	7.10E-01	1.75E-02
8.78E-05	1.71E+00	7.28E-01	1.80E-02
9.05E-05	1.75E+00	7.48E-01	1.84E-02
9.32E-05	1.80E+00	7.67E-01	1.89E-02
9.60E-05	1.84E+00	7.87E-01	1.94E-02
9.89E-05	1.89E+00	8.08E-01	1.98E-02
1.02E-04	1.94E+00	8.30E-01	2.03E-02
1.05E-04	1.98E+00	8.52E-01	2.09E-02
1.08E-04	2.03E+00	8.74E-01	2.14E-02
1.11E-04	2.08E+00	8.96E-01	2.19E-02
1.15E-04	2.13E+00	9.19E-01	2.24E-02
1.18E-04	2.18E+00	9.41E-01	2.29E-02

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.22E-04	2.23E+00	9.65E-01	2.35E-02
1.25E-04	2.29E+00	9.89E-01	2.40E-02
1.29E-04	2.34E+00	1.01E+00	2.46E-02
1.33E-04	2.40E+00	1.04E+00	2.52E-02
1.37E-04	2.46E+00	1.07E+00	2.58E-02
1.41E-04	2.51E+00	1.09E+00	2.64E-02
1.45E-04	2.57E+00	1.12E+00	2.71E-02
1.50E-04	2.64E+00	1.15E+00	2.77E-02
1.54E-04	2.70E+00	1.18E+00	2.83E-02
1.59E-04	2.76E+00	1.21E+00	2.90E-02
1.63E-04	2.83E+00	1.24E+00	2.97E-02
1.68E-04	2.89E+00	1.27E+00	3.04E-02
1.73E-04	2.96E+00	1.30E+00	3.11E-02
1.79E-04	3.04E+00	1.34E+00	3.19E-02
1.84E-04	3.12E+00	1.37E+00	3.27E-02
1.89E-04	3.19E+00	1.41E+00	3.35E-02
1.95E-04	3.25E+00	1.44E+00	3.42E-02
2.01E-04	3.34E+00	1.48E+00	3.51E-02
2.07E-04	3.42E+00	1.51E+00	3.59E-02
2.13E-04	3.50E+00	1.55E+00	3.68E-02
2.20E-04	3.58E+00	1.59E+00	3.77E-02
2.26E-04	3.67E+00	1.63E+00	3.85E-02
2.33E-04	3.75E+00	1.67E+00	3.94E-02
2.40E-04	3.84E+00	1.71E+00	4.04E-02
2.47E-04	3.93E+00	1.76E+00	4.13E-02
2.55E-04	4.02E+00	1.80E+00	4.22E-02
2.62E-04	4.11E+00	1.84E+00	4.32E-02
2.70E-04	4.21E+00	1.89E+00	4.42E-02
2.78E-04	4.32E+00	1.94E+00	4.53E-02
2.86E-04	4.41E+00	1.99E+00	4.63E-02
2.95E-04	4.50E+00	2.03E+00	4.73E-02
3.04E-04	4.60E+00	2.08E+00	4.84E-02
3.13E-04	4.70E+00	2.13E+00	4.94E-02
3.22E-04	4.81E+00	2.18E+00	5.05E-02
3.32E-04	4.92E+00	2.23E+00	5.16E-02
3.42E-04	5.02E+00	2.29E+00	5.28E-02
3.52E-04	5.13E+00	2.34E+00	5.39E-02

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.63E-04	5.24E+00	2.40E+00	5.51E-02
3.74E-04	5.37E+00	2.46E+00	5.64E-02
3.85E-04	5.50E+00	2.52E+00	5.77E-02
3.97E-04	5.62E+00	2.58E+00	5.90E-02
4.08E-04	5.75E+00	2.65E+00	6.03E-02
4.21E-04	5.87E+00	2.71E+00	6.17E-02
4.33E-04	6.01E+00	2.78E+00	6.31E-02
4.46E-04	6.14E+00	2.85E+00	6.45E-02
4.60E-04	6.28E+00	2.91E+00	6.60E-02
4.74E-04	6.43E+00	2.99E+00	6.75E-02
4.88E-04	6.57E+00	3.06E+00	6.90E-02
5.02E-04	6.72E+00	3.14E+00	7.05E-02
5.17E-04	6.87E+00	3.21E+00	7.21E-02
5.33E-04	7.02E+00	3.29E+00	7.37E-02
5.49E-04	7.17E+00	3.37E+00	7.53E-02
5.65E-04	7.33E+00	3.45E+00	7.70E-02
5.82E-04	7.49E+00	3.53E+00	7.87E-02
6.00E-04	7.65E+00	3.62E+00	8.04E-02
6.18E-04	7.82E+00	3.71E+00	8.21E-02
6.36E-04	7.99E+00	3.79E+00	8.39E-02
6.55E-04	8.16E+00	3.89E+00	8.57E-02
6.75E-04	8.34E+00	3.98E+00	8.76E-02
6.95E-04	8.52E+00	4.07E+00	8.95E-02
7.16E-04	8.70E+00	4.17E+00	9.14E-02
7.38E-04	8.89E+00	4.27E+00	9.33E-02
7.60E-04	9.08E+00	4.37E+00	9.53E-02
7.83E-04	9.27E+00	4.47E+00	9.74E-02
8.06E-04	9.47E+00	4.58E+00	9.94E-02
8.30E-04	9.67E+00	4.69E+00	1.02E-01
8.55E-04	9.88E+00	4.80E+00	1.04E-01
8.81E-04	1.01E+01	4.91E+00	1.06E-01
9.07E-04	1.03E+01	5.03E+00	1.08E-01
9.21E-04	1.04E+01	5.09E+00	1.09E-01
9.35E-04	1.05E+01	5.15E+00	1.10E-01
9.49E-04	1.06E+01	5.21E+00	1.12E-01
9.63E-04	1.07E+01	5.27E+00	1.13E-01
9.69E-04	1.08E+01	5.30E+00	1.13E-01

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
9.77E-04	1.09E+01	5.33E+00	1.14E-01
9.84E-04	1.09E+01	5.36E+00	1.15E-01
9.91E-04	1.10E+01	5.39E+00	1.15E-01
9.98E-04	1.10E+01	5.42E+00	1.16E-01
1.01E-03	1.11E+01	5.46E+00	1.16E-01
1.02E-03	1.12E+01	5.52E+00	1.18E-01
1.04E-03	1.13E+01	5.58E+00	1.19E-01
1.05E-03	1.14E+01	5.65E+00	1.20E-01
1.07E-03	1.16E+01	5.72E+00	1.21E-01
1.08E-03	1.17E+01	5.78E+00	1.23E-01
1.10E-03	1.18E+01	5.85E+00	1.24E-01
1.12E-03	1.19E+01	5.92E+00	1.25E-01
1.13E-03	1.20E+01	5.99E+00	1.26E-01
1.15E-03	1.22E+01	6.06E+00	1.28E-01
1.17E-03	1.23E+01	6.13E+00	1.29E-01
1.18E-03	1.24E+01	6.20E+00	1.30E-01
1.20E-03	1.25E+01	6.27E+00	1.32E-01
1.22E-03	1.27E+01	6.34E+00	1.33E-01
1.24E-03	1.28E+01	6.42E+00	1.34E-01
1.26E-03	1.29E+01	6.49E+00	1.36E-01
1.27E-03	1.31E+01	6.57E+00	1.37E-01
1.29E-03	1.32E+01	6.64E+00	1.39E-01
1.31E-03	1.33E+01	6.72E+00	1.40E-01
1.33E-03	1.35E+01	6.80E+00	1.41E-01
1.35E-03	1.36E+01	6.88E+00	1.43E-01
1.37E-03	1.38E+01	6.96E+00	1.44E-01
1.39E-03	1.39E+01	7.04E+00	1.46E-01
1.41E-03	1.40E+01	7.12E+00	1.47E-01
1.43E-03	1.42E+01	7.21E+00	1.49E-01
1.46E-03	1.43E+01	7.29E+00	1.50E-01
1.48E-03	1.45E+01	7.37E+00	1.52E-01
1.50E-03	1.46E+01	7.46E+00	1.54E-01
1.52E-03	1.48E+01	7.55E+00	1.55E-01
1.54E-03	1.49E+01	7.63E+00	1.57E-01
1.57E-03	1.51E+01	7.72E+00	1.58E-01
1.59E-03	1.52E+01	7.81E+00	1.60E-01
1.61E-03	1.54E+01	7.90E+00	1.62E-01

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.64E-03	1.55E+01	7.99E+00	1.63E-01
1.66E-03	1.57E+01	8.09E+00	1.65E-01
1.69E-03	1.59E+01	8.18E+00	1.67E-01
1.71E-03	1.60E+01	8.28E+00	1.68E-01
1.74E-03	1.62E+01	8.37E+00	1.70E-01
1.76E-03	1.64E+01	8.47E+00	1.72E-01
1.79E-03	1.65E+01	8.57E+00	1.73E-01
1.82E-03	1.67E+01	8.67E+00	1.75E-01
1.84E-03	1.69E+01	8.77E+00	1.77E-01
1.87E-03	1.74E+01	9.10E+00	1.83E-01
1.90E-03	1.92E+01	1.02E+01	2.02E-01
1.93E-03	1.96E+01	1.04E+01	2.06E-01
1.96E-03	1.80E+01	9.44E+00	1.89E-01
1.99E-03	1.79E+01	9.41E+00	1.88E-01
2.02E-03	1.81E+01	9.49E+00	1.89E-01
2.08E-03	1.84E+01	9.67E+00	1.93E-01
2.14E-03	1.87E+01	9.88E+00	1.96E-01
2.20E-03	1.91E+01	1.01E+01	2.00E-01
2.27E-03	1.94E+01	1.03E+01	2.04E-01
2.34E-03	1.98E+01	1.06E+01	2.08E-01
2.41E-03	2.02E+01	1.08E+01	2.12E-01
2.48E-03	2.06E+01	1.11E+01	2.16E-01
2.55E-03	2.10E+01	1.13E+01	2.21E-01
2.63E-03	2.14E+01	1.16E+01	2.25E-01
2.71E-03	2.19E+01	1.18E+01	2.29E-01
2.79E-03	2.23E+01	1.21E+01	2.34E-01
2.87E-03	2.28E+01	1.24E+01	2.39E-01
2.96E-03	2.32E+01	1.27E+01	2.43E-01
3.05E-03	2.37E+01	1.30E+01	2.48E-01
3.14E-03	2.41E+01	1.33E+01	2.53E-01
3.23E-03	2.46E+01	1.36E+01	2.58E-01
3.33E-03	2.51E+01	1.39E+01	2.63E-01
3.43E-03	2.56E+01	1.42E+01	2.69E-01
3.53E-03	2.61E+01	1.46E+01	2.74E-01
3.64E-03	2.66E+01	1.49E+01	2.79E-01
3.75E-03	2.79E+01	1.57E+01	2.92E-01
3.81E-03	2.82E+01	1.59E+01	2.96E-01

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.86E-03	2.69E+01	1.51E+01	2.83E-01
3.98E-03	2.73E+01	1.53E+01	2.87E-01
4.10E-03	2.78E+01	1.57E+01	2.91E-01
4.22E-03	2.83E+01	1.60E+01	2.97E-01
4.35E-03	2.88E+01	1.63E+01	3.02E-01
4.48E-03	2.94E+01	1.67E+01	3.08E-01
4.61E-03	2.99E+01	1.71E+01	3.14E-01
4.75E-03	3.05E+01	1.75E+01	3.20E-01
4.89E-03	3.11E+01	1.79E+01	3.26E-01
5.04E-03	3.30E+01	1.92E+01	3.47E-01
5.19E-03	3.41E+01	1.99E+01	3.57E-01
5.35E-03	3.48E+01	2.05E+01	3.65E-01
5.51E-03	3.56E+01	2.10E+01	3.73E-01
5.67E-03	3.63E+01	2.15E+01	3.81E-01
5.84E-03	3.70E+01	2.20E+01	3.88E-01
5.93E-03	3.74E+01	2.23E+01	3.92E-01
6.02E-03	3.78E+01	2.26E+01	3.96E-01
6.20E-03	3.85E+01	2.31E+01	4.04E-01
6.38E-03	3.93E+01	2.36E+01	4.12E-01
6.57E-03	4.01E+01	2.42E+01	4.20E-01
6.77E-03	4.08E+01	2.48E+01	4.28E-01
6.98E-03	4.16E+01	2.54E+01	4.37E-01
7.18E-03	4.25E+01	2.60E+01	4.45E-01
7.40E-03	4.33E+01	2.66E+01	4.54E-01
7.51E-03	4.37E+01	2.69E+01	4.58E-01
7.62E-03	4.35E+01	2.68E+01	4.57E-01
7.85E-03	4.42E+01	2.73E+01	4.64E-01
8.09E-03	4.50E+01	2.79E+01	4.72E-01
8.33E-03	4.59E+01	2.85E+01	4.81E-01
8.58E-03	4.68E+01	2.92E+01	4.90E-01
8.71E-03	4.72E+01	2.96E+01	4.95E-01
8.84E-03	4.77E+01	2.99E+01	5.00E-01
9.10E-03	4.86E+01	3.06E+01	5.10E-01
9.37E-03	4.95E+01	3.13E+01	5.19E-01
9.66E-03	5.05E+01	3.21E+01	5.29E-01
9.94E-03	5.15E+01	3.28E+01	5.40E-01
1.02E-02	5.25E+01	3.36E+01	5.50E-01

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.06E-02	5.35E+01	3.44E+01	5.61E-01
1.09E-02	5.45E+01	3.52E+01	5.72E-01
1.12E-02	5.56E+01	3.61E+01	5.83E-01
1.15E-02	5.67E+01	3.69E+01	5.94E-01
1.19E-02	5.74E+01	3.75E+01	6.02E-01
1.22E-02	5.85E+01	3.84E+01	6.13E-01
1.26E-02	5.96E+01	3.93E+01	6.25E-01
1.30E-02	6.11E+01	4.05E+01	6.40E-01
1.34E-02	6.23E+01	4.15E+01	6.53E-01
1.38E-02	6.35E+01	4.25E+01	6.66E-01
1.42E-02	6.48E+01	4.36E+01	6.80E-01
1.46E-02	6.70E+01	4.55E+01	7.03E-01
1.50E-02	6.79E+01	4.62E+01	7.12E-01
1.55E-02	6.86E+01	4.68E+01	7.20E-01
1.60E-02	6.99E+01	4.79E+01	7.33E-01
1.64E-02	7.12E+01	4.90E+01	7.47E-01
1.69E-02	7.26E+01	5.02E+01	7.61E-01
1.74E-02	7.39E+01	5.14E+01	7.75E-01
1.80E-02	7.54E+01	5.27E+01	7.90E-01
1.85E-02	7.68E+01	5.40E+01	8.06E-01
1.91E-02	7.83E+01	5.53E+01	8.21E-01
1.96E-02	8.07E+01	5.74E+01	8.46E-01
2.02E-02	8.20E+01	5.86E+01	8.60E-01
2.08E-02	8.34E+01	5.98E+01	8.75E-01
2.14E-02	8.45E+01	6.08E+01	8.86E-01
2.21E-02	8.61E+01	6.23E+01	9.03E-01
2.28E-02	8.78E+01	6.38E+01	9.20E-01
2.34E-02	8.95E+01	6.54E+01	9.38E-01
2.41E-02	9.12E+01	6.70E+01	9.57E-01
2.49E-02	9.32E+01	6.88E+01	9.77E-01
2.56E-02	9.50E+01	7.05E+01	9.96E-01
2.64E-02	9.68E+01	7.22E+01	1.01E+00
2.72E-02	9.86E+01	7.40E+01	1.03E+00
2.80E-02	1.00E+02	7.58E+01	1.05E+00
2.88E-02	1.02E+02	7.76E+01	1.07E+00
2.97E-02	1.04E+02	7.95E+01	1.09E+00
3.06E-02	1.06E+02	8.13E+01	1.11E+00

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.15E-02	1.08E+02	8.33E+01	1.13E+00
3.24E-02	1.10E+02	8.53E+01	1.16E+00
3.34E-02	1.12E+02	8.74E+01	1.18E+00
3.44E-02	1.15E+02	8.96E+01	1.20E+00
3.54E-02	1.17E+02	9.18E+01	1.22E+00
3.65E-02	1.19E+02	9.40E+01	1.25E+00
3.76E-02	1.21E+02	9.64E+01	1.27E+00
3.87E-02	1.24E+02	9.87E+01	1.30E+00
3.99E-02	1.26E+02	1.01E+02	1.32E+00
4.11E-02	1.28E+02	1.04E+02	1.35E+00
4.23E-02	1.31E+02	1.06E+02	1.37E+00
4.36E-02	1.33E+02	1.09E+02	1.40E+00
4.49E-02	1.36E+02	1.12E+02	1.42E+00
4.63E-02	1.38E+02	1.14E+02	1.45E+00
4.76E-02	1.41E+02	1.17E+02	1.48E+00
4.91E-02	1.44E+02	1.20E+02	1.51E+00
5.05E-02	1.47E+02	1.23E+02	1.54E+00
5.21E-02	1.49E+02	1.26E+02	1.57E+00
5.36E-02	1.52E+02	1.30E+02	1.60E+00
5.52E-02	1.55E+02	1.33E+02	1.63E+00
5.69E-02	1.59E+02	1.37E+02	1.66E+00
5.86E-02	1.62E+02	1.40E+02	1.70E+00
6.03E-02	1.64E+02	1.43E+02	1.72E+00
6.22E-02	1.67E+02	1.46E+02	1.75E+00
6.40E-02	1.70E+02	1.50E+02	1.78E+00
6.59E-02	1.73E+02	1.54E+02	1.82E+00
6.79E-02	1.77E+02	1.58E+02	1.86E+00
7.00E-02	1.81E+02	1.62E+02	1.89E+00
7.21E-02	1.84E+02	1.66E+02	1.93E+00
7.42E-02	1.88E+02	1.70E+02	1.97E+00
7.64E-02	1.91E+02	1.75E+02	2.01E+00
7.87E-02	1.95E+02	1.79E+02	2.05E+00
8.11E-02	1.99E+02	1.84E+02	2.08E+00
8.35E-02	2.03E+02	1.88E+02	2.12E+00
8.60E-02	2.06E+02	1.93E+02	2.16E+00
8.86E-02	2.10E+02	1.98E+02	2.21E+00
9.13E-02	2.14E+02	2.03E+02	2.25E+00

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
9.40E-02	2.19E+02	2.08E+02	2.29E+00
9.68E-02	2.23E+02	2.14E+02	2.34E+00
9.97E-02	2.28E+02	2.20E+02	2.39E+00
1.03E-01	2.32E+02	2.25E+02	2.43E+00
1.06E-01	2.37E+02	2.31E+02	2.48E+00
1.09E-01	2.41E+02	2.37E+02	2.53E+00
1.12E-01	2.46E+02	2.43E+02	2.58E+00
1.16E-01	2.51E+02	2.50E+02	2.63E+00
1.19E-01	2.55E+02	2.56E+02	2.68E+00
1.23E-01	2.60E+02	2.62E+02	2.72E+00
1.26E-01	2.65E+02	2.69E+02	2.78E+00
1.30E-01	2.70E+02	2.76E+02	2.83E+00
1.34E-01	2.75E+02	2.83E+02	2.89E+00
1.38E-01	2.81E+02	2.90E+02	2.94E+00
1.42E-01	2.86E+02	2.98E+02	3.00E+00
1.46E-01	2.92E+02	3.06E+02	3.06E+00
1.51E-01	2.97E+02	3.14E+02	3.12E+00
1.55E-01	3.03E+02	3.22E+02	3.18E+00
1.60E-01	3.09E+02	3.30E+02	3.24E+00
1.65E-01	3.15E+02	3.39E+02	3.30E+00
1.70E-01	3.21E+02	3.48E+02	3.37E+00
1.75E-01	3.27E+02	3.57E+02	3.43E+00
1.80E-01	3.34E+02	3.66E+02	3.50E+00
1.86E-01	3.40E+02	3.76E+02	3.57E+00
1.91E-01	3.47E+02	3.86E+02	3.64E+00
1.97E-01	3.54E+02	3.96E+02	3.71E+00
2.03E-01	3.61E+02	4.07E+02	3.78E+00
2.09E-01	3.68E+02	4.17E+02	3.85E+00
2.15E-01	3.75E+02	4.28E+02	3.93E+00
2.22E-01	3.82E+02	4.40E+02	4.01E+00
2.28E-01	3.90E+02	4.52E+02	4.09E+00
2.35E-01	3.98E+02	4.64E+02	4.17E+00
2.42E-01	4.05E+02	4.76E+02	4.25E+00
2.49E-01	4.13E+02	4.88E+02	4.33E+00
2.57E-01	4.21E+02	5.01E+02	4.42E+00
2.65E-01	4.30E+02	5.14E+02	4.50E+00
2.72E-01	4.38E+02	5.28E+02	4.59E+00

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
2.81E-01	4.47E+02	5.42E+02	4.68E+00
2.89E-01	4.56E+02	5.57E+02	4.78E+00
2.98E-01	4.65E+02	5.72E+02	4.87E+00
3.07E-01	4.74E+02	5.87E+02	4.97E+00
3.16E-01	4.83E+02	6.03E+02	5.06E+00
3.25E-01	4.93E+02	6.19E+02	5.16E+00
3.35E-01	5.02E+02	6.35E+02	5.26E+00
3.45E-01	5.12E+02	6.52E+02	5.37E+00
3.56E-01	5.23E+02	6.70E+02	5.48E+00
3.66E-01	5.33E+02	6.88E+02	5.59E+00
3.77E-01	5.44E+02	7.07E+02	5.70E+00
3.89E-01	5.55E+02	7.26E+02	5.81E+00
4.00E-01	5.65E+02	7.45E+02	5.93E+00
4.12E-01	5.77E+02	7.66E+02	6.05E+00
4.25E-01	5.89E+02	7.87E+02	6.17E+00
4.37E-01	6.00E+02	8.08E+02	6.29E+00
4.50E-01	6.12E+02	8.29E+02	6.42E+00
4.64E-01	6.25E+02	8.52E+02	6.55E+00
4.78E-01	6.37E+02	8.76E+02	6.68E+00
4.92E-01	6.50E+02	8.98E+02	6.81E+00
5.07E-01	6.63E+02	9.23E+02	6.95E+00
5.22E-01	6.76E+02	9.48E+02	7.09E+00
5.38E-01	6.90E+02	9.74E+02	7.23E+00
5.54E-01	7.04E+02	1.00E+03	7.38E+00
5.71E-01	7.18E+02	1.03E+03	7.53E+00
5.88E-01	7.32E+02	1.06E+03	7.68E+00
6.05E-01	7.47E+02	1.08E+03	7.83E+00
6.23E-01	7.62E+02	1.11E+03	7.99E+00
6.42E-01	7.78E+02	1.14E+03	8.15E+00
6.61E-01	7.94E+02	1.18E+03	8.32E+00
6.81E-01	8.10E+02	1.21E+03	8.49E+00
7.02E-01	8.26E+02	1.24E+03	8.66E+00
7.23E-01	8.43E+02	1.28E+03	8.84E+00
7.44E-01	8.61E+02	1.31E+03	9.02E+00
7.67E-01	8.78E+02	1.35E+03	9.21E+00
7.90E-01	8.96E+02	1.38E+03	9.40E+00
8.13E-01	9.15E+02	1.42E+03	9.59E+00

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
8.38E-01	9.33E+02	1.46E+03	9.79E+00
8.63E-01	9.53E+02	1.50E+03	9.99E+00
8.89E-01	9.72E+02	1.54E+03	1.02E+01
9.16E-01	9.93E+02	1.59E+03	1.04E+01
9.43E-01	1.01E+03	1.63E+03	1.06E+01
9.71E-01	1.03E+03	1.68E+03	1.08E+01
1.00E+00	1.06E+03	1.72E+03	1.11E+01
1.03E+00	1.08E+03	1.77E+03	1.13E+01
1.06E+00	1.10E+03	1.82E+03	1.15E+01
1.09E+00	1.12E+03	1.87E+03	1.18E+01
1.13E+00	1.15E+03	1.92E+03	1.20E+01
1.16E+00	1.17E+03	1.98E+03	1.23E+01
1.19E+00	1.20E+03	2.03E+03	1.25E+01
1.23E+00	1.22E+03	2.09E+03	1.28E+01
1.27E+00	1.25E+03	2.15E+03	1.31E+01
1.31E+00	1.27E+03	2.21E+03	1.33E+01
1.34E+00	1.30E+03	2.27E+03	1.36E+01
1.38E+00	1.33E+03	2.33E+03	1.39E+01
1.43E+00	1.35E+03	2.40E+03	1.42E+01
1.47E+00	1.38E+03	2.46E+03	1.45E+01
1.51E+00	1.41E+03	2.53E+03	1.48E+01
1.56E+00	1.44E+03	2.60E+03	1.51E+01
1.61E+00	1.47E+03	2.68E+03	1.55E+01
1.65E+00	1.51E+03	2.75E+03	1.58E+01
1.70E+00	1.54E+03	2.83E+03	1.61E+01
1.75E+00	1.57E+03	2.91E+03	1.65E+01
1.81E+00	1.61E+03	2.99E+03	1.68E+01
1.86E+00	1.64E+03	3.08E+03	1.72E+01
1.92E+00	1.68E+03	3.16E+03	1.76E+01
1.97E+00	1.71E+03	3.25E+03	1.79E+01
2.03E+00	1.75E+03	3.34E+03	1.83E+01
2.09E+00	1.79E+03	3.44E+03	1.87E+01
2.16E+00	1.83E+03	3.54E+03	1.91E+01
2.22E+00	1.87E+03	3.64E+03	1.96E+01
2.29E+00	1.91E+03	3.74E+03	2.00E+01
2.36E+00	1.95E+03	3.85E+03	2.04E+01
2.43E+00	1.99E+03	3.95E+03	2.09E+01

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
2.50E+00	2.04E+03	4.07E+03	2.13E+01
2.58E+00	2.08E+03	4.18E+03	2.18E+01
2.65E+00	2.13E+03	4.30E+03	2.23E+01
2.73E+00	2.17E+03	4.42E+03	2.28E+01
2.82E+00	2.22E+03	4.55E+03	2.33E+01
2.90E+00	2.27E+03	4.68E+03	2.38E+01
2.99E+00	2.32E+03	4.81E+03	2.44E+01
3.08E+00	2.38E+03	4.95E+03	2.49E+01
3.17E+00	2.43E+03	5.09E+03	2.55E+01
3.26E+00	2.48E+03	5.24E+03	2.60E+01
3.36E+00	2.54E+03	5.39E+03	2.66E+01
3.46E+00	2.60E+03	5.54E+03	2.72E+01
3.57E+00	2.66E+03	5.70E+03	2.79E+01
3.67E+00	2.72E+03	5.86E+03	2.85E+01
3.78E+00	2.78E+03	6.03E+03	2.91E+01
3.90E+00	2.84E+03	6.20E+03	2.98E+01
4.01E+00	2.91E+03	6.38E+03	3.05E+01
4.13E+00	2.98E+03	6.56E+03	3.12E+01
4.26E+00	3.04E+03	6.75E+03	3.19E+01
4.39E+00	3.12E+03	6.95E+03	3.27E+01
4.52E+00	3.19E+03	7.15E+03	3.34E+01
4.65E+00	3.26E+03	7.35E+03	3.42E+01
4.79E+00	3.34E+03	7.56E+03	3.50E+01
4.94E+00	3.42E+03	7.78E+03	3.58E+01
5.08E+00	3.50E+03	8.01E+03	3.66E+01
5.24E+00	3.58E+03	8.24E+03	3.75E+01
5.39E+00	3.66E+03	8.47E+03	3.84E+01
5.56E+00	3.75E+03	8.72E+03	3.93E+01
5.72E+00	3.84E+03	8.97E+03	4.02E+01
5.89E+00	3.93E+03	9.23E+03	4.12E+01
6.07E+00	4.02E+03	9.50E+03	4.22E+01
6.25E+00	4.12E+03	9.77E+03	4.32E+01
6.44E+00	4.22E+03	1.01E+04	4.42E+01
6.63E+00	4.32E+03	1.03E+04	4.53E+01
6.83E+00	4.42E+03	1.06E+04	4.64E+01
7.04E+00	4.53E+03	1.10E+04	4.75E+01
7.25E+00	4.64E+03	1.13E+04	4.86E+01

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.47E+00	4.75E+03	1.16E+04	4.98E+01
7.69E+00	4.87E+03	1.19E+04	5.10E+01
7.92E+00	4.99E+03	1.23E+04	5.23E+01
8.16E+00	5.11E+03	1.26E+04	5.36E+01
8.40E+00	5.24E+03	1.30E+04	5.49E+01
8.66E+00	5.37E+03	1.34E+04	5.62E+01
8.92E+00	5.50E+03	1.38E+04	5.76E+01
9.18E+00	5.63E+03	1.42E+04	5.91E+01
9.46E+00	5.77E+03	1.46E+04	6.05E+01
9.74E+00	5.92E+03	1.50E+04	6.20E+01
1.00E+01	6.07E+03	1.54E+04	6.36E+01
1.06E+01	6.37E+03	1.63E+04	6.68E+01
1.13E+01	6.69E+03	1.73E+04	7.01E+01
1.20E+01	7.03E+03	1.83E+04	7.37E+01
1.27E+01	7.39E+03	1.94E+04	7.74E+01
1.34E+01	7.76E+03	2.05E+04	8.14E+01
1.42E+01	8.16E+03	2.17E+04	8.56E+01
1.51E+01	8.59E+03	2.30E+04	9.00E+01
1.60E+01	9.03E+03	2.43E+04	9.47E+01
1.70E+01	9.50E+03	2.57E+04	9.96E+01
1.80E+01	1.00E+04	2.72E+04	1.05E+02
1.90E+01	1.05E+04	2.88E+04	1.10E+02
2.02E+01	1.11E+04	3.05E+04	1.16E+02
2.14E+01	1.17E+04	3.23E+04	1.22E+02
2.27E+01	1.23E+04	3.42E+04	1.29E+02
2.40E+01	1.30E+04	3.62E+04	1.36E+02
2.55E+01	1.37E+04	3.83E+04	1.43E+02
2.70E+01	1.44E+04	4.06E+04	1.51E+02
2.86E+01	1.52E+04	4.30E+04	1.59E+02
3.04E+01	1.60E+04	4.55E+04	1.68E+02
3.22E+01	1.69E+04	4.82E+04	1.77E+02
3.41E+01	1.78E+04	5.10E+04	1.87E+02
3.62E+01	1.88E+04	5.40E+04	1.97E+02
3.83E+01	1.99E+04	5.71E+04	2.08E+02
4.06E+01	2.10E+04	6.05E+04	2.20E+02
4.31E+01	2.21E+04	6.40E+04	2.32E+02
4.57E+01	2.34E+04	6.78E+04	2.45E+02

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.84E+01	2.47E+04	7.18E+04	2.59E+02
5.13E+01	2.61E+04	7.60E+04	2.73E+02
5.44E+01	2.75E+04	8.04E+04	2.89E+02
5.76E+01	2.91E+04	8.51E+04	3.05E+02
6.11E+01	3.08E+04	9.01E+04	3.22E+02
6.48E+01	3.25E+04	9.53E+04	3.41E+02
6.86E+01	3.44E+04	1.01E+05	3.60E+02
7.28E+01	3.63E+04	1.07E+05	3.81E+02
7.71E+01	3.84E+04	1.13E+05	4.03E+02
8.18E+01	4.06E+04	1.20E+05	4.26E+02
8.67E+01	4.30E+04	1.26E+05	4.51E+02
9.19E+01	4.55E+04	1.34E+05	4.77E+02
9.74E+01	4.81E+04	1.42E+05	5.04E+02
1.03E+02	5.09E+04	1.50E+05	5.33E+02
1.09E+02	5.38E+04	1.58E+05	5.64E+02
1.16E+02	5.70E+04	1.68E+05	5.97E+02
1.23E+02	6.03E+04	1.77E+05	6.32E+02
1.30E+02	6.38E+04	1.87E+05	6.69E+02
1.38E+02	6.76E+04	1.98E+05	7.08E+02
1.46E+02	7.15E+04	2.09E+05	7.50E+02

E.5. REFERENCES

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APPENDIX F

Epidemiologic Kinetic Modeling

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National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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APPENDIX F. EPIDEMIOLOGIC KINETIC MODELING

F.1. DERIVATION OF BACKGROUND CONCENTRATION

Background intakes for the Seveso cohort were estimated from information from two separate studies. The details of the modeling and the estimated background intakes are described in this section.

F.1.1. Needham Background Scenario

F.1.1.1. *Summary of Modeling Approach*

Needham et al. (1998) reported lipid adjusted serum concentrations in 11 pools of individuals in the non-ABR region near the site of the Seveso TCDD accident in July, 1976. The individuals in this region did not suffer exposure from the event and represent a reference (comparison) population in the study. There were 4−10 individuals per pool, and the median lipid-adjusted serum concentration (LASC) across the pools was reported by the study authors to be 15 ppt.

All subjects in the pooled samples were above age 25, but no further details about age are given in the study. Mocarelli et al. (1991) reported details about 10 subjects in the non-ABR region at the time of serum sample collection in 1976. The oldest individual in this sample was 46. In the absence of other information, this age was used as an upper bound, suggesting a median age (between 25 and 46) of approximately 35 years old.

The Emond model is not coded to allow the background intake to vary in time. Thus, it was assumed that the background intake remained constant over the lifetime of the individual. The Emond model was used to determine the continuous daily TCDD intake which gives a terminal concentration of 15 ppt at the age of 35 for both women and men. The background intakes were then rounded to the nearest 10^{-5} ng/kg-day. The corresponding male and female oral intakes were 3.5×10^{-4} ng/kg-day and 3.9×10^{-4} ng/kg-day, respectively.

For the modeled-TEQ method in the sensitivity analysis, TEQ background intake was estimated by assuming that TCDD LASC is 10% of total TEQ LASC and that all DLCs are kinetically-equivalent to TCDD. The TEQ intakes were then modeled as the continuous daily TCDD-equivalent intake which giving a terminal concentration of 150 ppt at the age of 35 for both women and men. The total TEQ intake matching 150 ppt (10 × TCDD) at 35 years was 8.91×10^{-3} ng/kg-day for males and 9.44×10^{-3} ng/kg-day for females.

For the additive DLC intake method, where DLC-TEQ intakes (ng/kg-day) are added to modeled TCDD intakes, a simple intake-scaling approach was used. The assumed ratio of TEQ LASC to TCDD LASC was applied to the TCDD intake estimate. For the Needham scenario, a total-TEQ LASC of 80.6 ppt is 1.88 times the TCDD LASC of 40.5 ppt. With the assumption that TCDD comprises 10% of the total background TEQ, the ratio of DLC-TEQ:TCDD is 9:1 for background exposures. Scaling the male TCDD background intake of 3.5×10^{-3} ng/kg-day by this factor gives a DLC-TEQ intake of 3.15×10^{-3} ng/kg-day. The corresponding female DLC-TEQ intake is 3.51×10^{-3} ng/kg-day ($3.9 \times 10^{-4} \times 1.88$).

F.1.1.2. *Input for Continuous Exposure to Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 306600. % AGE AT MEASUREMENT (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0. % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 306600. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 306600. % AGE AT MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.      % /KG-DAYBACKGROUND EXPOSURE INCLUDED IN MSTOT

% CONTINUOUS EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 3.5E-4  % TCDD-ONLY, MALES (15 ppt at 35 years)
      % 3.9E-4  % TCDD-ONLY, FEMALES (15 ppt at 35 years)
      % 8.91E-3 % TOTAL TEQ, MALES (150 ppt at 35 years)
      % 9.44E-3 % TOTAL TEQ, FEMALES (150 ppt at 35 years)

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ
```

F.1.1.3. *Needham Background Scenario Results*

Table F-1. Estimated background intakes for Needham scenario

Age at measurement (years)	Measured TCDD LASC (ppt)	Assumed TEQ LASC (ppt)	Continuous intake matching TCDD LASC (ng/kg-day)	Continuous intake matching TEQ LASC[a] (ng/kg-day)	Additive DLC-TEQ intake[b] (ng/kg-day)
35	15	150[a]	3.5E−04 (males)	8.91E−03 (males)	3.15E−03 (males)
			3.9E−04 (females)	9.44E−03 (females)	3.51E−03 (females)

Intakes rounded to the nearest 10^{-5} ng/kg-day
[a]For use in modeled-TEQ method
[b]For use in additive DLC-intake method

F.1.2. Eskenazi Background Scenario

F.1.2.1. *Summary of Modeling Approach*

Eskenazi et al. (2004) reported TCDD levels for the Seveso Women's Cohort from pooled samples from individuals living in zone non-ABR (unexposed regions) in 1976, representing background exposure levels to TCDD and total TEQ. Table 3 in that study reports mean TCDD and TEQ for three different age groups. As an alternative background intake for endpoints measured in children compared with the Needham background, the 0−12 age group (girls) was used to determine background exposure using the Emond model. The two pooled sample results were averaged to give an average background TCDD LASC of 40.5 ppt. It was assumed that both males and females had this average concentration. The Emond model was run until the intake resulted in an average LASC of 40.5 when averaged between ages 0 and 12. The corresponding male and female oral intakes were 4.22×10^{-3} ng/kg-day and 4.29×10^{-3} ng/kg-day, respectively. The background intake was then rounded to the nearest 10^{-5} ng/kg-day.

For direct modeling of total TEQ LASC, background TEQ LASC was estimated from Eskenazi et al. (2004). The average total TEQ levels for the 0−12 year-old group, as reported by Eskenazi et al. (2004), was 116.6 ppt, with 76.1 ppt attributed to DLCs. The Emond model was run until the TCDD-equivalent intake resulted in an average LASC of 116.6 when averaged between ages 0 and 12. The estimated male and female TEQ intakes were 0.01803 and

0.01807 ng/kg-day, respectively. These estimates were used for direct modeling of TEQ expressed as LASC to obtain corresponding TEQ intakes.

For the additive DLC method, where DLC-TEQ intakes (ng/kg-day) are added to modeled TCDD intakes, a simple intake-scaling approach was used. The assumed or measured ratio of TEQ LASC to TCDD LASC was applied to the TCDD intake estimate. For the Eskenazi scenario, measured DLC-TEQ LASC of 76.1 ppt is 1.88 times the TCDD LASC of 40.5 ppt. Scaling the male TCDD background intake of 4.22×10^{-3} ng/kg-day by this factor gives a DLC-TEQ intake of 7.93×10^{-3} ng/kg-day. The corresponding female DLC-TEQ intake is 8.07×10^{-3} ng/kg-day ($4.29 \times 10^{-3} \times 1.88$).

F.1.2.2. *Input for Continuous Exposure to Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 105120. % UPPER AGE RANGE IN SAMPLE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 105120. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 105120. % UPPER AGE RANGE IN SAMPLE (HOURS)
MSTOTBCKGR   = 0.      % /KG-DAYBACKGROUND EXPOSURE INCLUDED IN MSTOT

% CONTINUOUS EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 4.22E-3 % TCDD-ONLY, MALES (10-year avg = 40.5 ppt)
      % 4.29E-3 % TCDD-ONLY, FEMALES (10-year avg = 40.5 ppt)
      % 1.32E-2 % TOTAL TEQ, MALES (10-year avg = 93.7 ppt)
      % 1.33E-2 % TOTAL TEQ, FEMALES (10-year avg = 93.7 ppt)

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
mean(_cbsngkgliadj)
```

F.1.2.3. *Eskenazi et Background Scenario Results*

Table F-2. Estimated background intakes for Eskenazi background scenario

Age range at measurement (years)	Average measured TCDD LASC (ppt)	Average measured TEQ LASC (ppt)	Continuous intake matching measured TCDD LASC (ng/kg-day)	Continuous intake matching measured TEQ LASC[a] (ng/kg-day)	Additive DLC-TEQ intake[b] (ng/kg-day)
0−12	40.5	116.6	4.22E−03 (males)	1.32E−02 (males)	7.93E−03 (males)
			4.29E−03 (females)	1.33E−02 (females)	8.07E−03 (females)

Intakes rounded to the nearest 10^{-5} ng/kg-day
[a]For use in modeled-TEQ method
[b]For use in additive DLC-intake method

F.2. KINETIC MODELING OF EPIDEMIOLOGIC STUDIES CONSIDERED FOR RfD

F.2.1. Baccarelli et al. (2008)

F.2.1.1. *Input for Exposure During Pregnancy*

```
% EXPOSURE PARAMETERS
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 401190. % LENGTH OF CRITICAL WINDOW (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 401190. % AGE AT BEGINNING OF BACKGROUND EXPOSURE (HOURS)
BCK_TIME_OFF = 401190. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
CONCEPTION_T = 262800. % AGE AT CONCEPTION (HOURS)
TIMELIMIT    = 269184. % AGE AT END OF PREGNANCY (HOURS)
TRANSTIME_ON = 264312. % AGE AT MOTHER-FETUS EXCHANGE (HOURS)
MSTOTBCKGR   = 0.      % /KG-DAYBACKGROUND EXPOSURE INCLUDED IN MSTOT

% CONTINUOUS EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 0.021 % MATCHING MATERNAL LASC OF 235 NG/KG
```

F.2.1.2. *Baccarelli et al. (2008) Results*

Table F-3. Estimated continuous TCDD intake corresponding to maternal serum concentration

Variable	Value	Notes
Infant b-TSH	5 μU/mL	Adverse response level
Maternal lipid adjusted serum	235 ng/kg	From Figure 2A in Baccarelli et al. (2008)
Intake	0.020 ng/kg-day	From Emond model; pregnancy at 30 years

TSH = thyroid stimulating hormone.

F.2.2. Mocarelli et al. (2008)

F.2.2.1. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5.
CINT = 1.
EXP_TIME_ON  = 54312.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 54335.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 58692.  % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00035 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG-DAY)
```

```
% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 8.2   % 1ST QUARTILE
      % 22.5  % 2ND QUARTILE
      % 78.4  % 3RD QUARTILE
      % 231.9 % 4TH QUARTILE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==58524):length(_t)))
```

F.2.2.2. *Input for Exposure from Event to End of Critical Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5.
CINT = 1.
EXP_TIME_ON  = 54312.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 54335.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 87600.  % LENGTH OF CRITICAL WINDOW (HOURS)
MSTOTBCKGR   = 0.00035 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 8.2   % 1ST QUARTILE
      % 22.5  % 2ND QUARTILE
      % 78.4  % 3RD QUARTILE
      % 231.9 % 4TH QUARTILE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.2.2.3. *Input for Continuous Exposure over Critical Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG
```

```
% EXPOSURE PARAMETERS
MAXT = 0.5.
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 87601.  % LENGTH OF CRITICAL WINDOW (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 87600.  % LENGTH OF CRITICAL WINDOW (HOURS)
MSTOTBCKGR   = 0.      % /KG-DAYBACKGROUND EXPOSURE INCLUDED IN MSTOT

% CONTINUOUS EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 7.97E-3 % 1ST QUARTILE - MATCHING MEAN
      % 2.08E-2 % 2ND QUARTILE - MATCHING MEAN
      % 7.21E-2 % 3RD QUARTILE - MATCHING MEAN
      % 2.12E-1 % 4TH QUARTILE - MATCHING MEAN
      % 3.21E-2 % 1ST QUARTILE - MATCHING MAX
      % 1.41E-1 % 2ND QUARTILE - MATCHING MAX
      % 8.73E-1 % 3RD QUARTILE - MATCHING MAX
      % 3.89E+0 % 4TH QUARTILE - MATCHING MAX

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.2.2.4. *Mocarelli (2008) Results*

Table F-4. Matching peak and average after pulse to 10-year childhood intake for Mocarelli et al. (2008)

TCDD only								
Subject modeled	**Quartile**	**Measured LASC (ng/kg)**	**Event dose (ng/kg)**	**Average LASC after pulse dose (ng/kg)**	**Continuous intake matching average LASC (ng/kg-day)**	**Peak LASC after pulse dose (ng/kg)**	**Continuous intake matching peak LASC (ng/kg-day)**	**Average of continuous intake rates (ng/kg-day)**
TCDD Needham scenario; background LASC = 15 ppt (3.5E-04 ng/kg-day)[a]								
Male	1st	68	8.2	57.7	7.97E−03	249.0	3.21E−02	2.01E−02
Male	2nd	142	22.5	116.8	2.08E−02	668.7	1.41E−01	8.08E−02
Male	3rd	345	78.4	276.7	7.21E−02	2288.7	8.73E−01	4.73E−01
Male	4th	733	231.9	579.4	2.12E−01	6658.9	3.89E+00	2.05E+00

[a]See Table F-1.

F.2.3. Alaluusua et al. (2004)

F.2.3.1. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 21900.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 21923.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 26280.  % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00035 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 10.9   % 1ST TERTILE - MALE
      % 10.4   % 1ST TERTILE - FEMALE
      % 105.9  % 2ND TERTILE - MALE
      % 102.3  % 2ND TERTILE - FEMALE
      % 3419.2 % 3RD TERTILE - MALE
      % 4266.1 % 3RD TERTILE - FEMALE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==26112):length(_t)))
```

F.2.3.2. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 21900.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 21923.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 43800.  % LENGTH OF CRITICAL WINDOW (HOURS)
MSTOTBCKGR   = 0.00035 % NEEDHAM BACKGROUND EXPOSURE, MALES (NG/KG-DAY)
             % 0.00039 % NEEDHAM BACKGROUND EXPOSURE, FEMALES (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
```

```
MSTOT = 10.9   % 1ST TERTILE - MALE
      % 10.4   % 1ST TERTILE - FEMALE
      % 105.9  % 2ND TERTILE - MALE
      % 102.3  % 2ND TERTILE - FEMALE
      % 3419.2 % 3RD TERTILE - MALE
      % 4266.1 % 3RD TERTILE - FEMALE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.    % 0 FOR FEMALE SIMULATION
FEMALE = 0.    % 1 FOR FEMALE SIMULATION
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.2.3.3. *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG


% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 43801.  % LENGTH OF CRITICAL WINDOW (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 43800.  % LENGTH OF CRITICAL WINDOW (HOURS)
MSTOTBCKGR   = 0.      % /KG-DAYBACKGROUND EXPOSURE INCLUDED IN MSTOT

% CONTINUOUS EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 1.62E-2 % 1ST TERTILE - MALE   - MATCHING MEAN
      % 1.51E-2 % 1ST TERTILE - FEMALE - MATCHING MEAN
      % 1.53E-1 % 2ND TERTILE - MALE   - MATCHING MEAN
      % 1.44E-1 % 2ND TERTILE - FEMALE - MATCHING MEAN
      % 4.94E+0 % 3RD TERTILE - MALE   - MATCHING MEAN
      % 4.68E+0 % 3RD TERTILE - FEMALE - MATCHING MEAN
      % 6.95E-2 % 1ST TERTILE - MALE   - MATCHING MAX
      % 6.15E-2 % 1ST TERTILE - FEMALE - MATCHING MAX
      % 1.72E+0 % 2ND TERTILE - MALE   - MATCHING MAX
      % 1.58E+0 % 2ND TERTILE - FEMALE - MATCHING MAX
      % 1.14E+2 % 3RD TERTILE - MALE   - MATCHING MAX
      % 1.08E+2 % 3RD TERTILE - FEMALE - MATCHING MAX

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION
```

```
% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.2.3.4. *Alaluusua et al. (2004) Results*

Table F-5. Matching peak and average after pulse to chronic intake for Alaluusua et al. (2004)

Subject modeled	Tertile	TCDD Only								TEQ[a]
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of male and female continuous intake rates (ng/kg-day)	Average of male and female continuous intake rates (ng/kg-day)
Needham background										
Male	1st	72.1	10.9	61.8	1.62E−02	286.7	6.95E−02	4.28E−02	4.06E−02	4.39E−02
Female			10.4	62.1	1.51E−02	271.2	6.15E−02	3.83E−02		
Male	2nd	375.4	105.9	316.3	1.53E−01	2626.9	1.72E+00	9.34E−01	8.97E-01	9.01E-01
Female			102.3	318.1	1.44E−01	2536.8	1.58E+00	8.60E−01		
Male	3rd	4266.1	3419.2	3559.0	4.94E+00	79877.5	1.14E+02	5.95E+01	5.79E+01	5.79E+01
Female			4266.1	3581.9	4.68E+00	78251.9	1.08E+02	5.64E+01		

[a]TCDD male/female average + DLC background intake (3.3×10^{-3} ng/kg-day).

F.2.4. Eskanazi et al. (2002)

F.2.4.1. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 58692.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 58715.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 63072.  % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 5.4    % 28-DAY   EC GROUP
      % 2684.8 % Over 1000 ppt GROUP


% HUMAN VARIABLE PARAMETERS
```

```
MALE   = 0.
FEMALE = 1.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==62904):length(_t)))
```

F.2.4.2. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 58692.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 58715.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 113880. % LENGTH OF CRITICAL WINDOW (HOURS)
MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 5.4    % 28-DAY   EC GROUP
      % 2684.8 % Over 1000 ppt GROUP

% HUMAN VARIABLE PARAMETERS
MALE   = 0.
FEMALE = 1.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.2.4.3. *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 113881. % LENGTH OF CRITICAL WINDOW (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
```

```
TIMELIMIT    = 113880. % LENGTH OF CRITICAL WINDOW (HOURS)
MSTOTBCKGR   = 0.      % /KG-DAYBACKGROUND EXPOSURE INCLUDED IN MSTOT

% CONTINUOUS EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 3.64E-3 % 28-DAY   EC EXPOSURE GROUP - MATCHING MEAN
      % 1.51E+0 % Over 1000 ppt EXPOSURE GROUP - MATCHING MEAN
      % 1.68E-2 % 28-DAY   EC EXPOSURE GROUP - MATCHING MAX
      % 6.06E+1 % Over 1000 ppt EXPOSURE GROUP - MATCHING MAX

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.2.4.4. *Eskenazi et al. (2002) Results*

Table F-6. Matching peak and average after pulse to chronic intake for Eskenazi et al. (2002)

Subject modeled	Exposure group	TCDD Only							TEQ[a]
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of continuous intake rates (ng/kg-day)
Needham background									
Female	28-day EC	50	5.4	37.3	3.64E-03	166.9	1.68E−02	1.02E−02	1.37E−02
Female	Over 1,000 ppt	4,060	2684.8	2548.8	1.51E+00	74597.2	6.06E+01	3.11E+01	3.11E+01

[a]TCDD average + DLC background intake (3.5×10^{-3} ng/kg-day).
EC = estrous cycle.

F.3. KINETIC MODELING OF EPIDEMIOLOGIC STUDIES FOR SENSITIVITY ANALYSIS

F.3.1. Alaluusua et al. (2004)

F.3.1.1. *Summary of Modeling Approach*

For the sensitivity analysis, modeling for Alaluusua et al. (2004) (detailed in Section 4.2.3.3) was repeated using alternative male and female Eskenazi scenario background intakes for children aged 0−12 as described in Section F.1.2. EPA used the Emond human PBPK model to estimate continuous daily oral TCDD intakes for each exposure tertile from corresponding measured LASC values estimated by calculating the geometric mean of the tertile ranges provided by Alaluusua et al. (2004). Serum levels were measured within one year of the incident; in the absence of further specific information about measurement lag, a lag time of 6 months between the event and the measurement was assumed. This value was then used to model the associated peak and mean LASC from time of the event (average age 2.5 years) to the end of the critical window (5 years). Continuous daily intakes matching the peak and mean LASC were determined by modeling exposure from birth to the end of the critical exposure window. Male and female estimates were modeled separately and then averaged to give a single continuous intake estimate for each exposure tertile. Total TEQ intake was estimated using the additive method for both the Needham and Eskenazi scenarios as described previously (see Sections F.1.1 and F.1.2).

Table F-7. Model inputs derived from study details for Alaluusua et al. (2004)

Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Critical exposure window (years)
2.5	0.5	2.5	5

F.3.1.2. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG
```

```
% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 21900.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 21923.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 26280.  % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00422 % ESKENAZI BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 8.2    % 1ST TERTILE - MALE
      % 7.5    % 1ST TERTILE - FEMALE
      % 103.1  % 2ND TERTILE - MALE
      % 99.4   % 2ND TERTILE - FEMALE
      % 3416.5 % 3RD TERTILE - MALE
      % 3343.3 % 3RD TERTILE - FEMALE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==26112):length(_t)))
```

F.3.1.3. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 21900.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 21923.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 43800.  % LENGTH OF CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.00422 % ESKENAZI BACKGROUND EXPOSURE, MALES (NG/KG-DAY)
             % 0.00429 % ESKENAZI BACKGROUND EXPOSURE, FEMALES (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 8.2    % 1ST TERTILE - MALE
      % 7.5    % 1ST TERTILE - FEMALE
      % 103.1  % 2ND TERTILE - MALE
      % 99.4   % 2ND TERTILE - FEMALE
      % 3416.5 % 3RD TERTILE - MALE
      % 3343.3 % 3RD TERTILE - FEMALE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
```

```
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.3.1.4. *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 43801.  % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 43800.  % LENGTH OF CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.      % /KG-DAYBACKGROUND EXPOSURE INCLUDED IN MSTOT

% CONTINUOUS EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 1.81E-2 % 1ST TERTILE - MALE   - MATCHING MEAN
      % 1.69E-2 % 1ST TERTILE - FEMALE - MATCHING MEAN
      % 1.56E-1 % 2ND TERTILE - MALE   - MATCHING MEAN
      % 1.46E-1 % 2ND TERTILE - FEMALE - MATCHING MEAN
      % 4.94E+0 % 3RD TERTILE - MALE   - MATCHING MEAN
      % 4.68E+0 % 3RD TERTILE - FEMALE - MATCHING MEAN
      % 4.70E-2 % 1ST TERTILE - MALE   - MATCHING PEAK
      % 4.04E-2 % 1ST TERTILE - FEMALE - MATCHING PEAK
      % 1.58E+0 % 2ND TERTILE - MALE   - MATCHING PEAK
      % 1.45E+0 % 2ND TERTILE - FEMALE - MATCHING PEAK
      % 1.13E+2 % 3RD TERTILE - MALE   - MATCHING PEAK
      % 1.07E+2 % 3RD TERTILE - FEMALE - MATCHING PEAK

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.3.1.5. *Alaluusua et al. (2004) Results*

Table F-8. Matching peak and average after pulse to chronic intake for Alaluusua et al. (2004) using alternate background value

Subject modeled	Tertile	TCDD Only								TEQ[a]
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of male and female continuous intake rates (ng/kg-day)	Average of male and female continuous intake rates (ng/kg-day)
Eskenazi background										
Male	1st	72.1	8.2	67.5	1.81E−02	218.4	4.70E−02	3.25E−02	3.06E−02	3.86E−02
Female			7.5	68.0	1.69E−02	203.0	4.04E−02	2.87E−02		
Male	2nd	375.4	103.1	319.4	1.56E−01	2479.1	1.58E+00	8.68E−01	8.32E−01	8.40E−01
Female			99.4	321.2	1.46E−01	2390.4	1.45E+00	7.97E−01		
Male	3rd	4266.1	3416.5	3560.0	4.94E+00	79502.9	1.13E+02	5.92E+01	5.76E+01	5.76E+01
Female			3343.3	3582.9	4.68E+00	77847.7	1.07E+02	5.61E+01		

[a]TCDD male/female average + DLC male/female average background intake (8.0×10^{-3} ng/kg-day).

F.3.2. Baccarelli et al. (2008)

F.3.2.1. *Summary of Modeling Approach*

For the sensitivity analysis, total TEQ intakes were estimated. For Baccarelli et al. (2008), total TEQ exposure was obtained from the study author's Figure 2D by digitizing the figure and finding the TEQ concentration on the regression line associated with a b-TSH of 5 μU/mL (489 ppt). Modeling was then repeated as described in Section F.3.1.1 to determine the continuous daily intake associated with this concentration.

F.3.2.2. *Baccarelli et al. (2008) Results*

Table F-9. Estimated continuous intake corresponding to maternal serum concentration for TEQ

Variable	Value	Notes
Infant b-TSH	5 μU/mL	BMR
Maternal lipid adjusted serum TEQ	489 ng/kg	From Figure 2D in For Baccarelli et al. (2008)
Intake	0.059 ng/kg-day	From Emond model; pregnancy at 30 years

TSH = thyroid stimulating hormone; BMR = benchmark response.

F.3.3. Eskenazi et al. (2002)

F.3.3.1. *Summary of Modeling Approach*

For the sensitivity analysis, modeling for Eskenazi et al. (2002) (detailed in Section 4.2.3.4) was repeated using the Eskenazi scenario female background intake (see Section F.1.2). Modeling was carried out for the mid and high exposure tertiles as described in Section F.3.1.1 using this alternative background value. The measured LASC of the lowest exposure tertile was lower than the estimated background exposure; thus, for this tertile, the Emond human PBPK model was used to find the chronic intake over the critical exposure window (13 years) which matched the measured concentration.

As part of the sensitivity analysis, the total TEQ intakes were estimated. For the mid and high tertiles, this was done by adding the Eskenazi scenario female background DLC intake to the calculated TCDD intake as discussed in Section F.3.1.1. Total TEQ intake was estimated for the lowest tertile assuming that TEQ intake is equal to ten times the modeled TCDD intake.

Table F-10. Model inputs derived from study details for Eskenazi et al. (2002)

Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Critical exposure window (years)
6.7	0.5	6.7	13

F.3.3.2. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 58692.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 58715.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 63072.  % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00422 % ESKENAZI BACKGROUND EXPOSURE, FEMALES (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 2679.4  % Over 1000 ppt GROUP

% HUMAN VARIABLE PARAMETERS
```

```
MALE   = 0.
FEMALE = 1.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==62904):length(_t)))
```

F.3.3.3. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 58692.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 58715.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 113880. % LENGTH OF CRITICAL WINDOW (HOURS)
MSTOTBCKGR   = 0.00429 % ESKENAZI BACKGROUND EXPOSURE, FEMALES (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 2679.4  % Over 1000 ppt GROUP

% HUMAN VARIABLE PARAMETERS
MALE   = 0.
FEMALE = 1.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.3.3.4. *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 113881. % LENGTH OF CRITICAL WINDOW (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 113880. % LENGTH OF CRITICAL WINDOW (HOURS)
MSTOTBCKGR   = 0.      % /KG-DAYBACKGROUND EXPOSURE INCLUDED IN MSTOT
```

```
% CONTINUOUS EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 3.08E-3 % 28-DAY   EC EXPOSURE GROUP
      % 1.52E+0 % Over 1000 ppt EXPOSURE GROUP - MATCHING MEAN
      % 6.00E+1 % Over 1000 ppt EXPOSURE GROUP - MATCHING MAX

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.3.3.5. *Eskenazi et al. (2002) Results*

Table F-11. Matching peak and average after pulse to chronic intake for Eskenazi et al. (2002) using alternate background value

Subject modeled	Exposure group	TCDD Only							TEQ[a]
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC/ measured concentration (if LASC below background) (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of continuous intake rates (ng/kg-day)
Eskenazi background									
Female	28-day EC	50	Below background				3.08E−03	3.08E−03	1.12E−02
Female	Over 1000 ppt	4060	2679.4	2552.8	1.52E+00	73933.1	6.00E+01	3.08E+01	3.08E+01

[a]TCDD average + DLC background intake (8.07×10^{-3} ng/kg-day).

F.3.4. Eskenazi et al. (2005)

F.3.4.1. *Summary of Modeling Approach*

Eskenazi et al. (2005) investigated the association of TCDD exposure and age at menopause in women who were premenopausal in 1976 and living near Seveso, Italy. Study authors divided TCDD exposures into quintiles for analysis (reported in Table 3 inEskenazi et al., [2005]). Because the dose-response trend is not clear, it was difficult to determine a NOAEL and LOAEL for this study, and all quintiles were modeled. Measured LASC values for the

second, third, and fourth quintiles were estimated by calculating the geometric means of the quintile ranges rounded to the nearest tenth. No range was specified for the first quintile (defined as ≤20.4 ppt) and fifth quintile (defined as >300 ppt). Instead, for the first quintile, measured LASC was estimated by dividing the upper bound of the exposure range by 2 to give an estimate of 10.2 ppt. For the fifth quintile, the lower bound of the exposure range was used as the measured LASC estimate.

The mean age at time of the incident was not reported by Eskenazi et al.(2005). Thus, the age at incident was approximated by subtracting the lag between event and interview (21 years) from the mean age at menopause (56.6, Table 1 in the study report) to get an approximate mean age at incident of 35.6 years old. A critical susceptibility window for this endpoint could not be determined. Because women are susceptible to ovarian function effects until menopause, an assumed critical exposure window of 50 years was assigned for the sensitivity analysis. Serum levels were measured within one year of the incident, and an LASC measurement lag time of 0.5 years was assumed. Modeling was carried out as detailed in Section F.3.1.1 for the second, third, fourth, and fifth quintiles using the Needham background scenario intake estimated (see Section F.1.1). The measured LASC of the first quintile was lower than the estimated Needham background scenario exposure; thus, for this quintile, the Emond human PBPK model was used to find the intake over the assumed critical exposure window which matched the measured LASC value.

As part of the sensitivity analysis, total TEQ intakes were estimated for the second, third, fourth, and fifth quintiles by adding the Needham scenario background DLC intake to the modeled TCDD intake as discussed in Section F.3.1.1. Total TEQ intake for the first quintile was estimated assuming that total TEQ intake is equal to ten times the modeled TCDD intake.

Table F-12. Model inputs derived from study details for Eskenazi et al. (2005)

Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Assumed critical exposure window (years)
35.6	0.5	13.6	50

F.3.4.2. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 311856. % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 311879. % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 316236. % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 2.1  % 2ND QUINTILE
      % 5.5  % 3RD QUINTILE
      % 13.8 % 4TH QUINTILE
      % 23.4 % 5TH QUINTILE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==316068):length(_t)))
```

F.3.4.3. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 311856. % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 311879. % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 438000. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 2.1  % 2ND QUINTILE
      % 5.5  % 3RD QUINTILE
      % 13.8 % 4TH QUINTILE
      % 23.4 % 5TH QUINTILE

% HUMAN VARIABLE PARAMETERS
```

```
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.3.4.4. *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 438001. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 438000. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.      % /KG-DAYBACKGROUND EXPOSURE INCLUDED IN MSTOT

% CONTINUOUS EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 1.04E-3 % 2ND QUINTILE - MATCHING MEAN
      % 1.73E-3 % 3RD QUINTILE - MATCHING MEAN
      % 3.44E-3 % 4TH QUINTILE - MATCHING MEAN
      % 5.47E-3 % 5TH QUINTILE - MATCHING MEAN
      % 3.42E-3 % 2ND QUINTILE - MATCHING MAX
      % 1.29E-2 % 3RD QUINTILE - MATCHING MAX
      % 5.16E-2 % 4TH QUINTILE - MATCHING MAX
      % 1.15E-1 % 5TH QUINTILE - MATCHING MAX

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.3.4.5. *Eskenazi et al. (2005) Results*

Table F-13. Matching peak and average after pulse to chronic intake for Eskenazi et al. (2005)

Subject modeled	Quintile	TCDD only							TEQ[a]
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC/ measured concentration (if LASC below background) (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of continuous intake rates (ng/kg-day)
Female	1st	10.2	LASC below background				1.57E−04	1.57E−04	1.57E−03[b]
Female	2nd	26.4	2.1	25.9	1.04E−03	89.4	3.42E−03	2.23E−03	5.74E−03
Female	3rd	43.1	5.5	37.7	1.73E−03	209.4	1.29E−02	7.31E−03	1.08E−02
Female	4th	80.0	13.8	62.1	3.44E−03	506.1	5.16E−02	2.75E−02	3.10E−02
Female	5th	118.0	23.4	85.9	5.47E−03	848.3	1.15E−01	6.02E−02	6.37E−02

[a]TCDD average + DLC background intake (Needham = 3.51×10^{-3} ng/kg-day).
[a]Values below background multiplied by 10, assuming total TEQ = 10 × TCDD.

F.3.5. Mocarelli et al. (2000)

F.3.5.1. *Summary of Modeling Approach*

Mocarelli et al. (2000) examined sex ratio of offspring born to parents exposed to dioxin in Seveso, Italy. Sex and age at exposure were also tested as factors possibly affecting sex ratio. Because no difference in sex ratio was observed in groups in which only the mothers were exposed to TCDD, only male exposures were modeled. Because the authors conducted this statistical test using a dichotomous exposure variable (exposed vs. unexposed or <15 ppt), and because there is no clear dose-response trend in sex ratios of offspring and father's TCDD concentrations, a NOAEL and LOAEL were difficult to establish for this study. All quintiles (reported in Table 2 in the study report) of fathers' exposure were modeled using the Emond human PBPK model. Measured LASC values for all quintiles were estimated by calculating the geometric mean of the quintile ranges reported in Table 2 in the study.

Average ages at conception for various year ranges were provided in the study in Table 5. From these ages, a population-weighted average age at conception of 31.0 and average age at the time of exposure in 1976 of 20.5 were calculated. No critical susceptibility window could be determined for this study; however, an assumed critical exposure window of 31.0 years was

assumed to match the average age at time of conception. Modeling was carried out as detailed in Section F.3.1.1 using the Needham scenario background intake (see Section F.1.1) with the exception that a 5-year response surface was used to find continuous intakes matching the modeled peak and mean LASC values, as detailed in Section F.3.5.1.

As part of the sensitivity analysis, total TEQ intakes were estimated for all tertiles by adding the Needham scenario background DLC intake to the modeled TCDD intake as described in Section F.3.1.1.

Table F-14. Model inputs derived from study details for Mocarelli et al. (2000)

Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Assumed critical exposure window (years)
20.5	0.5	20	31.0

F.3.5.2. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 179580. % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 179603. % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 183960. % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00035 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 1.2    % 1ST QUINTILE
      % 4.2    % 2ND QUINTILE
      % 11.0   % 3RD QUINTILE
      % 30.2   % 4TH QUINTILE
      % 1420.0 % 5TH QUINTILE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
```

```
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==183792):length(_t)))
```

F.3.5.3. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 179580. % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 179603. % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 271560. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.00035 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 1.2    % 1ST QUINTILE
      % 4.2    % 2ND QUINTILE
      % 11.0   % 3RD QUINTILE
      % 30.2   % 4TH QUINTILE
      % 1420.0 % 5TH QUINTILE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.3.5.4. *Mocarelli et al. (2000) Results*

Table F-15. Matching peak and average after pulse to 5-year average response surface for Mocarelli et al. (2000)

Subject modeled	Quintile	TCDD only							TEQ
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	5-Year response surface matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	5-Year response surface matching peak LASC (ng/kg-day)	Average of 5-Year response surface values (ng/kg-day)	Average of 5-Year response surface values (ng/kg-day)
Male	1st	21.7	1.2	19.0	2.82E−04	52.4	1.35E−03	8.17E−04	3.97E−03
Male	2nd	44	4.2	33.0	6.56E−04	160.0	7.93E−03	4.30E−03	7.45E−03
Male	3rd	84.8	11.0	46.9	1.58E−03	397.3	3.41E−02	1.78E−02	2.10E−02
Male	4th	176.5	30.2	112.4	4.69E−03	1072.0	1.62E−01	8.31E−02	8.63E−02
Male	5th	2723.7	1420.0	1485.2	2.66E−01	48470.7	2.63E+01	1.33E+01	1.33E+01

F.3.6. Mocarelli et al. (2008)

F.3.6.1. *Summary of Modeling Approach*

For the sensitivity analysis, modeling for Mocarelli et al. (2008) (detailed in Section 4.2.3.2) was repeated for the 1st quartile (LOAEL group), only, using the male TCDD background intake of 4.22×10^{-3} ng/kg-day estimated for the Eskenazi scenario (see Table F-2) for children aged 0–12. Modeling was carried out as described in Section F.3.1.1 using this alternative background value.

As part of the sensitivity analysis, total TEQ intakes also were modeled for the 1st quartile using the Needham and Eskenazi scenario background TEQ intakes (see Tables F-2 and F-2). This approach models the exposure directly, by matching the total TEQ (as LASC ppt, TCDD included) at the time of TCDD measurement (i.e., serum sampling for boys 6.7 years old) with the corresponding intake using the Emond model. For the Needham scenario, background TEQ LASC at the time of measurement was estimated by running the Emond model from birth to age 6.7 with a constant exposure of 8.9×10^{-3} ng/kg-day. The resulting total TEQ background LASC of 80.6 ppt was multiplied by 0.9 to obtain the corresponding DLC-TEQ LASC (72.5 ppt), which was added to the measured TCDD LASC of 68 as an estimate of total TEQ LASC at time of measurement.

For the Eskenazi scenario, the background TCDD and TEQ LASC values are given as age-group averages, rather than time-point values. The averages were assumed to be the background levels at time of measurement. The total TEQ LASC is 93.7 ppt (see Table F-2). The DLC-TEQ contribution to background exposure is 53.2 ppt, which is added to the measured TCDD LASC of 68 as an estimate of total TEQ LASC at time of measurement.

An additional TCDD-only analysis was run for a Hill coefficient (HILL) value of 1 and an elimination constant (KELV) of 0.005, which was optimized.

Table F-16. Model inputs derived from study details for Mocarelli et al. (2008)

Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Critical exposure window (years)
6.2	0.5	3.8	10

F.3.6.2. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 54312.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 54335.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 58692.  % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00422 % ESKENAZI BACKGROUND TCDD INTAKE (NG/KG-DAY)
             % 0.0132  % ESKENAZI BACKGROUND TEQ INTAKE (NG/KG-DAY)
             % 0.0089  % NEEDHAM BACKGROUND TEQ INTAKE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 3.36 % TCDD only, ESKENAZI SCENARIO, 1ST QUARTILE
      % 2.9  % TOTAL TEQ, ESKENAZI SCENARIO, 1ST QUARTILE
      % 11.8 % TOTAL TEQ, NEEDHAM SCENARIO, 1ST QUARTILE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
```

```
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==58524):length(_t)))
```

F.3.6.3. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 54312.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 54335.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 87600.  % LENGTH OF CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.00422 % ESKENAZI BACKGROUND TCDD INTAKE (NG/KG-DAY)
             % 0.0132  % ESKENAZI BACKGROUND TEQ INTAKE (NG/KG-DAY)
             % 0.0089  % NEEDHAM BACKGROUND TEQ INTAKE (NG/KG-DAY)
/KG-DAY
% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 3.36  % TCDD only, ESKENAZI SCENARIO
      % 2.9   % TOTAL TEQ, ESKENAZI SCENARIO
      % 11.8  % TOTAL TEQ, NEEDHAM SCENARIO

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.3.6.4. *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 87601.  % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 87600.  % LENGTH OF CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.      % /KG-DAYBACKGROUND EXPOSURE INCLUDED IN MSTOT
```

```
% CONTINUOUS EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 1.03E-2 % TCDD, ESKENAZI SCENARIO - MATCHING MEAN
      % 1.34E-2 % TCDD, ESKENAZI SCENARIO - MATCHING PEAK
      % 2.45E-2 % TEQ, ESKENAZI SCENARIO - MATCHING MEAN
      % 2.02E-2 % TEQ, ESKENAZI SCENARIO - MATCHING PEAK
      % 2.56E-2 % TEQ, NEEDHAM SCENARIO - MATCHING MEAN
      % 6.66E-2 % TEQ, NEEDHAM SCENARIO - MATCHING PEAK

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.3.6.5. *Mocarelli et al. (2008) Results*

Table F-17. Matching peak and average after pulse to critical-window intake for Mocarelli et al. (2008) using alternate background value

Subject modeled	Quartile	Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC (ng/kg-day)	Average of continuous intake rates (ng/kg-day)
TCDD Eskenazi scenario; background LASC = 40.5 (4.22E-03 ng/kg-day)								
Male	1st	68	3.36	69.7	1.03E−02	137.6	1.34E−02	1.18E−02
TEQ Eskenazi scenario; background LASC = 93.7 (1.32E-03 ng/kg-day)								
Male	1st	121.2[a]	2.9	131.2	2.45E-02	181.7	2.02E−02	-[c]
TEQ Needham scenario; background LASC = 150 ppt (8.9E-03 ng/kg-day)								
Male	1st	140.5[b]	11.8	135.4	2.56E−02	403.7	6.66E−02	4.61E−02
TCDD alternate Hill coefficient scenario[d]; background intake = 1.9E-04 ng/kg-day								
Male	1st	86	4.11	64.2	3.73E−03	254.8	7.61E−03	5.67E−03

[a]68 ppt TCDD + 72.5 ppt DLC-TEQ.
[b]Window-average > Peak; overall average not meaningful.
[c]68 ppt TCDD + 53.2 ppt DLC-TEQ.
[d]HILL = 1, KELV= 0.005, Needham background scenario (15 ppt at 35 years).

F.3.7. Mocarelli et al. (2011)

F.3.7.1. *Summary of Modeling Approach*

Mocarelli et al. (2011) examined sperm effects in boys who experienced perinatal TCDD exposure during the Seveso event in 1976. Study authors used a model based on 1st-order kinetics to extrapolate the measured LASC concentrations to the concentration at conception.

For consistency with all other exposure estimates, EPA did not use the study authors' exposure estimates and instead used the Emond human PBPK model to estimate concentrations at conception. The median measured LASC for mothers who breastfed was provided in the study (reported in Table 2 of the study) and was selected as a LOAEL. Measured LASC of the comparison group was assumed by the study authors to be equal to the value reported in Eskenazi et al. (2004) (average of 10.4 ppt) for the 20–40 age group.

The average age of the women in the study was 24.8 years at the time of the incident, as reported in the study text in the Materials and Methods section. The average age of the women at conception in the exposed group was reported to be 28.2 years. Two mean ages-at-conception were evaluated by EPA: 30 and 45 years old. Serum levels were measured within one year of the incident, and an LASC measurement lag time of 0.5 years was assumed. Modeling was carried out for the exposure group that breastfed as detailed in Section F.3.1.1 using a scenario-specific background intake modeled for an assumption of 10.4 ppt TCDD at age 30; the background intake was assumed to be the same at age 45. Continuous daily TCDD intakes were modeled to delivery (age at conception + 9 months) for both alternative ages-at-conception.

As part of the sensitivity analysis, total TEQ intakes were estimated for the exposure group that breastfed by assuming that total TEQ intake is equal to ten times the modeled TCDD background intake. The resulting background DLC-TEQ intake of 2.61×10^{-3} ng/kg-day ($2.9 \times 10^{-4} \times 9$) was added to the modeled TCDD intakes to obtain the total TEQ intake estimates.

Table F-18. Model inputs derived from study details for Mocarelli et al. (2011)

Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Target population exposure window[a] (years)
24.8	0.5	5.2, 20.2	30.75, 45.75

[a]Age at delivery

F.3.7.2. *Input for Exposure from Event to LASC Measurement*

```
% EMOND HUMAN NON-GESTATION MODEL
% MODEL PARAMETERS
output @clear
```

```
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 217248. % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 217249. % AGE AT END OF EXPOSURE (HOURS)
BCK_TIME_ON  = 0.      % BEGIN BACKGROUND EXPOSURE (HOURS)
BCK_TIME_OFF = 613200. % END BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 221628. % AGE AT LASC MEASUREMENT (HOURS) (25.3 years)
MSTOTBCKGR   = 0.00029 % STUDY-SPECIFIC BACKGROUND EXPOSURE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 6.37 % BREASTFEEDING GROUP (46.8 ppt TCDD measured)

% HUMAN VARIABLE PARAMETERS
MALE   = 0.
FEMALE = 1.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==58524):length(_t)))
```

F.3.7.3. *Input for Exposure from Event to the Study-Average Age at Delivery*

```
% EMOND HUMAN GESTATION MODEL
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
BCK_TIME_ON  = 0.      % BEGIN BACKGROUND EXPOSURE (HOURS)
BCK_TIME_OFF = 613200. % END BACKGROUND EXPOSURE (HOURS)
EXP_TIME_ON  = 217248. % AGE AT EXPOSURE (HOURS) (24.8 years)
EXP_TIME_OFF = 217249. % AGE AT END OF EXPOSURE (HOURS)
CONCEPT      = 247032  % AGE AT CONCEPTION (HOURS) (28.2 years)
TIMELIMIT    = 253602. % AGE AT DELIVERY (HOURS) (28.95 years)
MSTOTBCKGR   = 0.00029 % MODELED BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 6.37 % BREASTFEEDING GROUP

MALE   = 0.
FEMALE = 1.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.3.7.4. *Input for Continuous Exposure until Age at Delivery for General Population*

```
% EMOND HUMAN GESTATION MODEL
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
CINT  = 1
MAXT  = 0.5
CONCEPT      = 262801. % AGE 30 AT CONCEPTION (HOURS)
             % 394201. % AGE 45 AT CONCEPTION (HOURS)
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 262801. % AGE 30.75 AT DELIVERY (HOURS)
             % 394201. % AGE 45.75 AT DELIVERY (HOURS)
TIMELIMIT    = EXP_TIME_OFF
MSTOTBCKGR   = 0.      % BACKGROUND EXPOSURE INCLUDED IN MSTOT

% CONTINUOUS EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 2.90E-4 % COMPARISON GROUP    - 10.4 PPT AT AGE 30 (BACKGROUND)
      % 1.50E-3 % BREASTFEEDING GROUP – 38.3 PPT AT AGE 30.75 AT DELIVERY
      % 1.04E-3 % BREASTFEEDING GROUP - 38.3 PPT AT AGE 45.75 AT DELIVERY

% HUMAN VARIABLE PARAMETERS
MALE   = 0.
FEMALE = 1.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.3.7.5. *Mocarelli et al. (2011) Results*

Table F-19. Matching concentration at conception for the study population to chronic intake for the general population for Mocarelli et al. (2011)

Subject modeled	Exposure group	General population age at conception	TCDD only				TEQ[a]
			Measured LASC (ng/kg)	Event dose (ng/kg)	Terminal LASC at conception (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Continuous intake matching average LASC (ng/kg-day)
Female	Comparison	30	10.4	LASC at background		2.90E−04	2.90E−03
Female		45					
Female	Breastfed	30	46.8	6.357	38.3	1.50E−03	4.11E−03
Female		45				1.04E−03	3.65E−03

[a]TCDD average + DLC background intake (2.61×10^{-3} ng/kg-day).

F.3.8. Warner et al. (2004)

F.3.8.1. *Summary of Modeling Approach*

Warner et al. (2004) studied age at onset of menarche in girls who were premenarcheal in 1976 at the time of first exposure. Study authors divided exposure groups into quartiles, and reported the exposures as ranges of measured TCDD LASC. EPA determined that the highest exposure group (4th quartile) was a NOAEL, so only the fourth quartile was evaluated for the sensitivity analysis. For the fourth quartile, the lower bound of the exposure range was used as the measured LASC estimate for estimating TCDD intakes.

The average age of the subjects on July 10, 1976 was reported to be 6.9 years in the text in the Results section. The critical susceptibility window for this endpoint could not be determined; however, an assumed critical exposure window of 12.8 was established for modeling purposes based on the age at menarche (12.8 ± 1.6 years) reported by Warner et al. (2004). Serum levels were measured within one year of the incident, therefore an LASC measurement lag time of 0.5 years was assumed. Modeling was carried out as detailed in Section F.3.3.1. Intakes were modeled with the Needham and Eskenazi background intakes as defined previously (see Section F.1.1 and F.1.2). Total TEQ was estimated by adding the background DLC intake for the corresponding scenario to the calculated TCDD intakes as described in Section F.3.1.1.

Table F-20. Model inputs derived from study details for Warner et al. (2004)

Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Assumed critical exposure window (years)
6.9	0.5	5.9	12.8

F.3.8.2. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 60444.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 60467.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 64824.  % AGE AT LASC MEASUREMENT (HOURS)
```

```
MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG-DAY)
             % 0.00429 % ESKENAZI BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 0.3  % 1ST QUARTILE LOW - NEEDHAM BACKGROUND
      % 3.0  % 1ST QUARTILE HIGH - NEEDHAM BACKGROUND
      % 11.9 % 2ND QUARTILE - NEEDHAM BACKGROUND
      % 37.9 % 3RD QUARTILE - NEEDHAM BACKGROUND
      % 64.8 % 4TH QUARTILE - NEEDHAM BACKGROUND
      % 6.4  % 2ND QUARTILE - ESKENAZI BACKGROUND
      % 32.5 % 3RD QUARTILE - ESKENAZI BACKGROUND
      % 59.3 % 4TH QUARTILE - ESKENAZI BACKGROUND

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==64656):length(_t)))
```

F.3.8.3. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG


% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 60444.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 60467.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 112128. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG-DAY)
             % 0.00429 % ESKENAZI BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 64.8 % 4TH QUARTILE - NEEDHAM BACKGROUND
      % 59.3 % 4TH QUARTILE - ESKENAZI BACKGROUND

% HUMAN VARIABLE PARAMETERS
MALE   = 0.
FEMALE = 1.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.3.8.4. *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 112129. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 112128. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.      % /KG-DAYBACKGROUND EXPOSURE INCLUDED IN MSTOT

% CONTINUOUS EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 3.94E-2. % 4TH QUARTILE - NEEDHAM  BACKGROUND - MATCHING MEAN
      % 4.24E-2. % 4TH QUARTILE - ESKENAZI BACKGROUND - MATCHING MEAN
      % 6.04E-1  % 4TH QUARTILE - NEEDHAM  BACKGROUND - MATCHING PEAK
      % 5.17E-1  % 4TH QUARTILE - ESKENAZI BACKGROUND - MATCHING PEAK

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.3.8.5. *Warner et al. (2004) Results*

Table F-21. Matching peak and average after pulse to chronic intake for Warner et al. (2004)

Subject modeled	Quartile	TCDD only							TEQ[a]
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC/ measured concentration (if LASC below background) (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of continuous intake rates (ng/kg-day)
Needham background									
Female	4th	300.0	64.8	207.2	3.94E−02	1896.6	6.04E−01	3.22E−01	3.25E−01
Eskenazi background									
Female	4th	300.0	59.3	218.2	4.24E−02	1708.9	5.17E−01	2.80E−01	2.88E−01

[a]TCDD average + DLC background intake (Needham = 3.5×10^{-3} ng/kg-day; Eskenazi = 8.1×10^{-3} ng/kg-day).

F.3.9. Warner et al. (2007)

F.3.9.1. *Summary of Modeling Approach*

Warner et al. (2007) examined ovarian function in women residents of Seveso, Italy in 1996−1998, approximately 21 years after the incident. For analysis of ovulation status, the study authors divided the exposure range into quartile groups (reported in Table 3 in the study report). EPA determined that the highest exposure group (4th quartile) was a NOAEL, so only the fourth quartile was evaluated for the sensitivity analysis. For the fourth quartile, the lower bound of the exposure group was used as the measured LASC estimate for estimating TCDD intakes.

Warner et al., (2007) reported the average age of women at the time of the interviews (1996–1998) to be 31.3 years old in the text in the Results section. Because interviews took place on average 21 years after the incident, average age at the time of the incident was estimated to be 10 years old. Serum values were collected within a year of the incident, and an LASC measurement lag time of 0.5 years was assumed. A critical susceptibility window for this endpoint could not be determined. Because women are susceptible to ovarian function effects until menopause, an assumed critical exposure window of 50 years was assigned as a

conservative estimate for the sensitivity analysis. Modeling was carried out as detailed in Section F.3.1.1 using the Needham scenario background intake (see Section F.1.1).

As part of the sensitivity analysis, the intake when including DLCs was estimated by adding the background DLC-TEQ intake to the modeled TCDD intake as described in Section F.1.1 using the Needham scenario female additive background DLC intake factor.

Table F-22. Model inputs derived from study details for Warner et al. (2007)

Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Assumed critical exposure window (years)
10	0.5	21	50

F.3.9.2. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 87600.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 87623.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 91980.  % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 0.1   % 1ST QUARTILE
      % 3.7   % 2ND QUARTILE
      % 127.8 % 3RD QUARTILE
      % 212.0 % 4TH QUARTILE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==91812):length(_t)))
```

F.3.9.3. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 87600.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 87623.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 438000. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG-DAY)

% EVENT EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 212.0 % 4TH QUARTILE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.3.9.4. *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 438001. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 438000. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.      % /KG-DAYBACKGROUND EXPOSURE INCLUDED IN MSTOT

% CONTINUOUS EXPOSURE DOSE (NG/KG-DAY)
MSTOT = 3.00E-3 % 4TH QUARTILE - MATCHING MEAN
      % 2.04E-1 % 4TH QUARTILE - MATCHING PEAK

% HUMAN VARIABLE PARAMETERS
MALE   = 0.
FEMALE = 1.
```

```
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.3.9.5. *Warner et al. (2007) Results*

Table F-23. Matching peak and average after pulse to chronic intake for Warner et al. (2007)

Subject modeled	Quartile	TCDD only							TEQ[a]
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of continuous intake rates (ng/kg-day)
Needham background									
Female	4th	212.0	39.4	56.3	3.00E−03	1229.7	2.04E−01	1.04E−01	1.07E−01

[a]TCDD average + DLC background intake (Needham = 3.5×10^{-3} ng/kg-day).

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APPENDIX G

Noncancer Benchmark Dose Modeling

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National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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APPENDIX G. NONCANCER BENCHMARK DOSE MODELING

G.1. BENCHMARK DOSE SOFTWARE (BMDS) INPUT TABLES

G.1.1. Amin et al. (2000)

Endpoint[c]	Administered dose (ng/kg-day)		
	0	25[a]	100
	Internal dose (ng/kg blood)[b]		
	0	3.38	10.57
	(*n* = 10)	(*n* = 10)	(*n* = 10)
Saccharin consumed, female rats (0.25%) (mL saccharin solution/100 g body weight)[c]	31.67 ± 6.53	24.60 ± 3.79	10.70 ± 1.68
Saccharin consumed, female rats (0.50%) (mL saccharin solution/100 g body weight)[c]	22.40 ± 5.05	11.38 ± 2.42	4.54 ± 1.05
Saccharin preference ratio, female rats (0.25%) (ratio of saccharin solution consumed to total fluid consumed)[d]	82.14 ± 4.22	58.12 ± 10.71	54.87 ± 6.17
Saccharin preference ratio, female rats (0.50%) (ratio of saccharin solution consumed to total fluid consumed)[d]	72.73 ± 7.79	44.48 ± 10.39	33.77 ± 7.79

[a] Lowest-observed-adverse-effect level (LOAEL) identified.
[b] From the Emond physiologically based pharmacokinetic (PBPK) model described in Section 3.3.
[c] Values are the mean ± standard error (SE). Data obtained from Figure 2 in Amin et al. (2000).
[d] Values are the ratio ± SE. Data obtained from Figure 3 in Amin et al. (2000).

G.1.2. Bell et al. (2007)

Endpoint	Administered dose (ng/kg-day)			
	0	2.4[a]	8	46
	Internal dose (ng/kg blood)[b]			
	0	2.20	5.14	18.41
	(*n* = 30)	(*n* = 30)	(*n* = 30)	(*n* = 30)
Proportion of male rat pups that had not undergone balano-preputial separation on PND 49[c]	1/30 (3%)	5/30 (17%)	6/30 (20%)	15/30 (50%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Data obtained from Figure 2 in Bell et al. (2007).

PND = postnatal day.

G.1.3. Cantoni et al. (1981)

Endpoint	Administered dose (ng/kg-day)			
	0	**1.43[a]**	**14.3**	**143**
	Internal dose (ng/kg blood)[b]			
	0	**1.85**	**8.84**	**50.05**
	(*n* = 4)	**(*n* = 4)**	**(*n* = 3)**	**(*n* = 3)**
Urinary coproporphyrins in female rats (µg coproporphyrin methyl ester/24 hr) at 3 months[c]	0.74 ± 0.17	1.81 ± 0.42[d]	2.73 ± 0.75[e]	3.00 ± 1.30[e]
Urinary porphyrins in rats (nmol/24 hr) after 45 weeks[c]	2.27 ± 0.49	5.55 ± 0.85[d]	7.62 ± 1.79[d]	196.89 ± 63.14[e]

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SE. Data for urinary coproporphyrins and urinary porphyrins obtained from Figure 1 and Table 1, respectively, in Cantoni et al. (1981).
[d] Statistically significant as compared to control ($p < 0.05$).
[e] Statistically significant as compared to control ($p < 0.01$).

G.1.4. Crofton et al. (2005)

Endpoint	Administered dose (ng/kg-day)									
	0	**0.1**	**3**	**10**	**30[a]**	**100[b]**	**300**	**1,000**	**3,000**	**10,000**
	Internal dose (ng/kg blood)[c]									
	0	**0.02**	**0.49**	**1.38**	**3.46**	**9.26**	**23.07**	**65.65**	**180.90**	**583.48**
	(*n* = 14)	**(*n* = 6)**	**(*n* = 12)**	**(*n* = 6)**	**(*n* = 6)**	**(*n* = 6)**	**(*n* = 6)**	**(*n* = 6)**	**(*n* = 6)**	**(*n* = 4)**
Serum T4 in female rats (% control)[d]	100.00 ± 15.44	96.27 ± 14.98	98.57 ± 18.11	99.76 ± 19.04	93.32 ± 12.11	70.94 ± 12.74	62.52 ± 14.75	52.68 ± 22.73	54.66 ± 19.71	49.15 ± 11.15

[a] No-observed-adverse-effect level (NOAEL) identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SD. Data were obtained from a Crofton et al. (2005) supplemental file, available at http://ehp.niehs.nih.gov/docs/2005/8195/supplemental.pdf.

G.1.5. DeCaprio et al. (1986)

Endpoint	Administered dose (ng/kg-day)				
	0	**0.12**	**0.61[a]**	**4.9[b]**	**26**
	Internal dose (ng/kg blood) [c]				
	NM	**NM**	**NM**	**NM**	**NM**
	(*n* = 10)	**(*n* = 10)**	**(*n* = 11)**	**(*n* = 10)**	**(*n* = 4)**
Absolute kidney weight (g), males[d]	5.49 ± 0.17	5.14 ± 0.12	4.71 ± 0.12	4.3 ± 0.15[f]	-
Absolute thymus weight (g), males[d]	0.56 ± 0.050	0.45 ± 0.022	0.44 ± 0.034	0.35 ± 0.167[g]	-
Body weight (g), males[e]	713 ± 15	682 ± 16	651 ± 19	603 ± 20[f]	433 ± 38[h]
Relative brain weight, males[d]	0.54 ± 0.015	0.56 ± 0.016	0.6 ± 0.016	0.65 ± 0.016[f]	-
Relative liver weight, males[d]	4.54 ± 0.23	4.1 ± 0.14	5.36 ± 0.61	5.63 ± 0.29[f]	-
Relative thymus weight, males[d]	0.078 ± 0.006	0.066 ± 0.003	0.068 ± 0.004	0.06±0.003[f]	-
Endpoint	**Administered dose (ng/kg-day)**				
	0	**0.12**	**0.68**	**4.86**	**31**
	Internal dose (ng/kg blood)[c]				
	0	**NM**	**NM**	**NM**	**NM**
	(*n* = 8)	**(*n* = 10)**	**(*n* = 9)**	**(*n* = 10)**	**(*n* = 4)**
Body weight (g), females[e]	602 ± 12	583 ± 22	570 ± 22	531 ± 14[f]	351 ± 49[h]
Relative liver weight, females[d]	4.3 ± 0.26	4.49 ± 0.35	4.27 ± 0.16	5.54 ± 0.43[f]	-

[a] NOAEL identified.
[b] LOAEL identified.
[c] Internal dose not calculated using the Emond PBPK (guinea pigs).
[d] Organ weight data in guinea pigs obtained from Table 2 of DeCaprio et al. (1986). Values are the mean ± SE. Relative organs weights were calculated as organ weight (g)/body weight (g) × 100.
[e] Body weight data in guinea pigs obtained from Table 1 of DeCaprio et al. (1986). Values are the mean ± SE.
[f] Statistically significant as compared to control ($p < 0.05$).
[g] Statistically significant as compared to control ($p < 0.01$).
[h] Statistically significant as compared to control ($p < 0.001$).

NM = not modeled.

G.1.6. Franc et al. (2001)

Endpoint	Administered dose (ng/kg-day)			
	0	**10[a]**	**30[b]**	**100**
	Internal dose (ng/kg blood) [c]			
	0	**6.59**	**14.48**	**36.43**
	(*n* = 8)	**(*n* = 8)**	**(*n* = 8)**	**(*n* = 8)**
S-D rats, relative liver weight[d]	100.0 ± 5.0	108.1 ± 6.0[e]	116.8 ± 9.2[e]	155.3 ± 10.9[e]
L-E rats, relative liver weight[d]	100.0 ± 3.5	106.3 ± 6.3	116.8 ± 3.2[e]	122.2 ± 7.0[e]
S-D rats, relative thymus weight[d]	100.2 ± 29.4	91.2 ± 17.0	51.4 ± 15.4[e]	22.8 ± 10.6[e]
L-E rats, relative thymus weight[d]	103.4 ± 19.3	95.4 ± 24.9	38.7 ± 17.0[e]	35.0 ± 27.6[e]
H/W rats, relative thymus weight[d]	101.2 ± 12.7	97.5 ± 11.7.0	71.0 ± 8.5[e]	49.3 ± 15.4[e]

[a] NOAEL identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 5 in Franc et al. (2001).
[e] Statistically significant as compared to control ($p < 0.05$).

H/W = Han/Wistar; L-E = Long-Evans; S-D = Sprague-Dawley.

G.1.7. Hojo et al. (2002)

Endpoint	Administered dose (ng/kg-day)			
	0	**20[a]**	**60**	**180**
	Internal dose (ng/kg blood)[b]			
	0	**1.62**	**4.17**	**10.70**
	(*n* = 5)	**(*n* = 5)**	**(*n* = 6)**	**(*n* = 5)**
DRL reinforcements/min, rat litters[c]	−0.814 ± 0.45	−0.364 ± 0.82	0.374 ± 0.54	−0.163 ± 0.44
DRL responses/min, rat litters[c]	18.44 ± 7.99	−0.99 ± 10.96	−4.52 ± 7.19	−0.41 ± 15.23

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] DRL = differential reinforcement of low rate. Values are the mean ± SD. Data obtained from Table 5 in Hojo et al. (2002).

G.1.8. Kattainen et al. (2001)

Endpoint	Administered dose (ng/kg-day)				
	0	**30[a]**	**100**	**300**	**1,000**
	Internal dose (ng/kg blood)[b]				
	0	**2.23**	**6.25**	**16.08**	**46.86**
	(*n* = 16)	**(*n* = 17)**	**(*n* = 15)**	**(*n* = 12)**	**(*n* = 19)**
3rd molar mesio-distal length in female rat offspring (molar development) (mm)[c]	1.86 ± 0.017	1.58 ± 0.045[d]	1.6 ± 0.069[d]	1.5 ± 0.064[d]	1.35 ± 0.118[d]
Proportion of female rat offspring without 3rd molar eruption on PND 35[e]	1/16 (10%)	3/17 (20%)	4/15 (30%)	6/12 (50%)[d]	13/19 (70%)[d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SE. Data were obtained from Figure 3 in Kattainen et al. (2001).
[d] Statistically significant as compared to control ($p < 0.05$).
[e] Data were obtained from Figure 2 in Kattainen et al. (2001).

G.1.9. Keller et al. (2008a; 2008b; 2007)

Endpoint	Administered dose (ng/kg-day)			
	0	**10[a]**	**100**	**1,000**
	Internal dose (ng/kg blood)[b]			
	0	**0.54**	**4.29**	**34.06**
Frequency of missing 3rd mandibular molars in CBA J mice[c]	0/29 (0%)	2/23 (10%)	6/29 (20%)	30/30 (100%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Data obtained from Table 1 in Keller et al. (2007).

G.1.10. Kociba et al. (1978)

Endpoint	Administered dose (ng/kg-day)			
	0	1[a]	10[b]	100
	Internal dose (ng/kg blood) [c]			
	0	1.55	7.15	38.56
	(*n* = 5)	(*n* = 5)	(*n* = 5)	(*n* = 5)
Urinary coproporphyrin (µg/48 h), female rats[d]	9.8 ± 1.3	8.6 ± 2	16.4 ± 4.7 [e]	17.4 ± 4[e]
µg uroporphyrin per mg creatinine, female rats[d]	0.157 ± 0.05	0.143 ± 0.037	0.181 ± 0.053	0.296 ± 0.074 [e]

[a] NOAEL identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SD. Data obtained from Table 2 in Kociba et al. (1978).
[e] Statistically significant as compared to control ($p < 0.05$).

G.1.11. Kuchiiwa et al. (2002)

Endpoint	Administered Dose (ng/kg-day)		
	0	0.7[a]	70
	Internal Dose (ng/kg blood)[b]		
	0	0.26	9.12
	(*n* = 6)	(*n* = 6)	(*n* = 6)
Immunoreactive neurons in dorsalis, males[c]	237.1 ± 29.0	136.6 ± 22.4[d]	86.0 ± 13.2[d,e]
Immunoreactive neurons in medianus, males[c]	91.1 ± 12.2	33.3 ± 4.55[d]	23.1 ± 8.10[d,e]
Immunoreactive neurons in B9, males[c]	152.1 ± 16.0	46.8 ± 12.1[d]	19.6 ± 15.2[d,e]
Immunoreactive neurons in magnus, males[c]	43.61 ± 3.40	19.82 ± 10.20[d]	11.10 ± 3.88[d,e]

[a] LOAEL identified.
[b] From the Emond PRPK model described in Section 3.3.
[c] Values are the mean ± SD. Data obtained from Figure 2 in Kuchiiwa et al. (2002).
[d] Statistically significant as compared to control ($p < 0.01$).
[e] Dose dropped from Benchmark Dose (BMD) modeling

G.1.12. Latchoumycandane and Mathur (2002)

Endpoint	Administered dose (ng/kg-day)			
	0	**1[a]**	**10**	**100**
	Internal dose (ng/kg blood)[b]			
	0	**0.78**	**4.65**	**27.27**
	(*n* = 6)	**(*n* = 6)**	**(*n* = 6)**	**(*n* = 6)**
Daily sperm production ($\times 10^6$) in adult male rats (mg)[c]	22.19 ± 2.67	15.67 ± 2.65[d]	13.65 ± 2.19[d]	13.1 ± 3.16[d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SD. Data obtained from Table 1 in Latchoumycandane and Mathur (2002).
[d] Statistically significant as compared to control ($p < 0.05$).

G.1.13. Li et al. (1997)

Endpoint	Administered dose (ng/kg-day)									
	0	**3[a]**	**10[b]**	**30**	**100**	**300**	**1,000**	**3,000**	**10,000**	**30,000**
	Internal dose (ng/kg blood)[c]									
	0	**0.27**	**0.80**	**2.1**	**5.87**	**15**	**43.33**	**119.94**	**385.96**	**1,171.90**
	(*n* = 10)	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**
Serum FSH (ng/mL) in female rats[d]	23.86 ± 9.38	22.16 ± 15.34	85.23 ± 29.83	73.30 ± 15.34	126.14 ± 50.28	132.10 ± 36.65	116.76 ± 16.19	304.26 ± 48.58	346.88 ± 47.73	455.11 ± 90.34

[a] NOAEL identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 3 in Li et al. (1997).

FSH = follicle stimulatin hormone.

G.1.14. Li et al. (2006)

Endpoint	Administered dose (ng/kg-day)			
	0	**2**[a]	**50**	**100**
	Internal dose (ng/kg blood)[b]			
	0	**0.16**	**2.84**	**5.12**
	(*n* = 10)	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**
Serum estradiol/(pg·mL)$^{-1}$ in female mice (1~3d)[c]	10.17 ± 3.85	19.91 ± 6.31	24.72 ± 4.60	18.09 ± 5.57
Serum progesterone (ng·mL)$^{-1}$ in female mice (1~3d)[c]	61.74 ± 3.51	30.56 ± 12.80[d]	16.93 ± 10.53	11.36 ± 13.83

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SE. Data obtained from Figures 3 (estradiol) and 4 (progesterone) in Li et al. (2006).
[d] Statistically significant as compared to control ($p < 0.01$).

G.1.15. Markowski et al. (2001)

Endpoint	Administered dose (ng/kg-day)			
	0	**20**[a]	**60**	**180**
	Internal dose (ng/kg blood)[b]			
	0	**1.56**	**4.03**	**10.32**
	(*n* = 7)	**(*n* = 4)**	**(*n* = 6)**	**(*n* = 7)**
FR10 earned run opportunities, adult female offspring[c]	13.29 ± 8.65	11.25 ± 5.56	5.75 ± 3.53	7 ± 6.01
FR2 total revolutions, adult female offspring[c]	119.29 ± 69.9	108.5 ± 61	56.5 ± 31.21	68.14 ± 33.23
FR5 earned run opportunities, adult female offspring[c]	26.14 ± 12.28	23.5 ± 7.04	12.8 ± 6.17	13.14 ± 7.14

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SD. Data obtained from Table 3 in Markowski et al. (2001).

G.1.16. Miettinen et al. (2006)

Endpoint	Administered dose (ng/kg-day)				
	0	**30[a]**	**100**	**300**	**1,000**
	Internal dose (ng/kg blood)[b]				
	0	**2.22**	**6.23**	**16.01**	**46.64**
	(*n* = 42)	**(*n* = 29)**	**(*n* = 15)**	**(*n* = 24)**	**(*n* = 32)**
Cariogenic lesions in rat pups[c]	25/42 (60%)	23/29 (79%)[d]	19/25 (76%)	20/24 (83%)[d]	29/32 (91%)[d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Data obtained from Table 2 in Miettinen et al. (2006).
[d] Statistically significant as compared to control ($p < 0.05$).

G.1.17. National Toxicology Program (1982)

Endpoint	Administered dose (ng/kg-day)			
	0	**1.43[a]**	**7.14**	**71.4**
	Internal dose (ng/kg blood)[b]			
	0	**0.77**	**2.27**	**11.24**
	(*n* = 73)	**(*n* = 49)**	**(*n* = 49)**	**(*n* = 50)**
Numbers of male mice with toxic hepatitis[c]	1/73 (1.4%)	5/49 (10%)	3/49 (6.1%)	44/50 (88%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Data obtained from Table 11 in NTP (1982).

G.1.18. National Toxicology Program (2006)

Endpoint[c]	Administered dose (ng/kg-day)					
	0	**2.14[a]**	**7.14**	**15.7**	**32.9**	**71.4**
	Internal dose (ng/kg blood)[b]					
	0	**2.56**	**5.69**	**9.79**	**16.57**	**29.70**
	(*n* = 10)	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**
Gingival squamous hyperplasia	1/53 (2%)	7/54 (13%)[d]	14/53 (26%)[e]	13/53 (25%)[e]	15/53 (28%)[e]	16/53 (30%)[e]
Liver, hepatocyte hypertrophy	0/53 (0%)	19/54 (40%)[e]	19/53 (40%)[c]	42/53 (80%)[e]	41/53 (80%)[e]	52/53 (100%)[e]
Heart, cardiomyopathy	10/53 (19%)	12/54 (22%)	22/53[e] (42%)	25/52[e] (48%)	32/53[e] (60%)	36/52[e] (69%)
Liver, eosinophilic focus, multiple	3/53 (6%)	8/54 (15%)	14/53 (26%)	17/53 (32%)	22/53 (42%)	42/53 (79%)
Liver, fatty change, diffuse	0/53 (0%)	2/54 (4%)	12/53[e] (23%)	17/53[e] (32%)	30/53[e] (57%)	48/53[e] (91%)
Liver, necrosis	1/53 (2%)	4/54 (7%)	4/53 (8%)	8/53[d] (15%)	10/53[e] (19%)	17/53[e] (32%)
Liver, pigmentation	4/53 (8%)	9/54 (17%)	34/53[e] (64%)	48/53[e] (91%)	52/53[e] (98%)	53/53[e] (100%)
Liver, toxic hepatopathy	0/53 (0%)	2/54 (4%)	8/53 (15%)	30/53 (57%)	45/50 (85%)	53/53 (100%)
Oval cell hyperplasia	0/53 (0%)	4/54 (10%)[d]	3/53 (10%)	20/53 (40%)[e]	38/53 (70%)[d]	53/53 (100%)[e]
Lung, alveolar to bronchiolar epithelial metaplasia (Alveolar epithelium, metaplasia, bronchiolar)	2/53 (4%)	19/54[e] (35%)	33/53[e] (62%)	35/52[e] (67%)	45/53[e] (85%)	46/52[e] (89%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Data are for female rats in 2-year gavage study. Data for all endpoints obtained from Table A5b in NTP (2006).
[d] Statistically significant as compared to control ($p < 0.05$).
[e] Statistically significant as compared to control ($p < 0.01$).

G.1.19. Ohsako et al. (2001)

Endpoint	Administered dose (ng/kg-day)				
	0	**12.5[a]**	**50[b]**	**200**	**800**
	Internal dose (ng/kg blood)[c]				
	0	**1.04**	**3.47**	**11.36**	**38.42**
	(*n* = 12)	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 12)**
Anogenital distance (mm) in male rat offspring, PND120[d]	28.91 ± 0.90	27.94 ± 0.79	25.17 ± 1.02[e]	26.01 ± 0.90[f]	23.80 ± 0.45[e]

[a] NOAEL for selected endpoint.
[b] LOAEL for selected endpoint.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 7 in Ohsako et al. (2001).
[e] Statistically significant as compared to control ($p < 0.01$).
[f] Statistically significant as compared to control ($p < 0.05$).

G.1.20. Sewall et al. (1995)

Endpoint	Administered dose (ng/kg-day)				
	0	**3.5**	**10.7[a]**	**35[b]**	**125**
	Internal dose (ng/kg blood)[c]				
	0	**3.29**	**7.11**	**16.63**	**44.66**
	(*n* = 9)	**(*n* = 9)**	**(*n* = 9)**	**(*n* = 9)**	**(*n* = 9)**
Serum levels of T4 (nmol/L), saline non noninitiated[d]	30.70 ± 1.55	27.88 ± 2.39	25.90 ± 2.27	23.56 ± 1.79[e]	18.40 ± 1.37[e]

[a] NOAEL for selected endpoint.
[b] LOAEL for selected endpoint.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 1 in Sewall et al. (1995).
[e] Statistically significant as compared to control ($p < 0.05$).

G.1.21. Shi et al. (2007)

Endpoint	Administered dose (ng/kg-day)				
	0	**0.143[a]**	**0.714[b]**	**7.14**	**28.6**
	Internal dose (ng/kg blood)[c]				
	0	**0.34**	**1.07**	**5.23**	**13.91**
	(*n* = 10)	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**	**(*n* = 10)**
Serum estradiol—17β at proestrus 9 in female rats at 9 mo. of age (pg/mL)[d]	102.86 ± 13.10	86.19 ± 6.19	63.33 ± 9.29[e]	48.1 ± 5.95[e]	38.57 ± 7.14[e]

[a] NOAEL identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 4 in Shi et al. (2007).
[e] Statistically significant as compared to control ($p < 0.05$).

G.1.22. Smialowicz et al. (2008)

Endpoint	Administered dose (ng/kg-day)				
	0	**1.07[a]**	**10.7**	**107**	**321**
	Internal dose (ng/kg blood)[b]				
	0	**0.44**	**2.46**	**13.40**	**31.65**
	(*n* = 15)	**(*n* = 14)**	**(*n* = 15)**	**(*n* = 15)**	**(*n* = 8)**
PFC per 10^6 cells in female mice[c]	1,491 ± 716	1,129 ± 171[d]	945 ± 516[d]	677 ± 465[d]	161 ± 117[d]
PFC × 10^4 per spleen in female mice[c]	27.8 ± 13.4	21 ± 13.6[d]	17.6 ± 9.4[d]	12.6 ± 8.7[d]	3.0 ± 3.1[d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SD. Data obtained from Table 4 in Smialowicz et al. (2008).
[d] Statistically significant as compared to control ($p < 0.05$).

G.1.23. Smith et al. (1976)

Endpoint	Administered Dose (ng/kg-day)					
	0	**1**	**10**	**100[a]**	**1,000[b]**	**3,000**
	Internal Dose (ng/kg blood)[c]					
	0	**0.12**	**1.01**	**7.11**	**50.59**	**138.07**
Cleft palate in pups[d]	0/34 (0%)	2/41 (4.9%)	0/19 (0%)	1/17 (5.9%)	4/19 (21%)[e]	10/14 (71%)[e]

[a] NOAEL identified
[b] LOAEL identified
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the incidence and number of litter groups. Data obtained from Table 3 in Smith et al. (1976).
[e] Statistically significant as compared to control ($p < 0.01$).

G.1.24. Sparschu et al. (1971)

Endpoint	Administered Dose (ng/kg-day)				
	0	**30[a]**	**125[b]**	**500**	**2,000**
	Internal Dose (ng/kg blood)[c]				
	0	**5.09**	**16.28**	**52.87**	**188.26**
	(*n* = 117)	**(*n* = 55)**	**(*n* = 66)**	**(*n* = 39)**	**(*n* = 3)**
Body weight of male fetuses[d]	4.03 ± 0.37	4.14 ± 0.26	3.85 ± 0.35[e]	3.86 ± 0.61[e]	2.72 ± 0.25[e]
	(*n* = 129)	**(*n* = 60)**	**(*n* = 58)**	**(*n* = 54)**	**(*n* = 4)**
Body weight of female fetuses[d]	3.89 ± 0.39	3.98 ± 0.35	3.71 ± 0.37[e]	3.78 ± 0.54[e]	2.69 ± 0.19[e]

[a] NOAEL identified
[b] LOAEL identified
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SD. Data obtained from Table 4 in Sparschu et al. (1971).
[e] Statistically significant as compared to control ($p < 0.05$).

G.1.25. Toth et al. (1979)

Endpoint	Administered dose (ng/kg-day)			
	0	1[a]	100	1,000
	Internal dose (ng/kg blood)[b]			
	0	0.57	14.21	91.21
	(*n* =38)	(*n* = 44)	(*n* = 44)	(*n* = 43)
Number with amyloidosis plus skin lesions in mice[c]	0/38 (0%)	5/44 (11%)	10/44 (23%)	17/43 (40%)
Number with skin lesions in mice[c]	0/38 (0%)	5/44 (11%)	13/44 (30%)	25/43 (58%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Data obtained from Table 2 in Toth et al. (1979).

G.1.26. van Birgelen et al. (1995)

Endpoint	Administered dose (ng/kg-day)					
	0	14[a]	26	47	320	1,024
	Internal dose (ng/kg blood)[b]					
	0	7.20	11.76	18.09	86.41	250.16
	(*n* = 8)	(*n* = 8)	(*n* = 8)	(*n* = 8)	(*n* = 8)	(*n* = 8)
Hepatic retinol (mg/g liver) in female rats[c]	14.9 ± 3.1	8.4 ± 1.2[d]	8.2 ± 0.8[d]	5.1 ± 0.3[d]	2.2 ± 0.3[d]	0.6 ± 0.2[d]
Hepatic retinol palmitate (mg/g liver) in female rats[c]	472 ± 96	94 ± 24[d]	107 ± 27[d]	74 ± 14[d]	22 ± 8[d]	3 ± 1[d]
Plasma FT4 (pmol/L) in female rats[c]	23.4 ± 1.1	24.5 ± 2.0	22.4 ± 1.0	19.3 ± 3.3	16.3 ± 1.5[d]	10.3 ± 1.7[d]
Plasma TT4 (nmol/L) in female rats[c]	40.9 ± 2.4	41.4 ± 1.9	41.4 ± 2.3	32.3 ± 2.6[d]	33.6 ± 2.2[d]	25.5 ± 2.7[d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SE. Data obtained from Table 3 in van Birgelen et al. (1995).
[d] Statistically significant as compared to control ($p < 0.05$).

FT4 = free thyroxine; TT4 = total thyroxine.

G.1.27. White et al. (1986)

Endpoint	Administered dose (ng/kg-day)						
	0	10[a]	50	100	500	1,000	2,000
	Internal dose (ng/kg blood)[b]						
	0	1.09	4.08	7.14	26.81	48.72	90.56
	(*n* = 8)	(*n* = 8)	(*n* = 8)	(*n* = 8)	(*n* = 8)	(*n* = 8)	(*n* = 8)
CH50 (U/mL) in female mice[c]	91 ± 5	54 ± 3[d]	63 ± 4[d]	56 ± 9[d]	41 ± 6[d]	32 ± 6[d]	17 ± 6[d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SE. Data obtained from Table 1 in White et al. (1986).
[d] Statistically significant as compared to control ($p < 0.05$).

G.2. ALTERNATE DOSE: WHOLE BLOOD BMDS RESULTS

G.2.1. Amin et al. (2000): 0.25% Saccharin Consumed, Female

G.2.1.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL[b] (ng/kg)	Notes
Linear[c]	**1**	**0.551**	**179.214**	**9.147E+00**	**6.094E+00**	
Polynomial, 2-degree	1	0.551	179.214	9.147E+00	6.094E+00	
Power	1	0.551	179.214	9.147E+00	6.094E+00	power bound hit (power = 1)
Power, unrestricted[d]	0	N/A	180.858	8.367E+00	3.419E+00	unrestricted (power = 0.736)

[a] Nonconstant variance model selected ($p = 0.0005$).
[b] BMDL = Benchmark Dose Level.
[c] Best-fitting model, BMDS output presented in this appendix.
[d] Alternate model, BMDS output also presented in this appendix.

G.2.1.2. *Output for Selected Model: Linear*

Amin et al. (2000): 0.25% Saccharin Consumed, Female

```
 ========================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\Blood\1_Amin_2000_25_SC_Linear_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\1_Amin_2000_25_SC_Linear_1.plt
                                          Mon Feb 08 10:44:22 2010
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The form of the response function is:

Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

Dependent variable = Mean
Independent variable = Dose
Signs of the polynomial coefficients are not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	5.29482
rho =	0
beta_0 =	31.5112
beta_1 =	-1.97726

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	-0.029	0.044
rho	-0.99	1	0.026	-0.04
beta_0	-0.029	0.026	1	-0.94
beta_1	0.044	-0.04	-0.94	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-2.54215	1.65048	-5.77702	0.692726
rho	2.40985	0.541771	1.34799	3.4717
beta_0	31.2644	4.1929	23.0464	39.4823
beta_1	-1.9414	0.436071	-2.79609	-1.08672

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	31.7	31.3	20.6	17.8	0.0727
3.378	10	24.6	24.7	12	13.4	-0.0264
10.57	10	10.7	10.8	5.33	4.91	-0.0362

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.841935	4	193.683870
A2	-85.255316	6	182.510632
A3	-85.429148	5	180.858295
fitted	-85.606998	4	179.213995
R	-98.136607	2	200.273213

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	25.7626	4	<.0001
Test 2	15.1732	2	0.0005072
Test 3	0.347663	1	0.5554
Test 4	0.3557	1	0.5509

```
The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


             Benchmark Dose Computation

Specified effect =             1

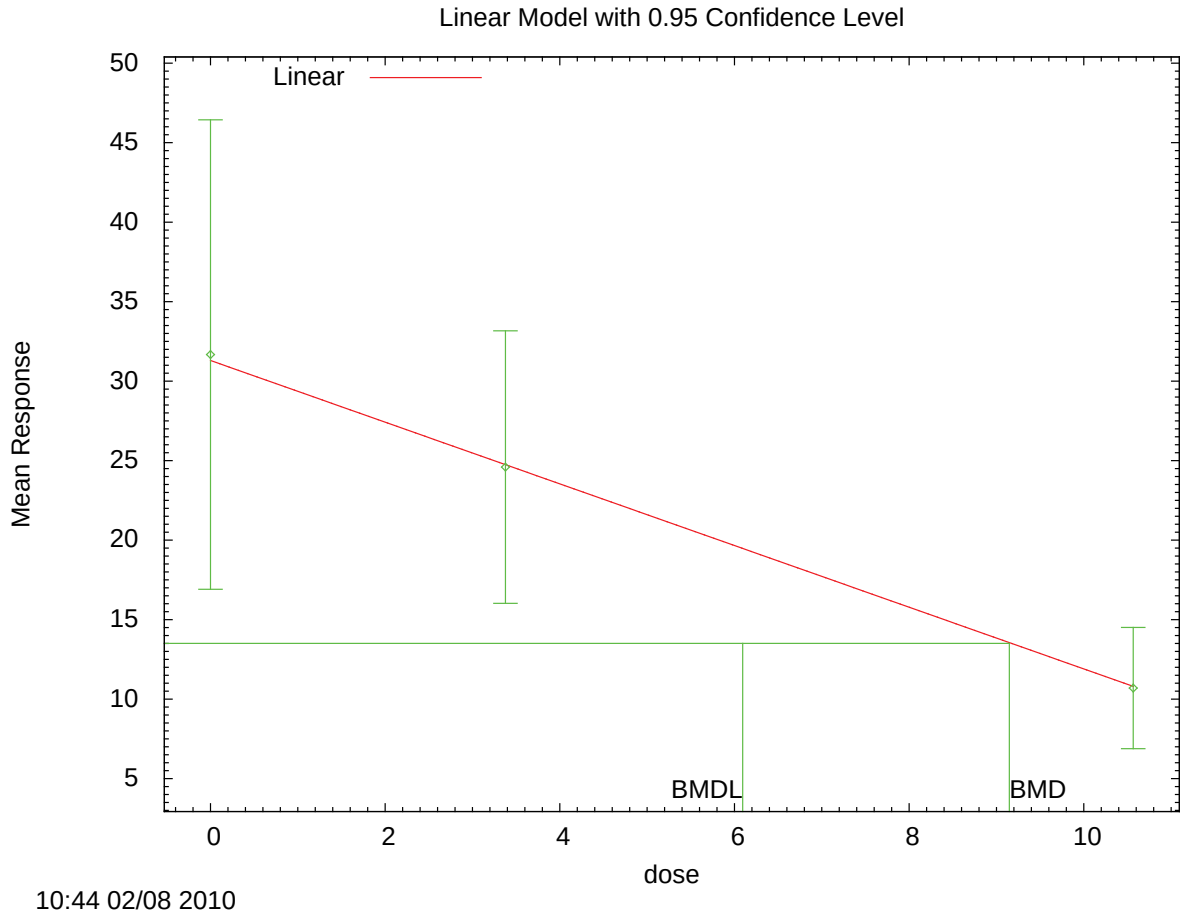
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        9.14709


            BMDL =        6.09414
```

G.2.1.3. *Figure for Selected Model: Linear*



G.2.1.4. *Output for Additional Model Presented: Power, Unrestricted*

Amin et al. (2000): 0.25% Saccharin Consumed, Female

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\1_Amin_2000_25_SC_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\1_Amin_2000_25_SC_Pwr_U_1.plt
                                          Mon Feb 08 10:44:22 2010
 ======================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
```

Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	5.29482
rho =	0
control =	31.6727
slope =	-2.2195
power =	0.952715

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.99	0.34	-0.17	-0.061
rho	-0.99	1	-0.42	0.19	0.068
control	0.34	-0.42	1	-0.72	-0.56
slope	-0.17	0.19	-0.72	1	0.97
power	-0.061	0.068	-0.56	0.97	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-2.48291	2.08669	-6.57274	1.60693
rho	2.38455	0.692047	1.02817	3.74094
control	32.99	5.40754	22.3914	43.5886
slope	-3.91099	3.83883	-11.435	3.61299
power	0.735877	0.350669	0.0485775	1.42318

Table of Data and Estimated Values of Interest

```
 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0    10       31.7           33         20.6         18.7         -0.223
3.378    10       24.6         23.4           12         12.4          0.302
10.57    10       10.7         10.8         5.33         4.94          -0.08

 Warning: Likelihood for fitted model larger than the Likelihood for model
A3.



 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1          -92.841935            4     193.683870
            A2          -85.255316            6     182.510632
            A3          -85.429148            5     180.858295
        fitted          -85.429148            5     180.858295
             R          -98.136607            2     200.273213


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              25.7626          4          <.0001
   Test 2              15.1732          2       0.0005072
```

```
   Test 3             0.347663          1          0.5554
   Test 4         -8.2423e-013          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


               Benchmark Dose Computation

Specified effect =             1

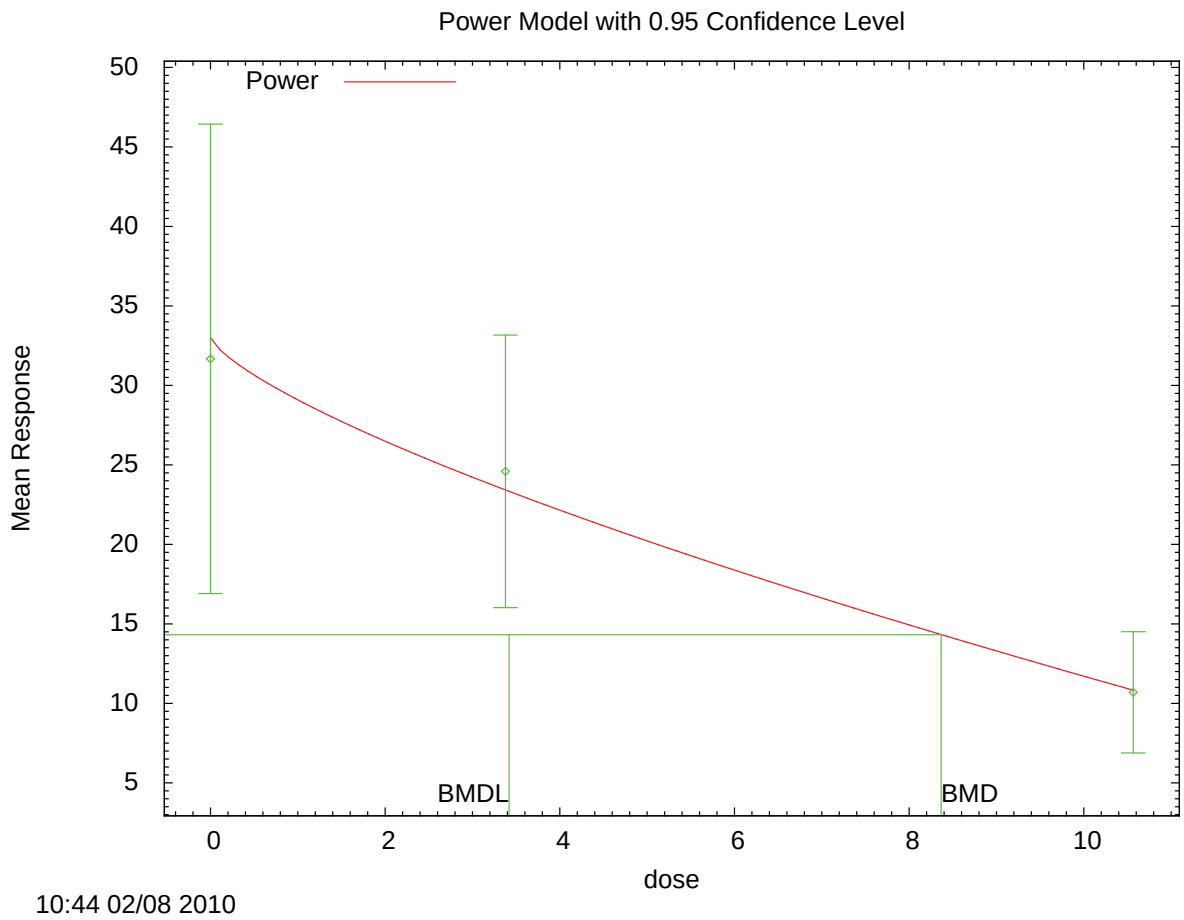
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 8.36678


            BMDL = 3.41906
```

G.2.1.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.2.2. Amin et al. (2000): 0.25% Saccharin Preference Ratio, Female

G.2.2.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Linear[b]	**1**	**0.002**	**227.807**	**1.162E+01**	**5.572E+00**	
Polynomial, 2-degree	1	0.002	227.807	1.162E+01	5.572E+00	
Power	1	0.002	227.807	1.162E+01	5.572E+00	power bound hit (power = 1)

[a] Nonconstant variance model selected (p = 0.0135).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.2.2. *Output for Selected Model: Linear*

Amin et al. (2000): 0.25% Saccharin Preference Ratio, Female

```
 ====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\Blood\2_Amin_2000_25_SP_Linear_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\2_Amin_2000_25_SP_Linear_1.plt
                                          Mon Feb 08 10:44:49 2010
 ====================================================================

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   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                         lalpha =      6.34368
                            rho =            0
                         beta_0 =      75.4888
                         beta_1 =     -2.24733


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho       beta_0       beta_1

    lalpha            1           -1         0.22        -0.31

       rho           -1            1        -0.22         0.31

    beta_0         0.22        -0.22            1        -0.77

    beta_1        -0.31         0.31        -0.77            1


                                     Parameter Estimates
```

95.0% Wald
Confidence Interval

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	3.00523	9.2122	-15.0503	21.0608
rho	0.797764	2.21138	-3.53646	5.13199
beta_0	75.1087	6.74312	61.8924	88.3249
beta_1	-2.16469	1.00825	-4.14082	-0.188553

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	82.1	75.1	13.3	25.2	0.884
3.378	10	58.1	67.8	33.9	24.2	-1.27
10.57	10	54.9	52.2	19.5	21.8	0.383

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-108.574798	4	225.149597
A2	-104.269377	6	220.538754
A3	-105.147952	5	220.295903
fitted	-109.903705	4	227.807410
R	-112.382522	2	228.765045

Explanation of Tests

```
 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.2263	4	0.00273
Test 2	8.61084	2	0.0135
Test 3	1.75715	1	0.185
Test 4	9.51151	1	0.002042

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

```
Specified effect =            1

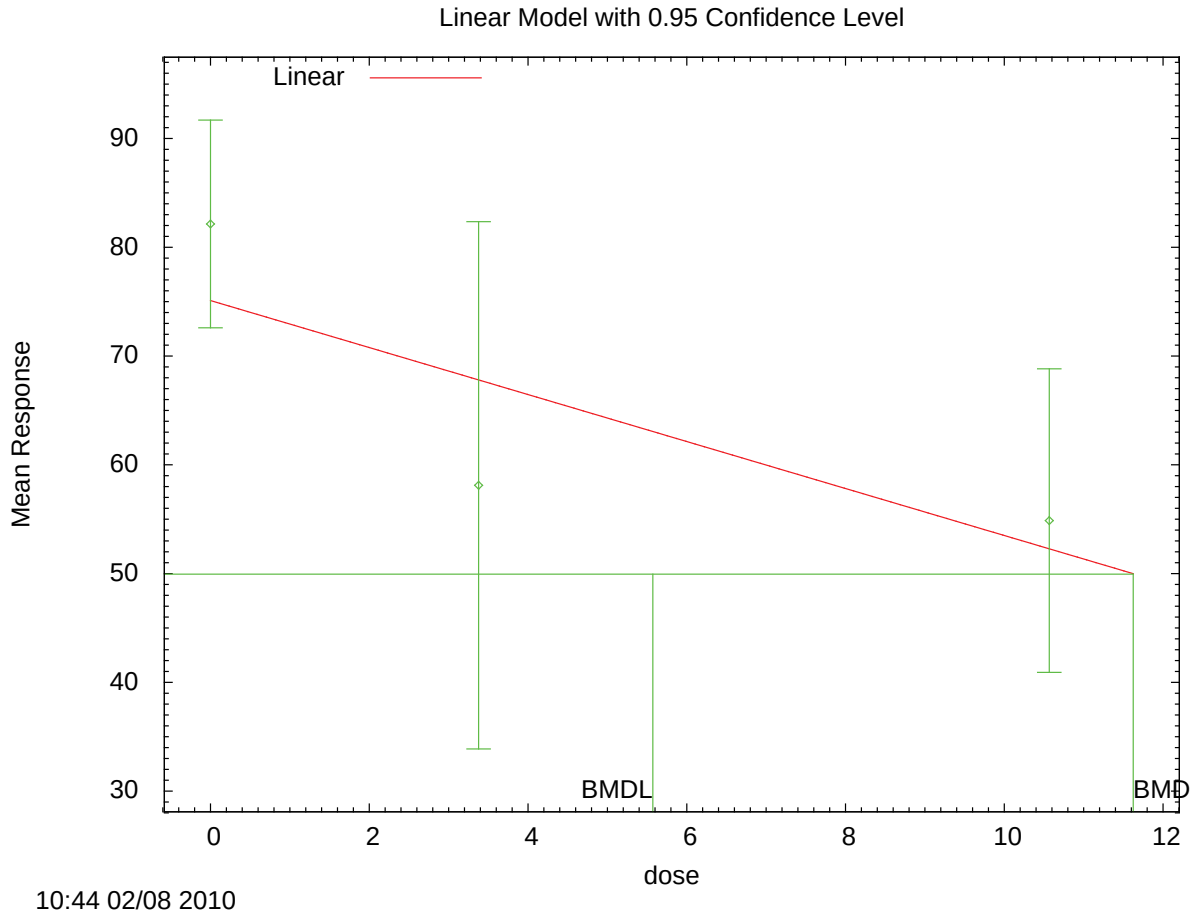
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        11.6241


            BMDL =        5.57215
```

G.2.2.3. *Figure for Selected Model: Linear*



G.2.3. Amin et al. (2000): 0.50% Saccharin Consumed, Female

G.2.3.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Linear[b]	**1**	**0.060**	**158.591**	**1.016E+01**	**6.567E+00**	
Polynomial, 2-degree	1	0.060	158.591	1.016E+01	6.567E+00	
Power	1	0.060	158.591	1.016E+01	6.567E+00	power bound hit (power = 1)
Power, unrestricted[c]	0	N/A	157.060	6.567E+00	1.155E+00	unrestricted (power = 0.396)

[a] Nonconstant variance model selected (p = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.3.2. *Output for Selected Model: Linear*

Amin et al. (2000): 0.50% Saccharin Consumed, Female

```
 ====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\Blood\3_Amin_2000_50_SC_Linear_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\3_Amin_2000_50_SC_Linear_1.plt
                                          Mon Feb 08 10:45:20 2010
 ====================================================================

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   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                         lalpha =      4.68512
                            rho =            0
                         beta_0 =      20.0631
                         beta_1 =     -1.57142


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho       beta_0       beta_1

    lalpha            1        -0.96        0.019      -0.0016

       rho        -0.96            1       -0.031        0.015

    beta_0        0.019       -0.031            1        -0.96

    beta_1      -0.0016        0.015        -0.96            1


                                   Parameter Estimates
```

95.0% Wald
Confidence Interval

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	-0.982115	0.982262	-2.90731	0.943084
rho	2.11808	0.401166	1.33181	2.90435
beta_0	18.6171	3.1782	12.3879	24.8462
beta_1	-1.33226	0.322037	-1.96344	-0.70108

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	22.4	18.6	16	13.5	0.873
3.378	10	11.4	14.1	7.66	10.1	-0.856
10.57	10	4.54	4.54	3.33	3.04	-0.00339

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-83.696404	4	175.392808
A2	-73.511830	6	159.023660
A3	-73.530233	5	157.060467
fitted	-75.295363	4	158.590726
R	-90.294746	2	184.589492

Explanation of Tests

```
 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	33.5658	4	<.0001
Test 2	20.3691	2	<.0001
Test 3	0.0368066	1	0.8479
Test 4	3.53026	1	0.06026

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

```
Specified effect =             1

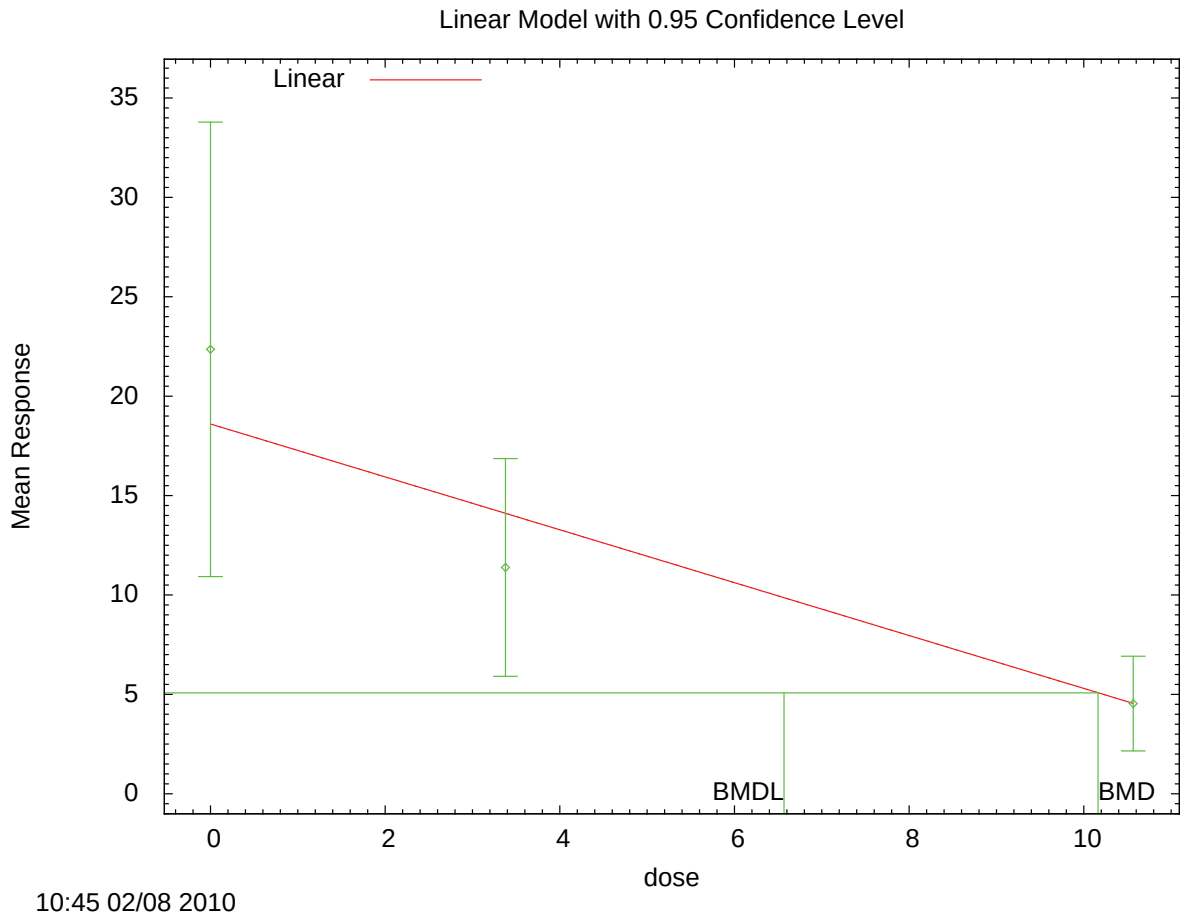
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        10.1633


            BMDL =        6.56742
```

G.2.3.3. *Figure for Selected Model: Linear*



G.2.3.4. *Output for Additional Model Presented: Power, Unrestricted*

Amin et al. (2000): 0.50% Saccharin Consumed, Female

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\3_Amin_2000_50_SC_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\3_Amin_2000_50_SC_Pwr_U_1.plt
                                          Mon Feb 08 10:45:20 2010
 ======================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
```

```
Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                Default Initial Parameter Values
                       lalpha =      4.68512
                          rho =            0
                      control =      22.3564
                        slope =     -6.53901
                        power =     0.425213


        Asymptotic Correlation Matrix of Parameter Estimates

              lalpha          rho      control        slope        power

    lalpha         1        -0.96         0.34        -0.31        -0.15

       rho     -0.96            1        -0.47         0.36         0.15

   control      0.34        -0.47            1        -0.81        -0.52

     slope     -0.31         0.36        -0.81            1         0.92

     power     -0.15         0.15        -0.52         0.92            1


                                Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha        -0.708629            1.298            -3.25267
1.83541
            rho          1.96142         0.529653            0.923323
2.99953
        control          22.6293          4.48416             13.8405
31.4181
          slope         -7.10123          4.04394            -15.0272
0.824743
          power         0.395571         0.168677           0.0649698
0.726173


     Table of Data and Estimated Values of Interest
```

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	22.4	22.6	16	15	-0.0577
3.378	10	11.4	11.1	7.66	7.46	0.105
10.57	10	4.54	4.58	3.33	3.12	-0.0475

Degrees of freedom for Test A3 vs fitted <= 0

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-83.696404	4	175.392808
A2	-73.511830	6	159.023660
A3	-73.530233	5	157.060467
fitted	-73.530233	5	157.060467
R	-90.294746	2	184.589492

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	33.5658	4	<.0001
Test 2	20.3691	2	<.0001
Test 3	0.0368066	1	0.8479

```
   Test 4                    0          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


               Benchmark Dose Computation

Specified effect =             1

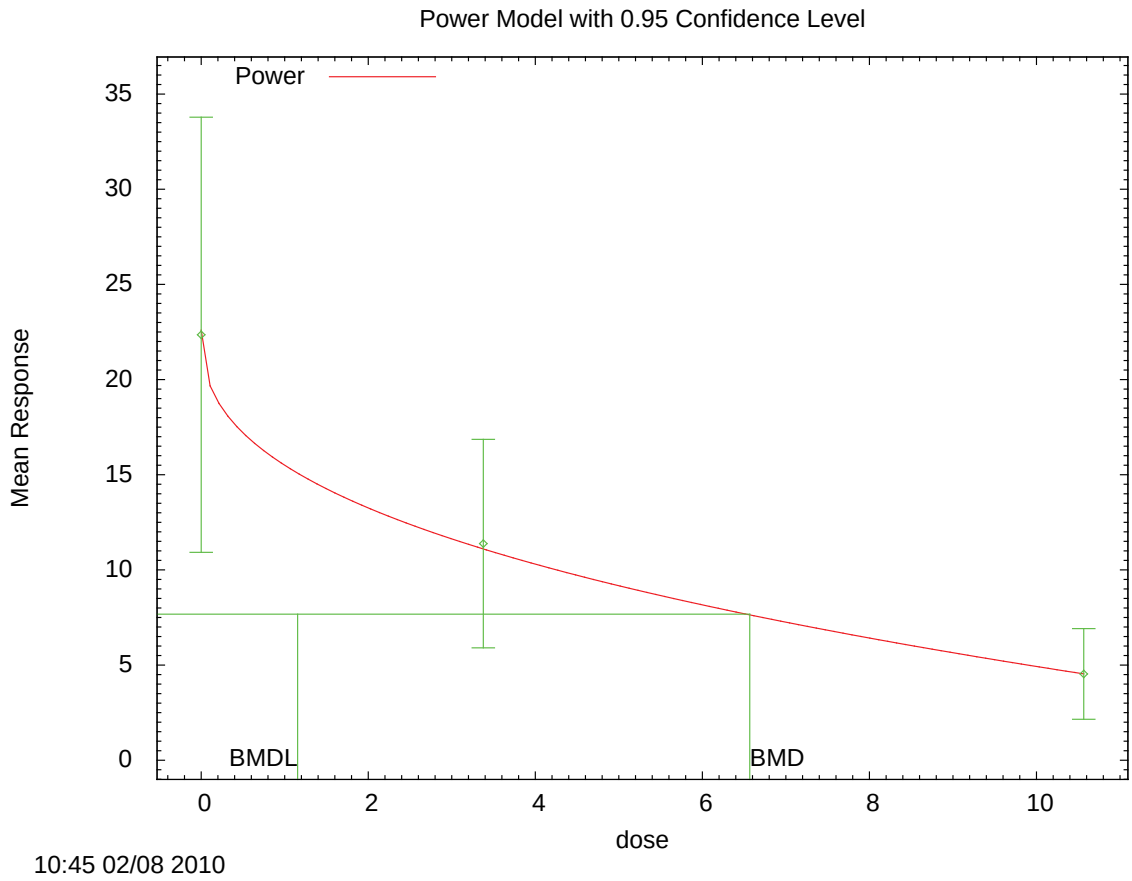
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 6.56719


            BMDL = 1.15476
```

G.2.3.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.2.4. Amin et al. (2000): 0.50% Saccharin Preference Ratio, Female

G.2.4.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Linear[b]	**1**	**0.135**	**234.250**	**8.144E+00**	**5.105E+00**	
Polynomial, 2-degree	1	0.135	234.250	8.144E+00	5.105E+00	
Power	1	0.135	234.250	8.144E+00	5.105E+00	power bound hit (power = 1)
Power, unrestricted[c]	0	N/A	234.020	2.598E+00	1.057E−14	unrestricted (power = 0.282)

[a] Constant variance model selected (p = 0.5593).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.4.2. *Output for Selected Model: Linear*

Amin et al. (2000): 0.50% Saccharin Preference Ratio, Female

```
 ====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\Blood\4_Amin_2000_50_SP_LinearCV_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\4_Amin_2000_50_SP_LinearCV_1.plt
                                          Mon Feb 08 10:45:50 2010
 ====================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                   Default Initial Parameter Values
                           alpha =      764.602
                             rho =            0   Specified
                          beta_0 =      65.8627
                          beta_1 =     -3.34297


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -rho
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                   alpha       beta_0       beta_1

     alpha             1     2.6e-008     2.1e-009

    beta_0     2.6e-008            1        -0.73

    beta_1     2.1e-009        -0.73            1
```

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	741.255	191.391	366.135	1116.38
beta_0	65.8627	7.22524	51.7015	80.0239
beta_1	-3.34297	1.12815	-5.55412	-1.13183

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	72.7	65.9	24.6	27.2	0.797
3.378	10	44.5	54.6	32.9	27.2	-1.17
10.57	10	33.8	30.5	24.6	27.2	0.375

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.009921	4	234.019841
A2	-112.428886	6	236.857773
A3	-113.009921	4	234.019841
fitted	-114.125184	3	234.250368
R	-117.976057	2	239.952114

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	11.0943	4	0.02552
Test 2	1.16207	2	0.5593
Test 3	1.16207	2	0.5593
Test 4	2.23053	1	0.1353

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

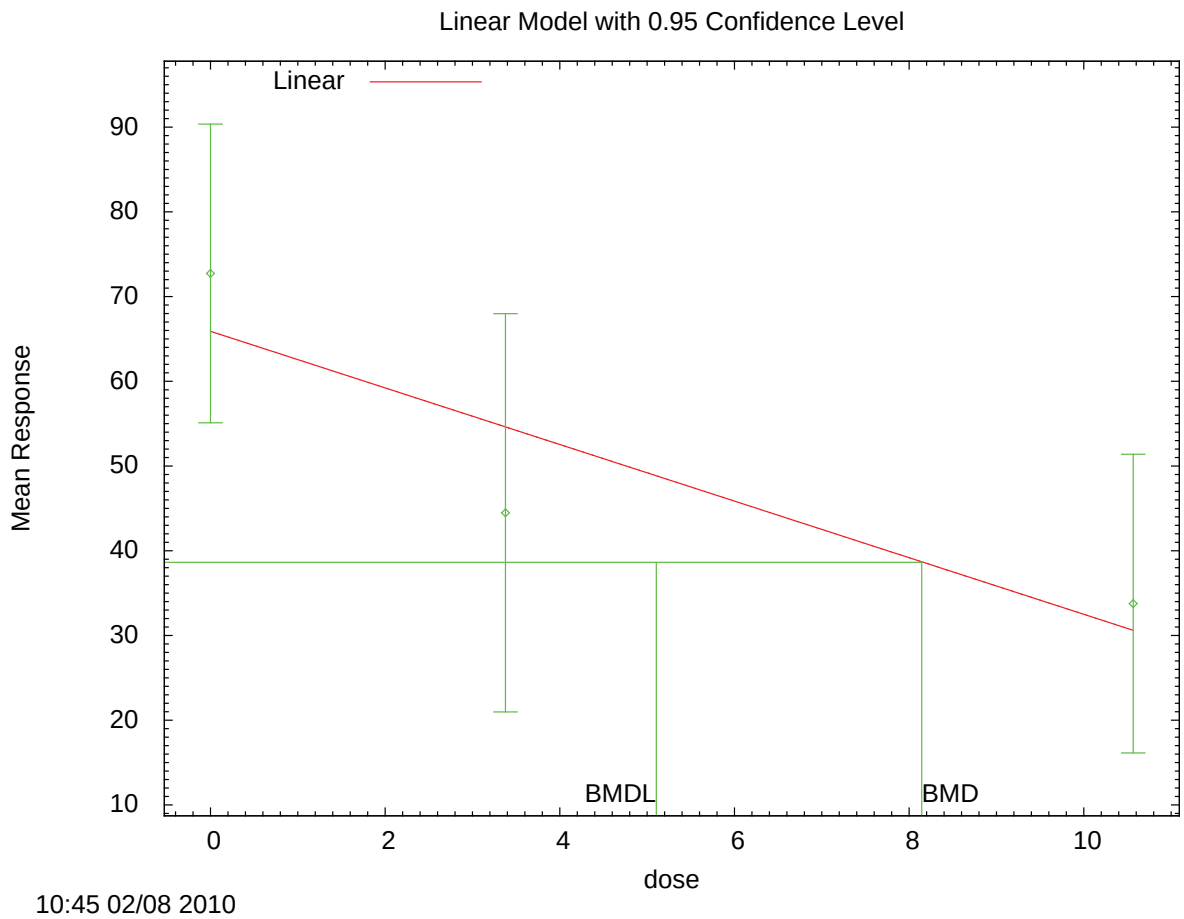
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 8.14425

BMDL = 5.10523

G.2.4.3. *Figure for Selected Model: Linear*



G.2.4.4. *Output for Additional Model Presented: Power, Unrestricted*

Amin et al. (2000): 0.50% Saccharin Preference Ratio, Female

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\4_Amin_2000_50_SP_PwrCV_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\4_Amin_2000_50_SP_PwrCV_U_1.plt
                                          Mon Feb 08 10:45:50 2010
 ======================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
```

```
Independent variable = Dose
rho is set to 0
The power is not restricted
A constant variance model is fit

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                         alpha =      764.602
                           rho =            0   Specified
                       control =      72.7273
                         slope =     -20.0402
                         power =     0.281985


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope        power

     alpha            1    -1.2e-009    -1.2e-009    -2.2e-010

   control    -1.2e-009            1        -0.51        -0.22

     slope    -1.2e-009        -0.51            1         0.92

     power    -2.2e-010        -0.22         0.92            1


                                 Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          688.142          177.677               339.9
1036.38
        control          72.7273          8.29543             56.4686
88.986
          slope         -20.0402          15.0576            -49.5526
9.47219
          power         0.281985         0.325861            -0.35669
0.920661
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	72.7	72.7	24.6	26.2	4.67e-009
3.378	10	44.5	44.5	32.9	26.2	1.52e-008
10.57	10	33.8	33.8	24.6	26.2	1.77e-008

Warning: Likelihood for fitted model larger than the Likelihood for model A3.

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.009921	4	234.019841
A2	-112.428886	6	236.857773
A3	-113.009921	4	234.019841
fitted	-113.009921	4	234.019841
R	-117.976057	2	239.952114

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	11.0943	4	0.02552
Test 2	1.16207	2	0.5593
Test 3	1.16207	2	0.5593
Test 4	-2.84217e-014	0	NA

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square test for fit is not valid

Benchmark Dose Computation

Specified effect = 1

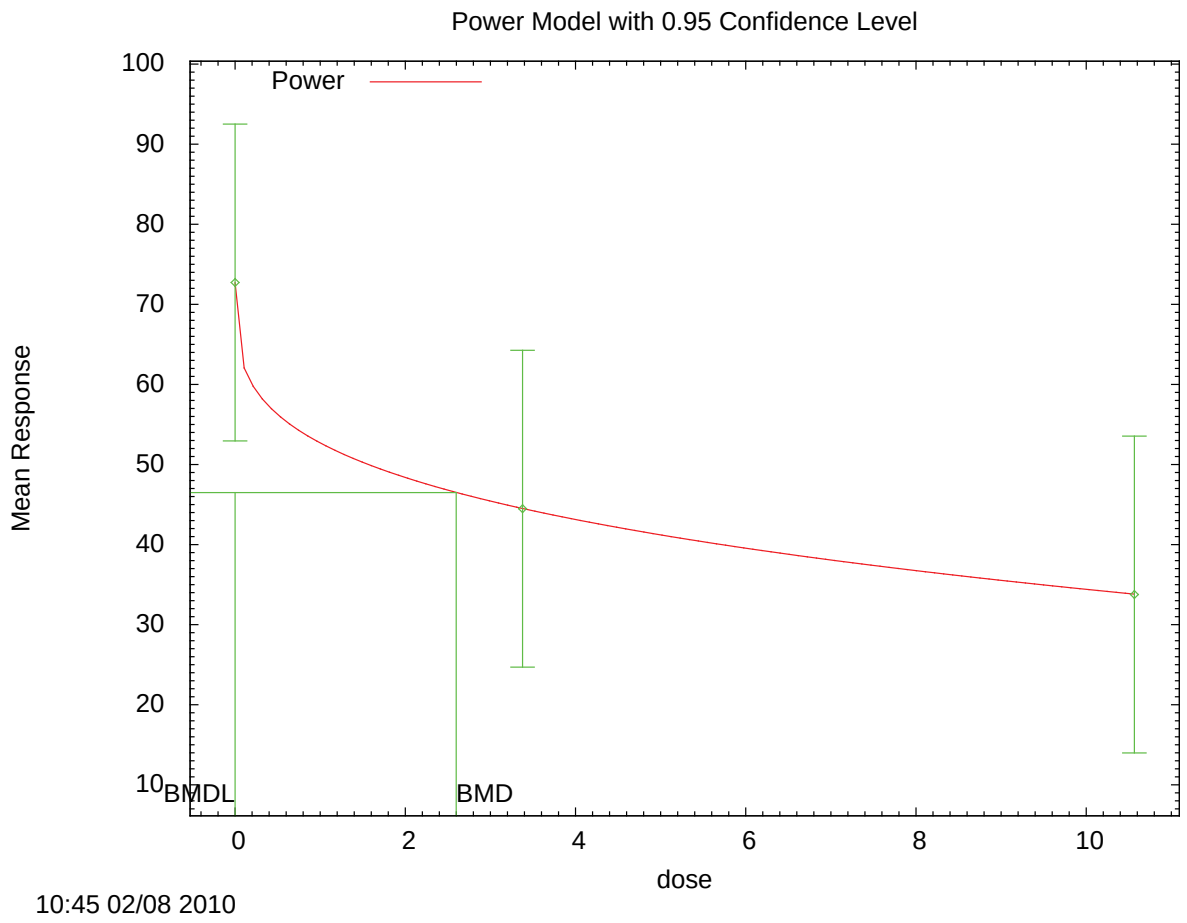
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 2.59831

BMDL = 1.05661e-014

G.2.4.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.2.5. Bell et al. (2007): Balano-Preputial Separation, Postnatal Day (PND) 49

G.2.5.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	2	0.684	112.136	2.867E+00	1.943E+00	power bound hit (power = 1)
Logistic	2	0.342	113.915	6.159E+00	4.746E+00	negative intercept (intercept = −2.246)
Log-logistic[a]	**2**	**0.777**	**111.908**	**2.246E+00**	**1.394E+00**	**slope bound hit (slope = 1)**
Log-probit	2	0.269	114.254	5.322E+00	3.512E+00	slope bound hit (slope = 1)
Multistage, 3-degree	2	0.684	112.136	2.867E+00	1.943E+00	final ß = 0
Probit	2	0.367	113.713	5.715E+00	4.422E+00	
Weibull	2	0.684	112.136	2.867E+00	1.943E+00	power bound hit (power = 1)
Gamma, unrestricted	1	0.566	113.746	1.862E+00	1.829E−01	unrestricted (power = 0.741)
Log-logistic, unrestricted[b]	1	0.501	113.871	1.998E+00	2.795E−01	unrestricted (slope = 0.93)
Log-probit, unrestricted	1	0.456	113.977	2.038E+00	3.250E−01	unrestricted (slope = 0.54)
Weibull, unrestricted	1	0.551	113.771	1.914E+00	2.346E−01	unrestricted (power = 0.795)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.2.5.2. *Output for Selected Model: Log-Logistic*

Bell et al. (2007): Balano-Preputial Separation, PND 49

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\5_Bell_2007_BPS_LogLogistic_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\5_Bell_2007_BPS_LogLogistic_1.plt
                                          Mon Feb 08 10:46:18 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.0333333
intercept = -2.99896
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -slope
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	background	intercept
background	1	-0.49
intercept	-0.49	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.038005	*	*	*
intercept	-3.00658	*	*	*
slope	1	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-53.7077	4			
Fitted model	-53.954	2	0.492596	2	0.7817
Reduced model	-63.9797	1	20.544	3	0.0001309

AIC: 111.908

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0380	1.140	1.000	30	-0.134
2.2040	0.1326	3.977	5.000	30	0.551
5.1378	0.2329	6.988	6.000	30	-0.427
18.4110	0.4965	14.895	15.000	30	0.038

Chi^2 = 0.50 d.f. = 2 P-value = 0.7769

Benchmark Dose Computation

Specified effect = 0.1

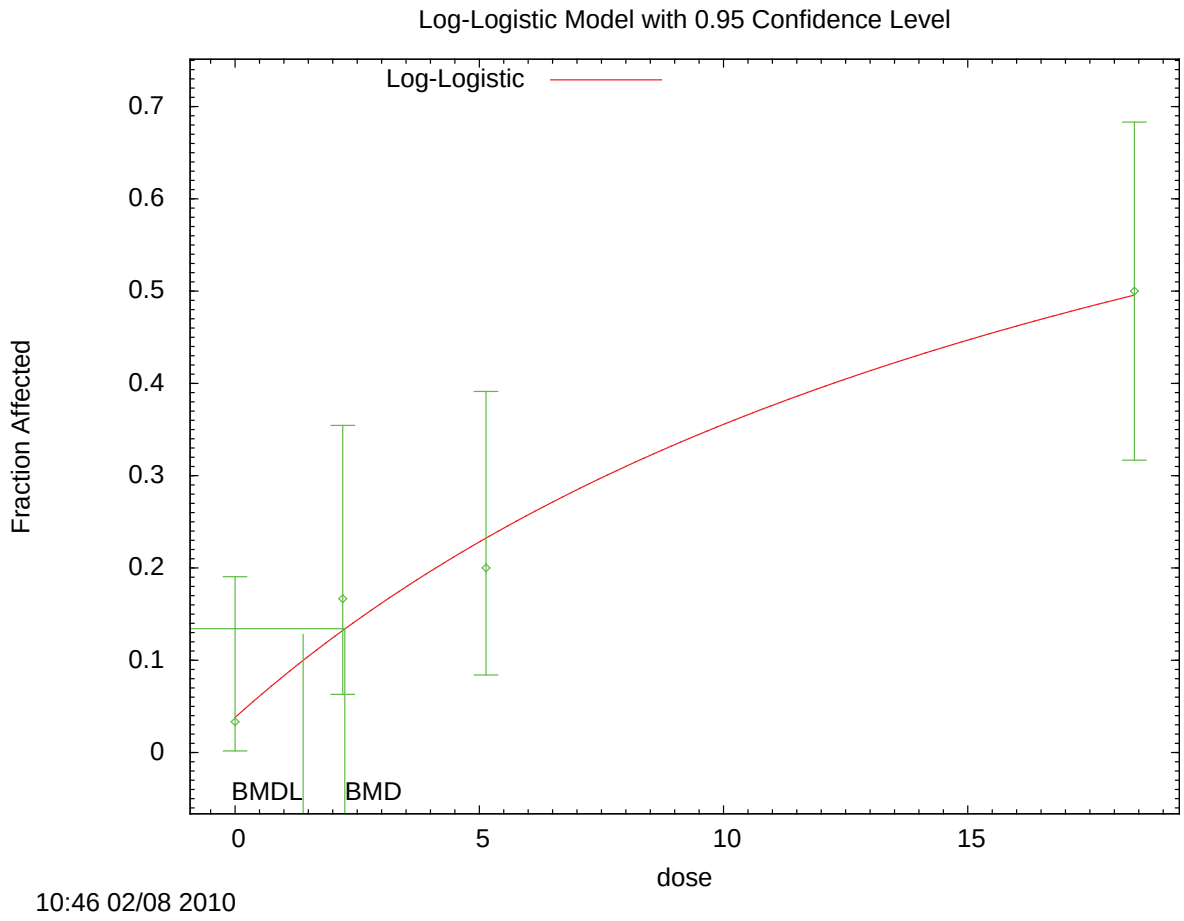
Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.24647

BMDL = 1.39385

G.2.5.3. *Figure for Selected Model: Log-Logistic*



G.2.5.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Bell et al. (2007): Balano-Preputial Separation, PND 49

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\5_Bell_2007_BPS_LogLogistic_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\5_Bell_2007_BPS_LogLogistic_U_1.plt
                                          Mon Feb 08 10:46:18 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]
```

```
Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



User has chosen the log transformed model


                Default Initial Parameter Values
                   background =    0.0333333
                    intercept =     -2.68464
                        slope =     0.858398


          Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.48         0.35

 intercept        -0.48            1        -0.94

     slope         0.35        -0.94            1



                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background        0.0353402            *                *
*
      intercept         -2.84051            *                *
*
          slope         0.929645            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -53.7077         4
   Fitted model        -53.9354         3      0.455534      1
0.4997
```

```
  Reduced model        -63.9797         1        20.544      3
0.0001309

           AIC:         113.871


                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.0353         1.060     1.000          30       -0.060
    2.2040     0.1400         4.201     5.000          30        0.420
    5.1378     0.2389         7.166     6.000          30       -0.499
   18.4110     0.4858        14.573    15.000          30        0.156

 Chi^2 = 0.45      d.f. = 1        P-value = 0.5005


   Benchmark Dose Computation

Specified effect =            0.1

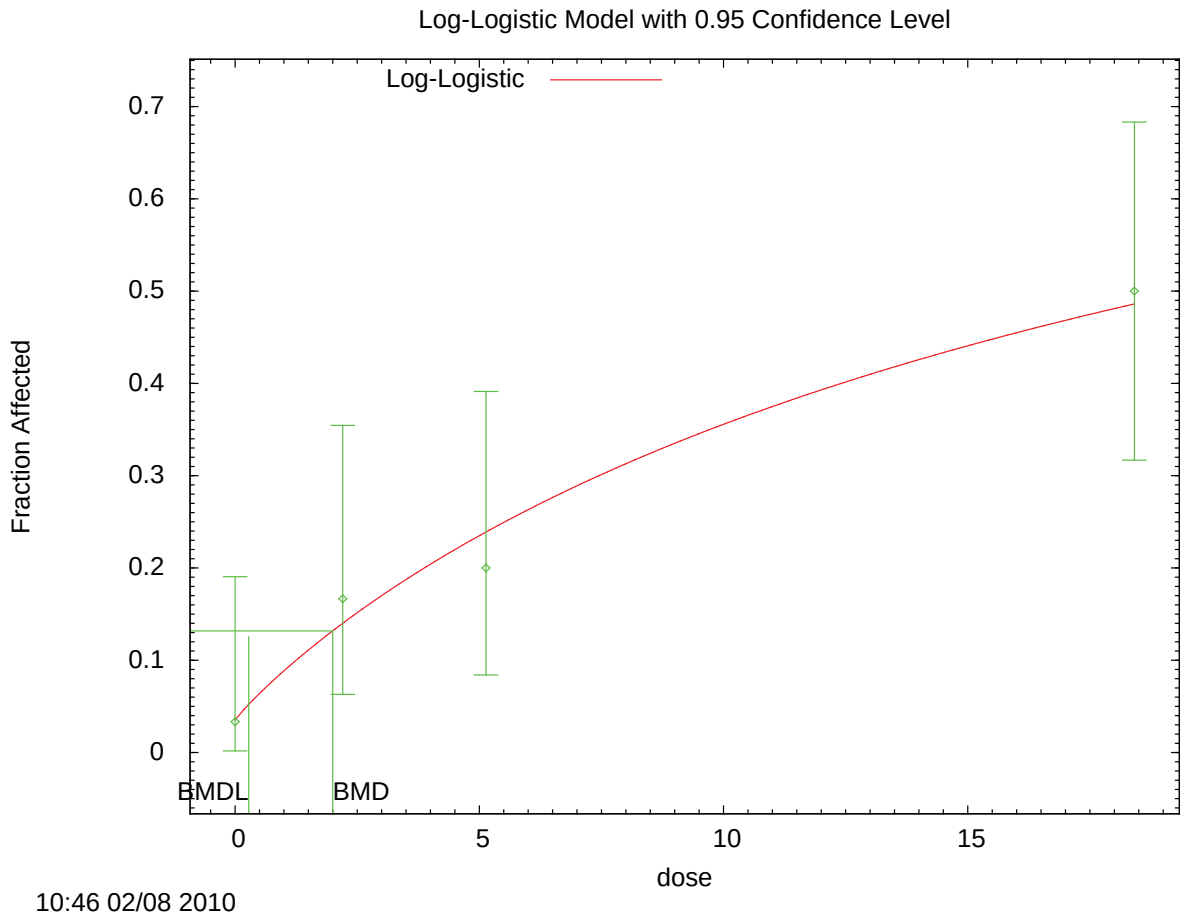
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        1.99765

            BMDL =       0.279534
```

G.2.5.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



G.2.6. Cantoni et al. (1981): Urinary Coproporhyrins, 3 Months

G.2.6.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.003	32.882	3.209E+01	1.567E+01	
Exponential (M3)	2	0.003	32.882	3.209E+01	1.567E+01	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.486**	**23.459**	**5.339E−01**	**1.803E−01**	
Exponential (M5)	1	0.486	23.459	5.339E−01	1.803E−01	power hit bound (*d* = 1)
Hill	1	0.788	23.047	4.333E−01	error	*n* lower bound hit (*n* = 1)
Linear	2	0.005	31.595	1.464E+01	2.753E+00	
Polynomial, 3-degree	2	0.005	31.595	1.464E+01	2.753E+00	
Power	2	0.005	31.595	1.464E+01	2.753E+00	power bound hit (power = 1)
Power, unrestricted[c]	1	0.610	23.235	2.766E−02	2.031E−05	unrestricted (power = 0.304)
Hill, unrestricted	0	N/A	24.974	2.602E−01	error	unrestricted (*n* = 0.739)

[a] Nonconstant variance model selected (*p* = 0.0039).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.6.2. *Output for Selected Model: Exponential (M4)*

Cantoni et al. (1981): Urinary Coproporhyrins, 3 Months

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\6_Cantoni_1981_UriCopro_Exp_1.(d)
        Gnuplot Plotting File:
                                            Mon Feb 08 10:46:46 2010
 ======================================================================

 Figure1-UrinaryCoproporphyrin_3months
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
```

```
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 4
lnalpha	-1.50063
rho	2.60979
a	0.704303
b	0.0604961
c	4.47268
d	1

Parameter Estimates

Variable	Model 4
lnalpha	-1.75302
rho	2.6322
a	0.761218
b	0.241561
c	4.15597
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	4	0.7414	0.3475
1.847	4	1.807	0.8341
8.839	4	2.734	1.506
50.05	4	3	2.6

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.7612	0.2907	-0.1366
1.847	1.626	0.7892	0.4588
8.839	2.88	1.674	-0.1743
50.05	3.164	1.895	-0.1725

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-12.90166	5	35.80333
A2	-6.203643	8	28.40729
A3	-6.487204	6	24.97441
R	-15.73713	2	35.47427
4	-6.729737	5	23.45947

Additive constant for all log-likelihoods = -14.7. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	19.07	6	0.004052
Test 2	13.4	3	0.003854
Test 3	0.5671	2	0.7531
Test 6a	0.4851	1	0.4861

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 1.000000

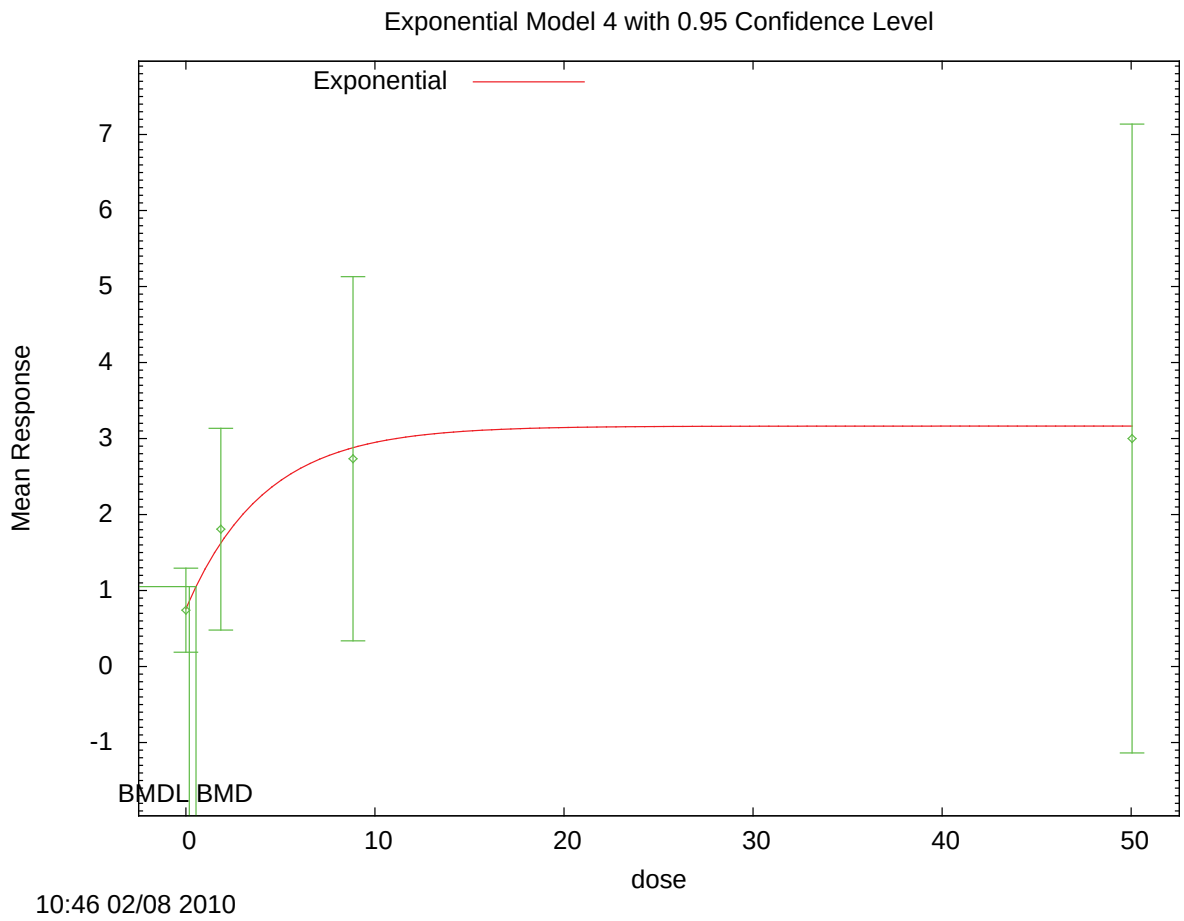
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 0.533855

BMDL = 0.180293

G.2.6.3. *Figure for Selected Model: Exponential (M4)*



G.2.6.4. *Output for Additional Model Presented: Power, Unrestricted*

Cantoni et al. (1981): Urinary Coproporhyrins, 3 Months

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\6_Cantoni_1981_UriCopro_Pwr_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\6_Cantoni_1981_UriCopro_Pwr_U_1.plt
                                          Mon Feb 08 10:46:47 2010
 ======================================================================

 Figure1-UrinaryCoproporphyrin_3months
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power
```

Dependent variable = Mean
Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	0.90039
rho =	0
control =	0.741372
slope =	0.93685
power =	0.224904

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.62	-0.53	-0.036	0.024
rho	-0.62	1	0.43	-0.2	-0.16
control	-0.53	0.43	1	-0.28	0.086
slope	-0.036	-0.2	-0.28	1	-0.77
power	0.024	-0.16	0.086	-0.77	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-1.78125	0.617807	-2.99213	-0.570373
rho	2.64332	0.744946	1.18325	4.10338
control	0.75678	0.139979	0.482426	1.03113
slope	0.845767	0.324854	0.209065	1.48247
power	0.304211	0.135053	0.0395119	0.568909

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	4	0.741	0.757	0.348	0.284	-0.109
1.847	4	1.81	1.78	0.834	0.877	0.0705
8.839	4	2.73	2.4	1.51	1.3	0.515
50.05	4	3	3.54	2.6	2.18	-0.493

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.901663	5	35.803325
A2	-6.203643	8	28.407287
A3	-6.487204	6	24.974409
fitted	-6.617347	5	23.234694
R	-15.737135	2	35.474269

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	19.067	6	0.004052
Test 2	13.396	3	0.003854
Test 3	0.567122	2	0.7531

```
   Test 4             0.260285          1          0.6099

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =             1

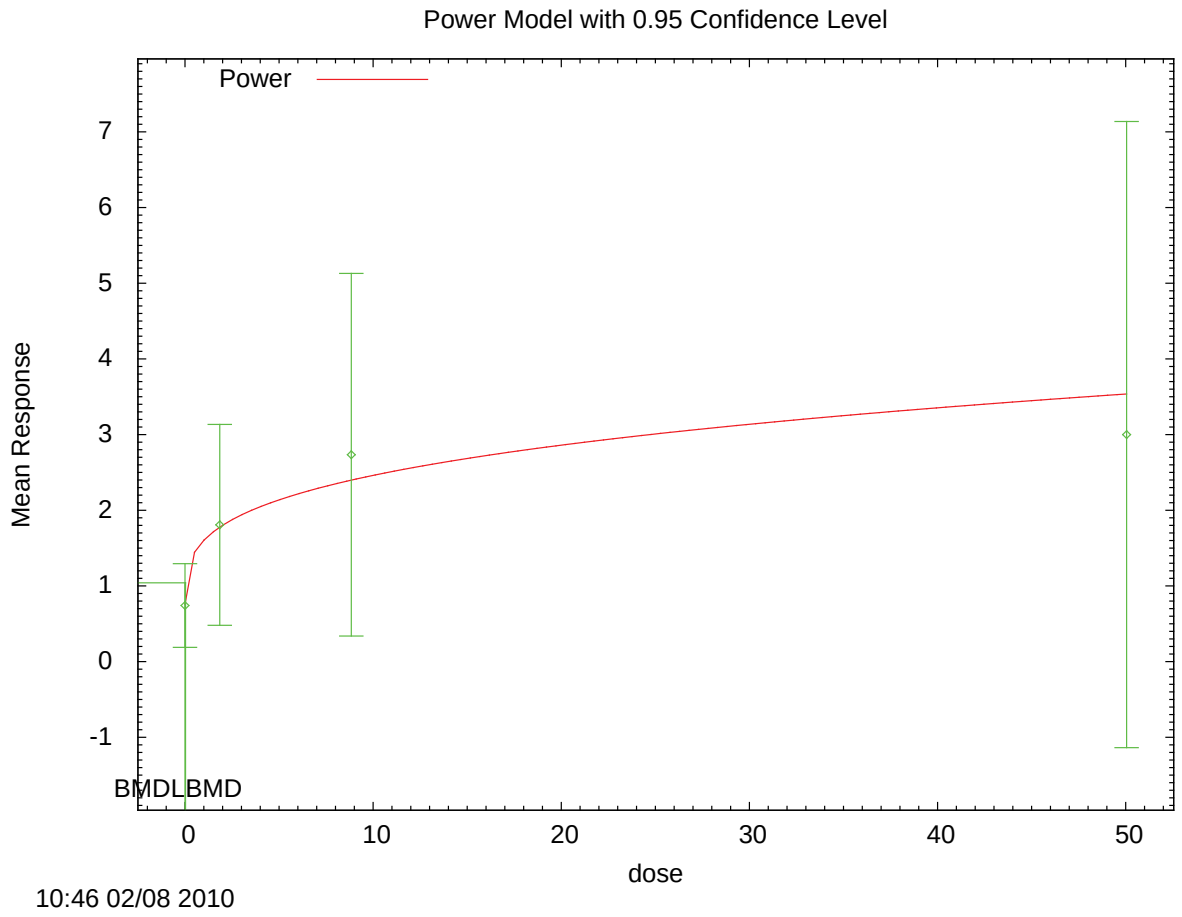
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 0.0276599


            BMDL = 2.03143e-005
```

G.2.6.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.2.7. Cantoni et al. (1981): Urinary Porphyrins

G.2.7.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)[b]	2	<0.001	55.465	3.760E+00	2.762E+00	
Exponential (M3)	2	<0.001	55.465	3.760E+00	2.762E+00	power hit bound (*d* = 1)
Exponential (M4)	1	<0.0001	59.187	2.484E−01	1.448E−01	
Exponential (M5)	0	N/A	61.084	2.878E−01	1.461E−01	
Hill	0	N/A	62.199	6.233E+00	3.341E+00	
Linear	2	<0.001	57.187	2.484E−01	1.448E−01	
Polynomial, 3-degree	1	<0.0001	10.000	error	error	
Power	1	<0.0001	59.084	2.878E−01	1.461E−01	

[a] Nonconstant variance model selected (*p* = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.7.2. *Output for Selected Model: Exponential (M2)*

Cantoni et al. (1981): Urinary Porphyrins

```
 ========================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\7_Cantoni_1981_UriPor_Exp_1.(d)
        Gnuplot Plotting File:
                                            Mon Feb 08 10:47:24 2010
 ========================================================================

 Table 1, dose converted to ng per kg per day
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 4
```

Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 2
lnalpha	-3.57509
rho	2.23456
a	3.36453
b	0.0819801
c	0
d	1

Parameter Estimates

Variable	Model 2
lnalpha	-1.85879
rho	1.82273
a	3.57896
b	0.0803347
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	4	2.27	0.49
1.847	4	5.55	0.85
8.839	3	7.62	1.79
50.05	3	196.9	63.14

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	3.579	1.262	-2.074
1.847	4.152	1.445	1.936
8.839	7.28	2.41	0.2441
50.05	199.5	49.25	-0.09069

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)

```
            Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
            Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-51.42175	5	112.8435
A2	-15.31211	8	46.62422
A3	-15.66963	6	43.33925
R	-68.75058	2	141.5012
2	-23.73254	4	55.46509

Additive constant for all log-likelihoods = -12.87. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	106.9	6	< 0.0001
Test 2	72.22	3	< 0.0001
Test 3	0.715	2	0.6994
Test 4	16.13	2	0.000315

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

```
The p-value for Test 4 is less than .1.  Model 2 may not adequately
describe the data; you may want to consider another model.


Benchmark Dose Computations:

  Specified Effect = 1.000000

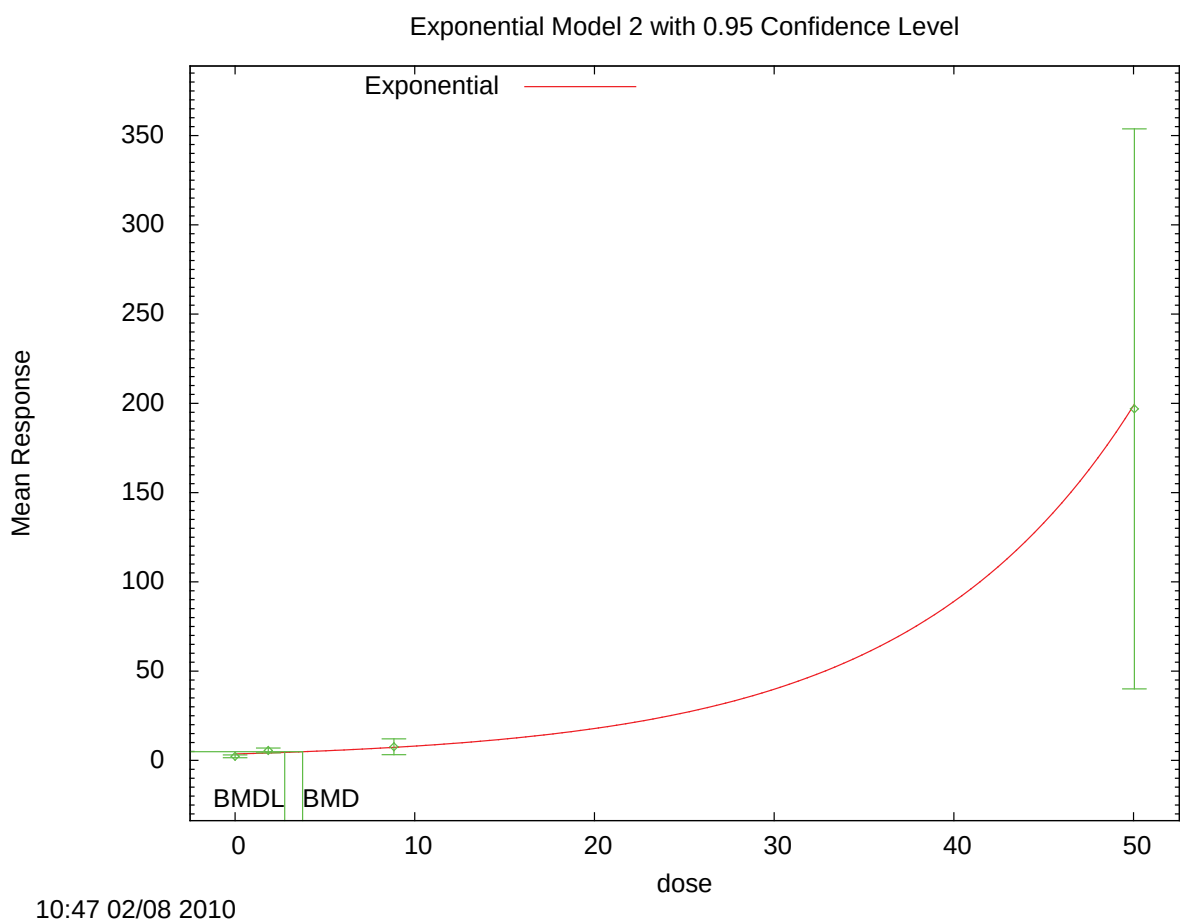
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      3.75968

              BMDL =      2.76247
```

G.2.7.3. *Figure for Selected Model: Exponential (M2)*



G.2.8. Crofton et al. (2005): Serum, T4

G.2.8.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	8	<0.0001	516.356	1.144E+02	6.239E+01	
Exponential (M3)	8	<0.0001	516.356	1.144E+02	6.239E+01	power hit bound (*d* = 1)
Exponential (M4)[b]	**7**	**0.942**	**476.449**	**5.190E+00**	**3.029E+00**	
Exponential (M5)	6	0.912	478.234	5.757E+00	3.094E+00	
Hill	6	0.972	477.450	5.724E+00	3.024E+00	
Linear	8	<0.0001	522.460	2.406E+02	1.761E+02	
Polynomial, 8-degree	8	<0.0001	522.460	2.406E+02	1.761E+02	
Power	8	<0.0001	522.460	2.406E+02	1.761E+02	power bound hit (power = 1)
Power, unrestricted	7	0.018	491.101	2.449E+00	3.307E−01	unrestricted (power = 0.243)

[a] Constant variance model selected (*p* = 0.7647).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.8.2. *Output for Selected Model: Exponential (M4)*

Crofton et al. (2005): Serum, T4

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\8_Crofton_2005_T4_ExpCV_1.(d)
        Gnuplot Plotting File:
                                             Mon Feb 08 10:48:04 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	5.47437
rho(S)	0
a	104.999
b	0.00641895
c	0.445764
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	5.50623
rho	0
a	100.332
b	0.076678
c	0.523626
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	14	100	15.44
0.0202	6	96.27	14.98
0.4882	12	98.57	18.11
1.384	6	99.76	19.04
3.455	6	93.32	12.11
9.257	6	70.94	12.74
23.07	6	62.52	14.75
65.65	6	52.68	22.73
180.9	6	54.66	19.71
583.5	4	49.15	11.15

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	100.3	15.69	-0.07952
0.0202	100.3	15.69	-0.6231
0.4882	98.58	15.69	-0.000744
1.384	95.52	15.69	0.6614
3.455	89.21	15.69	0.6422
9.257	76.04	15.69	-0.7962
23.07	60.69	15.69	0.2854
65.65	52.85	15.69	-0.02621
180.9	52.54	15.69	0.3319
583.5	52.54	15.69	-0.4323

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-233.0774	11	488.1549
A2	-230.2028	20	500.4056
A3	-233.0774	11	488.1549
R	-268.4038	2	540.8076
4	-234.2243	4	476.4486

Additive constant for all log-likelihoods = -66.16. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	76.4	18	< 0.0001
Test 2	5.749	9	0.7647
Test 3	5.749	9	0.7647
Test 6a	2.294	7	0.9418

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 1.000000

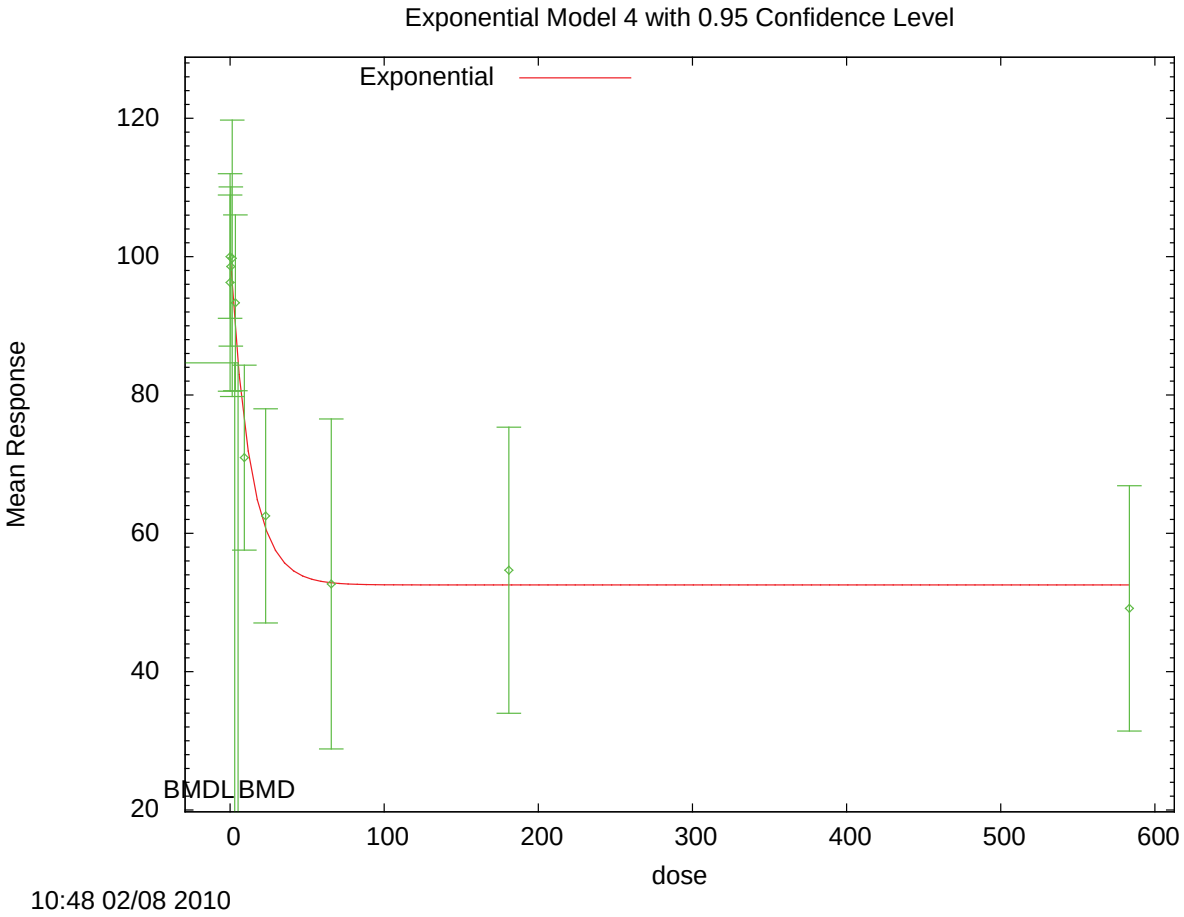
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 5.18983

BMDL = 3.02894

G.2.8.3. *Figure for Selected Model: Exponential (M4)*



G.2.9. Franc et al. (2001): Sprague-Dawley (S-D) Rats, Relative Liver Weight

G.2.9.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.968	234.369	7.800E+00	6.040E+00	
Exponential (M3)	1	0.880	236.327	9.201E+00	6.051E+00	
Exponential (M4)	1	0.580	236.610	6.365E+00	4.512E+00	
Exponential (M5)	0	N/A	238.346	9.474E+00	4.425E+00	
Hill	0	N/A	238.346	9.479E+00	3.004E+00	
Linear	2	0.858	234.610	6.365E+00	4.512E+00	
Polynomial, 3-degree	1	0.935	236.311	8.946E+00	4.598E+00	
Power[b]	1	0.839	236.346	9.474E+00	4.587E+00	

[a] Constant variance model selected ($p = 0.107$).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.9.2. *Output for Selected Model: Power*

Franc et al. (2001): S-D Rats, Relative Liver Weight

```
 ========================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\88_Franc_2001_SD_RelLivWt_PowerCV_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\88_Franc_2001_SD_RelLivWt_PowerCV_1.plt
                                          Thu Apr 15 11:46:32 2010
 ========================================================================

 Figure 5, SD rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is restricted to be greater than or equal to 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                            alpha =      527.447
                              rho =            0   Specified
```

control = 100
slope = 0.947018
power = 1.13144

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	control	slope	power
alpha	1	-6.3e-009	5.4e-009	-4.7e-009
control	-6.3e-009	1	-0.74	0.71
slope	5.4e-009	-0.74	1	-1
power	-4.7e-009	0.71	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	462.113	115.528	235.682	688.544
control	100.494	7.31114	86.1645	114.824
slope	0.593276	1.31535	-1.98476	3.17131
power	1.25841	0.597816	0.086712	2.43011

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	100	100	14	21.5	-0.065
6.587	8	108	107	16.9	21.5	0.158
14.48	8	117	118	25.9	21.5	-0.109
36.43	8	155	155	30.9	21.5	0.0157

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.152281	5	238.304562
A2	-111.103649	8	238.207299
A3	-114.152281	5	238.304562
fitted	-114.172940	4	236.345880
R	-125.052064	2	254.104127

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.8968	6	<.0001
Test 2	6.09726	3	0.107
Test 3	6.09726	3	0.107
Test 4	0.0413179	1	0.8389

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

```
                Benchmark Dose Computation

Specified effect =           0.1

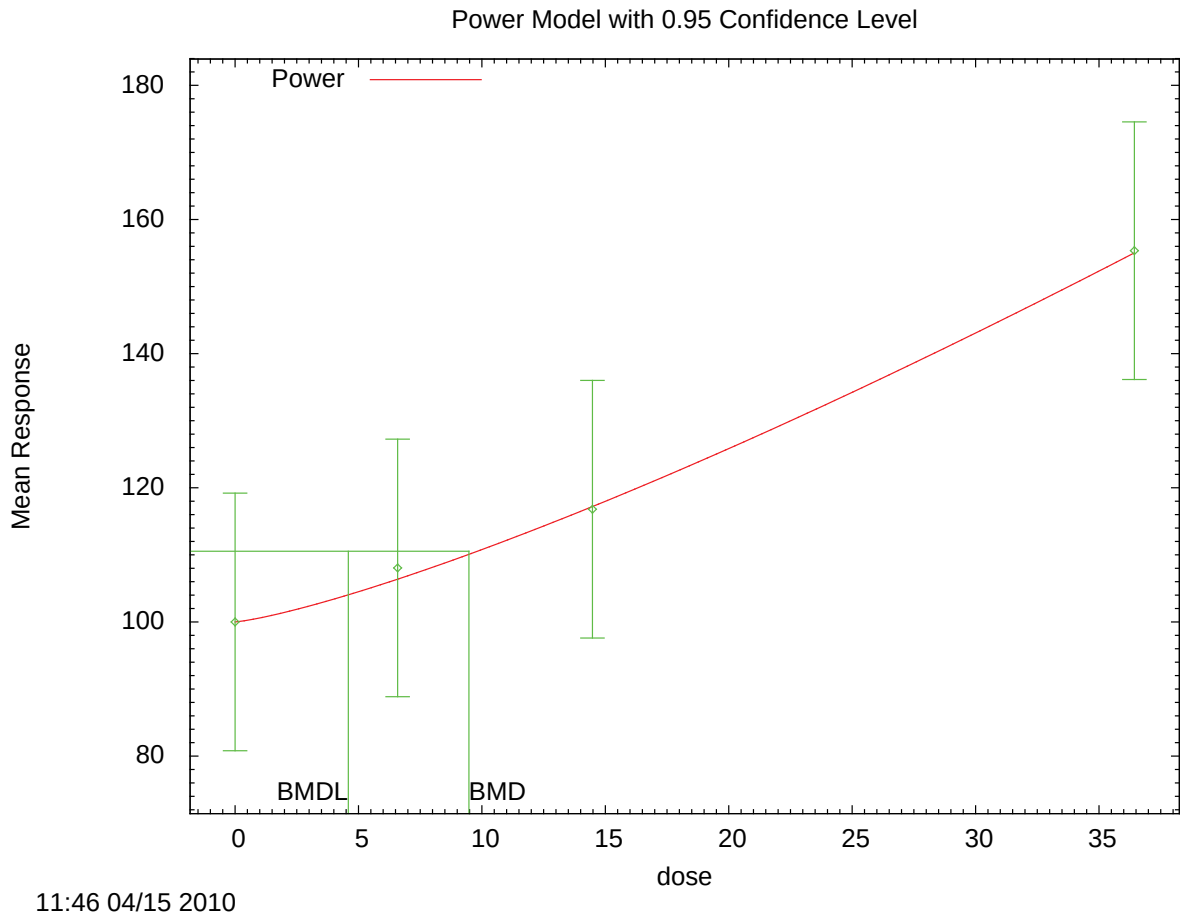
Risk Type        =     Relative risk

Confidence level =          0.95

             BMD = 9.47408


            BMDL = 4.5873
```

G.2.9.3. *Figure for Selected Model: Power*



G.2.10. Franc et al. (2001): Long-Evans (L-E) Rats, Relative Liver Weight

G.2.10.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.441	208.974	1.708E+01	1.098E+01	
Exponential (M3)	2	0.441	208.974	1.708E+01	1.098E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.785	209.408	7.997E+00	2.601E+00	
Exponential (M5)	1	0.785	209.408	7.997E+00	2.601E+00	power hit bound (*d* = 1)
Hill[b]	1	0.829	209.381	7.725E+00	1.225E+00	*n* lower bound hit (*n* = 1)
Linear	2	0.499	208.725	1.570E+01	9.619E+00	
Polynomial, 3-degree	1	<0.0001	10.000	8.604E+00	error	
Power	2	0.499	208.725	1.570E+01	9.619E+00	power bound hit (power = 1)
Hill, unrestricted[c]	0	N/A	211.337	7.217E+00	1.147E+00	unrestricted (*n* = 0.545)
Power, unrestricted	1	0.965	209.336	7.193E+00	error	unrestricted (power = 0.524)

[a] Nonconstant variance model selected (*p* = 0.0632).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.10.2. *Output for Selected Model: Hill*

Franc et al. (2001): L-E Rats, Relative Liver Weight

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\89_Franc_2001_LE_RelLivWt_Hill_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\89_Franc_2001_LE_RelLivWt_Hill_1.plt
                                          Thu Apr 15 11:48:44 2010
 ======================================================================

 Figure 5, L-E rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

lalpha =	5.41581
rho =	0
intercept =	100
v =	22.225
n =	0.443155
k =	18.746

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-1	-0.21	0.33	0.18
rho	-1	1	0.21	-0.33	-0.18
intercept	-0.21	0.21	1	0.028	0.35
v	0.33	-0.33	0.028	1	0.91
k	0.18	-0.18	0.35	0.91	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-17.2754	17.3066	-51.1957	16.6449
rho	4.77884	3.67625	-2.42648	11.9842
intercept	99.5348	3.61286	92.4538	106.616
v	36.3963	24.1862	-11.0079	83.8004
n	1	NA		
k	20.5223	28.2566	-34.8596	75.9042

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	100	99.5	10	10.5	0.125
6.584	8	106	108	17.9	12.9	-0.455
14.47	8	117	115	8.97	14.8	0.426
36.41	8	122	123	19.9	17.4	-0.0954

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-100.516456	5	211.032912
A2	-96.870820	8	209.741641
A3	-99.666984	6	211.333969
fitted	-99.690373	5	209.380746
R	-105.717087	2	215.434174

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.6925	6	0.007048
Test 2	7.29127	3	0.06317
Test 3	5.59233	2	0.06104

```
   Test 4            0.0467774          1          0.8288

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =           0.1

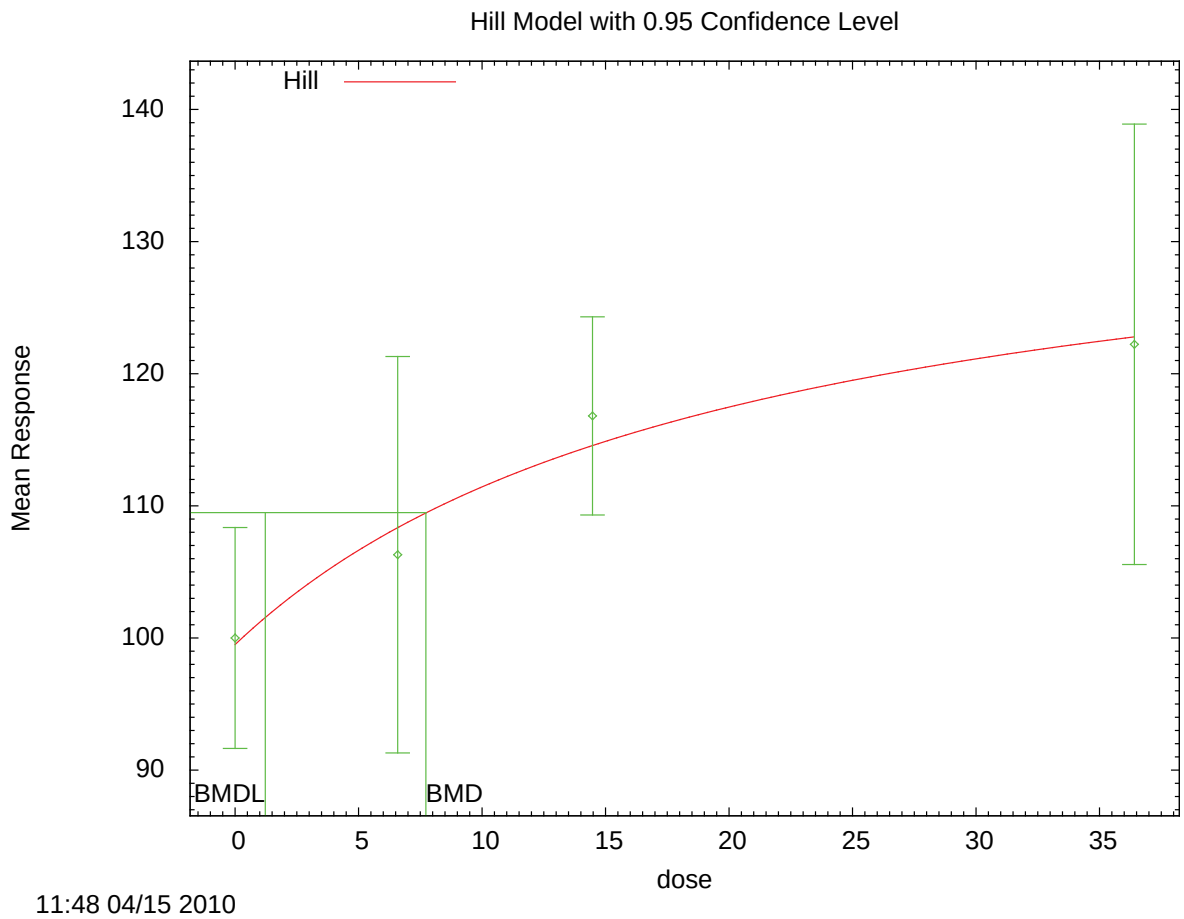
Risk Type        =     Relative risk

Confidence level =           0.95

             BMD =        7.72492

            BMDL =       1.22451
```

G.2.10.3. *Figure for Selected Model: Hill*



G.2.10.4. *Output for Additional Model Presented: Hill, Unrestricted*

Franc et al. (2001): L-E Rats, Relative Liver Weight

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\89_Franc_2001_LE_RelLivWt_Hill_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\89_Franc_2001_LE_RelLivWt_Hill_U_1.plt
                                          Thu Apr 15 11:48:50 2010
 ======================================================================

 Figure 5, L-E rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)
```

```
Dependent variable = Mean
Independent variable = Dose
Power parameter is not restricted
The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                        lalpha =      5.41581
                           rho =            0
                     intercept =          100
                             v =       22.225
                             n =     0.443155
                             k =       18.746


           Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho    intercept            v            n
k

    lalpha            1           -1        -0.22        -0.14         0.24
-0.15

       rho           -1            1         0.22         0.14        -0.24
0.15

 intercept        -0.22         0.22            1        0.022         0.11
0.013

         v        -0.14         0.14        0.022            1         -0.9
1

         n         0.24        -0.24         0.11         -0.9            1
-0.92

         k        -0.15         0.15        0.013            1        -0.92
1


                                 Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         -19.2405            18.21            -54.9315
16.4505
            rho          5.19575          3.86861            -2.38657
12.7781
```

```
      intercept          99.5348          3.51796             92.6398
106.43
              v          440.285          13708.5            -26427.9
27308.5
              n         0.544741         0.730981           -0.887956
1.97744
              k          7266.27           485402             -944104
958637


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0     8        100         99.5           10         10.3          0.128
6.584     8        106          109         17.9           13         -0.589
14.47     8        117          114         8.97         14.6          0.558
36.41     8        122          123         19.9         17.8        -0.0957

Degrees of freedom for Test A3 vs fitted <= 0


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -100.516456            5     211.032912
             A2          -96.870820            8     209.741641
             A3          -99.666984            6     211.333969
         fitted          -99.668321            6     211.336641
              R         -105.717087            2     215.434174


                    Explanation of Tests
```

```
 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.6925	6	0.007048
Test 2	7.29127	3	0.06317
Test 3	5.59233	2	0.06104
Test 4	0.00267242	0	NA

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is less than .1. You may want to consider a different variance model

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square test for fit is not valid

Benchmark Dose Computation

Specified effect = 0.1

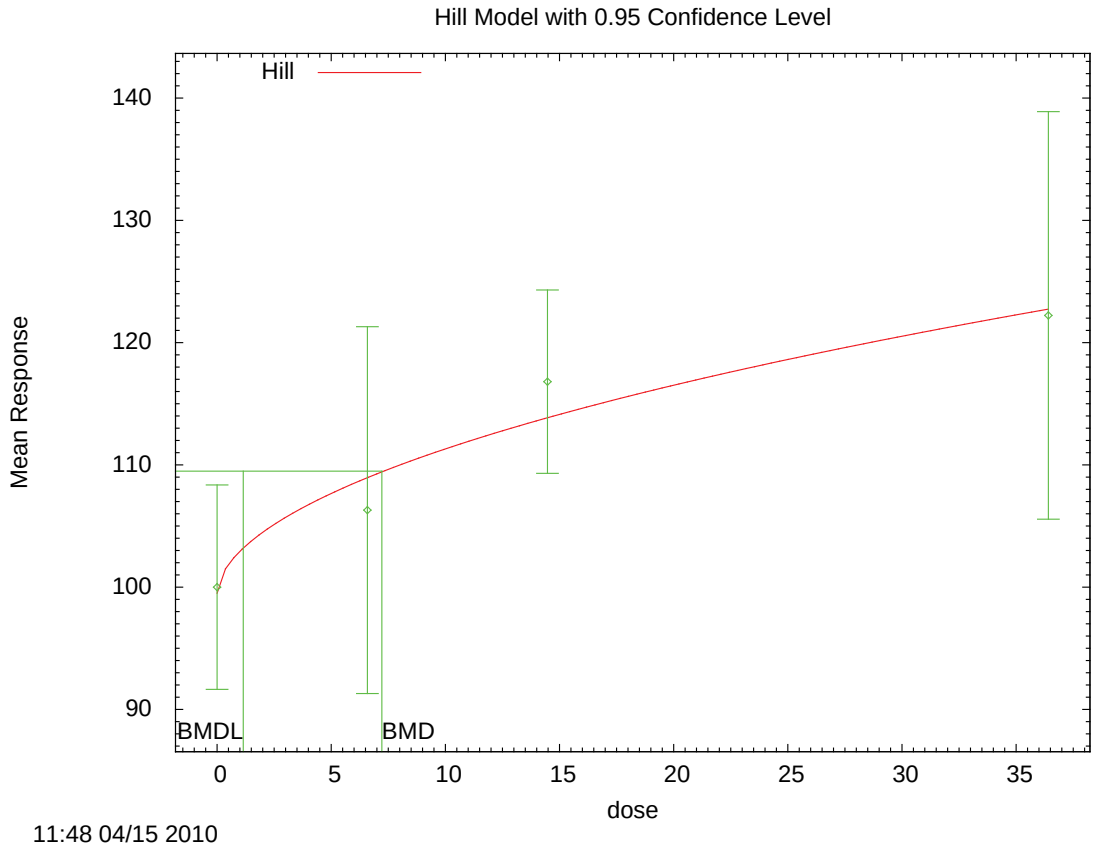
Risk Type = Relative risk

Confidence level = 0.95

BMD = 7.21718

BMDL = 1.14742

G.2.10.5. *Figure for Additional Model Presented: Hill, Unrestricted*



G.2.11. Franc et al. (2001): S-D Rats, Relative Thymus Weight

G.2.11.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.814	285.107	2.478E+00	1.535E+00	
Exponential (M3)	1	0.016	292.452	3.173E+01	1.007E+00	
Exponential (M4)[b]	1	0.720	286.825	1.878E+00	9.221E−01	
Exponential (M5)	0	N/A	288.696	3.296E+00	9.365E−01	
Hill	0	N/A	288.696	3.625E+00	6.199E−01	
Linear	2	0.404	286.508	4.783E+00	3.893E+00	
Polynomial, 3-degree[c]	2	0.404	286.508	4.783E+00	3.893E+00	
Power	2	0.404	286.508	4.783E+00	3.893E+00	power bound hit (power = 1)
Power, unrestricted	1	0.483	287.189	6.795E−01	3.271E−03	unrestricted (power = 0.515)

[a] Nonconstant variance model selected ($p = 0.0320$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.11.2. *Output for Selected Model: Exponential (M4)*

Franc et al. (2001): S-D Rats, Relative Thymus Weight

```
 ========================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\91_Franc_2001_SD_RelThyWt_Exp_1.(d)
        Gnuplot Plotting File:
                                             Thu Apr 15 11:51:19 2010
 ========================================================================

 Figure 5, SD rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
```

```
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 4
lnalpha	3.35464
rho	1.08199
a	105
b	0.0569979
c	0.108531
d	1

Parameter Estimates

Variable	Model 4
lnalpha	2.4312
rho	1.28672
a	110.959
b	0.0663498
c	0.146486
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	100	83.2
6.587	8	91.17	47.97
14.48	8	51.41	43.48
36.43	8	22.79	29.98

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	111	69.78	-0.4442
6.587	77.43	55.36	0.7019
14.48	52.49	43.11	-0.0709
36.43	24.7	26.54	-0.2031

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-141.9834	5	293.9669
A2	-137.5818	8	291.1637
A3	-138.3482	6	288.6964
R	-146.9973	2	297.9946
4	-138.4123	5	286.8245

Additive constant for all log-likelihoods = -29.41. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	18.83	6	0.004459
Test 2	8.803	3	0.03203
Test 3	1.533	2	0.4647
Test 6a	0.1282	1	0.7203

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 0.100000

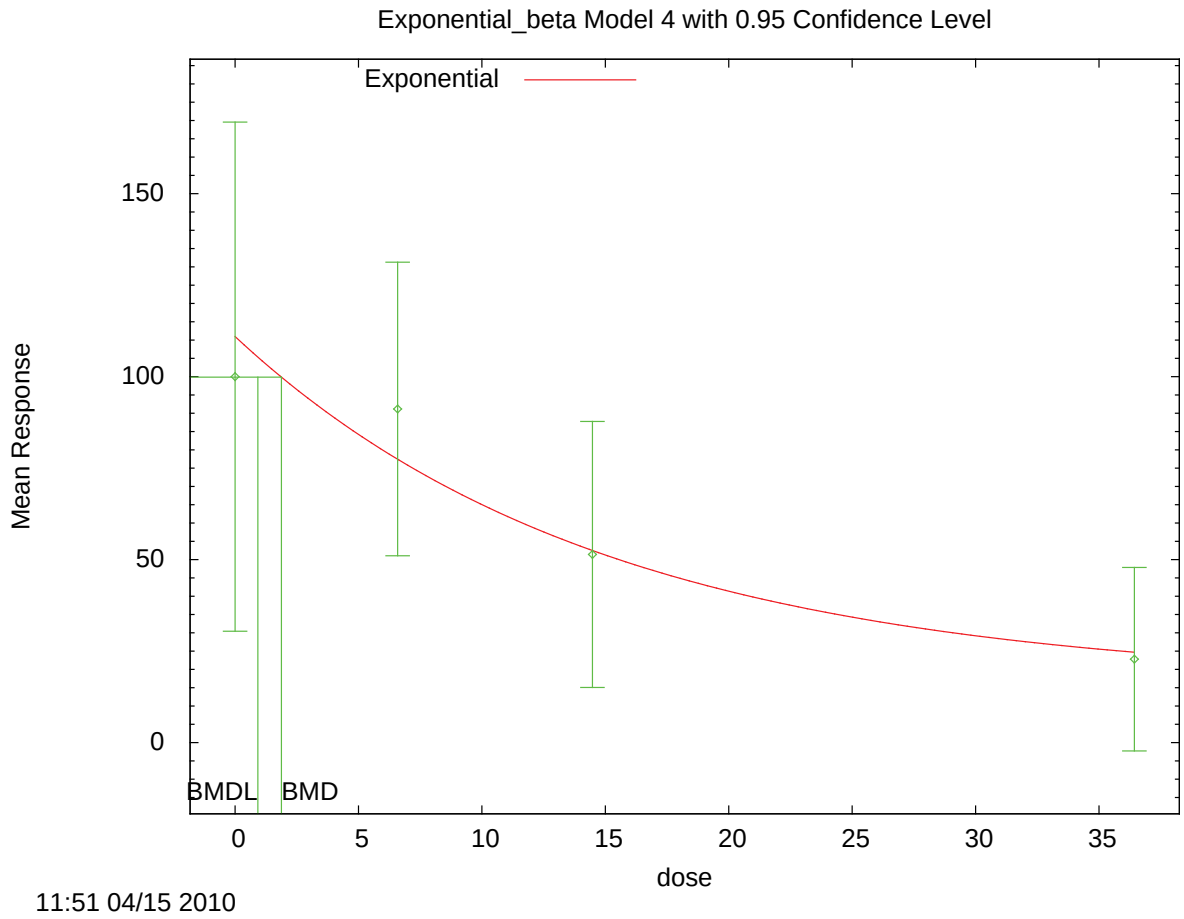
Risk Type = Relative deviation

Confidence Level = 0.950000

BMD = 1.87814

BMDL = 0.922136

G.2.11.3. *Figure for Selected Model: Exponential (M4)*



G.2.11.4. *Output for Additional Model Presented: Polynomial, 3-degree*

Franc et al. (2001): S-D Rats, Relative Thymus Weight

```
 ======================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\Blood\91_Franc_2001_SD_RelThyWt_Poly_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\91_Franc_2001_SD_RelThyWt_Poly_1.plt
                                          Thu Apr 15 11:51:20 2010
 ======================================================================

 Figure 5, SD rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
```

```
Dependent variable = Mean
Independent variable = Dose
The polynomial coefficients are restricted to be negative
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                        lalpha =       8.0075
                           rho =            0
                        beta_0 =          100
                        beta_1 =            0
                        beta_2 =    -0.475283
                        beta_3 =            0


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -beta_2    -beta_3
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                lalpha          rho       beta_0       beta_1

    lalpha           1        -0.99        0.018       0.0095

       rho        -0.99            1       -0.022      -0.0024

    beta_0        0.018       -0.022            1        -0.87

    beta_1       0.0095      -0.0024        -0.87            1


                                  Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha           2.8315          1.71297           -0.525852
6.18885
            rho          1.19884         0.416889            0.381756
2.01593
         beta_0          94.5944          14.6685             65.8446
123.344
         beta_1         -1.97776         0.509904            -2.97715
-0.978362
         beta_2                0               NA
         beta_3                0               NA
```

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	100	94.6	83.2	63	0.243
6.587	8	91.2	81.6	48	57.6	0.471
14.48	8	51.4	66	43.5	50.7	-0.811
36.43	8	22.8	22.5	30	26.7	0.0269

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-141.983433	5	293.966865
A2	-137.581833	8	291.163667
A3	-138.348184	6	288.696368
fitted	-139.254163	4	286.508326
R	-146.997301	2	297.994602

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.8309	6	0.004459
Test 2	8.8032	3	0.03203
Test 3	1.5327	2	0.4647
Test 4	1.81196	2	0.4041

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 0.1

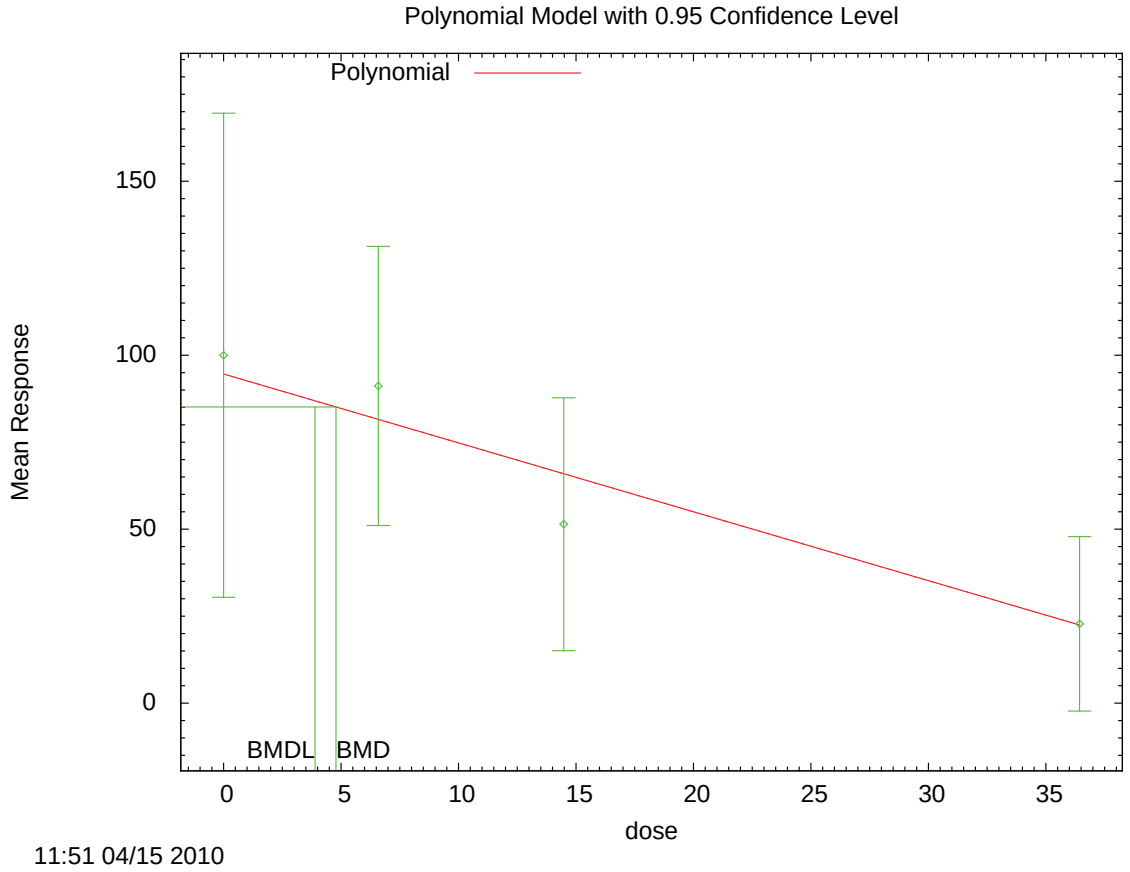
Risk Type = Relative risk

Confidence level = 0.95

BMD = 4.78292

BMDL = 3.8932

G.2.11.5. *Figure for Additional Model Presented: Polynomial, 3-degree*



G.2.12. Franc et al. (2001): L-E Rats, Relative Thymus Weight

G.2.12.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.440	301.449	2.726E+00	1.212E+00	
Exponential (M3)	2	0.440	301.449	2.726E+00	1.212E+00	power hit bound (*d* = 1)
Exponential (M4)[b]	1	0.227	303.266	2.084E+00	5.926E−01	
Exponential (M5)	0	N/A	303.805	7.859E+00	9.801E−01	
Hill	0	N/A	303.805	7.480E+00	7.512E−01	
Linear	2	0.304	302.186	5.045E+00	3.349E+00	
Polynomial, 3-degree	2	0.304	302.186	5.045E+00	3.349E+00	
Power	2	0.304	302.186	5.045E+00	3.349E+00	power bound hit (power = 1)
Power, unrestricted	1	0.168	303.710	1.374E+00	9.032E−09	unrestricted (power = 0.601)

[a] Constant variance model selected (*p* = 0.5063).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.12.2. *Output for Selected Model: Exponential (M4)*

Franc et al. (2001): L-E Rats, Relative Thymus Weight

```
 ========================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\92_Franc_2001_LE_RelThyWt_ExpCV_1.(d)
        Gnuplot Plotting File:
                                             Thu Apr 15 11:53:37 2010
 ========================================================================

 Figure 5, L-E rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   rho is set to 0.
```

A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	8.1814
rho(S)	0
a	105
b	0.0506168
c	0.166582
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	8.22706
rho	0
a	105.977
b	0.0660042
c	0.221786
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	100	54.72
6.584	8	95.41	70.46
14.47	8	38.69	47.97
36.41	8	34.98	77.96

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	106	61.16	-0.2764
6.584	76.91	61.16	0.8555
14.47	55.24	61.16	-0.765
36.41	30.96	61.16	0.186

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-146.9024	5	303.8049
A2	-145.7361	8	307.4723
A3	-146.9024	5	303.8049
R	-150.6049	2	305.2098
4	-147.6329	4	303.2658

Additive constant for all log-likelihoods = -29.41. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	9.738	6	0.1362
Test 2	2.333	3	0.5063
Test 3	2.333	3	0.5063
Test 6a	1.461	1	0.2268

The p-value for Test 1 is greater than .05. There may not be a diffence between responses and/or variances among the dose levels Modelling the data with a dose/response curve may not be appropriate.

```
  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 0.100000

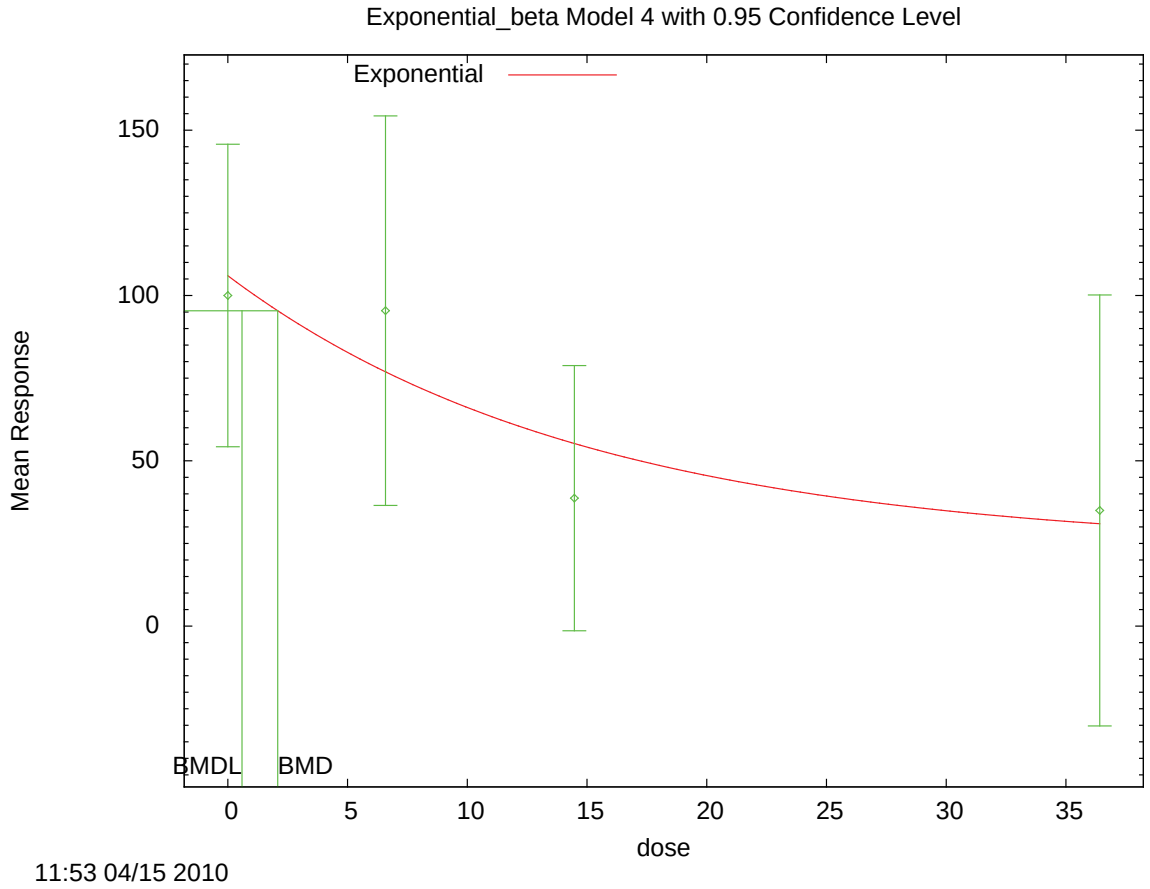
         Risk Type = Relative deviation

  Confidence Level = 0.950000

               BMD =      2.08379

              BMDL =     0.592601
```

G.2.12.3. *Figure for Selected Model: Exponential (M4)*



G.2.13. Franc et al. (2001): Han/Wistar (H/W) Rats, Relative Thymus Weight

G.2.13.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)[b]	2	0.698	261.646	5.094E+00	3.132E+00	
Exponential (M3)	1	0.407	263.616	5.944E+00	3.140E+00	
Exponential (M4)	1	0.396	263.646	5.063E+00	1.864E+00	
Exponential (M5)	0	N/A	264.927	9.945E+00	2.127E+00	
Hill	0	N/A	264.927	9.638E+00	1.853E+00	
Linear	2	0.645	261.804	6.874E+00	5.006E+00	
Polynomial, 3-degree	2	0.645	261.804	6.874E+00	5.006E+00	
Power	2	0.645	261.804	6.874E+00	5.006E+00	power bound hit (power = 1)
Power, unrestricted	1	0.363	263.755	5.487E+00	2.573E−01	unrestricted (power = 0.881)

[a] Constant variance model selected ($p = 0.4331$).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.13.2. *Output for Selected Model: Exponential (M2)*

Franc et al. (2001): H/W Rats, Relative Thymus Weight

```
 ========================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\93_Franc_2001_HW_RelThyWt_ExpCV_1.(d)
        Gnuplot Plotting File:
                                             Thu Apr 15 11:55:55 2010
 ========================================================================

 Figure 5, H/W rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 2
lnalpha	6.96647
rho(S)	0
a	56.9433
b	0.0204806
c	0
d	1

(S) = Specified

Parameter Estimates

Variable	Model 2
lnalpha	6.98895
rho	0
a	103.047
b	0.0206828
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	100	35.98
6.588	8	97.53	32.98
14.48	8	71.02	23.99
36.44	8	49.29	43.48

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	103	32.93	-0.2617
6.588	89.92	32.93	0.6532
14.48	76.38	32.93	-0.4596
36.44	48.49	32.93	0.06871

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-127.4636	5	264.9271
A2	-126.0925	8	268.185
A3	-127.4636	5	264.9271
R	-132.935	2	269.87
2	-127.8231	3	261.6463

Additive constant for all log-likelihoods = -29.41. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	13.69	6	0.03336
Test 2	2.742	3	0.4331
Test 3	2.742	3	0.4331
Test 4	0.7192	2	0.698

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

```
  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 4 is greater than .1.  Model 2 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 0.100000

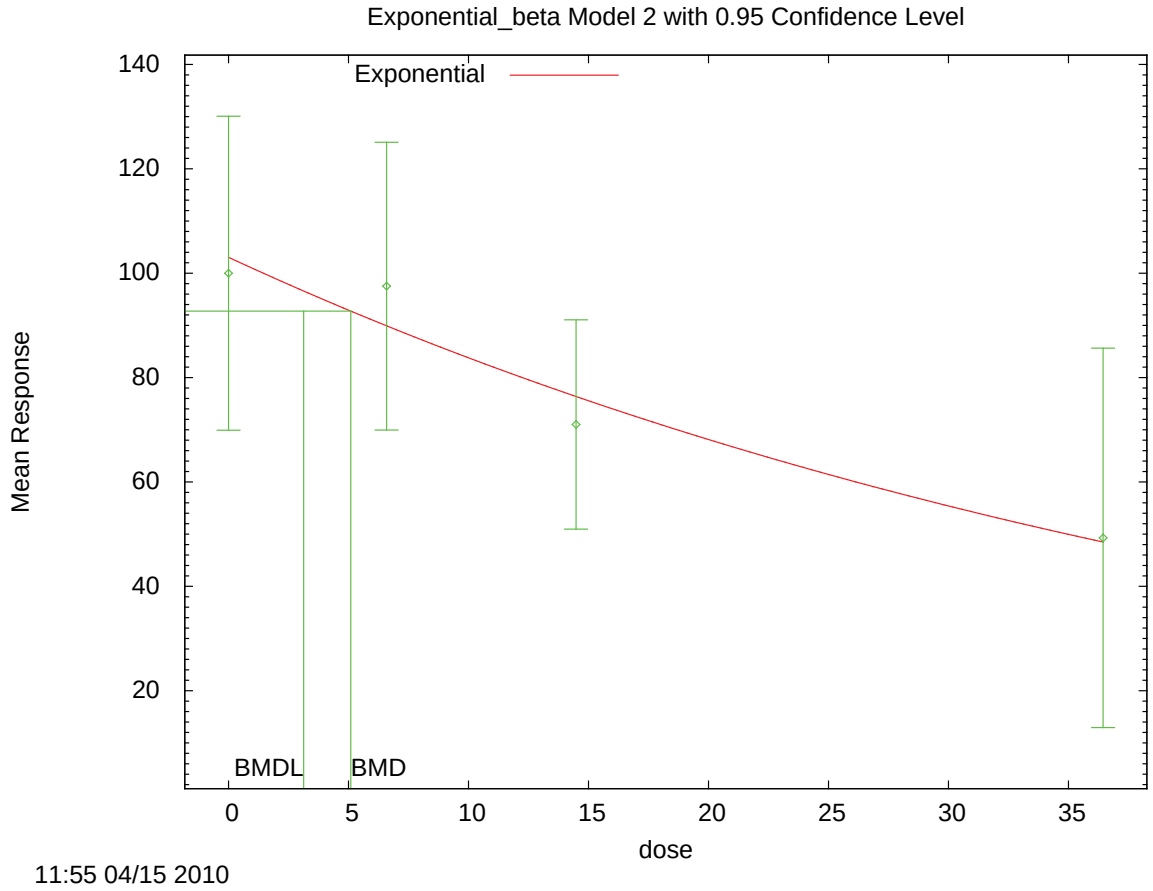
         Risk Type = Relative deviation

  Confidence Level = 0.950000

               BMD =      5.09411

              BMDL =      3.13214
```

G.2.13.3. *Figure for Selected Model: Exponential (M2)*



G.2.14. Hojo et al. (2002): DRL Reinforce per Minute

G.2.14.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Hill	1	0.101	4.465	1.667E+00	6.209E−08	*n* upper bound hit (*n* = 18)
Linear	2	0.009	9.124	1.352E+01	6.020E+00	
Polynomial, 3-degree	2	0.009	9.124	1.352E+01	6.020E+00	
Power	2	0.009	9.124	1.352E+01	6.020E+00	power bound hit (power = 1)
Power, unrestricted	1	0.025	6.780	2.428E−01	1.070E−14	unrestricted (power = 0.103)
Exponential (M2)	2	0.007	9.612	1.623E+01	8.673E+00	
Exponential (M3)	2	0.007	9.612	1.623E+01	8.673E+00	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.054**	**5.488**	**1.316E+00**	**2.367E−03**	
Exponential (M5)	0	N/A	6.465	1.728E+00	9.452E−03	

[a] Constant variance model selected (*p* = 0.4321).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.14.2. *Output for Selected Model: Exponential (M4)*

Hojo et al. (2002): DRL Reinforce Per Minute

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\21_Hojo_2002_DRLrein_ExpCV_1.(d)
        Gnuplot Plotting File:
                                             Mon Feb 08 10:49:08 2010
 ======================================================================

 Table 5, values adjusted by a constant to allow exponential model
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	-1.29672
rho(S)	0
a	0.0817
b	0.15642
c	16.3733
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	-1.11961
rho	0
a	0.0547452
b	0.708154
c	18.214
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	0.086	0.448
1.625	5	0.536	0.821
4.169	6	1.274	0.54
10.7	5	0.737	0.443

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.05475	0.5713	0.1223
1.625	0.6989	0.5713	-0.6375
4.169	0.9479	0.5713	1.398
10.7	0.9966	0.5713	-1.016

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	3.11555	5	3.7689
A2	4.489557	8	7.020886
A3	3.11555	5	3.7689
R	-2.435087	2	8.870174
4	1.255891	4	5.488219

Additive constant for all log-likelihoods = -19.3. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	13.85	6	0.03137
Test 2	2.748	3	0.4321
Test 3	2.748	3	0.4321
Test 6a	3.719	1	0.05379

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose

levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model.

Benchmark Dose Computations:

Specified Effect = 1.000000

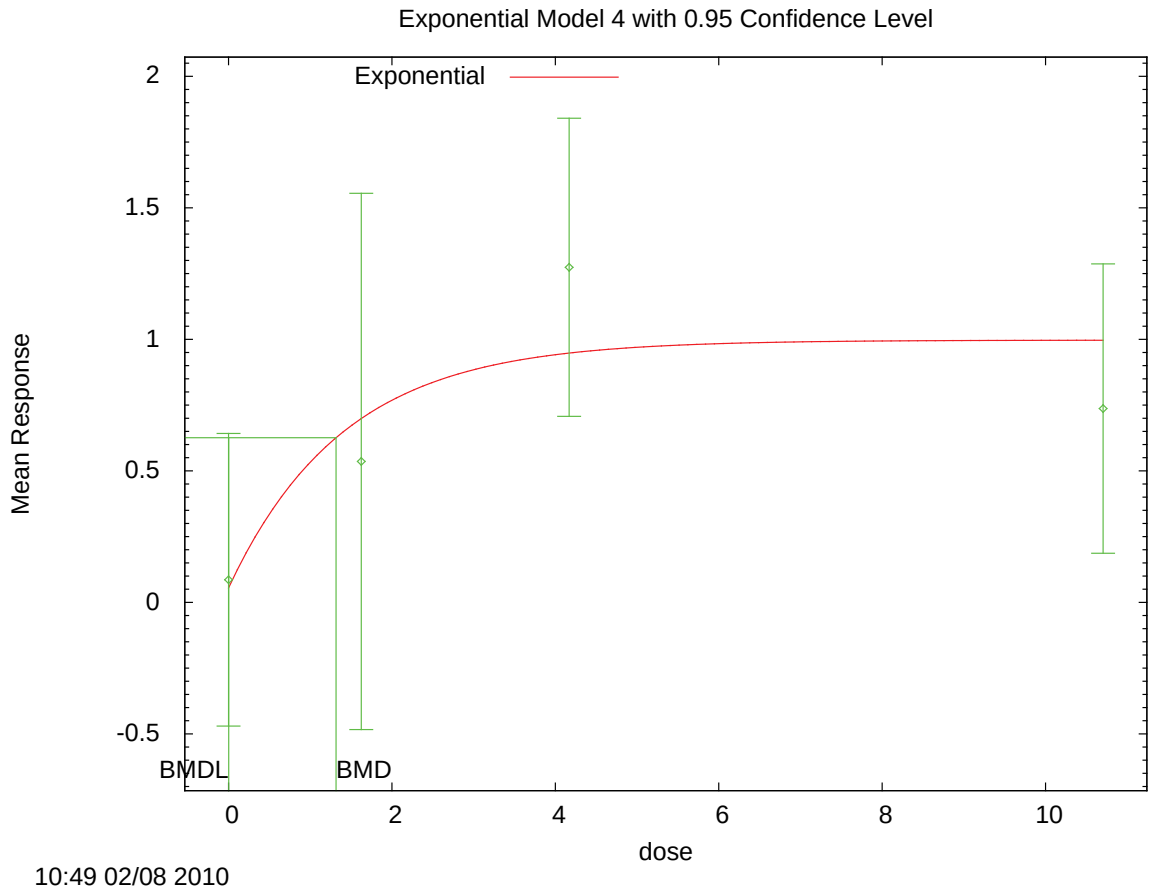
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 1.31616

BMDL = 0.00236664

G.2.14.3. *Figure for Selected Model: Exponential (M4)*



G.2.15. Hojo et al. (2002): DRL Response per Minute

G.2.15.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Hill	0	N/A	126.353	1.373E+00	1.070E−14	
Linear	2	0.006	132.243	1.064E+01	5.340E+00	
Polynomial, 3-degree	2	0.006	132.243	1.064E+01	5.340E+00	
Power	2	0.006	132.243	1.064E+01	5.340E+00	power bound hit (power = 1)
Power, unrestricted	2	0.741	122.455	1.070E+03	error	unrestricted (power = 0)
Exponential (M2)	2	0.570	122.980	5.027E−01	error	
Exponential (M3)	2	0.570	122.980	5.027E−01	error	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.477**	**124.360**	**3.813E−01**	**1.553E−02**	
Exponential (M5)	0	N/A	126.353	8.430E−01	2.221E−02	

[a] Constant variance model selected (*p* = 0.3004).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.15.2. *Output for Selected Model: Exponential (M4)*

Hojo et al. (2002): DRL Response Per Minute

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\23_Hojo_2002_DRLresp_ExpCV_1.(d)
        Gnuplot Plotting File:
                                            Mon Feb 08 10:50:10 2010
 ======================================================================

 Table 5, values adjusted by a constant to allow exponential model
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   rho is set to 0.
```

A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	4.51689
rho(S)	0
a	24.6362
b	0.379327
c	0.0184785
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	4.54096
rho	0
a	23.4674
b	1.61185
c	0.101317
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	23.46	7.986
1.625	5	4.013	10.96
4.169	6	0.478	7.194
10.7	5	4.594	15.23

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	23.47	9.684	-0.001008
1.625	3.915	9.684	0.02265
4.169	2.403	9.684	-0.4869
10.7	2.378	9.684	0.5118

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-57.92733	5	125.8547
A2	-56.09669	8	128.1934
A3	-57.92733	5	125.8547
R	-64.49611	2	132.9922
4	-58.1801	4	124.3602

Additive constant for all log-likelihoods = -19.3. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	16.8	6	0.01005
Test 2	3.661	3	0.3004
Test 3	3.661	3	0.3004
Test 6a	0.5056	1	0.4771

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

```
  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

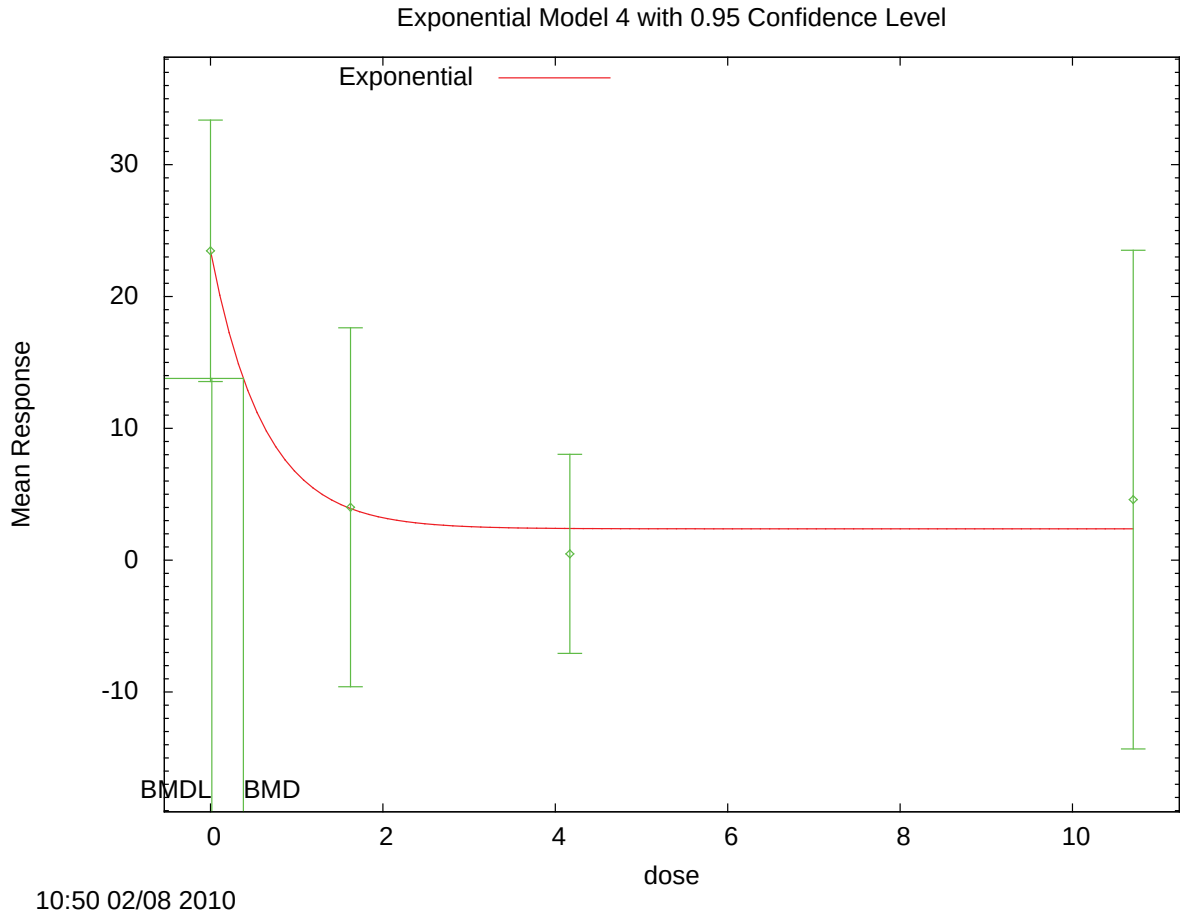
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =     0.381347

              BMDL =    0.0155267
```

G.2.15.3. *Figure for Selected Model: Exponential (M4)*



G.2.16. Kattainen et al. (2001): 3rd Molar Eruption, Female

G.2.16.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Logistic	3	0.360	88.508	9.223E+00	6.671E+00	
Log-logistic[a]	**3**	**0.982**	**85.227**	**2.399E+00**	**1.328E+00**	**slope bound hit (slope = 1)**
Log-probit	3	0.522	87.424	7.346E+00	4.561E+00	slope bound hit (slope = 1)
Probit	3	0.379	88.352	8.802E+00	6.549E+00	
Multistage, 4-degree	3	0.781	86.155	4.042E+00	2.626E+00	final ß = 0
Log-logistic, unrestricted[b]	2	0.949	87.162	1.931E+00	1.840E−01	unrestricted (slope = 0.91)
Log-probit, unrestricted	2	0.941	87.181	2.075E+00	2.395E−01	unrestricted (slope = 0.549)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.2.16.2. *Output for Selected Model: Log-Logistic*

Kattainen et al. (2001): 3rd Molar Eruption, Female

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\24_Katt_2001_Erup_LogLogistic_BMR1.(d)
        Gnuplot Plotting File:
C:\1\Blood\24_Katt_2001_Erup_LogLogistic_BMR1.plt
                                            Mon Feb 08 10:50:39 2010
 ======================================================================

 Figure 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.0625
intercept = -3.07535
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -slope
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	background	intercept
background	1	-0.53
intercept	-0.53	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0699339	*	*	*
intercept	-3.07219	*	*	*
slope	1	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-40.5286	5			
Fitted model	-40.6137	2	0.170195	3	0.9823
Reduced model	-50.7341	1	20.411	4	0.0004142

AIC: 85.2274

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual

0.0000	0.0699	1.119	1.000	16	-0.117
2.2297	0.1570	2.669	3.000	17	0.221
6.2523	0.2788	4.182	4.000	15	-0.105
16.0824	0.4670	5.604	6.000	12	0.229
46.8576	0.7066	13.426	13.000	19	-0.215

Chi^2 = 0.17 d.f. = 3 P-value = 0.9820

Benchmark Dose Computation

Specified effect = 0.1

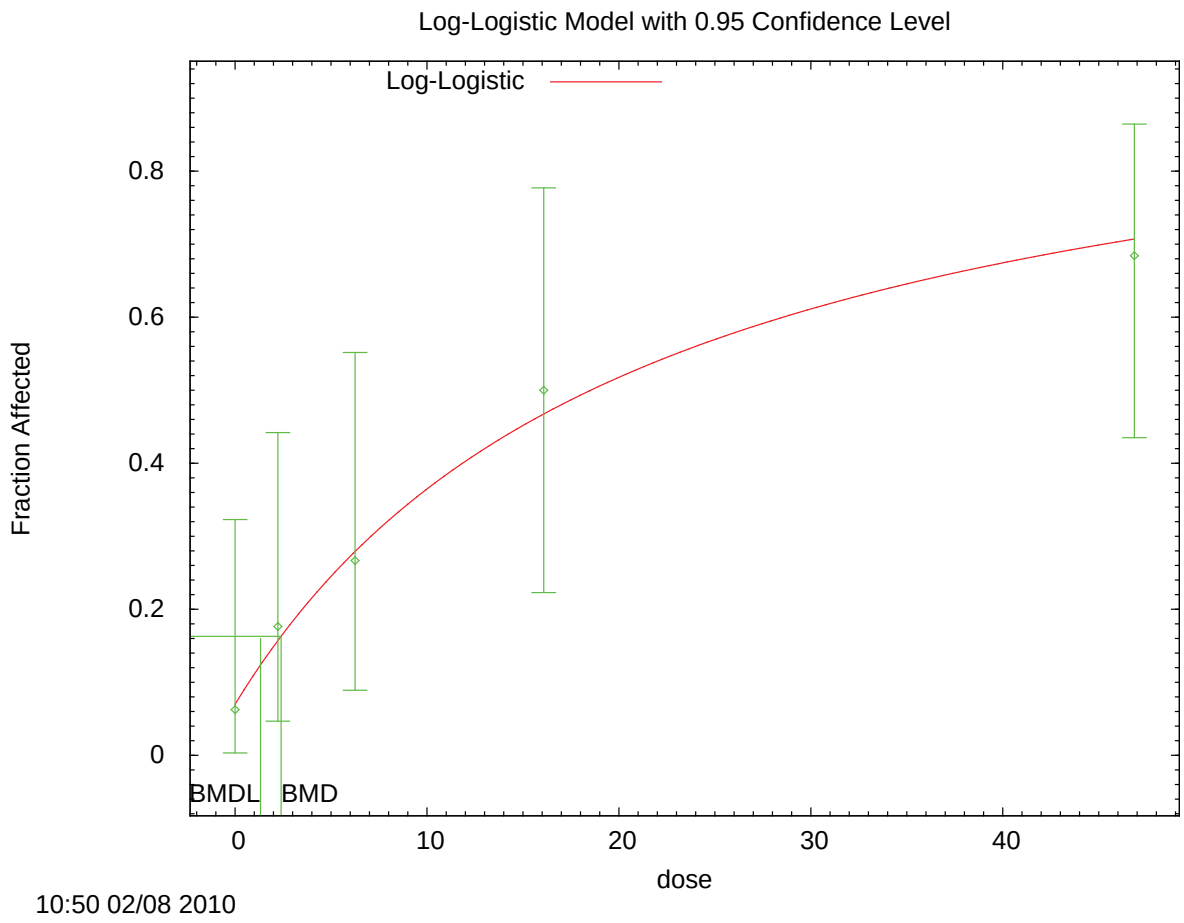
Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.39879

BMDL = 1.32815

G.2.16.3. *Figure for Selected Model: Log-Logistic*



G.2.16.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Kattainen et al. (2001): 3rd Molar Eruption, Female

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\24_Katt_2001_Erup_LogLogistic_U_BMR1.(d)
        Gnuplot Plotting File:
C:\1\Blood\24_Katt_2001_Erup_LogLogistic_U_BMR1.plt
                                          Mon Feb 08 10:50:40 2010
 ======================================================================

 Figure 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]
```

```
   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =       0.0625
                      intercept =      -2.7659
                          slope =     0.901885


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.52         0.38

 intercept        -0.52            1        -0.94

     slope         0.38        -0.94            1



                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background        0.0630045            *                *
*
      intercept         -2.79616            *                *
*
          slope         0.910333            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -40.5286         5
   Fitted model        -40.5811         3      0.105049      2
0.9488
```

```
  Reduced model        -50.7341         1        20.411      4
0.0004142

           AIC:         87.1622


                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ----------------------------------------------------------------------
    0.0000     0.0630         1.008     1.000          16        -0.008
    2.2297     0.1683         2.862     3.000          17         0.090
    6.2523     0.2922         4.383     4.000          15        -0.217
   16.0824     0.4692         5.631     6.000          12         0.214
   46.8576     0.6903        13.116    13.000          19        -0.058

 Chi^2 = 0.10      d.f. = 2        P-value = 0.9491


   Benchmark Dose Computation

Specified effect =            0.1

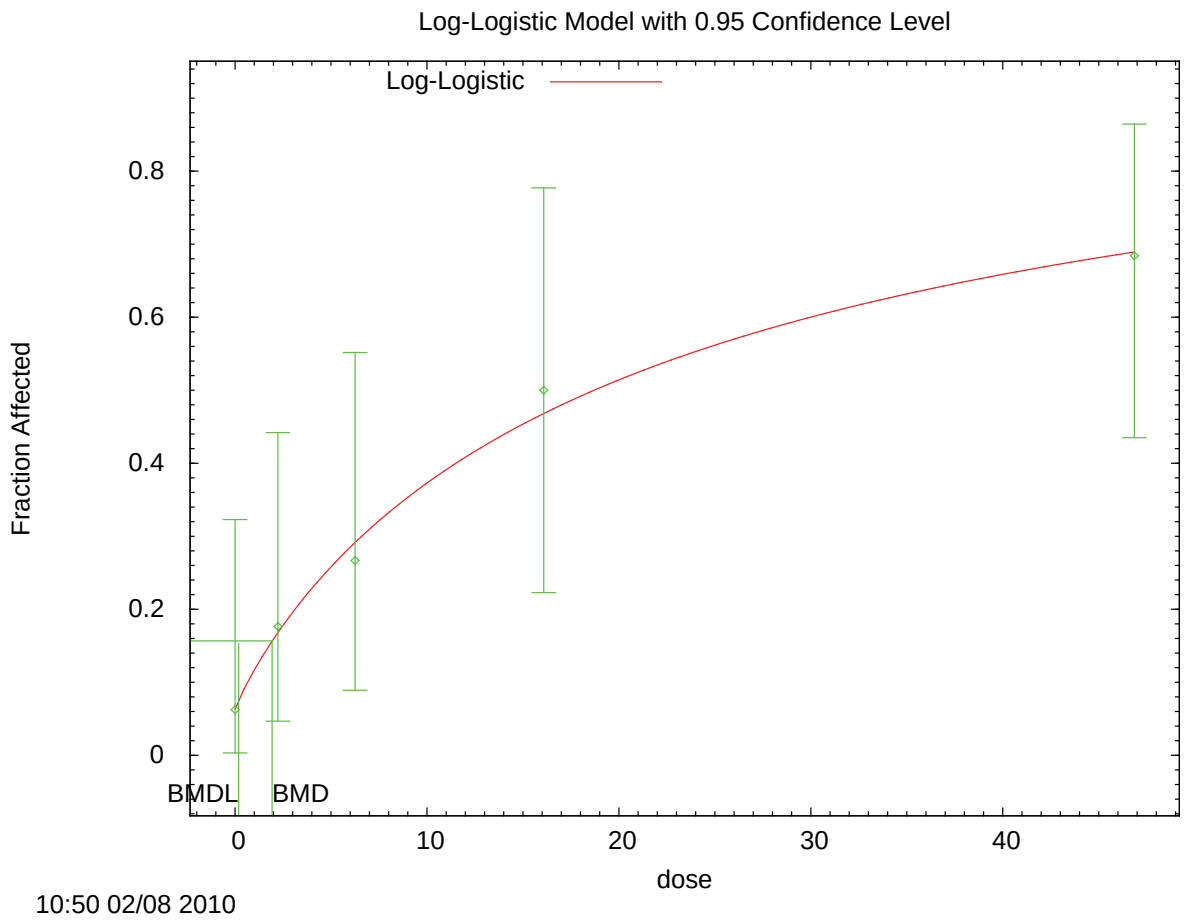
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        1.93079

            BMDL =        0.18403
```

G.2.16.5. ***Figure for Additional Model Presented: Log-Logistic, Unrestricted***



G.2.17. Kattainen et al. (2001): 3rd Molar Length, Female

G.2.17.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	3	<0.0001	−124.866	1.669E+01	9.933E+00	
Exponential (M3)	3	<0.0001	−124.866	1.669E+01	9.933E+00	power hit bound (*d* = 1)
Exponential (M4)	2	0.002	−147.120	4.237E−01	2.530E−01	
Exponential (M5)	2	0.002	−147.120	4.237E−01	2.530E−01	power hit bound (*d* = 1)
Hill[b]	**2**	**0.022**	**−152.239**	**3.132E−01**	**1.679E−01**	***n* lower bound hit (*n* = 1)**
Linear	3	<0.0001	−124.024	1.982E+01	1.277E+01	
Polynomial, 4-degree	3	<0.0001	−124.024	1.982E+01	1.277E+01	
Power	3	<0.0001	−124.024	1.982E+01	1.277E+01	power bound hit (power = 1)
Hill, unrestricted[c]	1	<0.0001	−130.856	1.215E−02	error	unrestricted (*n* = 13.042)
Power, unrestricted	2	0.263	−157.201	1.964E−03	8.002E−06	unrestricted (power = 0.195)

[a] Nonconstant variance model selected (*p* = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.17.2. *Output for Selected Model: Hill*

Kattainen et al. (2001): 3rd Molar Length, Female

```
 ========================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\25_Katt_2001_Length_Hill_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\25_Katt_2001_Length_Hill_1.plt
                                          Mon Feb 08 10:51:09 2010
 ========================================================================

 Figure 3 female only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 5
```

Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	-2.37155
rho =	0
intercept =	1.85591
v =	-0.507874
n =	0.845932
k =	2.03129

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-0.98	-0.16	0.84	-0.38
rho	-0.98	1	0.2	-0.79	0.4
intercept	-0.16	0.2	1	-0.3	-0.11
v	0.84	-0.79	-0.3	1	-0.52
k	-0.38	0.4	-0.11	-0.52	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	3.31084	1.404	0.559057	6.06262
rho	-14.2657	2.62739	-19.4153	-9.11612
intercept	1.85483	0.0159477	1.82357	1.88609
v	-0.453667	0.0620227	-0.575229	-0.332105
n	1	NA		
k	1.91219	0.624785	0.687636	3.13675

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus

has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	16	1.86	1.85	0.0661	0.0639	0.0674
2.23	17	1.58	1.61	0.185	0.175	-0.789
6.252	15	1.6	1.51	0.265	0.28	1.22
16.08	12	1.5	1.45	0.221	0.371	0.51
46.86	19	1.35	1.42	0.515	0.431	-0.716

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	56.758717	6	-101.517434
A2	85.856450	10	-151.712901
A3	84.934314	7	-155.868628
fitted	81.119648	5	-152.239295
R	45.373551	2	-86.747101

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	80.9658	8	<.0001
Test 2	58.1955	4	<.0001
Test 3	1.84427	3	0.6053
Test 4	7.62933	2	0.02205

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

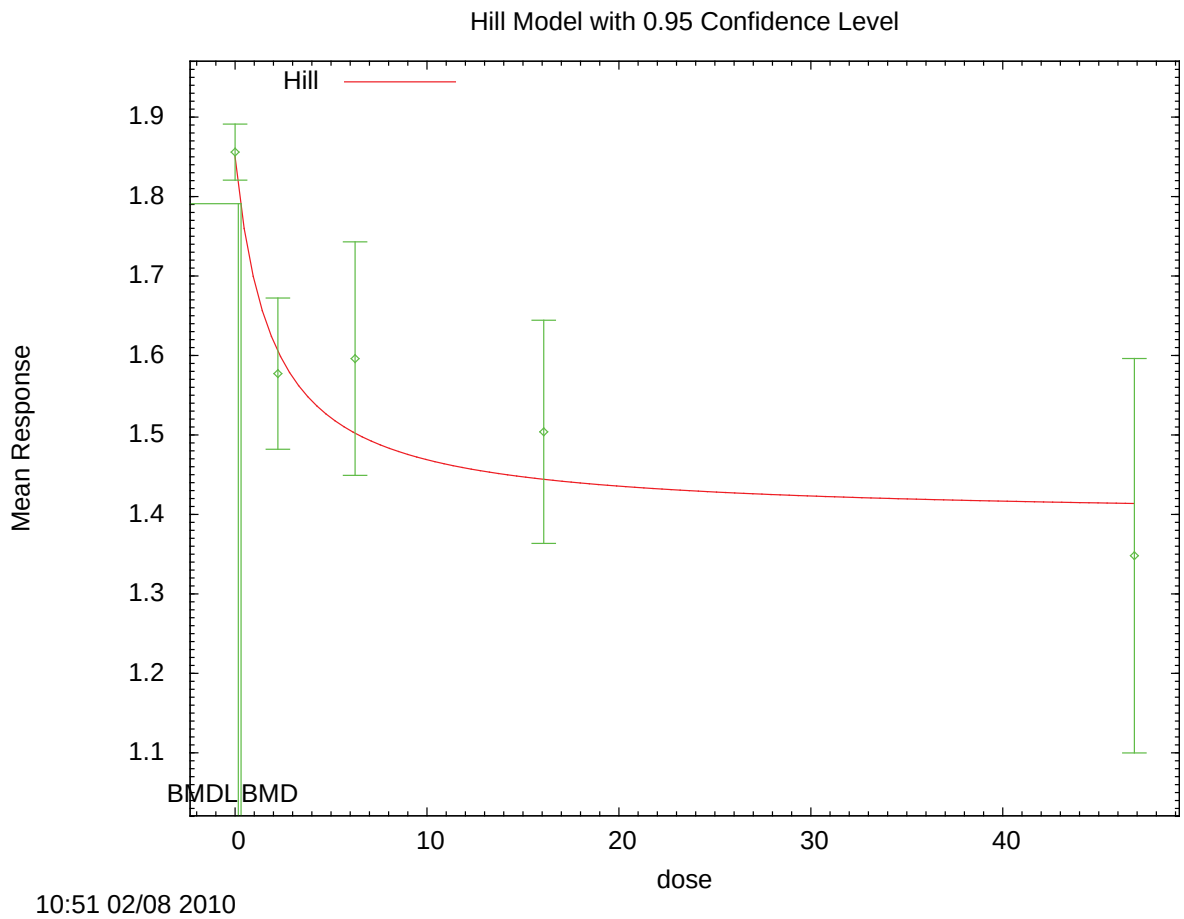
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.313211

BMDL = 0.167922

G.2.17.3. *Figure for Selected Model: Hill*



G.2.17.4. *Output for Additional Model Presented: Hill, Unrestricted*

Kattainen et al. (2001): 3rd Molar Length, Female

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\25_Katt_2001_Length_Hill_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\25_Katt_2001_Length_Hill_U_1.plt
                                          Mon Feb 08 10:51:09 2010
 ======================================================================

 Figure 3 female only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
```

```
Independent variable = Dose
Power parameter is not restricted
The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                        lalpha =     -2.37155
                           rho =            0
                     intercept =      1.85591
                             v =    -0.507874
                             n =     0.845932
                             k =      2.03129


           Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho    intercept            v            n
k

    lalpha            1        -0.98        -0.16         0.84     1.4e-016
3.3e-017

       rho        -0.98            1         0.22        -0.77    -2.2e-016
-5.1e-017

 intercept        -0.16         0.22            1        -0.35       6e-017
1.4e-017

         v         0.84        -0.77        -0.35            1    -2.6e-016
-6.2e-017

         n     1.4e-016    -2.2e-016       6e-017    -2.6e-016            1
1

         k     3.3e-017    -5.1e-017     1.4e-017    -6.2e-017            1
1


                                 Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha          4.25154           1.5913             1.13265
7.37044
            rho         -15.7639          2.90127            -21.4503
-10.0776
```

```
      intercept          1.85591        0.0160104             1.82453
1.88729
              v        -0.357293        0.0463784           -0.448193
-0.266393
              n          13.0417     4.64308e+013       -9.10027e+013
9.10027e+013
              k        0.0136512     2.57737e+011       -5.05155e+011
5.05155e+011


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0    16       1.86         1.86       0.0661        0.064      2.09e-009
 2.23    17       1.58          1.5        0.185        0.345          0.937
6.252    15        1.6          1.5        0.265        0.345           1.09
16.08    12        1.5          1.5        0.221        0.345         0.0534
46.86    19       1.35          1.5        0.515        0.345           -1.9


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1           56.758717            6    -101.517434
             A2           85.856450           10    -151.712901
             A3           84.934314            7    -155.868628
         fitted           71.427978            6    -130.855955
              R           45.373551            2     -86.747101


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
```

```
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	80.9658	8	<.0001
Test 2	58.1955	4	<.0001
Test 3	1.84427	3	0.6053
Test 4	27.0127	1	<.0001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

```
Specified effect =             1

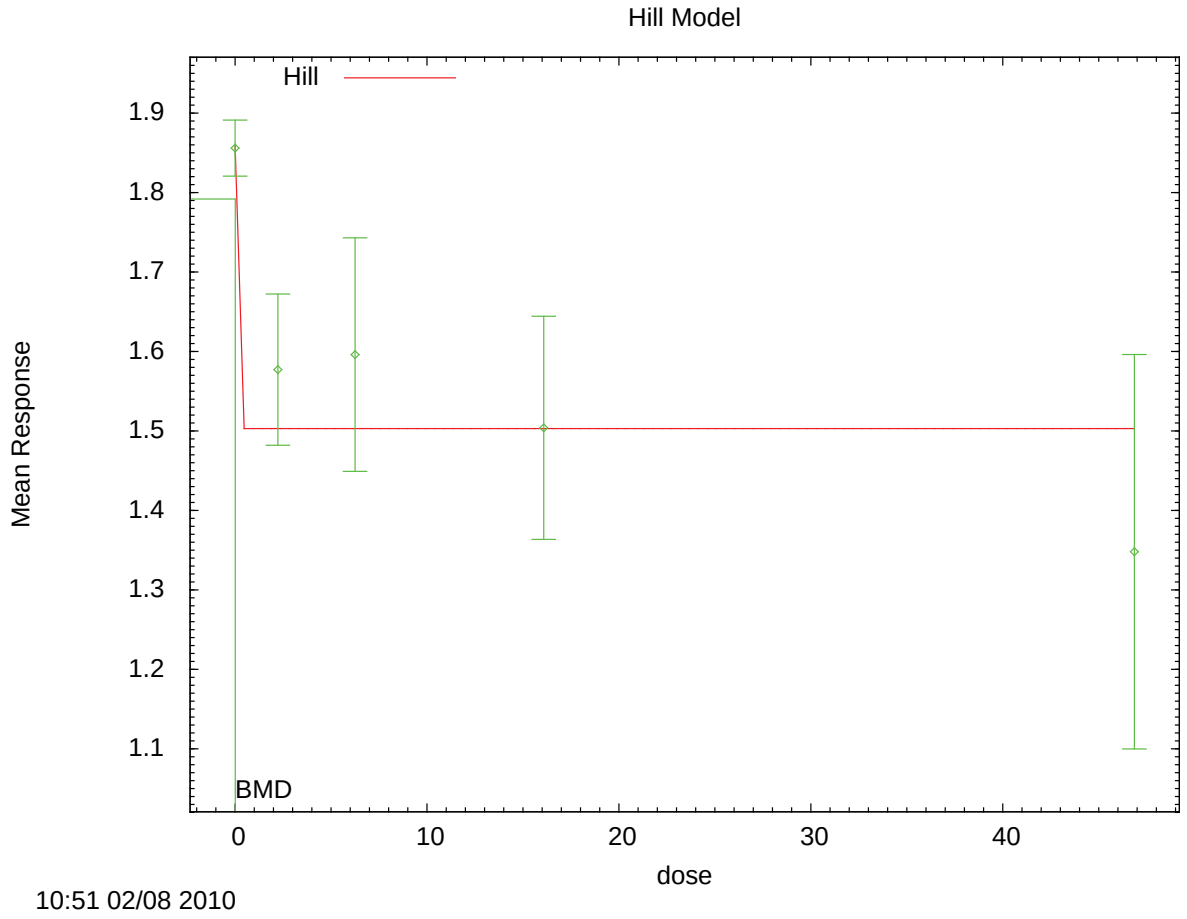
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =       0.012148
```

BMDL computation failed.

G.2.17.5. ***Figure for Additional Model Presented: Hill, Unrestricted***



G.2.18. Keller et al. (2007): Missing Mandibular Molars, CBA J

G.2.18.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	1	0.105	52.510	3.342E+00	8.986E−01	
Logistic	2	0.335	49.984	3.069E+00	2.212E+00	
Log-logistic	1	0.105	52.524	4.009E+00	2.411E+00	
Log-probit	1	0.105	52.524	3.845E+00	2.421E+00	
Multistage, 1-degree[a]	**3**	**0.255**	**50.425**	**1.091E+00**	**7.624E−01**	
Multistage, 2-degree	1	0.122	51.391	1.916E+00	9.654E−01	
Multistage, 3-degree	1	0.150	50.853	1.713E+00	9.584E−01	
Probit	2	0.342	49.904	2.927E+00	2.053E+00	
Weibull	1	0.108	52.219	2.744E+00	9.350E−01	

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.18.2. *Output for Selected Model: Multistage, 1-Degree*

Keller et al. (2007): Missing Mandibular Molars, CBA J

```
 ========================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\26_Keller_2007_Molars_Multi1_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\26_Keller_2007_Molars_Multi1_1.plt
                                          Mon Feb 08 10:51:47 2010
 ========================================================================

 Table 1 using mandibular molars only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values
Background = 0
Beta(1) = 3.03988e+018

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.096571	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-21.5798	4			
Fitted model	-24.2126	1	5.26564	3	0.1533
Reduced model	-71.326	1	99.4926	3	<.0001

AIC: 50.4251

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	29	0.000
0.5374	0.0506	1.163	2.000	23	0.796
4.2881	0.3391	9.833	6.000	29	-1.504
34.0560	0.9627	28.881	30.000	30	1.078

Chi^2 = 4.06 d.f. = 3 P-value = 0.2554

```
   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

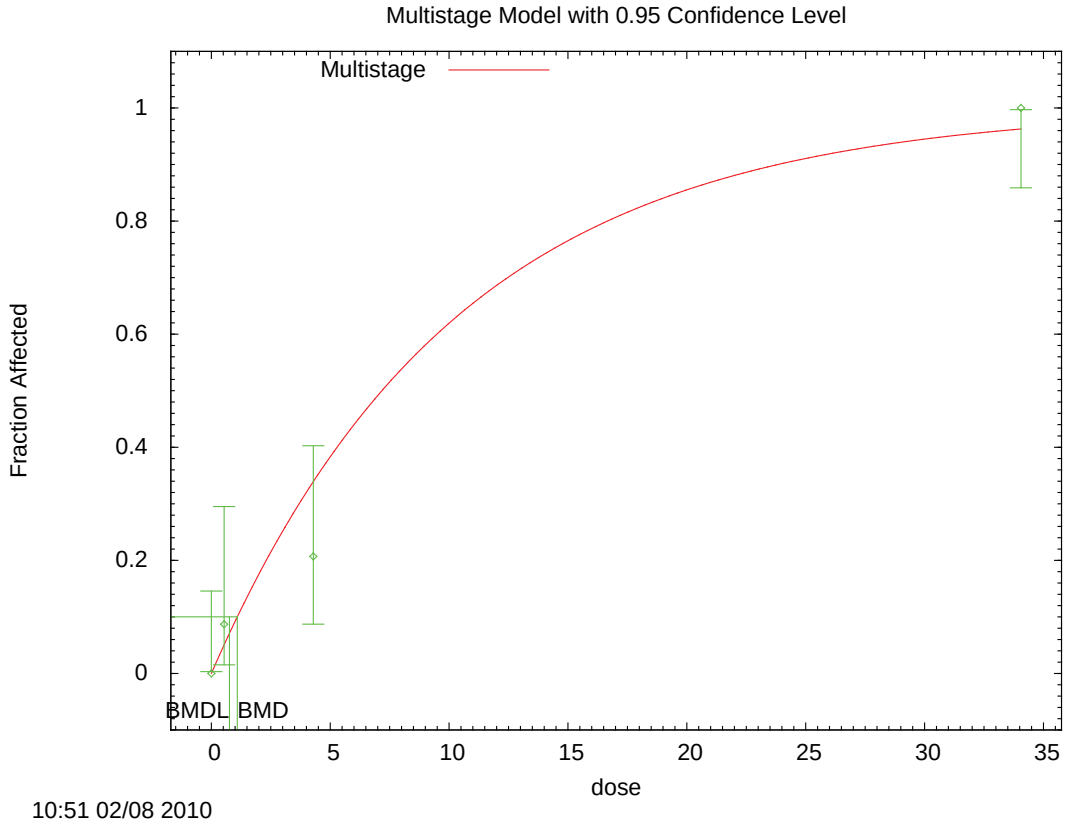
             BMD =        1.09102

            BMDL =       0.762404

            BMDU =        1.56496

Taken together, (0.762404, 1.56496) is a 90     % two-sided confidence
interval for the BMD
```

G.2.18.3. *Figure for Selected Model: Multistage, 1-Degree*



G.2.19. Kociba et al. (1978): Urinary Coproporphyrin, Females

G.2.19.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	<0.0001	82.975	2.378E+01	1.340E+01	
Exponential (M3)	2	<0.0001	82.975	2.378E+01	1.340E+01	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.006**	**73.823**	**1.566E+00**	**7.180E−01**	
Exponential (M5)	0	N/A	69.047	6.225E+00	1.586E+00	
Hill	0	N/A	69.047	5.473E+00	error	
Linear	2	<0.001	82.233	1.790E+01	3.862E+00	
Polynomial, 3-degree	2	<0.001	82.233	1.790E+01	3.862E+00	
Power	2	<0.001	82.233	1.790E+01	3.862E+00	power bound hit (power = 1)
Power, unrestricted	1	<0.001	78.691	1.148E+00	8.984E−09	unrestricted (power = 0.416)

[a] Nonconstant variance model selected (*p* = 0.0298).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.19.2. *Output for Selected Model: Exponential (M4)*

Kociba et al. (1978): Urinary Coproporphyrin, Females

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\29_Kociba_1978_Copro_Exp_1.(d)
        Gnuplot Plotting File:
                                          Mon Feb 08 10:52:47 2010
 ======================================================================

 Table2-UrinaryCoproporphyrin
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   MLE solution provided: Exact


                   Initial Parameter Values

                   Variable          Model 4
                   --------          --------
                     lnalpha             -5.58269
                         rho              2.98472
                           a                 8.17
                           b            0.0692478
                           c              2.23623
                           d                    1
```

Parameter Estimates

Variable	Model 4
lnalpha	-4.90852
rho	2.80743
a	8.91071
b	0.15304
c	1.97526
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	9.8	1.3
1.547	5	8.6	2
7.155	5	16.4	4.7
38.56	5	17.4	4

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	8.911	1.852	1.074
1.547	10.74	2.407	-1.991
7.155	14.69	3.736	1.021
38.56	17.58	4.805	-0.08246

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-31.69739	5	73.39478
A2	-27.21541	8	70.43081
A3	-28.16434	6	68.32868
R	-41.73188	2	87.46376

4	-31.91136	5	73.82272

Additive constant for all log-likelihoods = -18.38. This constant added to the
above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	29.03	6	< 0.0001
Test 2	8.964	3	0.02977
Test 3	1.898	2	0.3872
Test 6a	7.494	1	0.00619

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model.

Benchmark Dose Computations:

Specified Effect = 1.000000

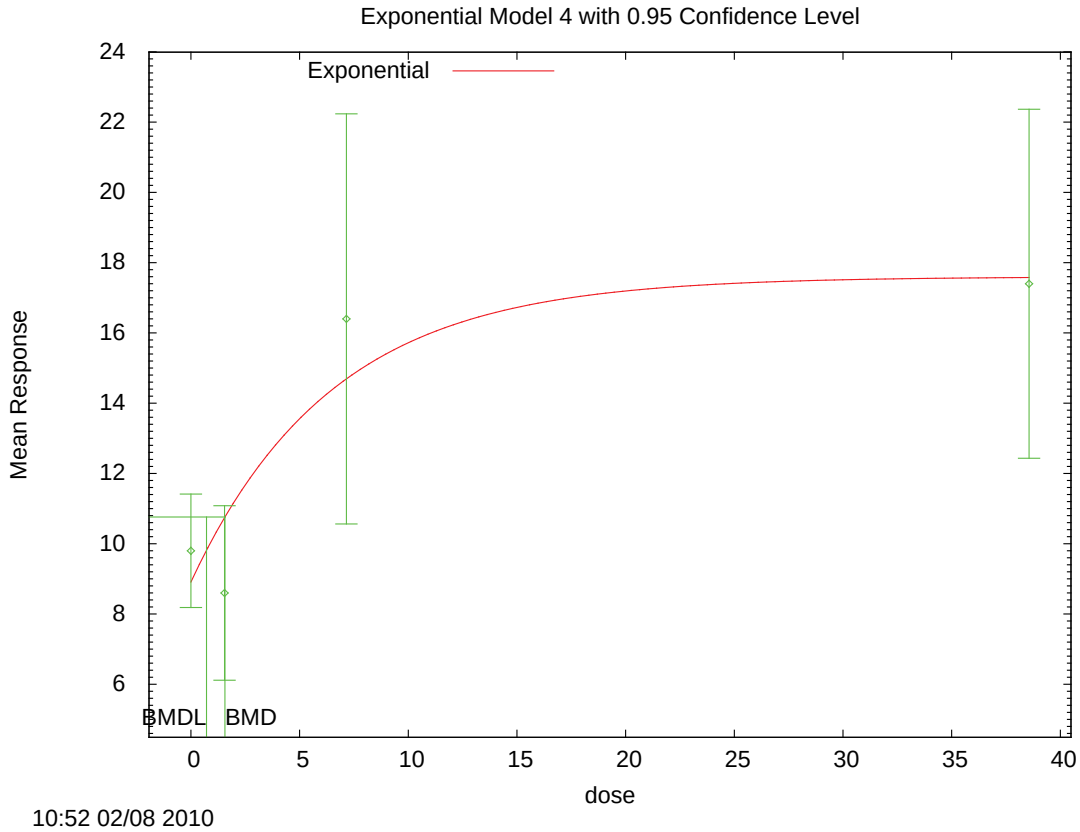
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 1.56562

BMDL = 0.718033

G.2.19.3. *Figure for Selected Model: Exponential (M4)*



G.2.20. Kociba et al. (1978): Uroporphyrin per Creatinine, Female

G.2.20.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.755	−93.828	1.641E+01	1.259E+01	
Exponential (M3)	2	0.755	−93.828	1.641E+01	1.259E+01	power hit bound (d = 1)
Exponential (M4)	1	0.499	−91.935	1.216E+01	3.958E+00	
Exponential (M5)	0	N/A	−90.190	7.542E+00	4.128E+00	
Hill	0	N/A	−90.190	7.607E+00	3.966E+00	
Linear[b]	**2**	**0.793**	**−93.928**	**1.306E+01**	**9.287E+00**	
Polynomial, 3-degree	2	0.793	−93.928	1.306E+01	9.287E+00	
Power	1	0.497	−91.928	1.326E+01	9.287E+00	

[a] Constant variance model selected (p = 0.4919).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.20.2. *Output for Selected Model: Linear*

Kociba et al. (1978): Uroporphyrin per Creatinine, Female

```
 ======================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\Blood\28_Kociba_1978_Uropor_LinearCV_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\28_Kociba_1978_Uropor_LinearCV_1.plt
                                          Mon Feb 08 10:52:17 2010
 ======================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                   Default Initial Parameter Values
                           alpha =    0.0030385
                             rho =            0   Specified
                          beta_0 =     0.149139
                          beta_1 =   0.00381789


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -rho
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                   alpha       beta_0       beta_1

     alpha             1     1.9e-009    -2.6e-009

    beta_0     1.9e-009            1         -0.6

    beta_1    -2.6e-009         -0.6            1
```

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.00248773	0.000786688	0.000945846	0.00402961
beta_0	0.149139	0.0139684	0.121761	0.176517
beta_1	0.00381789	0.000711776	0.00242284	0.00521295

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	5	0.157	0.149	0.05	0.0499	0.352
1.547	5	0.143	0.155	0.037	0.0499	-0.54
7.155	5	0.181	0.176	0.053	0.0499	0.204
38.56	5	0.296	0.296	0.074	0.0499	-0.0161

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	50.195349	5	-90.390697
A2	51.400051	8	-86.800103
A3	50.195349	5	-90.390697
fitted	49.963863	3	-93.927727
R	41.049755	2	-78.099510

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	20.7006	6	0.002076
Test 2	2.40941	3	0.4919
Test 3	2.40941	3	0.4919
Test 4	0.46297	2	0.7934

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

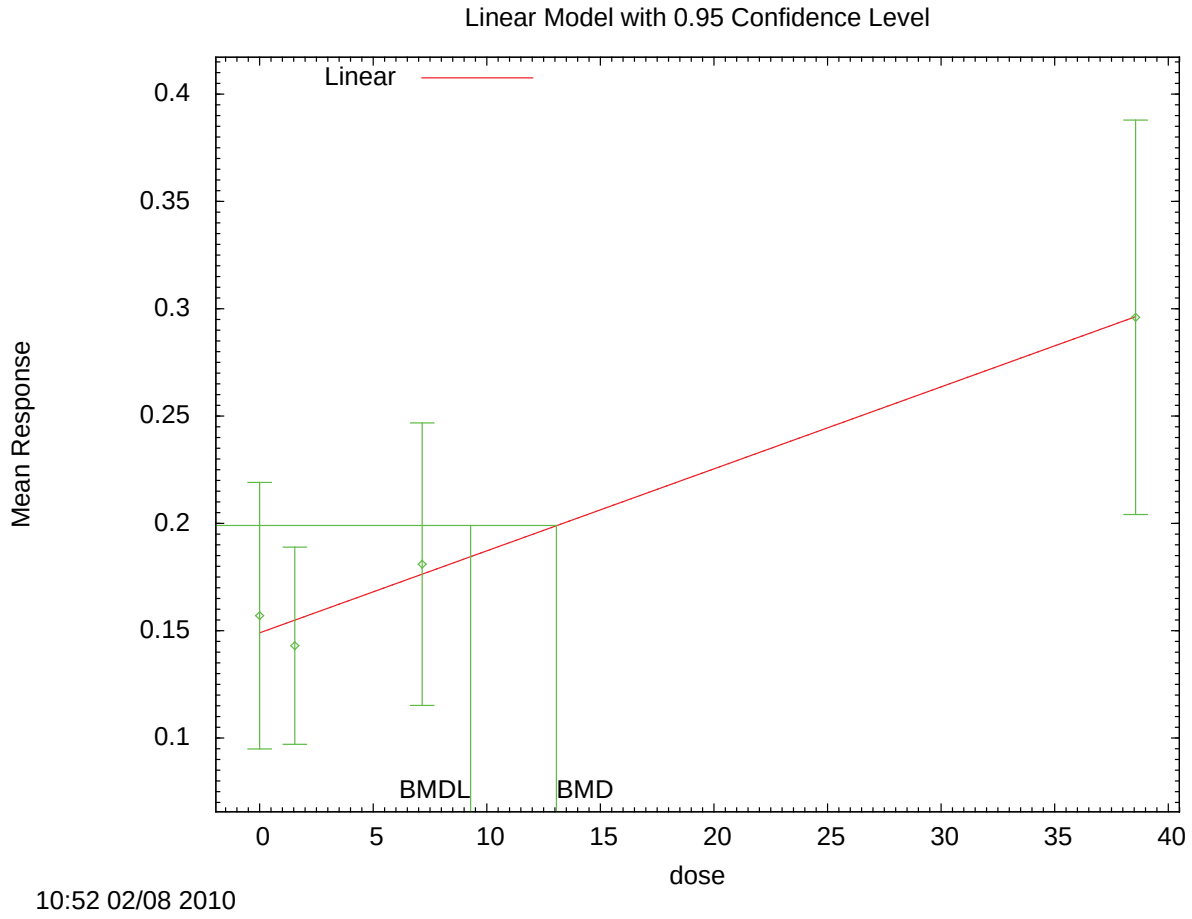
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 13.064

BMDL = 9.28715

G.2.20.3. *Figure for Selected Model: Linear*



G.2.21. Kuchiiwa et al. (2002): Immunoreactive Neurons in Dorsalis, Males

G.2.21.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	**0**	**N/A [c]**	**93.91**	**6.044E−02**	**4.270E−02**	

[a] Constant variance model selected (p = 0.530).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] p-value could not be calculated because there were no available degrees of freedom.

G.2.21.2. *Output for Selected Model: Linear*

```
=====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\USEPA\BMDS21\1\79_Kuchiiwa_2002_dors_blood_dd_LinearCV_1.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\1\79_Kuchiiwa_2002_dors_blood_dd_LinearCV_1.plt
                                          Tue Aug 16 13:54:37 2011
 ====================================================================

 number_labeled_cells_dorsalis_TWAblooddose
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 2
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =      670.324
                            rho =            0   Specified
                         beta_0 =      237.097
                         beta_1 =     -391.046


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                  alpha       beta_0       beta_1

     alpha            1    -4.2e-008     2.3e-008

    beta_0    -4.2e-008            1        -0.71

    beta_1     2.3e-008        -0.71            1
```

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	558.603	228.049	111.636	1005.57
beta_0	237.097	9.64886	218.186	256.008
beta_1	-391.046	53.0749	-495.071	-287.021

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	237	237	29	23.6	1.03e-007
0.2571	6	137	137	22.4	23.6	2.15e-008

Degrees of freedom for Test A3 vs fitted <= 0

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-43.952634	3	93.905267
A2	-43.755407	4	95.510815
A3	-43.952634	3	93.905267
fitted	-43.952634	3	93.905267
R	-54.206960	2	112.413921

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	20.9031	2	<.0001
Test 2	0.394453	1	0.53
Test 3	0.394453	1	0.53
Test 4	8.81073e-013	0	NA

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square
test for fit is not valid

Benchmark Dose Computation

Specified effect = 1

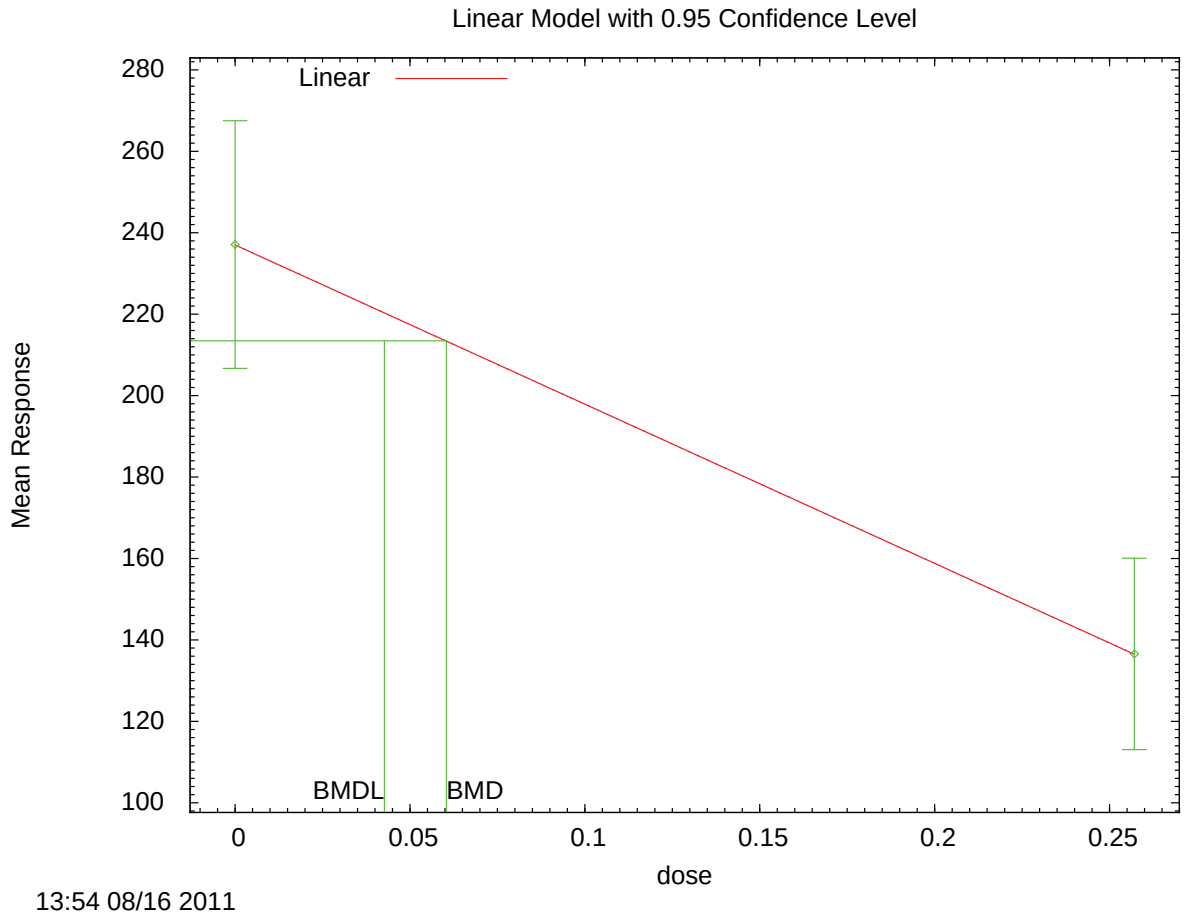
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.0604398

BMDL = 0.0427028

G.2.21.3. *Figure for Selected Model: Linear*



G.2.22. Kuchiiwa et al. (2002): Immunoreactive Neurons in Medianus, Males

G.2.22.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	**0**	**N/A [c]**	**65.97**	**4.928E−02**	**3.227E−02**	

[a] Modeled variance model selected ($p = 0.025$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] *p*-value could not be calculated because there were no available degrees of freedom.

G.2.22.2. *Output for Selected Model: Linear*

```
=====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\USEPA\BMDS21\1\80_Kuchiiwa_2002_med_blood_dd_Linear_1.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\1\80_Kuchiiwa_2002_med_blood_dd_Linear_1.plt
```

Tue Aug 16 13:55:40 2011

==========

number_labeled_cells_medianus_TWAblooddose

~~~
~~~

```
        beta_1         -225.014          18.8038            -261.869
-188.16



     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0     6       91.1         91.1         12.1         11.1      4.41e-009
0.2571     6       33.3         33.3         4.55         4.16     -4.19e-009

Degrees of freedom for Test A2 vs A3 <= 0

 Warning: Likelihood for fitted model larger than the Likelihood for model
A3.



 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -31.500916            3      69.001832
             A2          -28.985335            4      65.970670
             A3          -28.985335            4      65.970670
         fitted          -28.985335            4      65.970670
              R          -46.859574            2      97.719148


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
```

(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	35.7485	2	<.0001
Test 2	5.03116	1	0.0249
Test 3	2.47269e-012	0	NA
Test 4	-2.47269e-012	0	NA

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

NA - Degrees of freedom for Test 3 are less than or equal to 0. The Chi-Square
test for fit is not valid

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square
test for fit is not valid

Benchmark Dose Computation

Specified effect = 1

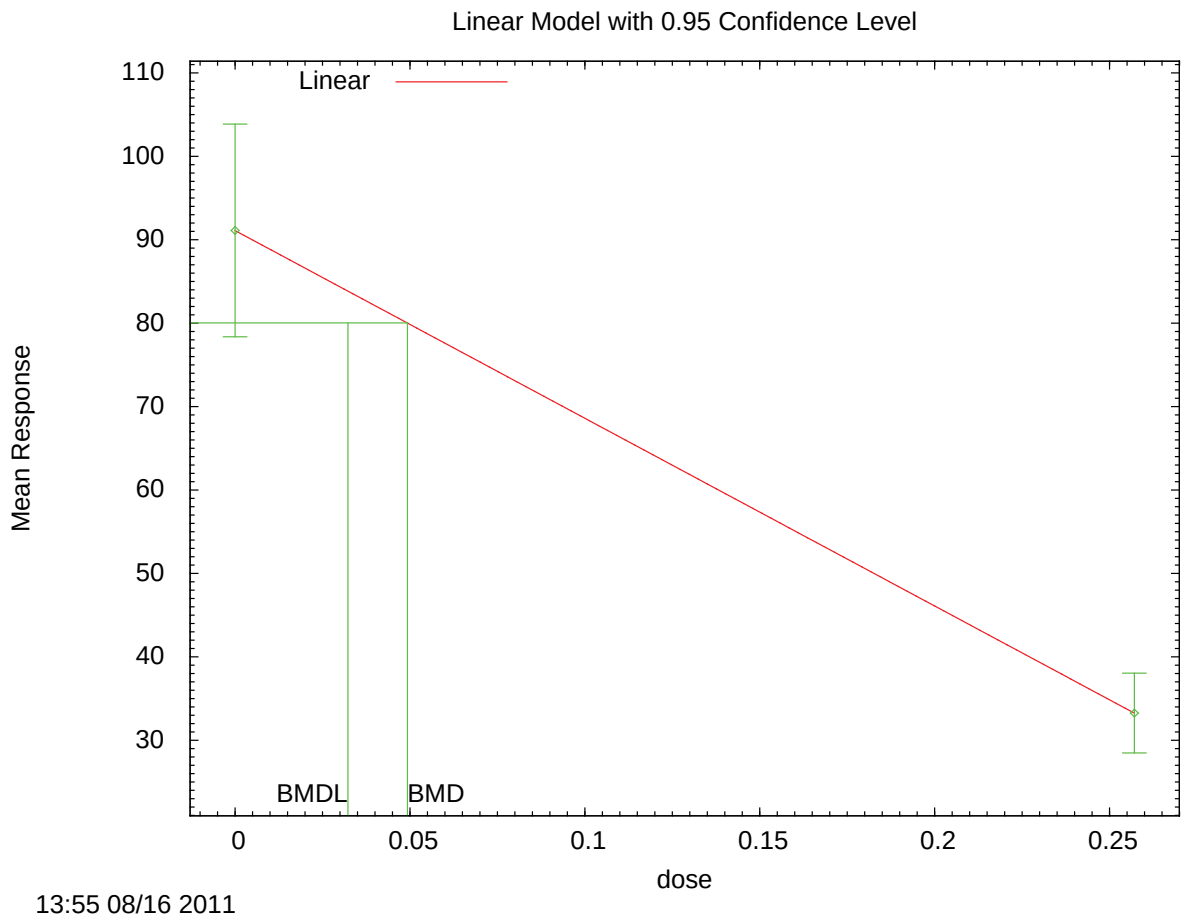
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.0492768

BMDL = 0.032269

G.2.22.3. *Figure for Selected Model: Linear*



G.2.23. Kuchiiwa et al. (2002): Immunoreactive Neurons in B9, Males

G.2.23.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	**0**	**N/A [c]**	**86.12**	**4.172E−02**	**3.015E−02**	

[a] Constant variance model selected ($p = 0.504$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] *p*-value could not be calculated because there were no available degrees of freedom.

G.2.23.2. *Output for Selected Model: Linear*

```
=====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\USEPA\BMDS21\1\81_Kuchiiwa_2002_b9_blood_dd_LinearCV_1.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\1\81_Kuchiiwa_2002_b9_blood_dd_LinearCV_1.plt
```

```
                                        Tue Aug 16 13:57:44 2011
 ======================================================================

 number_labeled_cells_b9_TWAblooddose
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 2
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =      350.225
                            rho =            0   Specified
                         beta_0 =      152.086
                         beta_1 =     -409.531


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                  alpha       beta_0       beta_1

     alpha            1     2.2e-007    -2.5e-007

    beta_0     2.2e-007            1        -0.71

    beta_1    -2.5e-007        -0.71            1



                                  Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          291.854          119.149             58.3265
525.381
```

```
         beta_0          152.086           6.9744             138.416
165.756
         beta_1         -409.531          38.3637            -484.722
-334.339



     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0     6        152          152           16         17.1      -5.3e-007
0.2571     6       46.8         46.8         21.1         17.1      3.27e-007

Degrees of freedom for Test A3 vs fitted <= 0



 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -40.057520            3      86.115041
             A2          -39.834453            4      87.668907
             A3          -40.057520            3      86.115041
         fitted          -40.057520            3      86.115041
              R          -54.163617            2     112.327234


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	28.6583	2	<.0001
Test 2	0.446134	1	0.5042
Test 3	0.446134	1	0.5042
Test 4	1.87583e-012	0	NA

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square test for fit is not valid

Benchmark Dose Computation

Specified effect = 1

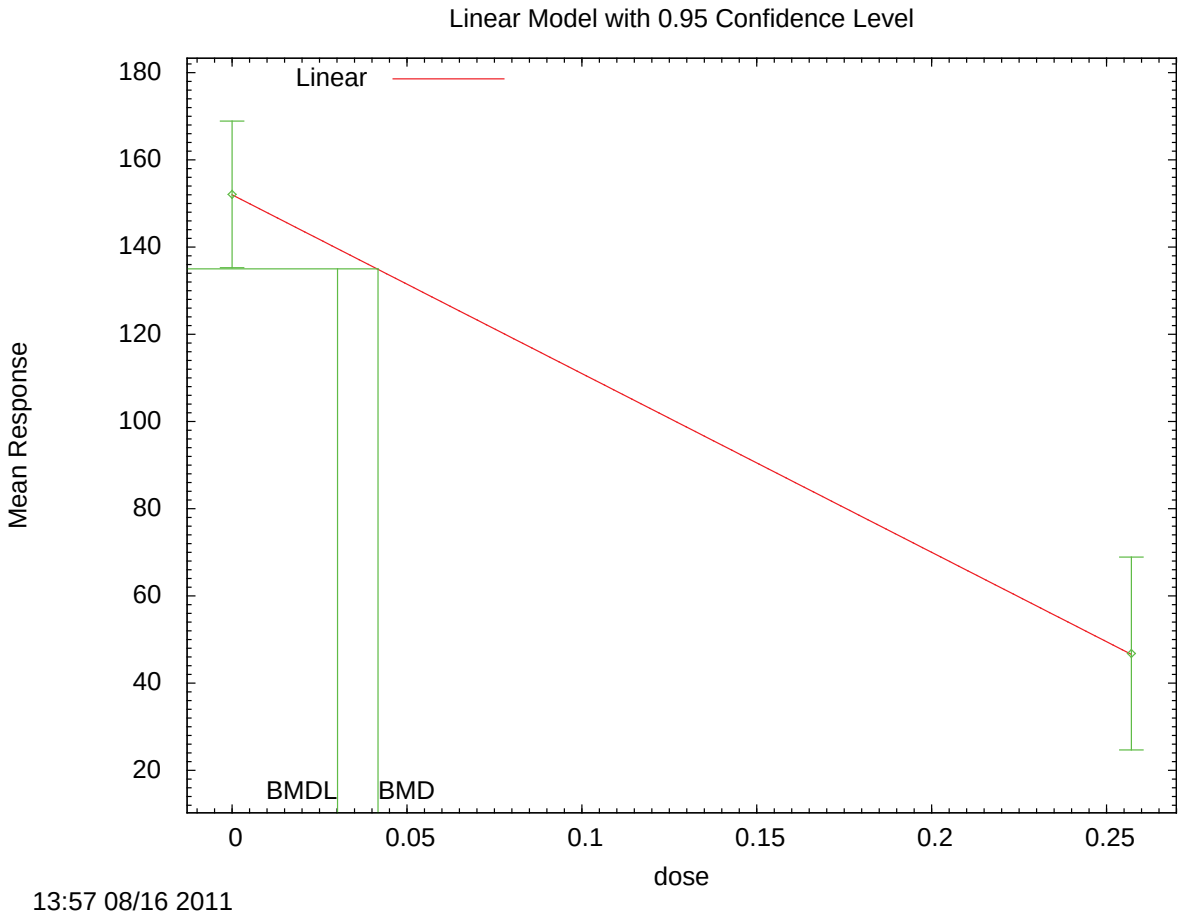
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.0417154

BMDL = 0.0301486

G.2.23.3. *Figure for Selected Model: Linear*



G.2.24. Kuchiiwa et al. (2002): Immunoreactive Neurons in Magnus, Males

G.2.24.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	**0**	**N/A [c]**	**60.36**	**3.354E−02**	**2.048E−02**	

[a] Modeled variance model selected (p = 0.013).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] p-value could not be calculated because there were no available degrees of freedom.

G.2.24.2. *Output for Selected Model: Linear*

```
=====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\USEPA\BMDS21\1\82_Kuchiiwa_2002_mag_blood_dd_Linear_1.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\1\82_Kuchiiwa_2002_mag_blood_dd_Linear_1.plt
```

Tue Aug 16 13:56:37 2011

==========

number_labeled_cells_magnus_TWAblooddose

~~~
~~~

```
        beta_1         -92.5263          15.5809            -123.064
-61.9882



     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0     6       43.6         43.6          3.4          3.1      1.13e-008
0.2571     6       19.8         19.8         10.2         9.31      1.88e-008

Degrees of freedom for Test A2 vs A3 <= 0

Degrees of freedom for Test A3 vs fitted <= 0



 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -29.244768            3      64.489536
             A2          -26.179929            4      60.359859
             A3          -26.179929            4      60.359859
         fitted          -26.179929            4      60.359859
              R          -37.469939            2      78.939878


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	22.58	2	<.0001
Test 2	6.12968	1	0.01329
Test 3	7.10543e-015	0	NA
Test 4	0	0	NA

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

NA - Degrees of freedom for Test 3 are less than or equal to 0. The Chi-Square test for fit is not valid

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square test for fit is not valid

Benchmark Dose Computation

Specified effect = 1

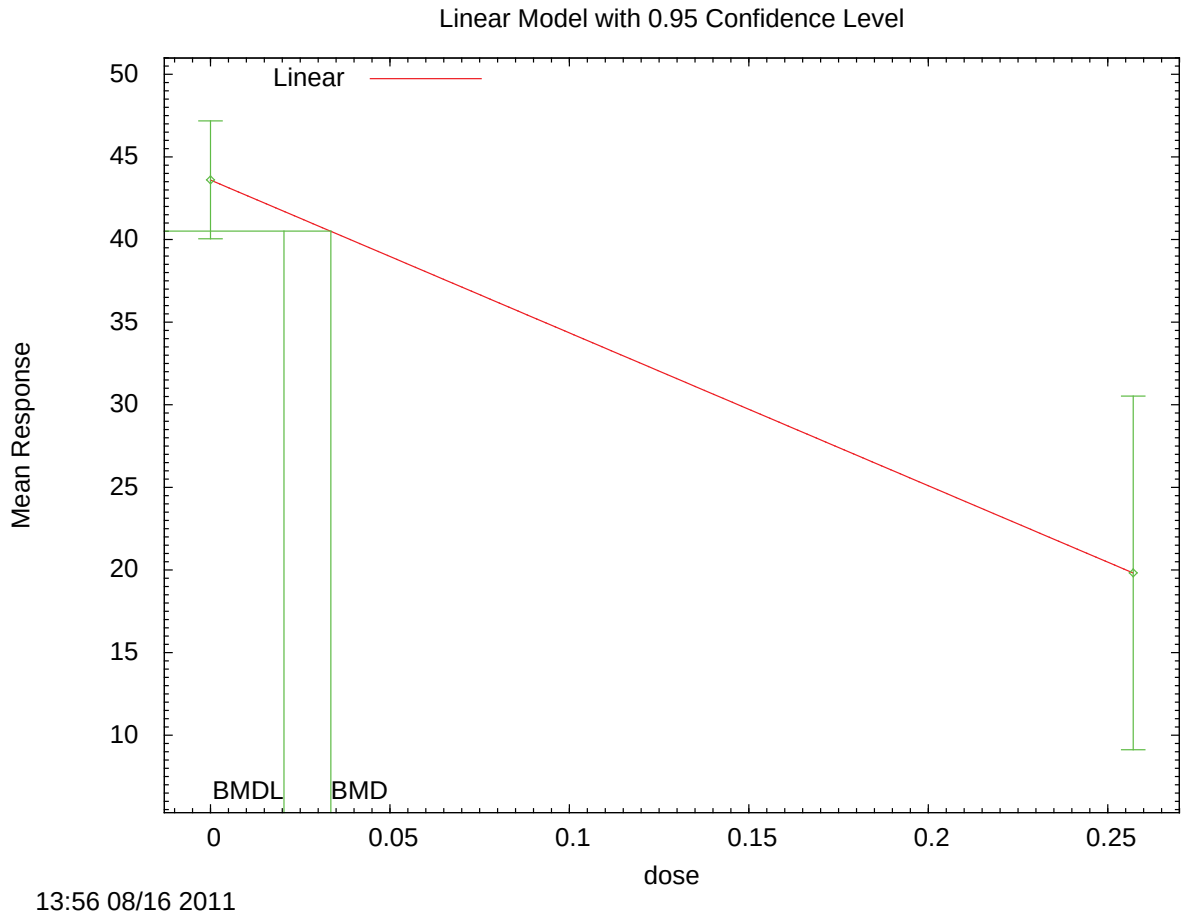
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.0335363

BMDL = 0.020483

G.2.24.3. *Figure for Selected Model: Linear*



G.2.25. Latchoumycandane and Mathur (2002): Sperm Production

G.2.25.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	<0.0001	93.831	1.739E+01	9.432E+00	
Exponential (M3)	2	<0.0001	93.831	1.739E+01	9.432E+00	power hit bound (*d* = 1)
Exponential (M4)	1	0.700	75.261	1.912E−01	7.976E−02	
Exponential (M5)	0	N/A	77.263	2.925E−01	7.970E−02	
Hill[b]	**1**	**0.962**	**75.115**	**1.171E−01**	**1.324E−02**	***n* lower bound hit (*n* = 1)**
Linear	2	<0.0001	94.250	1.995E+01	1.212E+01	
Polynomial, 3-degree	2	<0.0001	94.250	1.995E+01	1.212E+01	
Power	2	<0.0001	94.250	1.995E+01	1.212E+01	power bound hit (power = 1)
Hill, unrestricted[c]	0	N/A	77.113	9.955E−02	1.228E−09	unrestricted (*n* = 0.916)
Power, unrestricted	1	0.501	75.566	6.921E−06	6.921E−06	unrestricted (power = 0.087)

[a] Constant variance model selected (*p* = 0.8506).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.25.2. *Output for Selected Model: Hill*

Latchoumycandane and Mathur (2002): Sperm Production

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\30_Latch_2002_Sperm_HillCV_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\30_Latch_2002_Sperm_HillCV_1.plt
                                          Mon Feb 08 10:53:26 2010
 ======================================================================

 (x10^6) Table 1 without Vitamin E
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	7.23328	
rho =	0	Specified
intercept =	22.19	
v =	-9.09	
n =	1.93059	
k =	0.546864	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	-2.2e-009	-3.7e-008	-5.9e-009
intercept	-2.2e-009	1	-0.76	-0.23
v	-3.7e-008	-0.76	1	-0.24
k	-5.9e-009	-0.23	-0.24	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	6.0283	1.74022	2.61753	9.43907
intercept	22.1894	1.00236	20.2248	24.154
v	-9.16715	1.30966	-11.734	-6.60026
n	1	NA		
k	0.320198	0.220443	-0.111862	0.752259

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

```
------     ---   --------     --------   -----------  -----------   ---------
-

    0     6       22.2         22.2         2.67         2.46       0.000631
0.7845     6       15.7         15.7         2.65         2.46       -0.00931
4.651     6       13.7         13.6         2.19         2.46         0.0372
27.27     6       13.1         13.1         3.16         2.46        -0.0285


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -33.556444            5      77.112888
             A2          -33.158811            8      82.317623
             A3          -33.556444            5      77.112888
         fitted          -33.557588            4      75.115176
              R          -47.392394            2      98.784788


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              28.4672          6          <.0001
   Test 2             0.795266          3          0.8506
   Test 3             0.795266          3          0.8506
   Test 4           0.00228746          1          0.9619

The p-value for Test 1 is less than .05.  There appears to be a
```

```
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

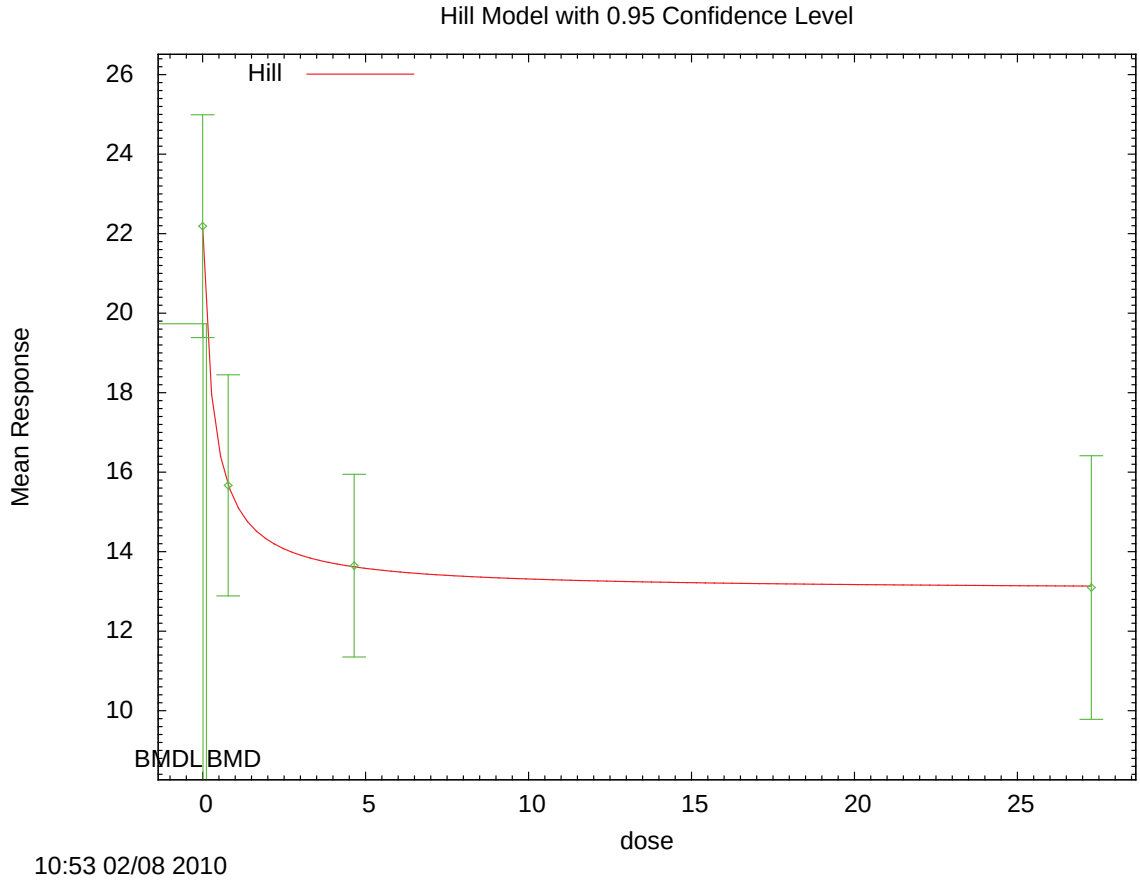
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =       0.117131

            BMDL =     0.0132353
```

G.2.25.3. *Figure for Selected Model: Hill*



G.2.25.4. *Output for Additional Model Presented: Hill, Unrestricted*

Latchoumycandane and Mathur (2002): Sperm Production

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\30_Latch_2002_Sperm_HillCV_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\30_Latch_2002_Sperm_HillCV_U_1.plt
                                          Mon Feb 08 10:53:26 2010
 ======================================================================

 (x10^6) Table 1 without Vitamin E
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

```
Power parameter is not restricted
A constant variance model is fit

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                         alpha =      7.23328
                           rho =            0   Specified
                     intercept =        22.19
                             v =        -9.09
                             n =      1.93059
                             k =     0.546864


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha    intercept            v            n            k

     alpha            1    -9.8e-009     1.6e-007     1.6e-007     1.2e-007

 intercept    -9.8e-009            1         -0.5       -0.015        -0.13

         v     1.6e-007         -0.5            1         0.76         0.56

         n     1.6e-007       -0.015         0.76            1         0.86

         k     1.2e-007        -0.13         0.56         0.86            1


                                 Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          6.02773          1.74006             2.61728
9.43818
      intercept            22.19          1.00231             20.2255
24.1545
              v         -9.23667          2.03204            -13.2194
-5.25394
              n         0.916265          1.66287            -2.34291
4.17544
              k         0.301742         0.440535           -0.561692
1.16518
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	22.2	22.2	2.67	2.46	3.4e-008
0.7845	6	15.7	15.7	2.65	2.46	-1.51e-007
4.651	6	13.7	13.6	2.19	2.46	2.62e-007
27.27	6	13.1	13.1	3.16	2.46	-5.45e-007

Degrees of freedom for Test A3 vs fitted <= 0

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-33.556444	5	77.112888
A2	-33.158811	8	82.317623
A3	-33.556444	5	77.112888
fitted	-33.556444	5	77.112888
R	-47.392394	2	98.784788

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	28.4672	6	<.0001
Test 2	0.795266	3	0.8506
Test 3	0.795266	3	0.8506
Test 4	6.96332e-013	0	NA

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square test for fit is not valid

Benchmark Dose Computation

Specified effect = 1

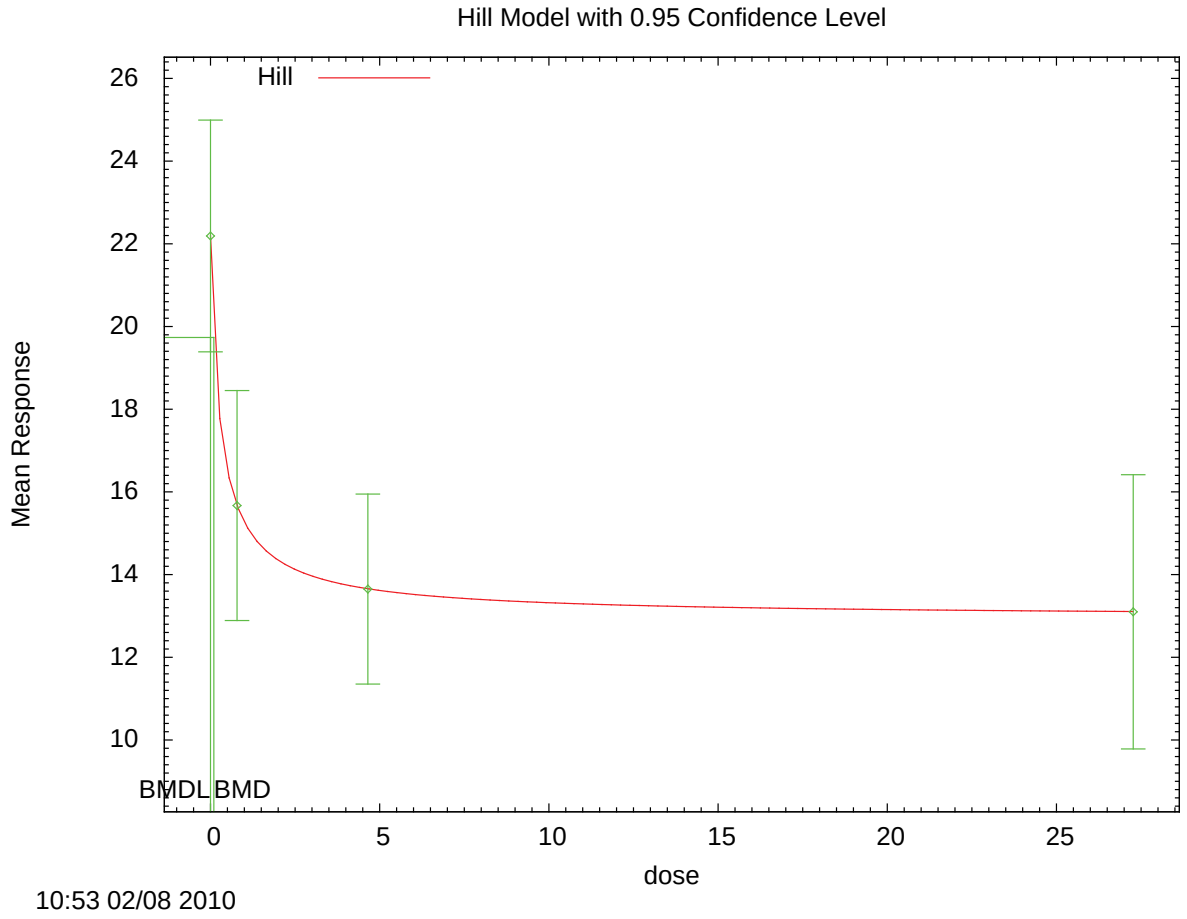
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.0995543

BMDL = 1.22818e-009

G.2.25.5. *Figure for Additional Model Presented: Hill, Unrestricted*



G.2.26. Li et al. (1997): Follicle-Stimulating Hormone (FSH)

G.2.26.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	8	<0.0001	1,095.292	5.222E+02	4.121E+02	
Exponential (M3)	8	<0.0001	1,095.292	5.222E+02	4.121E+02	power hit bound (*d* = 1)
Exponential (M4)	7	<0.0001	1,059.480	3.432E+01	9.930E+00	
Exponential (M5)	6	<0.0001	1,066.195	1.019E+02	8.583E−01	
Hill	7	<0.0001	1,056.459	5.423E+00	error	*n* lower bound hit (*n* = 1)
Linear	8	<0.0001	1,077.695	2.003E+02	1.357E+02	
Polynomial, 8-degree	9	<0.0001	1,155.670	error	1.916E+02	
Power[b]	**8**	**<0.0001**	**1,077.695**	**2.003E+02**	**1.357E+02**	**power bound hit (power = 1)**
Hill, unrestricted	6	0.001	1,039.481	2.204E−01	error	unrestricted (*n* = 0.32)
Power, unrestricted[c]	7	0.002	1,037.474	1.963E−01	2.484E−02	unrestricted (power = 0.305)

[a] Nonconstant variance model selected (*p* = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.26.2. *Output for Selected Model: Power*

Li et al. (1997): FSH

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\72_Li_1997_FSH_Pwr_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\72_Li_1997_FSH_Pwr_1.plt
                                          Mon Feb 08 13:36:35 2010
 ======================================================================

 Figure 3: FSH in female S-D rats 24hr after dosing, 22 day old rats
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is restricted to be greater than or equal to 1
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 10
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

lalpha =	9.8191
rho =	0
control =	22.1591
slope =	52.284
power =	0.294106

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -power
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	control	slope
lalpha	1	-0.99	-0.29	-0.033
rho	-0.99	1	0.2	0.033
control	-0.29	0.2	1	-0.36
slope	-0.033	0.033	-0.36	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	3.50054	1.225	1.09958	5.9015
rho	1.27087	0.241869	0.796814	1.74492
control	87.4348	12.9347	62.0833	112.786
slope	0.492306	0.0919718	0.312044	0.672567
power	1	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
---	---	---	---	---	---	---

0	10	23.9	87.4	29.6	98.6	-2.04
0.266	10	22.2	87.6	48.5	98.7	-2.1
0.7988	10	85.2	87.8	94.3	98.9	-0.0832
2.097	10	73.3	88.5	48.5	99.4	-0.483
5.867	10	126	90.3	159	101	1.12
15	10	132	94.8	116	104	1.14
43.33	10	117	109	51.2	113	0.223
119.9	10	304	146	154	137	3.65
386	10	347	277	151	205	1.07
1172	10	455	664	286	358	-1.85

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-535.687163	11	1093.374327
A2	-496.367061	20	1032.734122
A3	-502.709623	12	1029.419246
fitted	-534.847518	4	1077.695035
R	-574.835246	2	1153.670492

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	156.936	18	<.0001
Test 2	78.6402	9	<.0001

Test 3	12.6851	8	0.1232
Test 4	64.2758	8	<.0001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

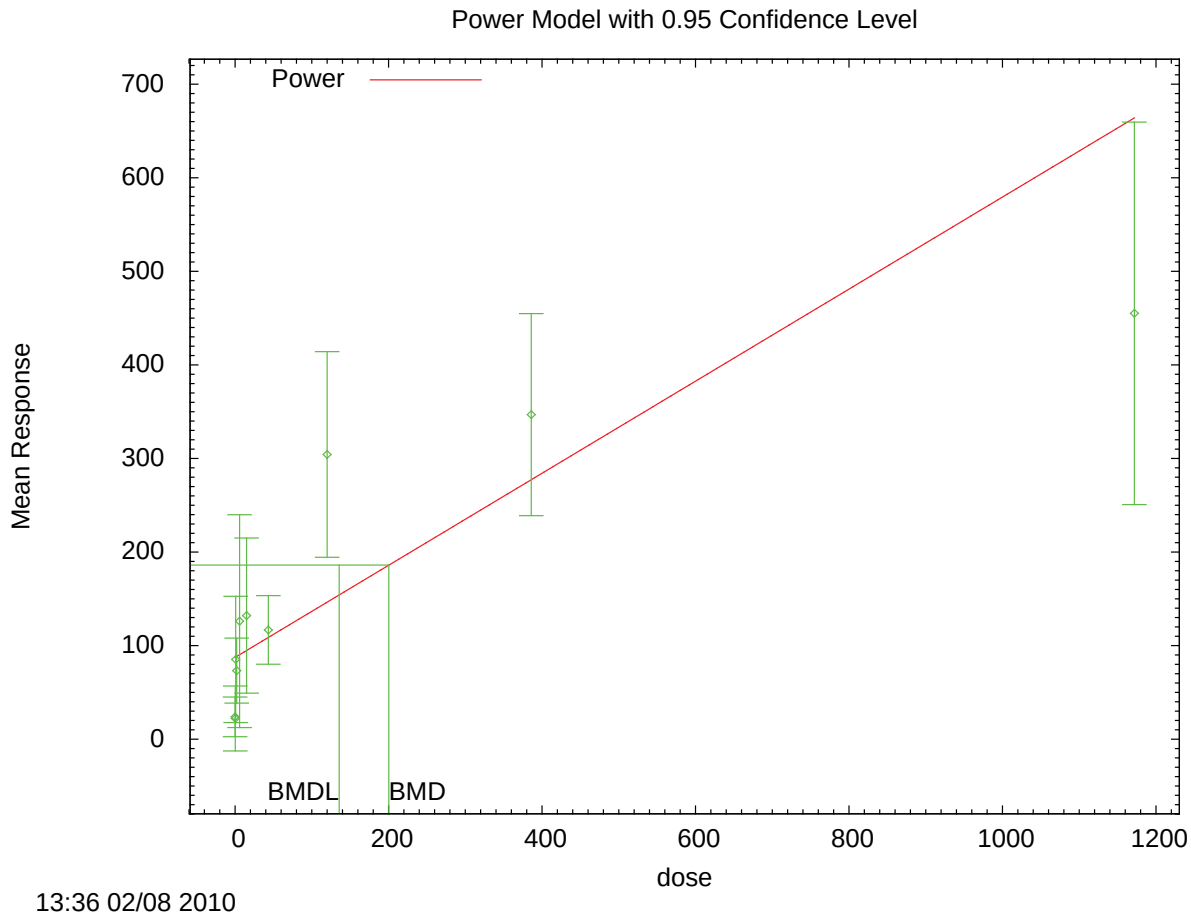
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 200.314

BMDL = 135.673

G.2.26.3. *Figure for Selected Model: Power*



G.2.26.4. *Output for Additional Model Presented: Power, Unrestricted*

Li et al. (1997): FSH

```
 ====================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\72_Li_1997_FSH_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\72_Li_1997_FSH_Pwr_U_1.plt
                                          Mon Feb 08 13:36:46 2010
 ====================================================================

 Figure 3: FSH in female S-D rats 24hr after dosing, 22 day old rats
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
```

```
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                Default Initial Parameter Values
                        lalpha =       9.8191
                           rho =            0
                       control =      22.1591
                         slope =       52.284
                         power =     0.294106


         Asymptotic Correlation Matrix of Parameter Estimates

               lalpha          rho      control        slope        power

    lalpha            1        -0.99        -0.69        -0.06         0.26

       rho        -0.99            1         0.65       0.0089        -0.23

   control        -0.69         0.65            1        -0.23        0.029

     slope        -0.06       0.0089        -0.23            1        -0.85

     power         0.26        -0.23        0.029        -0.85            1


                              Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha          3.67487          1.12134             1.47708
5.87265
            rho          1.17882         0.221526            0.744632
1.613
        control          15.8201          6.87715             2.34113
29.299
          slope           52.528          9.46821             33.9706
71.0853
          power         0.304867        0.0336805            0.238855
0.37088


     Table of Data and Estimated Values of Interest
```

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	23.9	15.8	29.6	32	0.795
0.266	10	22.2	50.9	48.5	63.7	-1.43
0.7988	10	85.2	64.9	94.3	73.5	0.876
2.097	10	73.3	81.7	48.5	84.1	-0.314
5.867	10	126	106	159	98.1	0.652
15	10	132	136	116	114	-0.102
43.33	10	117	182	51.2	135	-1.52
119.9	10	304	242	154	160	1.24
386	10	347	339	151	195	0.134
1172	10	455	469	286	236	-0.182

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-535.687163	11	1093.374327
A2	-496.367061	20	1032.734122
A3	-502.709623	12	1029.419246
fitted	-513.737215	5	1037.474431
R	-574.835246	2	1153.670492

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	156.936	18	<.0001
Test 2	78.6402	9	<.0001
Test 3	12.6851	8	0.1232
Test 4	22.0552	7	0.002485

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

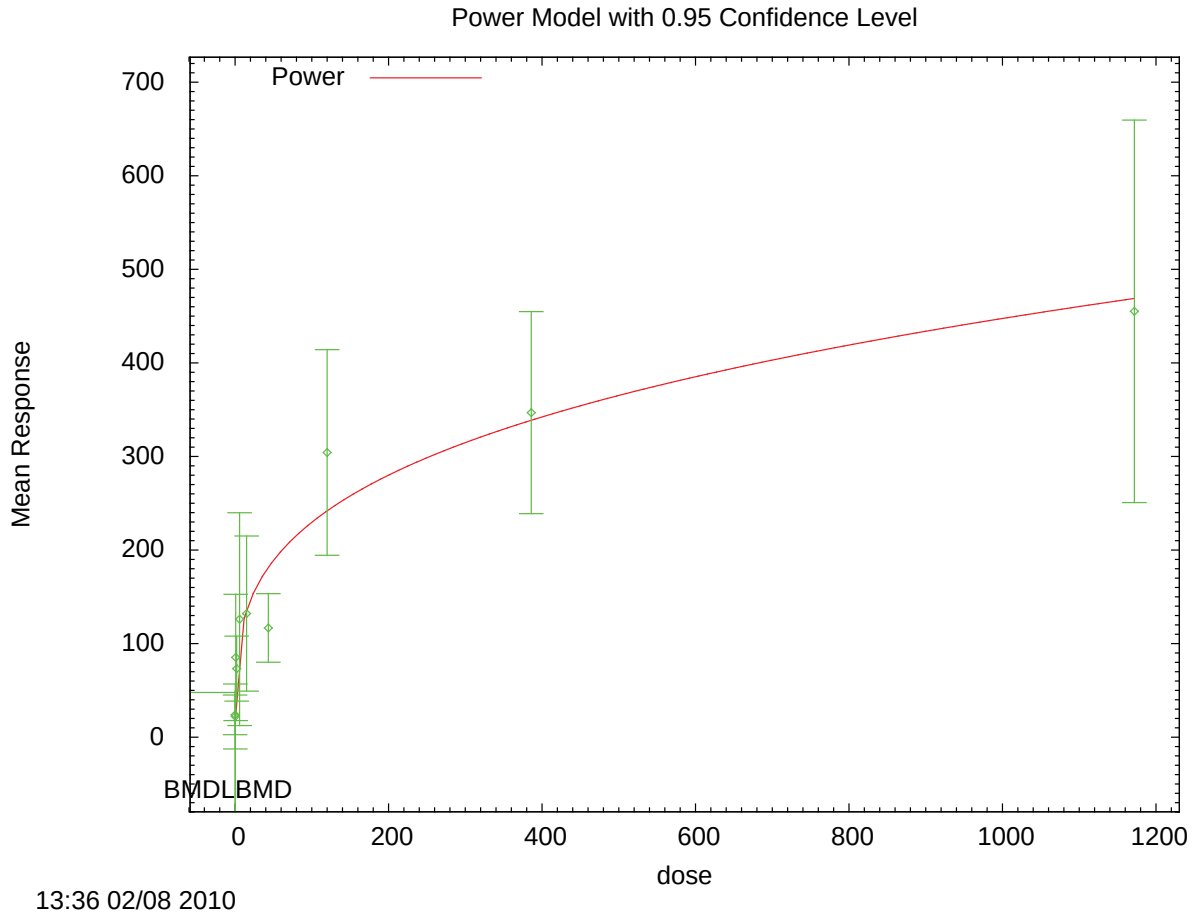
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.196278

BMDL = 0.0248364

G.2.26.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.2.27. Li et al. (2006): Estradiol, 3-Day

G.2.27.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.156	269.027	1.416E+01	5.544E+00	
Exponential (M3)	2	0.156	269.027	1.416E+01	5.544E+00	power hit bound (*d* = 1)
Exponential (M4)	1	0.341	268.212	error	error	
Exponential (M5)	0	N/A	270.212	error	error	
Hill	0	N/A	270.212	error	error	
Linear[b]	**2**	**0.162**	**268.952**	**1.606E+01**	**5.379E+00**	
Polynomial, 3-degree	2	0.162	268.952	1.606E+01	5.379E+00	
Power	2	0.162	268.952	1.606E+01	5.379E+00	power bound hit (power = 1)
Hill, unrestricted	0	N/A	270.265	9.273E+12	9.273E+12	unrestricted (*n* = 0.03)
Power, unrestricted	1	0.328	268.265	9.455E+10	error	unrestricted (power = 0.015)

[a] Constant variance model selected (*p* = 0.4372).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.27.2. *Output for Selected Model: Linear*

Li et al. (2006): Estradiol, 3-Day

```
 ========================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\Blood\31_Li_2006_Estra_LinearCV_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\31_Li_2006_Estra_LinearCV_1.plt
                                             Mon Feb 08 10:54:00 2010
 ========================================================================

 Figure 3, 3-day estradiol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	267.211	
rho =	0	Specified
beta_0 =	16.1705	
beta_1 =	1.0106	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	beta_0	beta_1
alpha	1	2.1e-012	5e-014
beta_0	2.1e-012	1	-0.69
beta_1	5e-014	-0.69	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	263.435	58.9057	147.981	378.888
beta_0	16.1705	3.55949	9.19407	23.147
beta_1	1.0106	1.2148	-1.37037	3.39156

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	10.2	16.2	12.2	16.2	-1.17
0.1588	10	19.9	16.3	20	16.2	0.697
2.839	10	24.7	19	14.6	16.2	1.11
5.124	10	18.1	21.3	17.6	16.2	-0.635

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-129.653527	5	269.307054
A2	-128.294657	8	272.589314
A3	-129.653527	5	269.307054
fitted	-131.476097	3	268.952193
R	-131.819169	2	267.638338

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	7.04902	6	0.3163
Test 2	2.71774	3	0.4372
Test 3	2.71774	3	0.4372
Test 4	3.64514	2	0.1616

The p-value for Test 1 is greater than .05. There may not be a diffence between responses and/or variances among the dose levels Modelling the data with a dose/response curve may not be appropriate

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

```
              Benchmark Dose Computation

Specified effect =             1

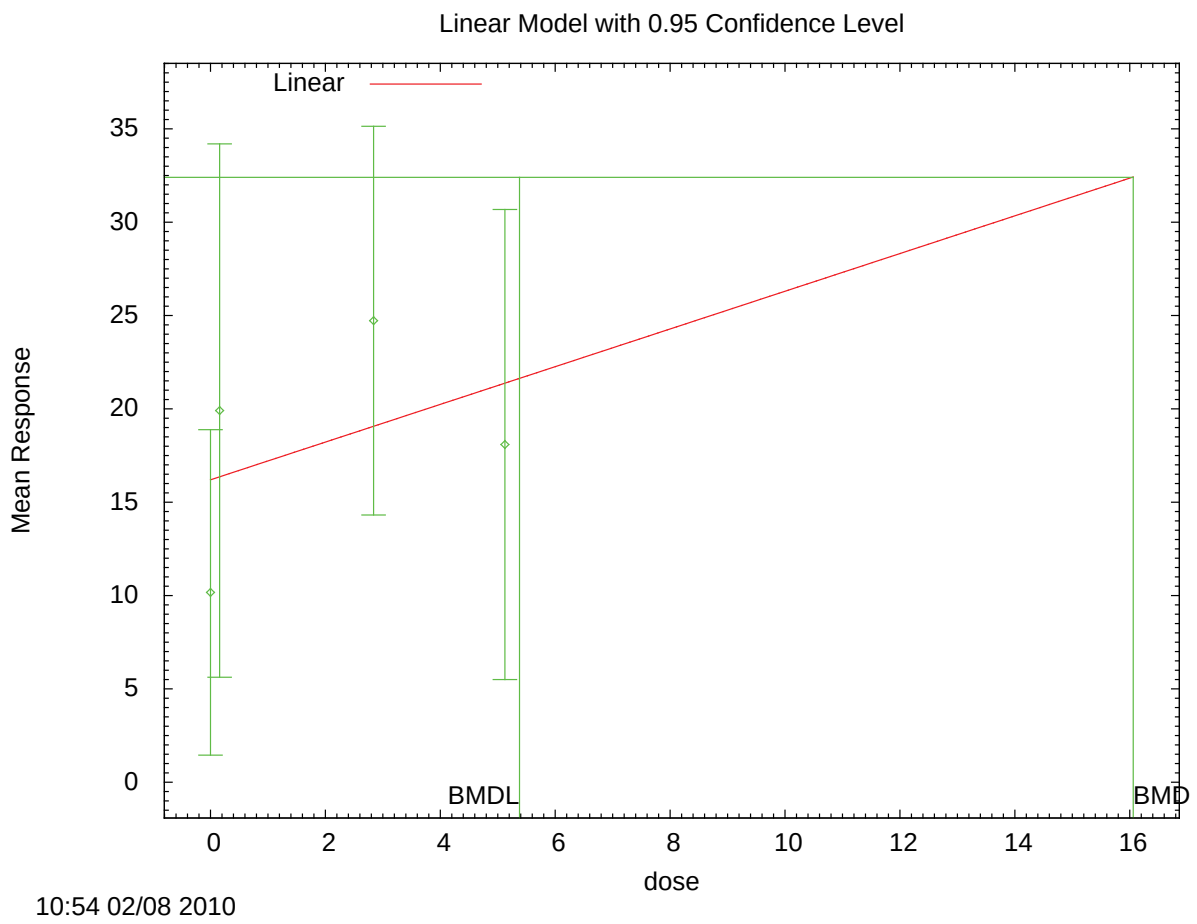
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        16.0605


            BMDL =        5.37895
```

G.2.27.3. *Figure for Selected Model: Linear*



G.2.28. Li et al. (2006): Progesterone, 3-Day

G.2.28.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	<0.001	329.928	2.619E+00	error	
Exponential (M3)	2	0.001	328.101	1.340E−01	error	power hit bound (*d* = 1)
Exponential (M4)	1	0.384	315.734	1.074E−02	6.633E−03	
Exponential (M5)	0	N/A	317.734	4.301E−02	4.272E−03	
Hill[b]	**1**	**0.386**	**315.728**	**9.461E−04**	**8.006E−11**	***n* lower bound hit (*n* = 1)**
Linear	2	<0.001	330.729	3.891E+00	2.626E+00	
Polynomial, 3-degree	2	<0.001	330.729	3.891E+00	2.626E+00	
Power	2	<0.001	330.729	3.891E+00	2.626E+00	power bound hit (power = 1)
Power, unrestricted	1	0.404	315.673	2.812E−59	2.812E−59	unrestricted (power = 0.01)

[a] Nonconstant variance model selected (*p* = 0.0013).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.28.2. *Output for Selected Model: Hill*

Li et al. (2006): Progesterone, 3-Day

```
 ========================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\32_Li_2006_Progest_Hill_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\32_Li_2006_Progest_Hill_1.plt
                                             Wed Feb 10 10:57:14 2010
 ========================================================================

 Figure 4, 3-day progesterone
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

lalpha =	7.08699
rho =	0
intercept =	61.7404
v =	-50.3835
n =	1.47286
k =	0.128302

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-0.99	-0.093	0.82	0.22
rho	-0.99	1	0.12	-0.79	-0.2
intercept	-0.093	0.12	1	-0.43	0.014
v	0.82	-0.79	-0.43	1	0.035
k	0.22	-0.2	0.014	0.035	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	14.0902	3.36095	7.50284	20.6775
rho	-2.27438	0.861553	-3.963	-0.585772
intercept	61.7488	3.3373	55.2078	68.2898
v	-42.1007	7.70852	-57.2091	-26.9922
n	1	NA		
k	0.00282851	0.020619	-0.037584	0.0432411

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	61.7	61.7	11.1	10.6	-0.00251
0.1588	10	30.6	20.4	40.5	37.2	0.865
2.839	10	16.9	19.7	33.3	38.7	-0.225
5.124	10	11.4	19.7	43.7	38.8	-0.678

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-159.632675	5	329.265349
A2	-151.812765	8	319.625529
A3	-152.488175	6	316.976349
fitted	-152.863841	5	315.727683
R	-165.698875	2	335.397750

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.7722	6	0.0001037
Test 2	15.6398	3	0.001344
Test 3	1.35082	2	0.5089
Test 4	0.751333	1	0.3861

```
The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

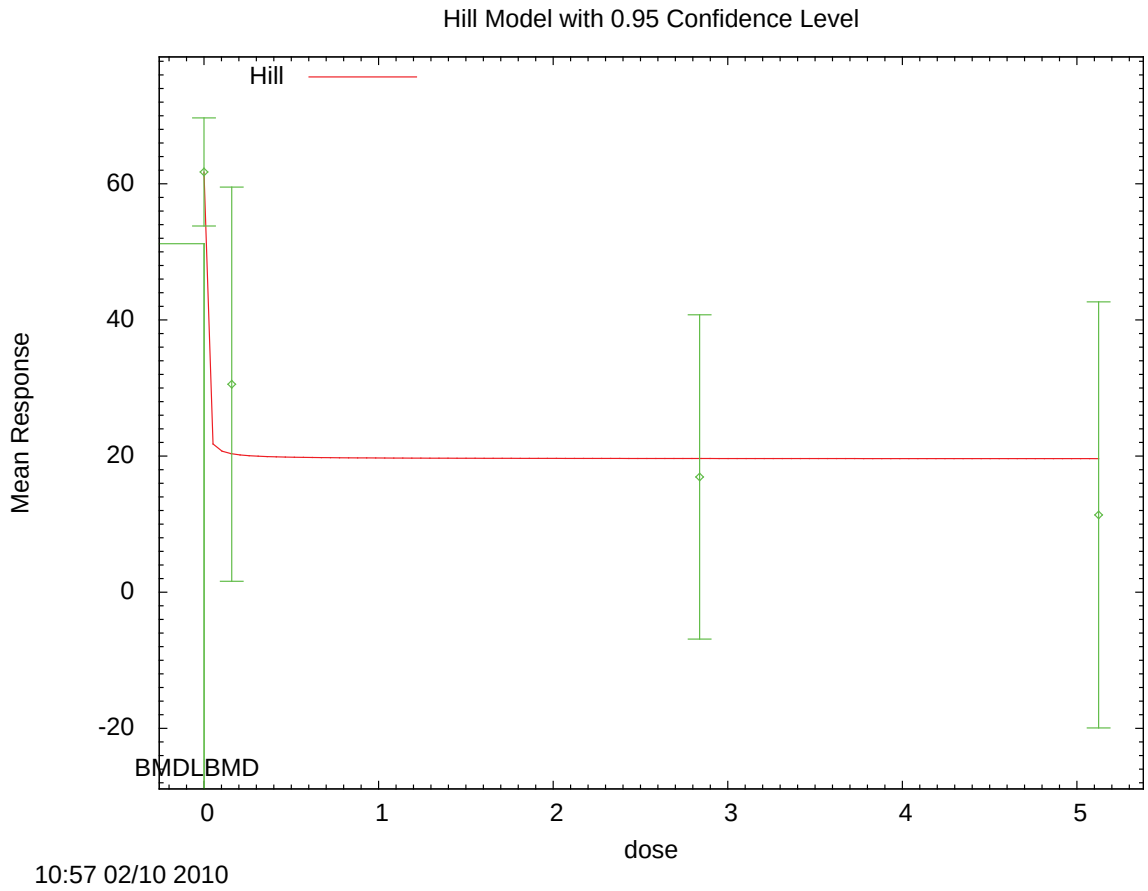
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =    0.000946102

            BMDL =  8.00639e-011
```

G.2.28.3. *Figure for Selected Model: Hill*



G.2.29. Markowski et al. (2001): FR10 Run Opportunities

G.2.29.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)[b]	**2**	**0.304**	**117.150**	**8.570E+00**	**2.887E+00**	
Exponential (M3)	2	0.304	117.150	8.570E+00	2.887E+00	power hit bound (*d* = 1)
Exponential (M4)	1	0.371	117.570	3.452E+00	1.299E−02	
Exponential (M5)	0	N/A	118.918	2.315E+00	1.391E−02	
Hill	0	N/A	118.918	1.801E+00	1.274E−09	
Linear	2	0.226	117.744	1.106E+01	5.741E+00	
Polynomial, 3-degree	2	0.226	117.744	1.106E+01	5.741E+00	
Power	2	0.226	117.744	1.106E+01	5.741E+00	power bound hit (power = 1)
Power, unrestricted	1	0.239	118.158	5.768E+00	1.032E−14	unrestricted (power = 0.276)

[a] Constant variance model selected ($p = 0.1719$).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.29.2. *Output for Selected Model: Exponential (M2)*

Markowski et al. (2001): FR10 Run Opportunities

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\33_Mark_2001_FR10opp_ExpCV_1.(d)
        Gnuplot Plotting File:
                                             Mon Feb 08 10:55:13 2010
 ======================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

```
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                Initial Parameter Values

                Variable          Model 2
                --------          --------
                  lnalpha               3.5321
                      rho(S)                 0
                        a              6.77975
                        b            0.0581937
                        c                    0
                        d                    1

  (S) = Specified


                  Parameter Estimates

                 Variable          Model 2
                 --------          -------
                  lnalpha           3.63127
                      rho                 0
                        a           12.2901
                        b         0.0808832
                        c                 0
                        d                 1


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      7        13.29         8.65
  1.557      4        11.25         5.56
   4.03      6         5.75         3.53
  10.32      7            7         6.01


               Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         12.29        6.145           0.4305
  1.557         10.84        6.145           0.1347
   4.03         8.871        6.145           -1.244
  10.32         5.335        6.145            0.717
```

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-54.38526	5	118.7705
A2	-51.88568	8	119.7714
A3	-54.38526	5	118.7705
R	-57.45429	2	118.9086
2	-55.57522	3	117.1504

Additive constant for all log-likelihoods = -22.05. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	11.14	6	0.08423
Test 2	4.999	3	0.1719
Test 3	4.999	3	0.1719
Test 4	2.38	2	0.3042

The p-value for Test 1 is greater than .05. There may not be a diffence between responses and/or variances among the dose levels Modelling the data with a dose/response curve may not be appropriate.

```
  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 4 is greater than .1.  Model 2 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

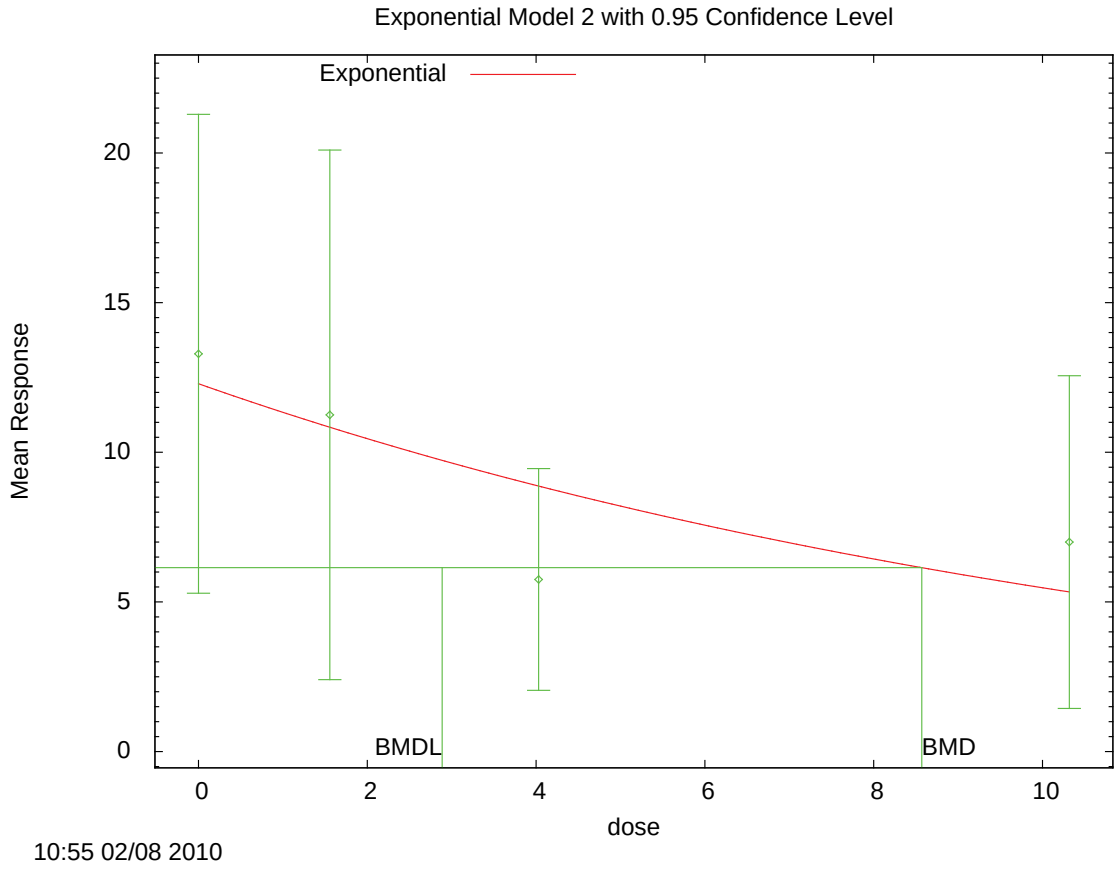
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      8.56961

              BMDL =      2.88708
```

G.2.29.3. *Figure for Selected Model: Exponential (M2)*



G.2.30. Markowski et al. (2001): FR2 Revolutions

G.2.30.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.236	217.219	8.486E+00	3.232E+00	
Exponential (M3)	2	0.236	217.219	8.486E+00	3.232E+00	power hit bound (*d* = 1)
Exponential (M4)	1	0.263	217.583	3.413E+00	1.766E−02	
Exponential (M5)	0	N/A	218.532	2.415E+00	9.313E−01	
Hill[b]	**1**	**0.654**	**216.532**	**1.840E+00**	**5.992E−01**	***n* upper bound hit (*n* = 18)**
Linear	2	0.180	217.764	1.058E+01	5.602E+00	
Polynomial, 3-degree	2	0.180	217.764	1.058E+01	5.602E+00	
Power	2	0.180	217.764	1.058E+01	5.602E+00	power bound hit (power = 1)
Power, unrestricted[c]	1	0.161	218.294	5.739E+00	1.032E−14	unrestricted (power = 0.318)

[a] Constant variance model selected (*p* = 0.1092).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.30.2. *Output for Selected Model: Hill*

Markowski et al. (2001): FR2 Revolutions

```
 ========================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\34_Mark_2001_FR2rev_HillCV_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\34_Mark_2001_FR2rev_HillCV_1.plt
                                          Mon Feb 08 10:55:47 2010
 ========================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	2598.74	
rho =	0	Specified
intercept =	119.29	
v =	-62.79	
n =	2.13752	
k =	2.53662	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	1.2e-008	1e-009	3.5e-008
intercept	1.2e-008	1	-0.81	-0.52
v	1e-009	-0.81	1	0.37
k	3.5e-008	-0.52	0.37	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	2183.85	630.425	948.245	3419.46
intercept	119.29	17.6629	84.6713	153.909
v	-56.5223	21.9082	-99.4615	-13.5831
n	18	NA		
k	1.68653	0.295154	1.10804	2.26502

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

0	7	119	119	69.9	46.7	-2.41e-007
1.557	4	109	108	61	46.7	2.29e-007
4.03	6	56.5	62.8	31.2	46.7	-0.329
10.32	7	68.1	62.8	33.2	46.7	0.304

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-104.165520	5	218.331040
A2	-101.140174	8	218.280349
A3	-104.165520	5	218.331040
fitted	-104.266162	4	216.532324
R	-107.599268	2	219.198536

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	12.9182	6	0.04435
Test 2	6.05069	3	0.1092
Test 3	6.05069	3	0.1092
Test 4	0.201284	1	0.6537

The p-value for Test 1 is less than .05. There appears to be a

```
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

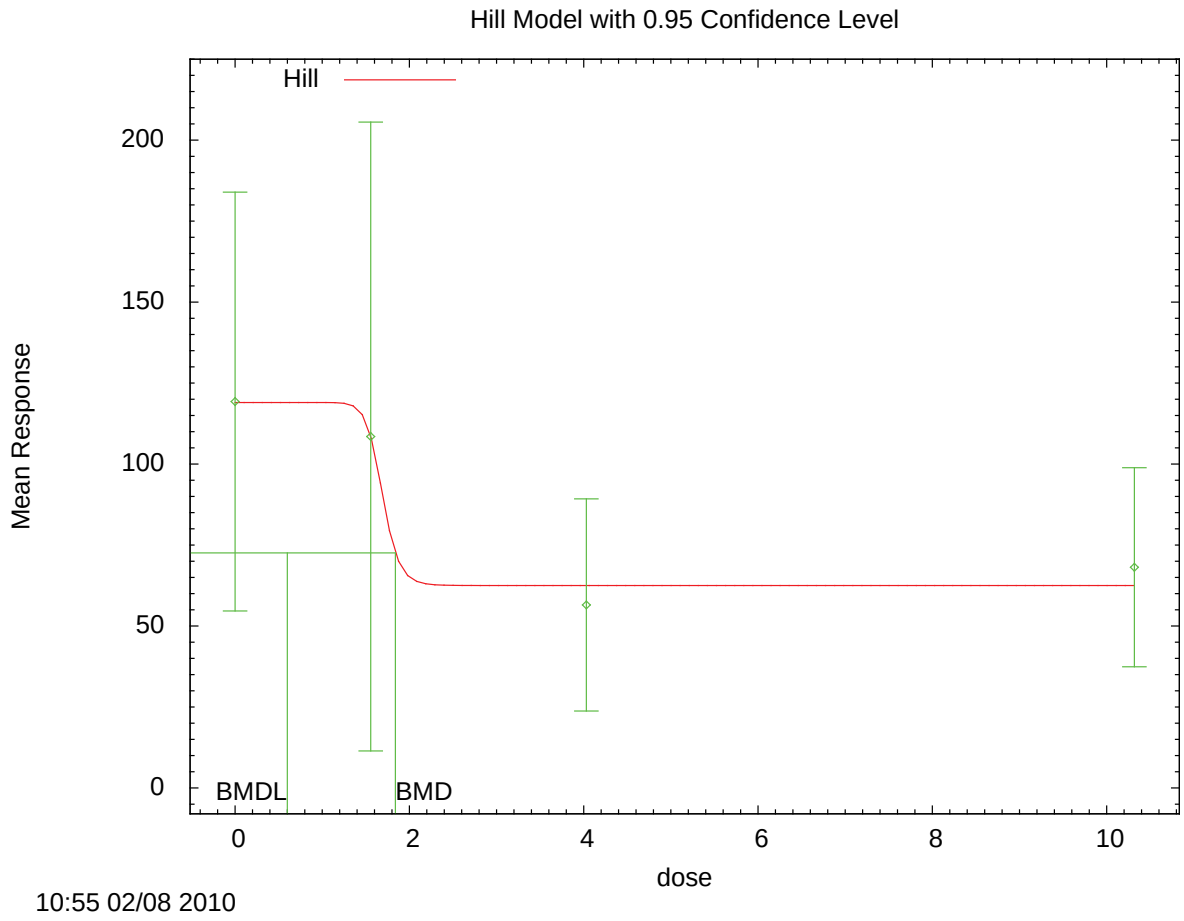
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =        1.83952

            BMDL =      0.599228
```

G.2.30.3. *Figure for Selected Model: Hill*



G.2.30.4. *Output for Additional Model Presented: Power, Unrestricted*

Markowski et al. (2001): FR2 Revolutions

```
 ==================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\34_Mark_2001_FR2rev_PowerCV_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\34_Mark_2001_FR2rev_PowerCV_U_1.plt
                                          Mon Feb 08 10:55:49 2010
 ==================================================================

 Table 3
~~~
```

```
Independent variable = Dose
rho is set to 0
The power is not restricted
A constant variance model is fit

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                         alpha =      2598.74
                           rho =            0   Specified
                       control =       119.29
                         slope =     -10.3599
                         power =     0.824761


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope        power

     alpha            1      -3e-010     6.9e-010     9.9e-010

   control      -3e-010            1        -0.63        -0.28

     slope     6.9e-010        -0.63            1         0.87

     power     9.9e-010        -0.28         0.87            1


                                 Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          2350.22          678.449             1020.48
3679.95
        control          120.082          18.0782             84.6491
155.514
          slope         -27.8164          24.2447            -75.3352
19.7023
          power         0.317923         0.350841           -0.369713
1.00556
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	7	119	120	69.9	48.5	-0.0432
1.557	4	109	88.1	61	48.5	0.843
4.03	6	56.5	76.8	31.2	48.5	-1.02
10.32	7	68.1	61.7	33.2	48.5	0.353

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-104.165520	5	218.331040
A2	-101.140174	8	218.280349
A3	-104.165520	5	218.331040
fitted	-105.147159	4	218.294317
R	-107.599268	2	219.198536

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	12.9182	6	0.04435
Test 2	6.05069	3	0.1092

```
   Test 3              6.05069          3          0.1092
   Test 4              1.96328          1          0.1612

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =             1

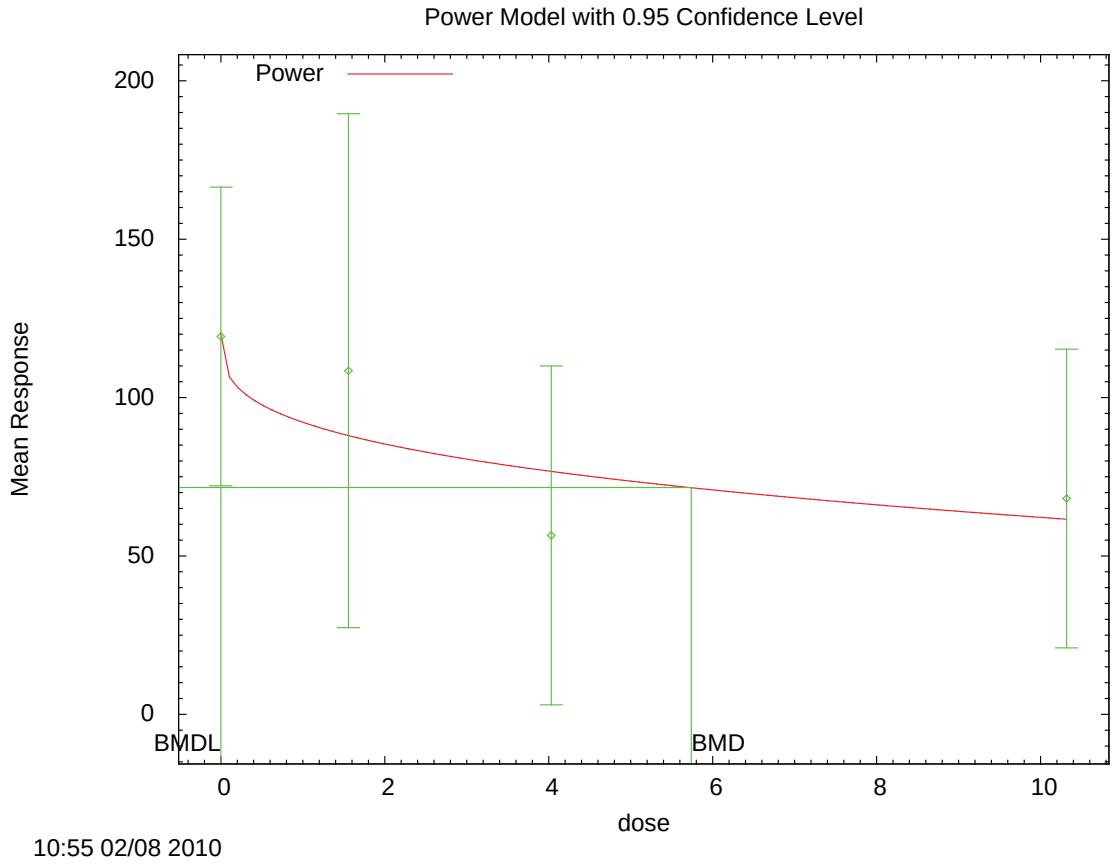
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 5.73906


            BMDL = 1.03181e-014
```

G.2.30.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.2.31. Markowski et al. (2001): FR5 Run Opportunities

G.2.31.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.205	133.193	5.078E+00	2.439E+00	
Exponential (M3)	2	0.205	133.193	5.078E+00	2.439E+00	power hit bound (*d* = 1)
Exponential (M4)	1	0.254	133.328	2.160E+00	6.854E−01	
Exponential (M5)	0	N/A	134.032	2.124E+00	9.667E−01	
Hill[b]	**1**	**0.939**	**132.032**	**1.723E+00**	**9.085E−01**	***n* upper bound hit (*n* = 18)**
Linear	2	0.122	134.229	7.234E+00	4.430E+00	
Polynomial, 3-degree	2	0.122	134.229	7.234E+00	4.430E+00	
Power	2	0.122	134.229	7.234E+00	4.430E+00	power bound hit (power = 1)
Power, unrestricted[c]	1	0.134	134.268	2.666E+00	1.032E−14	unrestricted (power = 0.392)

[a] Constant variance model selected (*p* = 0.2262).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.31.2. *Output for Selected Model: Hill*

Markowski et al. (2001): FR5 Run Opportunities

```
 ========================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\35_Mark_2001_FR5opp_HillCV_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\35_Mark_2001_FR5opp_HillCV_1.plt
                                          Mon Feb 08 10:56:24 2010
 ========================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	77.4849	
rho =	0	Specified
intercept =	26.14	
v =	-13.34	
n =	2.77257	
k =	2.48811	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	-3.2e-009	1.9e-008	6.2e-008
intercept	-3.2e-009	1	-0.81	-0.51
v	1.9e-008	-0.81	1	0.36
k	6.2e-008	-0.51	0.36	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	64.5863	18.6445	28.0438	101.129
intercept	26.14	3.03753	20.1865	32.0935
v	-13.1569	3.7676	-20.5413	-5.77257
n	18	NA		
k	1.68073	0.208677	1.27173	2.08973

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

```
------     ---   --------     --------   -----------  -----------   ---------
-

    0     7       26.1         26.1         12.3         8.04      -1.9e-008
1.557     4       23.5         23.5         7.04         8.04     -1.94e-007
 4.03     6       12.8           13         6.17         8.04        -0.0558
10.32     7       13.1           13         7.14         8.04         0.0517


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -62.013133            5     134.026266
             A2          -59.839035            8     135.678070
             A3          -62.013133            5     134.026266
         fitted          -62.016025            4     132.032049
              R          -67.530040            2     139.060081


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1               15.382          6         0.01748
   Test 2               4.3482          3          0.2262
   Test 3               4.3482          3          0.2262
   Test 4           0.00578335          1          0.9394

The p-value for Test 1 is less than .05.  There appears to be a
```

```
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

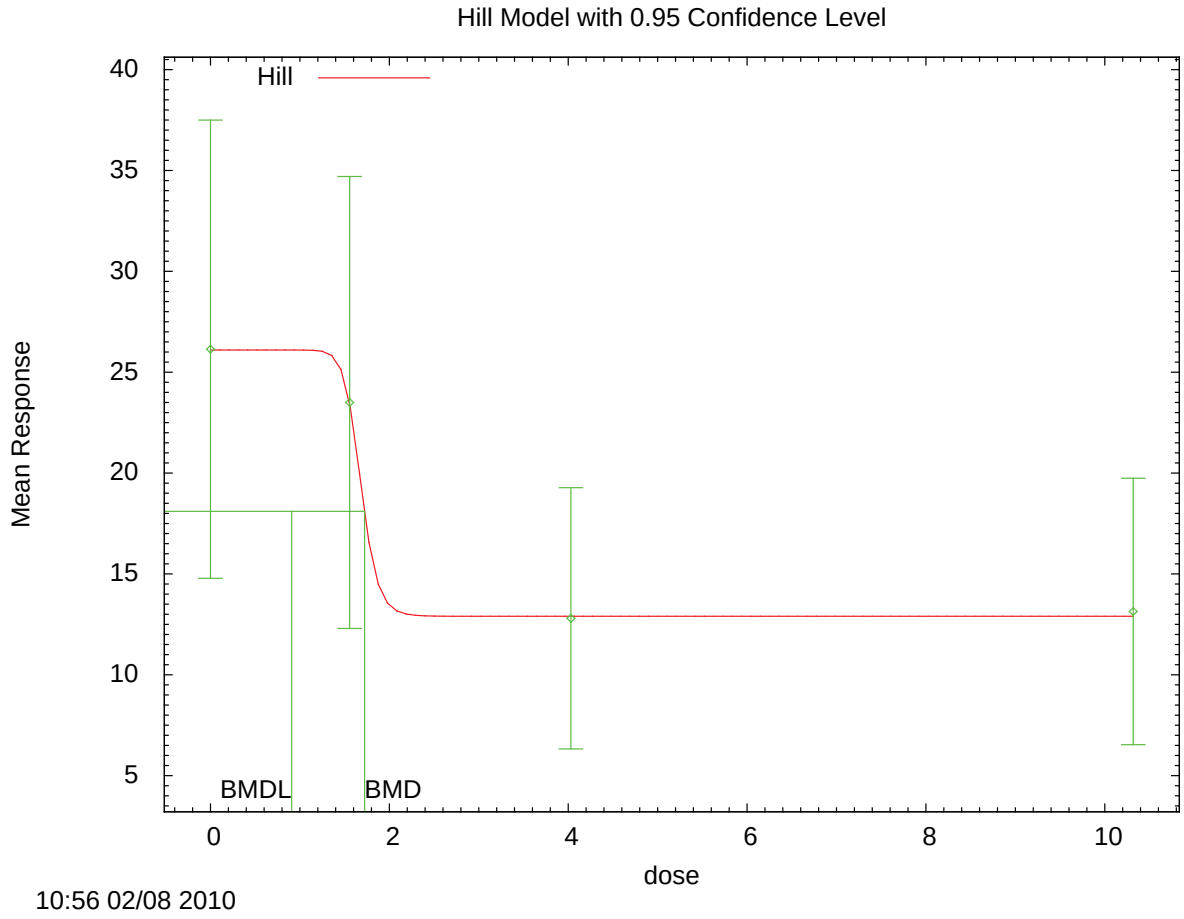
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =        1.72335

            BMDL =      0.908491
```

G.2.31.3. *Figure for Selected Model: Hill*



G.2.31.4. *Output for Additional Model Presented: Power, Unrestricted*

Markowski et al. (2001): FR5 Run Opportunities

```
 ==================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\35_Mark_2001_FR5opp_PwrCV_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\35_Mark_2001_FR5opp_PwrCV_U_1.plt
                                          Mon Feb 08 10:56:24 2010
 ==================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
```

```
Independent variable = Dose
rho is set to 0
The power is not restricted
A constant variance model is fit

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                         alpha =      77.4849
                           rho =            0   Specified
                       control =        26.14
                         slope =      -2.3827
                         power =     0.844532


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope        power

     alpha            1    -9.3e-009     1.4e-008     9.3e-009

   control    -9.3e-009            1        -0.64        -0.34

     slope     1.4e-008        -0.64            1          0.9

     power     9.3e-009        -0.34          0.9            1


                                 Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          70.8926          20.4649             30.7821
111.003
        control          26.3582          3.12902             20.2254
32.4909
          slope         -5.73309          4.02937            -13.6305
2.16433
          power         0.391903         0.281862           -0.160536
0.944342
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	7	26.1	26.4	12.3	8.42	-0.0686
1.557	4	23.5	19.5	7.04	8.42	0.941
4.03	6	12.8	16.5	6.17	8.42	-1.06
10.32	7	13.1	12	7.14	8.42	0.343

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-62.013133	5	134.026266
A2	-59.839035	8	135.678070
A3	-62.013133	5	134.026266
fitted	-63.134001	4	134.268002
R	-67.530040	2	139.060081

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	15.382	6	0.01748
Test 2	4.3482	3	0.2262

Test 3	4.3482	3	0.2262
Test 4	2.24174	1	0.1343

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

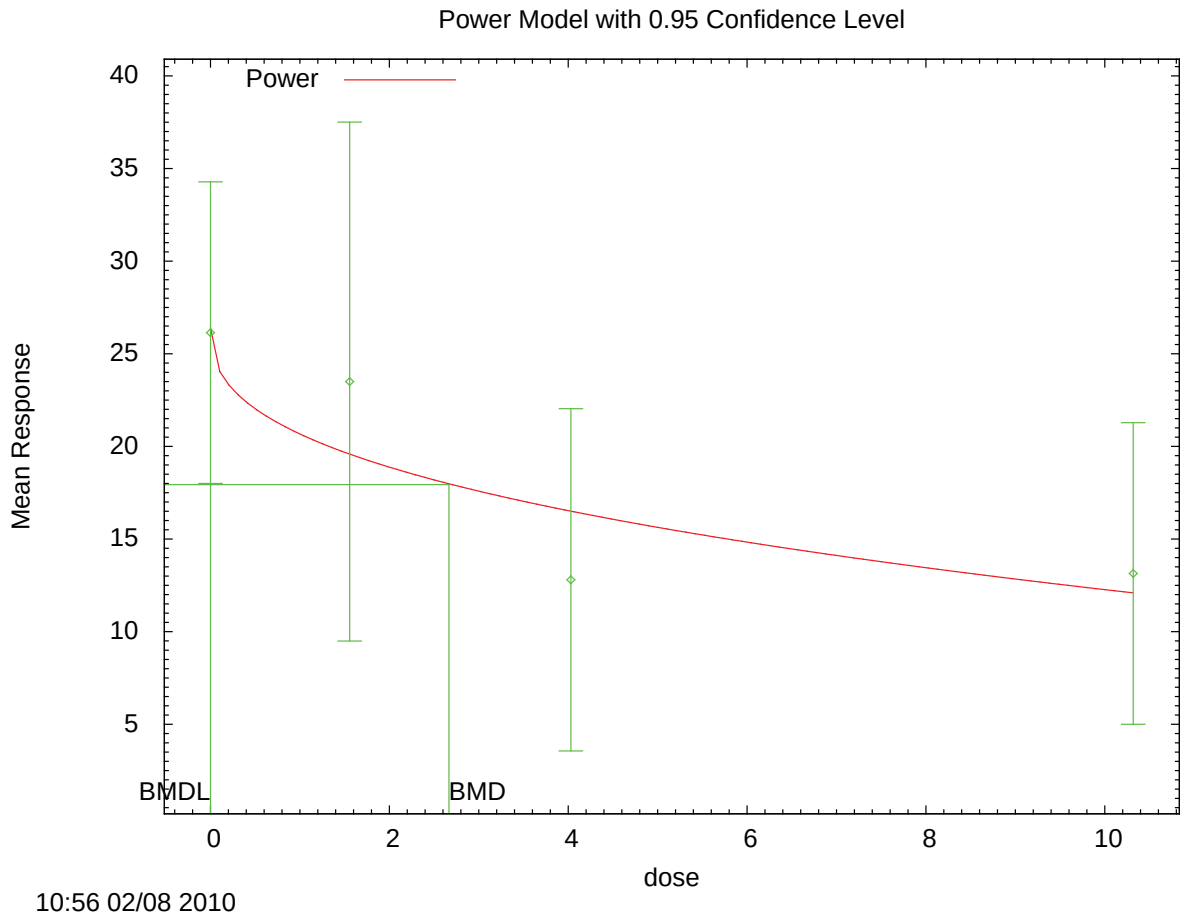
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 2.66625

BMDL = 1.03181e-014

G.2.31.5. ***Figure for Additional Model Presented: Power, Unrestricted***



G.2.32. Miettinen et al. (2006): Cariogenic Lesions, Pups

G.2.32.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	3	0.410	162.280	3.401E+00	1.889E+00	power bound hit (power = 1)
Logistic	3	0.371	162.518	4.108E+00	2.450E+00	
Log-logistic[a]	**3**	**0.602**	**161.292**	**1.428E+00**	**5.175E−01**	**slope bound hit (slope = 1)**
Log-probit	3	0.300	163.040	6.321E+00	3.127E+00	slope bound hit (slope = 1)
Multistage, 4-degree	3	0.410	162.280	3.401E+00	1.889E+00	final ß = 0
Probit	3	0.350	162.656	4.548E+00	2.889E+00	
Weibull	3	0.410	162.280	3.401E+00	1.889E+00	power bound hit (power = 1)
Gamma, unrestricted	2	0.798	161.801	3.374E−03	8.884E−242	unrestricted (power = 0.215)
Log-logistic, unrestricted[b]	2	0.728	161.983	4.942E−02	error	unrestricted (slope = 0.465)
Log-probit, unrestricted	2	0.732	161.972	6.495E−02	error	unrestricted (slope = 0.289)
Weibull, unrestricted	2	0.766	161.884	1.792E−02	error	unrestricted (power = 0.324)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.2.32.2. *Output for Selected Model: Log-Logistic*

Miettinen et al. (2006): Cariogenic Lesions, Pups

```
 ========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\36_Miet_2006_Cariogenic_LogLogistic_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\36_Miet_2006_Cariogenic_LogLogistic_1.plt
                                                Mon Feb 08 10:56:59 2010
 ========================================================================

 Table 2 converting the percentage into the number of animals, and control is
Control II from the study. Dose is in ng per kg and is from Table 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
```

```
Slope parameter is restricted as slope >= 1

Total number of observations = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =     0.595238
                     intercept =       -2.494
                         slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.66

 intercept        -0.66            1



                                 Parameter Estimates

                                                                 95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background         0.644165            *                *
*
      intercept         -2.55354            *                *
*
          slope                1            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -77.6769         5
   Fitted model         -78.646         2       1.93832      3
0.5853
```

```
  Reduced model        -83.2067         1       11.0597      4
0.0259

           AIC:         161.292


                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ----------------------------------------------------------------------
    0.0000     0.6442        27.055    25.000          42        -0.662
    2.2195     0.6966        20.200    23.000          29         1.131
    6.2259     0.7603        19.007    19.000          25        -0.003
   16.0142     0.8416        20.198    20.000          24        -0.111
   46.6355     0.9231        29.540    29.000          32        -0.358

 Chi^2 = 1.86      d.f. = 3        P-value = 0.6024


   Benchmark Dose Computation

Specified effect =            0.1

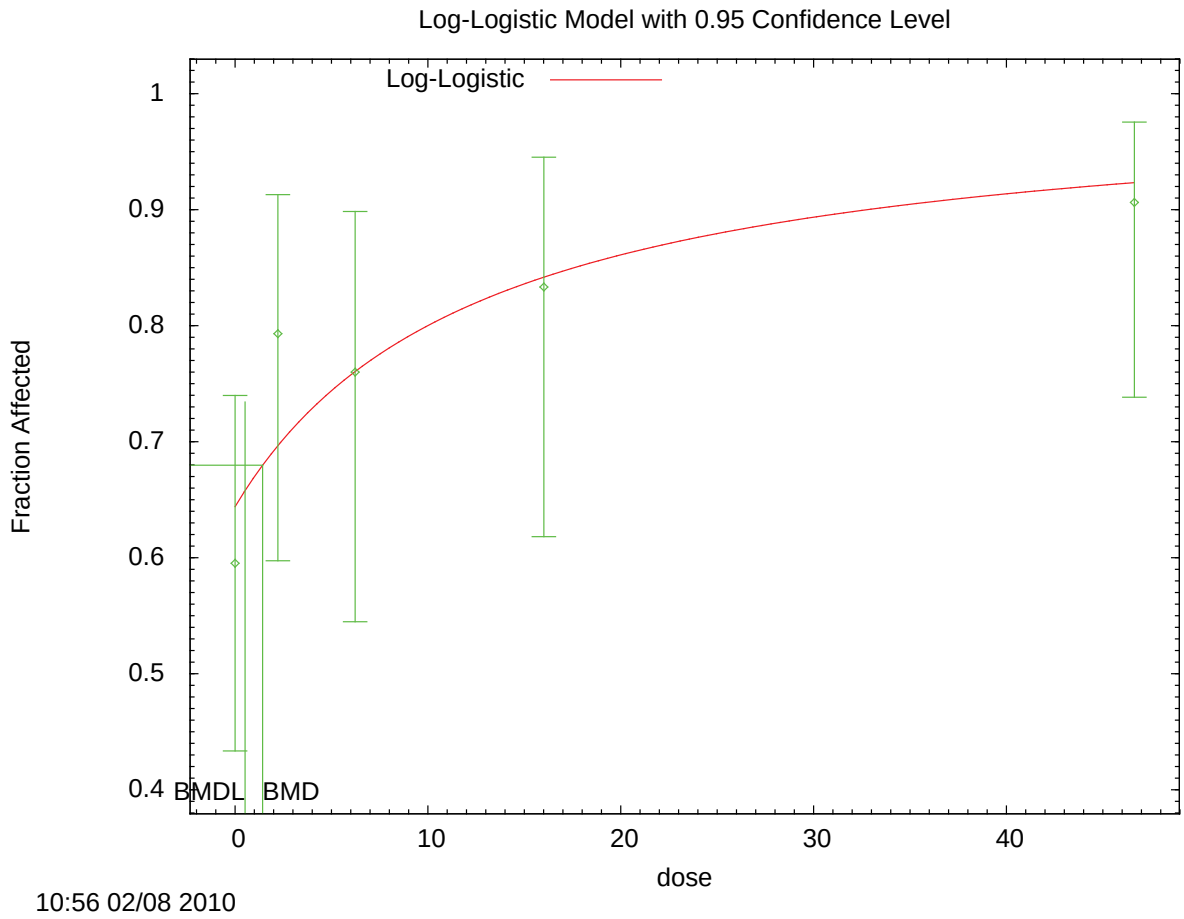
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        1.42805

            BMDL =       0.517495
```

G.2.32.3. *Figure for Selected Model: Log-Logistic*



G.2.32.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Miettinen et al. (2006): Cariogenic Lesions, Pups

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File:
C:\1\Blood\36_Miet_2006_Cariogenic_LogLogistic_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\36_Miet_2006_Cariogenic_LogLogistic_U_1.plt
                                          Mon Feb 08 10:56:59 2010
 ======================================================================

 Table 2 converting the percentage into the number of animals, and control is
Control II from the study. Dose is in ng per kg and is from Table 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]
```

```
Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



User has chosen the log transformed model


                Default Initial Parameter Values
                   background =     0.595238
                    intercept =    -0.739403
                        slope =     0.442847


          Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.51         0.24

 intercept        -0.51            1        -0.89

     slope         0.24        -0.89            1



                                Parameter Estimates

                                                                  95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background         0.597745            *                *
*
      intercept        -0.798024            *                *
*
          slope         0.465259            *                *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -77.6769         5
```

```
   Fitted model        -77.9915         3      0.629204      2
0.7301
  Reduced model        -83.2067         1       11.0597      4
0.0259

           AIC:         161.983


                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.5977        25.105    25.000          42       -0.033
    2.2195     0.7566        21.940    23.000          29        0.458
    6.2259     0.8042        20.105    19.000          25       -0.557
   16.0142     0.8474        20.338    20.000          24       -0.192
   46.6355     0.8910        28.512    29.000          32        0.277

 Chi^2 = 0.63      d.f. = 2        P-value = 0.7281


   Benchmark Dose Computation

Specified effect =            0.1

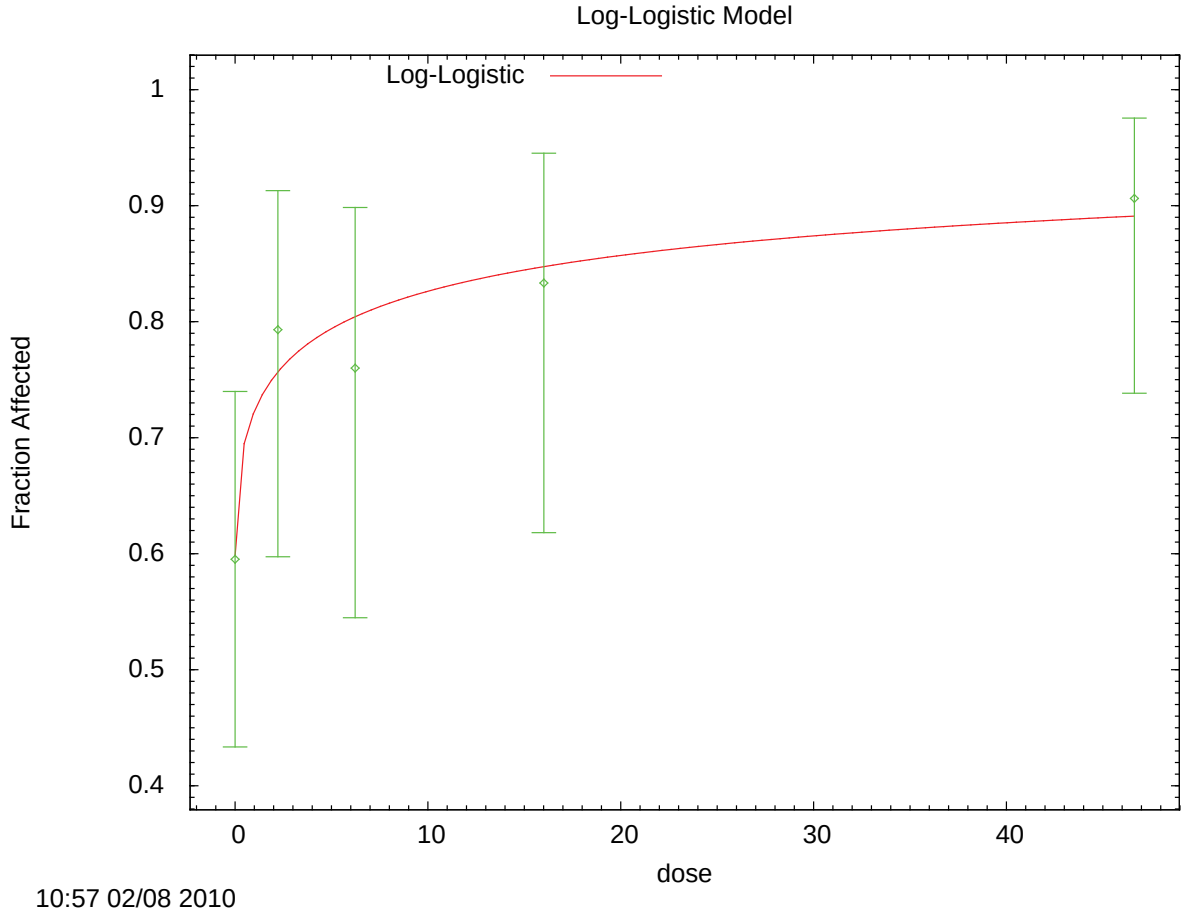
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.049422

            Benchmark dose computation failed.  Lower limit includes zero.
```

G.2.32.5. ***Figure for Additional Model Presented: Log-Logistic, Unrestricted***



G.2.33. Murray et al. (1979): Fertility in F2 Generation

G.2.33.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	0	N/A	61.729	4.481E+00	1.590E+00	
Logistic	1	0.051	61.318	2.420E+00	1.722E+00	
Log-logistic	0	N/A	61.729	4.971E+00	1.565E+00	
Multistage, 1-degree	1	0.031	63.154	1.598E+00	8.747E−01	
Multistage, 2-degree[a]	**1**	**0.079**	**60.464**	**2.733E+00**	**1.366E+00**	
Probit	1	0.048	61.544	2.250E+00	1.590E+00	
Weibull	0	N/A	61.729	5.042E+00	1.604E+00	
Log-probit, unrestricted	0	N/A	61.729	4.244E+00	1.506E+00	unrestricted (slope = 3.182)

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.33.2. *Output for Selected Model: Multistage, 2-Degree*

Murray et al. (1979): Fertility in F2 Generation

```
 ========================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\Murray_1979_fert_index_f2_Multi2_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\Murray_1979_fert_index_f2_Multi2_1.plt
                                          Wed Feb 10 16:06:28 2010
 ========================================================================

 Table 1 but expressed as number of dams who do not produce offspring
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
```

Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 0.0567204
Beta(1) = 0
Beta(2) = 0.0155037

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(1)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(2)
Background	1	-0.45
Beta(2)	-0.45	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0780188	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.0141051	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-25.8194	3			
Fitted model	-28.2318	2	4.82474	1	0.02805
Reduced model	-34.0009	1	16.363	2	0.0002798

AIC: 60.4636

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual

```
  ----------------------------------------------------------------------
    0.0000     0.0780         2.497     4.000          32        0.991
    1.1242     0.0943         1.886     0.000          20       -1.443
    5.8831     0.4341         8.683     9.000          20        0.143

 Chi^2 = 3.08      d.f. = 1        P-value = 0.0790


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

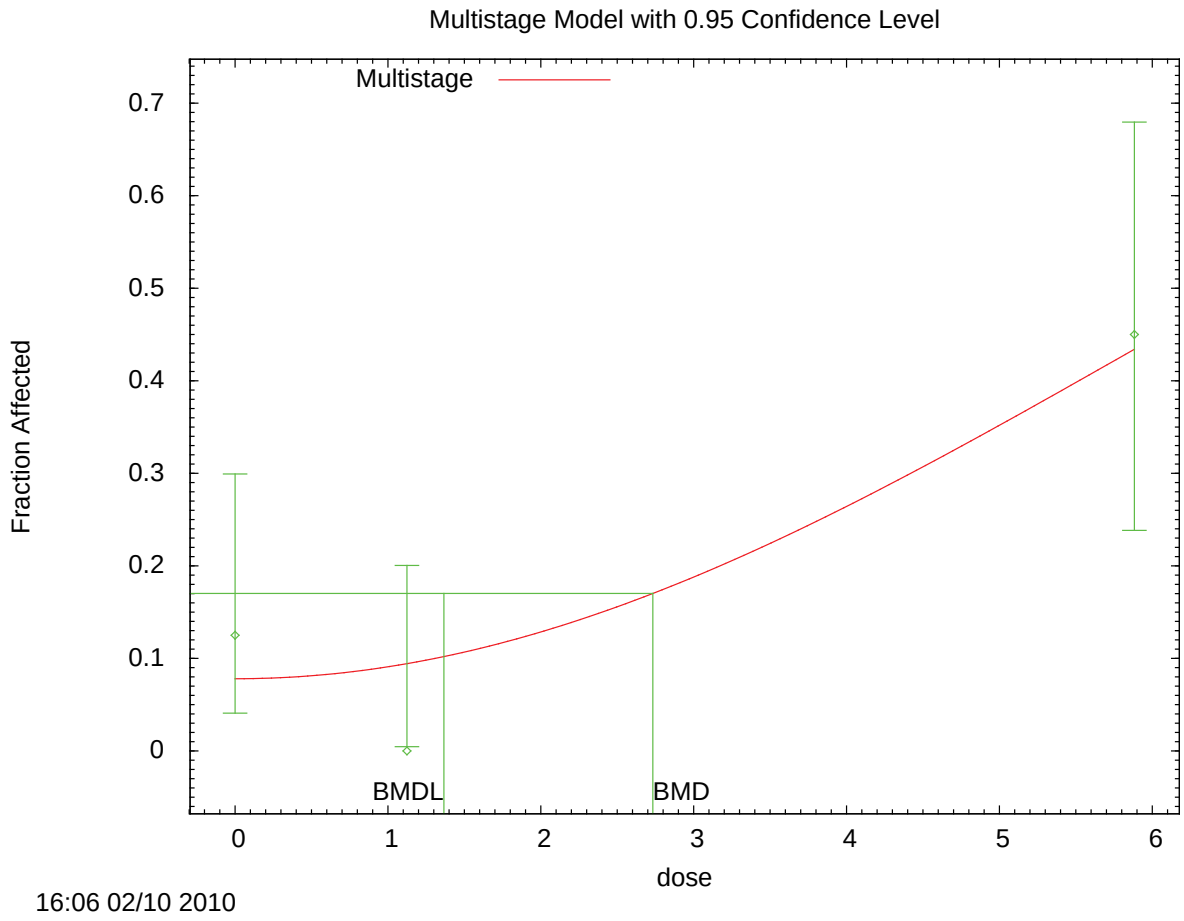
             BMD =        2.73307

            BMDL =        1.36619

            BMDU =        4.10938

Taken together, (1.36619, 4.10938) is a 90     % two-sided confidence
interval for the BMD
```

G.2.33.3. *Figure for Selected Model: Multistage, 2-Degree*



G.2.34. National Toxicology Program (1982): Toxic Hepatitis, Male Mice

G.2.34.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	1	0.027	113.103	3.823E+00	2.005E+00	
Logistic	2	0.092	110.352	3.108E+00	2.465E+00	
Log-logistic	1	0.026	113.089	3.797E+00	2.141E+00	
Log-probit	1	0.027	113.111	3.565E+00	2.294E+00	
Multistage, 3-degree[a]	**1**	**0.036**	**112.045**	**2.782E+00**	**1.343E+00**	
Probit	2	0.082	110.512	2.763E+00	2.241E+00	
Weibull	1	0.025	113.044	3.967E+00	1.704E+00	

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.34.2. *Output for Selected Model: Multistage, 3-Degree*

National Toxicology Program (1982): Toxic Hepatitis, Male Mice

```
 ======================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\37_NTP_1982_ToxHep_Multi3_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\37_NTP_1982_ToxHep_Multi3_1.plt
                                          Mon Feb 08 10:57:32 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0471757
                        Beta(1) =   0.00749116
                        Beta(2) =            0
                        Beta(3) =   0.00139828


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(1)      Beta(3)

Background            1        -0.77         0.69
```

Beta(1)	-0.77	1	-0.95
Beta(3)	0.69	-0.95	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0267933	*	*	*
Beta(1)	0.0283198	*	*	*
Beta(2)	0	*	*	*
Beta(3)	0.0012342	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-51.0633	4			
Fitted model	-53.0224	3	3.91812	1	0.04777
Reduced model	-121.743	1	141.358	3	<.0001

AIC: 112.045

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0268	1.956	1.000	73	-0.693
0.7665	0.0482	2.363	5.000	49	1.759
2.2711	0.1005	4.925	3.000	49	-0.915
11.2437	0.8775	43.877	44.000	50	0.053

Chi^2 = 4.41 d.f. = 1 P-value = 0.0357

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

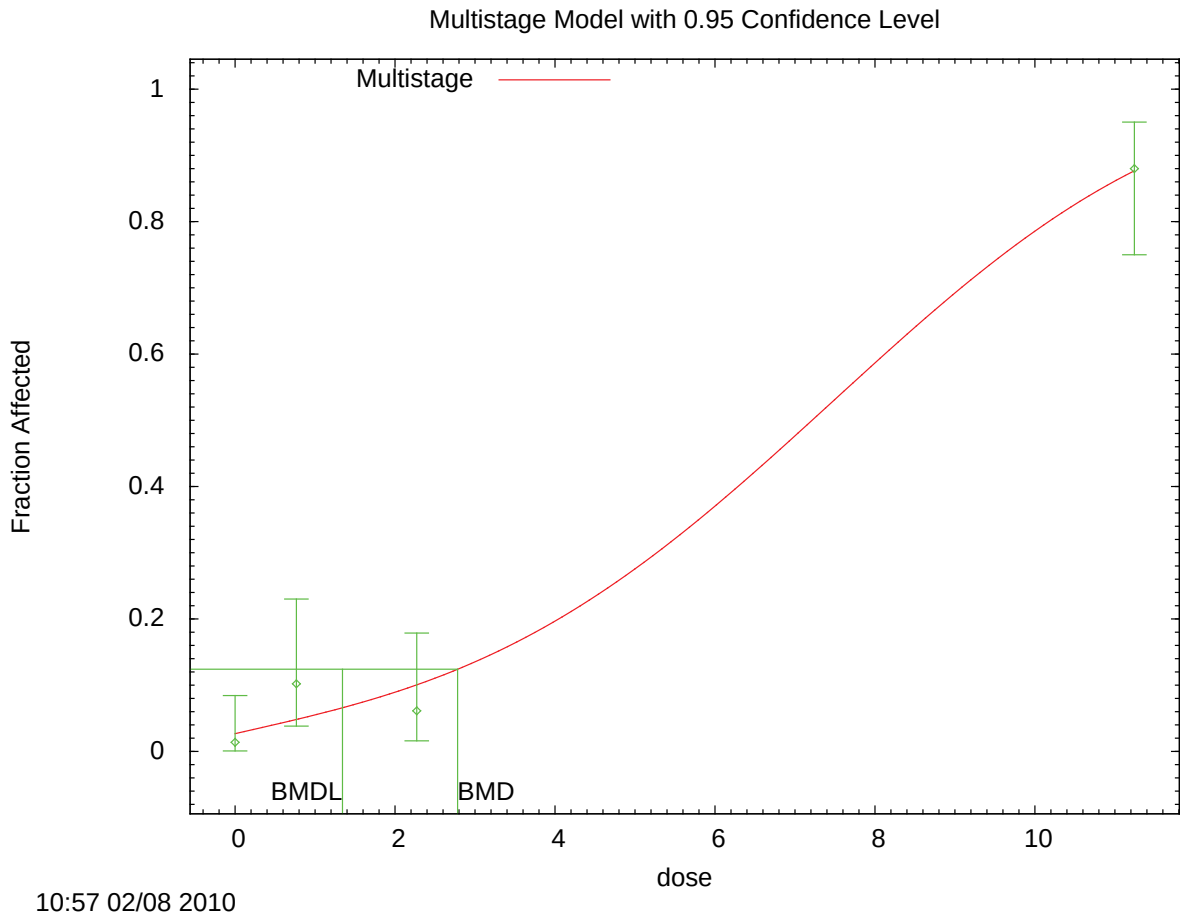
BMD = 2.78201

```
            BMDL =        1.34308

            BMDU =         4.5214

Taken together, (1.34308, 4.5214 ) is a 90     % two-sided confidence
interval for the BMD
```

G.2.34.3. *Figure for Selected Model: Multistage, 3-Degree*



G.2.35. National Toxicology Program (2006): Alveolar Metaplasia

G.2.35.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	4	0.010	320.093	9.886E−01	8.393E−01	power bound hit (power = 1)
Logistic	4	<0.001	343.283	2.389E+00	2.052E+00	
Log-logistic[a]	**3**	**0.723**	**312.558**	**6.497E−01**	**3.751E−01**	
Log-probit	4	0.024	318.680	1.566E+00	1.318E+00	slope bound hit (slope = 1)
Multistage, 5-degree	4	0.010	320.093	9.886E−01	8.393E−01	final ß = 0
Probit	4	<0.001	347.071	2.542E+00	2.219E+00	
Weibull	4	0.010	320.093	9.886E−01	8.393E−01	power bound hit (power = 1)
Gamma, unrestricted	3	0.426	314.011	1.642E−01	1.874E−02	unrestricted (power = 0.503)
Log-probit, unrestricted	3	0.696	312.677	6.818E−01	2.740E−01	unrestricted (slope = 0.677)
Weibull, unrestricted	3	0.522	313.492	2.644E−01	6.947E−02	unrestricted (power = 0.661)

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.35.2. *Output for Selected Model: Log-Logistic*

National Toxicology Program (2006): Alveolar Metaplasia

```
 ========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\40_NTP_2006_AlvMeta_LogLogistic_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\40_NTP_2006_AlvMeta_LogLogistic_1.plt
                                            Mon Feb 08 10:58:58 2010
 ========================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
```

Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.0377358
intercept = -1.69494
slope = 1.12282

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.21	0.1
intercept	-0.21	1	-0.93
slope	0.1	-0.93	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0373462	*	*	*
intercept	-1.70923	*	*	*
slope	1.13164	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-152.615	6			
Fitted model	-153.279	3	1.32728	3	0.7227
Reduced model	-216.802	1	128.374	5	<.0001

AIC: 312.558

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual

```
    0.0000     0.0373         1.979     2.000          53        0.015
    2.5565     0.3682        19.881    19.000          54       -0.249
    5.6937     0.5807        30.776    33.000          53        0.619
    9.7882     0.7162        37.243    35.000          52       -0.690
   16.5688     0.8197        43.446    45.000          53        0.555
   29.6953     0.8976        46.674    46.000          52       -0.308

 Chi^2 = 1.33      d.f. = 3        P-value = 0.7232


   Benchmark Dose Computation

Specified effect =            0.1

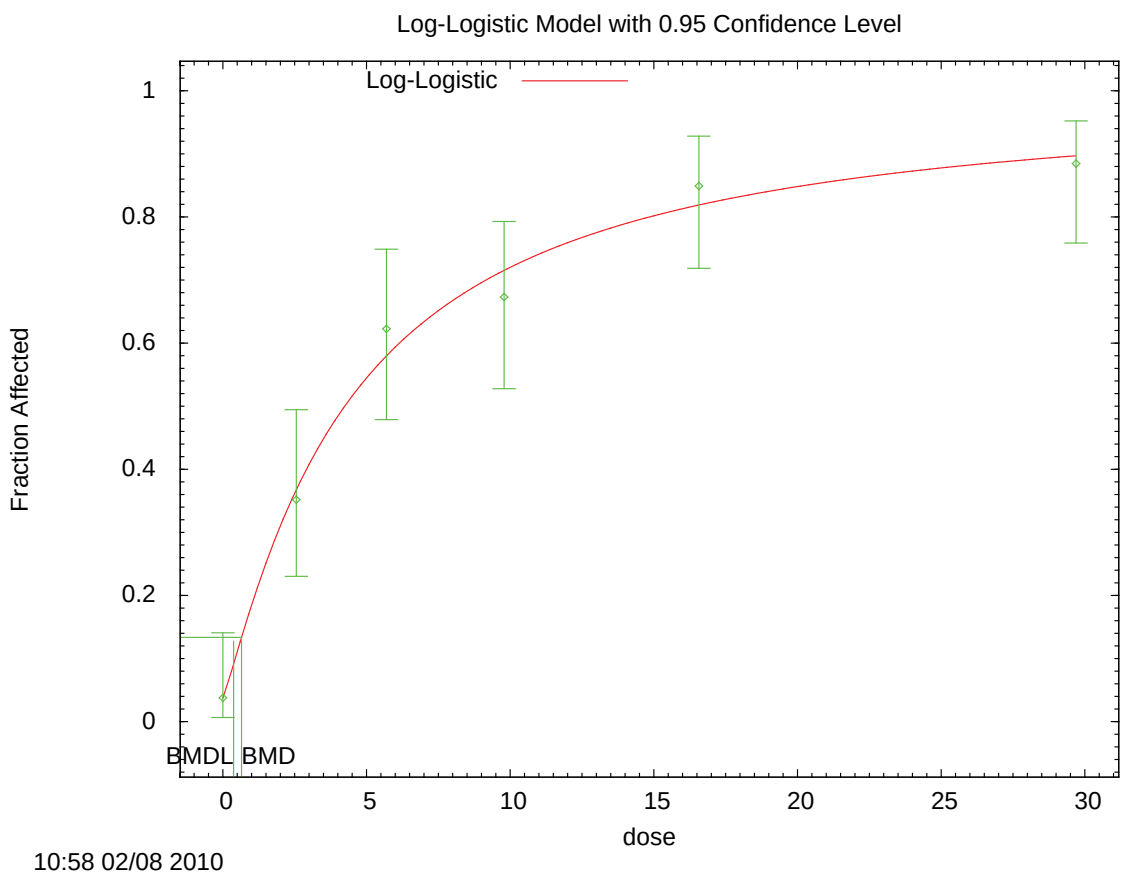
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        0.64971

            BMDL =       0.375051
```

G.2.35.3. *Figure for Selected Model: Log-Logistic*



G.2.36. National Toxicology Program (2006): Eosinophilic Focus, Liver

G.2.36.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	3	0.293	331.902	3.573E+00	2.225E+00	
Logistic	4	0.405	330.400	5.949E+00	5.137E+00	
Log-logistic	3	0.152	333.515	4.139E+00	2.077E+00	
Log-probit	4	0.192	332.312	4.889E+00	3.980E+00	slope bound hit (slope = 1)
Multistage, 5-degree	3	0.752	329.328	3.393E+00	2.466E+00	
Probit[a]	**4**	**0.459**	**329.945**	**5.583E+00**	**4.864E+00**	
Weibull	3	0.324	331.628	3.770E+00	2.249E+00	
Log-probit, unrestricted	3	0.116	334.150	4.146E+00	2.152E+00	unrestricted (slope = 0.895)

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.36.2. *Output for Selected Model: Probit*

National Toxicology Program (2006): Eosinophilic Focus, Liver

```
 ========================================================================
        Probit Model. (Version: 3.1;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\45_NTP_2006_LivEosFoc_Probit_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\45_NTP_2006_LivEosFoc_Probit_1.plt
                                          Mon Feb 08 11:00:54 2010
 ========================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = CumNorm(Intercept+Slope*Dose),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial (and Specified) Parameter Values
                     background =            0   Specified
```

```
                    intercept =     -1.28017
                        slope =    0.0712441


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -background
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

             intercept        slope

 intercept            1        -0.77

     slope        -0.77            1



                                Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
      intercept         -1.23453         0.125132            -1.47979
-0.989279
          slope        0.0688678       0.00823346           0.0527305
0.085005



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -161.07         6
   Fitted model        -162.972         2       3.80461      4
0.4331
  Reduced model        -202.816         1       83.4925      5         <.0001

          AIC:         329.945


                               Goodness  of  Fit
                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.1085         5.751     3.000          53       -1.215
    2.5565     0.1449         7.826     8.000          54        0.067
    5.6937     0.1998        10.588    14.000          53        1.172
    9.7882     0.2876        15.242    17.000          53        0.533
   16.5688     0.4628        24.526    22.000          53       -0.696
   29.6953     0.7912        41.932    42.000          53        0.023

 Chi^2 = 3.62      d.f. = 4        P-value = 0.4593
```

```
   Benchmark Dose Computation

Specified effect =            0.1

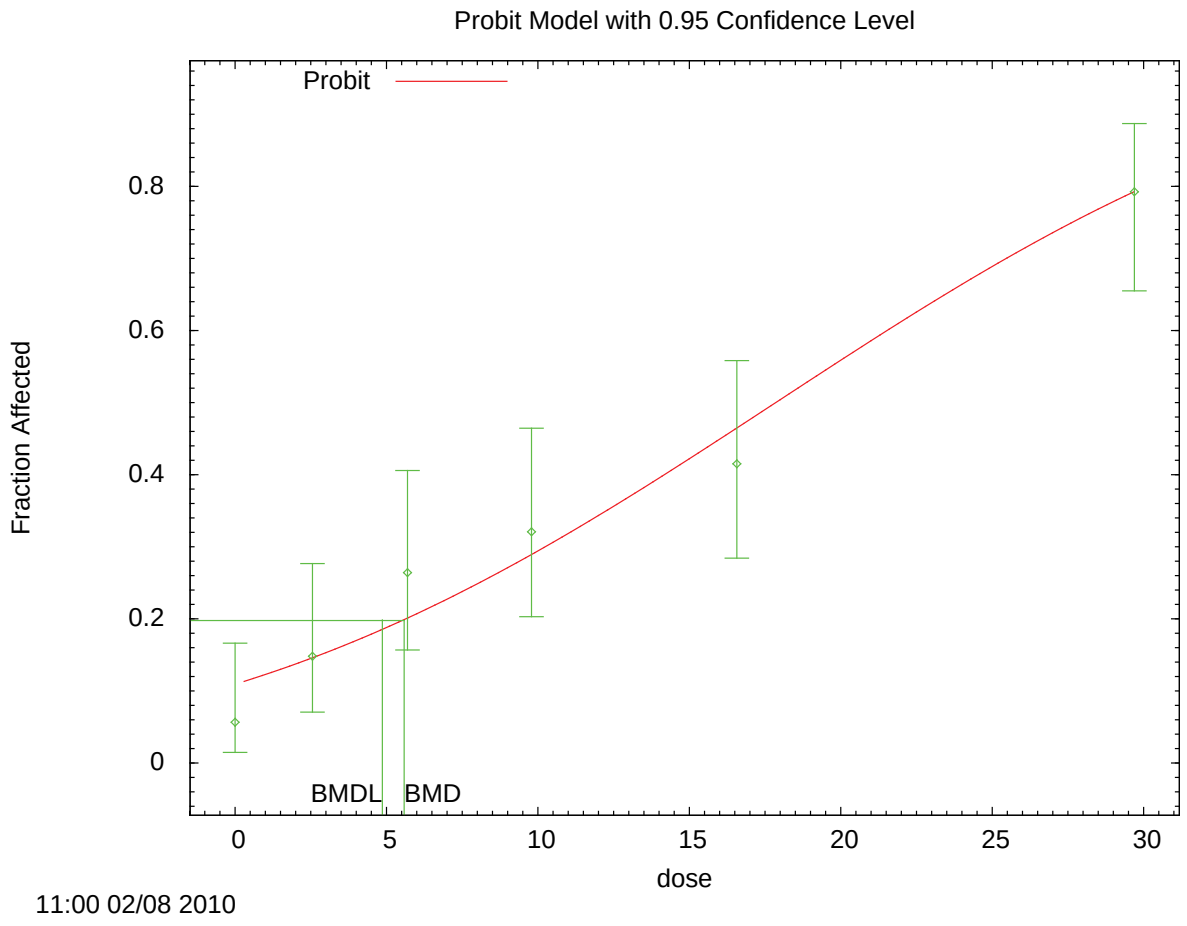
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        5.58309

            BMDL =        4.86394
```

G.2.36.3. *Figure for Selected Model: Probit*



G.2.37. National Toxicology Program (2006): Fatty Change Diffuse, Liver

G.2.37.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	4	0.659	252.348	4.028E+00	2.923E+00	
Logistic	4	0.056	262.132	5.890E+00	5.042E+00	
Log-logistic	4	0.359	254.413	4.254E+00	3.228E+00	
Log-probit	4	0.367	254.428	4.204E+00	3.277E+00	
Multistage, 5-degree	3	0.581	254.045	3.524E+00	2.234E+00	
Probit	4	0.075	260.915	5.567E+00	4.784E+00	
Weibull[a]	**4**	**0.724**	**251.989**	**3.917E+00**	**2.856E+00**	

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.37.2. *Output for Selected Model: Weibull*

National Toxicology Program (2006): Fatty Change Diffuse, Liver

```
 ========================================================================
        Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\47_NTP_2006_LivFatDiff_Weibull_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\47_NTP_2006_LivFatDiff_Weibull_1.plt
                                          Mon Feb 08 11:01:56 2010
 ========================================================================

 NTP_liver_fatty_change_diffuse
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]


   Dependent variable = DichEff
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial (and Specified) Parameter Values
                     Background =   0.00925926
                          Slope =   0.00721355
                          Power =      1.69678
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Slope	Power
Slope	1	-0.98
Power	-0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Slope	0.0135075	0.00640459	0.00095478	0.0260603
Power	1.50444	0.168981	1.17324	1.83564

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-122.992	6			
Fitted model	-123.995	2	2.00444	4	0.7349
Reduced model	-204.846	1	163.708	5	<.0001

AIC: 251.989

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	53	0.000
2.5565	0.0539	2.912	2.000	54	-0.550
5.6937	0.1688	8.949	12.000	53	1.119
9.7882	0.3415	18.102	17.000	53	-0.319
16.5688	0.6024	31.929	30.000	53	-0.542
29.6953	0.8913	47.238	48.000	53	0.336

Chi^2 = 2.06 d.f. = 4 P-value = 0.7243

```
   Benchmark Dose Computation

Specified effect =            0.1

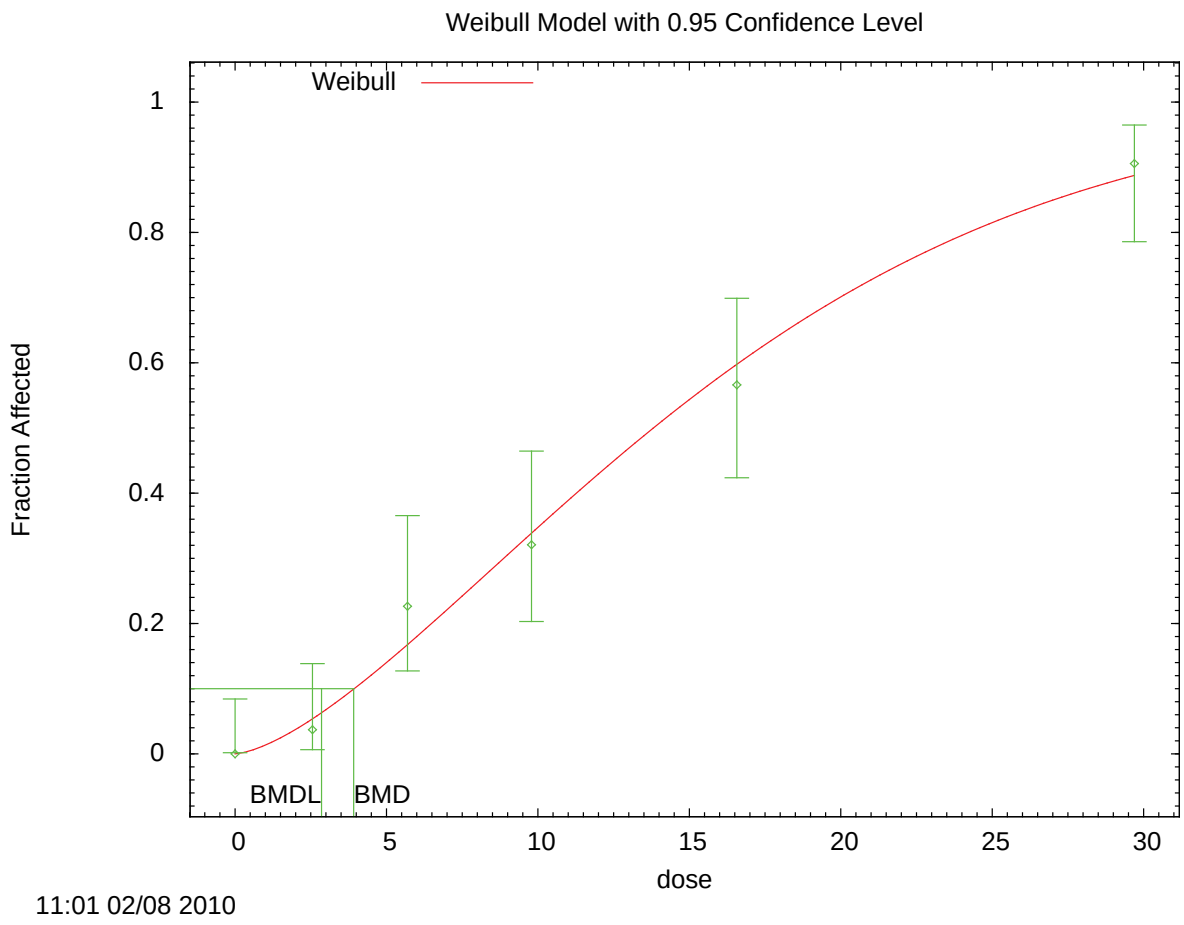
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        3.91723

            BMDL =       2.85566
```

G.2.37.3. *Figure for Selected Model: Weibull*



G.2.38. National Toxicology Program (2006): Gingival Hyperplasia, Squamous, 2 Years

G.2.38.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	4	0.036	314.985	7.743E+00	5.166E+00	power bound hit (power = 1)
Logistic	4	0.016	318.602	1.392E+01	1.056E+01	
Log-logistic[a]	**4**	**0.055**	**313.351**	**5.850E+00**	**3.730E+00**	**slope bound hit (slope = 1)**
Log-probit	4	0.005	321.426	1.535E+01	1.038E+01	slope bound hit (slope = 1)
Multistage, 5-degree	4	0.036	314.985	7.743E+00	5.166E+00	final ß = 0
Probit	4	0.018	318.240	1.318E+01	9.924E+00	
Weibull	4	0.036	314.985	7.743E+00	5.166E+00	power bound hit (power = 1)
Gamma, unrestricted	3	0.633	307.618	5.309E−01	9.859E−07	unrestricted (power = 0.282)
Log-logistic, unrestricted[b]	3	0.655	307.507	7.049E−01	1.260E−05	unrestricted (slope = 0.374)
Log-probit, unrestricted	3	0.668	307.444	8.357E−01	4.796E−05	unrestricted (slope = 0.22)
Weibull, unrestricted	3	0.644	307.562	6.143E−01	3.872E−06	unrestricted (power = 0.325)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.2.38.2. *Output for Selected Model: Log-Logistic*

National Toxicology Program (2006): Gingival Hyperplasia, Squamous, 2 Years

```
 ========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\42_NTP_2006_GingHypSq_LogLogistic_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\42_NTP_2006_GingHypSq_LogLogistic_1.plt
                                                Mon Feb 08 10:59:57 2010
 ========================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

```
   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =    0.0188679
                      intercept =     -3.75308
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.79

 intercept        -0.79            1



                                 Parameter Estimates

                                                                 95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background        0.0671812            *                *
*
      intercept         -3.96371            *                *
*
          slope                1            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -149.95         6
   Fitted model        -154.675         2       9.45085      4
0.05077
```

```
  Reduced model        -162.631         1       25.3627      5
0.0001186

           AIC:         313.351


                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ----------------------------------------------------------------------
    0.0000     0.0672         3.561     1.000          53        -1.405
    2.5565     0.1104         5.960     7.000          54         0.452
    5.6937     0.1582         8.385    14.000          53         2.113
    9.7882     0.2134        11.311    13.000          53         0.566
   16.5688     0.2905        15.394    15.000          53        -0.119
   29.6953     0.4036        21.389    16.000          53        -1.509

 Chi^2 = 9.26      d.f. = 4        P-value = 0.0550


   Benchmark Dose Computation

Specified effect =            0.1

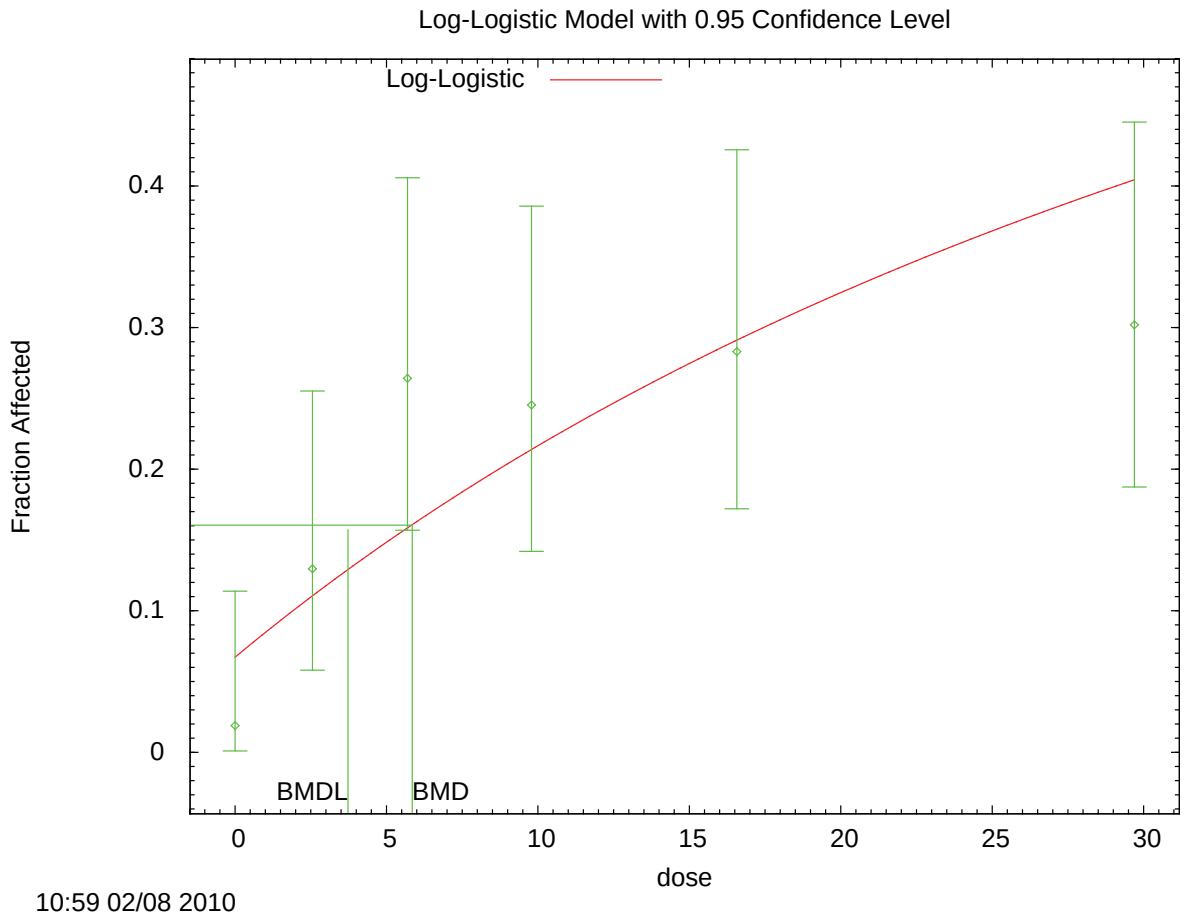
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        5.85026

            BMDL =         3.7296
```

G.2.38.3. *Figure for Selected Model: Log-Logistic*



G.2.38.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

National Toxicology Program (2006): Gingival Hyperplasia, Squamous, 2 Years

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\42_NTP_2006_GingHypSq_LogLogistic_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\42_NTP_2006_GingHypSq_LogLogistic_U_1.plt
                                          Mon Feb 08 10:59:57 2010
 ======================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]
```

```
Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



User has chosen the log transformed model


                Default Initial Parameter Values
                   background =    0.0188679
                    intercept =         -2.2
                        slope =     0.424326


          Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.27         0.11

 intercept        -0.27            1        -0.93

     slope         0.11        -0.93            1



                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background        0.0185138            *                *
*
      intercept         -2.06653            *                *
*
          slope         0.373721            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -149.95         6
   Fitted model        -150.753         3       1.60697      3
0.6578
```

```
  Reduced model        -162.631         1       25.3627      5
0.0001186

           AIC:         307.507


                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ----------------------------------------------------------------------
    0.0000     0.0185         0.981     1.000          53         0.019
    2.5565     0.1681         9.078     7.000          54        -0.756
    5.6937     0.2101        11.136    14.000          53         0.966
    9.7882     0.2433        12.893    13.000          53         0.034
   16.5688     0.2792        14.795    15.000          53         0.063
   29.6953     0.3230        17.117    16.000          53        -0.328

 Chi^2 = 1.62      d.f. = 3        P-value = 0.6554


   Benchmark Dose Computation

Specified effect =            0.1

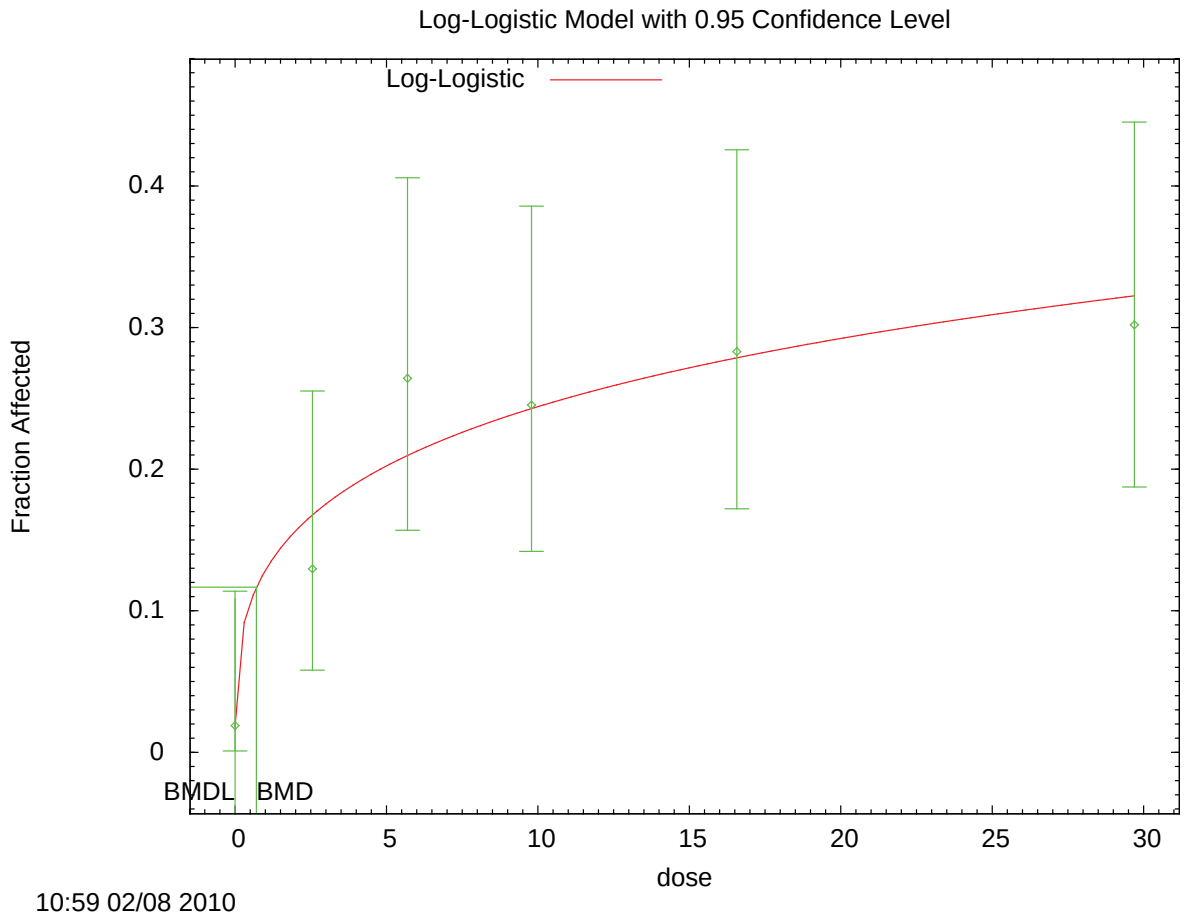
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.704898

            BMDL =   1.26034e-005
```

G.2.38.5. ***Figure for Additional Model Presented: Log-Logistic, Unrestricted***



G.2.39. National Toxicology Program (2006): Hepatocyte Hypertrophy, 2 Years

G.2.39.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	5	0.034	273.875	9.091E−01	7.868E−01	power bound hit (power = 1)
Logistic	4	<0.001	297.895	2.475E+00	2.122E+00	
Log-logistic	4	0.006	279.210	1.137E+00	6.491E−01	
Log-probit	5	0.006	277.800	1.530E+00	1.321E+00	
Multistage, 5-degree[a]	**4**	**0.018**	**275.693**	**9.272E−01**	**7.906E−01**	
Probit	4	<0.001	299.731	2.453E+00	2.137E+00	
Weibull	5	0.034	273.875	9.091E−01	7.868E−01	power bound hit (power = 1)
Gamma, unrestricted	4	0.027	275.270	error	error	unrestricted (power = 0.844)
Log-probit, unrestricted	4	0.008	278.360	1.191E+00	7.038E−01	unrestricted (slope = 0.864)
Weibull, unrestricted	4	0.024	275.439	7.345E−01	3.588E−01	unrestricted (power = 0.92)

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.39.2. *Output for Selected Model: Multistage, 5-Degree*

National Toxicology Program (2006): Hepatocyte Hypertrophy, 2 Years

```
 ======================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\43_NTP_2006_HepHyper_Multi5_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\43_NTP_2006_HepHyper_Multi5_1.plt
                                          Mon Feb 08 11:00:25 2010
 ======================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-
beta5*dose^5)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 6
 Total number of specified parameters = 0
```

Degree of polynomial = 5

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Background =	0.112745
Beta(1) =	0.0950808
Beta(2) =	0
Beta(3) =	0
Beta(4) =	0
Beta(5) =	4.39515e-008

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Beta(2) -Beta(3) -Beta(4)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)	Beta(5)
Beta(1)	1	-0.5
Beta(5)	-0.5	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.113632	*	*	*
Beta(2)	0	*	*	*
Beta(3)	0	*	*	*
Beta(4)	0	*	*	*
Beta(5)	1.71322e-008	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-129.986	6			
Fitted model	-135.847	2	11.7216	4	0.01955
Reduced model	-219.97	1	179.968	5	<.0001

AIC: 275.693

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	53	0.000
2.5565	0.2521	13.614	19.000	54	1.688
5.6937	0.4764	25.251	19.000	53	-1.719
9.7882	0.6717	35.599	42.000	53	1.872
16.5688	0.8510	45.106	41.000	53	-1.584
29.6953	0.9769	51.778	52.000	53	0.203

Chi^2 = 11.86 d.f. = 4 P-value = 0.0184

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

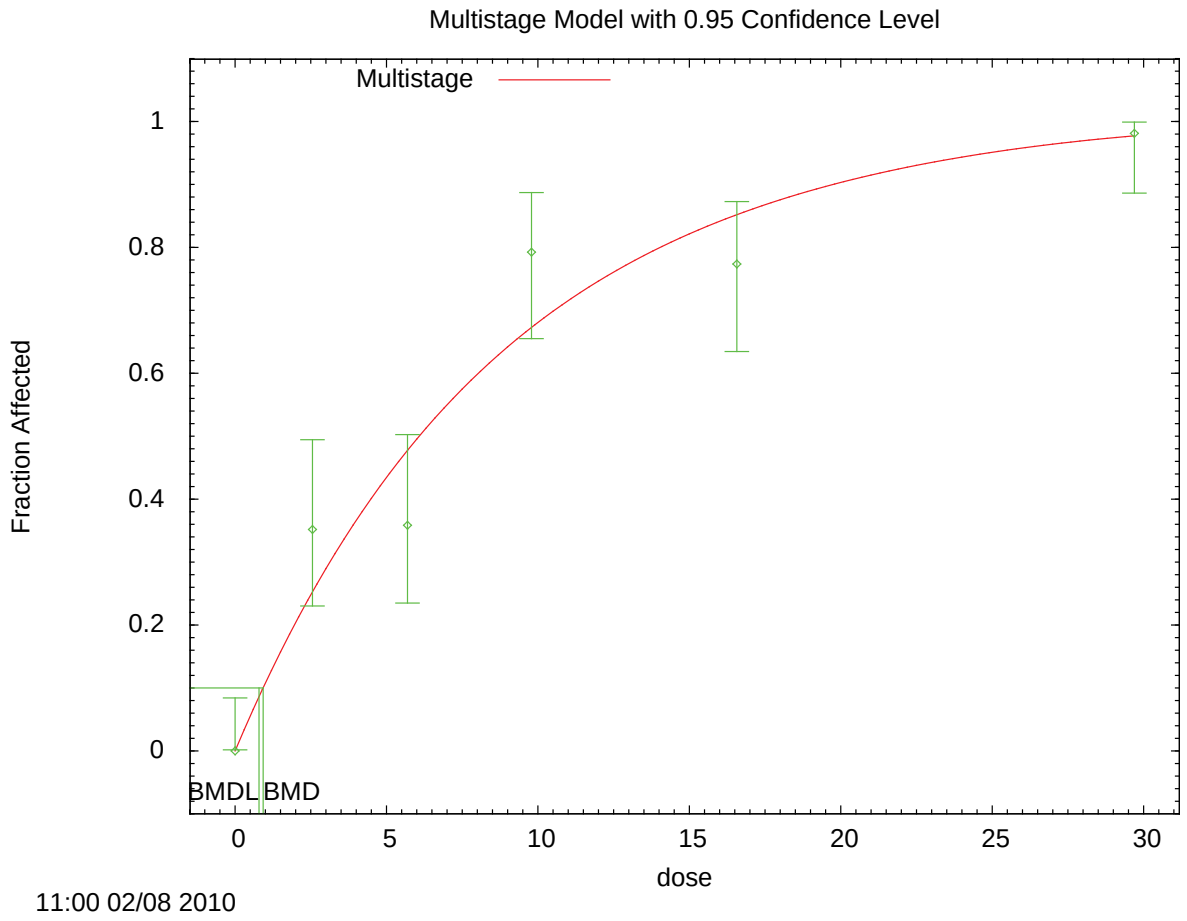
BMD = 0.92721

BMDL = 0.790637

BMDU = 1.14523

Taken together, (0.790637, 1.14523) is a 90 % two-sided confidence interval for the BMD

G.2.39.3. *Figure for Selected Model: Multistage, 5-Degree*



G.2.40. National Toxicology Program (2006): Necrosis, Liver

G.2.40.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	4	0.939	234.400	8.655E+00	6.340E+00	power bound hit (power = 1)
Logistic	4	0.601	236.742	1.484E+01	1.240E+01	
Log-logistic	4	0.943	234.382	7.928E+00	5.605E+00	slope bound hit (slope = 1)
Log-probit	4	0.572	236.863	1.333E+01	1.024E+01	slope bound hit (slope = 1)
Multistage, 5-degree	4	0.939	234.400	8.655E+00	6.340E+00	final ß = 0
Probit	4	0.666	236.293	1.393E+01	1.154E+01	
Weibull	4	0.939	234.400	8.655E+00	6.340E+00	power bound hit (power = 1)
Gamma, unrestricted	3	0.883	236.290	7.726E+00	3.453E+00	unrestricted (power = 0.87)
Log-logistic, unrestricted	3	0.860	236.377	7.733E+00	3.536E+00	unrestricted (slope = 0.974)
Log-probit, unrestricted[a]	**3**	**0.805**	**236.598**	**7.501E+00**	**3.504E+00**	**unrestricted (slope = 0.517)**
Weibull, unrestricted	3	0.879	236.302	7.763E+00	3.508E+00	unrestricted (power = 0.895)

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.40.2. *Output for Selected Model: Log-Probit, Unrestricted*

National Toxicology Program (2006): Necrosis, Liver

```
 ========================================================================
        Probit Model. (Version: 3.1;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\50_NTP_2006_LivNec_LogProbit_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\50_NTP_2006_LivNec_LogProbit_U_1.plt
                                          Mon Feb 08 11:29:30 2010
 ========================================================================

 NTP_liver_necrosis
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted
```

```
Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


User has chosen the log transformed model


                Default Initial (and Specified) Parameter Values
                   background =    0.0188679
                    intercept =     -2.16223
                        slope =     0.457376


          Asymptotic Correlation Matrix of Parameter Estimates

            background    intercept        slope

background            1        -0.65         0.55

 intercept        -0.65            1        -0.97

     slope         0.55        -0.97            1


                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background        0.0221151        0.0221351          -0.0212689
0.065499
      intercept         -2.32352         0.556343            -3.41393
-1.23311
          slope         0.517104         0.185064            0.154385
0.879823


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -114.813         6
   Fitted model        -115.299         3      0.972184      3
0.808
  Reduced model         -127.98         1       26.3331      5         <.0001

          AIC:         236.598


                                 Goodness  of  Fit
```

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0221	1.172	1.000	53	-0.161
2.5565	0.0544	2.938	4.000	54	0.637
5.6937	0.0976	5.174	4.000	53	-0.543
9.7882	0.1457	7.720	8.000	53	0.109
16.5688	0.2096	11.106	10.000	53	-0.373
29.6953	0.3002	15.908	17.000	53	0.327

```
Chi^2 = 0.99      d.f. = 3        P-value = 0.8048


   Benchmark Dose Computation

Specified effect =            0.1

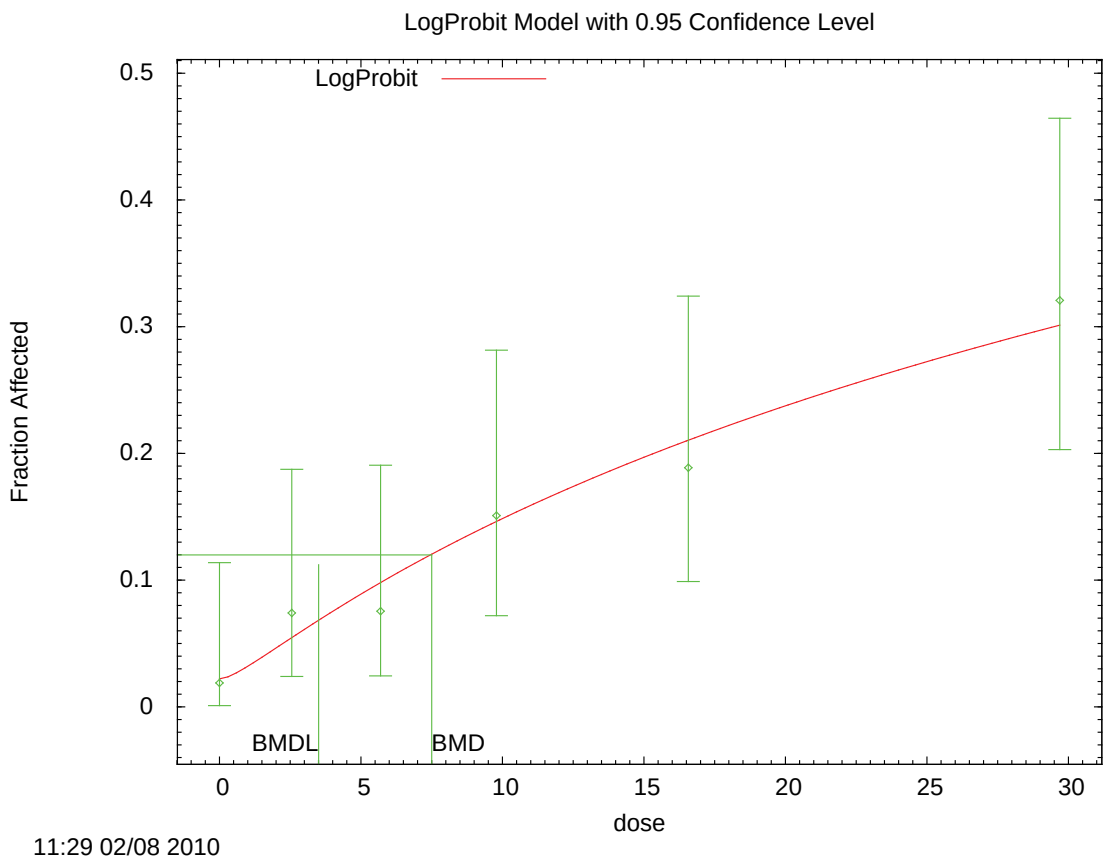
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        7.50077

            BMDL =         3.5039
```

G.2.40.3. *Figure for Selected Model: Log-Probit, Unrestricted*



G.2.41. National Toxicology Program (2006): Oval Cell Hyperplasia

G.2.41.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	3	0.074	199.468	6.739E+00	5.074E+00	
Logistic	4	0.171	196.803	6.064E+00	5.145E+00	
Log-logistic	3	0.042	201.659	6.936E+00	5.604E+00	
Log-probit	3	0.072	200.121	7.090E+00	5.931E+00	
Multistage, 5-degree	3	0.207	195.962	4.785E+00	3.105E+00	
Probit[a]	**4**	**0.227**	**195.448**	**5.673E+00**	**4.793E+00**	
Weibull[b]	3	0.077	198.375	5.718E+00	4.088E+00	

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.2.41.2. *Output for Selected Model: Probit*

National Toxicology Program (2006): Oval Cell Hyperplasia

```
 ======================================================================
        Probit Model. (Version: 3.1;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\53_NTP_2006_OvalHyper_Probit_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\53_NTP_2006_OvalHyper_Probit_1.plt
                                          Mon Feb 08 13:25:23 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = CumNorm(Intercept+Slope*Dose),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                    Default Initial (and Specified) Parameter Values
```

```
                    background =            0   Specified
                     intercept =     -2.29925
                         slope =     0.169545


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

              intercept        slope

 intercept            1        -0.87

     slope        -0.87            1



                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
      intercept         -2.18988         0.208021             -2.5976
-1.78217
          slope         0.172453        0.0182446            0.136694
0.208211



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -92.4898         6
   Fitted model        -95.7242         2       6.46873      4
0.1668
  Reduced model        -210.191         1       235.402      5         <.0001

           AIC:         195.448


                                 Goodness  of  Fit
                                                                   Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.0143         0.756     0.000          53       -0.876
    2.5565     0.0401         2.168     4.000          54        1.270
    5.6937     0.1135         6.017     3.000          53       -1.306
    9.7882     0.3079        16.317    20.000          53        1.096
   16.5688     0.7478        39.631    38.000          53       -0.516
   29.6953     0.9983        52.911    53.000          53        0.299

 Chi^2 = 5.64      d.f. = 4        P-value = 0.2274
```

```
   Benchmark Dose Computation

Specified effect =           0.1

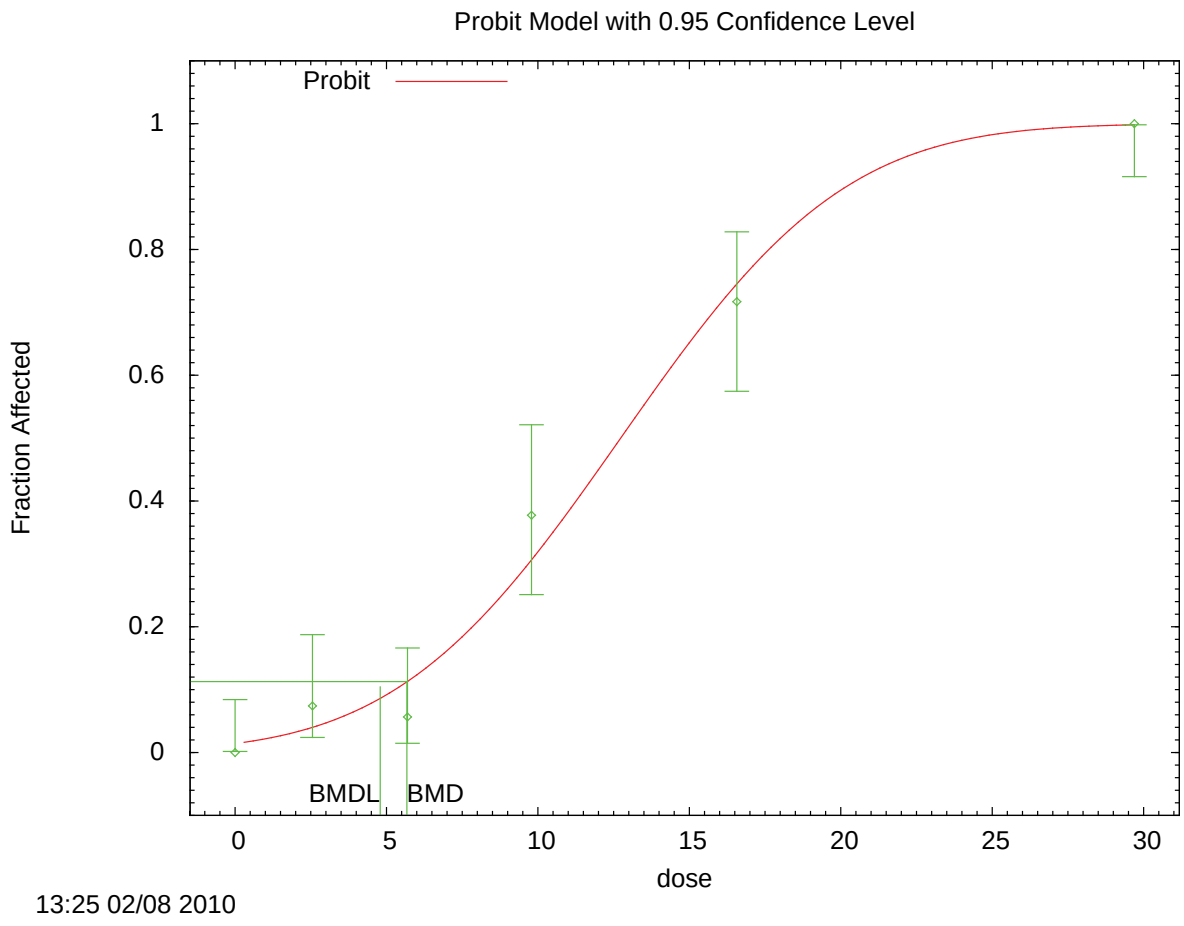
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        5.67298

            BMDL =        4.79341
```

G.2.41.3. *Figure for Selected Model: Probit*



G.2.41.4. *Output for Additional Model Presented: Weibull*

National Toxicology Program (2006): Oval Cell Hyperplasia

```
 ======================================================================
        Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\53_NTP_2006_OvalHyper_Weibull_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\53_NTP_2006_OvalHyper_Weibull_1.plt
                                          Mon Feb 08 13:25:23 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]


   Dependent variable = DichEff
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial (and Specified) Parameter Values
                     Background =   0.00925926
                          Slope =   0.00296825
                          Power =      2.17092


           Asymptotic Correlation Matrix of Parameter Estimates

             Background        Slope        Power

Background            1        -0.72          0.7

     Slope        -0.72            1        -0.99

     Power          0.7        -0.99            1



                                  Parameter Estimates

                                                                  95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
```

```
     Background        0.0164137        0.0221488          -0.0269971
0.0598245
          Slope       0.00162074       0.00202897         -0.00235596
0.00559745
          Power          2.39427         0.455116             1.50226
3.28628



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -92.4898         6
   Fitted model        -96.1875         3        7.3953      3
0.06031
  Reduced model        -210.191         1       235.402      5         <.0001

           AIC:         198.375


                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ----------------------------------------------------------------------
    0.0000     0.0164         0.870     0.000          53        -0.940
    2.5565     0.0314         1.695     4.000          54         1.799
    5.6937     0.1138         6.034     3.000          53        -1.312
    9.7882     0.3285        17.411    20.000          53         0.757
   16.5688     0.7440        39.431    38.000          53        -0.450
   29.6953     0.9957        52.774    53.000          53         0.476

 Chi^2 = 6.85      d.f. = 3        P-value = 0.0770


   Benchmark Dose Computation

Specified effect =            0.1

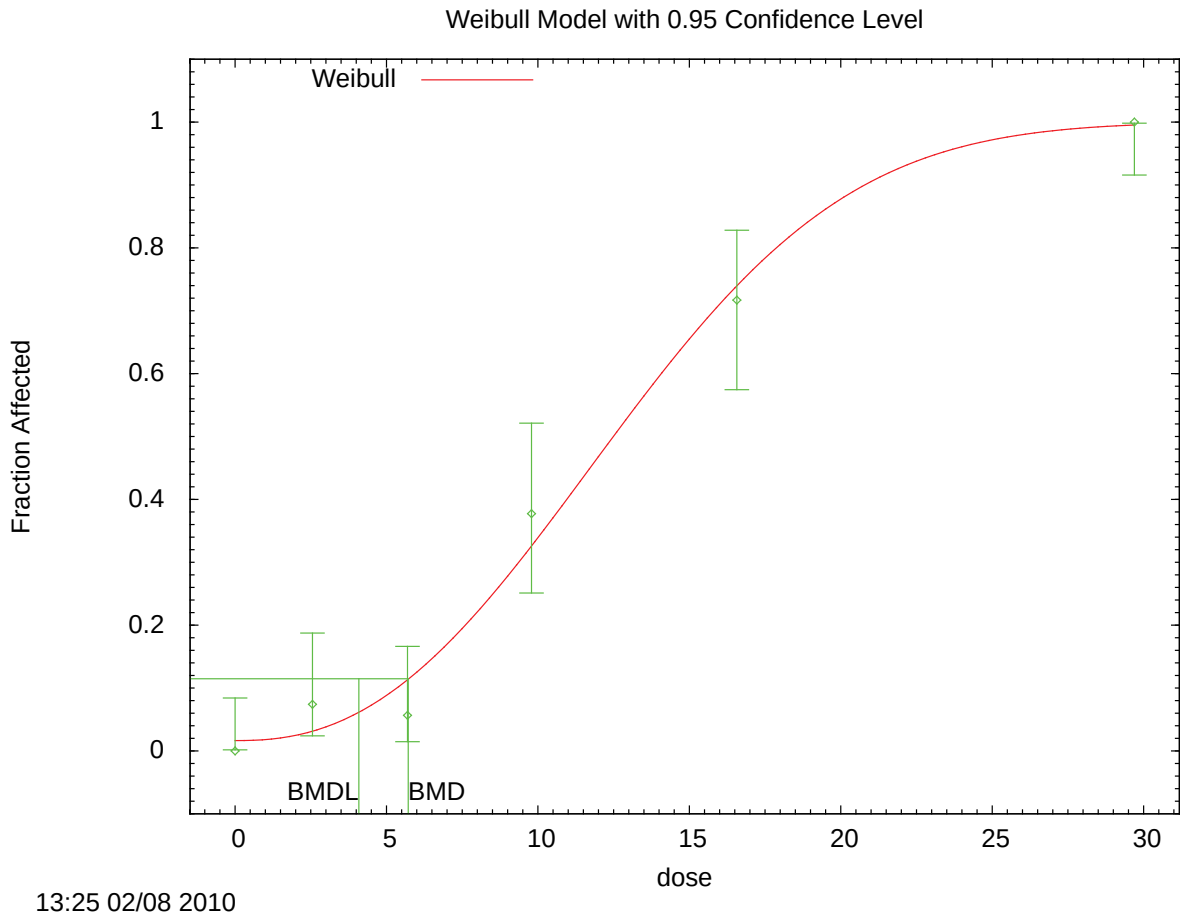
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        5.71754

            BMDL =       4.08823
```

G.2.41.5. *Figure for Additional Model Presented: Weibull*



G.2.42. National Toxicology Program (2006): Pigmentation, Liver

G.2.42.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	3	0.552	196.971	2.172E+00	1.493E+00	
Logistic	4	0.247	197.066	1.853E+00	1.521E+00	
Log-logistic	3	0.984	195.530	2.566E+00	1.937E+00	
Log-probit[a]	**3**	**0.962**	**195.526**	**2.463E+00**	**1.890E+00**	
Multistage, 5-degree	3	0.058	199.955	1.822E+00	9.916E−01	final ß = 0
Probit	4	0.004	200.504	1.710E+00	1.430E+00	
Weibull	3	0.219	199.007	1.756E+00	1.190E+00	

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.42.2. *Output for Selected Model: Log-Probit*

National Toxicology Program (2006): Pigmentation, Liver

```
 ======================================================================
        Probit Model. (Version: 3.1;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\54_NTP_2006_Pigment_LogProbit_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\54_NTP_2006_Pigment_LogProbit_1.plt
                                          Mon Feb 08 13:25:55 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                   Default Initial (and Specified) Parameter Values
                      background =    0.0754717
                       intercept =     -2.48683
                           slope =      1.53221


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.42         0.33

 intercept        -0.42            1        -0.96

     slope         0.33        -0.96            1
```

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0725473	0.0338856	0.00613263	0.138962
intercept	-2.93268	0.487158	-3.8875	-1.97787
slope	1.83184	0.246868	1.34798	2.31569

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-94.6177	6			
Fitted model	-94.7632	3	0.291072	3	0.9617
Reduced model	-210.717	1	232.198	5	<.0001

AIC: 195.526

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0725	3.845	4.000	53	0.082
2.5565	0.1769	9.553	9.000	54	-0.197
5.6937	0.6291	33.342	34.000	53	0.187
9.7882	0.9013	47.771	48.000	53	0.105
16.5688	0.9874	52.334	52.000	53	-0.412
29.6953	0.9995	52.974	53.000	53	0.160

Chi^2 = 0.29 d.f. = 3 P-value = 0.9624

Benchmark Dose Computation

Specified effect = 0.1

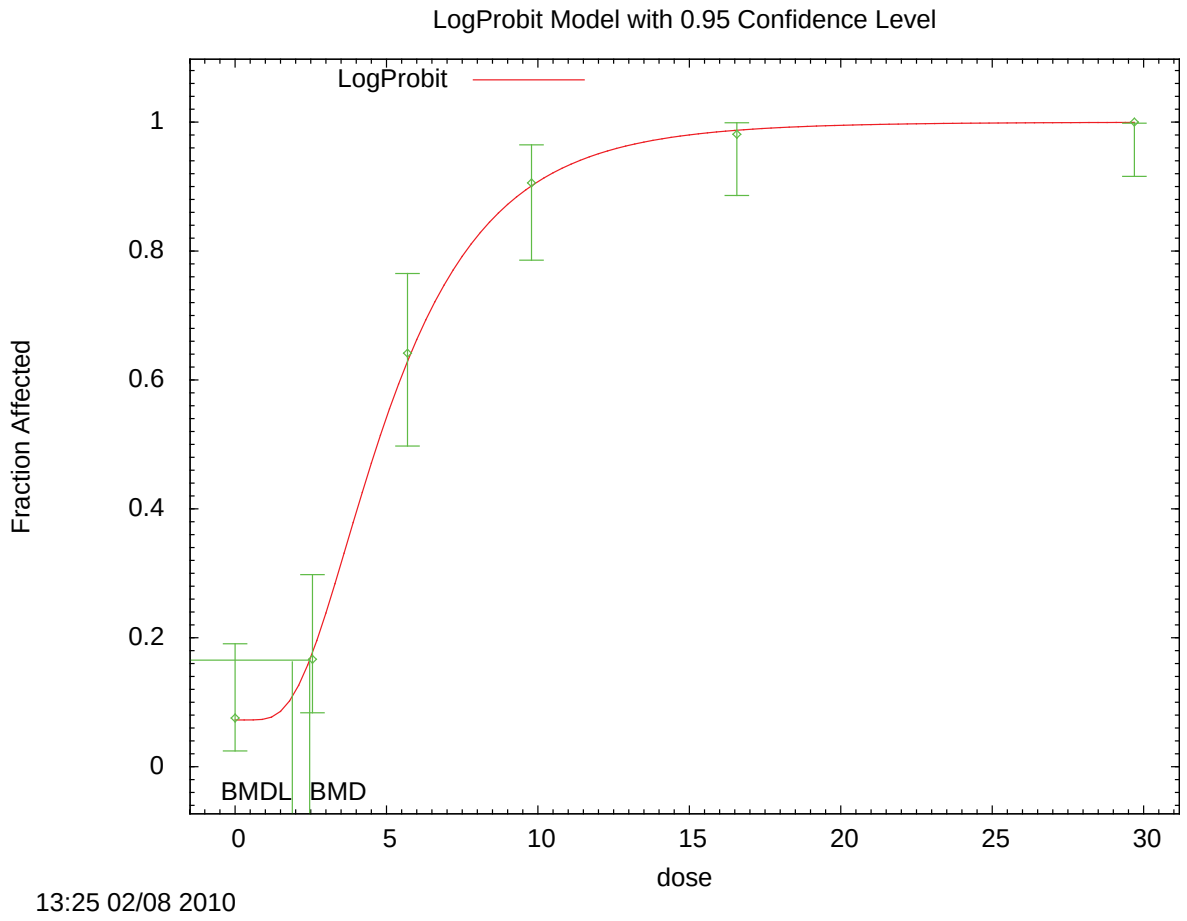
Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.46293

BMDL = 1.88981

G.2.42.3. *Figure for Selected Model: Log-Probit*



G.2.43. National Toxicology Program (2006): Toxic Hepatopathy

G.2.43.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	4	0.754	185.763	4.302E+00	3.463E+00	
Logistic	4	0.159	191.136	4.833E+00	4.068E+00	
Log-logistic	3	0.391	189.577	4.697E+00	3.818E+00	
Log-probit	3	0.394	189.580	4.972E+00	3.780E+00	
Multistage, 5-degree[a]	**4**	**0.693**	**185.924**	**3.980E+00**	**3.059E+00**	**final ß = 0**
Probit	4	0.231	189.820	4.621E+00	3.860E+00	
Weibull	4	0.716	185.785	4.089E+00	3.215E+00	

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.43.2. *Output for Selected Model: Multistage, 5-Degree*

National Toxicology Program (2006): Toxic Hepatopathy

```
 ======================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\55_NTP_2006_ToxHepa_Multi5_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\55_NTP_2006_ToxHepa_Multi5_1.plt
                                          Mon Feb 08 13:26:28 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                  -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-
beta5*dose^5)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 6
 Total number of specified parameters = 0
 Degree of polynomial = 5


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                   Default Initial Parameter Values
                      Background =            0
                         Beta(1) =            0
                         Beta(2) =            0
                         Beta(3) =            0
                         Beta(4) =            0
                         Beta(5) = 4.36963e+012


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(4)
-Beta(5)
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )
```

	Beta(2)	Beta(3)
Beta(2)	1	-0.95
Beta(3)	-0.95	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.00639021	*	*	*
Beta(3)	6.5404e-005	*	*	*
Beta(4)	0	*	*	*
Beta(5)	0	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-89.8076	6			
Fitted model	-90.9619	2	2.30853	4	0.6792
Reduced model	-218.207	1	256.799	5	<.0001

AIC: 185.924

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	53	0.000
2.5565	0.0420	2.265	2.000	54	-0.180
5.6937	0.1969	10.434	8.000	53	-0.841
9.7882	0.4901	25.976	30.000	53	1.106
16.5688	0.8715	46.189	45.000	53	-0.488
29.6953	0.9994	52.966	53.000	53	0.185

Chi^2 = 2.23 d.f. = 4 P-value = 0.6928

Benchmark Dose Computation

```
Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

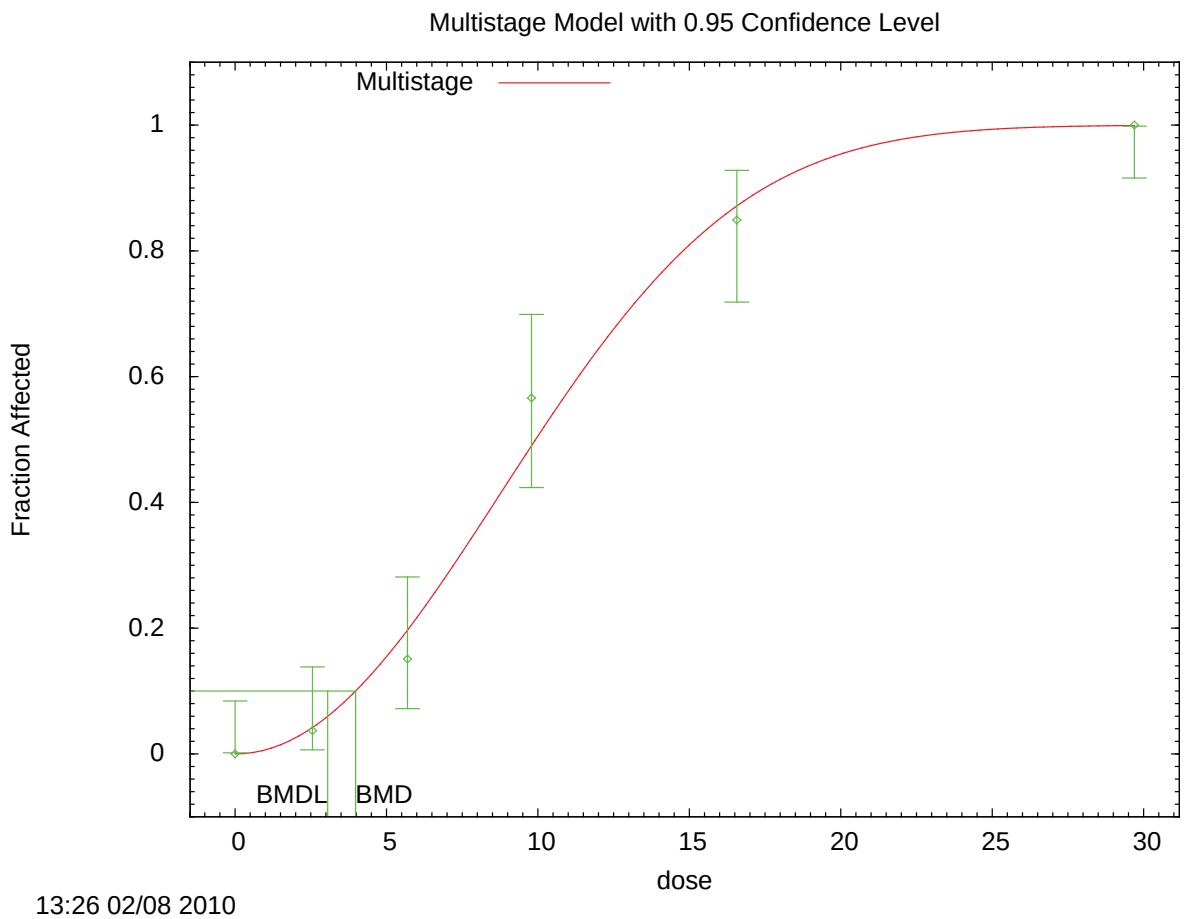
             BMD =        3.98025

            BMDL =        3.05855

            BMDU =        4.89735

Taken together, (3.05855, 4.89735) is a 90     % two-sided confidence
interval for the BMD
```

G.2.43.3. *Figure for Selected Model: Multistage, 5-Degree*



G.2.44. Ohsako et al. (2001): Ano-Genital Length, PND 120

G.2.44.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	3	0.027	171.073	2.592E+01	1.750E+01	
Exponential (M3)	3	0.027	171.073	2.592E+01	1.750E+01	power hit bound (*d* = 1)
Exponential (M4)	2	0.106	168.392	2.248E+00	8.445E−01	
Exponential (M5)	1	0.049	169.789	2.193E+00	9.382E−01	
Hill[b]	**2**	**0.154**	**167.647**	**2.879E+00**	**8.028E−01**	***n* lower bound hit (*n* = 1)**
Linear	3	0.025	171.258	2.700E+01	1.881E+01	
Polynomial, 4-degree	3	0.025	171.258	2.700E+01	1.881E+01	
Power	3	0.025	171.258	2.700E+01	1.881E+01	power bound hit (power = 1)
Hill, unrestricted[c]	1	0.056	169.555	3.494E+00	3.046E−01	unrestricted (*n* = 0.591)
Power, unrestricted	2	0.153	167.654	4.151E+00	2.395E−01	unrestricted (power = 0.291)

[a] Constant variance model selected (*p* = 0.165).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.44.2. *Output for Selected Model: Hill*

Ohsako et al. (2001): Ano-Genital Length, PND 120

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\56_Ohsako_2001_Anogen_HillCV_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\56_Ohsako_2001_Anogen_HillCV_1.plt
                                          Mon Feb 08 13:27:02 2010
 ======================================================================

 Figure 7
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	7.27386	
rho =	0	Specified
intercept =	28.905	
v =	-5.1065	
n =	1.57046	
k =	2.4317	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	4.4e-008	-9.8e-008	7.2e-008
intercept	4.4e-008	1	-0.57	-0.52
v	-9.8e-008	-0.57	1	-0.23
k	7.2e-008	-0.52	-0.23	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	7.07394	1.36138	4.40568	9.7422
intercept	28.9732	0.74996	27.5034	30.4431
v	-5.02686	1.05086	-7.08651	-2.9672
n	1	NA		
k	2.56203	2.11462	-1.58255	6.70661

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

0	12	28.9	29	3.13	2.66	-0.0889
1.04	10	27.9	27.5	2.5	2.66	0.495
3.471	10	25.2	26.1	3.21	2.66	-1.09
11.36	10	26	24.9	2.85	2.66	1.35
38.42	12	23.8	24.3	1.56	2.66	-0.602

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-77.952340	6	167.904680
A2	-74.703868	10	169.407736
A3	-77.952340	6	167.904680
fitted	-79.823277	4	167.646555
R	-89.824703	2	183.649405

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	30.2417	8	0.0001916
Test 2	6.49694	4	0.165
Test 3	6.49694	4	0.165
Test 4	3.74187	2	0.154

```
The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

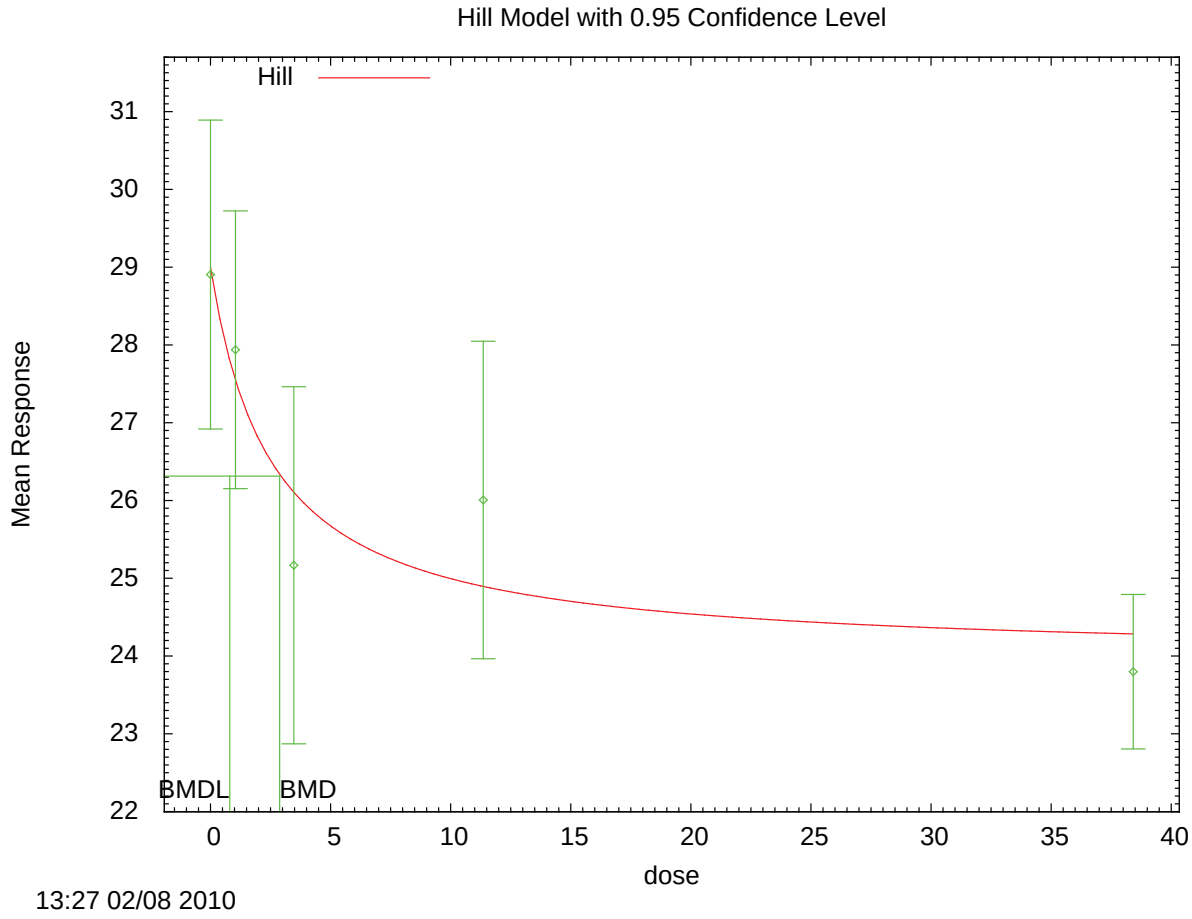
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =        2.87863

            BMDL =      0.802782
```

G.2.44.3. *Figure for Selected Model: Hill*



G.2.44.4. *Output for Additional Model Presented: Hill, Unrestricted*

Ohsako et al. (2001): Ano-Genital Length, PND 120

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\56_Ohsako_2001_Anogen_HillCV_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\56_Ohsako_2001_Anogen_HillCV_U_1.plt
                                          Mon Feb 08 13:27:04 2010
 ======================================================================

 Figure 7
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)
```

Dependent variable = Mean
Independent variable = Dose
rho is set to 0
Power parameter is not restricted
A constant variance model is fit

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	7.27386	
rho =	0	Specified
intercept =	28.905	
v =	-5.1065	
n =	1.57046	
k =	2.4317	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	n	k
alpha	1	-3.1e-008	7.5e-009	1.7e-008	-8.8e-009
intercept	-3.1e-008	1	0.001	0.0016	-0.13
v	7.5e-009	0.001	1	0.98	-0.99
n	1.7e-008	0.0016	0.98	1	-0.97
k	-8.8e-009	-0.13	-0.99	-0.97	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	7.06192	1.35907	4.3982	9.72564
intercept	28.9618	0.754441	27.4831	30.4404
v	-6.82284	11.1104	-28.5989	14.9532

```
              n         0.591421             1.04            -1.44695
2.62979
              k          7.47064           48.002            -86.6115
101.553


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0    12       28.9           29         3.13         2.66         -0.074
 1.04    10       27.9         27.3          2.5         2.66           0.71
3.471    10       25.2         26.3         3.21         2.66          -1.36
11.36    10         26         25.1         2.85         2.66           1.04
38.42    12       23.8           24         1.56         2.66         -0.284


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1          -77.952340            6     167.904680
            A2          -74.703868           10     169.407736
            A3          -77.952340            6     167.904680
         fitted         -79.777354            5     169.554709
             R          -89.824703            2     183.649405


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
```

(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	30.2417	8	0.0001916
Test 2	6.49694	4	0.165
Test 3	6.49694	4	0.165
Test 4	3.65003	1	0.05607

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

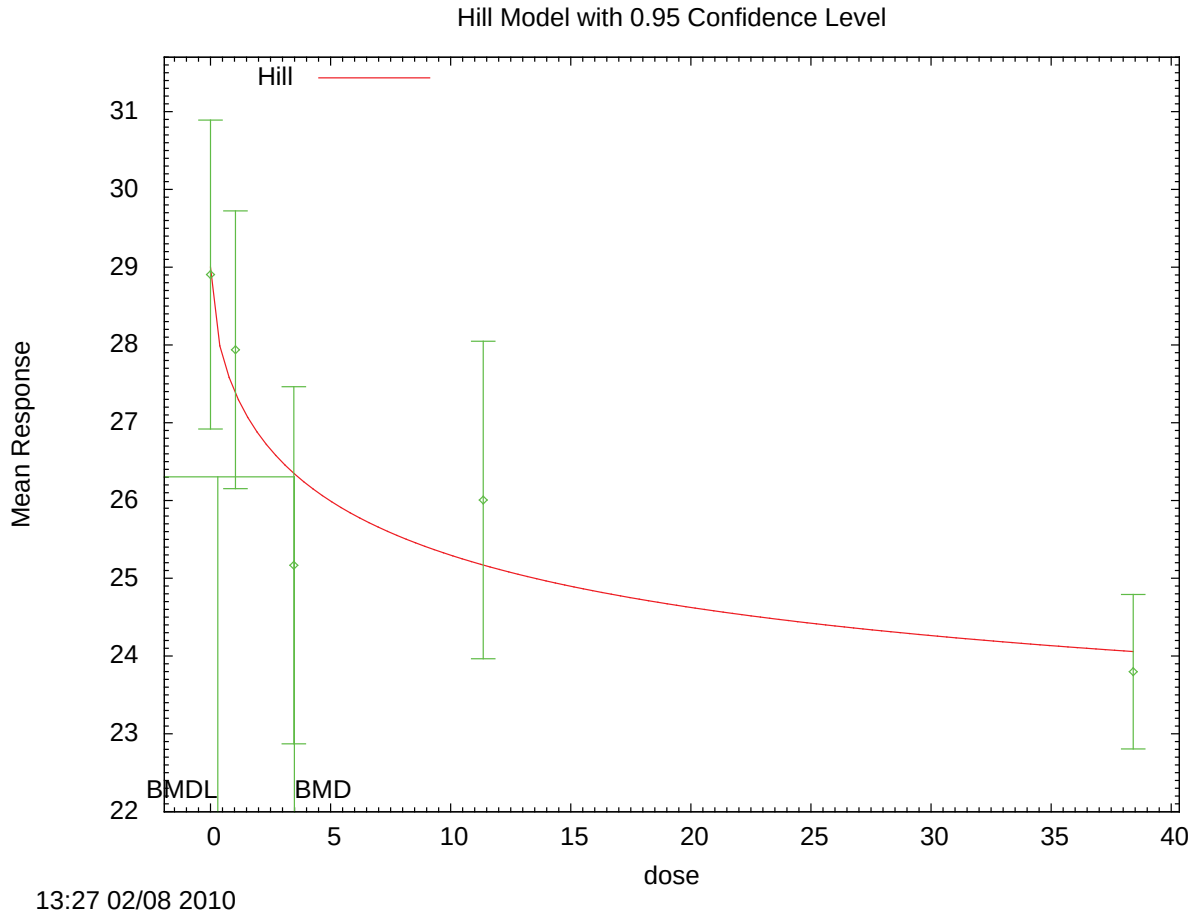
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 3.49389

BMDL = 0.304602

G.2.44.5. *Figure for Additional Model Presented: Hill, Unrestricted*



G.2.45. Sewall et al. (1995): T4 In Serum

G.2.45.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	3	0.722	204.495	1.869E+01	1.243E+01	
Exponential (M3)	3	0.722	204.495	1.869E+01	1.243E+01	power hit bound (*d* = 1)
Exponential (M4)	2	0.854	205.483	1.106E+01	4.650E+00	
Exponential (M5)	2	0.854	205.483	1.106E+01	4.650E+00	power hit bound (*d* = 1)
Hill[b]	**2**	**0.898**	**205.382**	**1.031E+01**	**3.603E+00**	***n* lower bound hit (*n* = 1)**
Linear	3	0.576	205.150	2.238E+01	1.619E+01	
Polynomial, 4-degree	3	0.576	205.150	2.238E+01	1.619E+01	
Power	3	0.576	205.150	2.238E+01	1.619E+01	power bound hit (power = 1)
Hill, unrestricted[c]	1	0.864	207.196	9.706E+00	1.973E+00	unrestricted (*n* = 0.569)
Power, unrestricted	2	0.985	205.197	9.726E+00	1.914E+00	unrestricted (power = 0.538)

[a] Constant variance model selected (*p* = 0.4078).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.45.2. *Output for Selected Model: Hill*

Sewall et al. (1995): T4 In Serum

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\58_Sewall_1995_T4_HillCV_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\58_Sewall_1995_T4_HillCV_1.plt
                                             Mon Feb 08 13:28:15 2010
 ======================================================================

 Figure 1, Saline noninitiated
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

```
                 Default Initial Parameter Values
                         alpha =      33.0913
                           rho =            0   Specified
                     intercept =      30.6979
                             v =     -12.2937
                             n =     0.950815
                             k =      12.5808


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -n
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                  alpha    intercept            v            k

     alpha            1    -1.2e-009    -1.8e-008     1.5e-008

 intercept    -1.2e-009            1          0.3        -0.65

         v    -1.8e-008          0.3            1        -0.89

         k     1.5e-008        -0.65        -0.89            1


                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          29.5556          6.23087             17.3433
41.7679
      intercept          30.3957          1.68747             27.0883
33.7031
              v         -18.2488          7.72836            -33.3961
-3.10154
              n                1               NA
              k          24.2883           26.743             -28.127
76.7035

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-
```

0	9	30.7	30.4	4.66	5.44	0.167
3.291	9	27.9	28.2	7.17	5.44	-0.188
7.107	9	25.9	26.3	6.81	5.44	-0.204
16.63	9	23.6	23	5.38	5.44	0.319
44.66	9	18.4	18.6	4.12	5.44	-0.0942

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-98.583448	6	209.166896
A2	-96.590204	10	213.180407
A3	-98.583448	6	209.166896
fitted	-98.691143	4	205.382286
R	-109.013252	2	222.026503

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	24.8461	8	0.001651
Test 2	3.98649	4	0.4078
Test 3	3.98649	4	0.4078
Test 4	0.21539	2	0.8979

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

```
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

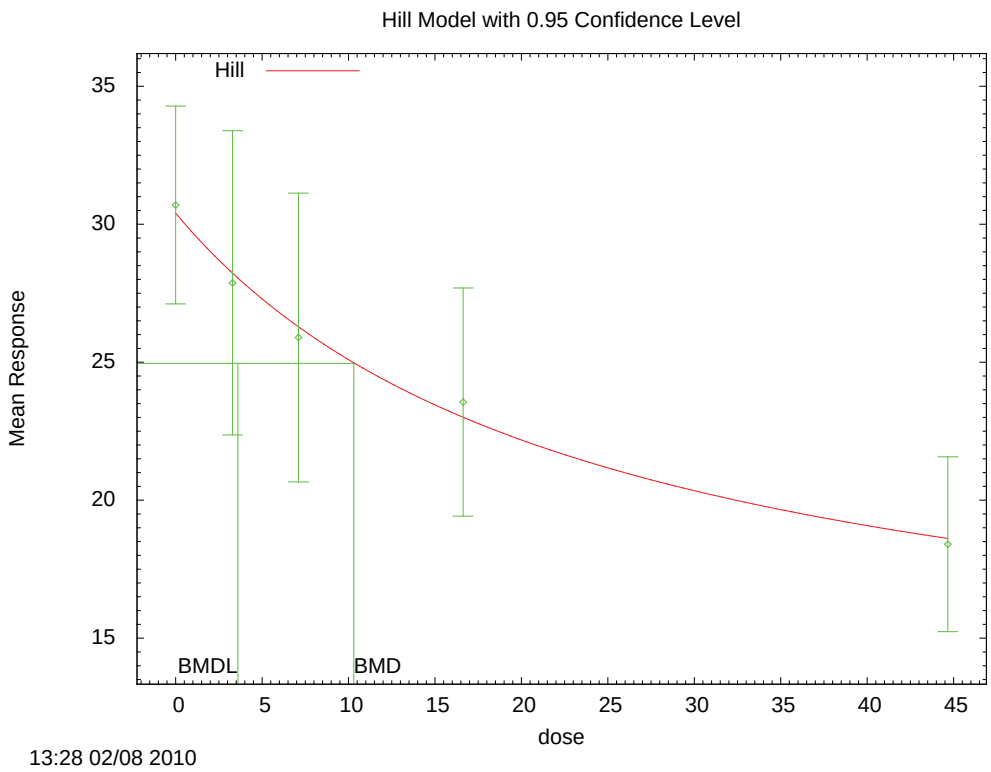
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =         10.306

            BMDL =       3.60269
```

G.2.45.3. *Figure for Selected Model: Hill*



G.2.45.4. *Output for Additional Model Presented: Hill, Unrestricted*

Sewall et al. (1995): T4 In Serum

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\58_Sewall_1995_T4_HillCV_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\58_Sewall_1995_T4_HillCV_U_1.plt
                                          Mon Feb 08 13:28:15 2010
 ======================================================================

 Figure 1, Saline noninitiated
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter is not restricted
   A constant variance model is fit

   Total number of dose groups = 5
```

Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	33.0913	
rho =	0	Specified
intercept =	30.6979	
v =	-12.2937	
n =	0.950815	
k =	12.5808	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	n	k
alpha	1	-3.9e-005	0.00022	0.00021	-0.00022
intercept	-3.9e-005	1	-0.17	-0.31	0.18
v	0.00022	-0.17	1	0.97	-1
n	0.00021	-0.31	0.97	1	-0.98
k	-0.00022	0.18	-1	-0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	29.4337	6.20518	17.2718	41.5957
intercept	30.7096	1.79801	27.1855	34.2336
v	-143.244	3972.28	-7928.78	7642.29
n	0.569063	0.947248	-1.28751	2.42564
k	2856.29	171186	-332662	338374

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	9	30.7	30.7	4.66	5.43	-0.00646
3.291	9	27.9	27.7	7.17	5.43	0.0842
7.107	9	25.9	26.1	6.81	5.43	-0.134
16.63	9	23.6	23.4	5.38	5.43	0.0657
44.66	9	18.4	18.4	4.12	5.43	-0.00948

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-98.583448	6	209.166896
A2	-96.590204	10	213.180407
A3	-98.583448	6	209.166896
fitted	-98.598183	5	207.196367
R	-109.013252	2	222.026503

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	24.8461	8	0.001651
Test 2	3.98649	4	0.4078

Test 3	3.98649	4	0.4078
Test 4	0.0294713	1	0.8637

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

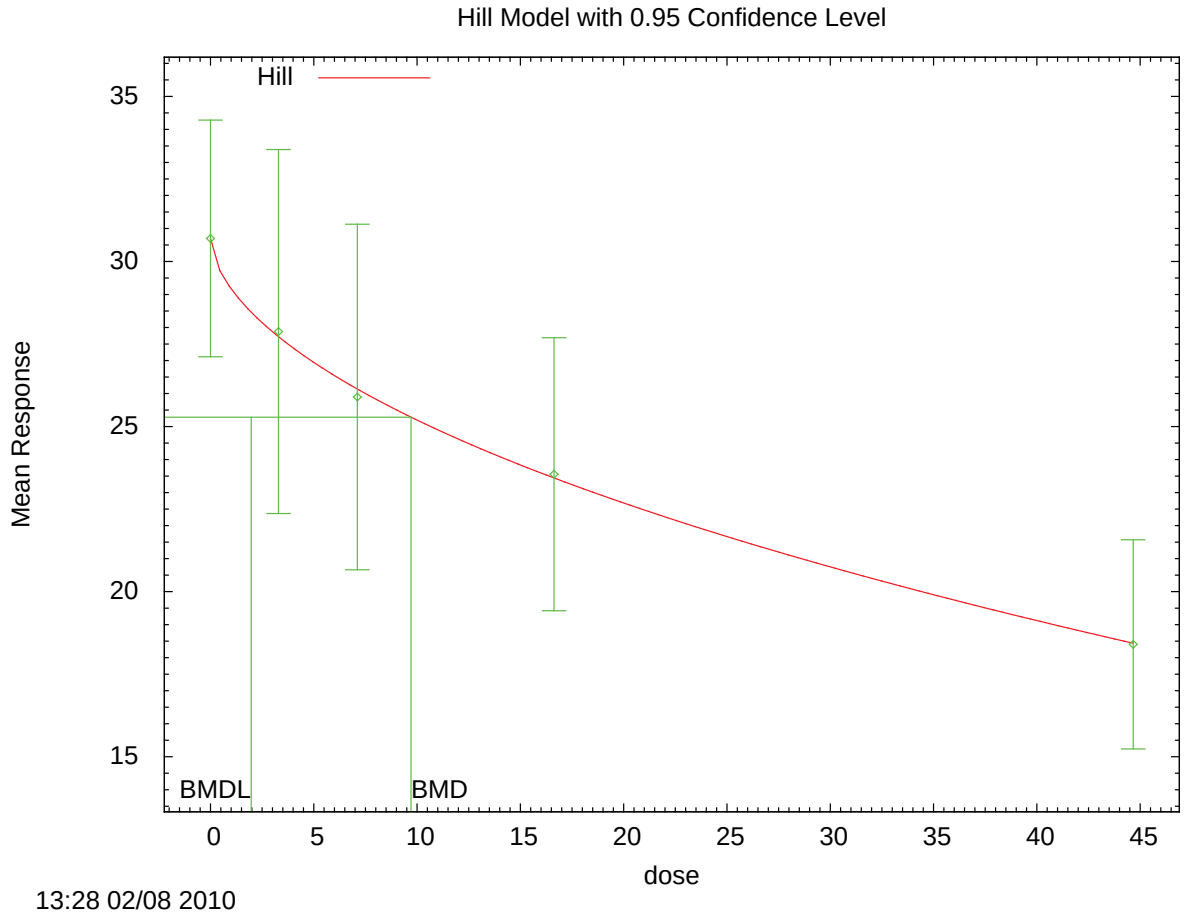
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 9.70574

BMDL = 1.97319

G.2.45.5. *Figure for Additional Model Presented: Hill, Unrestricted*



G.2.46. Shi et al. (2007): Estradiol 17B, PE9

G.2.46.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	3	0.010	391.638	6.976E+00	3.761E+00	
Exponential (M3)	3	0.010	391.638	6.976E+00	3.761E+00	power hit bound (*d* = 1)
Exponential (M4)[b]	**2**	**0.690**	**382.969**	**8.068E−01**	**3.544E−01**	
Exponential (M5)	2	0.690	382.969	8.068E−01	3.544E−01	power hit bound (*d* = 1)
Hill	2	0.975	382.278	7.239E−01	error	*n* lower bound hit (*n* = 1)
Linear	3	0.003	394.308	9.841E+00	6.687E+00	
Polynomial, 4-degree	3	0.003	394.308	9.841E+00	6.687E+00	
Power	3	0.003	394.308	9.841E+00	6.687E+00	power bound hit (power = 1)
Hill, unrestricted	1	0.897	384.243	7.086E−01	error	unrestricted (*n* = 0.875)
Power, unrestricted	2	0.506	383.590	6.280E−01	3.304E−02	unrestricted (power = 0.222)

[a] Nonconstant variance model selected (*p* = 0.0521).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.46.2. *Output for Selected Model: Exponential (M4)*

Shi et al. (2007): Estradiol 17B, PE9

```
 ========================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\59_Shi_2007_Estradiol_Exp_1.(d)
        Gnuplot Plotting File:
                                             Mon Feb 08 13:28:52 2010
 ========================================================================

 Figure 4 PE9 only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	2.65881
rho	0.913414
a	108
b	0.277637
c	0.340136
d	1

Parameter Estimates

Variable	Model 4
lnalpha	1.66773
rho	1.15314
a	103.146
b	1.00685
c	0.418742
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	102.9	41.41
0.3418	10	86.19	19.58
1.075	10	63.33	29.36
5.23	10	48.1	18.82
13.91	10	38.57	22.59

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	103.1	33.35	-0.02738
0.3418	85.69	29.96	0.05296
1.075	63.51	25.21	-0.02238
5.23	43.5	20.27	0.7167
13.91	43.19	20.19	-0.7237

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-188.3615	6	388.7231
A2	-183.667	10	387.3339
A3	-186.1132	7	386.2263
R	-203.3606	2	410.7211
4	-186.4844	5	382.9687

Additive constant for all log-likelihoods = -45.95. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	39.39	8	< 0.0001
Test 2	9.389	4	0.05208
Test 3	4.892	3	0.1798
Test 6a	0.7424	2	0.6899

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

```
  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

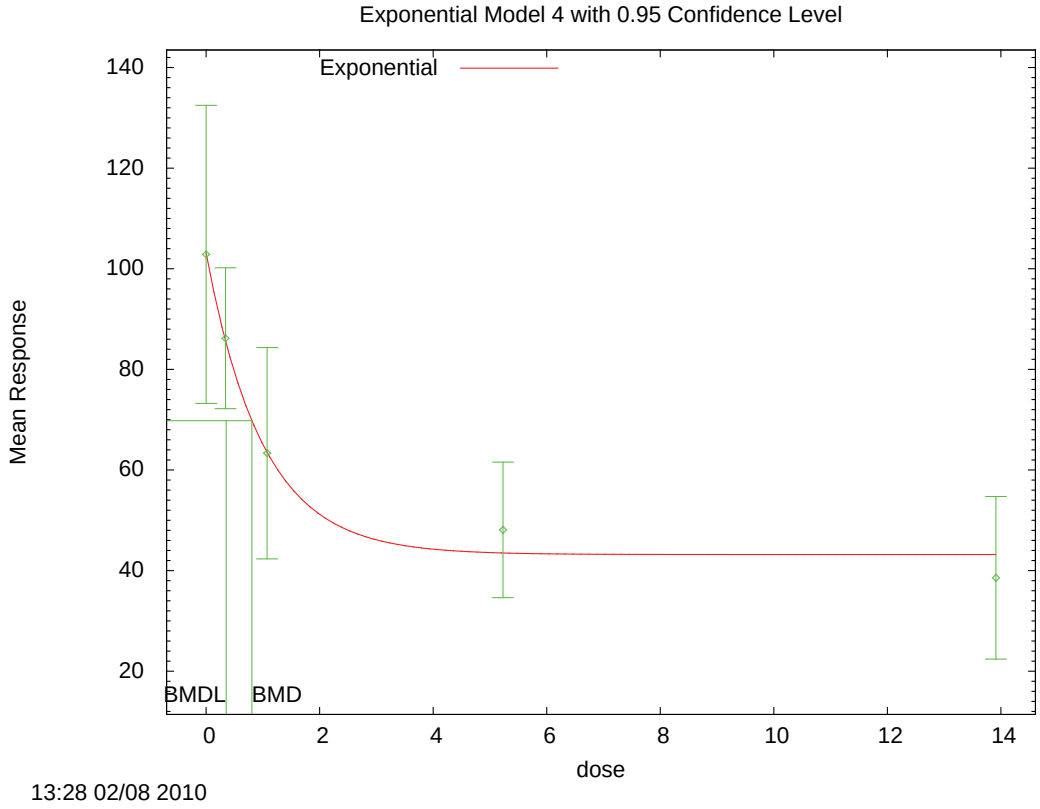
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =     0.806817

              BMDL =     0.354366
```

G.2.46.3. *Figure for Selected Model: Exponential (M4)*



G.2.47. Smialowicz et al. (2008): PFC per 10^6 Cells

G.2.47.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	3	0.101	901.897	8.343E+00	5.064E+00	
Exponential (M3)	3	0.101	901.897	8.343E+00	5.064E+00	power hit bound (*d* = 1)
Exponential (M4)	2	0.044	903.897	8.325E+00	1.465E+00	
Exponential (M5)	2	0.044	903.897	8.325E+00	1.465E+00	power hit bound (*d* = 1)
Hill	2	0.063	903.192	3.669E+00	6.970E−01	*n* lower bound hit (*n* = 1)
Linear	3	0.048	903.585	1.373E+01	1.053E+01	
Polynomial, 4-degree	3	0.048	903.585	1.374E+01	1.053E+01	
Power	3	0.048	903.585	1.373E+01	1.053E+01	power bound hit (power = 1)
Hill, unrestricted	1	0.213	901.219	1.928E+00	2.208E−01	unrestricted (*n* = 0.35)
Power, unrestricted[b]	**2**	**0.481**	**899.130**	**1.902E+00**	**2.158E−01**	**unrestricted (power = 0.333)**

[a] Constant variance model selected (p = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.47.2. *Output for Selected Model: Power, Unrestricted*

Smialowicz et al. (2008): PFC per 10^6 Cells

```
 ========================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\60_Smial_2008_PFCcells_PwrCV_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\60_Smial_2008_PFCcells_PwrCV_U_1.plt
                                          Mon Feb 08 13:29:38 2010
 ========================================================================

 Anti Response to SRBCs, PFC per 10to6 cells, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is not restricted
   A constant variance model is fit

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	232385	
rho =	0	Specified
control =	1491	
slope =	-491.716	
power =	0.288021	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	control	slope	power
alpha	1	-3.4e-009	1.8e-009	-1.2e-010
control	-3.4e-009	1	-0.82	-0.65
slope	1.8e-009	-0.82	1	0.94
power	-1.2e-010	-0.65	0.94	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	219793	37974.5	145365	294222
control	1470.48	123.73	1227.98	1712.99
slope	-378.406	157.002	-686.125	-70.6872
power	0.333124	0.113501	0.110666	0.555581

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	15	1.49e+003	1.47e+003	716	469	0.169
0.438	14	1.13e+003	1.18e+003	171	469	-0.431
2.464	15	945	959	516	469	-0.12
13.4	15	677	572	465	469	0.867

31.65	8	161	274	117	469	-0.684

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-444.832859	6	901.665718
A2	-425.402825	10	870.805651
A3	-444.832859	6	901.665718
fitted	-445.564823	4	899.129647
R	-463.753685	2	931.507371

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	76.7017	8	<.0001
Test 2	38.8601	4	<.0001
Test 3	38.8601	4	<.0001
Test 4	1.46393	2	0.481

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. Consider running a non-homogeneous variance model

```
The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =             1

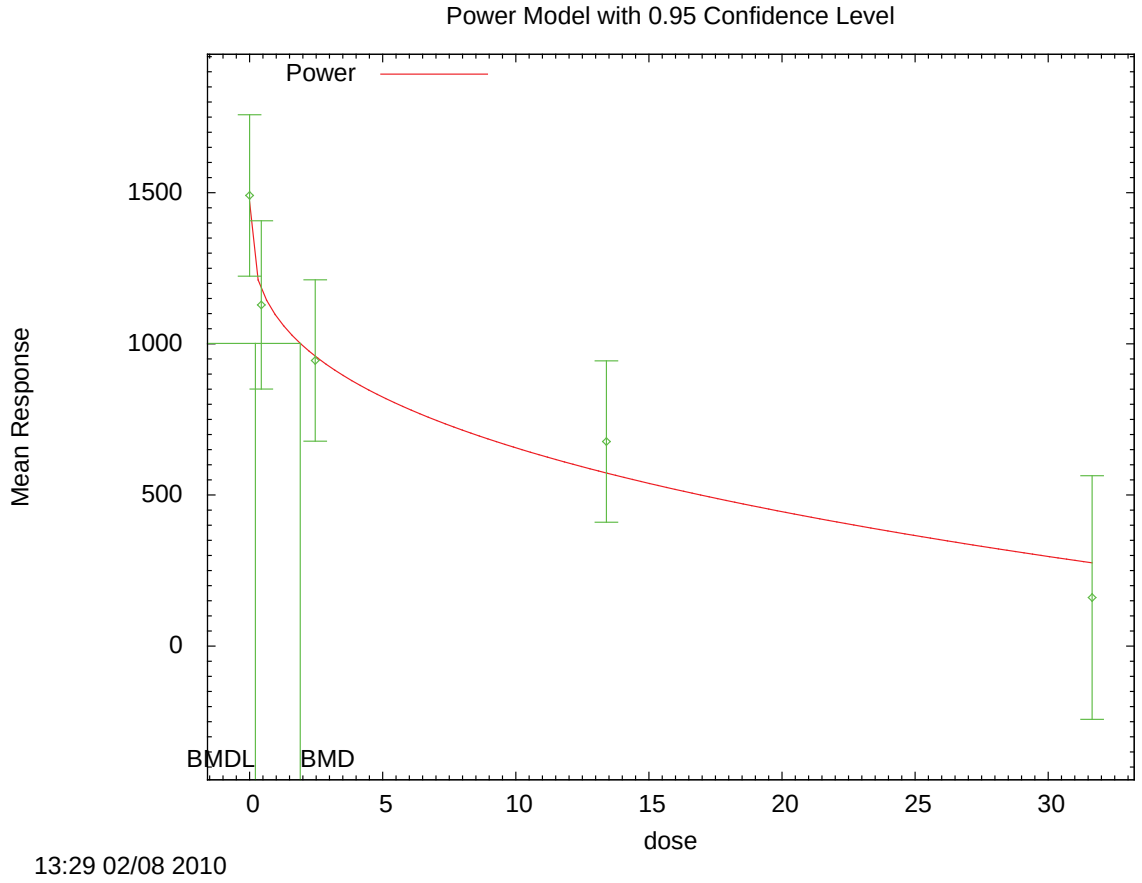
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 1.90249


            BMDL = 0.215843
```

G.2.47.3. *Figure for Selected Model: Power, Unrestricted*



G.2.48. Smialowicz et al. (2008): PFC per Spleen

G.2.48.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	3	0.124	377.565	1.334E+01	8.593E+00	
Exponential (M3)	2	0.069	379.138	1.536E+01	8.895E+00	
Exponential (M4)	3	0.124	377.565	1.334E+01	8.593E+00	
Exponential (M5)	1	0.021	381.138	1.536E+01	8.895E+00	
Hill	2	0.116	378.108	1.568E+01	error	*n* lower bound hit (*n* = 1)
Linear	3	0.126	377.522	2.055E+01	1.624E+01	
Polynomial, 4-degree	3	0.126	377.522	2.055E+01	1.624E+01	
Power	3	0.126	377.522	2.055E+01	1.624E+01	power bound hit (power = 1)
Hill, unrestricted	1	0.103	378.463	1.202E+01	error	unrestricted (*n* = 0.544)
Power, unrestricted[b]	**2**	**0.270**	**376.420**	**1.187E+01**	**3.762E+00**	**unrestricted (power = 0.531)**

[a] Nonconstant variance model selected (*p* = 0.0011).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.48.2. *Output for Selected Model: Power, Unrestricted*

Smialowicz et al. (2008): PFC per Spleen

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\61_Smial_2008_PFCspleen_Pwr_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\61_Smial_2008_PFCspleen_Pwr_U_1.plt
                                          Mon Feb 08 13:30:16 2010
 ======================================================================

 Anti Response to SRBCs - PFC x 10 to the 4 per spleen, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

lalpha =	4.76607
rho =	0
control =	27.8
slope =	-9.21898
power =	0.286443

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.98	0.25	-0.28	-0.22
rho	-0.98	1	-0.3	0.28	0.22
control	0.25	-0.3	1	-0.83	-0.74
slope	-0.28	0.28	-0.83	1	0.99
power	-0.22	0.22	-0.74	0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	0.746922	1.02058	-1.25337	2.74721
rho	1.36826	0.355827	0.67085	2.06567
control	25.3816	2.96691	19.5666	31.1967
slope	-3.5662	2.52558	-8.51626	1.38385
power	0.531216	0.175728	0.186796	0.875637

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	15	27.8	25.4	13.4	13.3	0.706
0.438	14	21	23.1	13.6	12.4	-0.626
2.464	15	17.6	19.6	9.4	11.1	-0.704
13.4	15	12.6	11.2	8.7	7.6	0.702
31.65	8	3	3.03	3.1	3.1	-0.0313

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-190.565019	6	393.130038
A2	-181.476284	10	382.952569
A3	-181.900030	7	377.800059
fitted	-183.210137	5	376.420274
R	-204.636496	2	413.272993

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.3204	8	<.0001
Test 2	18.1775	4	0.001139
Test 3	0.84749	3	0.8381
Test 4	2.62021	2	0.2698

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

```
The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


                Benchmark Dose Computation

Specified effect =             1

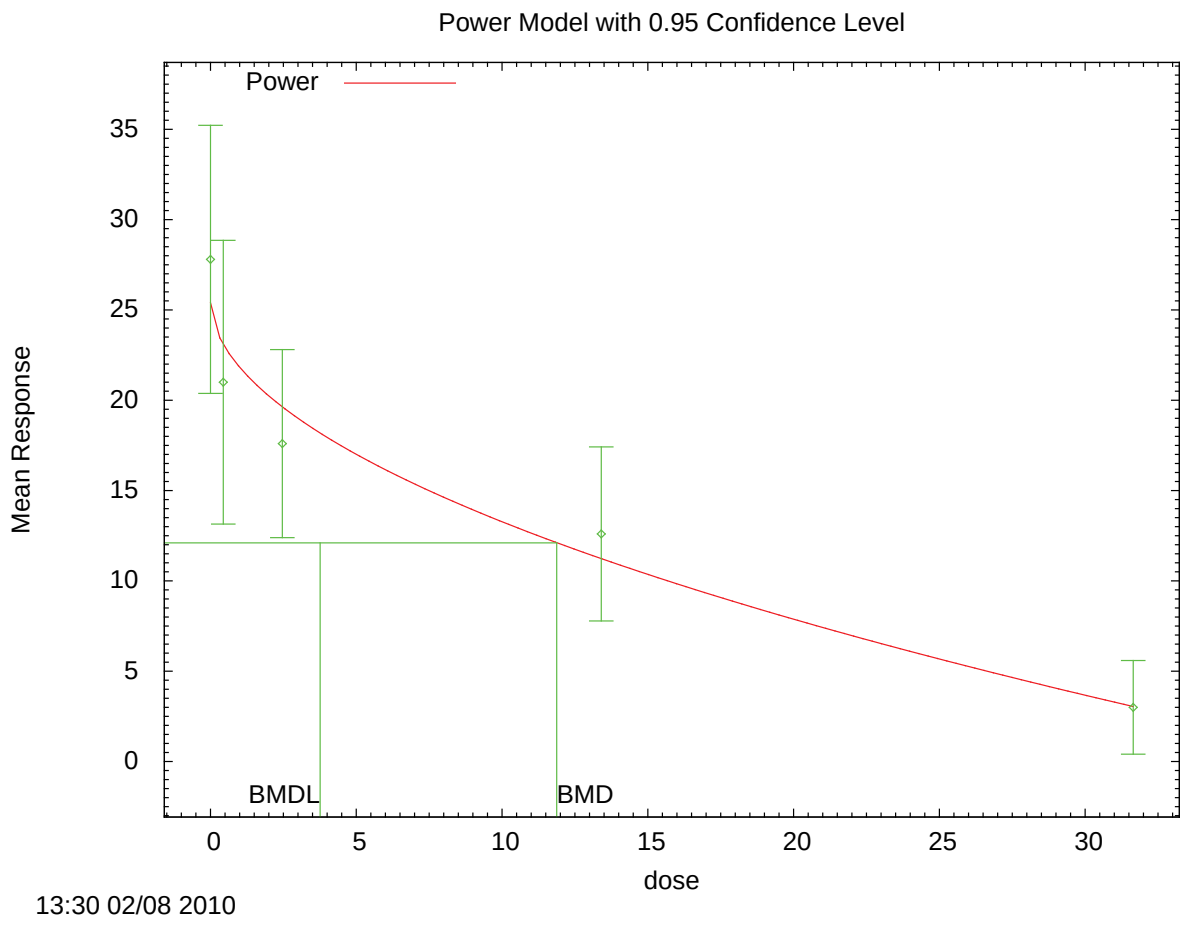
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 11.8748


            BMDL = 3.76161
```

G.2.48.3. *Figure for Selected Model: Power, Unrestricted*



G.2.49. Smith et al. (1976): Cleft Palate in Pups

G.2.49.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	3	0.4216	69.75	3.242E+01	1.123E+01	
Logistic	4	0.5620	68.48	4.592E+01	3.437E+01	
Log-logistic [a]	**3**	**0.4218**	**69.79**	**3.525E+01**	**1.064E+01**	
Log-probit	3	0.4667	69.96	3.854E+01	1.903E+01	
Multistage, 5th degree	3	0.4490	69.41	2.504E+01	1.165E+01	
Probit	4	0.6133	67.98	4.096E+01	3.113E+01	
Weibull	3	0.4340	69.64	3.104E+01	1.136E+01	
Gamma, unrestricted	3	0.4216	69.75	3.242E+01	8.310E+00	
Log-logistic, unrestricted	3	0.4218	69.79	3.525E+01	1.064E+01	
Log-probit, unrestricted	3	0.4134	69.89	3.806E+01	1.086E+01	
Weibull, unrestricted	3	0.4339	69.64	3.104E+01	9.231E+00	

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.49.2. *Output for Selected Model: Log-Logistic*

```
=====================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File:
C:\USEPA\BMDS21\1a\76_Smith_1976_cleft_palate_b_LogLogistic_1.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\1a\76_Smith_1976_cleft_palate_b_LogLogistic_1.plt
                                          Fri Sep 02 08:12:55 2011
 ====================================================================

 Table 3 cleft palate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model
```

Default Initial Parameter Values

background =	0
intercept =	-4.88569
slope =	1

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.22	0.21
intercept	-0.22	1	-0.99
slope	0.21	-0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0259253	*	*	*
intercept	-10.1275	*	*	*
slope	2.22613	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-29.9486	6			
Fitted model	-31.8949	3	3.89258	3	0.2733
Reduced model	-52.2767	1	44.6562	5	<.0001

AIC: 69.7899

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0259	0.881	0.000	34	-0.951
0.1242	0.0259	1.063	2.000	41	0.921
1.0125	0.0260	0.493	0.000	19	-0.712
7.1100	0.0290	0.493	1.000	17	0.733
50.5906	0.2197	4.175	4.000	19	-0.097
138.0663	0.7067	9.894	10.000	14	0.062

```
 Chi^2 = 2.81      d.f. = 3        P-value = 0.4218

   Benchmark Dose Computation

Specified effect =            0.1

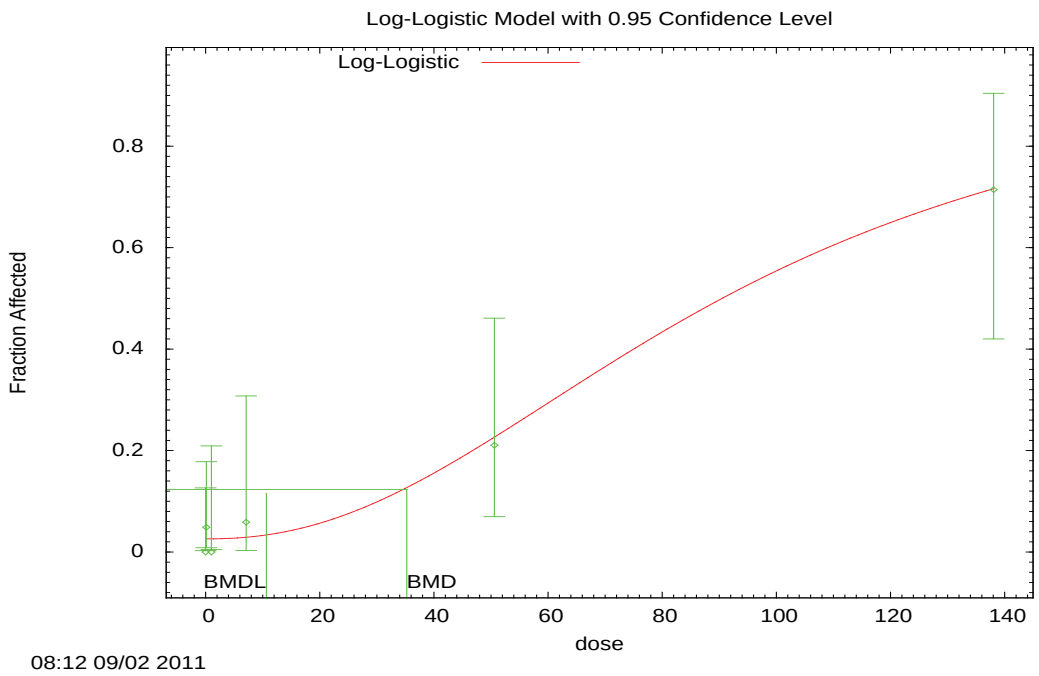
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        35.2466

            BMDL =        10.6443
```

G.2.49.3. *Figure for Selected Model: Log-Logistic*



G.2.50. Sparschu et al. (1976): Fetal Body Weight, Male

G.2.50.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	0.0002	-247.04	6.844E+01	4.399E+01	
Exponential (M3)	3	0.0002	-247.04	6.844E+01	4.399E+01	
Exponential (M4)	2	0.0001	-246.68	6.436E+01	3.808E+01	
Exponential (M5) [b]	**1**	**<0.0001**	**-246.18**	**5.736E+01**	**1.685E+01**	
Hill	1	<.0001	-246.76	5.421E+01	error	
Linear	3	0.0001	-246.33	7.217E+01	4.697E+01	
Polynomial, 3-degree	0	NA	-151.65	6.931E+01	2.162E+01	
Power	3	0.0001	-246.33	7.217E+01	4.697E+01	
Hill, unrestricted	1	<.0001	-246.76	5.421E+01	error	
Power, unrestricted	2	<.0001	-244.93	7.132E+01	4.420E+01	

[a] Modeled variance model presented ($p < 0.0001$); variance not appropriately captured (*p*-test 3 = 0.008).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.50.2. *Output for Selected Model: exponential (M5)*

```
=====================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File:
C:\USEPA\BMDS21\1a\74_Sparschu_1971_pup_bw_male_b_Exp_1.(d)
        Gnuplot Plotting File:
                                          Thu Sep 01 14:59:46 2011
 ====================================================================

 Table 4 males
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 5
```

Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 5
lnalpha	-4.28192
rho	1.66816
a	4.347
b	0.0041752
c	0.312859
d	1

Parameter Estimates

Variable	Model 5
lnalpha	16.8213
rho	-13.5946
a	4.04383
b	0.0163183
c	0.86046
d	1.40496

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	117	4.03	0.37
5.09	55	4.14	0.26
16.28	66	3.85	0.35
52.87	39	3.86	0.61
188.3	3	2.72	0.25

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	4.044	0.3374	-0.4433
5.09	4.027	0.3471	2.415
16.28	3.963	0.3873	-2.363
52.87	3.73	0.5844	1.39
188.3	3.484	0.929	-1.424

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	126.4055	6	-240.8109
A2	145.7666	10	-271.5331
A3	137.4206	7	-260.8413
R	101.5293	2	-199.0587
5	129.0908	6	-246.1816

Additive constant for all log-likelihoods = -257.3. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 7a: Does Model 5 fit the data? (A3 vs 5)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	88.47	8	< 0.0001
Test 2	38.72	4	< 0.0001
Test 3	16.69	3	0.0008177
Test 7a	16.66	1	< 0.0001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

```
The p-value for Test 3 is less than .1.  You may want to
consider a different variance model.

The p-value for Test 7a is less than .1.  Model 5 may not adequately
describe the data; you may want to consider another model.


Benchmark Dose Computations:

Specified Effect = 1.000000

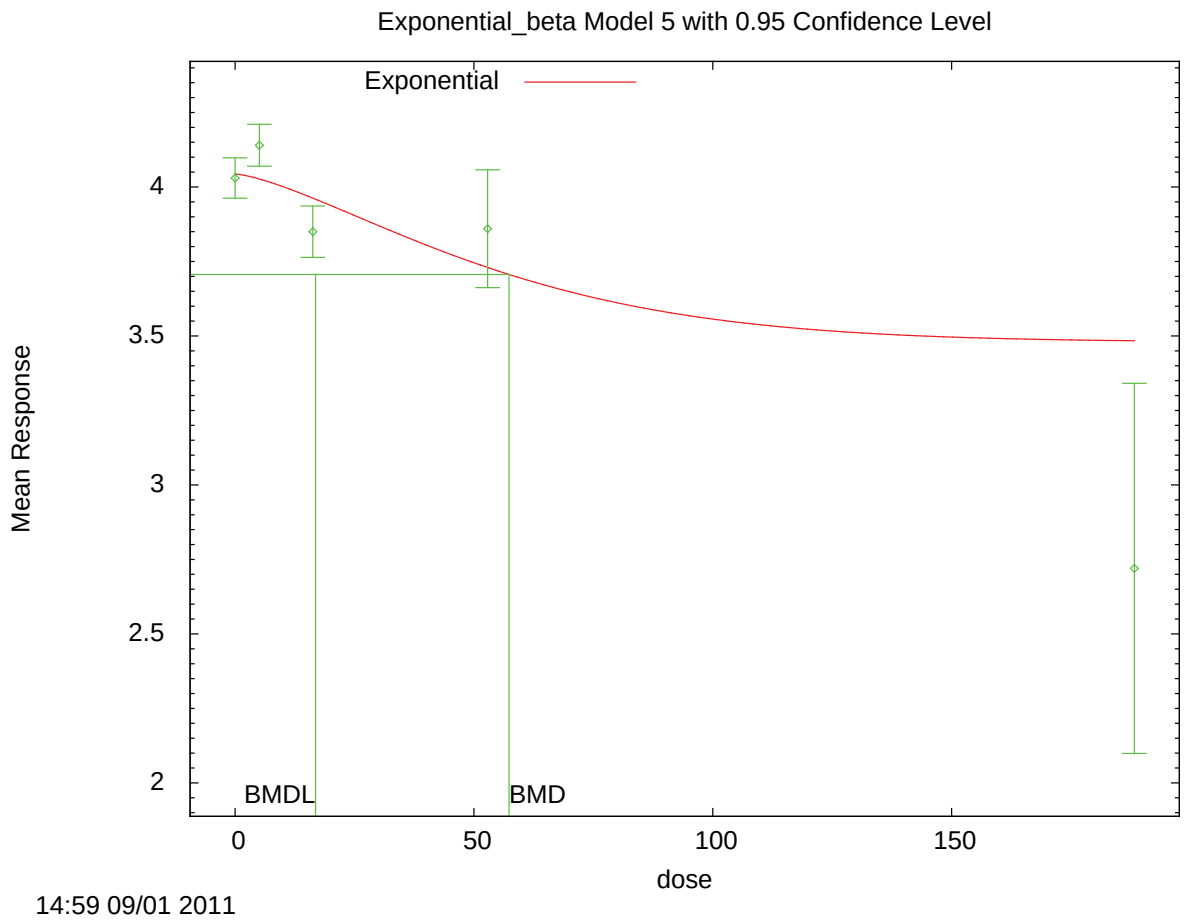
       Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

             BMD =      57.3555

            BMDL =      16.8535
```

G.2.50.3. *Figure for Selected Model: Exponential (M5)*



G.2.51. Sparschu et al. (1971): Fetal Body Weight, Female

G.2.51.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2) [b]	**3**	**0.0340**	**-229.963**	**1.027E+02**	**6.523E+01**	
Exponential (M3)	2	0.0025	-224.657	1.713E+02	5.467E+01	
Exponential (M4)	2	0.0146	-228.182	1.044E+02	6.131E+01	
Exponential (M5)	1	0.0037	-226.196	1.037E+02	6.028E+01	
Hill	1	0.0037	-226.226	1.044E+02	6.055E+01	
Linear	3	0.0315	-229.794	1.035E+02	6.725E+01	
Polynomial, 3-degree	3	0.0315	-229.794	1.035E+02	6.725E+01	
Power	2	0.0025	-224.657	1.746E+02	5.742E+01	
Hill, unrestricted	1	0.0037	-226.226	1.044E+02	6.055E+01	
Power, unrestricted	2	0.0136	-228.035	1.054E+02	6.491E+01	

[a] Modeled variance model presented (p = 0.001)); variance not appropriately captured (p-test 3 = 0.005).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.51.2. *Output for Selected Model: Exponential (M2)*

```
=====================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File:
C:\USEPA\BMDS21\1a\75_Sparschu_1971_pup_bw_fm_b_Exp_1.(d)
        Gnuplot Plotting File:
                                          Thu Sep 01 15:03:28 2011
 ====================================================================

 Table 4 females
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 5
```

Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 2
lnalpha	-7.22746
rho	4.02075
a	3.74918
b	0.00140938
c	0
d	1

Parameter Estimates

Variable	Model 2
lnalpha	11.1109
rho	-9.58142
a	3.90142
b	0.000999148
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	129	3.89	0.39
5.09	60	3.98	0.35
16.28	58	3.71	0.37
52.87	54	3.78	0.54
188.3	4	2.69	0.19

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	3.901	0.3805	-0.3408
5.09	3.882	0.3899	1.955
16.28	3.838	0.4113	-2.379
52.87	3.701	0.49	1.189
188.3	3.232	0.9369	-1.158

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	123.0729	6	-234.1458
A2	132.131	10	-244.262
A3	123.3163	7	-232.6326
R	100.5646	2	-197.1292
2	118.9813	4	-229.9626

Additive constant for all log-likelihoods = -280.3. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	63.13	8	< 0.0001
Test 2	18.12	4	0.001171
Test 3	17.63	3	0.0005244
Test 4	8.67	3	0.03402

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

```
The p-value for Test 3 is less than .1.  You may want to
consider a different variance model.

The p-value for Test 4 is less than .1.  Model 2 may not adequately
describe the data; you may want to consider another model.


Benchmark Dose Computations:

Specified Effect = 1.000000

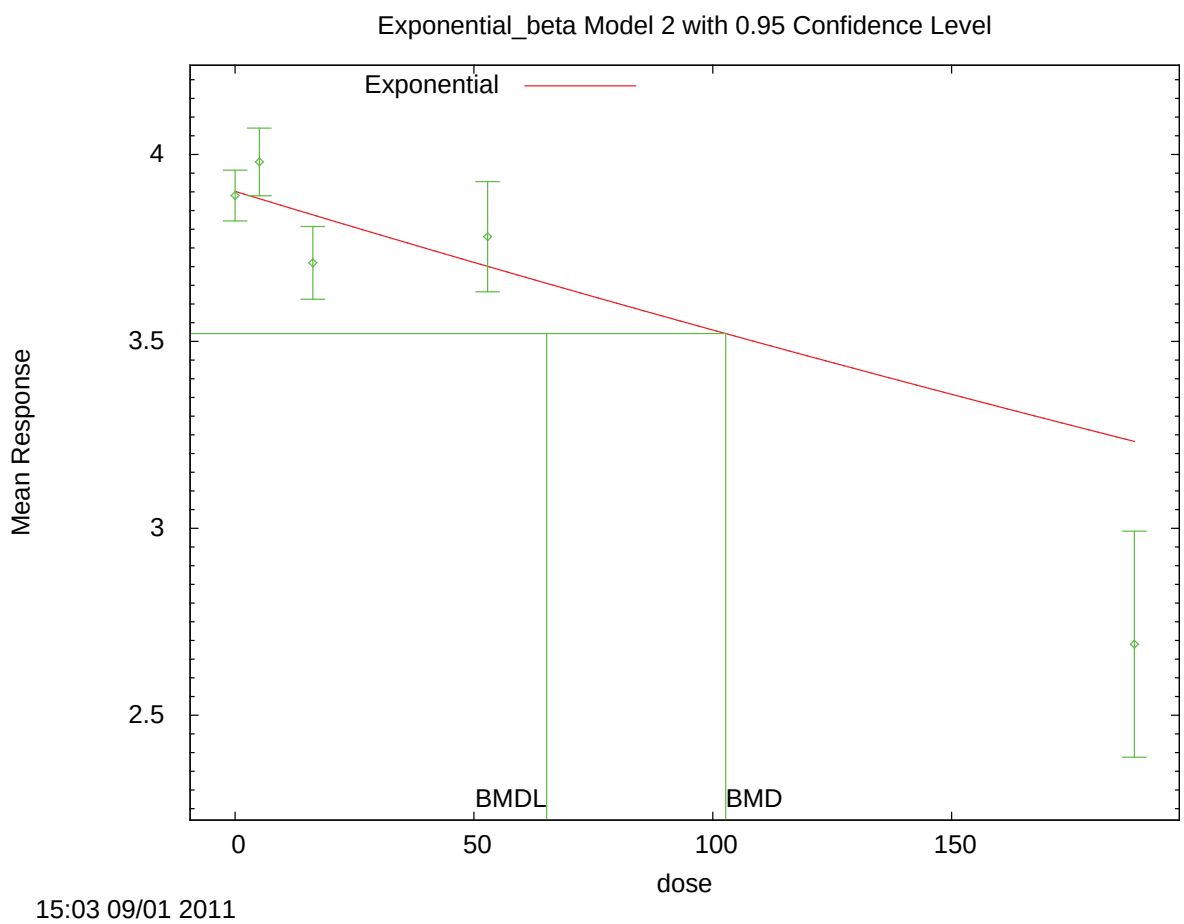
       Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

             BMD =      102.699

            BMDL =      65.2254
```

G.2.51.3. *Figure for Selected Model: Exponential (M2)*



G.2.52. Toth et al. (1979): Amyloidosis

G.2.52.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	2	0.040	149.120	1.965E+01	1.283E+01	power bound hit (power = 1)
Logistic	2	0.019	151.340	3.701E+01	2.858E+01	
Log-logistic[a]	**2**	**0.053**	**148.269**	**1.503E+01**	**8.747E+00**	**slope bound hit (slope = 1)**
Log-probit	2	0.009	152.855	3.782E+01	2.502E+01	slope bound hit (slope = 1)
Multistage, 3-degree	2	0.040	149.120	1.965E+01	1.283E+01	final ß = 0
Probit	2	0.021	151.115	3.467E+01	2.657E+01	
Weibull	2	0.040	149.120	1.965E+01	1.283E+01	power bound hit (power = 1)
Gamma, unrestricted	2	0.959	140.119	4.349E−01	2.891E−03	unrestricted (power = 0.254)
Log-logistic, unrestricted[b]	2	0.903	140.240	4.843E−01	5.312E−03	unrestricted (slope = 0.326)
Log-probit, unrestricted	2	0.870	140.315	4.960E−01	7.292E−03	unrestricted (slope = 0.186)
Weibull, unrestricted	2	0.933	140.174	4.641E−01	4.069E−03	unrestricted (power = 0.289)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.2.52.2. *Output for Selected Model: Log-Logistic*

Toth et al. (1979): Amyloidosis

```
 ========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\62_Toth_1979_Amy1yr_LogLogistic_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\62_Toth_1979_Amy1yr_LogLogistic_1.plt
                                          Mon Feb 08 13:30:54 2010
 ========================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

```
   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =            0
                      intercept =     -4.54593
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.49

 intercept        -0.49            1



                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background        0.0699918            *                *
*
      intercept         -4.90704            *                *
*
          slope                1            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -68.017         4
   Fitted model        -72.1346         2       8.23525      2
0.01628
  Reduced model        -82.0119         1         27.99      3         <.0001
```

AIC: 148.269

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0700	2.660	0.000	38	-1.691
0.5732	0.0739	3.252	5.000	44	1.007
14.2123	0.1584	6.971	10.000	44	1.251
91.2070	0.4446	19.117	17.000	43	-0.650

Chi^2 = 5.86 d.f. = 2 P-value = 0.0534

Benchmark Dose Computation

Specified effect = 0.1

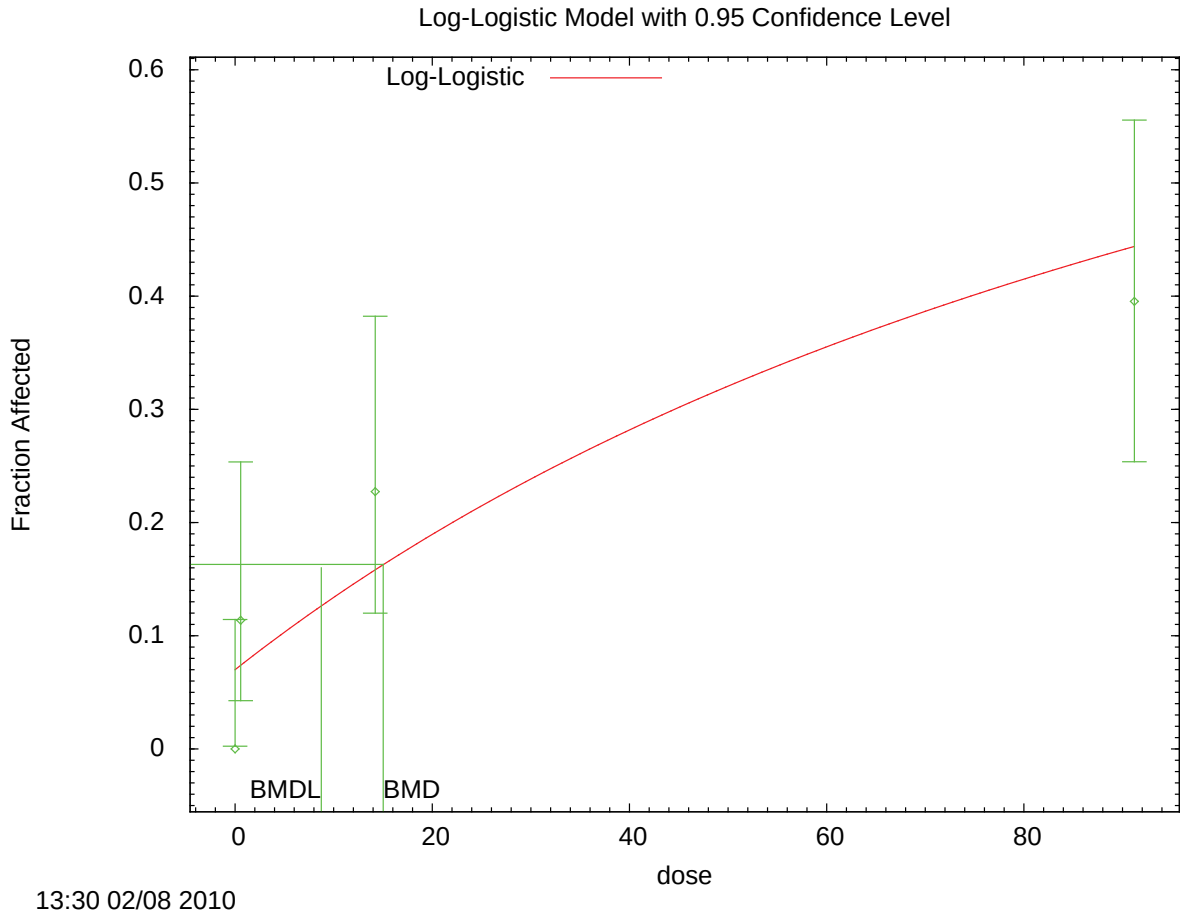
Risk Type = Extra risk

Confidence level = 0.95

BMD = 15.0264

BMDL = 8.74665

G.2.52.3. *Figure for Selected Model: Log-Logistic*



G.2.52.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Toth et al. (1979): Amyloidosis

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\62_Toth_1979_Amy1yr_LogLogistic_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\62_Toth_1979_Amy1yr_LogLogistic_U_1.plt
                                          Mon Feb 08 13:30:54 2010
 ======================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]
```

```
Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =            0
                     intercept =     -1.92722
                         slope =     0.314472


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

              intercept        slope

 intercept            1        -0.84

     slope        -0.84            1



                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background                0            *                *
*
      intercept         -1.96073            *                *
*
          slope         0.326156            *                *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
```

```
     Full model         -68.017         4
   Fitted model        -68.1201         2      0.206341      2
0.902
  Reduced model        -82.0119         1         27.99      3         <.0001

           AIC:          140.24


                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  -----------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          38        0.000
    0.5732     0.1051         4.623     5.000          44        0.186
   14.2123     0.2507        11.029    10.000          44       -0.358
   91.2070     0.3802        16.348    17.000          43        0.205

 Chi^2 = 0.20      d.f. = 2        P-value = 0.9028


   Benchmark Dose Computation

Specified effect =            0.1

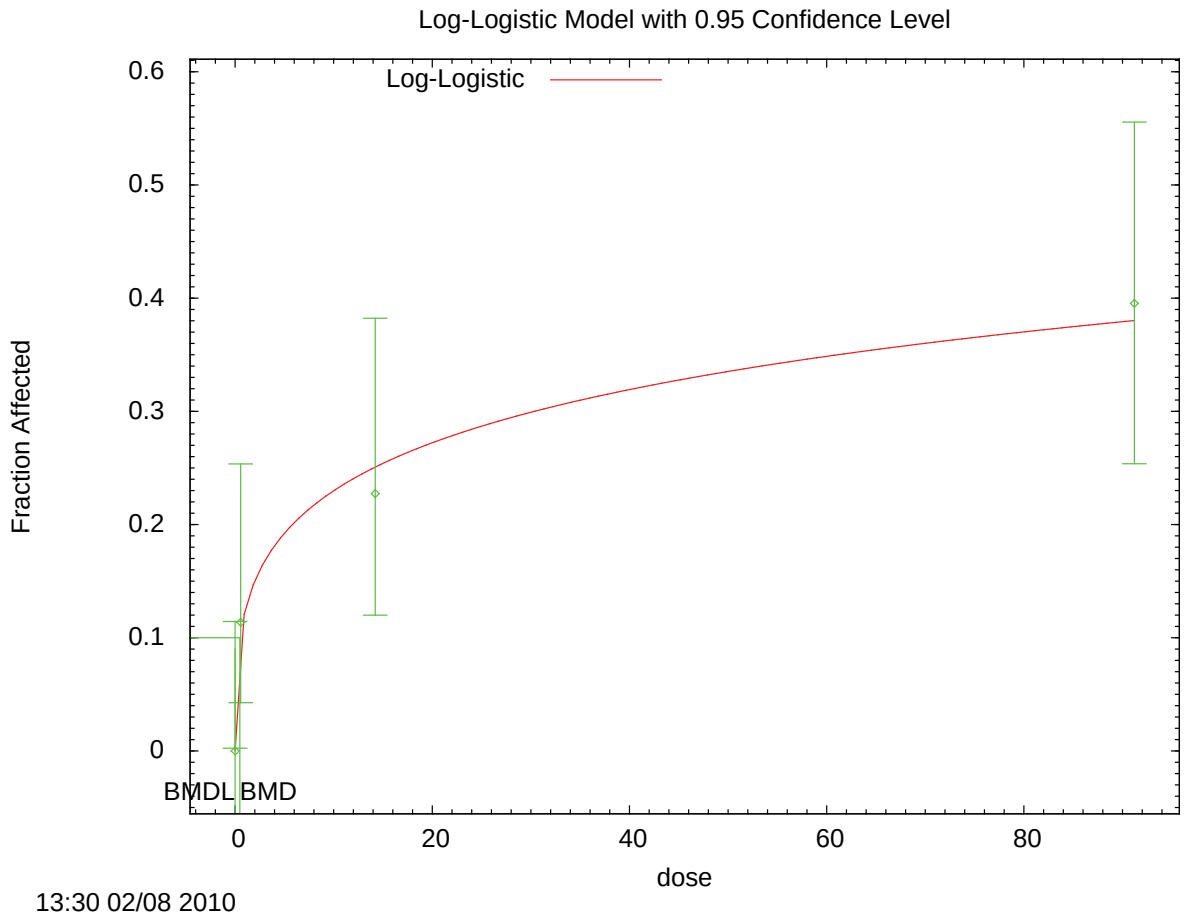
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.484272

            BMDL =     0.00531211
```

G.2.52.5. ***Figure for Additional Model Presented: Log-Logistic, Unrestricted***



G.2.53. Toth et al. (1979): Skin Lesions

G.2.53.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	2	0.032	156.346	1.037E+01	7.470E+00	power bound hit (power = 1)
Logistic	2	0.005	161.421	2.487E+01	1.982E+01	
Log-logistic[a]	**2**	**0.078**	**153.963**	**6.413E+00**	**4.025E+00**	**slope bound hit (slope = 1)**
Log-probit	2	0.003	161.788	1.887E+01	1.280E+01	slope bound hit (slope = 1)
Multistage, 3-degree	2	0.032	156.346	1.037E+01	7.470E+00	final ß = 0
Probit	2	0.006	160.991	2.309E+01	1.858E+01	
Weibull	2	0.032	156.346	1.037E+01	7.470E+00	power bound hit (power = 1)
Gamma, unrestricted	2	0.945	147.148	error	error	unrestricted (power = 0.341)
Log-logistic, unrestricted[b]	2	0.744	147.631	5.969E−01	6.773E−02	unrestricted (slope = 0.48)
Log-probit, unrestricted	2	0.670	147.844	5.939E−01	8.147E−02	unrestricted (slope = 0.279)
Weibull, unrestricted	2	0.866	147.324	5.539E−01	5.181E−02	unrestricted (power = 0.405)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.2.53.2. *Output for Selected Model: Log-Logistic*

Toth et al. (1979): Skin Lesions

```
 ========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\63_Toth_1979_SkinLes_LogLogistic_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\63_Toth_1979_SkinLes_LogLogistic_1.plt
                                          Wed Feb 10 14:47:53 2010
 ========================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

```
   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =            0
                      intercept =     -3.94312
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.43

 intercept        -0.43            1



                                  Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background        0.0564562            *                *
*
      intercept         -4.05558            *                *
*
          slope                1            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -71.5177         4
   Fitted model        -74.9813         2       6.92722      2
0.03132
  Reduced model        -95.8498         1       48.6642      3         <.0001
```

AIC: 153.963

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0565	2.145	0.000	38	-1.508
0.5732	0.0657	2.892	5.000	44	1.282
14.2123	0.2429	10.687	13.000	44	0.813
91.2070	0.6343	27.275	25.000	43	-0.720

Chi^2 = 5.10 d.f. = 2 P-value = 0.0782

Benchmark Dose Computation

Specified effect = 0.1

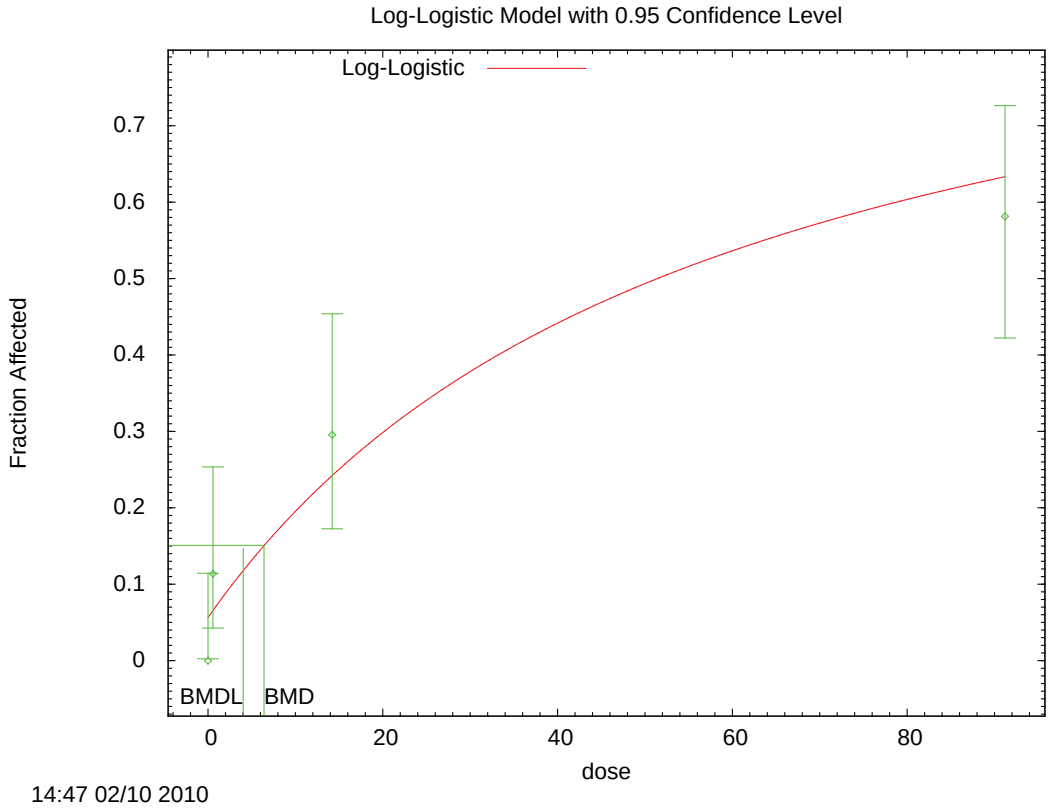
Risk Type = Extra risk

Confidence level = 0.95

BMD = 6.4132

BMDL = 4.0249

G.2.53.3. *Figure for Selected Model: Log-Logistic*



G.2.53.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Toth et al. (1979): Skin Lesions

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\63_Toth_1979_SkinLes_LogLogistic_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\63_Toth_1979_SkinLes_LogLogistic_U_1.plt
                                          Wed Feb 10 14:47:54 2010
 ======================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted
```

```
   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =            0
                      intercept =     -1.87608
                          slope =     0.458888


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

              intercept        slope

 intercept            1        -0.86

     slope        -0.86            1



                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background                0            *                *
*
      intercept         -1.94946            *                *
*
          slope           0.4802            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -71.5177         4
   Fitted model        -71.8153         2       0.59526      2
0.7426
  Reduced model        -95.8498         1       48.6642      3         <.0001
```

AIC: 147.631

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	38	0.000
0.5732	0.0983	4.323	5.000	44	0.343
14.2123	0.3374	14.845	13.000	44	-0.588
91.2070	0.5542	23.832	25.000	43	0.358

Chi^2 = 0.59 d.f. = 2 P-value = 0.7438

Benchmark Dose Computation

Specified effect = 0.1

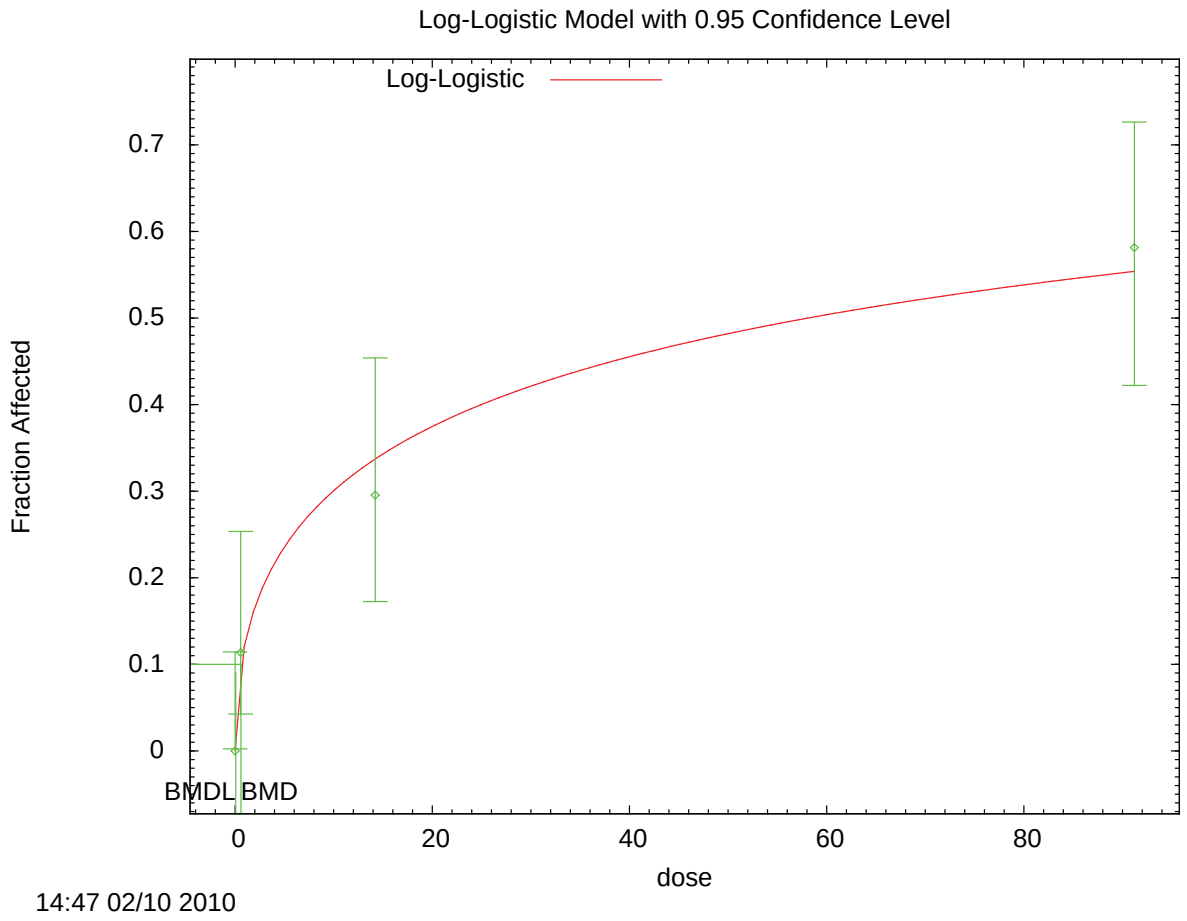
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.596932

BMDL = 0.06773

G.2.53.5. ***Figure for Additional Model Presented: Log-Logistic, Unrestricted***



G.2.54. van Birgelen et al. (1995): Hepatic Retinol

G.2.54.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	4	<0.0001	159.735	7.790E+00	4.150E+00	
Exponential (M3)	4	<0.0001	3,222.700	5.542E+01	error	power hit bound (*d* = 1)
Exponential (M4)[b]	**3**	**<0.001**	**141.454**	**2.488E+01**	**3.363E+00**	
Exponential (M5)	3	<0.001	141.454	2.488E+01	3.363E+00	power hit bound (*d* = 1)
Hill	3	0.239	124.865	5.316E+00	error	*n* lower bound hit (*n* = 1)
Linear	4	<0.0001	176.828	1.877E+02	1.437E+02	
Polynomial, 5-degree	4	<0.0001	176.828	1.877E+02	1.437E+02	
Power	4	<0.0001	176.828	1.877E+02	1.437E+02	power bound hit (power = 1)
Hill, unrestricted	2	0.241	125.495	3.595E+00	error	unrestricted (*n* = 0.763)
Power, unrestricted[c]	3	0.011	131.771	3.802E−01	1.393E−02	unrestricted (power = 0.14)

[a] Nonconstant variance model selected (*p* = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.54.2. *Output for Selected Model: Exponential (M4)*

van Birgelen et al. (1995): Hepatic Retinol

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\65_VanB_1995a_HepRet_Exp_1.(d)
        Gnuplot Plotting File:
                                            Mon Feb 08 13:32:00 2010
 ======================================================================

 Tbl3, hepatic retinol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
```

```
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 4
lnalpha	-1.16065
rho	1.53688
a	15.645
b	0.0254351
c	0.0365247
d	1

Parameter Estimates

Variable	Model 4
lnalpha	-0.92683
rho	1.77262
a	11.5049
b	0.0286598
c	0.0653043
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	14.9	8.768
7.204	8	8.4	3.394
11.76	8	8.2	2.263
18.09	8	5.1	0.8485
86.41	8	2.2	0.8485
250.2	8	0.6	0.5657

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	11.5	5.483	1.751
7.204	9.499	4.627	-0.6719
11.76	8.428	4.161	-0.1552

18.09	7.154	3.599	-1.615
86.41	1.655	0.9832	1.568
250.2	0.7596	0.4931	-0.9155

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-87.1567	7	188.3134
A2	-47.28742	12	118.5748
A3	-55.32422	8	126.6484
R	-109.967	2	223.934
4	-65.72714	5	141.4543

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	125.4	10	< 0.0001
Test 2	79.74	5	< 0.0001
Test 3	16.07	4	0.002922
Test 6a	20.81	3	0.0001155

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model.

Benchmark Dose Computations:

Specified Effect = 1.000000

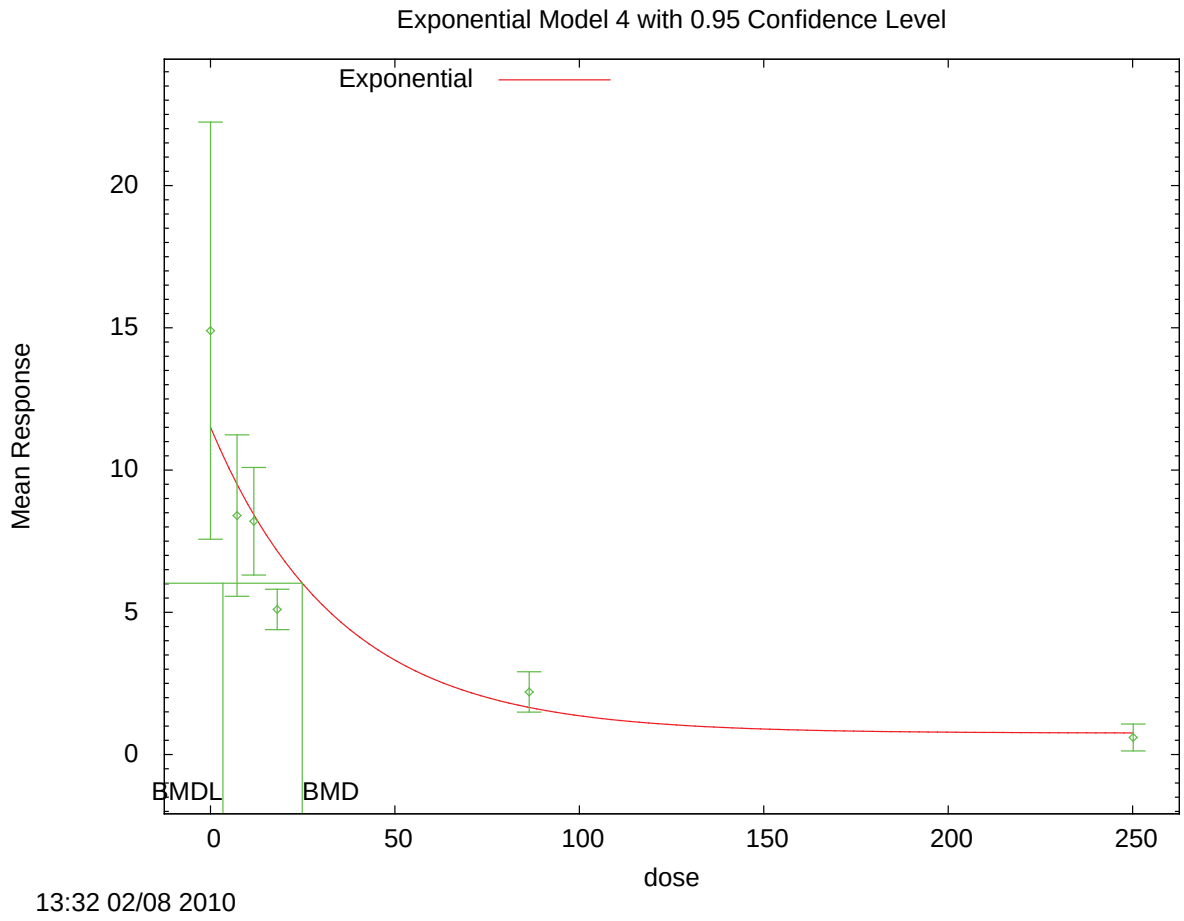
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 24.8811

BMDL = 3.36281

G.2.54.3. *Figure for Selected Model: Exponential (M4)*



G.2.54.4. *Output for Additional Model Presented: Power, Unrestricted*

van Birgelen et al. (1995): Hepatic Retinol

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\65_VanB_1995a_HepRet_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\65_VanB_1995a_HepRet_Pwr_U_1.plt
                                          Mon Feb 08 13:32:03 2010
 ======================================================================

 Tbl3, hepatic retinol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is not restricted
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	2.76506
rho =	0
control =	14.9
slope =	-3.98831
power =	0.231232

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.8	-0.042	0.038	0.063
rho	-0.8	1	-0.089	0.0044	-0.1
control	-0.042	-0.089	1	-0.95	-0.81
slope	0.038	0.0044	-0.95	1	0.95
power	0.063	-0.1	-0.81	0.95	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-0.986251	0.394722	-1.75989	-0.212609
rho	1.67858	0.202896	1.28091	2.07625
control	16.9266	2.23237	12.5513	21.302
slope	-7.51118	2.04379	-11.5169	-3.50543
power	0.139871	0.0269576	0.0870351	0.192707

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

0	8	14.9	16.9	8.77	6.56	-0.874
7.204	8	8.4	7.03	3.39	3.14	1.24
11.76	8	8.2	6.32	2.26	2.87	1.85
18.09	8	5.1	5.67	0.849	2.62	-0.611
86.41	8	2.2	2.91	0.849	1.5	-1.34
250.2	8	0.6	0.666	0.566	0.434	-0.427

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-87.156698	7	188.313395
A2	-47.287416	12	118.574833
A3	-55.324218	8	126.648436
fitted	-60.885746	5	131.771493
R	-109.967018	2	223.934036

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	125.359	10	<.0001
Test 2	79.7386	5	<.0001
Test 3	16.0736	4	0.002922
Test 4	11.1231	3	0.01108

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is less than .1. You may want to consider a different variance model

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

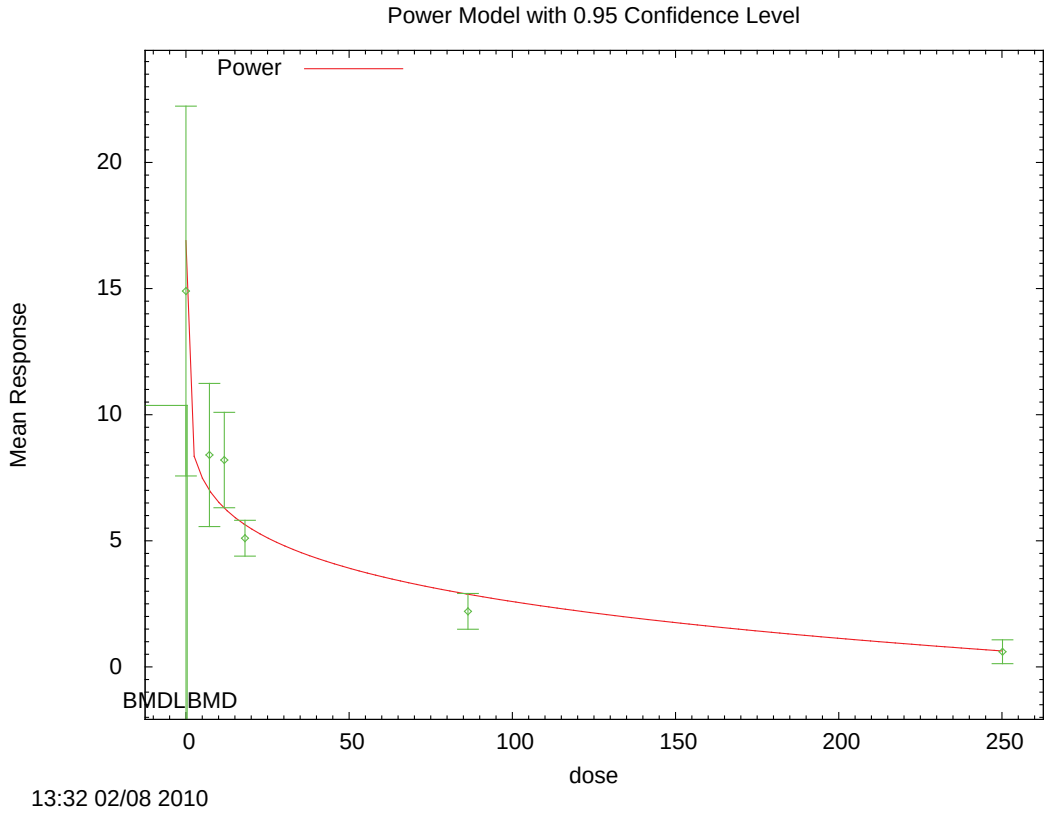
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.380208

BMDL = 0.013927

G.2.54.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.2.55. van Birgelen et al. (1995): Hepatic Retinol Palmitate

G.2.55.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	4	<0.0001	460.282	error	error	
Exponential (M3)	4	<0.0001	460.282	error	error	power hit bound (*d* = 1)
Exponential (M4)[b]	**3**	**<0.0001**	**446.995**	**1.415E+02**	**3.647E+01**	
Exponential (M5)	3	<0.0001	446.995	1.415E+02	3.647E+01	power hit bound (*d* = 1)
Hill	3	0.009	416.233	3.657E+00	error	*n* lower bound hit (*n* = 1)
Linear	4	<0.0001	486.375	3.487E+02	2.412E+02	
Polynomial, 5-degree	0	N/A	584.170	error	5.617E+02	
Power	4	<0.0001	486.375	3.487E+02	2.412E+02	power bound hit (power = 1)
Hill, unrestricted	3	<0.0001	527.310	6.875E−14	6.875E−14	unrestricted (*n* = 0.613)
Power, unrestricted[c]	3	0.239	408.982	5.262E−02	5.889E−05	unrestricted (power = 0.064)

[a] Nonconstant variance model selected (*p* = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.55.2. *Output for Selected Model: Exponential (M4)*

van Birgelen et al. (1995): Hepatic Retinol Palmitate

```
 ========================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\66_VanB_1995a_HepRetPalm_Exp_1.(d)
        Gnuplot Plotting File:
                                            Mon Feb 08 13:32:41 2010
 ========================================================================

 Tbl3, hepatic retinol palmitate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
```

Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	0.284674
rho	1.77158
a	495.6
b	0.0337826
c	0.00576502
d	1

Parameter Estimates

Variable	Model 4
lnalpha	-0.241601
rho	2.03456
a	223.848
b	0.0300737
c	0.0129253
d	1

NC = No Convergence

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	472	271.5
7.204	8	94	67.88
11.76	8	107	76.37
18.09	8	74	39.6
86.41	8	22	22.63
250.2	8	3	2.828

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	223.8	217.8	3.222

7.204	180.8	175.3	-1.401
11.76	158	152.9	-0.9443
18.09	131.1	126.4	-1.278
86.41	19.33	18.03	0.4197
250.2	3.013	2.721	-0.01317

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-250.5548	7	515.1096
A2	-196.7557	12	417.5115
A3	-197.3832	8	410.7663
R	-276.7896	2	557.5793
4	-218.4977	5	446.9954

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	160.1	10	< 0.0001
Test 2	107.6	5	< 0.0001
Test 3	1.255	4	0.869

Test 6a	42.23	3	< 0.0001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model.

Benchmark Dose Computations:

Specified Effect = 1.000000

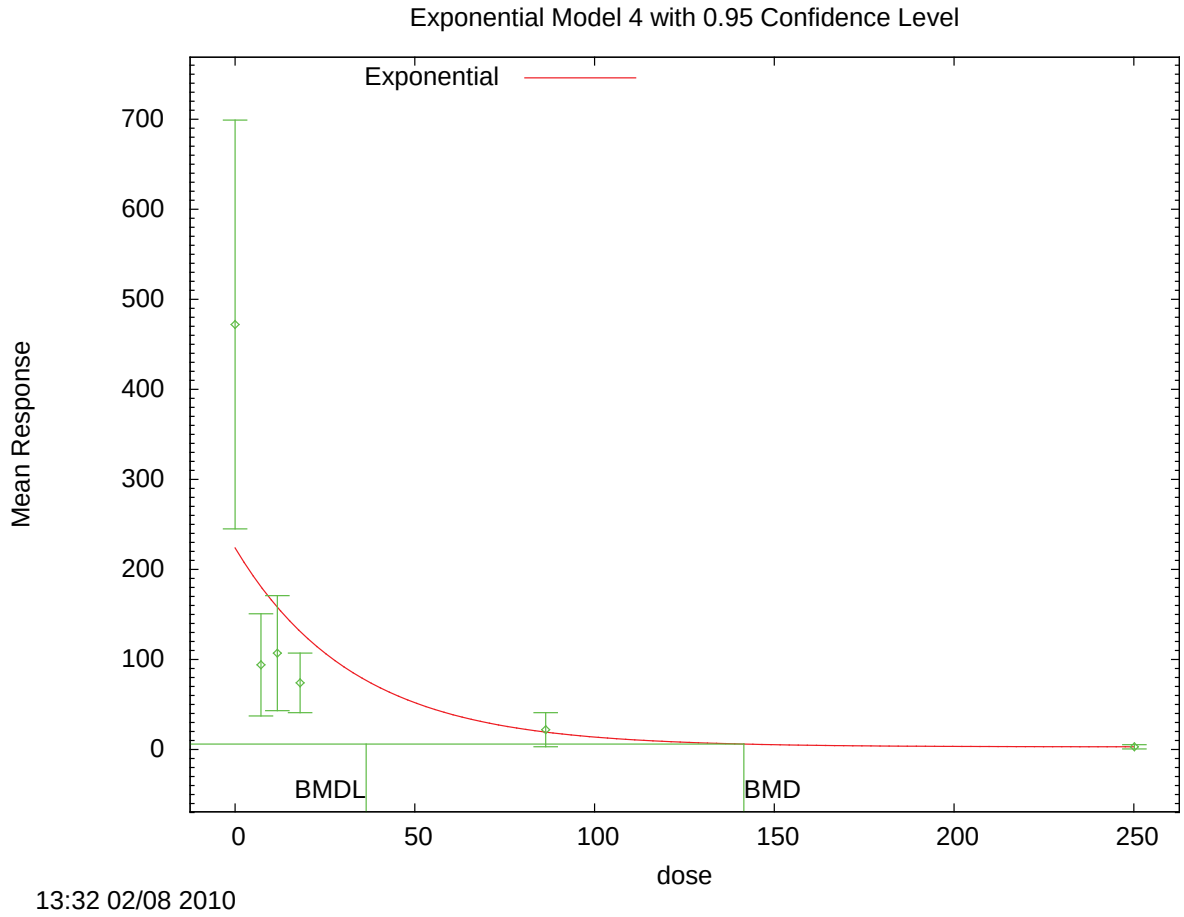
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 141.528

BMDL = 36.4721

G.2.55.3. *Figure for Selected Model: Exponential (M4)*



G.2.55.4. *Output for Additional Model Presented: Power, Unrestricted*

van Birgelen et al. (1995): Hepatic Retinol Palmitate

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\66_VanB_1995a_HepRetPalm_Pwr_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\66_VanB_1995a_HepRetPalm_Pwr_U_1.plt
                                          Mon Feb 08 13:32:47 2010
 ======================================================================

 Tbl3, hepatic retinol palmitate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power
```

```
Dependent variable = Mean
Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                Default Initial Parameter Values
                       lalpha =      9.57332
                          rho =            0
                      control =          472
                        slope =     -320.514
                        power =    0.0711173


        Asymptotic Correlation Matrix of Parameter Estimates

              lalpha          rho      control        slope        power

    lalpha         1        -0.95          0.3        -0.31         -0.3

       rho     -0.95            1        -0.41         0.39         0.29

   control       0.3        -0.41            1        -0.98        -0.82

     slope     -0.31         0.39        -0.98            1          0.9

     power      -0.3         0.29        -0.82          0.9            1


                              Parameter Estimates

                                                                 95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha        0.0640168         0.859472            -1.62052
1.74855
            rho          1.81132         0.197468             1.42429
2.19835
        control           464.29          87.5705             292.655
635.925
          slope         -324.216          83.3327            -487.545
-160.887
          power        0.0639088        0.0139778           0.0365129
0.0913048


     Table of Data and Estimated Values of Interest
```

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	472	464	272	269	0.0812
7.204	8	94	96.5	67.9	64.7	-0.108
11.76	8	107	84.8	76.4	57.6	1.09
18.09	8	74	74.2	39.6	51	-0.00941
86.41	8	22	33.2	22.6	24.6	-1.28
250.2	8	3	2.86	2.83	2.68	0.145

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-250.554817	7	515.109634
A2	-196.755746	12	417.511491
A3	-197.383174	8	410.766347
fitted	-199.490808	5	408.981615
R	-276.789644	2	557.579287

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	160.068	10	<.0001

Test 2	107.598	5	<.0001
Test 3	1.25486	4	0.869
Test 4	4.21527	3	0.2391

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

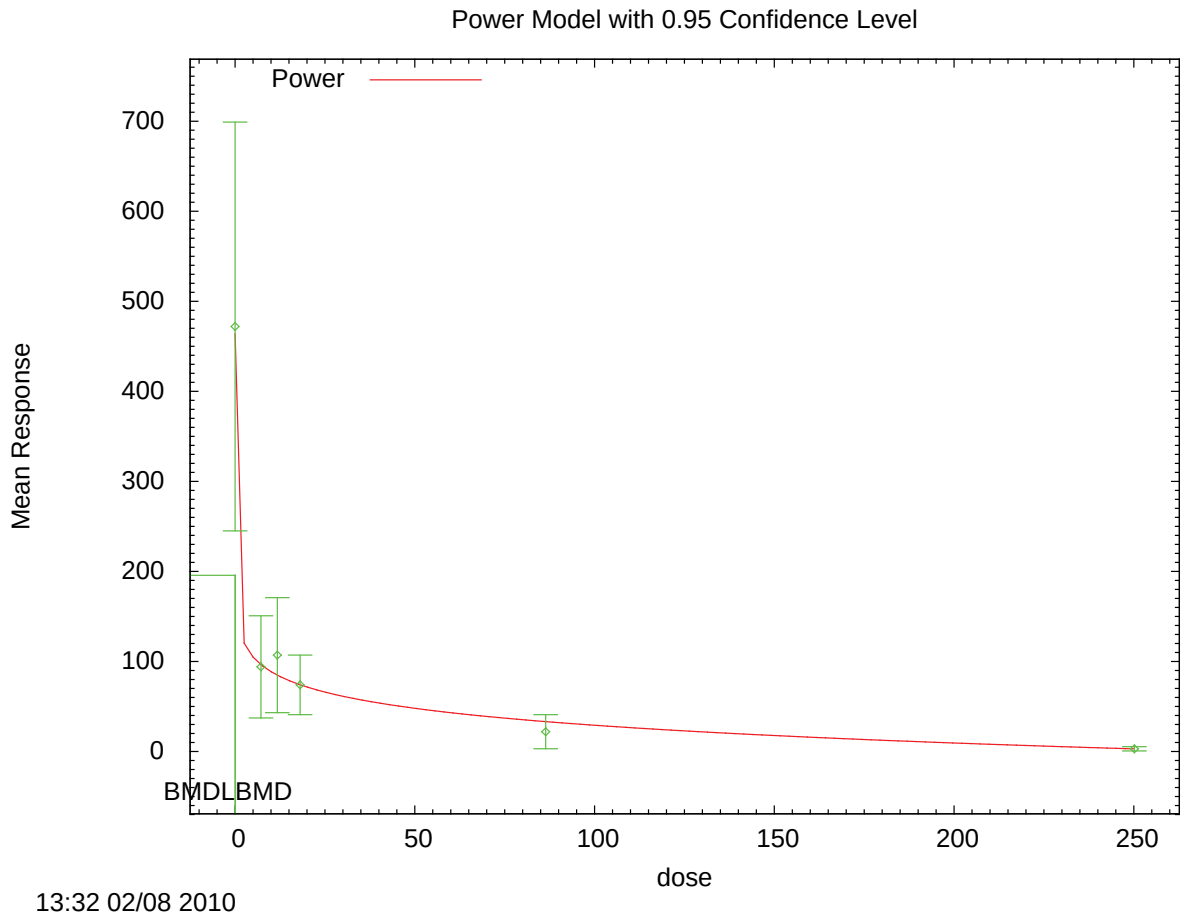
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.0526247

BMDL = 5.88883e-005

G.2.55.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.2.56. White et al. (1986): CH50

G.2.56.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	5	0.002	389.664	1.957E+01	1.261E+01	
Exponential (M3)	5	0.002	389.664	1.957E+01	1.261E+01	power hit bound (*d* = 1)
Exponential (M4)	4	0.001	390.632	1.411E+01	5.177E+00	
Exponential (M5)	4	0.001	390.632	1.411E+01	5.177E+00	power hit bound (*d* = 1)
Hill[b]	**4**	**0.002**	**389.601**	**8.632E+00**	**1.498E+00**	***n* lower bound hit (*n* = 1)**
Linear	5	<0.001	394.446	3.497E+01	2.568E+01	
Polynomial, 6-degree	5	<0.001	394.446	3.497E+01	2.568E+01	
Power	5	<0.001	394.446	3.497E+01	2.568E+01	power bound hit (power = 1)
Hill, unrestricted[c]	3	0.071	381.520	1.481E−01	4.351E−03	unrestricted (*n* = 0.246)
Power, unrestricted	4	0.148	379.265	1.211E−01	1.225E−03	unrestricted (power = 0.227)

[a] Nonconstant variance model selected (*p* = 0.0871).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.56.2. *Output for Selected Model: Hill*

White et al. (1986): CH50

```
 ========================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\71_White_1986_CH50_Hill_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\71_White_1986_CH50_Hill_1.plt
                                          Mon Feb 08 13:35:56 2010
 ========================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 7
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

lalpha =	5.60999
rho =	0
intercept =	91
v =	-74
n =	0.118036
k =	1.094

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-0.99	0.27	0.23	-0.32
rho	-0.99	1	-0.28	-0.24	0.33
intercept	0.27	-0.28	1	0.39	-0.78
v	0.23	-0.24	0.39	1	-0.85
k	-0.32	0.33	-0.78	-0.85	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	4.581	1.66273	1.32211	7.83989
rho	0.31293	0.431616	-0.533022	1.15888
intercept	74.6365	6.33673	62.2167	87.0562
v	-66.2096	14.7876	-95.1928	-37.2264
n	1	NA		
k	20.8286	21.3237	-20.965	62.6223

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	91	74.6	14.1	19.4	2.39
1.094	8	54	71.3	8.49	19.3	-2.54
4.085	8	63	63.8	11.3	18.9	-0.117
7.14	8	56	57.7	25.5	18.6	-0.263
26.81	8	41	37.4	17	17.4	0.589
48.72	8	32	28.3	17	16.7	0.636
90.56	8	17	20.8	17	15.9	-0.678

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-181.340979	8	378.681959
A2	-175.820265	14	379.640529
A3	-181.238690	9	380.477380
fitted	-189.800288	5	389.600575
R	-212.367055	2	428.734109

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	73.0936	12	<.0001

Test 2	11.0414	6	0.0871
Test 3	10.8369	5	0.05471
Test 4	17.1232	4	0.001829

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is less than .1. You may want to consider a different variance model

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

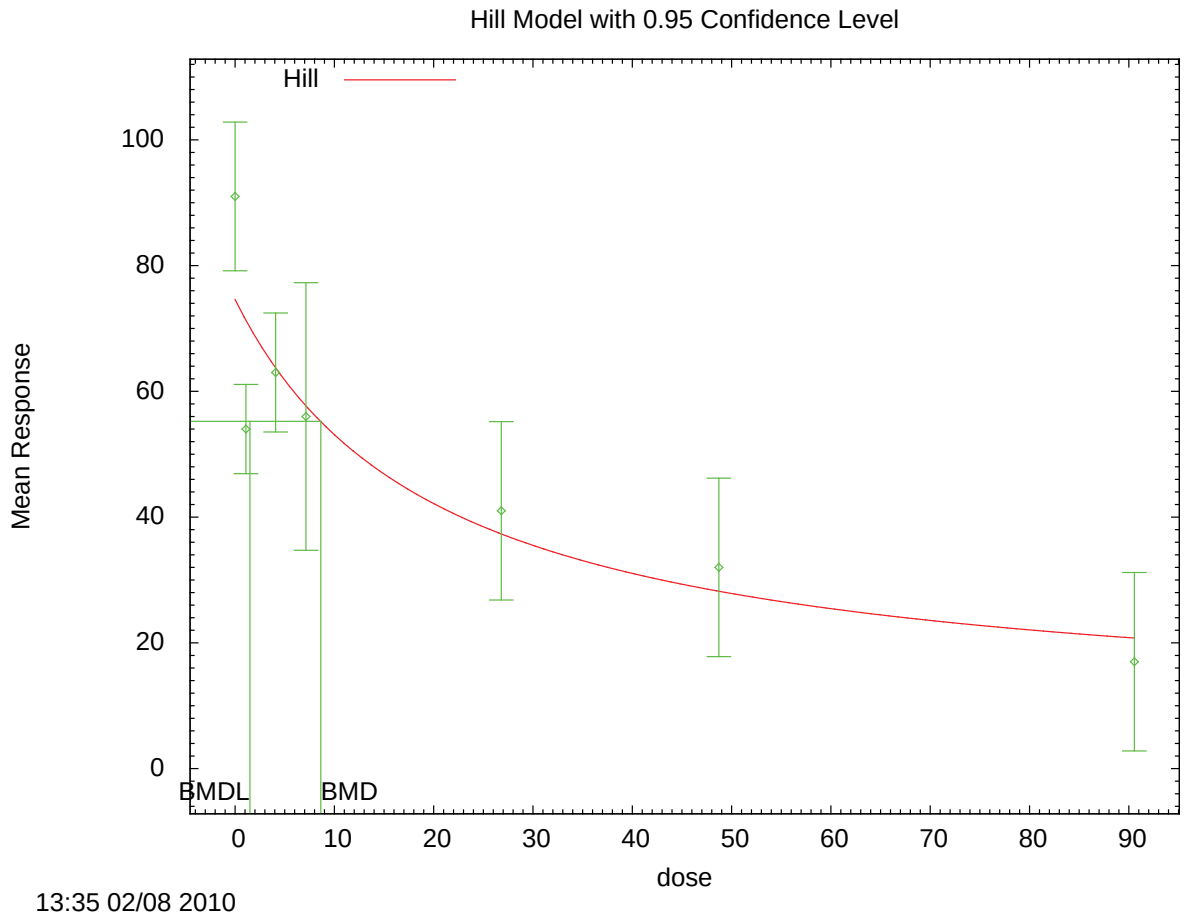
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 8.63239

BMDL = 1.49823

G.2.56.3. *Figure for Selected Model: Hill*



G.2.56.4. *Output for Additional Model Presented: Hill, Unrestricted*

White et al. (1986): CH50

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\71_White_1986_CH50_Hill_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\71_White_1986_CH50_Hill_U_1.plt
                                          Mon Feb 08 13:35:57 2010
 ======================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
```

```
Power parameter is not restricted
The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

Total number of dose groups = 7
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                Default Initial Parameter Values
                       lalpha =      5.60999
                          rho =            0
                    intercept =           91
                            v =          -74
                            n =     0.118036
                            k =        1.094


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n
k

    lalpha            1           -1         0.16         0.19         -0.4
-0.014

       rho           -1            1        -0.16        -0.19          0.4
0.011

 intercept         0.16        -0.16            1         0.15        -0.58
0.015

         v         0.19        -0.19         0.15            1        -0.02
-0.93

         n         -0.4          0.4        -0.58        -0.02            1
-0.35

         k       -0.014        0.011        0.015        -0.93        -0.35
1


                                  Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha          6.54093          2.08879             2.44698
10.6349
            rho        -0.245847         0.541645            -1.30745
0.815757
      intercept          89.6302          5.59428             78.6656
100.595
```

```
              v         -628.486          727.973            -2055.29
798.315
              n         0.246409         0.058636            0.131484
0.361333
              k           493877     2.74838e+006       -4.89284e+006
5.88059e+006


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0     8         91         89.6         14.1         15.1          0.256
1.094     8         54         65.2         8.49         15.8          -2.01
4.085     8         63         56.3         11.3           16           1.17
 7.14     8         56         51.7         25.5         16.2          0.746
26.81     8         41         38.3           17         16.8          0.453
48.72     8         32         30.9           17         17.3          0.175
90.56     8         17         22.3           17           18         -0.831


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -181.340979            8     378.681959
             A2         -175.820265           14     379.640529
             A3         -181.238690            9     380.477380
         fitted         -184.759769            6     381.519538
              R         -212.367055            2     428.734109


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
```

```
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              73.0936         12          <.0001
   Test 2              11.0414          6          0.0871
   Test 3              10.8369          5         0.05471
   Test 4              7.04216          3         0.07057

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =             1

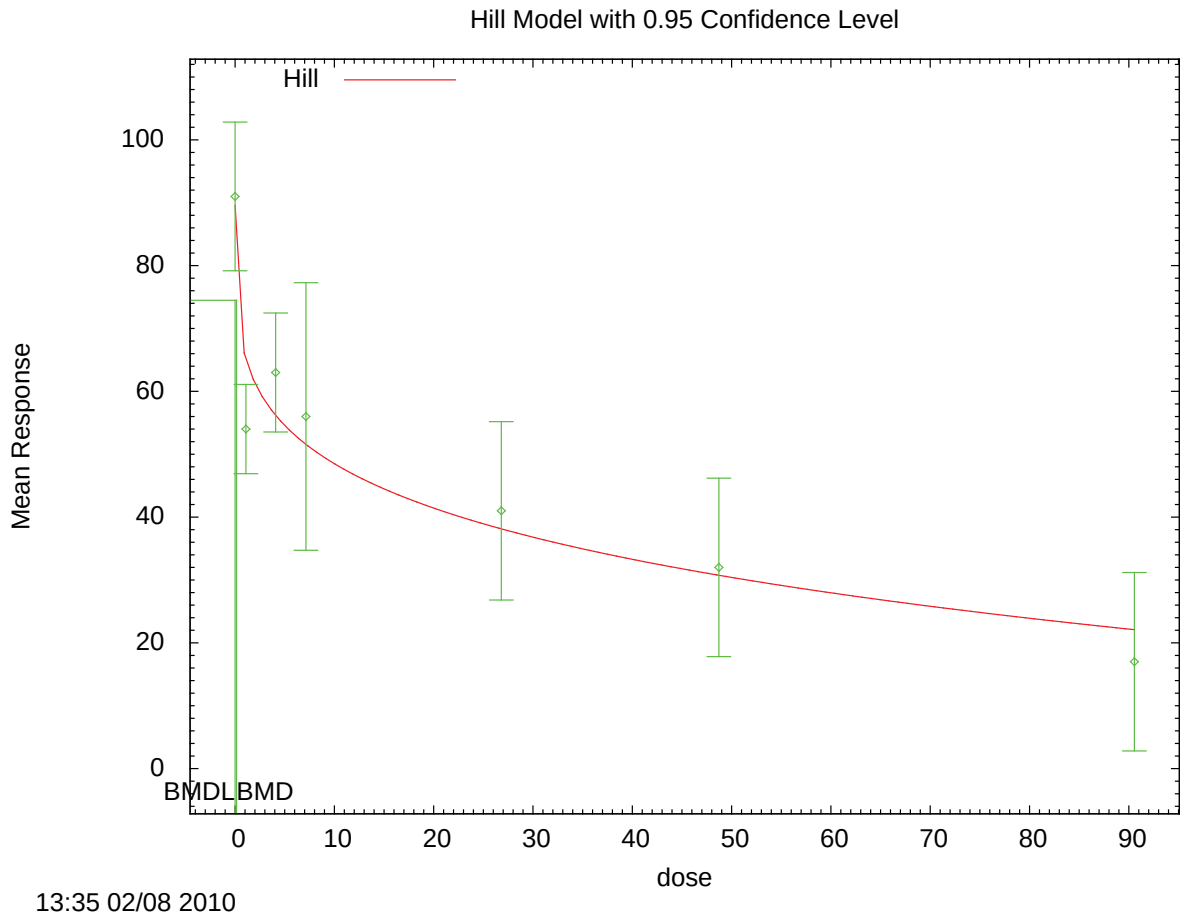
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =       0.148074

            BMDL =    0.00435112
```

G.2.56.5. *Figure for Additional Model Presented: Hill, Unrestricted*



G.3. ADMINISTERED DOSE: BMDS RESULTS

G.3.1. Amin et al. (2000): 0.25% Saccharin Consumed, Female

G.3.1.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear[b]	**1**	**0.358**	**179.702**	**8.816E+01**	**5.890E+01**	
Polynomial, 2-degree	1	0.358	179.702	8.816E+01	5.890E+01	
Power	1	0.358	179.702	8.816E+01	5.890E+01	power bound hit (power = 1)
Power, unrestricted[c]	0	N/A	180.858	7.530E+01	2.537E+01	unrestricted (power = 0.605)

[a] Nonconstant variance model selected (p = 0.0005).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.1.2. *Output for Selected Model: Linear*

Amin et al. (2000): 0.25% Saccharin Consumed, Female

```
 ====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\1_Amin_2000_25_SC_Linear_1.(d)
        Gnuplot Plotting File:  C:\1\1_Amin_2000_25_SC_Linear_1.plt
                                          Tue Feb 16 17:22:16 2010
 ====================================================================

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~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                         lalpha =      5.29482
                            rho =            0
                         beta_0 =      30.8266
                         beta_1 =    -0.204134


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho       beta_0       beta_1

    lalpha            1        -0.99       -0.016         0.03

       rho        -0.99            1        0.013       -0.026

    beta_0       -0.016        0.013            1        -0.94

    beta_1         0.03       -0.026        -0.94            1


                                   Parameter Estimates
```

95.0% Wald
Confidence Interval

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	-2.55843	1.66185	-5.8156	0.698746
rho	2.42056	0.545617	1.35117	3.48995
beta_0	30.3968	4.03582	22.4868	38.3069
beta_1	-0.196699	0.0443352	-0.283594	-0.109803

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	31.7	30.4	20.6	17.3	0.233
25	10	24.6	25.5	12	14	-0.2
100	10	10.7	10.7	5.33	4.92	-0.0204

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.841935	4	193.683870
A2	-85.255316	6	182.510632
A3	-85.429148	5	180.858295
fitted	-85.851107	4	179.702213
R	-98.136607	2	200.273213

Explanation of Tests

```
 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              25.7626          4          <.0001
   Test 2              15.1732          2       0.0005072
   Test 3             0.347663          1          0.5554
   Test 4             0.843918          1          0.3583

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


             Benchmark Dose Computation

Specified effect =             1

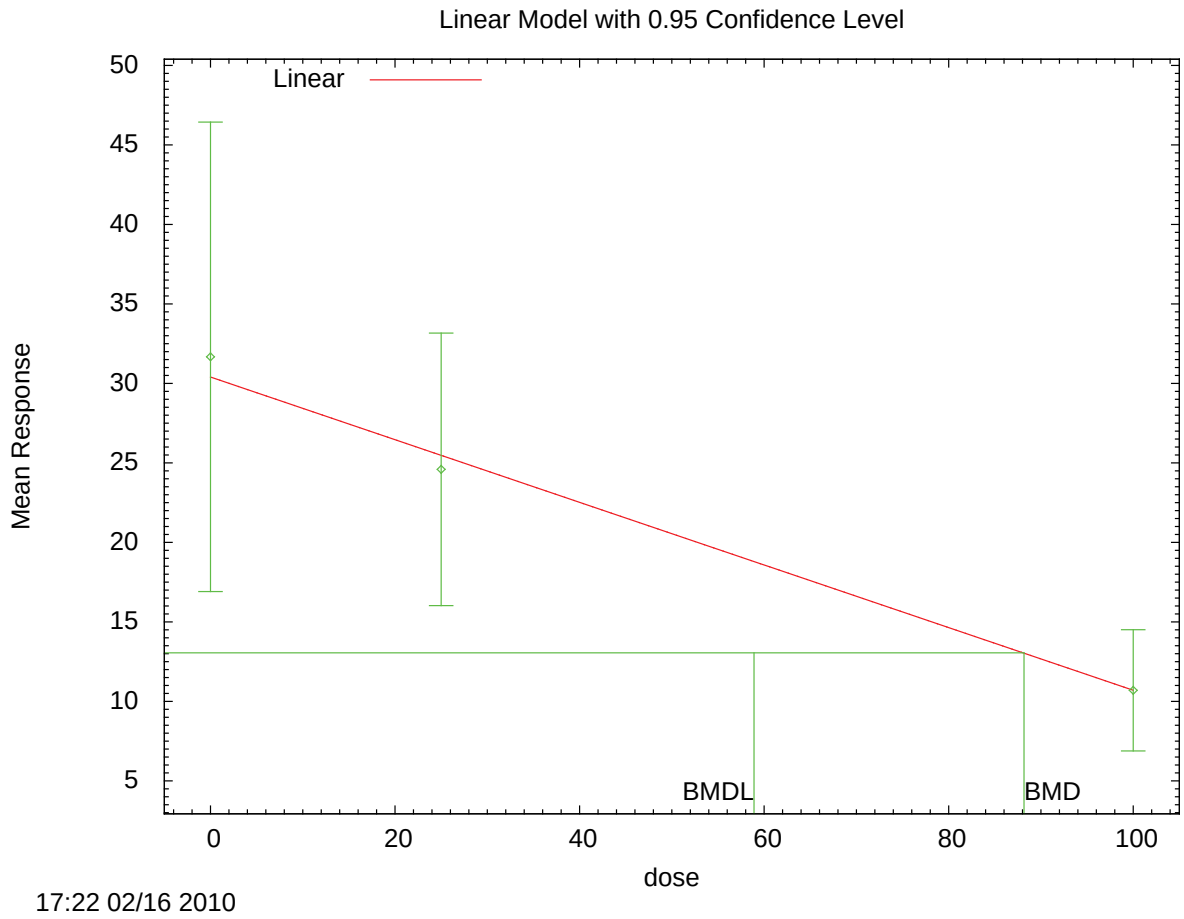
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        88.1623


            BMDL =        58.9029
```

G.3.1.3. *Figure for Selected Model: Linear*



G.3.1.4. *Output for Additional Model Presented: Power, Unrestricted*

Amin et al. (2000): 0.25% Saccharin Consumed, Female

```
=====================================================================
       Power Model. (Version: 2.15;  Date: 04/07/2008)
       Input Data File: C:\1\1_Amin_2000_25_SC_Pwr_U_1.(d)
       Gnuplot Plotting File:  C:\1\1_Amin_2000_25_SC_Pwr_U_1.plt
                                          Tue Feb 16 17:22:17 2010
=====================================================================

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~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
```

```
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                Default Initial Parameter Values
                        lalpha =      5.29482
                           rho =            0
                       control =      31.6727
                         slope =    -0.567889
                         power =     0.783745


         Asymptotic Correlation Matrix of Parameter Estimates

                lalpha          rho      control        slope        power

    lalpha           1        -0.99         0.34        -0.14       -0.061

       rho        -0.99            1        -0.42         0.15        0.068

   control         0.34        -0.42            1        -0.67        -0.56

     slope        -0.14         0.15        -0.67            1         0.99

     power       -0.061        0.068        -0.56         0.99            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         -2.48291          2.08669            -6.57274
1.60693
            rho          2.38455         0.692047             1.02817
3.74094
        control            32.99          5.40754             22.3914
43.5886
          slope         -1.36469          2.01258            -5.30927
2.5799
          power         0.605364         0.288476           0.0399625
1.17077


     Table of Data and Estimated Values of Interest
```

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	31.7	33	20.6	18.7	-0.223
25	10	24.6	23.4	12	12.4	0.302
100	10	10.7	10.8	5.33	4.94	-0.08

Warning: Likelihood for fitted model larger than the Likelihood for model A3.

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.841935	4	193.683870
A2	-85.255316	6	182.510632
A3	-85.429148	5	180.858295
fitted	-85.429148	5	180.858295
R	-98.136607	2	200.273213

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	25.7626	4	<.0001
Test 2	15.1732	2	0.0005072

```
   Test 3             0.347663          1          0.5554
   Test 4         -8.2423e-013          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


               Benchmark Dose Computation

Specified effect =             1

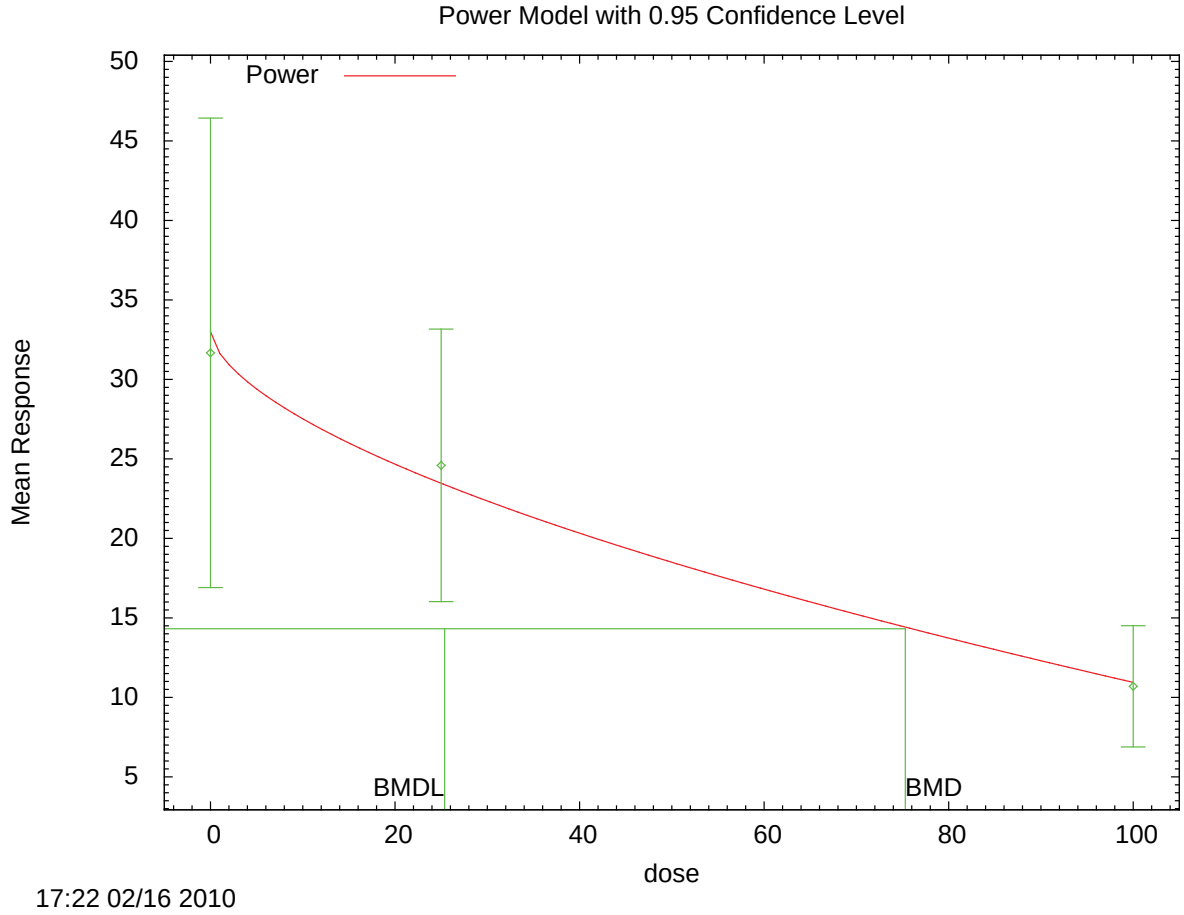
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 75.2994


            BMDL = 25.3717
```

G.3.1.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.3.2. Amin et al. (2000): 0.25% Saccharin Preference Ratio, Female

G.3.2.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear[b]	**1**	**0.002**	**228.094**	**1.264E+02**	**6.128E+01**	
Polynomial, 2-degree	1	0.002	228.094	1.264E+02	6.128E+01	
Power	1	0.002	228.094	1.264E+02	6.128E+01	power bound hit (power = 1)

[a] Nonconstant variance model selected ($p = 0.0135$).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.2.2. *Output for Selected Model: Linear*

Amin et al. (2000): 0.25% Saccharin Preference Ratio, Female

```
 ====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\2_Amin_2000_25_SP_Linear_1.(d)
        Gnuplot Plotting File:  C:\1\2_Amin_2000_25_SP_Linear_1.plt
                                          Tue Feb 16 17:22:44 2010
 ====================================================================

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   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                         lalpha =      6.34368
                            rho =            0
                         beta_0 =      74.2008
                         beta_1 =    -0.219781


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho       beta_0       beta_1

    lalpha            1           -1          0.2        -0.28

       rho           -1            1        -0.19         0.28

    beta_0          0.2        -0.19            1        -0.76

    beta_1        -0.28         0.28        -0.76            1


                                     Parameter Estimates
```

95.0% Wald
Confidence Interval

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	0.338774	9.23768	-17.7667	18.4443
rho	1.43998	2.21674	-2.90476	5.78472
beta_0	73.6633	6.6623	60.6054	86.7211
beta_1	-0.207175	0.101074	-0.405276	-0.00907442

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	82.1	73.7	13.3	26.2	1.02
25	10	58.1	68.5	33.9	24.8	-1.32
100	10	54.9	52.9	19.5	20.6	0.295

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-108.574798	4	225.149597
A2	-104.269377	6	220.538754
A3	-105.147952	5	220.295903
fitted	-110.046917	4	228.093834
R	-112.382522	2	228.765045

Explanation of Tests

```
 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              16.2263          4         0.00273
   Test 2              8.61084          2          0.0135
   Test 3              1.75715          1           0.185
   Test 4              9.79793          1        0.001747

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


             Benchmark Dose Computation

Specified effect =             1

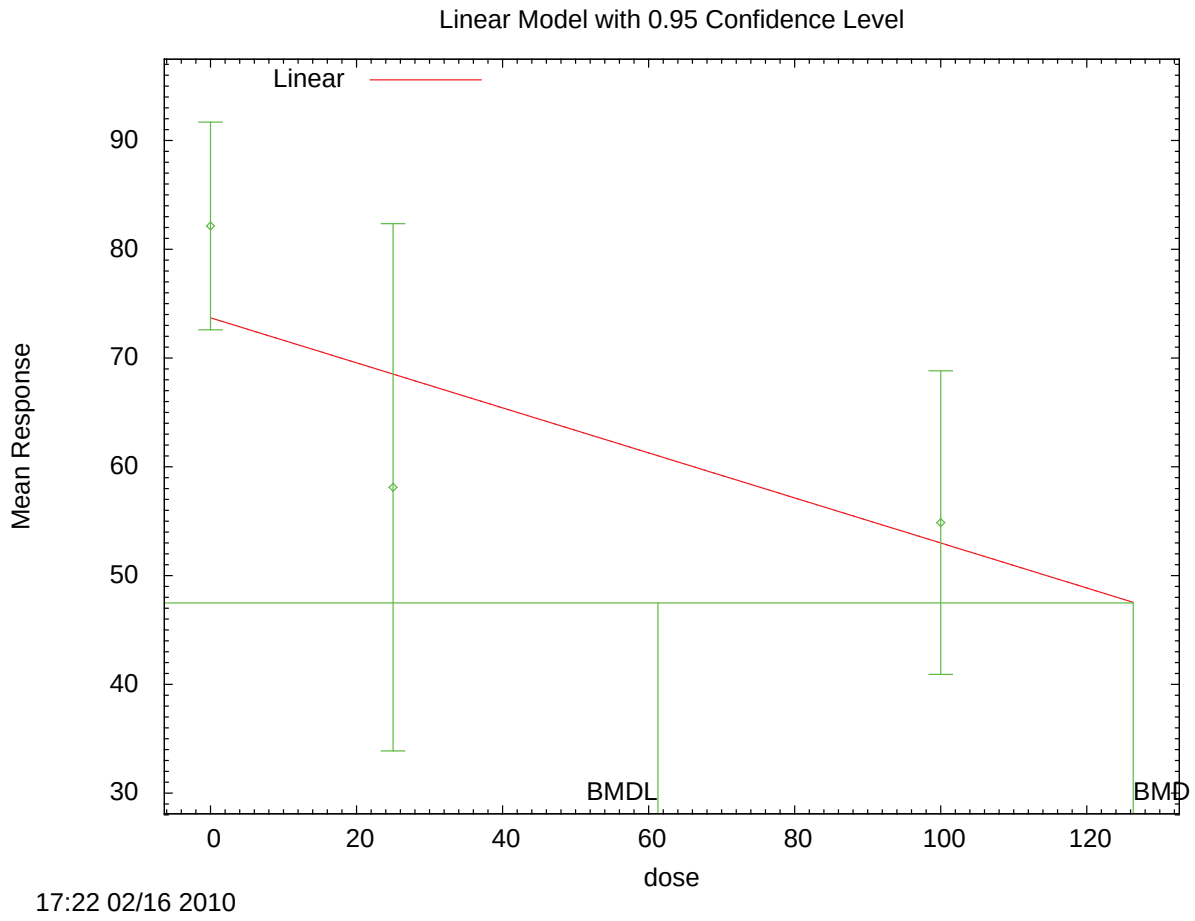
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        126.365


            BMDL =        61.2812
```

G.3.2.3. *Figure for Selected Model: Linear*



G.3.3. Amin et al. (2000): 0.50% Saccharin Consumed, Female

G.3.3.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear[b]	**1**	**0.031**	**159.737**	**9.874E+01**	**6.417E+01**	
Polynomial, 2-degree	1	0.031	159.737	9.874E+01	6.417E+01	
Power	1	0.031	159.737	9.874E+01	6.417E+01	power bound hit (power = 1)
Power, unrestricted[c]	0	N/A	157.060	5.610E+01	6.781E+00	unrestricted (power = 0.325)

[a] Nonconstant variance model selected (p = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.3.2. *Output for Selected Model: Linear*

Amin et al. (2000): 0.50% Saccharin Consumed, Female

```
 ====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\3_Amin_2000_50_SC_Linear_1.(d)
        Gnuplot Plotting File:  C:\1\3_Amin_2000_50_SC_Linear_1.plt
                                          Tue Feb 16 17:23:14 2010
 ====================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                         lalpha =      4.68512
                            rho =            0
                         beta_0 =      19.3484
                         beta_1 =    -0.158141


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho       beta_0       beta_1

    lalpha            1        -0.97        0.018      -0.0021

       rho        -0.97            1       -0.027        0.014

    beta_0        0.018       -0.027            1        -0.95

    beta_1      -0.0021        0.014        -0.95            1


                                     Parameter Estimates
```

95.0% Wald
Confidence Interval

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	-0.997428	0.992786	-2.94325	0.948397
rho	2.13634	0.404989	1.34257	2.9301
beta_0	18.1144	3.10302	12.0326	24.1962
beta_1	-0.135736	0.0331501	-0.200709	-0.0707631

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	22.4	18.1	16	13.4	1
25	10	11.4	14.7	7.66	10.7	-0.983
100	10	4.54	4.54	3.33	3.06	-0.00393

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-83.696404	4	175.392808
A2	-73.511830	6	159.023660
A3	-73.530233	5	157.060467
fitted	-75.868688	4	159.737377
R	-90.294746	2	184.589492

Explanation of Tests

```
 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	33.5658	4	<.0001
Test 2	20.3691	2	<.0001
Test 3	0.0368066	1	0.8479
Test 4	4.67691	1	0.03057

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

```
Specified effect =             1

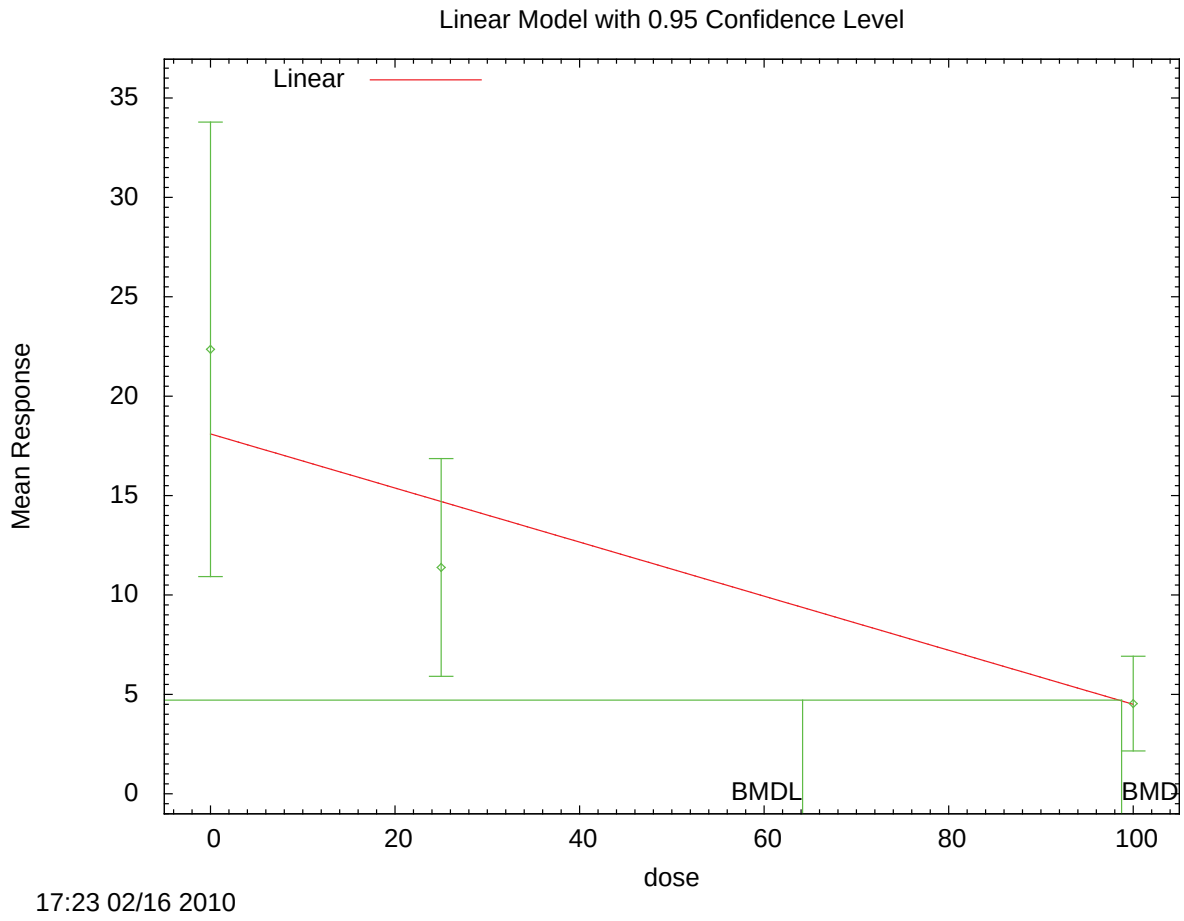
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        98.7409


            BMDL =         64.169
```

G.3.3.3. *Figure for Selected Model: Linear*



G.3.3.4. *Output for Additional Model Presented: Power, Unrestricted*

Amin et al. (2000): 0.50% Saccharin Consumed, Female

```
 ====================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\3_Amin_2000_50_SC_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\3_Amin_2000_50_SC_Pwr_U_1.plt
                                          Tue Feb 16 17:23:15 2010
 ====================================================================

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~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
```

The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	4.68512
rho =	0
control =	22.3564
slope =	-3.55874
power =	0.349799

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.96	0.34	-0.26	-0.15
rho	-0.96	1	-0.47	0.3	0.15
control	0.34	-0.47	1	-0.73	-0.52
slope	-0.26	0.3	-0.73	1	0.96
power	-0.15	0.15	-0.52	0.96	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-0.708629	1.298	-3.25267	1.83541
rho	1.96142	0.529653	0.923323	2.99953
control	22.6293	4.48416	13.8405	31.4181
slope	-4.03215	3.21302	-10.3296	2.26526
power	0.325414	0.138761	0.053447	0.597381

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	22.4	22.6	16	15	-0.0577
25	10	11.4	11.1	7.66	7.46	0.105
100	10	4.54	4.58	3.33	3.12	-0.0475

Warning: Likelihood for fitted model larger than the Likelihood for model A3.

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-83.696404	4	175.392808
A2	-73.511830	6	159.023660
A3	-73.530233	5	157.060467
fitted	-73.530233	5	157.060467
R	-90.294746	2	184.589492

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	33.5658	4	<.0001
Test 2	20.3691	2	<.0001

```
   Test 3            0.0368066          1          0.8479
   Test 4        -2.84217e-014          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


               Benchmark Dose Computation

Specified effect =             1

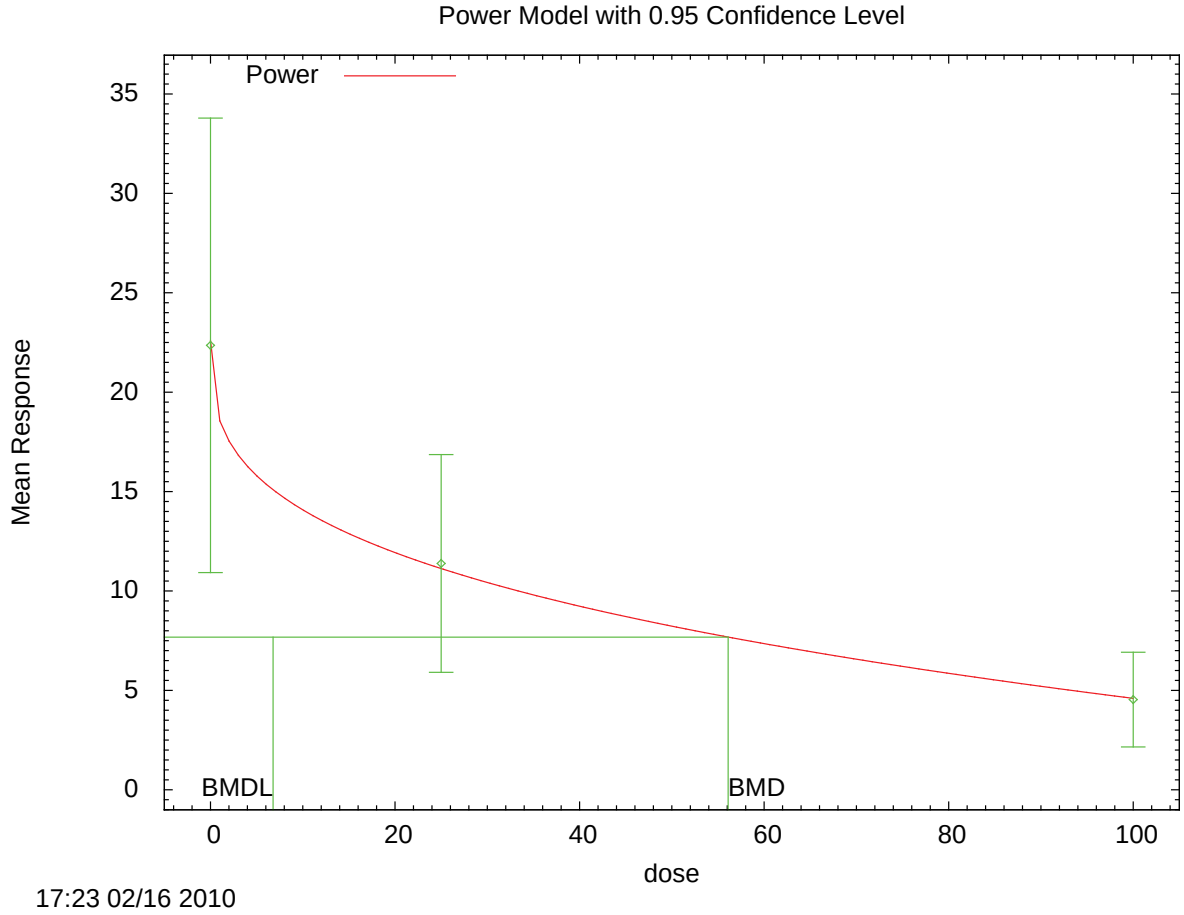
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 56.0967


            BMDL = 6.78112
```

G.3.3.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.3.4. Amin et al. (2000): 0.50% Saccharin Preference Ratio, Female

G.3.4.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear[b]	**1**	**0.088**	**234.936**	**8.278E+01**	**5.100E+01**	
Polynomial, 2-degree	1	0.088	234.936	8.278E+01	5.100E+01	
Power	1	0.088	234.936	8.278E+01	5.100E+01	power bound hit (power = 1)
Power, unrestricted[c]	0	N/A	234.020	1.817E+01	1.000E−13	unrestricted (power = 0.232)

[a] Constant variance model selected ($p = 0.5593$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.4.2. *Output for Selected Model: Linear*

Amin et al. (2000): 0.50% Saccharin Preference Ratio, Female

```
 ====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\4_Amin_2000_50_SP_LinearCV_1.(d)
        Gnuplot Plotting File:  C:\1\4_Amin_2000_50_SP_LinearCV_1.plt
                                          Tue Feb 16 17:23:43 2010
 ====================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                   Default Initial Parameter Values
                           alpha =      764.602
                             rho =            0   Specified
                          beta_0 =      64.1858
                          beta_1 =    -0.332668


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -rho
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                   alpha       beta_0       beta_1

     alpha             1       2e-008     1.4e-009

    beta_0       2e-008            1         -0.7

    beta_1     1.4e-009         -0.7            1
```

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	758.396	195.817	374.602	1142.19
beta_0	64.1858	7.04184	50.3841	77.9876
beta_1	-0.332668	0.118327	-0.564584	-0.100752

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	72.7	64.2	24.6	27.5	0.981
25	10	44.5	55.9	32.9	27.5	-1.31
100	10	33.8	30.9	24.6	27.5	0.327

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.009921	4	234.019841
A2	-112.428886	6	236.857773
A3	-113.009921	4	234.019841
fitted	-114.468091	3	234.936183
R	-117.976057	2	239.952114

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	11.0943	4	0.02552
Test 2	1.16207	2	0.5593
Test 3	1.16207	2	0.5593
Test 4	2.91634	1	0.08769

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

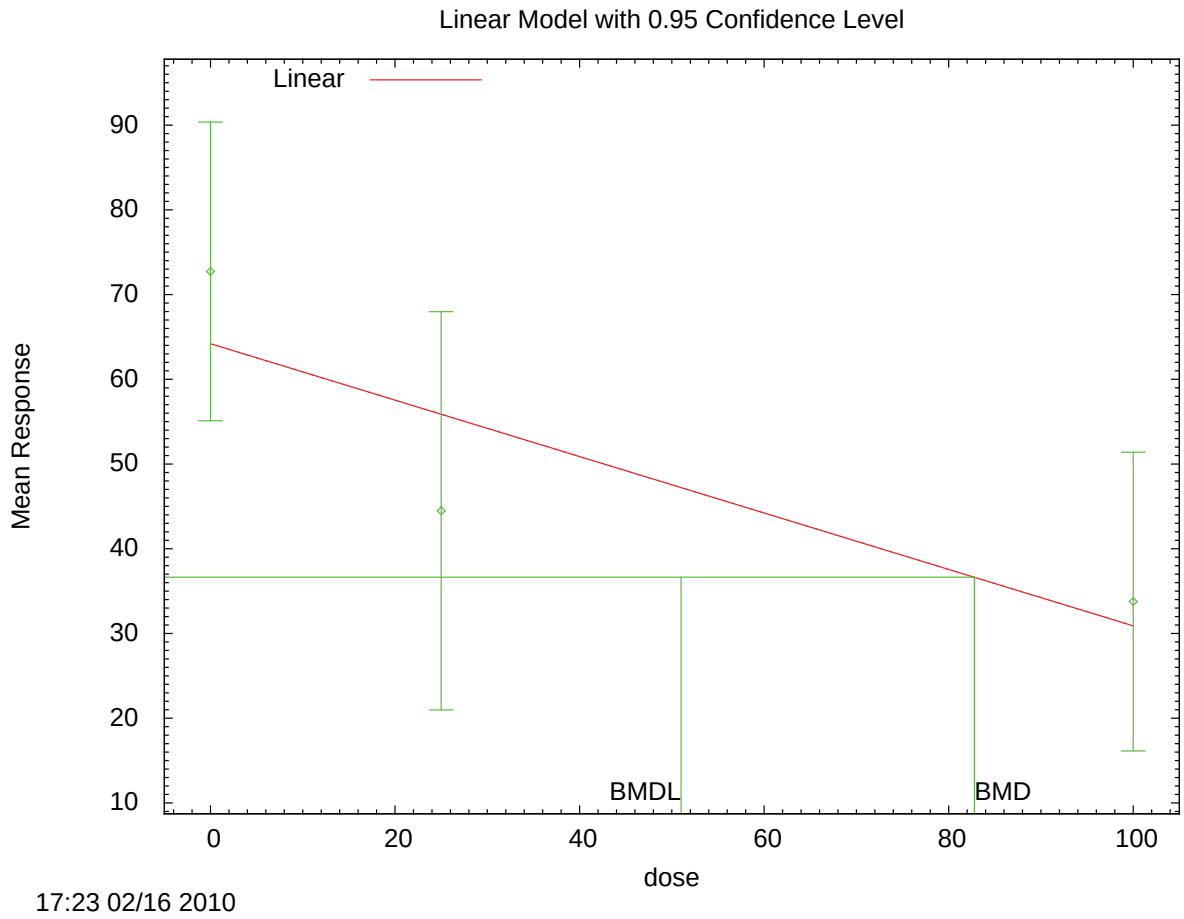
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 82.7823

BMDL = 50.9971

G.3.4.3. *Figure for Selected Model: Linear*



G.3.4.4. *Output for Additional Model Presented: Power, Unrestricted*

Amin et al. (2000): 0.50% Saccharin Preference Ratio, Female

```
=====================================================================
       Power Model. (Version: 2.15;  Date: 04/07/2008)
       Input Data File: C:\1\4_Amin_2000_50_SP_PwrCV_U_1.(d)
       Gnuplot Plotting File:  C:\1\4_Amin_2000_50_SP_PwrCV_U_1.plt
                                         Tue Feb 16 17:23:44 2010
=====================================================================

-
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
```

```
rho is set to 0
The power is not restricted
A constant variance model is fit

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                         alpha =      764.602
                           rho =            0   Specified
                       control =      72.7273
                         slope =      -13.387
                         power =     0.231973


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope        power

     alpha            1    -1.3e-008     5.9e-009     2.5e-009

   control    -1.3e-008            1         -0.4        -0.22

     slope     5.9e-009         -0.4            1         0.97

     power     2.5e-009        -0.22         0.97            1


                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          688.142          177.677               339.9
1036.38
        control          72.7273          8.29543             56.4686
88.986
          slope          -13.387          15.9957             -44.738
17.9639
          power         0.231973         0.268067           -0.293429
0.757376


     Table of Data and Estimated Values of Interest
```

```
 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0    10       72.7         72.7         24.6         26.2      5.16e-008
   25    10       44.5         44.5         32.9         26.2     -1.27e-008
  100    10       33.8         33.8         24.6         26.2        -2e-008

Degrees of freedom for Test A3 vs fitted <= 0



 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -113.009921            4     234.019841
             A2         -112.428886            6     236.857773
             A3         -113.009921            4     234.019841
         fitted         -113.009921            4     234.019841
              R         -117.976057            2     239.952114


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              11.0943          4         0.02552
   Test 2              1.16207          2          0.5593
```

```
   Test 3              1.16207          2          0.5593
   Test 4                    0          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


               Benchmark Dose Computation

Specified effect =             1

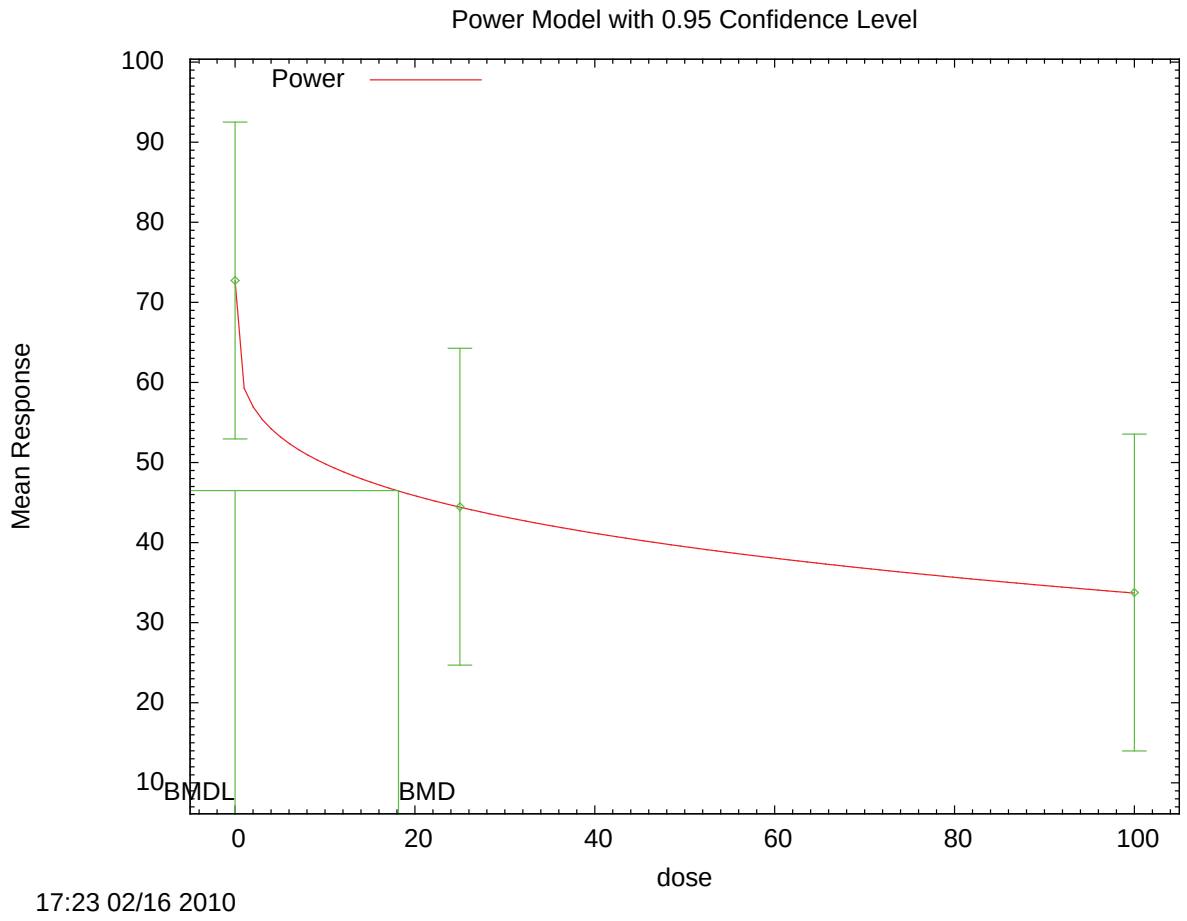
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 18.1732


            BMDL = 1e-013
```

G.3.4.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.3.5. Bell et al. (2007): Balano-Preputial Separation, PND 49

G.3.5.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	2	0.369	113.514	7.332E+00	4.687E+00	power bound hit (power = 1)
Logistic	2	0.237	114.853	1.501E+01	1.137E+01	
Log-logistic[a]	**2**	**0.456**	**112.952**	**5.209E+00**	**2.870E+00**	**slope bound hit (slope = 1)**
Log-probit	2	0.178	115.488	1.428E+01	9.138E+00	slope bound hit (slope = 1)
Multistage, 3-degree	2	0.369	113.514	7.332E+00	4.687E+00	final ß = 0
Probit	2	0.248	114.723	1.399E+01	1.061E+01	
Weibull	2	0.369	113.514	7.332E+00	4.687E+00	power bound hit (power = 1)
Gamma, unrestricted	1	0.566	113.746	1.894E+00	7.609E−02	unrestricted (power = 0.506)
Log-logistic, unrestricted[b]	1	0.484	113.908	2.127E+00	1.363E−01	unrestricted (slope = 0.67)
Log-probit, unrestricted	1	0.439	114.021	2.179E+00	1.671E−01	unrestricted (slope = 0.389)
Weibull, unrestricted	1	0.534	113.802	2.007E+00	1.075E−01	unrestricted (power = 0.574)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.5.2. *Output for Selected Model: Log-Logistic*

Bell et al. (2007): Balano-Preputial Separation, PND 49

```
 ========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\5_Bell_2007_BPS_LogLogistic_1.(d)
        Gnuplot Plotting File:  C:\1\5_Bell_2007_BPS_LogLogistic_1.plt
                                          Tue Feb 16 17:24:10 2010
 ========================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
```

```
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =    0.0333333
                      intercept =     -3.75371
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.58

 intercept        -0.58            1



                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background        0.0635251            *                *
*
      intercept         -3.84765            *                *
*
          slope                1            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -53.7077         4
   Fitted model         -54.476         2       1.53661      2
0.4638
  Reduced model        -63.9797         1        20.544      3
0.0001309
```

```
          AIC:         112.952


                                 Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
   0.0000     0.0635         1.906     1.000          30       -0.678
   2.4000     0.1091         3.274     5.000          30        1.011
   8.0000     0.2000         6.001     6.000          30       -0.000
  46.0000     0.5273        15.819    15.000          30       -0.300

 Chi^2 = 1.57      d.f. = 2        P-value = 0.4559


   Benchmark Dose Computation

Specified effect =           0.1

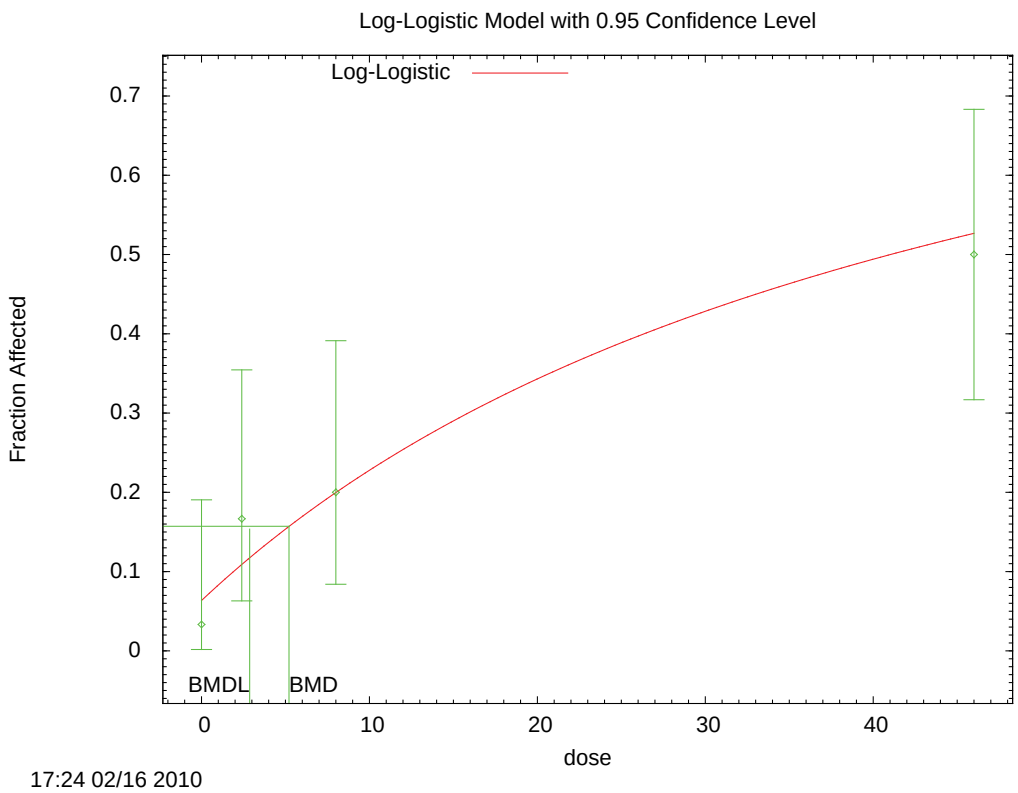
Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =        5.20918

            BMDL =        2.86991
```

G.3.5.3. *Figure for Selected Model: Log-Logistic*



G.3.5.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Bell et al. (2007): Balano-Preputial Separation, PND 49

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\5_Bell_2007_BPS_LogLogistic_U_1.(d)
        Gnuplot Plotting File:  C:\1\5_Bell_2007_BPS_LogLogistic_U_1.plt
                                          Tue Feb 16 17:24:10 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 4
```

Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.0333333
intercept = -2.54947
slope = 0.615936

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.49	0.35
intercept	-0.49	1	-0.93
slope	0.35	-0.93	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0354714	*	*	*
intercept	-2.70296	*	*	*
slope	0.670238	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-53.7077	4			
Fitted model	-53.9541	3	0.492844	1	0.4827
Reduced model	-63.9797	1	20.544	3	0.0001309

AIC: 113.908

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0355	1.064	1.000	30	-0.063
2.4000	0.1392	4.176	5.000	30	0.435
8.0000	0.2405	7.216	6.000	30	-0.520
46.0000	0.4848	14.544	15.000	30	0.167

Chi^2 = 0.49 d.f. = 1 P-value = 0.4836

Benchmark Dose Computation

Specified effect = 0.1

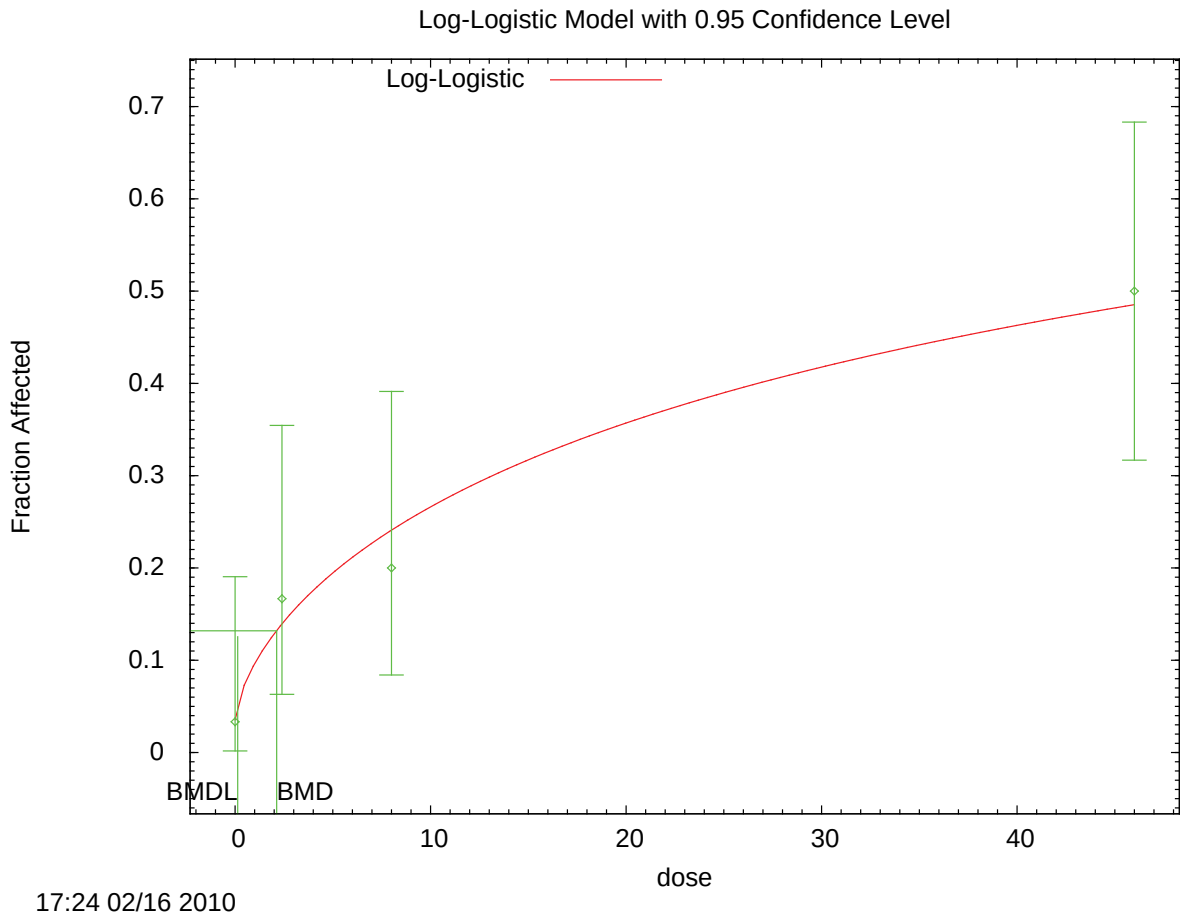
Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.12667

BMDL = 0.13633

G.3.5.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



G.3.6. Cantoni et al. (1981): Urinary Coproporhyrins, 3 Months

G.3.6.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.002	33.792	1.101E+02	5.318E+01	
Exponential (M3)	2	0.002	33.792	1.101E+02	5.318E+01	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.341**	**23.881**	**3.741E−01**	**1.253E−01**	
Exponential (M5)	1	0.341	23.881	3.741E−01	1.253E−01	power hit bound (*d* = 1)
Hill	1	0.535	23.359	3.273E−01	error	*n* lower bound hit (*n* = 1)
Linear	2	0.002	33.301	7.734E+01	1.975E+01	
Polynomial, 3-degree	2	0.002	33.301	7.734E+01	1.975E+01	
Power	2	0.002	33.301	7.734E+01	1.975E+01	power bound hit (power = 1)
Power, unrestricted[c]	1	0.665	23.162	4.637E−03	8.796E−08	unrestricted (power = 0.22)
Hill, unrestricted	0	N/A	24.974	7.264E−02	1.656E−04	unrestricted (*n* = 0.48)

[a] Nonconstant variance model selected (*p* = 0.0039).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.6.2. *Output for Selected Model: Exponential (M4)*

Cantoni et al. (1981): Urinary Coproporhyrins, 3 Months

```
 ========================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\6_Cantoni_1981_UriCopro_Exp_1.(d)
        Gnuplot Plotting File:
                                            Tue Feb 16 17:24:39 2010
 ========================================================================

 Figure1-UrinaryCoproporphyrin_3months
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
```

```
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 4
lnalpha	-1.50063
rho	2.60979
a	0.704303
b	0.0205927
c	4.47268
d	1

Parameter Estimates

Variable	Model 4
lnalpha	-1.74154
rho	2.66803
a	0.755982
b	0.3715
c	3.93845
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	4	0.7414	0.3475
1.43	4	1.807	0.8341
14.3	4	2.734	1.506
143	4	3	2.6

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.756	0.2882	-0.1014
1.43	1.671	0.8307	0.3265
14.3	2.966	1.786	-0.2607
143	2.977	1.794	0.02532

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-12.90166	5	35.80333
A2	-6.203643	8	28.40729
A3	-6.487204	6	24.97441
R	-15.73713	2	35.47427
4	-6.940389	5	23.88078

Additive constant for all log-likelihoods = -14.7. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	19.07	6	0.004052
Test 2	13.4	3	0.003854
Test 3	0.5671	2	0.7531
Test 6a	0.9064	1	0.3411

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

```
  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

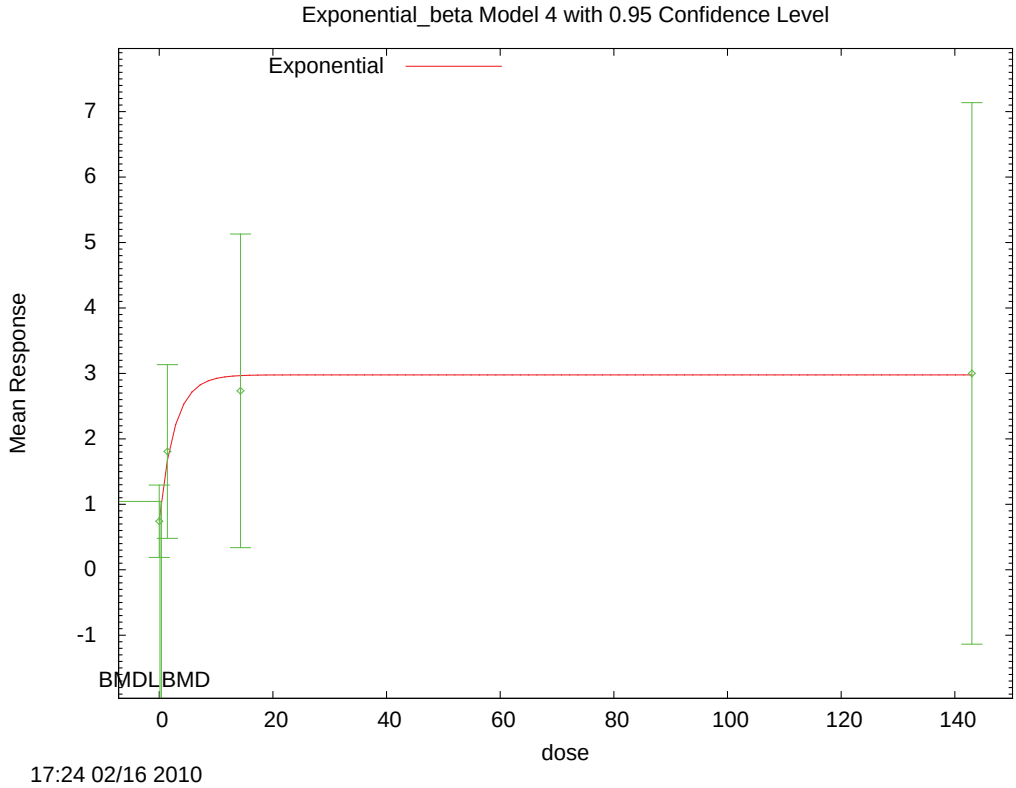
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =     0.374114

              BMDL =     0.125287
```

G.3.6.3. *Figure for Selected Model: Exponential (M4)*



G.3.6.4. *Output for Additional Model Presented: Power, Unrestricted*

Cantoni et al. (1981): Urinary Coproporhyrins, 3 Months

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\6_Cantoni_1981_UriCopro_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\6_Cantoni_1981_UriCopro_Pwr_U_1.plt
                                          Tue Feb 16 17:24:41 2010
 ======================================================================

 Figure1-UrinaryCoproporphyrin_3months
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 4
```

Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	0.90039
rho =	0
control =	0.741372
slope =	1.00533
power =	0.163111

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.62	-0.53	-0.038	0.027
rho	-0.62	1	0.43	-0.24	-0.16
control	-0.53	0.43	1	-0.3	0.09
slope	-0.038	-0.24	-0.3	1	-0.72
power	0.027	-0.16	0.09	-0.72	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-1.78404	0.61698	-2.9933	-0.57478
rho	2.6428	0.74449	1.18363	4.10197
control	0.757242	0.139966	0.482915	1.03157
slope	0.927009	0.325923	0.288212	1.56581
power	0.220276	0.0964599	0.031218	0.409334

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
---	---	---	---	---	---	---

0	4	0.741	0.757	0.348	0.284	-0.112
1.43	4	1.81	1.76	0.834	0.865	0.108
14.3	4	2.73	2.42	1.51	1.32	0.471
143	4	3	3.52	2.6	2.16	-0.483

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.901663	5	35.803325
A2	-6.203643	8	28.407287
A3	-6.487204	6	24.974409
fitted	-6.580755	5	23.161510
R	-15.737135	2	35.474269

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	19.067	6	0.004052
Test 2	13.396	3	0.003854
Test 3	0.567122	2	0.7531
Test 4	0.187101	1	0.6653

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

```
The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =             1

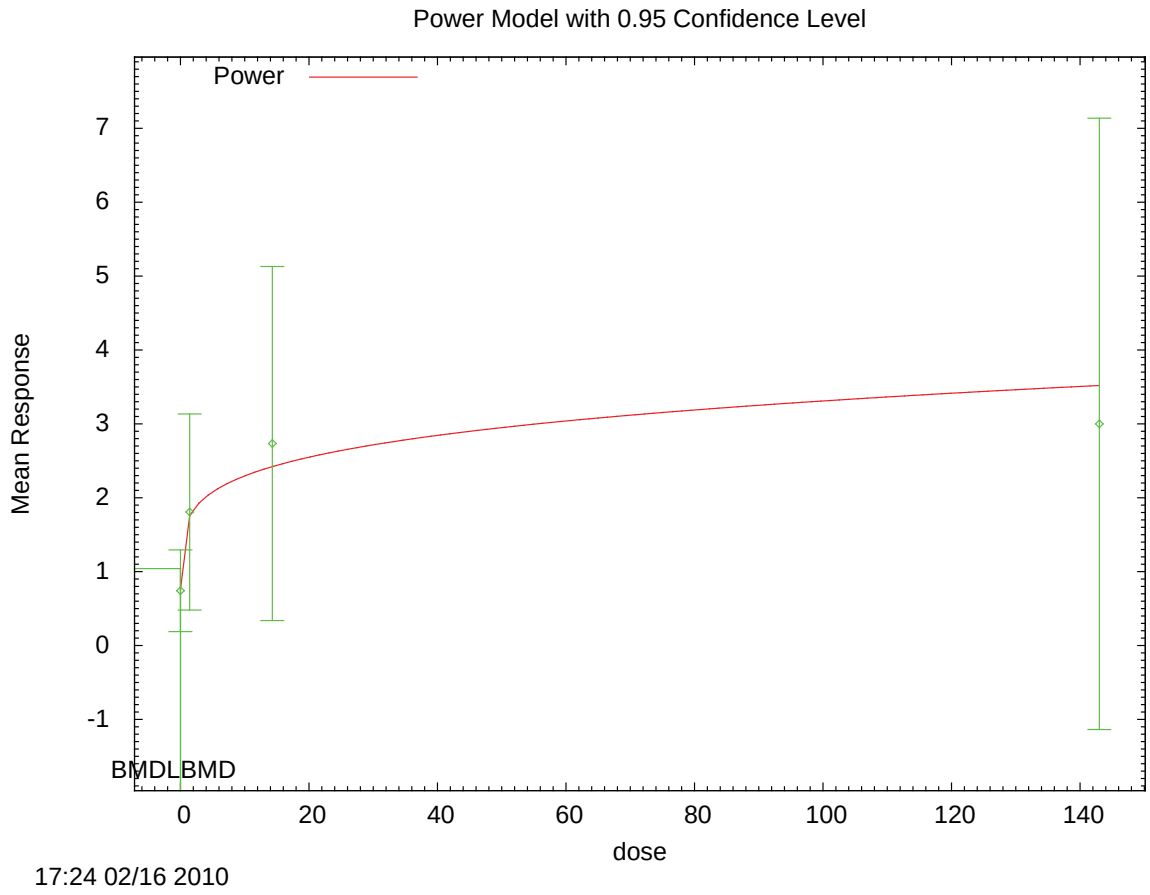
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 0.00463746


            BMDL = 8.79634e-008
```

G.3.6.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.3.7. Cantoni et al. (1981): Urinary Porphyrins

G.3.7.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)[b]	**2**	**<0.0001**	**58.753**	**1.223E+01**	**9.037E+00**	
Exponential (M3)	2	<0.0001	58.753	1.223E+01	9.037E+00	power hit bound (*d* = 1)
Exponential (M4)	1	<0.0001	63.138	2.227E−01	1.137E−01	
Exponential (M5)	1	<0.0001	63.138	2.227E−01	1.137E−01	power hit bound (*d* = 1)
Hill	0	N/A	62.356	9.363E+00	4.664E+00	
Linear	2	<0.0001	62.487	7.732E−01	2.816E−01	
Polynomial, 3-degree	1	<0.0001	10.000	error	error	
Power	2	<0.0001	62.487	7.732E−01	2.816E−01	power bound hit (power = 1)
Power, unrestricted	1	<0.0001	59.914	1.025E−01	2.389E−02	unrestricted (power = 0.746)

[a] Nonconstant variance model selected (*p* = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.7.2. *Output for Selected Model: Exponential (M2)*

Cantoni et al. (1981): Urinary Porphyrins

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\7_Cantoni_1981_UriPor_Exp_1.(d)
        Gnuplot Plotting File:
                                            Tue Feb 16 17:25:14 2010
 ======================================================================

 Table 1, dose converted to ng per kg per day
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
```

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 2
lnalpha	-3.57509
rho	2.23456
a	3.83141
b	0.0277822
c	0
d	1

Parameter Estimates

Variable	Model 2
lnalpha	-1.55886
rho	1.77962
a	4.17268
b	0.0270415
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	4	2.27	0.49
1.43	4	5.55	0.85
14.3	3	7.62	1.79
143	3	196.9	63.14

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	4.173	1.635	-2.327
1.43	4.337	1.692	1.433
14.3	6.143	2.307	1.109
143	199.4	51.04	-0.08645

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-51.42175	5	112.8435
A2	-15.31211	8	46.62422
A3	-15.66963	6	43.33925
R	-68.75058	2	141.5012
2	-25.37651	4	58.75302

Additive constant for all log-likelihoods = -12.87. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	106.9	6	< 0.0001
Test 2	72.22	3	< 0.0001
Test 3	0.715	2	0.6994
Test 4	19.41	2	< 0.0001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

```
The p-value for Test 3 is greater than .1.  The modeled
variance appears to be appropriate here.

The p-value for Test 4 is less than .1.  Model 2 may not adequately
describe the data; you may want to consider another model.


Benchmark Dose Computations:

Specified Effect = 1.000000

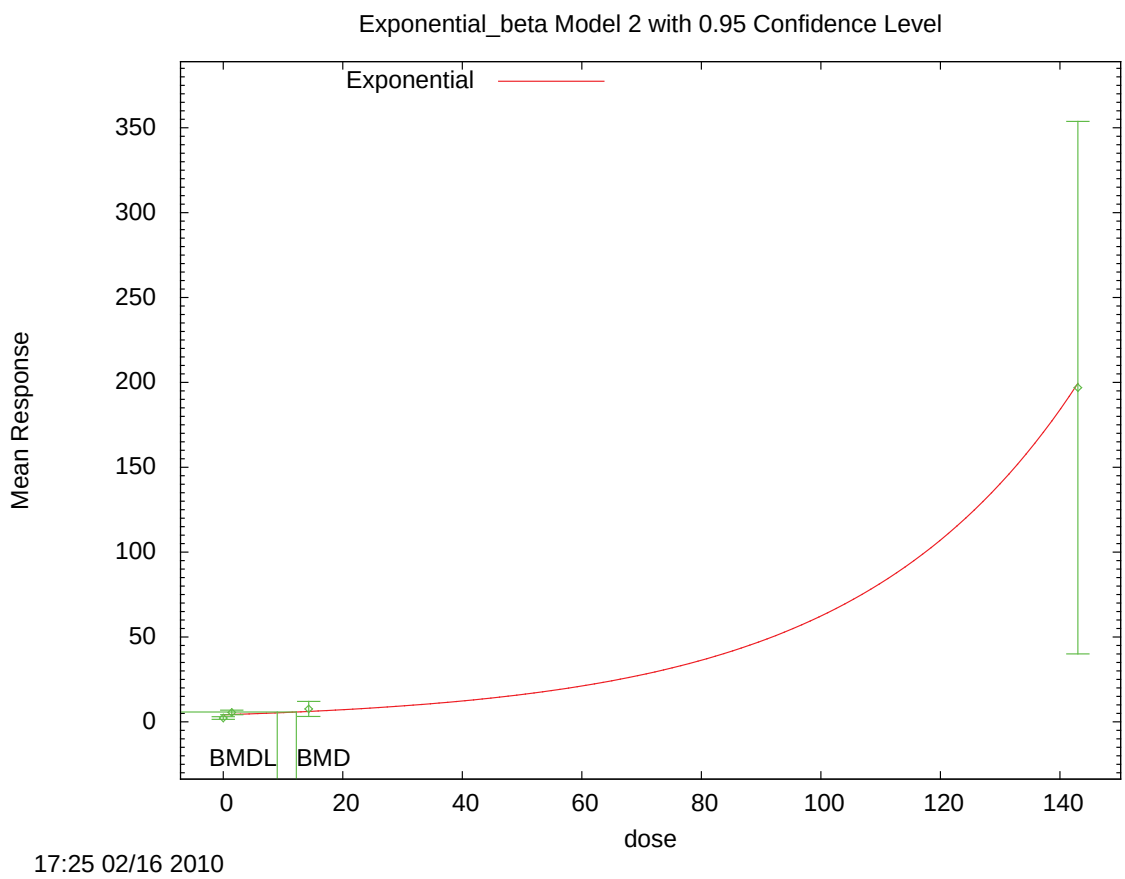
       Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

             BMD =      12.2272

            BMDL =      9.03732
```

G.3.7.3. *Figure for Selected Model: Exponential (M2)*



G.3.8. Crofton et al. (2005): Serum, T4

G.3.8.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	8	<0.0001	518.241	2.136E+03	1.157E+03	
Exponential (M3)	8	<0.0001	518.241	2.136E+03	1.157E+03	power hit bound (*d* = 1)
Exponential (M4)[b]	**7**	**0.957**	**476.204**	**5.633E+01**	**3.006E+01**	
Exponential (M5)	7	0.957	476.204	5.633E+01	3.006E+01	power hit bound (*d* = 1)
Hill	6	0.973	477.434	5.564E+01	2.590E+01	
Linear	8	<0.0001	523.518	4.246E+03	3.086E+03	
Polynomial, 8-degree	8	<0.0001	523.518	4.246E+03	3.086E+03	
Power	8	<0.0001	523.518	4.246E+03	3.086E+03	power bound hit (power = 1)
Power, unrestricted	7	0.030	489.670	2.179E+01	2.271E+00	unrestricted (power = 0.217)

[a] Constant variance model selected (*p* = 0.7647).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.8.2. *Output for Selected Model: Exponential (M4)*

Crofton et al. (2005): Serum, T4

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\8_Crofton_2005_T4_ExpCV_1.(d)
        Gnuplot Plotting File:
                                             Tue Feb 16 17:26:01 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	5.47437
rho(S)	0
a	104.999
b	0.000371694
c	0.445764
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	5.50283
rho	0
a	99.776
b	0.00728387
c	0.533516
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	14	100	15.44
0.1	6	96.27	14.98
3	12	98.57	18.11
10	6	99.76	19.04
30	6	93.32	12.11
100	6	70.94	12.74
300	6	62.52	14.75
1000	6	52.68	22.73
3000	6	54.66	19.71
1e+004	4	49.15	11.15

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	99.78	15.66	0.05325
0.1	99.74	15.66	-0.5434
3	98.77	15.66	-0.04357
10	96.51	15.66	0.5085
30	90.64	15.66	0.4195
100	75.7	15.66	-0.744
300	58.47	15.66	0.6334
1000	53.26	15.66	-0.09133
3000	53.23	15.66	0.2237
1e+004	53.23	15.66	-0.5218

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-233.0774	11	488.1549
A2	-230.2028	20	500.4056
A3	-233.0774	11	488.1549
R	-268.4038	2	540.8076
4	-234.1019	4	476.2038

Additive constant for all log-likelihoods = -66.16. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	76.4	18	< 0.0001
Test 2	5.749	9	0.7647
Test 3	5.749	9	0.7647
Test 6a	2.049	7	0.9571

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 1.000000

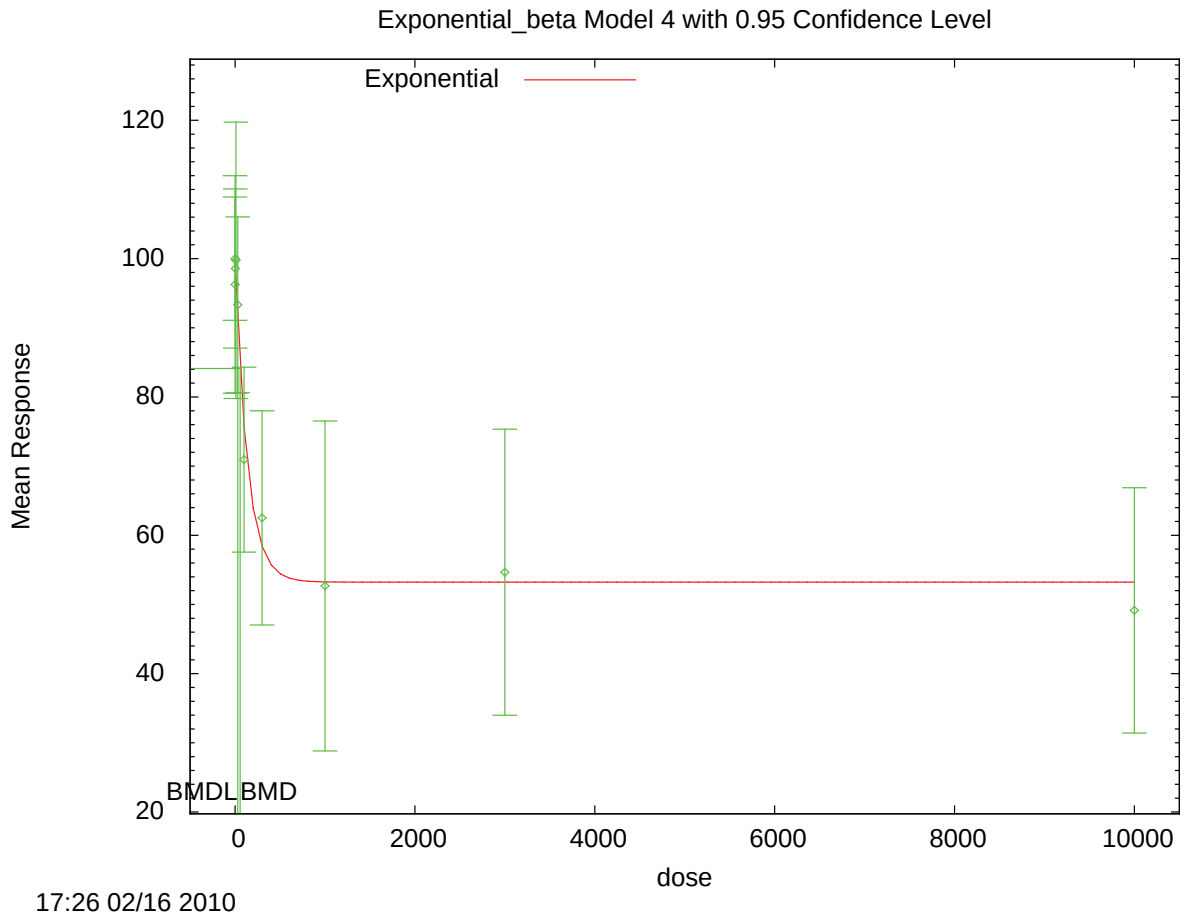
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 56.3321

BMDL = 30.0635

G.3.8.3. *Figure for Selected Model: Exponential (M4)*



G.3.9. Franc et al. (2001): S-D Rats, Relative Liver Weight

G.3.9.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Hill	1	0.797	236.371	1.826E+01	5.463E+00	*n* lower bound hit (*n* = 1)
Exponential (M2)	2	0.935	234.440	2.262E+01	1.757E+01	
Exponential (M3)	2	0.935	234.440	2.262E+01	1.757E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.797	236.371	1.827E+01	6.112E+00	
Exponential (M5)	1	0.797	236.371	1.827E+01	6.112E+00	power hit bound (*d* = 1)
Linear	2	0.967	234.372	1.861E+01	1.339E+01	
Polynomial, 3-degree	2	0.967	234.372	1.861E+01	1.339E+01	
Power[b]	**2**	**0.967**	**234.372**	**1.861E+01**	**1.339E+01**	**power bound hit (power = 1)**
Hill, unrestricted	0	N/A	238.366	1.726E+01	2.022E+00	unrestricted (*n* = 0.965)
Power, unrestricted[c]	1	0.805	236.365	1.725E+01	2.003E+00	unrestricted (power = 0.962)

[a] Constant variance model selected (*p* = 0.107).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.9.2. *Output for Selected Model: Power*

Franc et al. (2001): S-D Rats, Relative Liver Weight

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\88_Franc_2001_SD_RelLivWt_PowerCV_1.(d)
        Gnuplot Plotting File:  C:\1\88_Franc_2001_SD_RelLivWt_PowerCV_1.plt
                                          Fri Apr 16 16:28:45 2010
 ======================================================================

 Figure 5, SD rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is restricted to be greater than or equal to 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	527.447	
rho =	0	Specified
control =	100	
slope =	1.15946	
power =	0.839423	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -power
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	control	slope
alpha	1	1.3e-012	-6.2e-013
control	1.3e-012	1	-0.67
slope	-6.2e-013	-0.67	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	462.485	115.621	235.872	689.099
control	101.047	5.10511	91.0415	111.053
slope	0.542984	0.0973507	0.352181	0.733788
power	1	NA		

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	100	101	14	21.5	-0.138
10	8	108	106	16.9	21.5	0.208

30	8	117	117	25.9	21.5	-0.0702
100	8	155	155	30.9	21.5	0.000298

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.152281	5	238.304562
A2	-111.103649	8	238.207299
A3	-114.152281	5	238.304562
fitted	-114.185827	3	234.371654
R	-125.052064	2	254.104127

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.8968	6	<.0001
Test 2	6.09726	3	0.107
Test 3	6.09726	3	0.107
Test 4	0.0670927	2	0.967

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 0.1

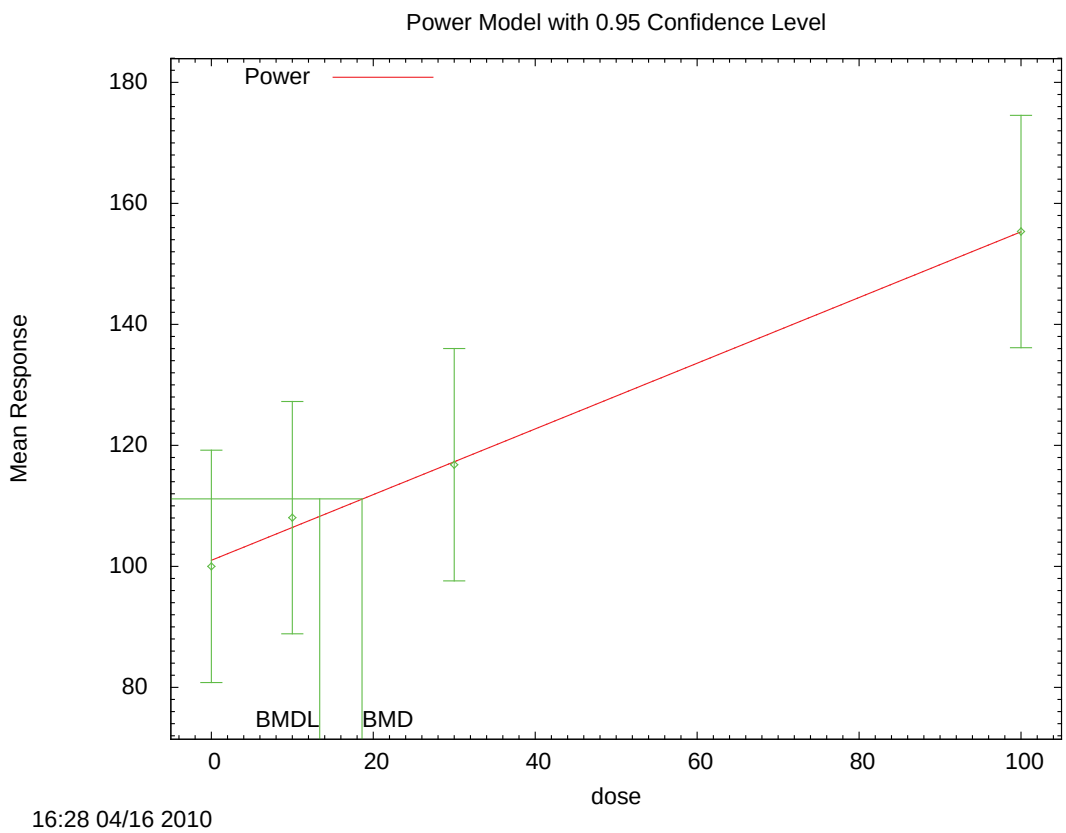
Risk Type = Relative risk

Confidence level = 0.95

BMD = 18.6096

BMDL = 13.3879

G.3.9.3. *Figure for Selected Model: Power*



G.3.9.4. *Output for Additional Model Presented: Power, Unrestricted*

Franc et al. (2001): S-D Rats, Relative Liver Weight

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\88_Franc_2001_SD_RelLivWt_PowerCV_U_1.(d)
        Gnuplot Plotting File:
C:\1\88_Franc_2001_SD_RelLivWt_PowerCV_U_1.plt
                                          Fri Apr 16 16:28:46 2010
 ======================================================================

 Figure 5, SD rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is not restricted
```

A constant variance model is fit

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	527.447	
rho =	0	Specified
control =	100	
slope =	1.15946	
power =	0.839423	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	control	slope	power
alpha	1	1e-009	-6.2e-010	4.7e-010
control	1e-009	1	-0.74	0.71
slope	-6.2e-010	-0.74	1	-1
power	4.7e-010	0.71	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	462.394	115.598	235.825	688.963
control	100.636	7.29156	86.3448	114.927
slope	0.650456	1.43713	-2.16627	3.46718
power	0.961853	0.465182	0.0501134	1.87359

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	100	101	14	21.5	-0.0836
10	8	108	107	16.9	21.5	0.192
30	8	117	118	25.9	21.5	-0.128
100	8	155	155	30.9	21.5	0.0192

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.152281	5	238.304562
A2	-111.103649	8	238.207299
A3	-114.152281	5	238.304562
fitted	-114.182670	4	236.365340
R	-125.052064	2	254.104127

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.8968	6	<.0001
Test 2	6.09726	3	0.107
Test 3	6.09726	3	0.107
Test 4	0.0607785	1	0.8053

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 0.1

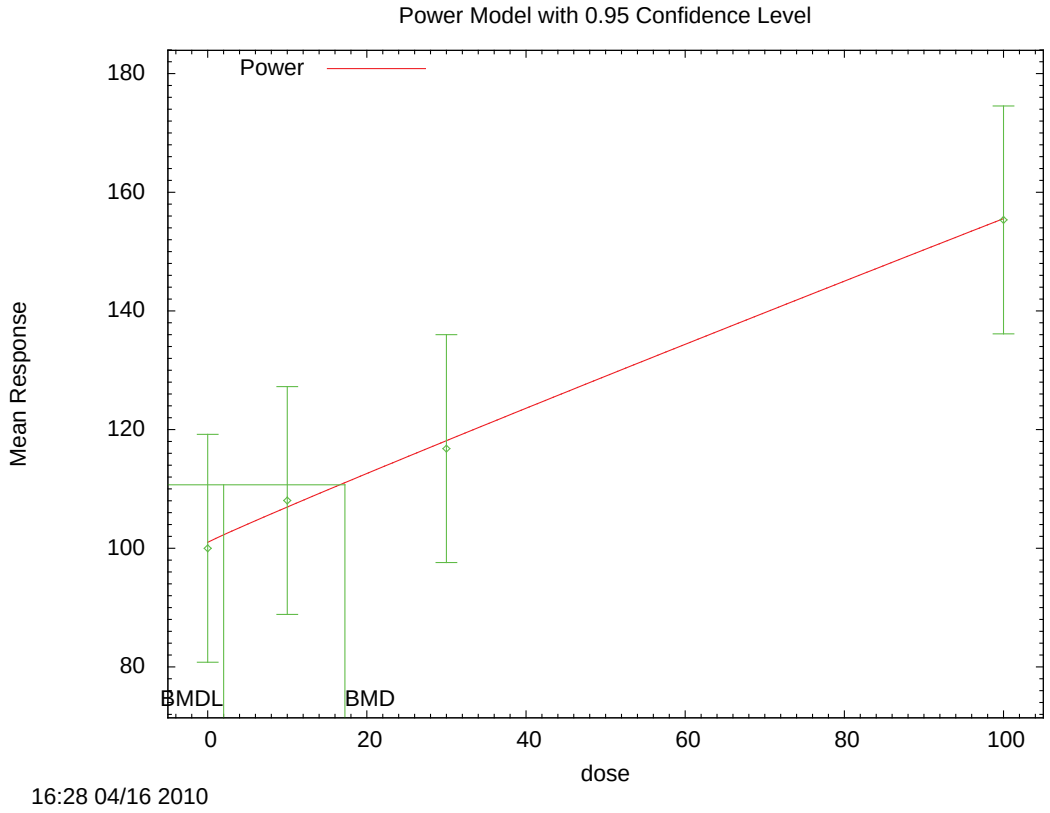
Risk Type = Relative risk

Confidence level = 0.95

BMD = 17.2469

BMDL = 2.00336

G.3.9.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.3.10. Franc et al. (2001): L-E Rats, Relative Liver Weight

G.3.10.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.245	210.148	5.143E+01	3.188E+01	
Exponential (M3)	2	0.245	210.148	5.143E+01	3.188E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.607	209.599	1.476E+01	3.702E+00	
Exponential (M5)	1	0.607	209.599	1.476E+01	3.702E+00	power hit bound (*d* = 1)
Hill[b]	**1**	**0.703**	**209.480**	**1.321E+01**	**1.591E+00**	***n* lower bound hit (*n* = 1)**
Linear	2	0.273	209.933	4.753E+01	2.788E+01	
Polynomial, 3-degree	1	<0.0001	10.000	1.505E+01	error	
Power	2	0.273	209.933	4.753E+01	2.788E+01	power bound hit (power = 1)
Hill, unrestricted[c]	0	N/A	211.341	1.163E+01	9.756E−01	unrestricted (*n* = 0.418)
Power, unrestricted	1	0.940	209.340	1.155E+01	1.513E−02	unrestricted (power = 0.394)

[a] Nonconstant variance model selected (*p* = 0.0632).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.10.2. *Output for Selected Model: Hill*

Franc et al. (2001): L-E Rats, Relative Liver Weight

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\89_Franc_2001_LE_RelLivWt_Hill_1.(d)
        Gnuplot Plotting File:  C:\1\89_Franc_2001_LE_RelLivWt_Hill_1.plt
                                          Fri Apr 16 16:29:20 2010
 ======================================================================

 Figure 5, L-E rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

lalpha =	5.41581
rho =	0
intercept =	100
v =	22.225
n =	0.329526
k =	40.8403

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-1	-0.18	0.38	0.2
rho	-1	1	0.17	-0.38	-0.2
intercept	-0.18	0.17	1	-0.13	0.39
v	0.38	-0.38	-0.13	1	0.77
k	0.2	-0.2	0.39	0.77	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-15.3958	17.0376	-48.7889	17.9973
rho	4.38043	3.61867	-2.71204	11.4729
intercept	99.5667	3.7178	92.28	106.853
v	28.8965	12.6477	4.10739	53.6856
n	1	NA		
k	25.1273	30.138	-33.9421	84.1966

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	100	99.6	10	10.8	0.114
10	8	106	108	17.9	12.8	-0.329
30	8	117	115	8.97	14.9	0.288
100	8	122	123	19.9	17	-0.0723

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-100.516456	5	211.032912
A2	-96.870820	8	209.741641
A3	-99.666984	6	211.333969
fitted	-99.739888	5	209.479776
R	-105.717087	2	215.434174

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.6925	6	0.007048
Test 2	7.29127	3	0.06317

```
   Test 3              5.59233          2         0.06104
   Test 4             0.145807          1          0.7026

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =           0.1

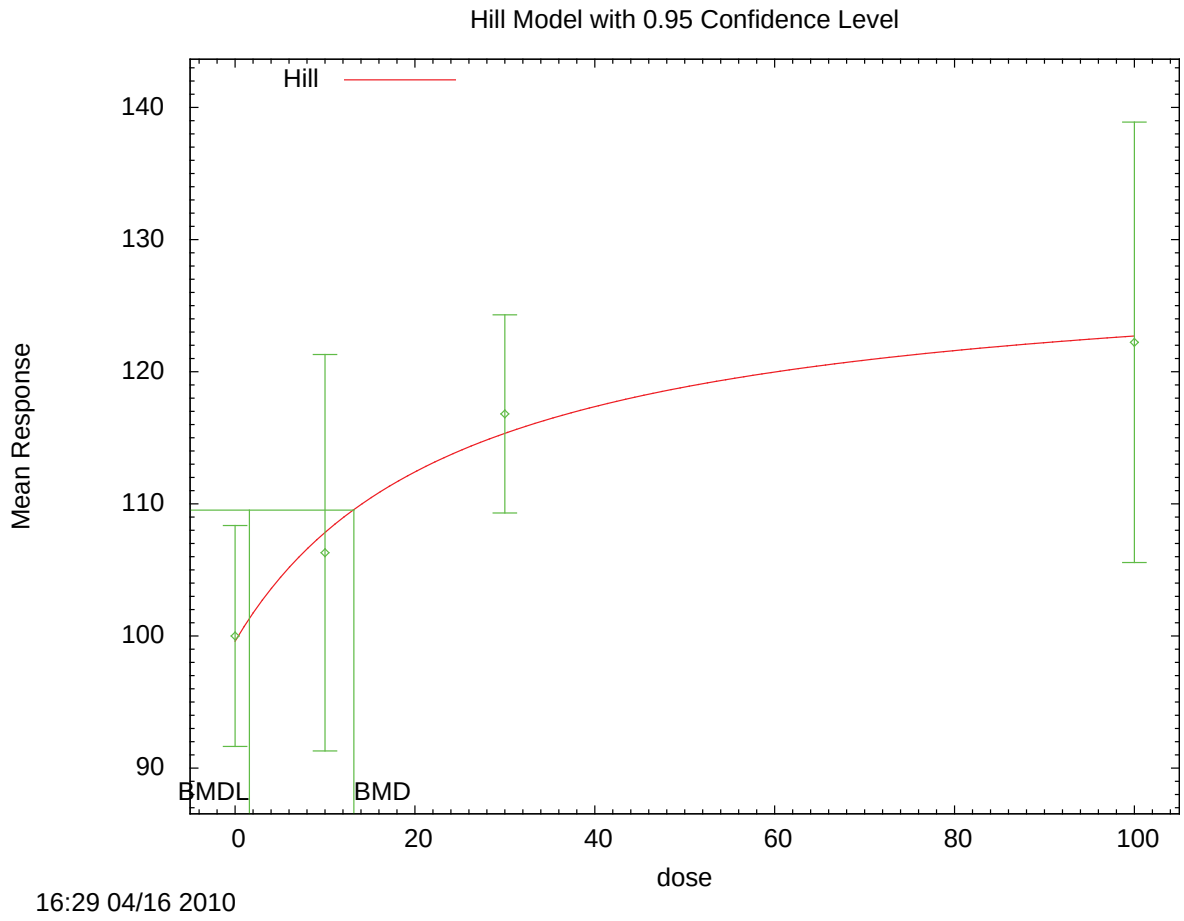
Risk Type        =     Relative risk

Confidence level =           0.95

             BMD =        13.2094

            BMDL =       1.59127
```

G.3.10.3. *Figure for Selected Model: Hill*



G.3.10.4. *Output for Additional Model Presented: Hill, Unrestricted*

Franc et al. (2001): L-E Rats, Relative Liver Weight

```
 ====================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\89_Franc_2001_LE_RelLivWt_Hill_U_1.(d)
        Gnuplot Plotting File:  C:\1\89_Franc_2001_LE_RelLivWt_Hill_U_1.plt
                                          Fri Apr 16 16:29:27 2010
 ====================================================================

 Figure 5, L-E rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
```

```
Power parameter is not restricted
The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                Default Initial Parameter Values
                       lalpha =      5.41581
                          rho =            0
                    intercept =          100
                            v =       22.225
                            n =     0.329526
                            k =      40.8403


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n
k

    lalpha            1           -1        -0.21       -0.099         0.23
-0.13

       rho           -1            1         0.21        0.099        -0.23
0.13

 intercept        -0.21         0.21            1        0.023         0.14
0.011

         v       -0.099        0.099        0.023            1        -0.84
1

         n         0.23        -0.23         0.14        -0.84            1
-0.88

         k        -0.13         0.13        0.011            1        -0.88
1


                                 Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         -18.8355          18.0637            -54.2397
16.5688
            rho           5.1098          3.83743            -2.41144
12.631
      intercept           99.526          3.53402             92.5994
106.453
```

```
              v          286.422           4487.2            -8508.33
9081.17
              n         0.418159         0.457476           -0.478477
1.31479
              k          32981.9     1.52481e+006       -2.95559e+006
3.02155e+006


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0     8        100         99.5           10         10.3           0.13
   10     8        106          109         17.9           13         -0.563
   30     8        117          114         8.97         14.6          0.529
  100     8        122          123         19.9         17.7        -0.0942

Degrees of freedom for Test A3 vs fitted <= 0


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -100.516456            5     211.032912
             A2          -96.870820            8     209.741641
             A3          -99.666984            6     211.333969
         fitted          -99.670736            6     211.341472
              R         -105.717087            2     215.434174


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
```

```
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              17.6925          6        0.007048
   Test 2              7.29127          3         0.06317
   Test 3              5.59233          2         0.06104
   Test 4           0.00750301          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


        Benchmark Dose Computation

Specified effect =           0.1

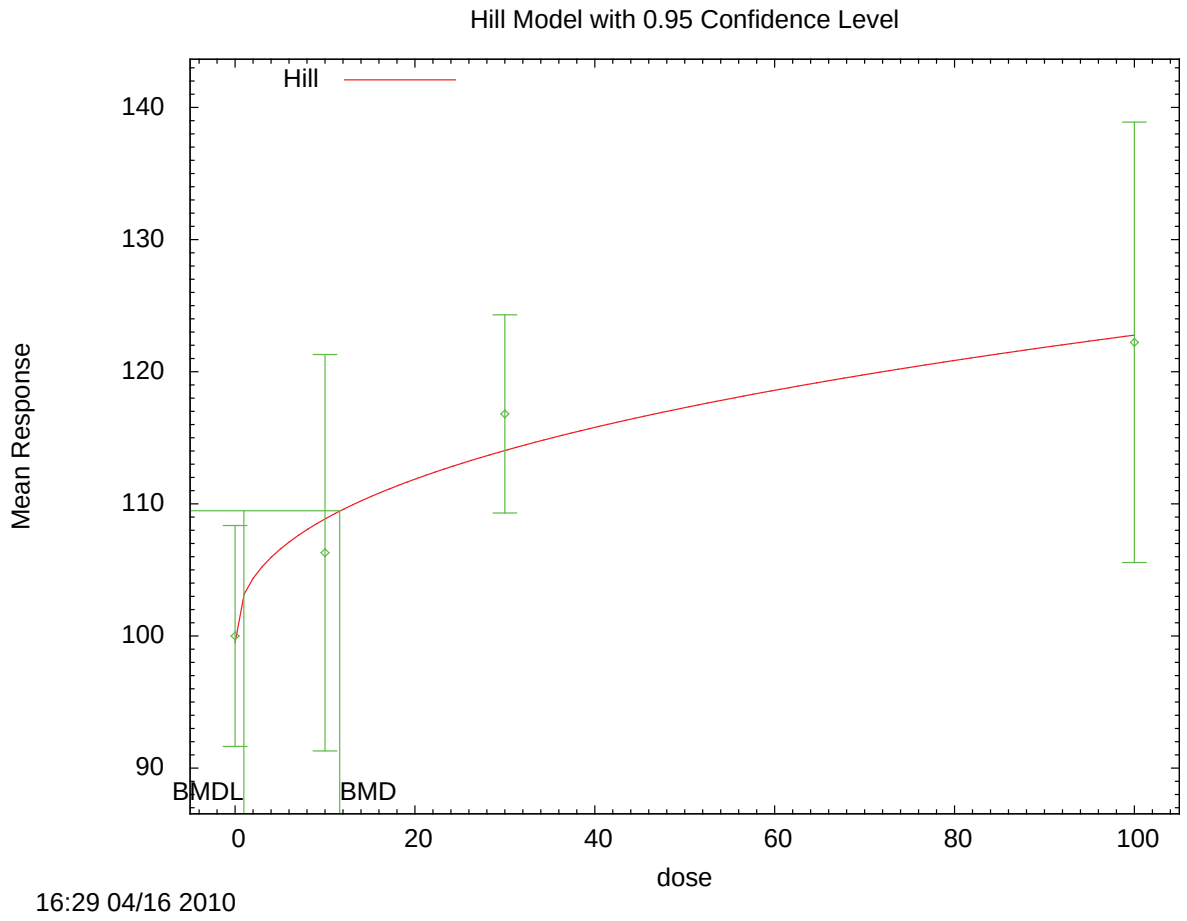
Risk Type        =     Relative risk

Confidence level =           0.95

             BMD =        11.6342

            BMDL =      0.975601
```

G.3.10.5. *Figure for Additional Model Presented: Hill, Unrestricted*



G.3.11. Franc et al. (2001): S-D Rats, Relative Thymus Weight

G.3.11.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.551	285.890	6.730E+00	3.627E+00	
Exponential (M3)	1	<0.0001	303.995	3.858E+02	6.615E−01	
Exponential (M4)[b]	**1**	**0.972**	**286.698**	**3.559E+00**	**1.714E+00**	
Exponential (M5)	0	N/A	288.696	3.796E+00	1.714E+00	
Hill	0	N/A	288.696	4.299E+00	9.311E−01	
Linear	2	0.252	287.456	1.330E+01	1.062E+01	
Polynomial, 3-degree[c]	2	0.252	287.456	1.330E+01	1.062E+01	
Power	2	0.252	287.456	1.330E+01	1.062E+01	power bound hit (power = 1)
Power, unrestricted	1	0.510	287.131	5.049E−01	4.411E−04	unrestricted (power = 0.388)

[a] Nonconstant variance model selected ($p = 0.0320$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.11.2. *Output for Selected Model: Exponential (M4)*

Franc et al. (2001): S-D Rats, Relative Thymus Weight

```
 ========================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\91_Franc_2001_SD_RelThyWt_Exp_1.(d)
        Gnuplot Plotting File:
                                             Fri Apr 16 16:30:07 2010
 ========================================================================

 Figure 5, SD rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	3.35464
rho	1.08199
a	105
b	0.0424361
c	0.206726
d	1

Parameter Estimates

Variable	Model 4
lnalpha	2.54324
rho	1.25901
a	108.904
b	0.0379343
c	0.208146
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	100	83.2
10	8	91.17	47.97
30	8	51.41	43.48
100	8	22.79	29.98

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	108.9	68.33	-0.3686
10	81.68	57.01	0.4706
30	50.3	42.02	0.0748
100	24.61	26.79	-0.192

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-141.9834	5	293.9669
A2	-137.5818	8	291.1637
A3	-138.3482	6	288.6964
R	-146.9973	2	297.9946
4	-138.3488	5	286.6976

Additive constant for all log-likelihoods = -29.41. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	18.83	6	0.004459
Test 2	8.803	3	0.03203
Test 3	1.533	2	0.4647
Test 6a	0.001216	1	0.9722

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous

```
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 0.100000

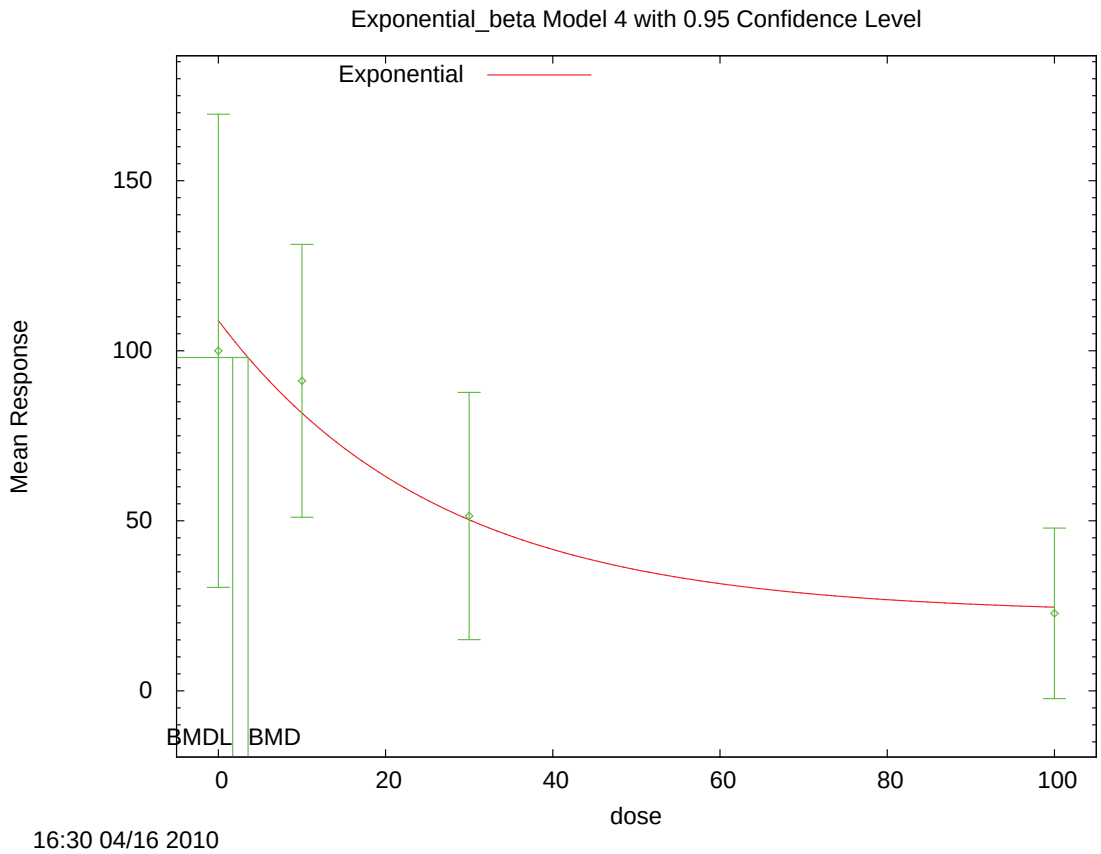
         Risk Type = Relative deviation

  Confidence Level = 0.950000

               BMD =      3.55883

              BMDL =      1.71399
```

G.3.12. Figure for Selected Model: Exponential (M4)



G.3.13. Output for Additional Model Presented: Polynomial, 3-Degree

Franc et al. (2001): S-D Rats, Relative Thymus Weight

```
 ====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\91_Franc_2001_SD_RelThyWt_Poly_1.(d)
        Gnuplot Plotting File:  C:\1\91_Franc_2001_SD_RelThyWt_Poly_1.plt
                                          Fri Apr 16 16:30:11 2010
 ====================================================================

 Figure 5, SD rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   The polynomial coefficients are restricted to be negative
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	8.0075
rho =	0
beta_0 =	100
beta_1 =	-0.352259
beta_2 =	-0.0585481
beta_3 =	0

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -beta_2 -beta_3
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.031	-0.016
rho	-0.99	1	-0.034	0.022
beta_0	0.031	-0.034	1	-0.84
beta_1	-0.016	0.022	-0.84	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	2.92328	1.7394	-0.485884	6.33243
rho	1.18295	0.423359	0.353177	2.01271
beta_0	89.841	13.7418	62.9076	116.774
beta_1	-0.675682	0.175538	-1.01973	-0.331634
beta_2	0	NA		
beta_3	0	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus

has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	100	89.8	83.2	61.7	0.466
10	8	91.2	83.1	48	58.9	0.388
30	8	51.4	69.6	43.5	53	-0.968
100	8	22.8	22.3	30	27	0.0543

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-141.983433	5	293.966865
A2	-137.581833	8	291.163667
A3	-138.348184	6	288.696368
fitted	-139.728204	4	287.456407
R	-146.997301	2	297.994602

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.8309	6	0.004459
Test 2	8.8032	3	0.03203
Test 3	1.5327	2	0.4647
Test 4	2.76004	2	0.2516

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 0.1

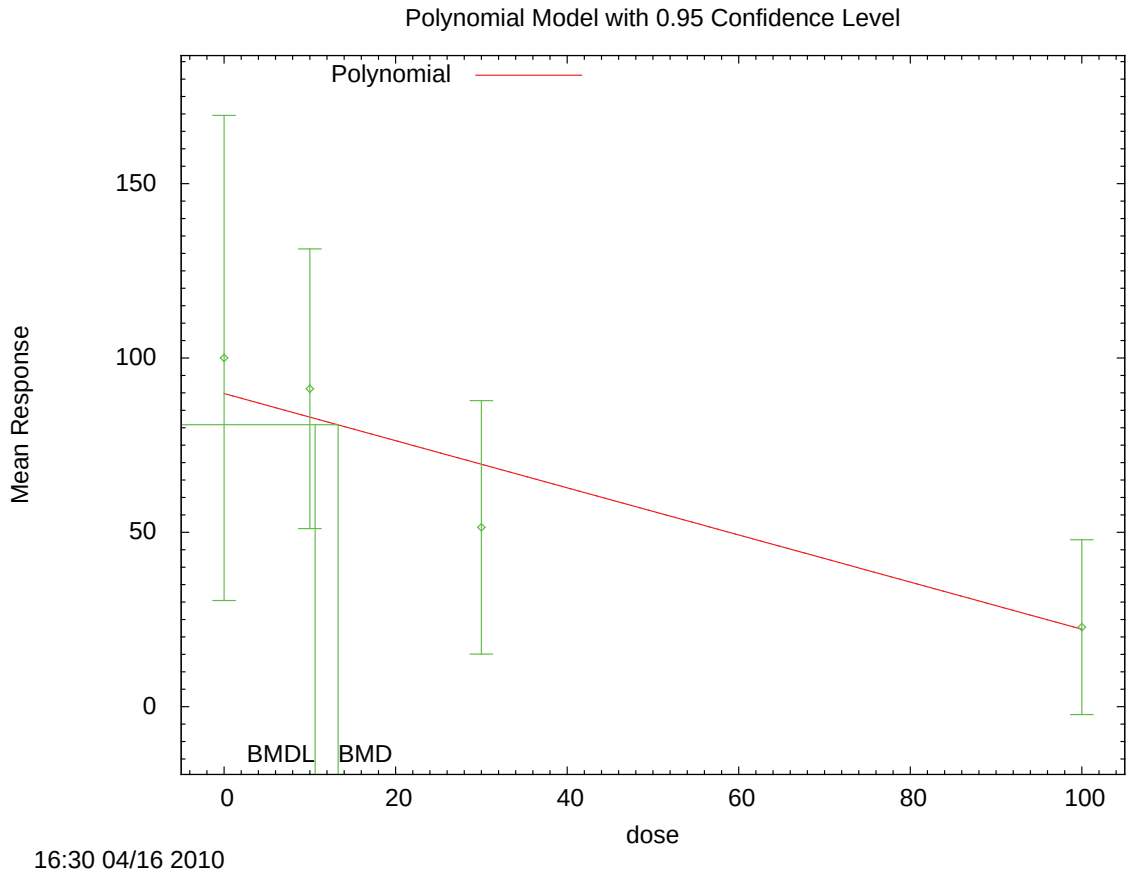
Risk Type = Relative risk

Confidence level = 0.95

BMD = 13.2963

BMDL = 10.6163

G.3.13.1. ***Figure for Additional Model Presented: Polynomial, 3-Degree***



G.3.14. Franc et al. (2001): L-E Rats, Relative Thymus Weight

G.3.14.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.394	301.666	6.406E+00	2.122E+00	
Exponential (M3)	2	0.394	301.666	6.406E+00	2.122E+00	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.317**	**302.808**	**3.520E+00**	**1.067E+00**	
Exponential (M5)	0	N/A	303.805	1.280E+01	1.450E+00	
Hill	0	N/A	303.805	1.195E+01	9.965E−01	
Linear	2	0.236	302.690	1.429E+01	9.087E+00	
Polynomial, 3-degree	2	0.236	302.690	1.429E+01	9.087E+00	
Power	2	0.236	302.690	1.429E+01	9.087E+00	power bound hit (power = 1)
Power, unrestricted	1	0.175	303.643	1.297E+00	2.703E−08	unrestricted (power = 0.454)

[a] Constant variance model selected (*p* = 0.5063).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.14.2. *Output for Selected Model: Exponential (M4)*

Franc et al. (2001): L-E Rats, Relative Thymus Weight

```
 ========================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\92_Franc_2001_LE_RelThyWt_ExpCV_1.(d)
        Gnuplot Plotting File:
                                             Fri Apr 16 16:30:58 2010
 ========================================================================

 Figure 5, L-E rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

```
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                Initial Parameter Values

                Variable          Model 4
                --------          --------
                  lnalpha               8.1814
                      rho(S)                 0
                        a                  105
                        b            0.0413945
                        c               0.3173
                        d                    1

  (S) = Specified


                  Parameter Estimates

                 Variable          Model 4
                 --------          -------
                  lnalpha             8.21275
                      rho                   0
                        a              106.57
                        b           0.0425967
                        c             0.28189
                        d                   1


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      8          100        54.72
     10      8        95.41        70.46
     30      8        38.69        47.97
    100      8        34.98        77.96


               Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         106.6        60.73           -0.306
     10         80.03        60.73           0.7164
     30         51.36        60.73          -0.5902
    100         31.12        60.73           0.1798
```

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-146.9024	5	303.8049
A2	-145.7361	8	307.4723
A3	-146.9024	5	303.8049
R	-150.6049	2	305.2098
4	-147.404	4	302.8079

Additive constant for all log-likelihoods = -29.41. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	9.738	6	0.1362
Test 2	2.333	3	0.5063
Test 3	2.333	3	0.5063
Test 6a	1.003	1	0.3166

The p-value for Test 1 is greater than .05. There may not be a diffence between responses and/or variances among the dose levels

```
  Modelling the data with a dose/response curve may not be appropriate.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 0.100000

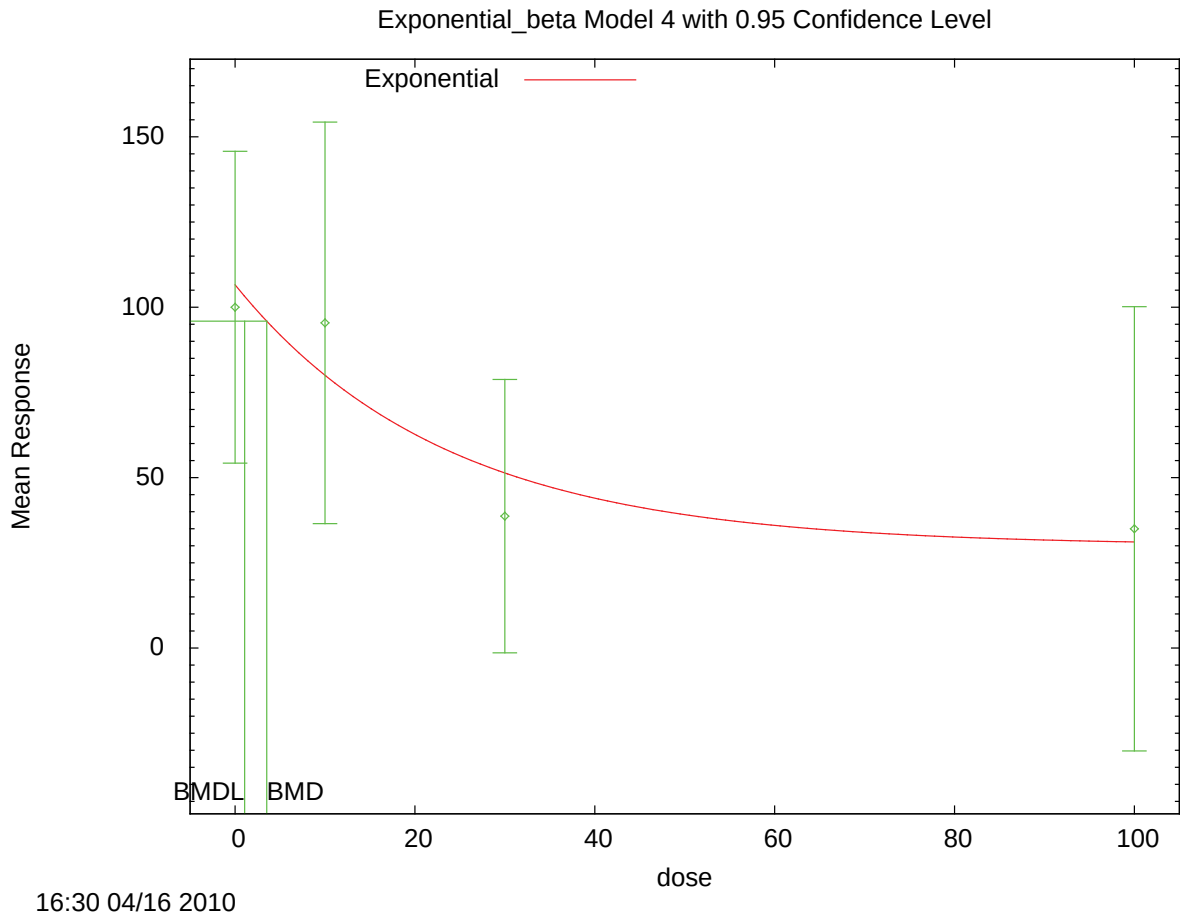
         Risk Type = Relative deviation

  Confidence Level = 0.950000

               BMD =      3.52038

              BMDL =      1.06729
```

G.3.14.3. *Figure for Selected Model: Exponential (M4)*



G.3.15. Franc et al. (2001): H/W Rats, Relative Thymus Weight

G.3.15.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)[b]	2	0.682	261.694	1.366E+01	8.014E+00	
Exponential (M3)	2	0.682	261.694	1.366E+01	8.014E+00	power hit bound (*d* = 1)
Exponential (M4)[c]	**1**	**0.512**	**263.358**	**8.820E+00**	**3.219E+00**	
Exponential (M5)	0	N/A	264.927	1.776E+01	3.500E+00	
Hill	0	N/A	264.927	1.701E+01	2.729E+00	
Linear	2	0.543	262.148	1.919E+01	1.373E+01	
Polynomial, 3-degree	2	0.543	262.148	1.919E+01	1.373E+01	
Power	2	0.543	262.148	1.919E+01	1.373E+01	power bound hit (power = 1)
Power, unrestricted	1	0.381	263.694	8.127E+00	1.406E−01	unrestricted (power = 0.665)

[a] Constant variance model selected (*p* = 0.4331).
[b] Alternate model, BMDS output also presented in this appendix.
[c] Best-fitting model, BMDS output presented in this appendix.

G.3.15.2. *Output for Selected Model: Exponential (M2)*

Franc et al. (2001): H/W Rats, Relative Thymus Weight

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\93_Franc_2001_HW_RelThyWt_ExpCV_1.(d)
        Gnuplot Plotting File:
                                          Fri Apr 16 16:31:40 2010
 ======================================================================

 Figure 5, H/W rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
```

```
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 2
lnalpha	6.96647
rho(S)	0
a	59.5084
b	0.00715458
c	0
d	1

(S) = Specified

Parameter Estimates

Variable	Model 2
lnalpha	6.99043
rho	0
a	99.7761
b	0.00771341
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	100	35.98
10	8	97.53	32.98
30	8	71.02	23.99
100	8	49.29	43.48

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	99.78	32.96	0.01921
10	92.37	32.96	0.4426
30	79.16	32.96	-0.6986

100	46.14	32.96	0.271

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-127.4636	5	264.9271
A2	-126.0925	8	268.185
A3	-127.4636	5	264.9271
R	-132.935	2	269.87
2	-127.8469	3	261.6939

Additive constant for all log-likelihoods = -29.41. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	13.69	6	0.03336
Test 2	2.742	3	0.4331
Test 3	2.742	3	0.4331
Test 4	0.7668	2	0.6815

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose

levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 0.100000

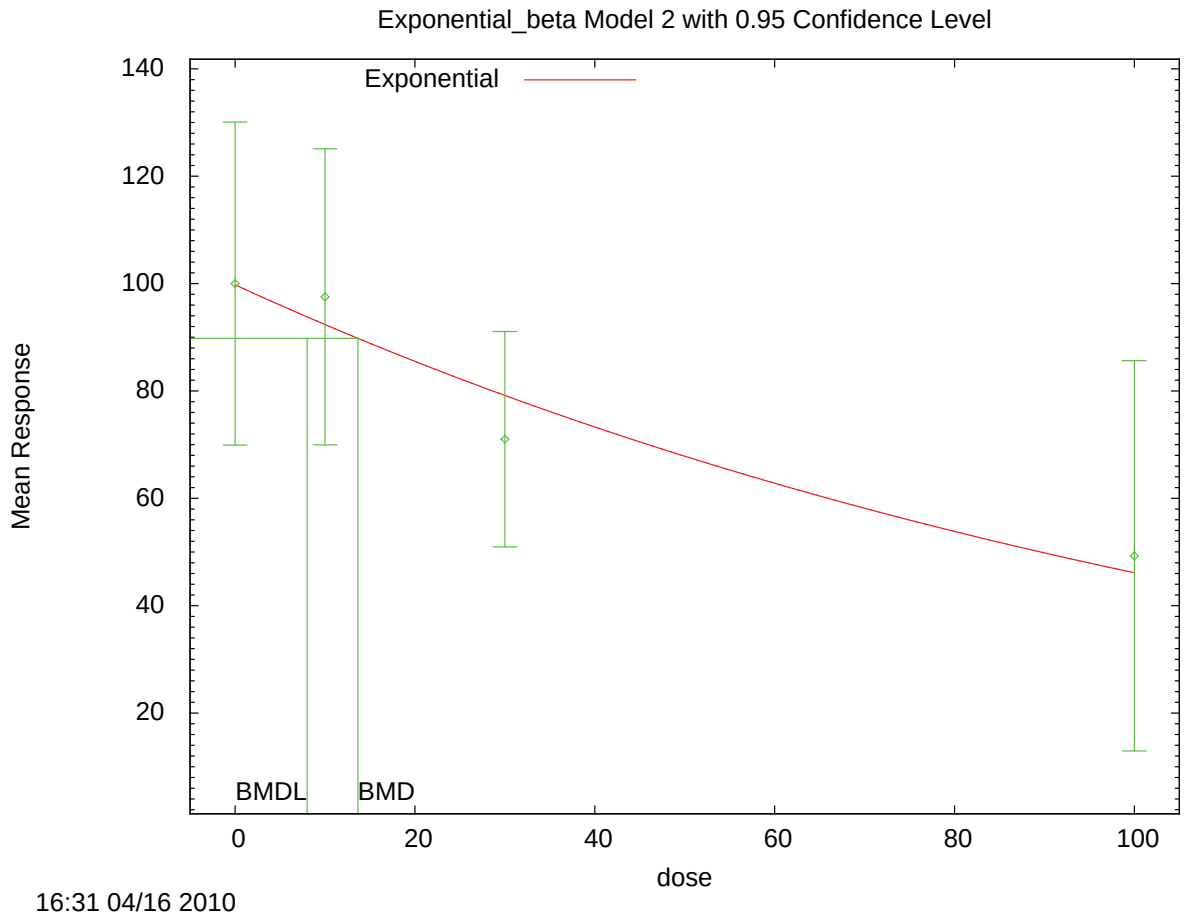
Risk Type = Relative deviation

Confidence Level = 0.950000

BMD = 13.6594

BMDL = 8.01373

G.3.15.3. *Figure for Selected Model: Exponential (M2)*



G.3.15.4. *Output for Additional Model Presented: Exponential (M4)*

Franc et al. (2001): H/W Rats, Relative Thymus Weight

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\93_Franc_2001_HW_RelThyWt_ExpCV_1.(d)
        Gnuplot Plotting File:
                                          Fri Apr 16 16:31:40 2010
 ======================================================================

 Figure 5, H/W rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
```

```
      sign = +1 for increasing trend in data;
      sign = -1 for decreasing trend.

   Model 2 is nested within Models 3 and 4.
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


               Initial Parameter Values

               Variable          Model 4
               --------          --------
                 lnalpha              6.96647
                     rho(S)                 0
                       a                  105
                       b              0.03169
                       c             0.447105
                       d                    1

  (S) = Specified


                  Parameter Estimates

                Variable          Model 4
                --------          -------
                 lnalpha             6.97993
                     rho                   0
                       a             103.091
                       b             0.02048
                       c            0.394904
                       d                   1


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      8          100        35.98
     10      8        97.53        32.98
```

30	8	71.02	23.99
100	8	49.29	43.48

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	103.1	32.78	-0.2667
10	91.54	32.78	0.5166
30	74.46	32.78	-0.2961
100	48.76	32.78	0.04621

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-127.4636	5	264.9271
A2	-126.0925	8	268.185
A3	-127.4636	5	264.9271
R	-132.935	2	269.87
4	-127.6789	4	263.3577

Additive constant for all log-likelihoods = -29.41. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	13.69	6	0.03336
Test 2	2.742	3	0.4331
Test 3	2.742	3	0.4331
Test 6a	0.4306	1	0.5117

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 0.100000

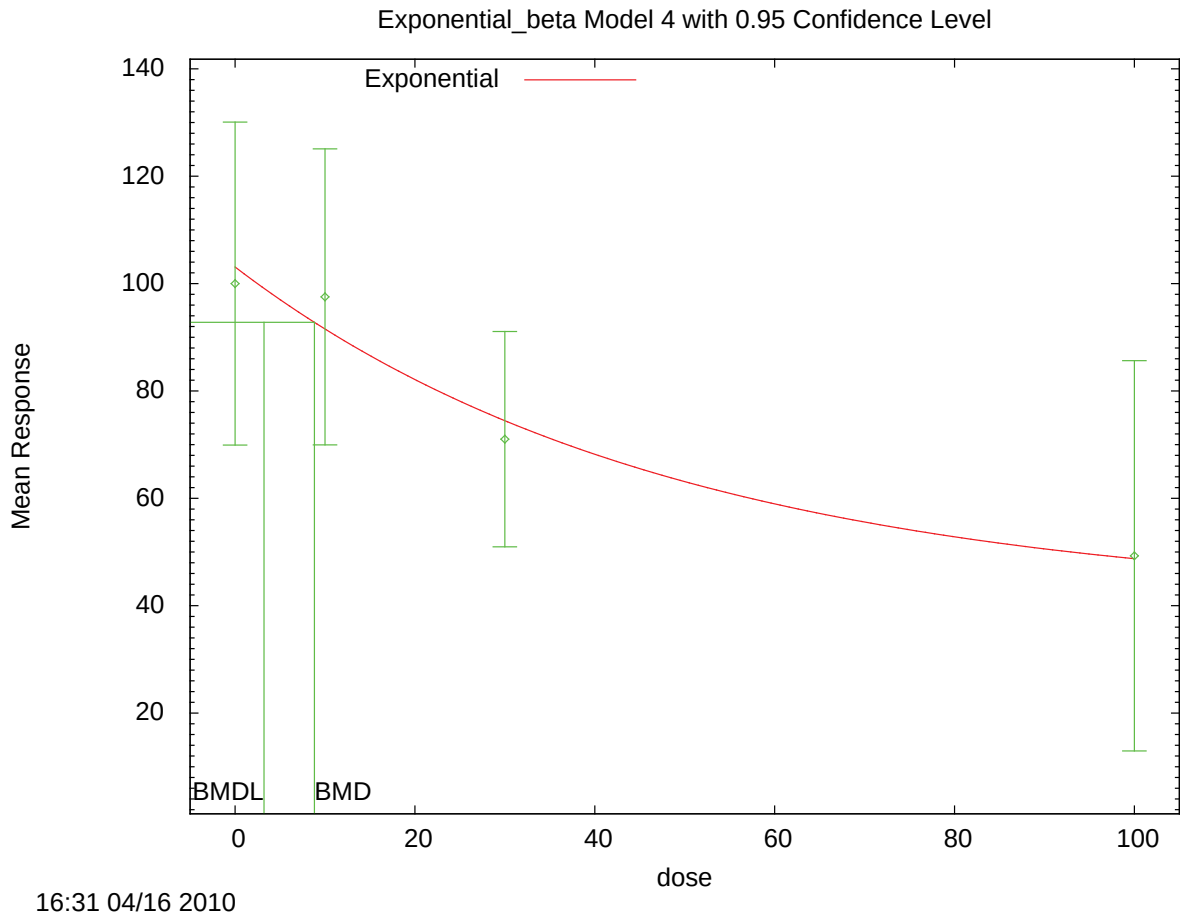
Risk Type = Relative deviation

Confidence Level = 0.950000

BMD = 8.82023

BMDL = 3.21928

G.3.15.5. *Figure for Additional Model Presented: Exponential (M4)*



G.3.16. Hojo et al. (2002): DRL Reinforce per Minute

G.3.16.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Hill	0	N/A	6.465	2.060E+01	1.713E−05	
Linear[b]	**2**	**0.008**	**9.552**	**2.677E+02**	**1.100E+02**	
Polynomial, 3-degree	2	0.008	9.552	2.677E+02	1.100E+02	
Power	2	0.008	9.552	2.677E+02	1.100E+02	power bound hit (power = 1)
Power, unrestricted	1	0.025	6.780	2.187E+00	4.612E−08	unrestricted (power = 0.089)
Exponential (M2)	2	0.006	9.894	3.043E+02	1.505E+02	
Exponential (M3)	2	0.006	9.894	3.043E+02	1.505E+02	power hit bound (*d* = 1)
Exponential (M4)[c]	1	0.062	5.241	1.734E+01	3.827E−02	
Exponential (M5)	0	N/A	6.465	2.140E+01	1.240E−05	

[a] Constant variance model selected (*p* = 0.4321).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.16.2. *Output for Selected Model: Linear*

Hojo et al. (2002): DRL Reinforce Per Minute

```
 ======================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\20_Hojo_2002_DRLrein_LinearCV_1.(d)
        Gnuplot Plotting File:  C:\1\20_Hojo_2002_DRLrein_LinearCV_1.plt
                                          Tue Feb 16 17:29:42 2010
 ======================================================================

 Table 5
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	0.337763	
rho =	0	Specified
beta_0 =	-0.404	
beta_1 =	0.00249615	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	beta_0	beta_1
alpha	1	-1.4e-008	2.2e-008
beta_0	-1.4e-008	1	-0.69
beta_1	2.2e-008	-0.69	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.435671	0.134451	0.172152	0.69919
beta_0	-0.372098	0.198702	-0.761547	0.017352
beta_1	0.00246548	0.00211361	-0.00167711	0.00660807

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	5	-0.814	-0.372	0.448	0.66	-1.5
20	5	-0.364	-0.323	0.821	0.66	-0.14
60	6	0.374	-0.224	0.54	0.66	2.22
180	5	-0.163	0.0717	0.443	0.66	-0.795

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	3.115550	5	3.768900
A2	4.489557	8	7.020886
A3	3.115550	5	3.768900
fitted	-1.775882	3	9.551763
R	-2.435087	2	8.870174

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	13.8493	6	0.03137
Test 2	2.74801	3	0.4321
Test 3	2.74801	3	0.4321
Test 4	9.78286	2	0.007511

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

```
              Benchmark Dose Computation

Specified effect =             1

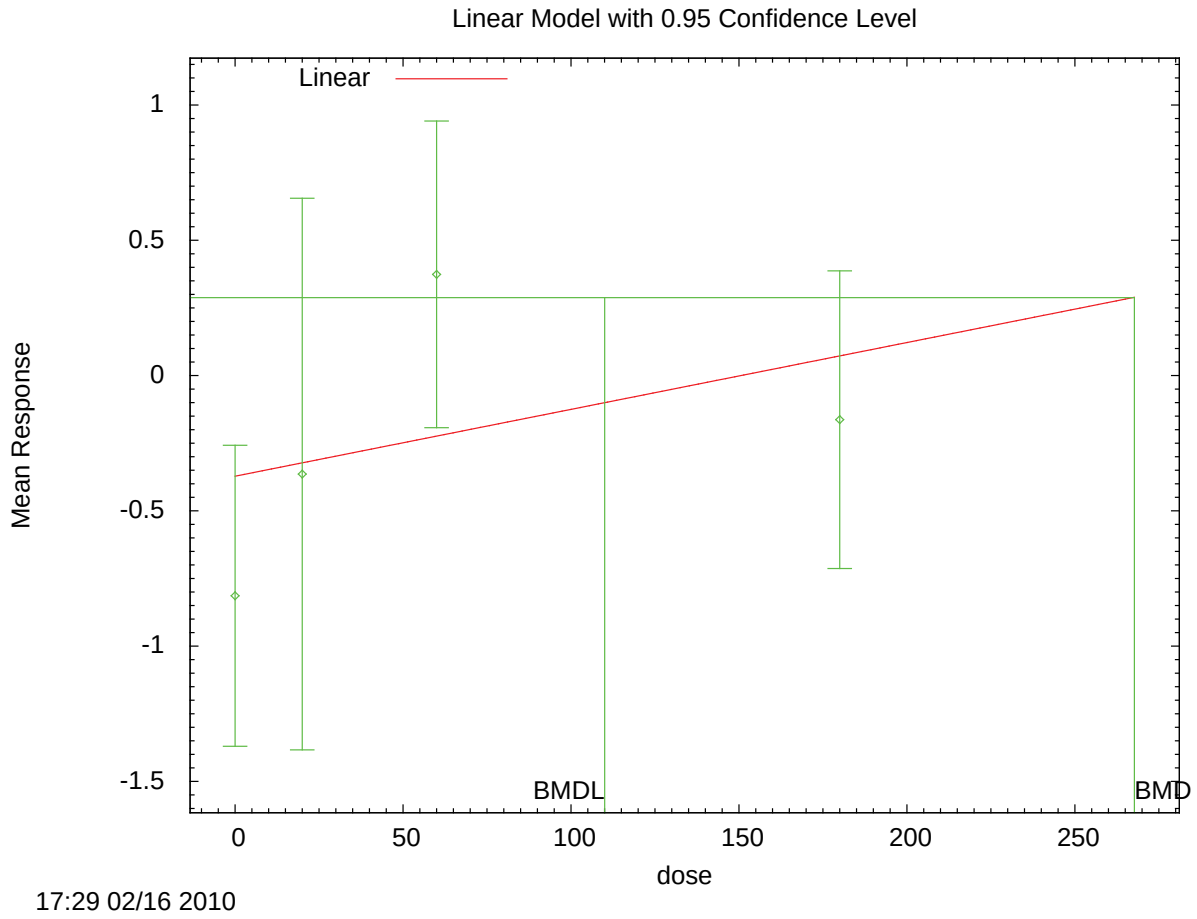
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        267.718


            BMDL =        110.032
```

G.3.16.3. *Figure for Selected Model: Linear*



G.3.16.4. *Output for Additional Model Presented: Exponential (M4)*

Hojo et al. (2002): DRL Reinforce Per Minute

```
 ====================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\21_Hojo_2002_DRLrein_ExpCV_1.(d)
        Gnuplot Plotting File:
                                          Tue Feb 16 17:30:21 2010
 ====================================================================

 Table 5, values adjusted by a constant to allow exponential model
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   rho is set to 0.
   A constant variance model is fit.

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   MLE solution provided: Exact


                   Initial Parameter Values

                   Variable          Model 4
                   --------          --------
                     lnalpha             -1.29672
                         rho(S)                 0
                           a               0.0817
                           b           0.00880867
                           c              16.3733
                           d                    1
```

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	-1.13136
rho	0
a	0.0542868
b	0.0525016
c	18.5072
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	0.086	0.448
20	5	0.536	0.821
60	6	1.274	0.54
180	5	0.737	0.443

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.05429	0.568	0.1249
20	0.6721	0.568	-0.5359
60	0.964	0.568	1.337
180	1.005	0.568	-1.054

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	3.11555	5	3.7689

A2	4.489557	8	7.020886
A3	3.11555	5	3.7689
R	-2.435087	2	8.870174
4	1.379312	4	5.241376

Additive constant for all log-likelihoods = -19.3. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	13.85	6	0.03137
Test 2	2.748	3	0.4321
Test 3	2.748	3	0.4321
Test 6a	3.472	1	0.0624

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model.

Benchmark Dose Computations:

Specified Effect = 1.000000

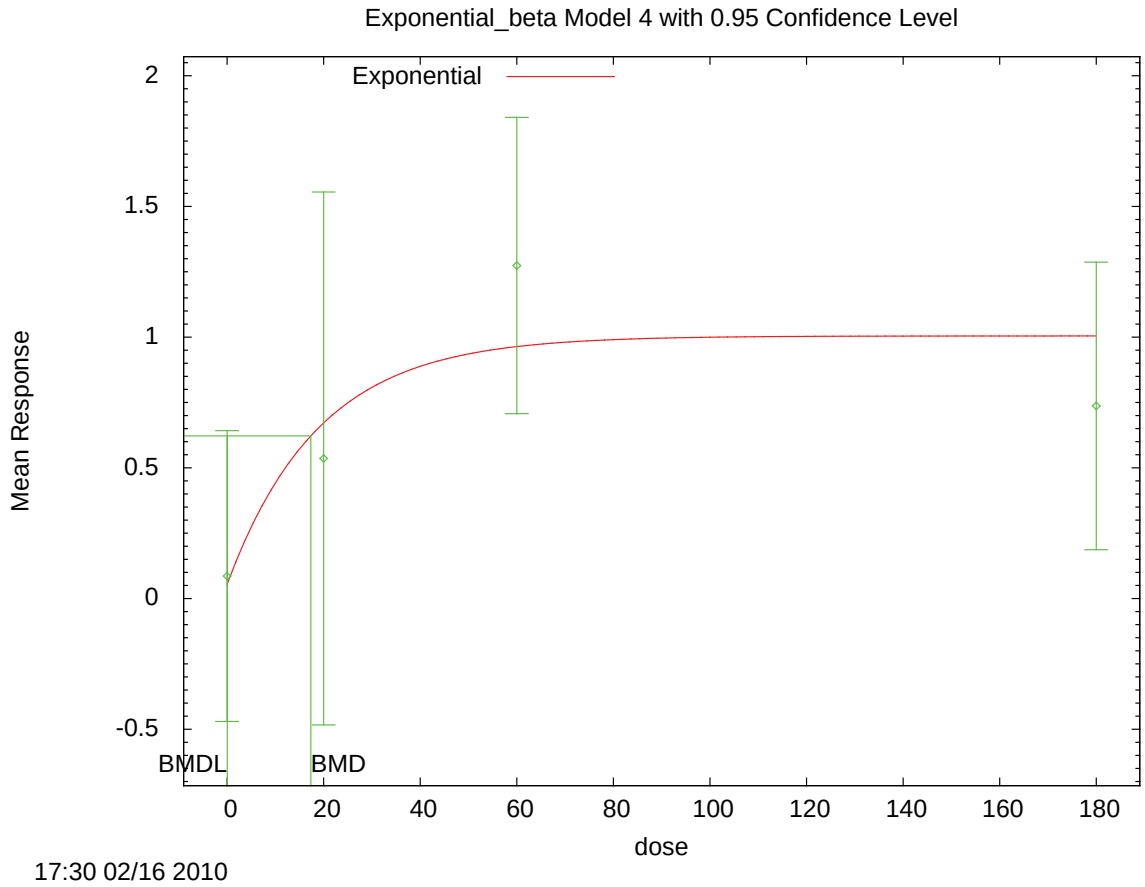
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 17.3391

BMDL = 0.0382689

G.3.16.5. *Figure for Additional Model Presented: Exponential (M4)*



G.3.17. Hojo et al. (2002): DRL Response per Minute

G.3.17.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Hill	0	N/A	126.353	1.646E+01	1.800E−13	
Linear	2	0.004	132.825	2.067E+02	9.757E+01	
Polynomial, 3-degree	2	0.004	132.825	2.067E+02	9.757E+01	
Power	2	0.004	132.825	2.067E+02	9.757E+01	power bound hit (power = 1)
Power, unrestricted	2	0.741	122.455	1.800E+04	error	unrestricted (power = 0)
Exponential (M2)	2	0.568	122.985	6.184E+00	error	
Exponential (M3)	2	0.568	122.985	6.184E+00	error	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.479**	**124.356**	**4.775E+00**	**2.704E−01**	
Exponential (M5)	0	N/A	126.353	1.118E+01	2.127E−01	

[a] Constant variance model selected (*p* = 0.3004).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.17.2. *Output for Selected Model: Exponential (M4)*

Hojo et al. (2002): DRL Response Per Minute

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\23_Hojo_2002_DRLresp_ExpCV_1.(d)
        Gnuplot Plotting File:
                                            Tue Feb 16 17:31:24 2010
 ======================================================================

 Table 5, values adjusted by a constant to allow exponential model
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   rho is set to 0.
```

A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	4.51689
rho(S)	0
a	24.6362
b	0.0212679
c	0.0184785
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	4.54075
rho	0
a	23.465
b	0.12859
c	0.100615
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	23.46	7.986
20	5	4.013	10.96
60	6	0.478	7.194
180	5	4.594	15.23

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	23.47	9.683	-0.0004677
20	3.973	9.683	0.009182
60	2.37	9.683	-0.4787
180	2.361	9.683	0.5157

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-57.92733	5	125.8547
A2	-56.09669	8	128.1934
A3	-57.92733	5	125.8547
R	-64.49611	2	132.9922
4	-58.17787	4	124.3557

Additive constant for all log-likelihoods = -19.3. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	16.8	6	0.01005
Test 2	3.661	3	0.3004
Test 3	3.661	3	0.3004
Test 6a	0.5011	1	0.479

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

```
  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

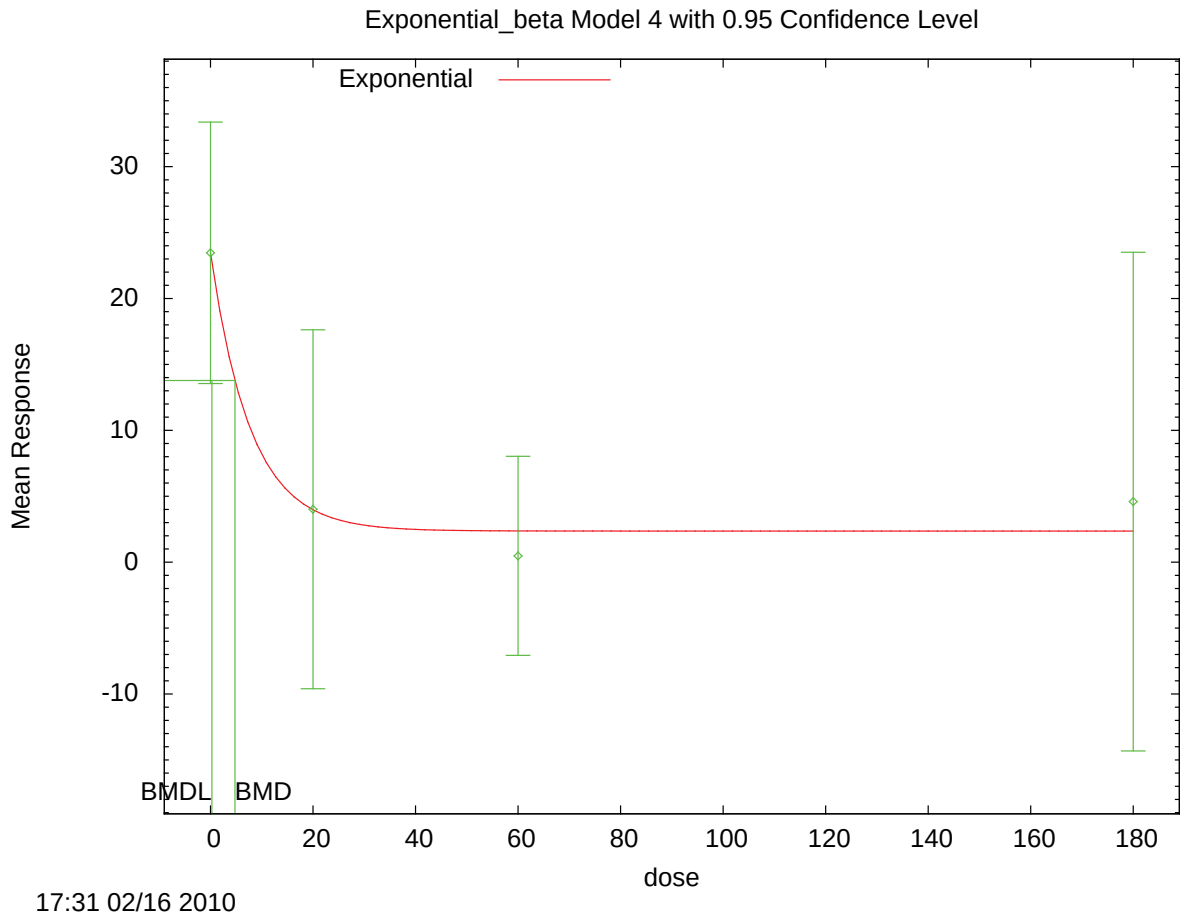
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      4.77493

              BMDL =     0.270447
```

G.3.17.3. *Figure for Selected Model: Exponential (M4)*



G.3.18. Kattainen et al. (2001): 3rd Molar Eruption, Female

G.3.18.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Logistic	3	0.292	89.060	1.941E+02	1.390E+02	negative intercept (intercept = −1.508)
Log-logistic[a]	**3**	**0.923**	**85.535**	**4.763E+01**	**2.481E+01**	**slope bound hit (slope = 1)**
Log-probit	3	0.390	88.231	1.574E+02	9.512E+01	slope bound hit (slope = 1)
Probit	3	0.306	88.919	1.858E+02	1.370E+02	negative intercept (intercept = −0.927)
Multistage, 4-degree	3	0.641	86.798	8.677E+01	5.520E+01	final ß = 0
Log-logistic, unrestricted[b]	2	0.952	87.157	2.599E+01	1.730E+00	unrestricted (slope = 0.794)
Log-probit, unrestricted	2	0.941	87.179	2.813E+01	2.334E+00	unrestricted (slope = 0.478)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.18.2. *Output for Selected Model: Log-Logistic*

Kattainen et al. (2001): 3rd Molar Eruption, Female

```
 ========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\24_Katt_2001_Erup_LogLogistic_BMR1.(d)
        Gnuplot Plotting File:  C:\1\24_Katt_2001_Erup_LogLogistic_BMR1.plt
                                          Tue Feb 16 17:31:52 2010
 ========================================================================

 Figure 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.0625
intercept = -6.063
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -slope
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	background	intercept
background	1	-0.56
intercept	-0.56	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0846785	*	*	*
intercept	-6.06063	*	*	*
slope	1	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-40.5286	5			
Fitted model	-40.7674	2	0.477533	3	0.9238
Reduced model	-50.7341	1	20.411	4	0.0004142

AIC: 85.5347

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual

```
  ----------------------------------------------------------------------
    0.0000     0.0847         1.355     1.000          16       -0.319
   30.0000     0.1445         2.457     3.000          17        0.374
  100.0000     0.2578         3.867     4.000          15        0.078
  300.0000     0.4615         5.538     6.000          12        0.267
 1000.0000     0.7254        13.782    13.000          19       -0.402

 Chi^2 = 0.48      d.f. = 3        P-value = 0.9231


   Benchmark Dose Computation

Specified effect =            0.1

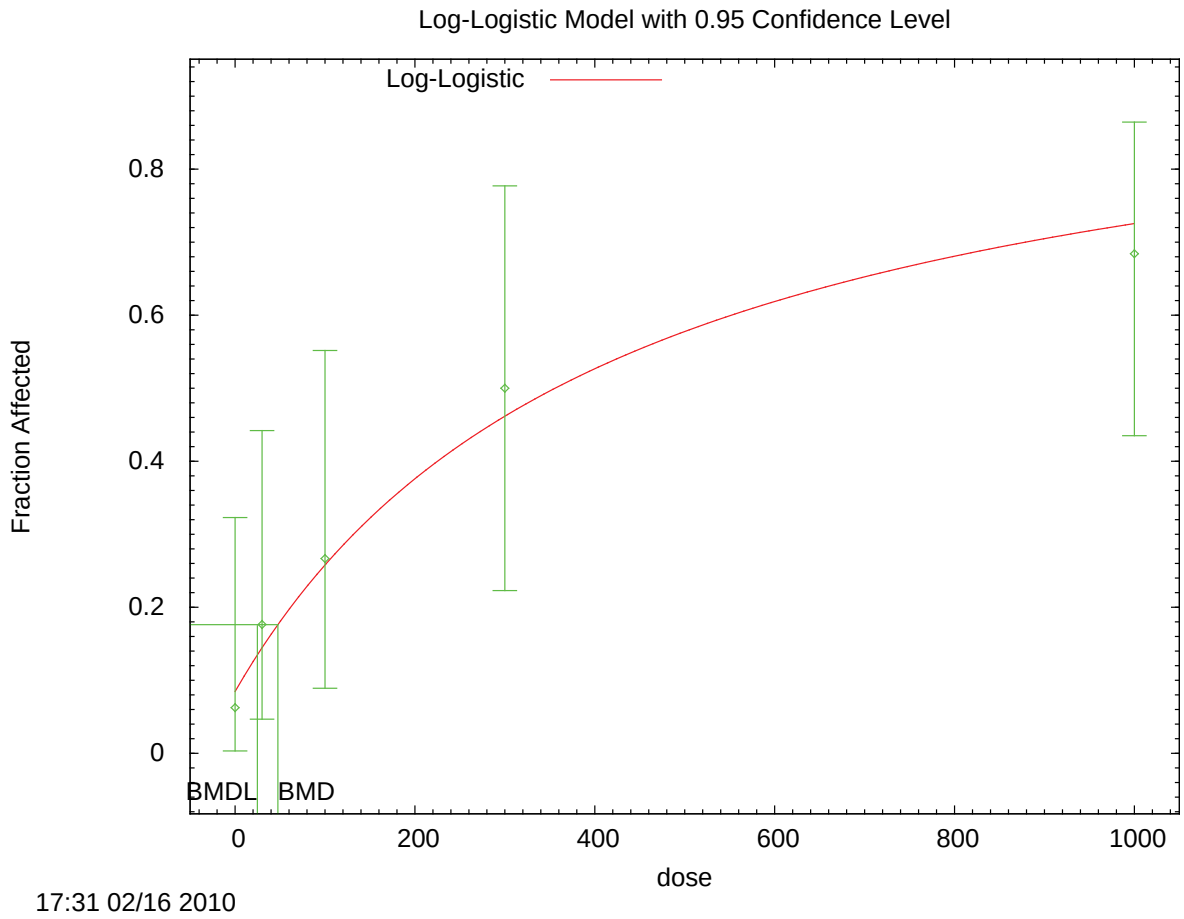
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        47.6274

            BMDL =        24.8121
```

G.3.18.3. *Figure for Selected Model: Log-Logistic*



G.3.18.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Kattainen et al. (2001): 3rd Molar Eruption, Female

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\24_Katt_2001_Erup_LogLogistic_U_BMR1.(d)
        Gnuplot Plotting File:  C:\1\24_Katt_2001_Erup_LogLogistic_U_BMR1.plt
                                          Tue Feb 16 17:31:53 2010
 ======================================================================

 Figure 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
```

Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values

background =	0.0625
intercept =	-4.71231
slope =	0.782659

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.48	0.39
intercept	-0.48	1	-0.98
slope	0.39	-0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0633217	*	*	*
intercept	-4.78282	*	*	*
slope	0.793723	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-40.5286	5			
Fitted model	-40.5783	3	0.0994416	2	0.9515
Reduced model	-50.7341	1	20.411	4	0.0004142

AIC: 87.1566

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0633	1.013	1.000	16	-0.013
30.0000	0.1670	2.840	3.000	17	0.104
100.0000	0.2924	4.387	4.000	15	-0.219
300.0000	0.4721	5.666	6.000	12	0.193
1000.0000	0.6892	13.095	13.000	19	-0.047

Chi^2 = 0.10 d.f. = 2 P-value = 0.9518

Benchmark Dose Computation

Specified effect = 0.1

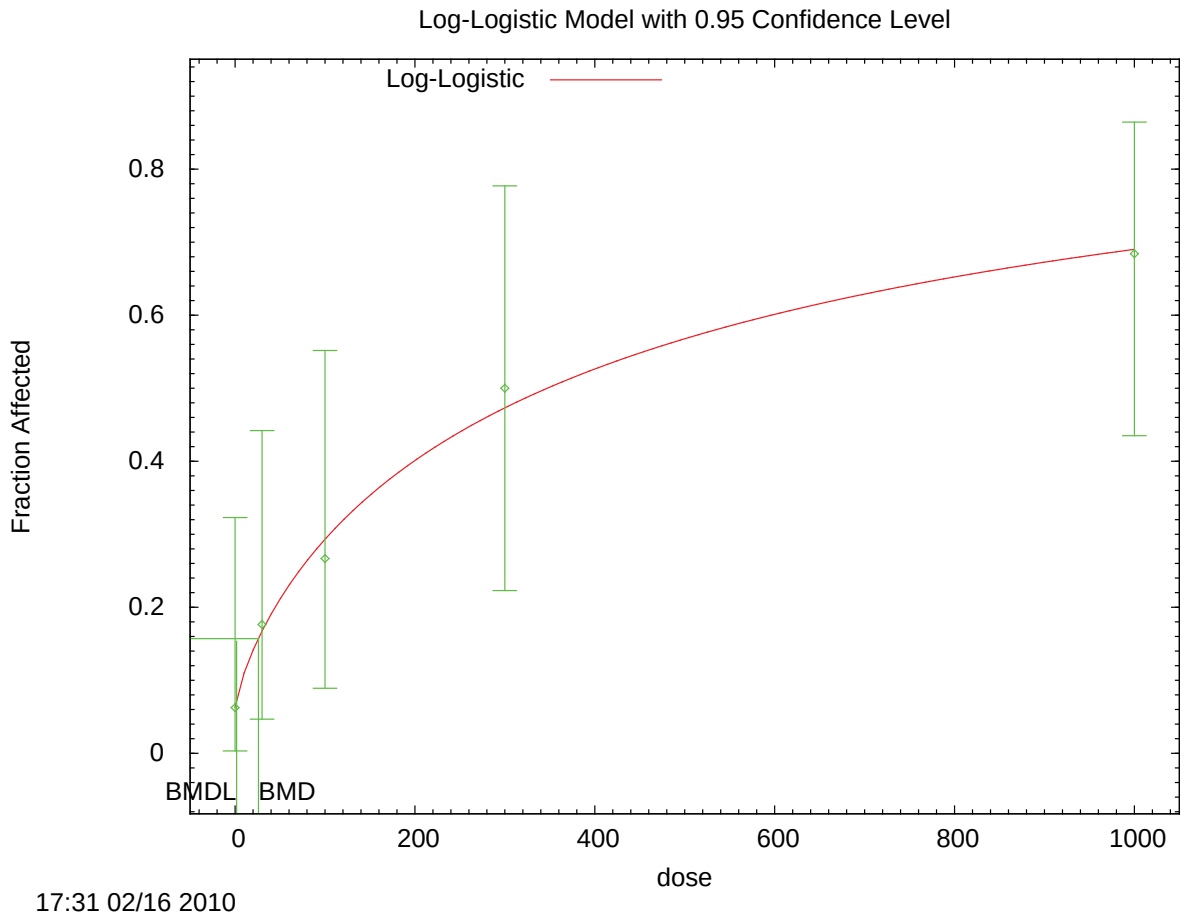
Risk Type = Extra risk

Confidence level = 0.95

BMD = 25.986

BMDL = 1.73001

G.3.18.5. ***Figure for Additional Model Presented: Log-Logistic, Unrestricted***



G.3.19. Kattainen et al. (2001): 3rd Molar Length, Female

G.3.19.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	<0.0001	−122.954	4.027E+02	2.366E+02	
Exponential (M3)	3	<0.0001	−122.954	4.027E+02	2.366E+02	power hit bound (*d* = 1)
Exponential (M4)	2	<0.0001	−80.747	error	error	
Exponential (M5)	1	<0.0001	−78.747	error	error	
Hill[b]	**2**	**0.013**	**−151.152**	**4.052E+00**	**2.144E+00**	***n* lower bound hit (*n* = 1)**
Linear	3	<0.0001	−122.325	4.659E+02	2.963E+02	
Polynomial, 4-degree	3	<0.0001	−122.325	4.659E+02	2.963E+02	
Power	3	<0.0001	−122.325	4.659E+02	2.963E+02	power bound hit (power = 1)
Hill, unrestricted[c]	1	0.087	−154.939	1.913E−02	1.928E−04	unrestricted (*n* = 0.197)
Power, unrestricted	2	0.250	−157.093	9.098E−03	9.097E−03	unrestricted (power = 0.169)

[a] Nonconstant variance model selected (*p* = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.19.2. *Output for Selected Model: Hill*

Kattainen et al. (2001): 3rd Molar Length, Female

```
 ========================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\25_Katt_2001_Length_Hill_1.(d)
        Gnuplot Plotting File:  C:\1\25_Katt_2001_Length_Hill_1.plt
                                          Tue Feb 16 17:32:21 2010
 ========================================================================

 Figure 3 female only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

lalpha =	-2.37155
rho =	0
intercept =	1.85591
v =	-0.507874
n =	0.826204
k =	27.3305

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-0.98	-0.16	0.84	-0.37
rho	-0.98	1	0.2	-0.79	0.39
intercept	-0.16	0.2	1	-0.31	-0.11
v	0.84	-0.79	-0.31	1	-0.48
k	-0.37	0.39	-0.11	-0.48	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	3.34561	1.40443	0.592981	6.09824
rho	-14.3325	2.62129	-19.4701	-9.19484
intercept	1.8548	0.0159017	1.82364	1.88597
v	-0.441166	0.058852	-0.556513	-0.325818
n	1	NA		
k	24.0343	7.84495	8.65852	39.4101

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	16	1.86	1.85	0.0661	0.0637	0.0692
30	17	1.58	1.61	0.185	0.176	-0.768
100	15	1.6	1.5	0.265	0.293	1.28
300	12	1.5	1.45	0.221	0.378	0.527
1000	19	1.35	1.42	0.515	0.423	-0.783

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	56.758717	6	-101.517434
A2	85.856450	10	-151.712901
A3	84.934314	7	-155.868628
fitted	80.575940	5	-151.151880
R	45.373551	2	-86.747101

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	80.9658	8	<.0001
Test 2	58.1955	4	<.0001

```
   Test 3              1.84427          3          0.6053
   Test 4              8.71675          2          0.0128

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =             1

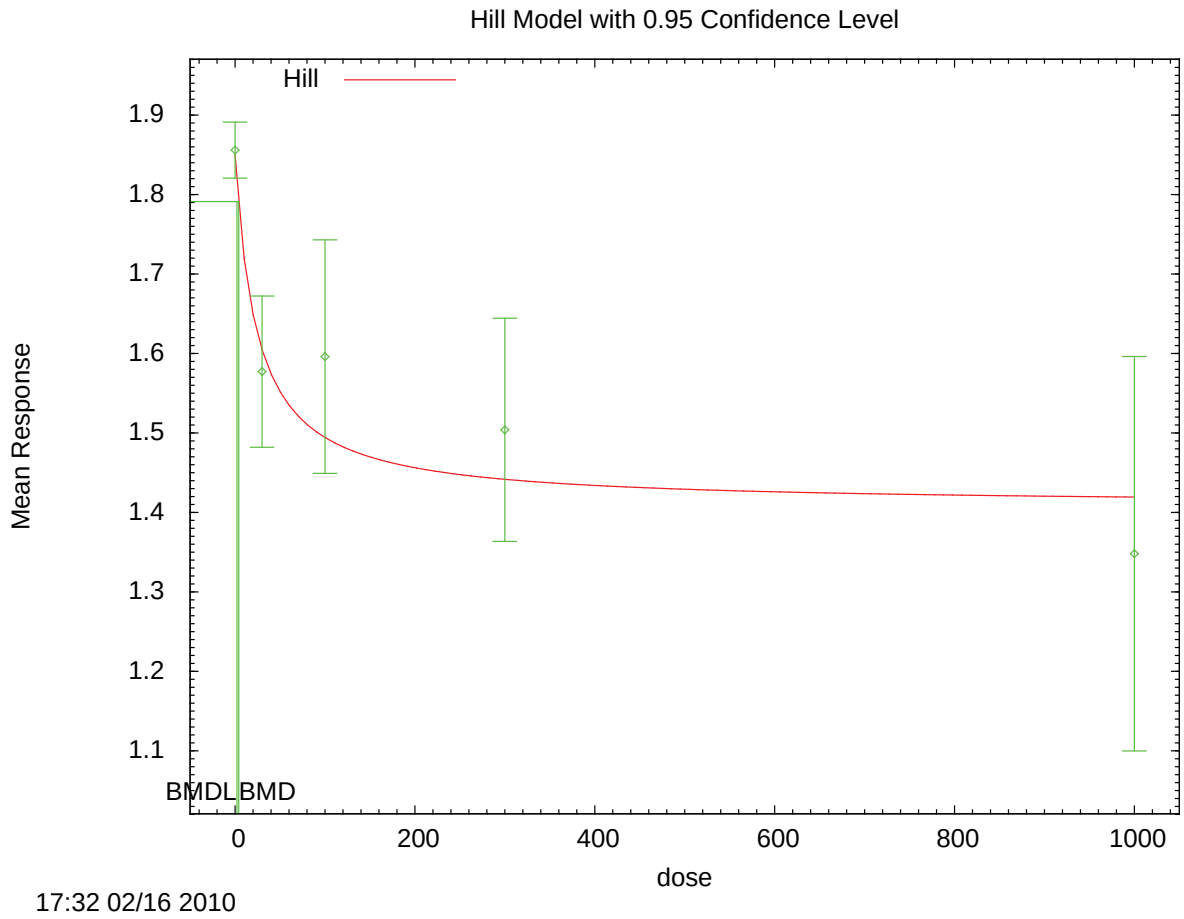
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =        4.05231

            BMDL =       2.14357
```

G.3.19.3. *Figure for Selected Model: Hill*



G.3.19.4. *Output for Additional Model Presented: Hill, Unrestricted*

Kattainen et al. (2001): 3rd Molar Length, Female

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\25_Katt_2001_Length_Hill_U_1.(d)
        Gnuplot Plotting File:  C:\1\25_Katt_2001_Length_Hill_U_1.plt
                                             Tue Feb 16 17:32:21 2010
 ======================================================================

 Figure 3 female only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
```

```
Power parameter is not restricted
The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                Default Initial Parameter Values
                       lalpha =     -2.37155
                          rho =            0
                    intercept =      1.85591
                            v =    -0.507874
                            n =     0.826204
                            k =      27.3305


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n
k

    lalpha            1        -0.98        -0.18         0.18        -0.28
-0.011

       rho        -0.98            1         0.22        -0.18         0.29
0.011

 intercept        -0.18         0.22            1       -0.025       -0.059
0.0019

         v         0.18        -0.18       -0.025            1         0.51
-0.96

         n        -0.28         0.29       -0.059         0.51            1
-0.71

         k       -0.011        0.011       0.0019        -0.96        -0.71
1


                                Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha          3.21882           1.4221            0.431563
6.00607
            rho         -14.0862          2.68292            -19.3446
-8.82777
      intercept          1.85564        0.0160224             1.82424
1.88704
```

```
              v         -2.48572          2.89658            -8.16291
3.19148
              n         0.196925        0.0499318           0.0990606
0.29479
              k     1.92967e+006     1.60869e+007          -2.96e+007
3.34593e+007


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0    16       1.86         1.86       0.0661       0.0643         0.0164
   30    17       1.58          1.6        0.185         0.18         -0.598
  100    15        1.6         1.54        0.265        0.234          0.857
  300    12        1.5         1.48        0.221        0.316          0.259
 1000    19       1.35          1.4        0.515        0.471         -0.466


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1           56.758717            6    -101.517434
            A2           85.856450           10    -151.712901
            A3           84.934314            7    -155.868628
        fitted           83.469680            6    -154.939361
             R           45.373551            2     -86.747101


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
```

Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	80.9658	8	<.0001
Test 2	58.1955	4	<.0001
Test 3	1.84427	3	0.6053
Test 4	2.92927	1	0.08699

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

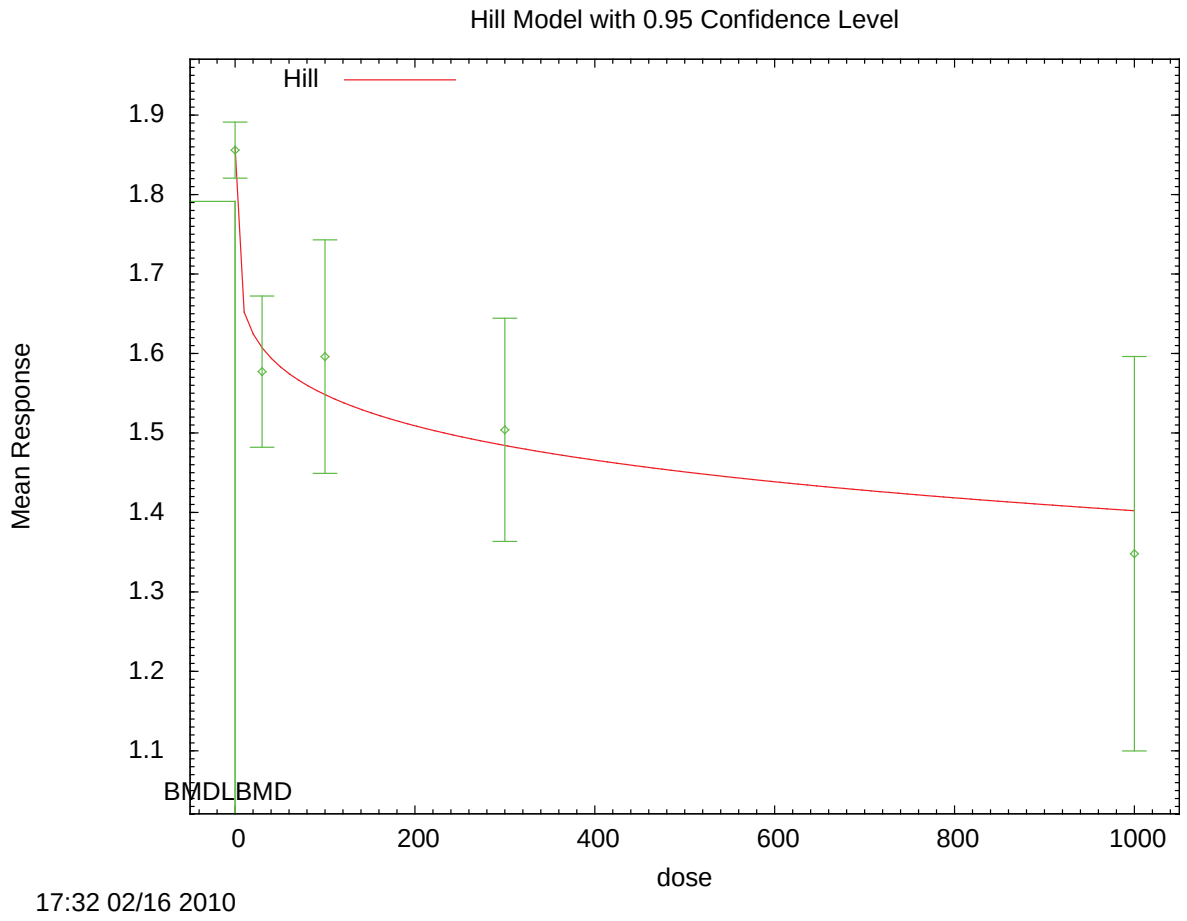
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.0191282

BMDL = 0.0001928

G.3.19.5. *Figure for Additional Model Presented: Hill, Unrestricted*



G.3.20. Keller et al. (2007): Missing Mandibular Molars, CBA J

G.3.20.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	1	0.105	52.490	7.293E+01	2.027E+01	
Logistic	2	0.320	50.095	7.168E+01	5.142E+01	
Log-logistic	1	0.105	52.524	9.278E+01	5.273E+01	
Log-probit	1	0.105	52.524	8.849E+01	5.297E+01	
Multistage, 1-degree[a]	**3**	**0.276**	**49.409**	**2.778E+01**	**1.884E+01**	
Multistage, 2-degree	1	0.126	51.515	4.619E+01	2.214E+01	
Multistage, 3-degree	1	0.141	51.222	4.253E+01	2.212E+01	
Probit	2	0.325	50.032	6.848E+01	4.775E+01	
Weibull	1	0.108	52.216	6.079E+01	2.078E+01	

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.20.2. *Output for Selected Model: Multistage, 1-Degree*

Keller et al. (2007): Missing Mandibular Molars, CBA J

```
 ========================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\1\26_Keller_2007_Molars_Multi1_1.(d)
        Gnuplot Plotting File:  C:\1\26_Keller_2007_Molars_Multi1_1.plt
                                          Tue Feb 16 17:32:56 2010
 ========================================================================

 Table 1 using mandibular molars only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values
Background = 0
Beta(1) = 1.02909e+017

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.00379264	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-21.5798	4			
Fitted model	-23.7044	1	4.24924	3	0.2358
Reduced model	-71.326	1	99.4926	3	<.0001

AIC: 49.4088

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	29	0.000
10.0000	0.0372	0.856	2.000	23	1.260
100.0000	0.3156	9.153	6.000	29	-1.260
1000.0000	0.9775	29.324	30.000	30	0.832

Chi^2 = 3.87 d.f. = 3 P-value = 0.2762

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

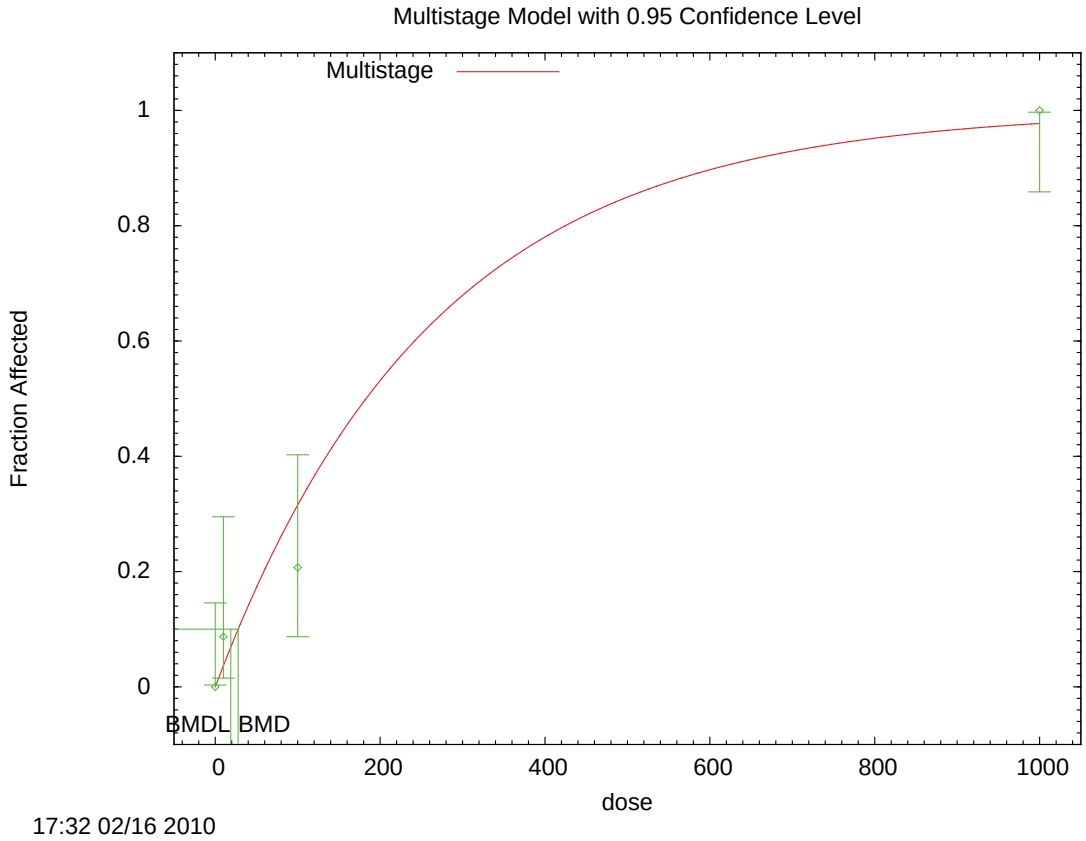
             BMD =        27.7803

            BMDL =        18.8447

            BMDU =        41.7256

Taken together, (18.8447, 41.7256) is a 90     % two-sided confidence
interval for the BMD
```

G.3.20.3. *Figure for Selected Model: Multistage, 1-Degree*



G.3.21. Kociba et al. (1978): Urinary Coproporphyrin, Females

G.3.21.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	<0.0001	84.006	7.054E+01	4.341E+01	
Exponential (M3)	2	<0.0001	84.006	7.054E+01	4.341E+01	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.040**	**70.556**	**1.625E+00**	**7.300E−01**	
Exponential (M5)	0	N/A	69.092	3.128E+00	1.024E+00	
Hill	0	N/A	69.047	6.677E+00	error	
Linear	2	<0.0001	83.713	6.195E+01	3.112E+01	
Polynomial, 3-degree	2	<0.0001	83.713	6.195E+01	3.112E+01	
Power	2	<0.0001	83.713	6.195E+01	3.112E+01	power bound hit (power = 1)
Power, unrestricted	1	0.001	78.260	7.808E−01	1.693E−08	unrestricted (power = 0.306)

[a] Nonconstant variance model selected (*p* = 0.0298).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.21.2. *Output for Selected Model: Exponential (M4)*

Kociba et al. (1978): Urinary Coproporphyrin, Females

```
 ========================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\29_Kociba_1978_Copro_Exp_1.(d)
        Gnuplot Plotting File:
                                             Tue Feb 16 17:34:45 2010
 ========================================================================

 Table2-UrinaryCoproporphyrin
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	-5.58269
rho	2.98472
a	8.17
b	0.0259469
c	2.23623
d	1

Parameter Estimates

Variable	Model 4
lnalpha	-4.94473
rho	2.76088
a	8.93039
b	0.136554
c	1.9753
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	9.8	1.3
1	5	8.6	2
10	5	16.4	4.7
100	5	17.4	4

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	8.93	1.733	1.122
1	10.04	2.038	-1.582
10	15.42	3.683	0.5967
100	17.64	4.436	-0.1211

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-31.69739	5	73.39478
A2	-27.21541	8	70.43081
A3	-28.16434	6	68.32868
R	-41.73188	2	87.46376
4	-30.27804	5	70.55608

Additive constant for all log-likelihoods = -18.38. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	29.03	6	< 0.0001
Test 2	8.964	3	0.02977
Test 3	1.898	2	0.3872
Test 6a	4.227	1	0.03978

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous

```
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is less than .1.  Model 4 may not adequately
  describe the data; you may want to consider another model.


Benchmark Dose Computations:

  Specified Effect = 1.000000

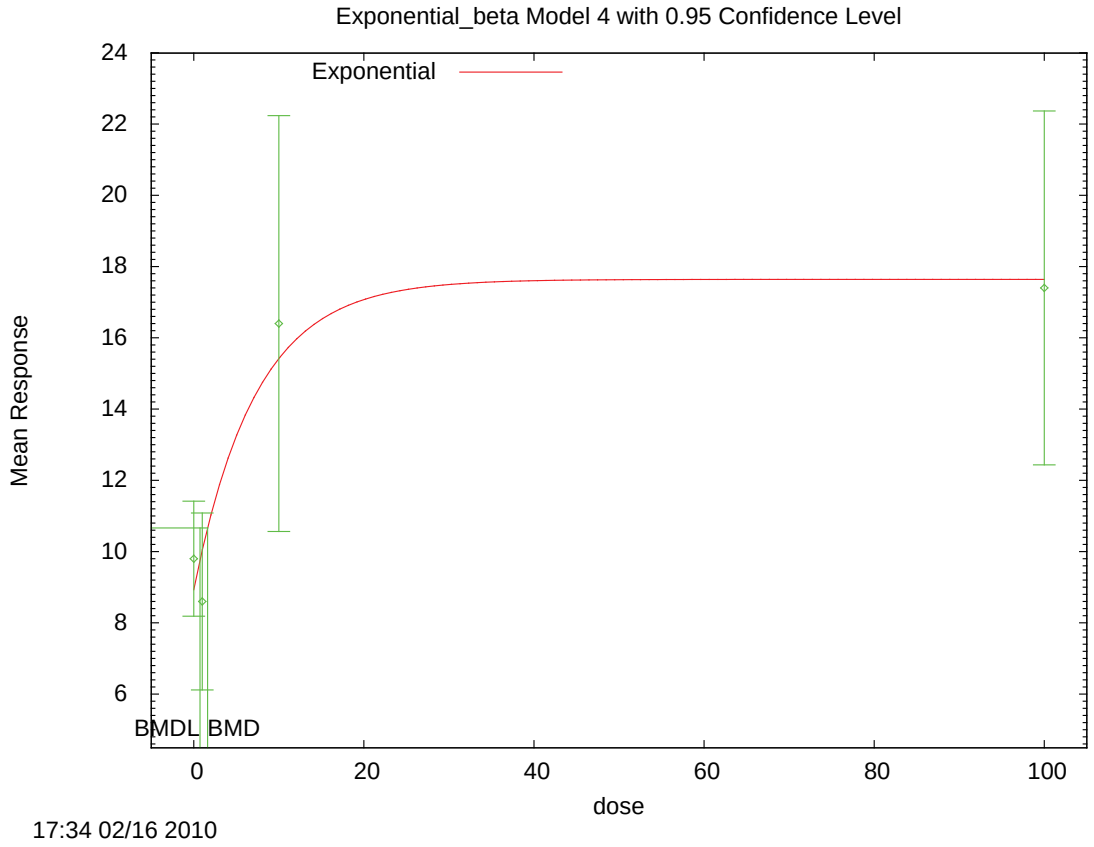
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      1.62505

              BMDL =     0.729987
```

G.3.21.3. *Figure for Selected Model: Exponential (M4)*



G.3.22. Kociba et al. (1978): Uroporphyrin per Creatinine, Female

G.3.22.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.661	−93.561	4.357E+01	3.328E+01	
Exponential (M3)	2	0.661	−93.561	4.357E+01	3.328E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.576	−92.078	1.719E+01	5.516E+00	
Exponential (M5)	0	N/A	−90.190	1.080E+01	5.613E+00	
Hill	0	N/A	−90.190	1.099E+01	5.088E+00	
Linear[b]	**2**	**0.720**	**−93.735**	**3.522E+01**	**2.500E+01**	
Polynomial, 3-degree	2	0.720	−93.735	3.522E+01	2.500E+01	
Power	2	0.720	−93.735	3.522E+01	2.500E+01	power bound hit (power = 1)
Power, unrestricted	1	0.515	−91.967	2.274E+01	3.334E+00	unrestricted (power = 0.731)

[a] Constant variance model selected ($p = 0.4919$).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.22.2. *Output for Selected Model: Linear*

Kociba et al. (1978): Uroporphyrin per Creatinine, Female

```
 ======================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\28_Kociba_1978_Uropor_LinearCV_1.(d)
        Gnuplot Plotting File:  C:\1\28_Kociba_1978_Uropor_LinearCV_1.plt
                                             Tue Feb 16 17:34:12 2010
 ======================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

```
alpha =    0.0030385
  rho =            0   Specified
beta_0 =     0.154759
beta_1 =    0.0014231
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	beta_0	beta_1
alpha	1	-2.2e-009	3.5e-009
beta_0	-2.2e-009	1	-0.55
beta_1	3.5e-009	-0.55	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.00251184	0.000794315	0.000955015	0.00406867
beta_0	0.154759	0.0134422	0.128413	0.181105
beta_1	0.0014231	0.000267497	0.000898818	0.00194739

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	5	0.157	0.155	0.05	0.0501	0.1
1	5	0.143	0.156	0.037	0.0501	-0.588
10	5	0.181	0.169	0.053	0.0501	0.536
100	5	0.296	0.297	0.074	0.0501	-0.0477

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)

```
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	50.195349	5	-90.390697
A2	51.400051	8	-86.800103
A3	50.195349	5	-90.390697
fitted	49.867385	3	-93.734769
R	41.049755	2	-78.099510

Explanation of Tests

```
 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	20.7006	6	0.002076
Test 2	2.40941	3	0.4919
Test 3	2.40941	3	0.4919
Test 4	0.655928	2	0.7204

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

```
            Benchmark Dose Computation

Specified effect =             1

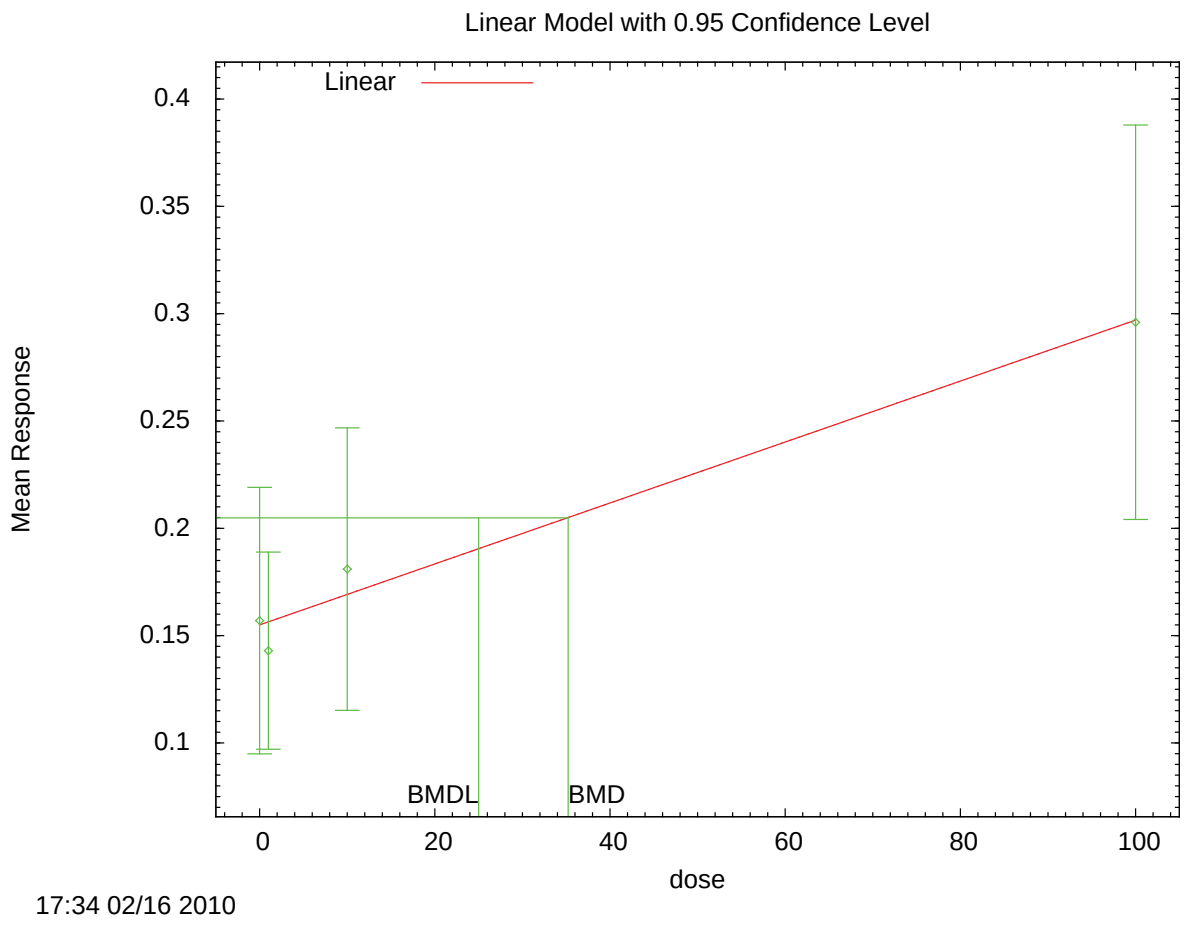
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        35.2176


            BMDL =        25.0024
```

G.3.22.3. *Figure for Selected Model: Linear*



G.3.23. Kuchiiwa et al. (2002): Immunoreactive Neurons in Dorsalis, Males

G.3.23.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	**0**	**N/A [c]**	**93.91**	**1.646E−01**	**1.163E−01**	

[a] Constant variance model selected (p = 0.530).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] p-value could not be calculated because there were no available degrees of freedom.

G.3.23.2. *Output for Selected Model: Linear*

```
=====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\USEPA\BMDS21\1\75_Kuchiiwa_2002_dors_admin_dd_LinearCV_1.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\1\75_Kuchiiwa_2002_dors_admin_dd_LinearCV_1.plt
                                          Tue Aug 16 13:41:50 2011
 ====================================================================

 number_labeled_cells_dorsalis
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 2
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =      670.324
                            rho =            0   Specified
                         beta_0 =      237.097
                         beta_1 =     -143.626


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -rho
```

have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	beta_0	beta_1
alpha	1	3.8e-008	-1.9e-008
beta_0	3.8e-008	1	-0.71
beta_1	-1.9e-008	-0.71	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	558.603	228.049	111.636	1005.57
beta_0	237.097	9.64886	218.186	256.008
beta_1	-143.626	19.4936	-181.833	-105.419

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	237	237	29	23.6	-9.42e-008
0.7	6	137	137	22.4	23.6	-2.9e-008

Degrees of freedom for Test A3 vs fitted <= 0

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

```
 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -43.952634            3      93.905267
             A2          -43.755407            4      95.510815
             A3          -43.952634            3      93.905267
         fitted          -43.952634            3      93.905267
              R          -54.206960            2     112.413921


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              20.9031          2          <.0001
   Test 2             0.394453          1            0.53
   Test 3             0.394453          1            0.53
   Test 4         8.95284e-013          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


             Benchmark Dose Computation

Specified effect =             1

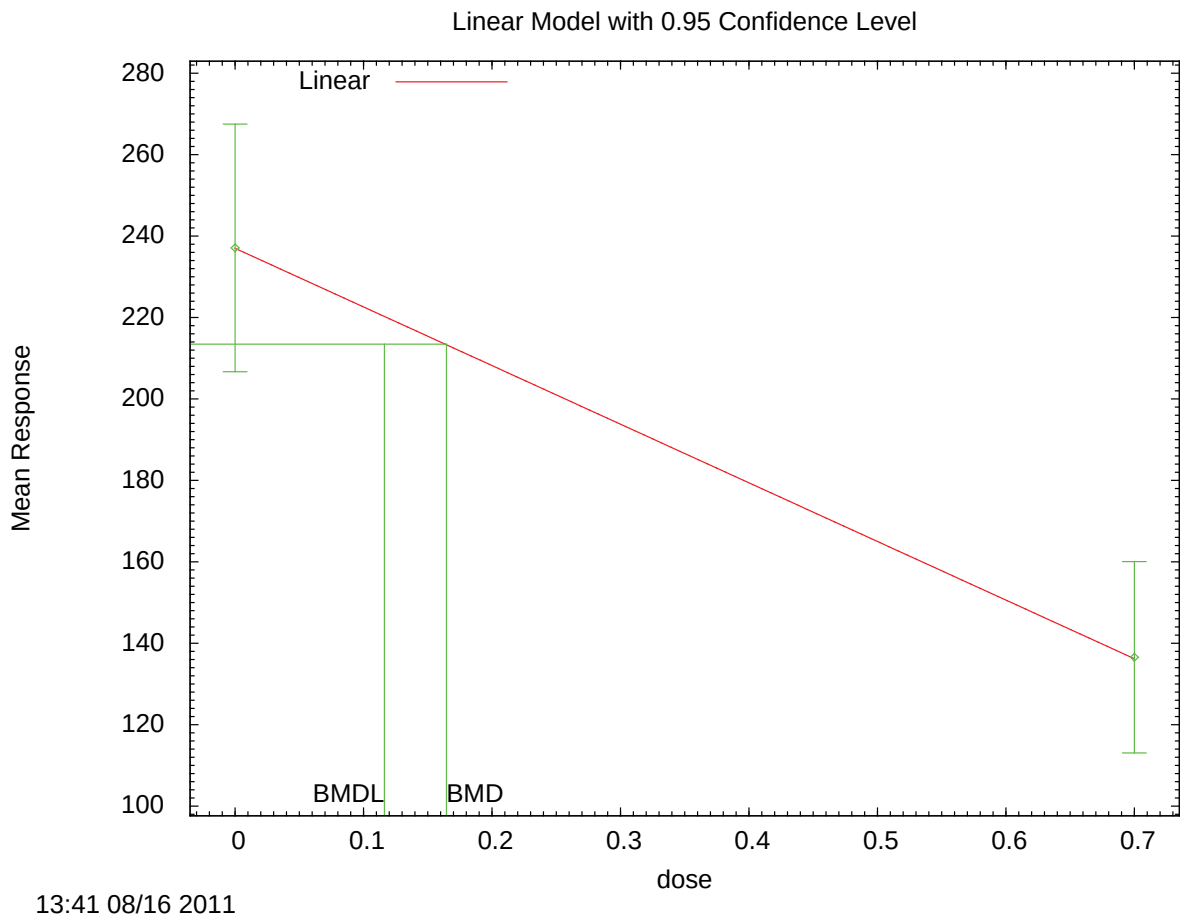
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       0.164558
```

```
BMDL =        0.116266
```

G.3.23.3. *Figure for Selected Model: Linear*



G.3.24. Kuchiiwa et al. (2002): Immunoreactive Neurons in Medianus, Males

G.3.24.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	0	N/A [c]	65.97	1.342E−01	8.786E−02	

[a] Modeled variance model selected (p = 0.025).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] p-value could not be calculated because there were no available degrees of freedom.

G.3.24.2. *Output for Selected Model: Linear*

```
=====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\USEPA\BMDS21\1\76_Kuchiiwa_2002_med_admin_dd_Linear_1.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\1\76_Kuchiiwa_2002_med_admin_dd_Linear_1.plt
                                          Tue Aug 16 13:44:08 2011
 ====================================================================

 number_labeled_cells_medianus
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 2
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                         lalpha =      4.43247
                            rho =            0
                         beta_0 =      91.1157
                         beta_1 =     -82.6446


            Asymptotic Correlation Matrix of Parameter Estimates
```

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	2.7e-009	-1.9e-009
rho	-0.99	1	-3e-009	2.2e-009
beta_0	2.7e-009	-3e-009	1	-0.94
beta_1	-1.9e-009	2.2e-009	-0.94	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-3.97249	3.27352	-10.3885	2.44349
rho	1.9468	0.810306	0.358628	3.53497
beta_0	91.1157	4.52665	82.2436	99.9878
beta_1	-82.6446	6.90638	-96.1808	-69.1083

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	91.1	91.1	12.1	11.1	4.41e-009
0.7	6	33.3	33.3	4.55	4.16	-4.19e-009

Degrees of freedom for Test A2 vs A3 <= 0

Warning: Likelihood for fitted model larger than the Likelihood for model A3.

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))

Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-31.500916	3	69.001832
A2	-28.985335	4	65.970670
A3	-28.985335	4	65.970670
fitted	-28.985335	4	65.970670
R	-46.859574	2	97.719148

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	35.7485	2	<.0001
Test 2	5.03116	1	0.0249
Test 3	2.47269e-012	0	NA
Test 4	-2.47269e-012	0	NA

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

NA - Degrees of freedom for Test 3 are less than or equal to 0. The Chi-
Square
test for fit is not valid

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-
Square
test for fit is not valid

Benchmark Dose Computation

Specified effect = 1

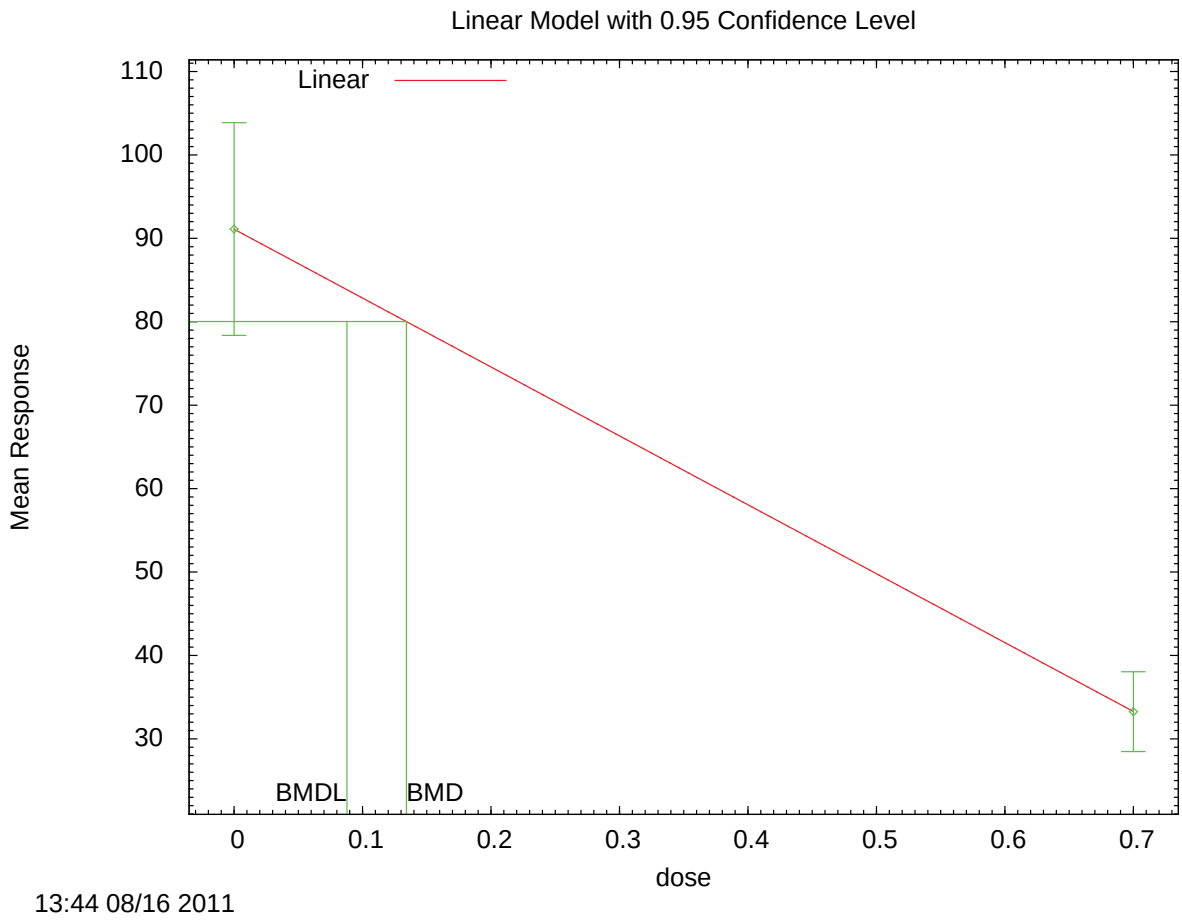
Risk Type = Estimated standard deviations from the control mean

```
Confidence level =          0.95

              BMD =       0.134165

             BMDL =      0.0878581
```

G.3.24.3. *Figure for Selected Model: Linear*



G.3.25. Kuchiiwa et al. (2002): Immunoreactive Neurons in B9, Males

G.3.25.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	0	N/A [c]	86.12	1.136E−01	8.208E−02	

[a] Constant variance model selected (p = 0.504).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] p-value could not be calculated because there were no available degrees of freedom.

G.3.25.2. *Output for Selected Model: Linear*

```
=====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\USEPA\BMDS21\1\77_Kuchiiwa_2002_b9_admin_dd_LinearCV_1.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\1\77_Kuchiiwa_2002_b9_admin_dd_LinearCV_1.plt
                                          Tue Aug 16 13:48:05 2011
 ====================================================================

 number_labeled_cells_b9
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 2
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =      350.225
                            rho =            0   Specified
                         beta_0 =      152.086
                         beta_1 =     -150.415


           Asymptotic Correlation Matrix of Parameter Estimates
```

```
           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                  alpha       beta_0       beta_1

     alpha            1       1e-031    -2.9e-016

    beta_0     9.2e-032            1        -0.71

    beta_1    -2.9e-016        -0.71            1



                                  Parameter Estimates

                                                                  95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          291.854          119.149             58.3265
525.381
         beta_0          152.086           6.9744             138.416
165.756
         beta_1         -150.415          14.0904            -178.031
-122.798



     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0     6        152          152           16         17.1              0
  0.7     6       46.8         46.8         21.1         17.1      1.02e-015

Degrees of freedom for Test A3 vs fitted <= 0



 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
```

were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-40.057520	3	86.115041
A2	-39.834453	4	87.668907
A3	-40.057520	3	86.115041
fitted	-40.057520	3	86.115041
R	-54.163617	2	112.327234

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	28.6583	2	<.0001
Test 2	0.446134	1	0.5042
Test 3	0.446134	1	0.5042
Test 4	1.37845e-012	0	NA

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square
test for fit is not valid

Benchmark Dose Computation

Specified effect = 1

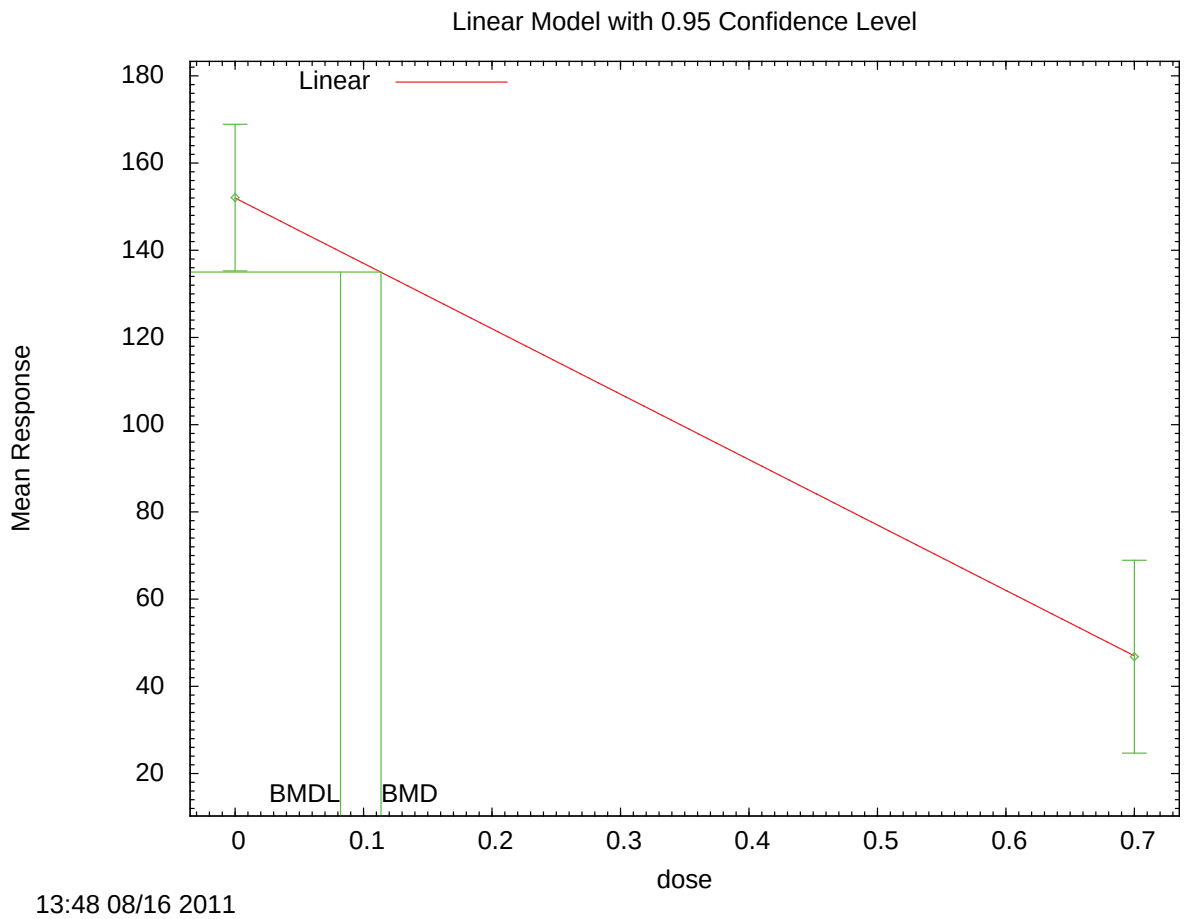
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

```
BMD =        0.113578

BMDL =       0.0820848
```

G.3.25.3. *Figure for Selected Model: Linear*



G.3.26. Kuchiiwa et al. (2002): Immunoreactive Neurons in Magnus, Males

G.3.26.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	**0**	**N/A [c]**	**60.36**	**9.131E−02**	**5.577E−02**	

[a] Modeled variance model selected ($p = 0.013$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] *p*-value could not be calculated because there were no available degrees of freedom.

G.3.26.2. *Output for Selected Model: Linear*

```
=====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\USEPA\BMDS21\1\78_Kuchiiwa_2002_mag_admin_dd_Linear_1.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\1\78_Kuchiiwa_2002_mag_admin_dd_Linear_1.plt
                                          Tue Aug 16 13:46:34 2011
 ====================================================================

 number_labeled_cells_magnus
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 2
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                           lalpha =      4.05645
                              rho =            0
                           beta_0 =      43.6123
                           beta_1 =     -33.9836


             Asymptotic Correlation Matrix of Parameter Estimates

                   lalpha          rho       beta_0       beta_1
```

lalpha	1	-0.99	4.1e-009	-5.6e-008
rho	-0.99	1	-4.6e-009	5.3e-008
beta_0	4.1e-009	-4.6e-009	1	-0.32
beta_1	-5.6e-008	5.3e-008	-0.32	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	12.7854	3.52508	5.87638	19.6944
rho	-2.78668	1.03556	-4.81635	-0.757015
beta_0	43.6123	1.26679	41.1294	46.0952
beta_1	-33.9836	5.72265	-45.1998	-22.7674

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	43.6	43.6	3.4	3.1	1.13e-008
0.7	6	19.8	19.8	10.2	9.31	1.88e-008

Degrees of freedom for Test A2 vs A3 <= 0

Degrees of freedom for Test A3 vs fitted <= 0

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

```
 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -29.244768            3      64.489536
             A2          -26.179929            4      60.359859
             A3          -26.179929            4      60.359859
         fitted          -26.179929            4      60.359859
              R          -37.469939            2      78.939878


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1                 22.58          2          <.0001
   Test 2               6.12968          1         0.01329
   Test 3          7.10543e-015          0              NA
   Test 4                     0          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

NA - Degrees of freedom for Test 3 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


             Benchmark Dose Computation

Specified effect =             1

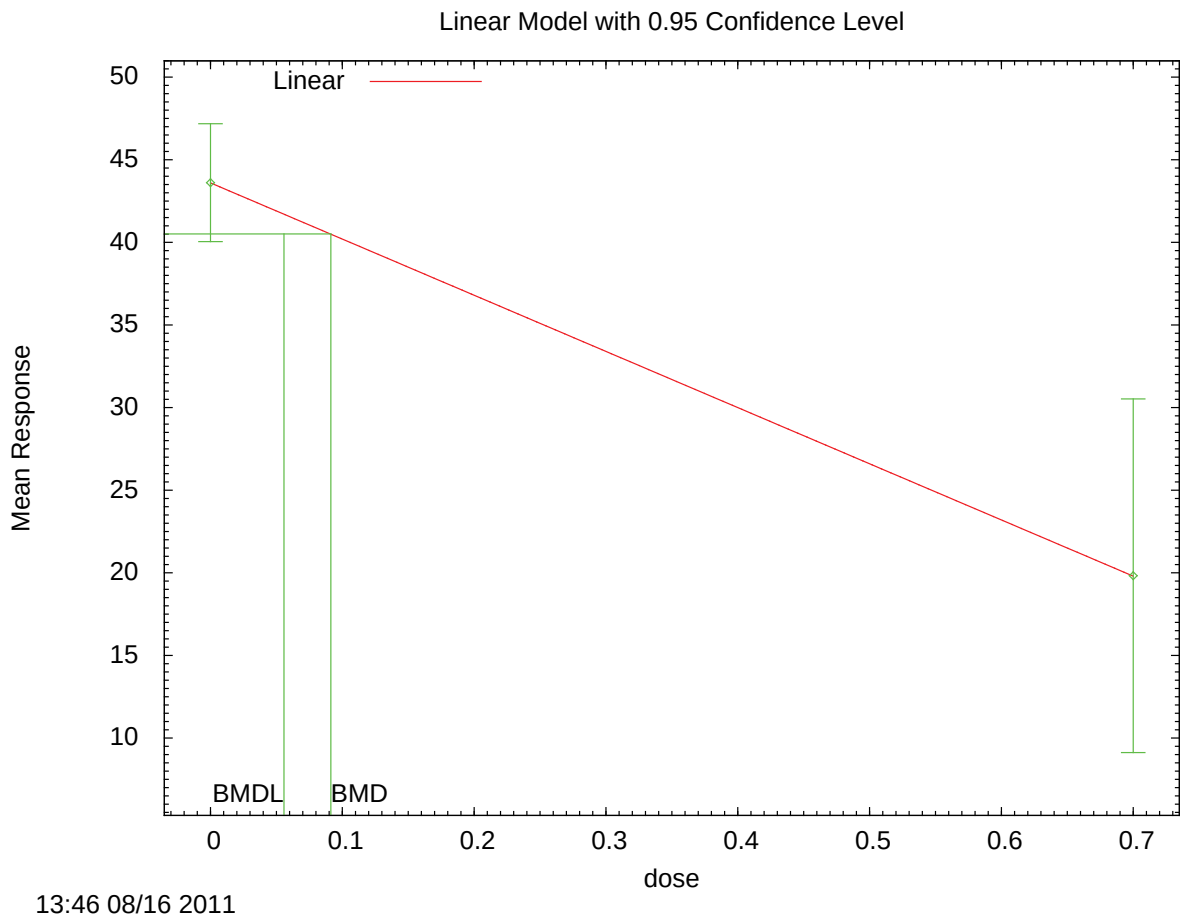
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =      0.0913086
```

```
BMDL =       0.0557686
```

G.3.26.3. *Figure for Selected Model: Linear*



G.3.27. Latchoumycandane and Mathur (2002): Sperm Production

G.3.27.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	<0.0001	95.106	7.640E+01	3.992E+01	
Exponential (M3)	2	<0.0001	95.106	7.640E+01	3.992E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.699	75.263	2.435E−01	1.016E−01	
Exponential (M5)	0	N/A	77.263	3.697E−01	1.016E−01	
Hill[b]	1	0.859	75.144	1.450E−01	1.559E−02	*n* lower bound hit (*n* = 1)
Linear	2	<0.0001	95.308	8.275E+01	4.852E+01	
Polynomial, 3-degree	2	<0.0001	95.308	8.275E+01	4.852E+01	
Power	2	<0.0001	95.308	8.275E+01	4.852E+01	power bound hit (power = 1)
Hill, unrestricted[c]	0	N/A	77.113	6.943E−02	2.060E−06	unrestricted (*n* = 0.709)
Power, unrestricted	1	0.499	75.570	2.706E−07	2.706E−07	unrestricted (power = 0.067)

[a] Constant variance model selected (*p* = 0.8506).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.27.2. *Output for Selected Model: Hill*

Latchoumycandane and Mathur (2002): Sperm Production

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\30_Latch_2002_Sperm_HillCV_1.(d)
        Gnuplot Plotting File:  C:\1\30_Latch_2002_Sperm_HillCV_1.plt
                                          Tue Feb 16 18:13:20 2010
 ======================================================================

 (x10^6) Table 1 without Vitamin E
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	7.23328	
rho =	0	Specified
intercept =	22.19	
v =	-9.09	
n =	1.80484	
k =	0.697086	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	6.3e-010	3e-008	8.3e-009
intercept	6.3e-010	1	-0.78	-0.23
v	3e-008	-0.78	1	-0.17
k	8.3e-009	-0.23	-0.17	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	6.03567	1.74235	2.62073	9.45061
intercept	22.1885	1.00316	20.2223	24.1547
v	-9.00869	1.26801	-11.4939	-6.52343
n	1	NA		
k	0.386669	0.265663	-0.134021	0.907359

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

0	6	22.2	22.2	2.67	2.46	0.00151
1	6	15.7	15.7	2.65	2.46	-0.0218
10	6	13.7	13.5	2.19	2.46	0.134
100	6	13.1	13.2	3.16	2.46	-0.114

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-33.556444	5	77.112888
A2	-33.158811	8	82.317623
A3	-33.556444	5	77.112888
fitted	-33.572245	4	75.144490
R	-47.392394	2	98.784788

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	28.4672	6	<.0001
Test 2	0.795266	3	0.8506
Test 3	0.795266	3	0.8506
Test 4	0.031602	1	0.8589

The p-value for Test 1 is less than .05. There appears to be a

```
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

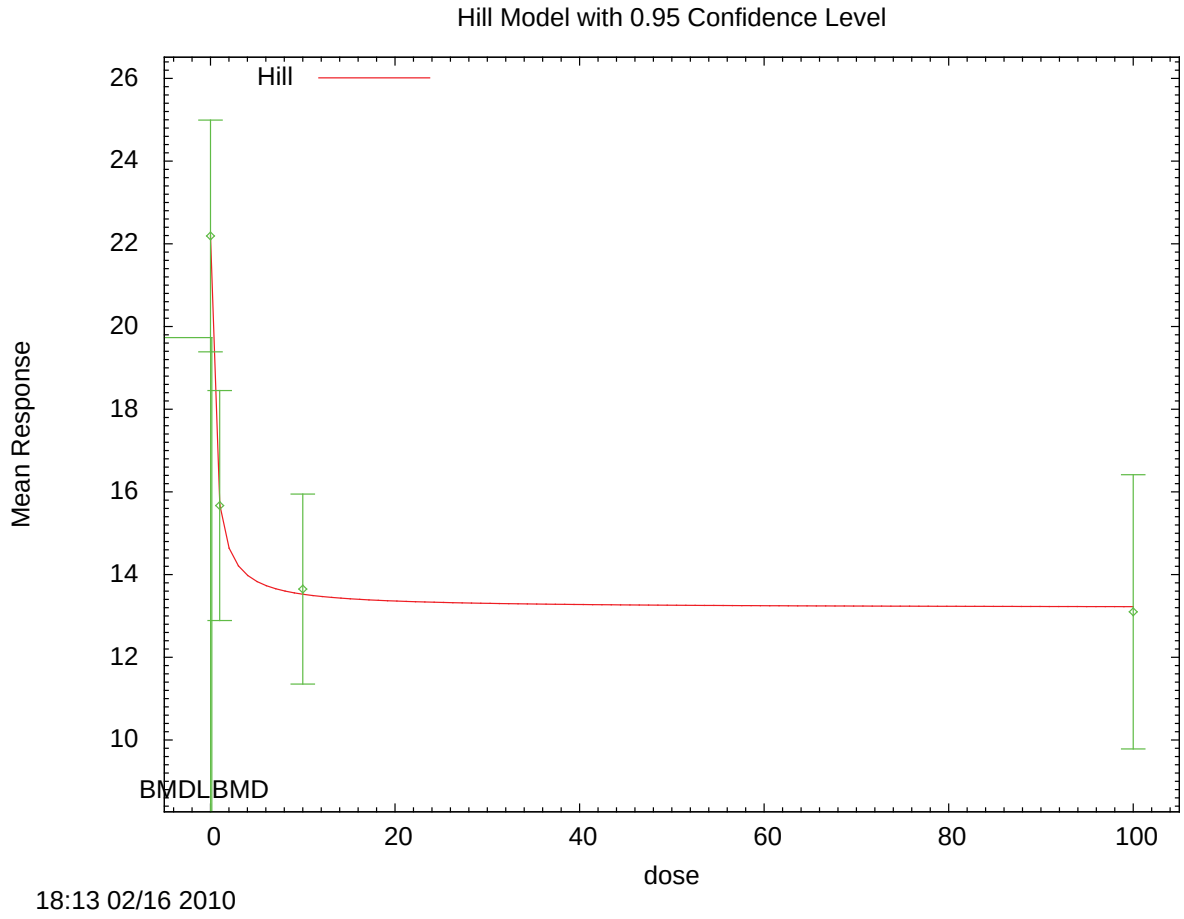
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =       0.144988

            BMDL =     0.0155926
```

G.3.27.3. *Figure for Selected Model: Hill*



G.3.27.4. *Output for Additional Model Presented: Hill, Unrestricted*

Latchoumycandane and Mathur (2002): Sperm Production

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\30_Latch_2002_Sperm_HillCV_U_1.(d)
        Gnuplot Plotting File:  C:\1\30_Latch_2002_Sperm_HillCV_U_1.plt
                                          Tue Feb 16 18:13:21 2010
 ======================================================================

 (x10^6) Table 1 without Vitamin E
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
```

```
Independent variable = Dose
rho is set to 0
Power parameter is not restricted
A constant variance model is fit

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                         alpha =      7.23328
                           rho =            0   Specified
                     intercept =        22.19
                             v =        -9.09
                             n =      1.80484
                             k =     0.697086


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha    intercept            v            n            k

     alpha            1    -7.6e-009       8e-008       5e-008     1.9e-008

 intercept    -7.6e-009            1         -0.5       -0.015        -0.13

         v       8e-008         -0.5            1         0.75         0.55

         n       5e-008       -0.015         0.75            1         0.86

         k     1.9e-008        -0.13         0.55         0.86            1


                                  Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          6.02773          1.74006             2.61728
9.43818
      intercept            22.19          1.00231             20.2255
24.1545
              v         -9.23433          2.02073            -13.1949
-5.27378
              n         0.709305          1.28329             -1.8059
3.22451
```

```
              k         0.290697         0.548737           -0.784807
1.3662


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0     6       22.2         22.2         2.67         2.46      2.62e-008
    1     6       15.7         15.7         2.65         2.46      -1.5e-008
   10     6       13.7         13.7         2.19         2.46     -4.56e-008
  100     6       13.1         13.1         3.16         2.46     -3.52e-007

Degrees of freedom for Test A3 vs fitted <= 0



 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1          -33.556444            5      77.112888
            A2          -33.158811            8      82.317623
            A3          -33.556444            5      77.112888
         fitted         -33.556444            5      77.112888
             R          -47.392394            2      98.784788


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	28.4672	6	<.0001
Test 2	0.795266	3	0.8506
Test 3	0.795266	3	0.8506
Test 4	2.84217e-014	0	NA

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square test for fit is not valid

Benchmark Dose Computation

Specified effect = 1

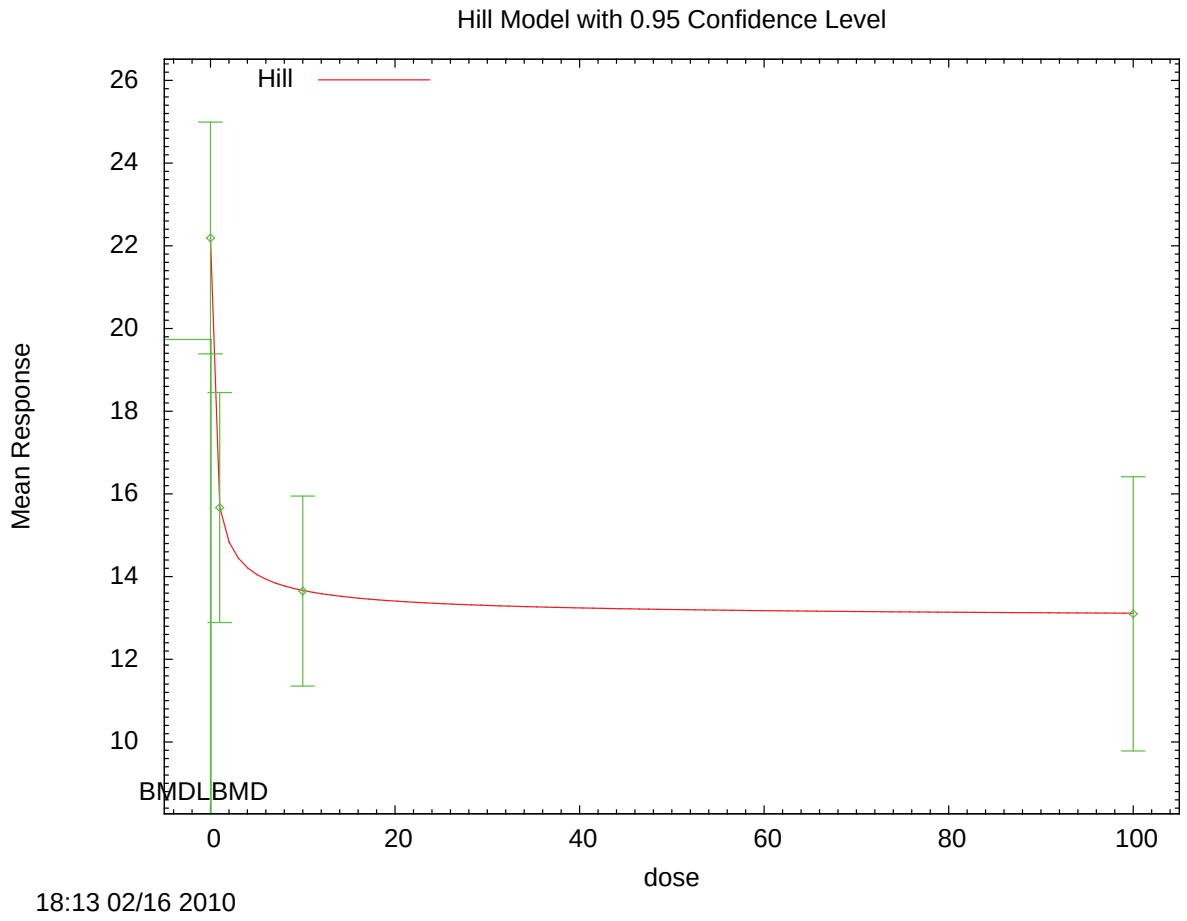
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.0694325

BMDL = 2.06007e-006

G.3.27.5. *Figure for Additional Model Presented: Hill, Unrestricted*



G.3.28. Li et al. (1997): FSH

G.3.28.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	8	<0.0001	1,095.240	1.340E+04	1.060E+04	
Exponential (M3)	8	<0.0001	1,095.240	1.340E+04	1.060E+04	power hit bound (*d* = 1)
Exponential (M4)	7	<0.0001	1,061.243	1.031E+03	4.015E+02	
Exponential (M5)	7	<0.0001	1,061.243	1.031E+03	4.015E+02	power hit bound (*d* = 1)
Hill	7	<0.0001	1,059.547	6.645E+02	error	*n* lower bound hit (*n* = 1)
Linear	8	<0.0001	1,078.221	5.287E+03	3.602E+03	
Polynomial, 8-degree	9	<0.0001	1,155.670	error	error	
Power [b]	**8**	**<0.0001**	**1,078.221**	**5.287E+03**	**3.602E+03**	**power bound hit (power = 1)**
Hill, unrestricted	6	0.001	1,039.902	2.809E+00	6.602E−01	unrestricted (*n* = 0.291)
Power, unrestricted [c]	7	0.002	1,037.821	2.508E+00	2.525E−01	unrestricted (power = 0.279)

[a] Nonconstant variance model selected (*p* = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.28.2. *Output for Selected Model: Power*

Li et al. (1997): FSH

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\72_Li_1997_FSH_Pwr_1.(d)
        Gnuplot Plotting File:  C:\1\72_Li_1997_FSH_Pwr_1.plt
                                          Tue Feb 16 20:07:31 2010
 ======================================================================

 Figure 3: FSH in female S-D rats 24hr after dosing, 22 day old rats
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is restricted to be greater than or equal to 1
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 10
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

lalpha =	9.8191
rho =	0
control =	22.1591
slope =	26.1213
power =	0.264963

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -power
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	control	slope
lalpha	1	-0.99	-0.29	-0.023
rho	-0.99	1	0.2	0.023
control	-0.29	0.2	1	-0.35
slope	-0.023	0.023	-0.35	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	3.5473	1.23656	1.12369	5.9709
rho	1.26137	0.244246	0.782659	1.74009
control	88.9479	12.9114	63.6419	114.254
slope	0.0188972	0.00351723	0.0120035	0.0257908
power	1	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
---	---	---	---	---	---	---

0	10	23.9	88.9	29.6	99.9	-2.06
3	10	22.2	89	48.5	99.9	-2.12
10	10	85.2	89.1	94.3	100	-0.124
30	10	73.3	89.5	48.5	100	-0.511
100	10	126	90.8	159	101	1.1
300	10	132	94.6	116	104	1.14
1000	10	117	108	51.2	113	0.25
3000	10	304	146	154	136	3.68
1e+004	10	347	278	151	205	1.06
3e+004	10	455	656	286	352	-1.8

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-535.687163	11	1093.374327
A2	-496.367061	20	1032.734122
A3	-502.709623	12	1029.419246
fitted	-535.110448	4	1078.220896
R	-574.835246	2	1153.670492

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	156.936	18	<.0001
Test 2	78.6402	9	<.0001

Test 3	12.6851	8	0.1232
Test 4	64.8016	8	<.0001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

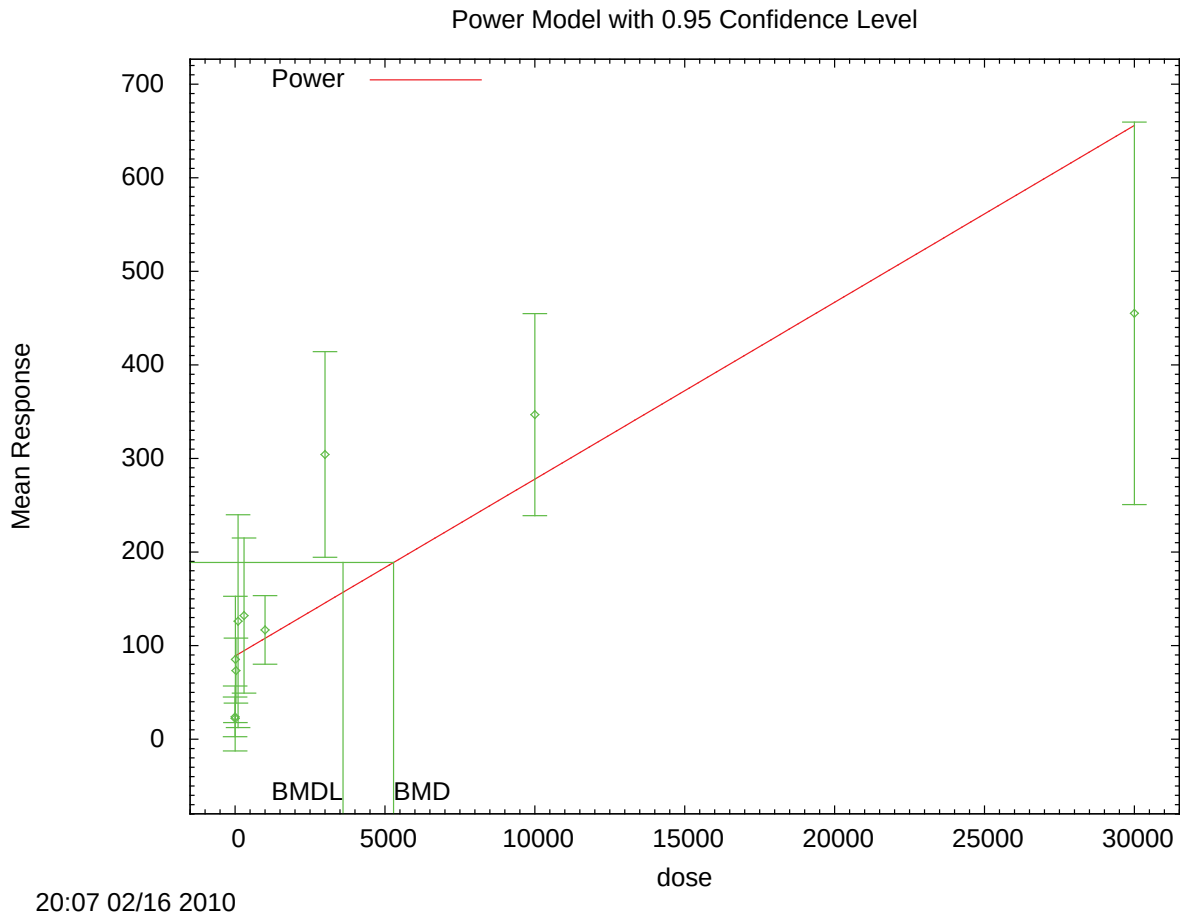
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 5286.67

BMDL = 3601.91

G.3.28.3. *Figure for Selected Model: Power*



G.3.28.4. *Output for Additional Model Presented: Power, Unrestricted*

Li et al. (1997): FSH

```
 ====================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\72_Li_1997_FSH_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\72_Li_1997_FSH_Pwr_U_1.plt
                                          Tue Feb 16 20:07:33 2010
 ====================================================================

 Figure 3: FSH in female S-D rats 24hr after dosing, 22 day old rats
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
```

```
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                Default Initial Parameter Values
                        lalpha =       9.8191
                           rho =            0
                       control =      22.1591
                         slope =      26.1213
                         power =     0.264963


         Asymptotic Correlation Matrix of Parameter Estimates

               lalpha          rho      control        slope        power

    lalpha            1        -0.99        -0.69        -0.15         0.28

       rho        -0.99            1         0.65         0.11        -0.26

   control        -0.69         0.65            1        -0.17        0.024

     slope        -0.15         0.11        -0.17            1        -0.93

     power         0.28        -0.26        0.024        -0.93            1


                              Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha          3.72156          1.13117              1.5045
5.93861
            rho          1.17032         0.223249            0.732758
1.60788
        control          15.7412          6.97367             2.07307
29.4094
          slope           24.963          6.42976             12.3609
37.5651
          power         0.278637        0.0312355            0.217417
0.339857


     Table of Data and Estimated Values of Interest
```

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	23.9	15.7	29.6	32.3	0.796
3	10	22.2	49.6	48.5	63.2	-1.38
10	10	85.2	63.2	94.3	72.7	0.96
30	10	73.3	80.1	48.5	83.6	-0.259
100	10	126	106	159	98.4	0.654
300	10	132	138	116	115	-0.164
1000	10	117	187	51.2	137	-1.62
3000	10	304	248	154	162	1.1
1e+004	10	347	341	151	195	0.0999
3e+004	10	455	457	286	232	-0.0271

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-535.687163	11	1093.374327
A2	-496.367061	20	1032.734122
A3	-502.709623	12	1029.419246
fitted	-513.910636	5	1037.821272
R	-574.835246	2	1153.670492

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	156.936	18	<.0001
Test 2	78.6402	9	<.0001
Test 3	12.6851	8	0.1232
Test 4	22.402	7	0.002165

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

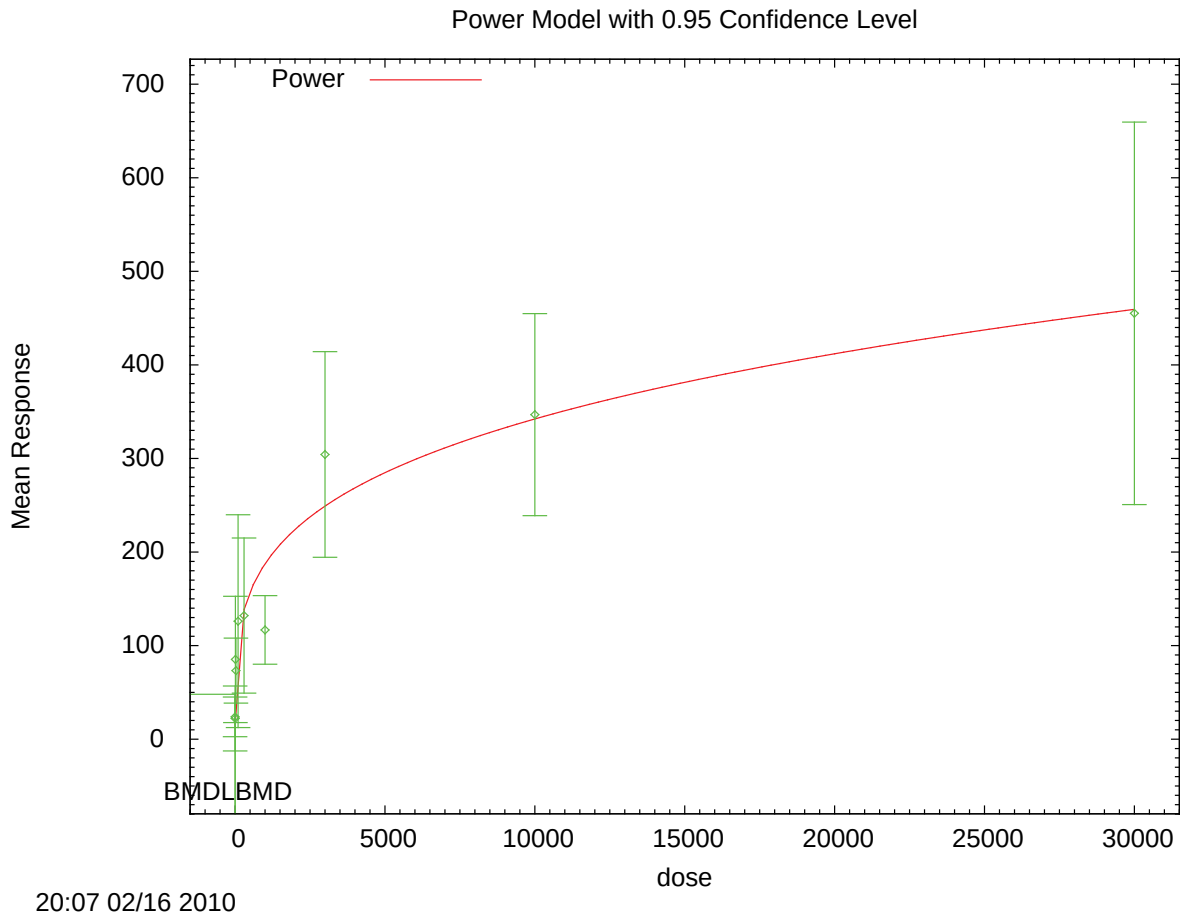
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 2.50839

BMDL = 0.252541

G.3.28.5. ***Figure for Additional Model Presented: Power, Unrestricted***



G.3.29. Li et al. (2006): Estradiol, 3-Day

G.3.29.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.147	269.146	3.044E+02	1.108E+02	
Exponential (M3)	2	0.147	269.146	3.044E+02	1.108E+02	power hit bound (*d* = 1)
Exponential (M4)	1	0.341	268.212	error	error	
Exponential (M5)	0	N/A	270.212	error	error	
Hill	0	N/A	270.212	error	error	
Linear[b]	**2**	**0.151**	**269.084**	**3.471E+02**	**1.082E+02**	
Polynomial, 3-degree	2	0.151	269.084	3.471E+02	1.082E+02	
Power	2	0.151	269.084	3.471E+02	1.082E+02	power bound hit (power = 1)
Hill, unrestricted	0	N/A	270.266	1.059E+17	1.059E+17	unrestricted (*n* = 0.025)
Power, unrestricted	1	0.327	268.266	3.727E+14	error	unrestricted (power = 0.012)

[a] Constant variance model selected (*p* = 0.4372).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.29.2. *Output for Selected Model: Linear*

Li et al. (2006): Estradiol, 3-Day

```
 ========================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\31_Li_2006_Estra_LinearCV_1.(d)
        Gnuplot Plotting File:  C:\1\31_Li_2006_Estra_LinearCV_1.plt
                                          Tue Feb 16 18:13:56 2010
 ========================================================================

 Figure 3, 3-day estradiol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	267.211	
rho =	0	Specified
beta_0 =	16.4428	
beta_1 =	0.0468351	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	beta_0	beta_1
alpha	1	-2.6e-013	-4.5e-015
beta_0	-2.6e-013	1	-0.68
beta_1	-4.5e-015	-0.68	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	264.303	59.1	148.469	380.137
beta_0	16.4428	3.50431	9.57445	23.3111
beta_1	0.0468351	0.062677	-0.0760095	0.16968

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	10.2	16.4	12.2	16.3	-1.22
2	10	19.9	16.5	20	16.3	0.656
50	10	24.7	18.8	14.6	16.3	1.16
100	10	18.1	21.1	17.6	16.3	-0.591

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-129.653527	5	269.307054
A2	-128.294657	8	272.589314
A3	-129.653527	5	269.307054
fitted	-131.541911	3	269.083823
R	-131.819169	2	267.638338

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	7.04902	6	0.3163
Test 2	2.71774	3	0.4372
Test 3	2.71774	3	0.4372
Test 4	3.77677	2	0.1513

The p-value for Test 1 is greater than .05. There may not be a diffence between responses and/or variances among the dose levels Modelling the data with a dose/response curve may not be appropriate

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

```
              Benchmark Dose Computation

Specified effect =             1

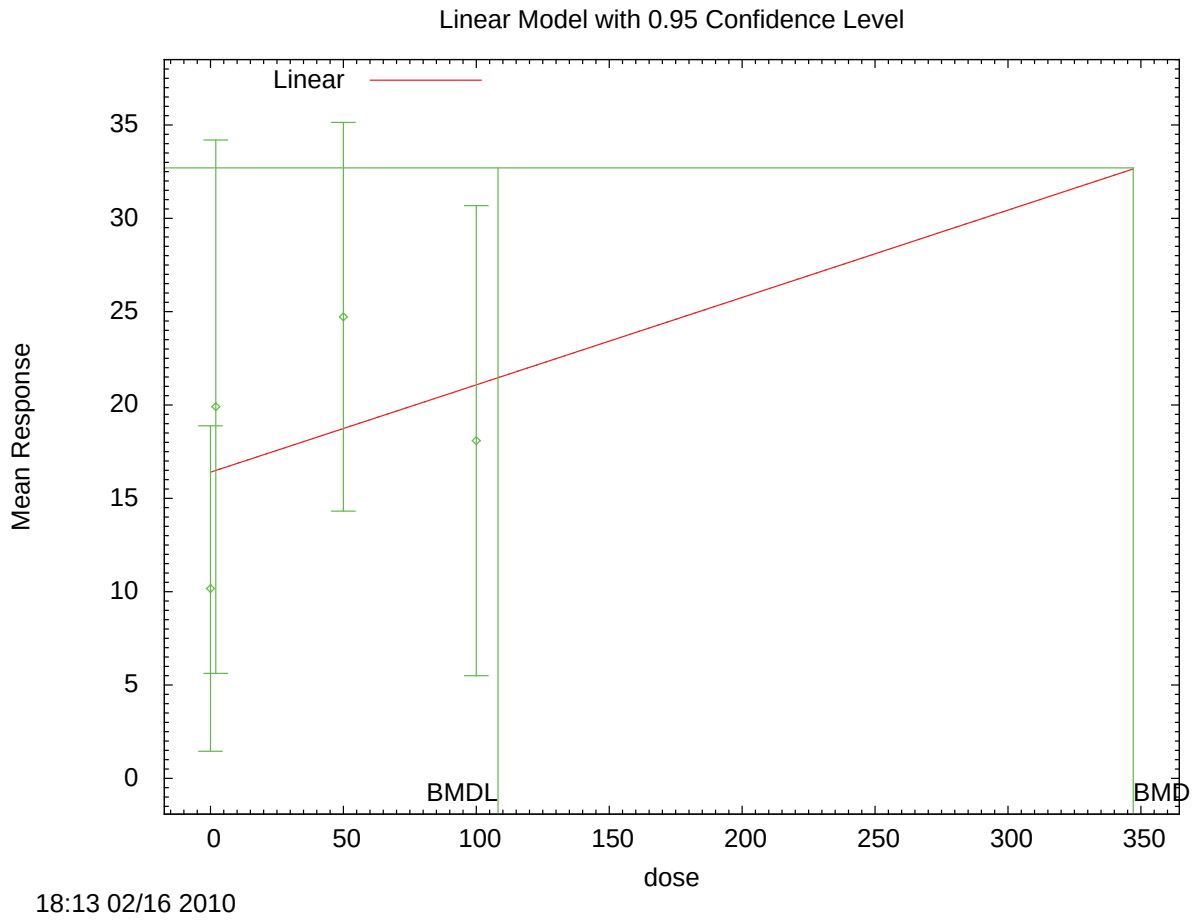
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =         347.12


            BMDL =        108.173
```

G.3.29.3. *Figure for Selected Model: Linear*



G.3.30. Li et al. (2006): Progesterone, 3-Day

G.3.30.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	<0.001	330.234	5.252E+01	error	
Exponential (M3)	2	<0.001	330.234	5.252E+01	error	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.384**	**315.734**	**1.353E−01**	**8.351E−02**	
Exponential (M5)	0	N/A	317.734	5.225E−01	7.503E−02	
Hill	1	0.386	315.729	1.135E−02	1.161E−05	*n* lower bound hit (*n* = 1)
Linear	2	<0.001	331.121	7.765E+01	5.264E+01	
Polynomial, 3-degree	2	<0.001	331.121	7.765E+01	5.264E+01	
Power	2	<0.001	331.121	7.765E+01	5.264E+01	power bound hit (power = 1)
Power, unrestricted	1	0.405	315.670	1.066E−63	1.066E−63	unrestricted (power = 0.009)

[a] Nonconstant variance model selected (*p* = 0.0013).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.30.2. *Output for Selected Model: Exponential (M4)*

Li et al. (2006): Progesterone, 3-Day

```
 ========================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\32_Li_2006_Progest_Exp_1.(d)
        Gnuplot Plotting File:
                                             Tue Feb 16 18:14:31 2010
 ========================================================================

 Figure 4, 3-day progesterone
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
```

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	11.3313
rho	-1.44835
a	64.8274
b	0.0456906
c	0.166844
d	1

Parameter Estimates

Variable	Model 4
lnalpha	14.074
rho	-2.27065
a	61.7474
b	2.13327
c	0.318566
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	61.74	11.1
2	10	30.56	40.48
50	10	16.93	33.3
100	10	11.36	43.75

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	61.75	10.55	-0.002085
2	20.26	37.38	0.8713
50	19.67	38.66	-0.224
100	19.67	38.66	-0.6801

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-159.6327	5	329.2653
A2	-151.8128	8	319.6255
A3	-152.4882	6	316.9763
R	-165.6989	2	335.3978
4	-152.8668	5	315.7335

Additive constant for all log-likelihoods = -36.76. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	27.77	6	0.0001037
Test 2	15.64	3	0.001344
Test 3	1.351	2	0.5089
Test 6a	0.7572	1	0.3842

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

```
  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

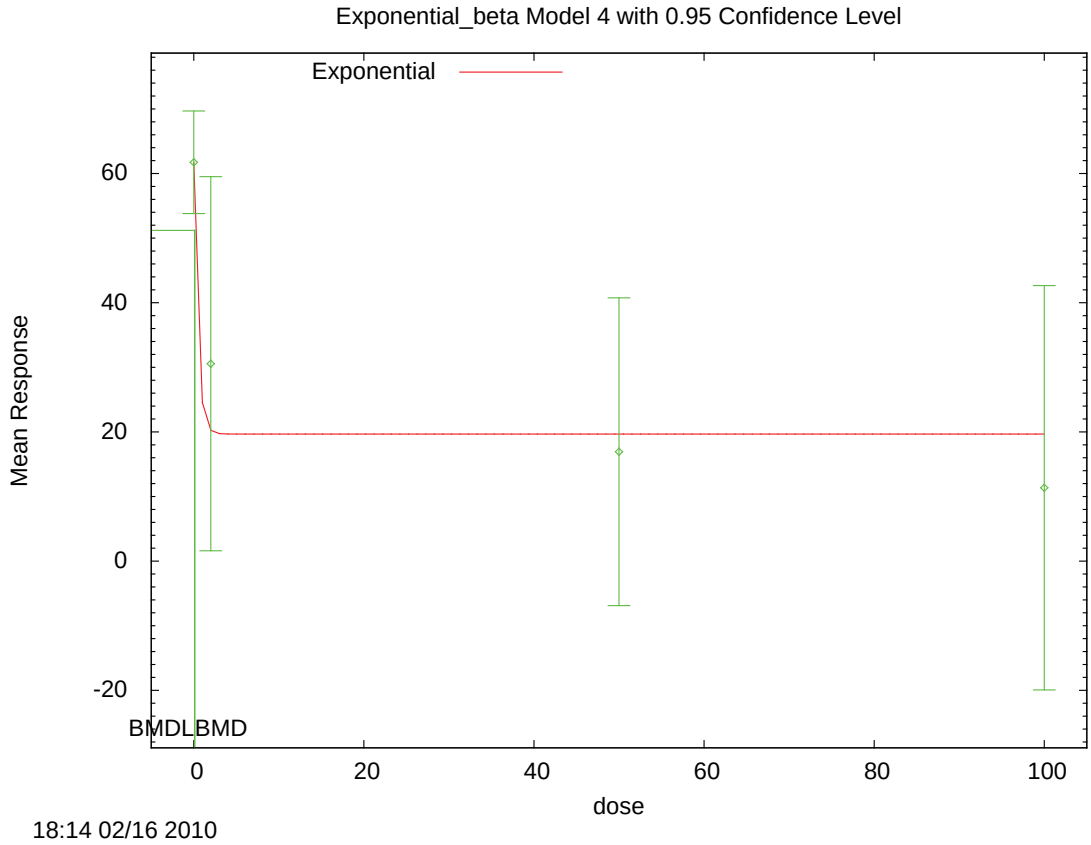
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =     0.135296

              BMDL =    0.0835054
```

G.3.30.3. *Figure for Selected Model: Exponential (M4)*



G.3.30.4. *Output for Additional Model Presented: Hill, Unrestricted*

Li et al. (2006): Progesterone, 3-Day

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\32_Li_2006_Progest_Hill_U_1.(d)
        Gnuplot Plotting File:  C:\1\32_Li_2006_Progest_Hill_U_1.plt
                                          Tue Feb 16 18:14:41 2010
 ======================================================================

 Figure 4, 3-day progesterone
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))
```

```
Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                        lalpha =      7.08699
                           rho =            0
                     intercept =      61.7404
                             v =     -50.3835
                             n =      1.43997
                             k =       1.6159


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -k
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                 lalpha          rho    intercept            v            n

    lalpha            1        -0.99       -0.097         0.84      NA

       rho        -0.99            1         0.13        -0.81      NA

 intercept       -0.097         0.13            1        -0.43      NA

         v         0.84        -0.81        -0.43            1      NA

         n      NA             NA             NA             NA
NA


NA - This parameter's variance has been estimated as zero or less.
THE MODEL HAS PROBABLY NOT CONVERGED!!!



                                  Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha          13.9863               NA                  NA
NA
            rho         -2.25026               NA                  NA
NA
      intercept          61.7404               NA                  NA
NA
```

```
              v         -42.1239               NA                   NA
NA
              n          2.02774               NA                   NA
NA
              k           1e-013               NA

At least some variance estimates are negative.
THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!
Try again from another starting point.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0    10       61.7         61.7         11.1         10.5      9.74e-008
    2    10       30.6         19.6         40.5         38.3          0.905
   50    10       16.9         19.6         33.3         38.3         -0.222
  100    10       11.4         19.6         43.7         38.3         -0.683


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -159.632675            5     329.265349
             A2         -151.812765            8     319.625529
             A3         -152.488175            6     316.976349
         fitted         -152.873643            5     315.747285
              R         -165.698875            2     335.397750


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
```

```
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              27.7722          6       0.0001037
   Test 2              15.6398          3        0.001344
   Test 3              1.35082          2          0.5089
   Test 4             0.770936          1          0.3799

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

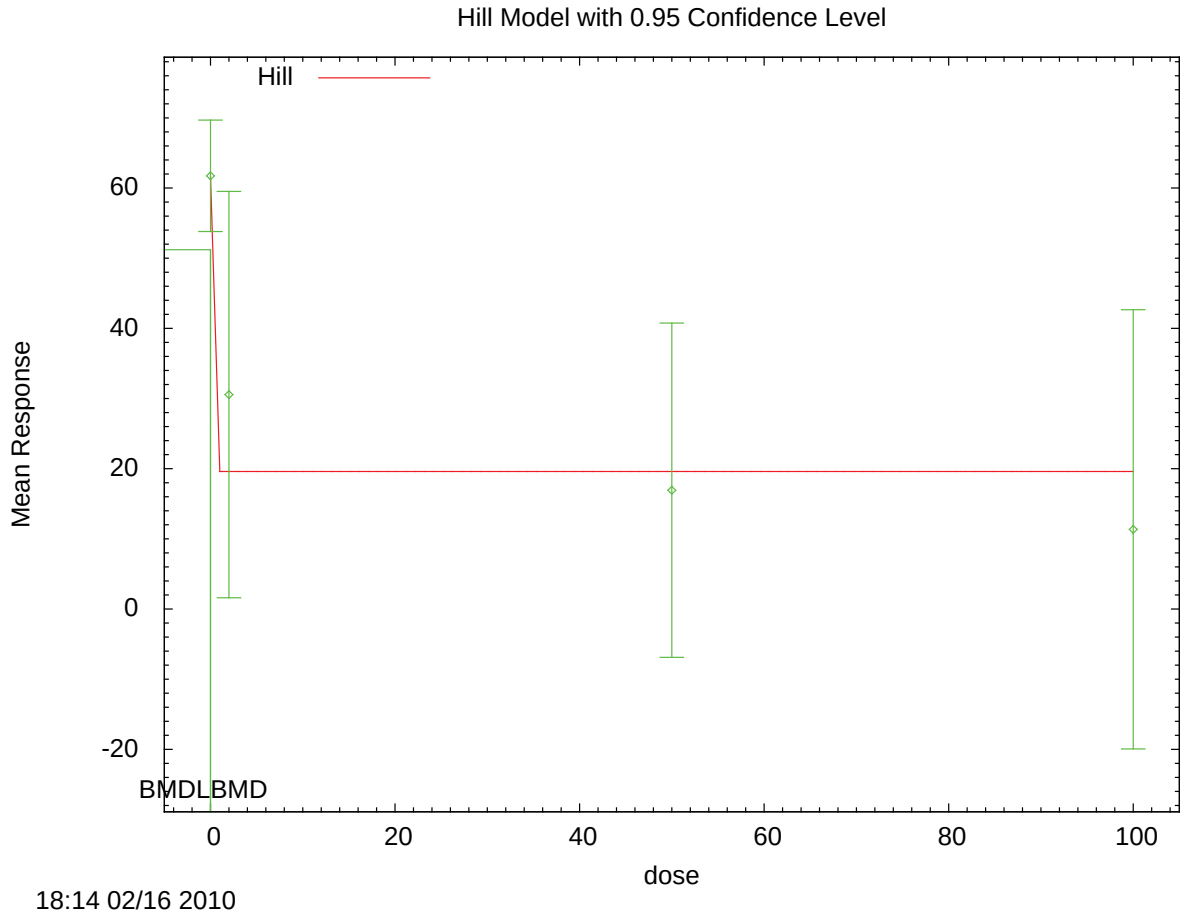
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =   5.81703e-014

            BMDL =  5.81703e-014
```

G.3.30.5. *Figure for Additional Model Presented: Hill, Unrestricted*



G.3.31. Markowski et al. (2001): FR10 Run Opportunities

G.3.31.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)[b]	**2**	**0.248**	**117.557**	**1.653E+02**	**5.025E+01**	
Exponential (M3)	2	0.248	117.557	1.653E+02	5.025E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.412	117.445	4.742E+01	1.729E−01	
Exponential (M5)	0	N/A	118.918	3.178E+01	3.967E−05	
Hill	0	N/A	118.918	2.348E+01	6.728E−06	
Linear	2	0.190	118.089	2.081E+02	1.051E+02	
Polynomial, 3-degree	2	0.190	118.089	2.081E+02	1.051E+02	
Power	2	0.190	118.089	2.081E+02	1.051E+02	power bound hit (power = 1)
Power, unrestricted	1	0.238	118.164	9.153E+01	5.911E−07	unrestricted (power = 0.237)

[a] Constant variance model selected (*p* = 0.1719).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.31.2. *Output for Selected Model: Exponential (M2)*

Markowski et al. (2001): FR10 Run Opportunities

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\33_Mark_2001_FR10opp_ExpCV_1.(d)
        Gnuplot Plotting File:
                                             Tue Feb 16 18:15:26 2010
 ======================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 2
lnalpha	3.5321
rho(S)	0
a	6.98169
b	0.00309891
c	0
d	1

(S) = Specified

Parameter Estimates

Variable	Model 2
lnalpha	3.64823
rho	0
a	11.9443
b	0.0044262
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	7	13.29	8.65
20	4	11.25	5.56
60	6	5.75	3.53
180	7	7	6.01

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	11.94	6.197	0.5745
20	10.93	6.197	0.1025
60	9.158	6.197	-1.347
180	5.385	6.197	0.6897

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-54.38526	5	118.7705
A2	-51.88568	8	119.7714
A3	-54.38526	5	118.7705
R	-57.45429	2	118.9086
2	-55.77871	3	117.5574

Additive constant for all log-likelihoods = -22.05. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	11.14	6	0.08423
Test 2	4.999	3	0.1719
Test 3	4.999	3	0.1719
Test 4	2.787	2	0.2482

The p-value for Test 1 is greater than .05. There may not be a diffence between responses and/or variances among the dose levels Modelling the data with a dose/response curve may not be appropriate.

```
  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 4 is greater than .1.  Model 2 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

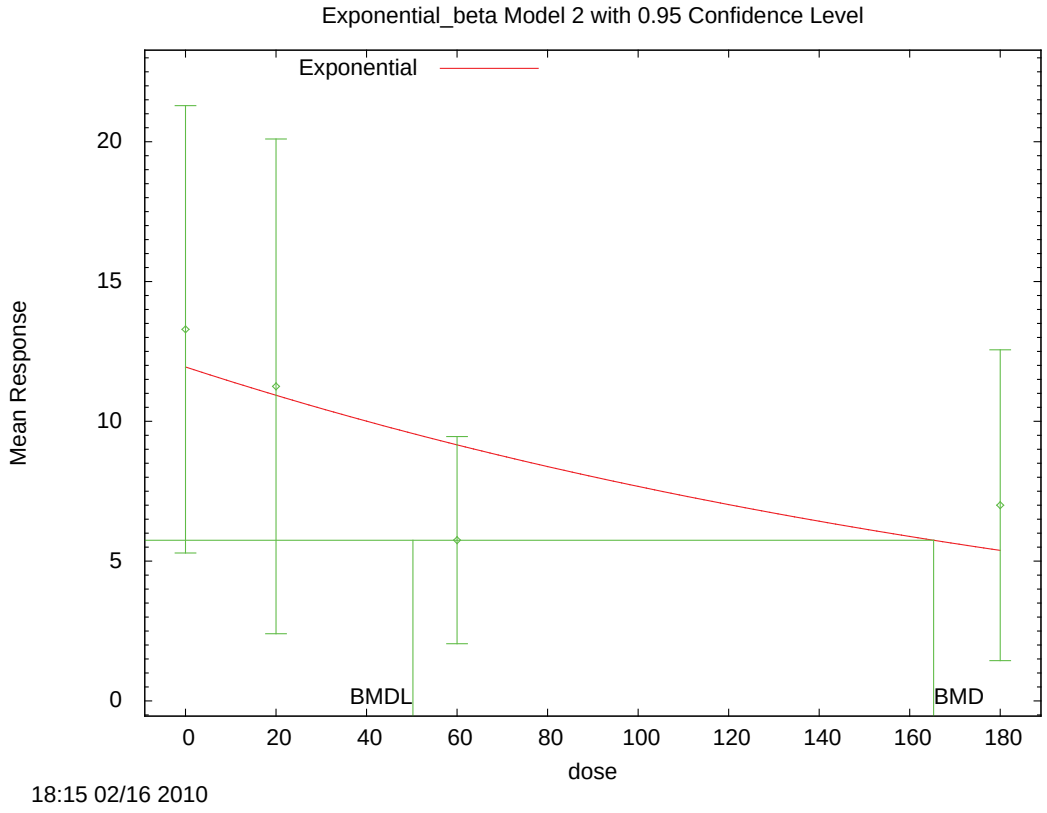
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      165.284

              BMDL =      50.2488
```

G.3.31.3. *Figure for Selected Model: Exponential (M2)*



G.3.32. Markowski et al. (2001): FR2 Revolutions

G.3.32.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.192	217.636	1.627E+02	5.807E+01	
Exponential (M3)	2	0.192	217.636	1.627E+02	5.807E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.298	217.415	4.668E+01	1.965E−01	
Exponential (M5)	0	N/A	218.532	3.308E+01	1.193E+01	
Hill[b]	**0**	**N/A**	**218.532**	**2.364E+01**	**7.336E+00**	***n* upper bound hit (*n* = 18)**
Linear	2	0.150	218.129	1.989E+02	1.025E+02	
Polynomial, 3-degree	2	0.150	218.129	1.989E+02	1.025E+02	
Power	2	0.150	218.129	1.989E+02	1.025E+02	power bound hit (power = 1)
Power, unrestricted[c]	1	0.160	218.302	9.101E+01	1.800E−13	unrestricted (power = 0.272)

[a] Constant variance model selected (*p* = 0.1092).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.32.2. *Output for Selected Model: Hill*

Markowski et al. (2001): FR2 Revolutions

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\34_Mark_2001_FR2rev_HillCV_1.(d)
        Gnuplot Plotting File:  C:\1\34_Mark_2001_FR2rev_HillCV_1.plt
                                          Tue Feb 16 18:16:03 2010
 ======================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	2598.74	
rho =	0	Specified
intercept =	119.29	
v =	-62.79	
n =	1.80602	
k =	35.85	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	n	k
alpha	1	-8.1e-009	4.5e-008	-3e-005	3e-005
intercept	-8.1e-009	1	-0.81	-0.00013	-0.0022
v	4.5e-008	-0.81	1	0.0002	0.0014
n	-3e-005	-0.00013	0.0002	1	-1
k	3e-005	-0.0022	0.0014	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	2183.85	630.425	948.245	3419.46
intercept	119.29	17.6629	84.6713	153.909
v	-56.5223	21.9082	-99.4615	-13.5831
n	18	8854.08	-17335.7	17371.7
k	21.6708	855.263	-1654.61	1697.95

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

```
------     ---   --------     --------   -----------  -----------   ---------
-

    0     7        119          119         69.9         46.7      2.74e-008
   20     4        109          108           61         46.7      8.42e-010
   60     6       56.5         62.8         31.2         46.7         -0.329
  180     7       68.1         62.8         33.2         46.7          0.304

Degrees of freedom for Test A3 vs fitted <= 0



 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1         -104.165520            5     218.331040
            A2         -101.140174            8     218.280349
            A3         -104.165520            5     218.331040
        fitted         -104.266162            5     218.532324
             R         -107.599268            2     219.198536


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              12.9182          6         0.04435
   Test 2              6.05069          3          0.1092
   Test 3              6.05069          3          0.1092
   Test 4             0.201283          0              NA
```

```
The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


        Benchmark Dose Computation

Specified effect =             1

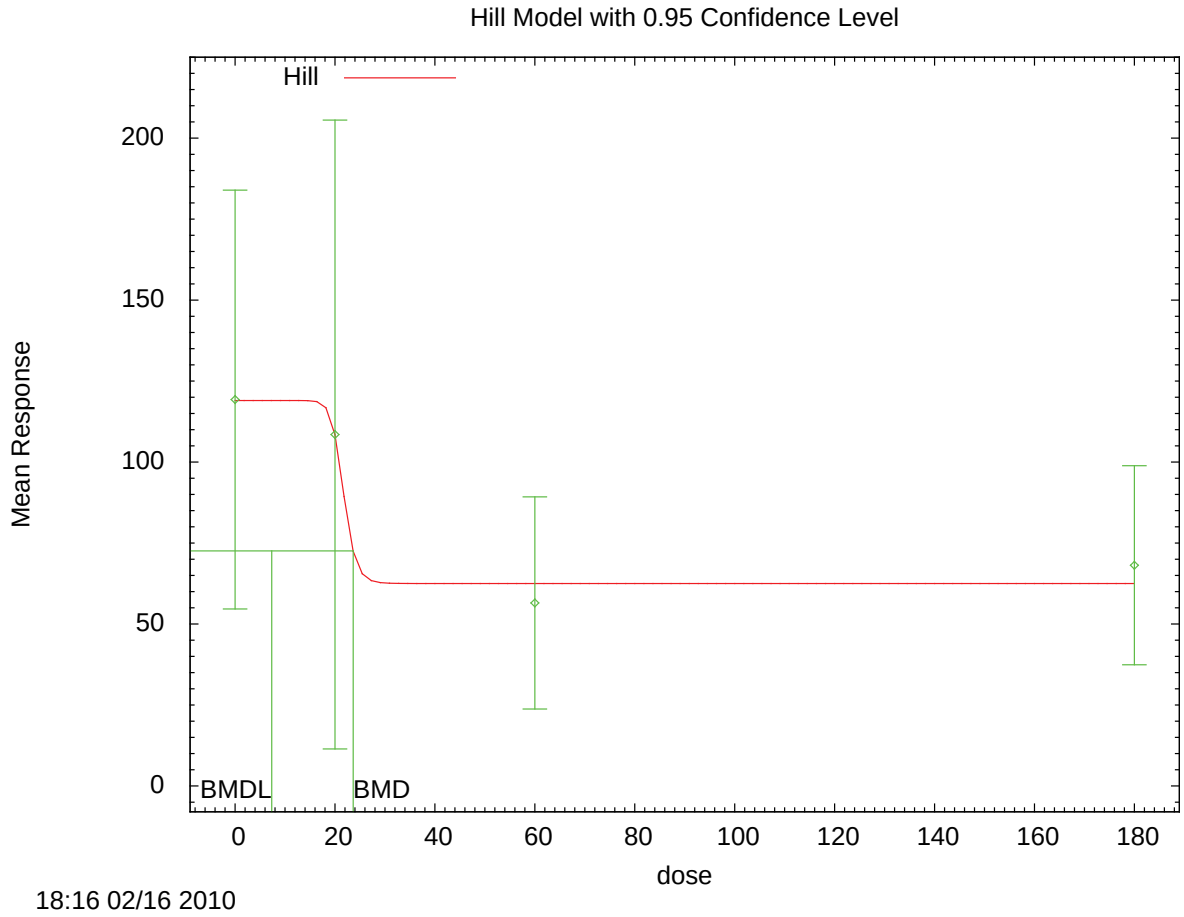
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =        23.6366

            BMDL =       7.33648
```

G.3.32.3. *Figure for Selected Model: Hill*



G.3.32.4. *Output for Additional Model Presented: Power, Unrestricted*

Markowski et al. (2001): FR2 Revolutions

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\34_Mark_2001_FR2rev_PowerCV_U_1.(d)
        Gnuplot Plotting File:  C:\1\34_Mark_2001_FR2rev_PowerCV_U_1.plt
                                          Tue Feb 16 18:16:04 2010
 ======================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
```

```
Independent variable = Dose
rho is set to 0
The power is not restricted
A constant variance model is fit

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                         alpha =      2598.74
                           rho =            0   Specified
                       control =       119.29
                         slope =     -1.79436
                         power =     0.708231


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope        power

     alpha            1     9.7e-009    -1.9e-008    -1.6e-008

   control     9.7e-009            1        -0.49        -0.28

     slope    -1.9e-008        -0.49            1         0.96

     power    -1.6e-008        -0.28         0.96            1


                                 Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha             2351          678.674             1020.82
3681.17
        control          120.074          18.0837             84.6305
155.517
          slope         -14.1965          22.2073             -57.722
29.329
          power          0.27229         0.301344           -0.318334
0.862913
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	7	119	120	69.9	48.5	-0.0428
20	4	109	88	61	48.5	0.846
60	6	56.5	76.8	31.2	48.5	-1.02
180	7	68.1	61.7	33.2	48.5	0.352

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-104.165520	5	218.331040
A2	-101.140174	8	218.280349
A3	-104.165520	5	218.331040
fitted	-105.151136	4	218.302271
R	-107.599268	2	219.198536

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	12.9182	6	0.04435
Test 2	6.05069	3	0.1092

Test 3	6.05069	3	0.1092
Test 4	1.97123	1	0.1603

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

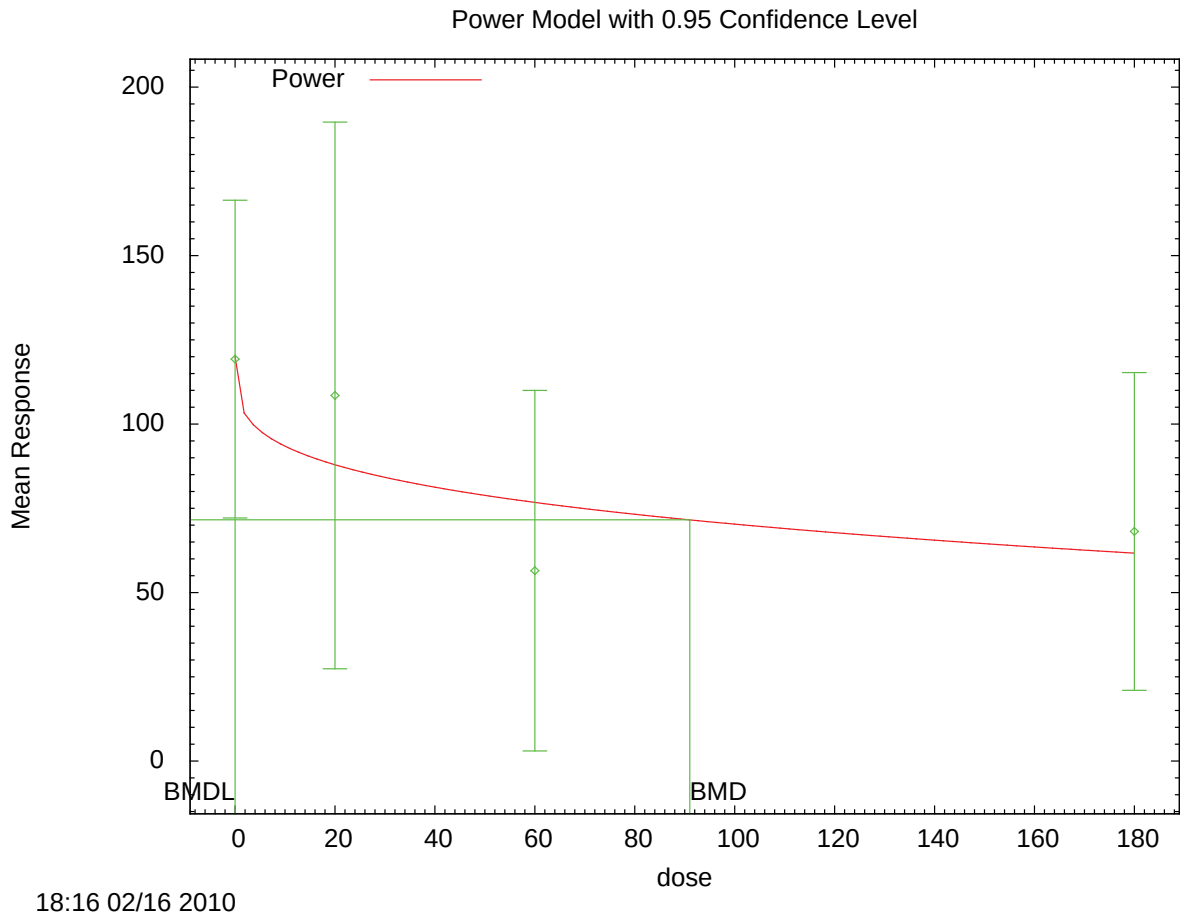
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 91.0145

BMDL = 1.8e-013

G.3.32.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.3.33. Markowski et al. (2001): FR5 Run Opportunities

G.3.33.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.149	133.830	9.491E+01	4.324E+01	
Exponential (M3)	2	0.149	133.830	9.491E+01	4.324E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.303	133.087	2.961E+01	9.356E+00	
Exponential (M5)	0	N/A	134.032	2.871E+01	1.226E+01	
Hill[b]	**1**	**0.939**	**132.032**	**2.214E+01**	**1.117E+01**	***n* upper bound hit (*n* = 18)**
Linear	2	0.091	134.825	1.349E+02	8.118E+01	
Polynomial, 3-degree	2	0.091	134.825	1.349E+02	8.118E+01	
Power	2	0.091	134.825	1.349E+02	8.118E+01	power bound hit (power = 1)
Power, unrestricted[c]	1	0.133	134.281	3.721E+01	1.439E−07	unrestricted (power = 0.336)

[a] Constant variance model selected (*p* = 0.2262).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.33.2. *Output for Selected Model: Hill*

Markowski et al. (2001): FR5 Run Opportunities

```
 ========================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\35_Mark_2001_FR5opp_HillCV_1.(d)
        Gnuplot Plotting File:  C:\1\35_Mark_2001_FR5opp_HillCV_1.plt
                                          Tue Feb 16 18:16:39 2010
 ========================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	77.4849	
rho =	0	Specified
intercept =	26.14	
v =	-13.34	
n =	2.36002	
k =	35.0654	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	-3.6e-009	9.8e-009	3.6e-008
intercept	-3.6e-009	1	-0.81	-0.51
v	9.8e-009	-0.81	1	0.36
k	3.6e-008	-0.51	0.36	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	64.5863	18.6445	28.0438	101.129
intercept	26.14	3.03753	20.1865	32.0935
v	-13.1569	3.7676	-20.5413	-5.77257
n	18	NA		
k	21.5963	2.68136	16.3409	26.8517

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

0	7	26.1	26.1	12.3	8.04	1.02e-008
20	4	23.5	23.5	7.04	8.04	-1.39e-007
60	6	12.8	13	6.17	8.04	-0.0558
180	7	13.1	13	7.14	8.04	0.0517

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-62.013133	5	134.026266
A2	-59.839035	8	135.678070
A3	-62.013133	5	134.026266
fitted	-62.016024	4	132.032049
R	-67.530040	2	139.060081

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	15.382	6	0.01748
Test 2	4.3482	3	0.2262
Test 3	4.3482	3	0.2262
Test 4	0.0057833	1	0.9394

The p-value for Test 1 is less than .05. There appears to be a

```
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

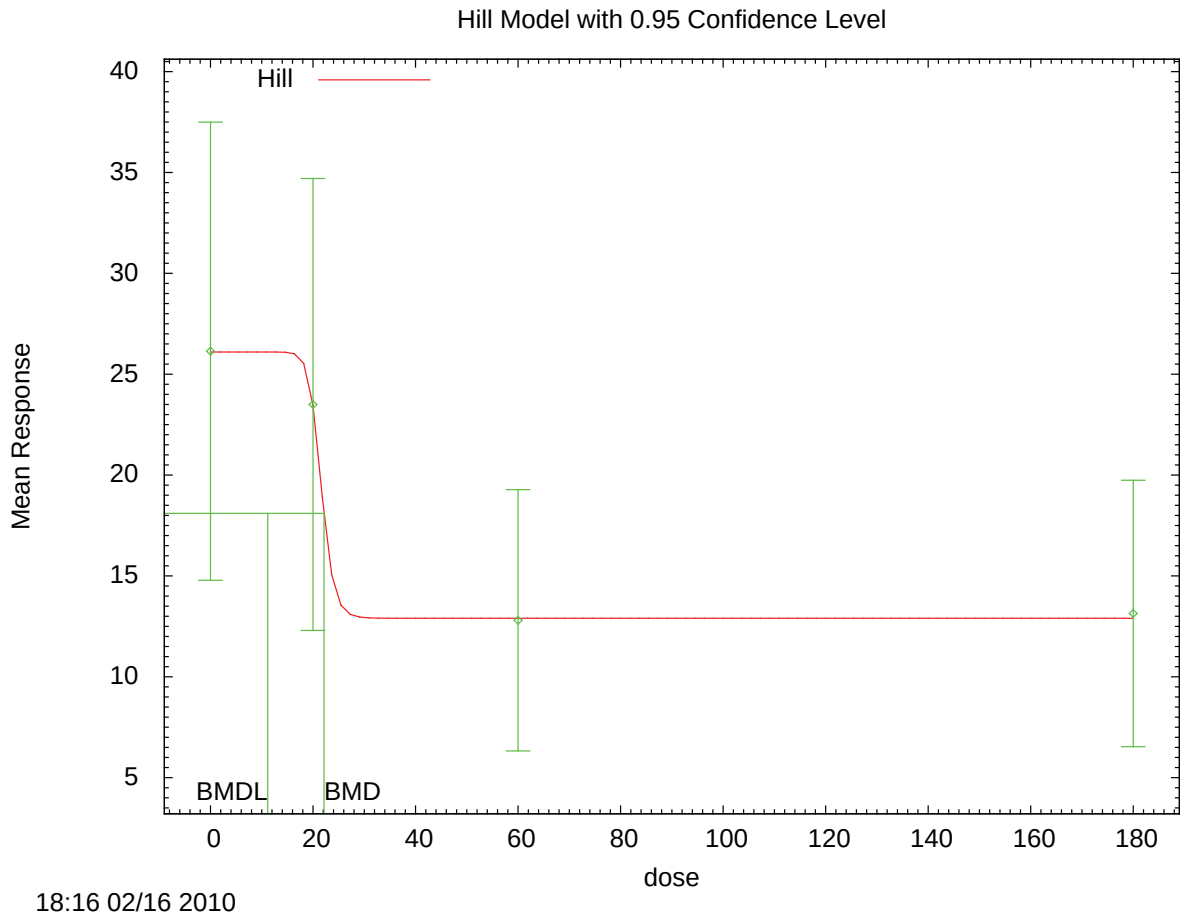
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =         22.144

            BMDL =        11.165
```

G.3.33.3. *Figure for Selected Model: Hill*



G.3.33.4. *Output for Additional Model Presented: Power, Unrestricted*

Markowski et al. (2001): FR5 Run Opportunities

```
 ==================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\35_Mark_2001_FR5opp_PwrCV_U_1.(d)
        Gnuplot Plotting File:  C:\1\35_Mark_2001_FR5opp_PwrCV_U_1.plt
                                          Tue Feb 16 18:16:40 2010
 ==================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
```

```
rho is set to 0
The power is not restricted
A constant variance model is fit

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                         alpha =      77.4849
                           rho =            0   Specified
                       control =        26.14
                         slope =     -0.39517
                         power =     0.725538


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope        power

     alpha            1     7.4e-009     4.3e-008     4.8e-008

   control     7.4e-009            1        -0.51        -0.34

     slope     4.3e-008        -0.51            1         0.97

     power     4.8e-008        -0.34         0.97            1


                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          70.9323          20.4764             30.7993
111.065
        control          26.3567          3.13032             20.2213
32.492
          slope         -2.49841          3.16984            -8.71118
3.71437
          power         0.336003         0.242031           -0.138368
0.810375


     Table of Data and Estimated Values of Interest
```

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	7	26.1	26.4	12.3	8.42	-0.0681
20	4	23.5	19.5	7.04	8.42	0.945
60	6	12.8	16.5	6.17	8.42	-1.07
180	7	13.1	12.1	7.14	8.42	0.341

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-62.013133	5	134.026266
A2	-59.839035	8	135.678070
A3	-62.013133	5	134.026266
fitted	-63.140714	4	134.281428
R	-67.530040	2	139.060081

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	15.382	6	0.01748
Test 2	4.3482	3	0.2262
Test 3	4.3482	3	0.2262

```
   Test 4              2.25516          1          0.1332

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =             1

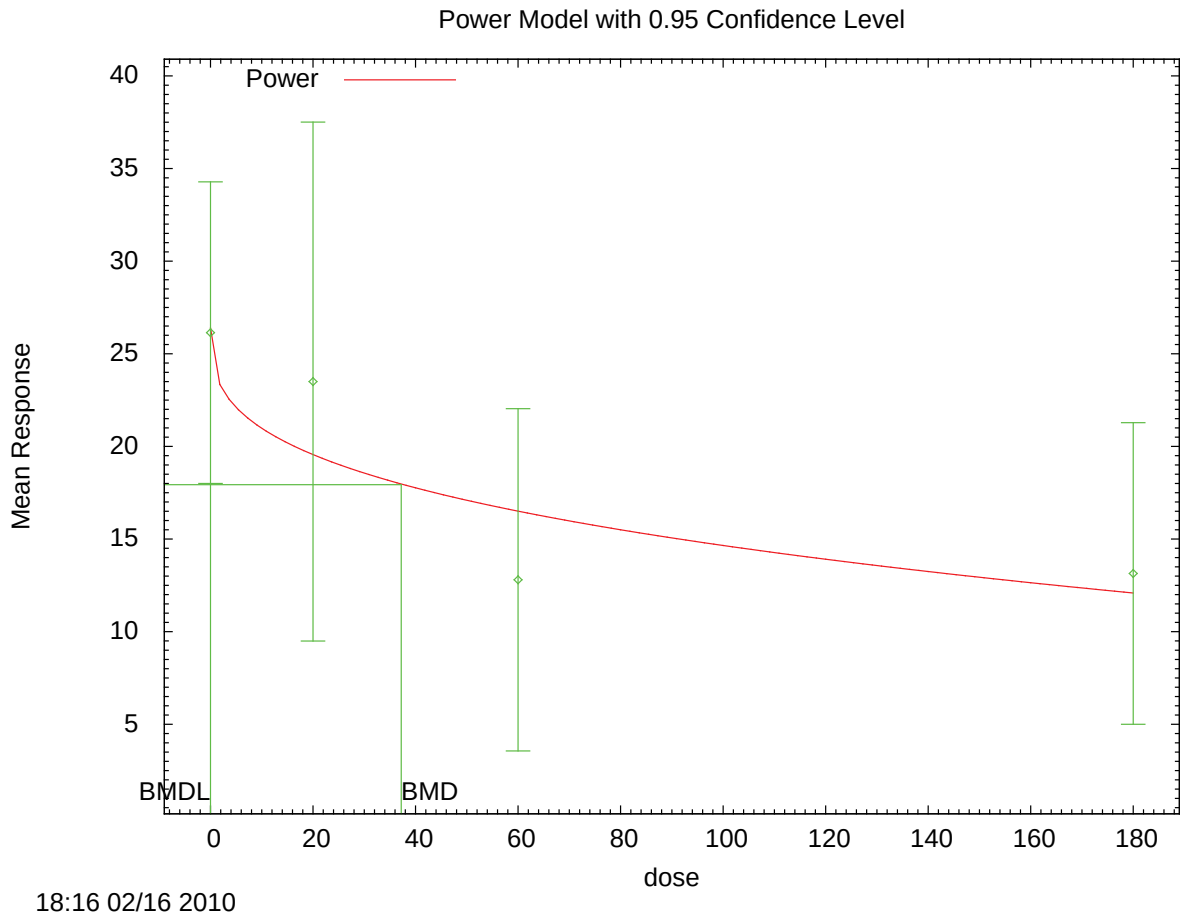
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 37.2131


            BMDL = 1.43926e-007
```

G.3.33.5. *Figure for Additional Model Presented: Power, Unrestricted*



G.3.34. Miettinen et al. (2006): Cariogenic Lesions, Pups

G.3.34.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	3	0.345	162.699	7.505E+01	4.086E+01	power bound hit (power = 1)
Logistic	3	0.315	162.909	8.991E+01	5.250E+01	
Log-logistic[a]	**3**	**0.506**	**161.767**	**3.130E+01**	**1.054E+01**	**slope bound hit (slope = 1)**
Log-probit	3	0.257	163.393	1.390E+02	6.729E+01	slope bound hit (slope = 1)
Multistage, 4-degree	3	0.345	162.699	7.505E+01	4.086E+01	final ß = 0
Probit	3	0.299	163.031	9.941E+01	6.208E+01	
Weibull	3	0.345	162.699	7.505E+01	4.086E+01	power bound hit (power = 1)
Gamma, unrestricted	2	0.797	161.805	1.591E−02	1.335E−240	unrestricted (power = 0.184)
Log-logistic, unrestricted[b]	2	0.723	161.998	3.713E−01	error	unrestricted (slope = 0.403)
Log-probit, unrestricted	2	0.726	161.987	5.098E−01	error	unrestricted (slope = 0.25)
Weibull, unrestricted	2	0.761	161.897	1.174E−01	error	unrestricted (power = 0.281)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.34.2. *Output for Selected Model: Log-Logistic*

Miettinen et al. (2006): Cariogenic Lesions, Pups

```
 ==================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\36_Miet_2006_Cariogenic_LogLogistic_1.(d)
        Gnuplot Plotting File:
C:\1\36_Miet_2006_Cariogenic_LogLogistic_1.plt
                                          Tue Feb 16 18:17:16 2010
 ==================================================================

 Table 2 converting the percentage into the number of animals, and control is
Control II from the study. Dose is in ng per kg and is from Table 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
```

```
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =     0.595238
                      intercept =     -5.52519
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.64

 intercept        -0.64            1



                                 Parameter Estimates

                                                                 95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background         0.658158            *                *
*
      intercept         -5.64068            *                *
*
          slope                1            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -77.6769         5
   Fitted model        -78.8837         2       2.41374      3
0.4911
```

```
  Reduced model        -83.2067         1       11.0597      4
0.0259

           AIC:         161.767


                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ----------------------------------------------------------------------
    0.0000     0.6582        27.643    25.000          42        -0.860
   30.0000     0.6911        20.041    23.000          29         1.189
  100.0000     0.7477        18.693    19.000          25         0.141
  300.0000     0.8345        20.027    20.000          24        -0.015
 1000.0000     0.9249        29.596    29.000          32        -0.400

 Chi^2 = 2.33      d.f. = 3        P-value = 0.5062


   Benchmark Dose Computation

Specified effect =            0.1

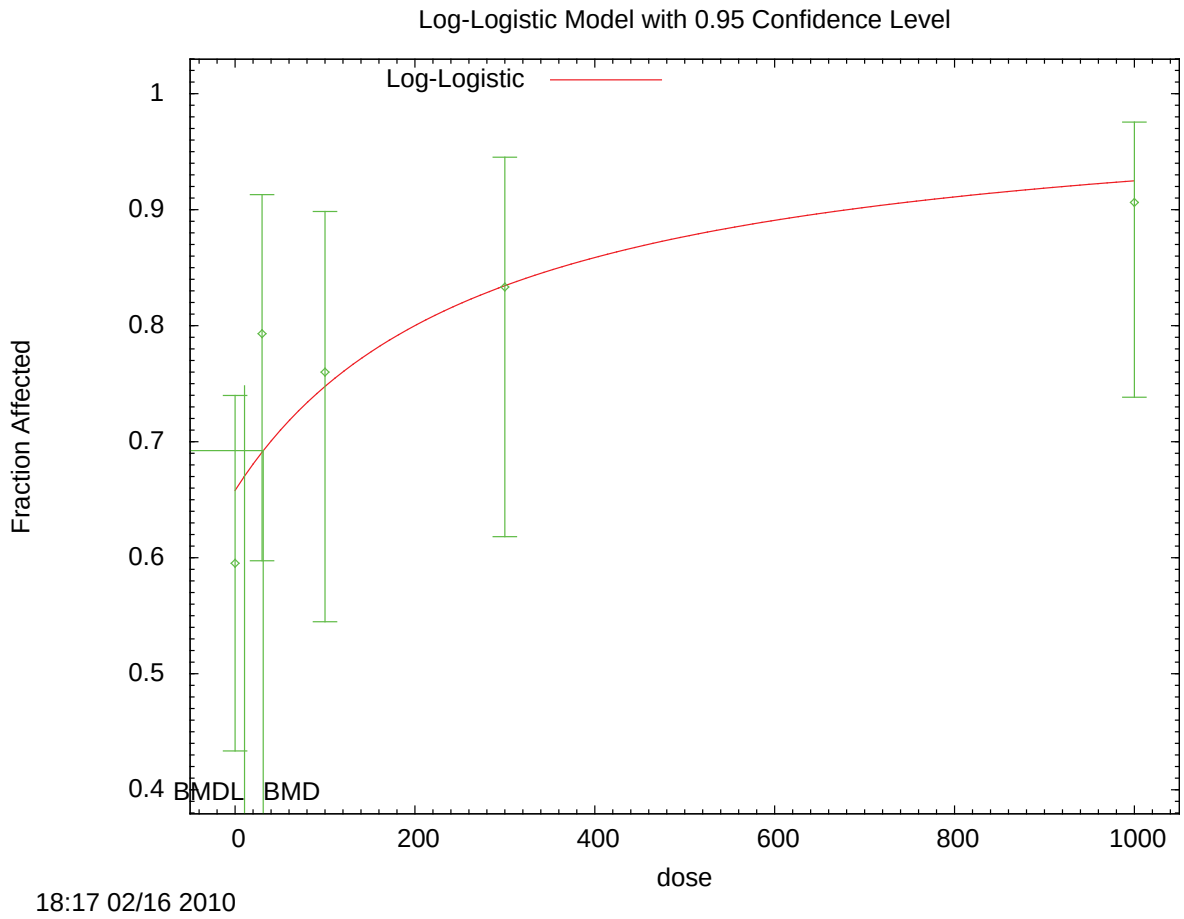
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        31.2951

            BMDL =        10.5354
```

G.3.34.3. *Figure for Selected Model: Log-Logistic*



G.3.34.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Miettinen et al. (2006): Cariogenic Lesions, Pups

```
 ==================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\36_Miet_2006_Cariogenic_LogLogistic_U_1.(d)
        Gnuplot Plotting File:
C:\1\36_Miet_2006_Cariogenic_LogLogistic_U_1.plt
                                          Tue Feb 16 18:17:18 2010
 ==================================================================

 Table 2 converting the percentage into the number of animals, and control is
Control II from the study. Dose is in ng per kg and is from Table 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]
```

```
   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =     0.595238
                      intercept =     -1.68849
                          slope =     0.382632


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.41         0.24

 intercept        -0.41            1        -0.96

     slope         0.24        -0.96            1



                                 Parameter Estimates

                                                                  95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background         0.597778            *                *
*
      intercept         -1.79836            *                *
*
          slope         0.402606            *                *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -77.6769         5
   Fitted model        -77.9988         3      0.643944      2
0.7247
```

```
  Reduced model        -83.2067         1       11.0597      4
0.0259

           AIC:         161.998


                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ----------------------------------------------------------------------
    0.0000     0.5978        25.107    25.000          42        -0.034
   30.0000     0.7564        21.936    23.000          29         0.460
  100.0000     0.8045        20.112    19.000          25        -0.561
  300.0000     0.8480        20.351    20.000          24        -0.200
 1000.0000     0.8905        28.495    29.000          32         0.286

 Chi^2 = 0.65      d.f. = 2        P-value = 0.7227


   Benchmark Dose Computation

Specified effect =            0.1

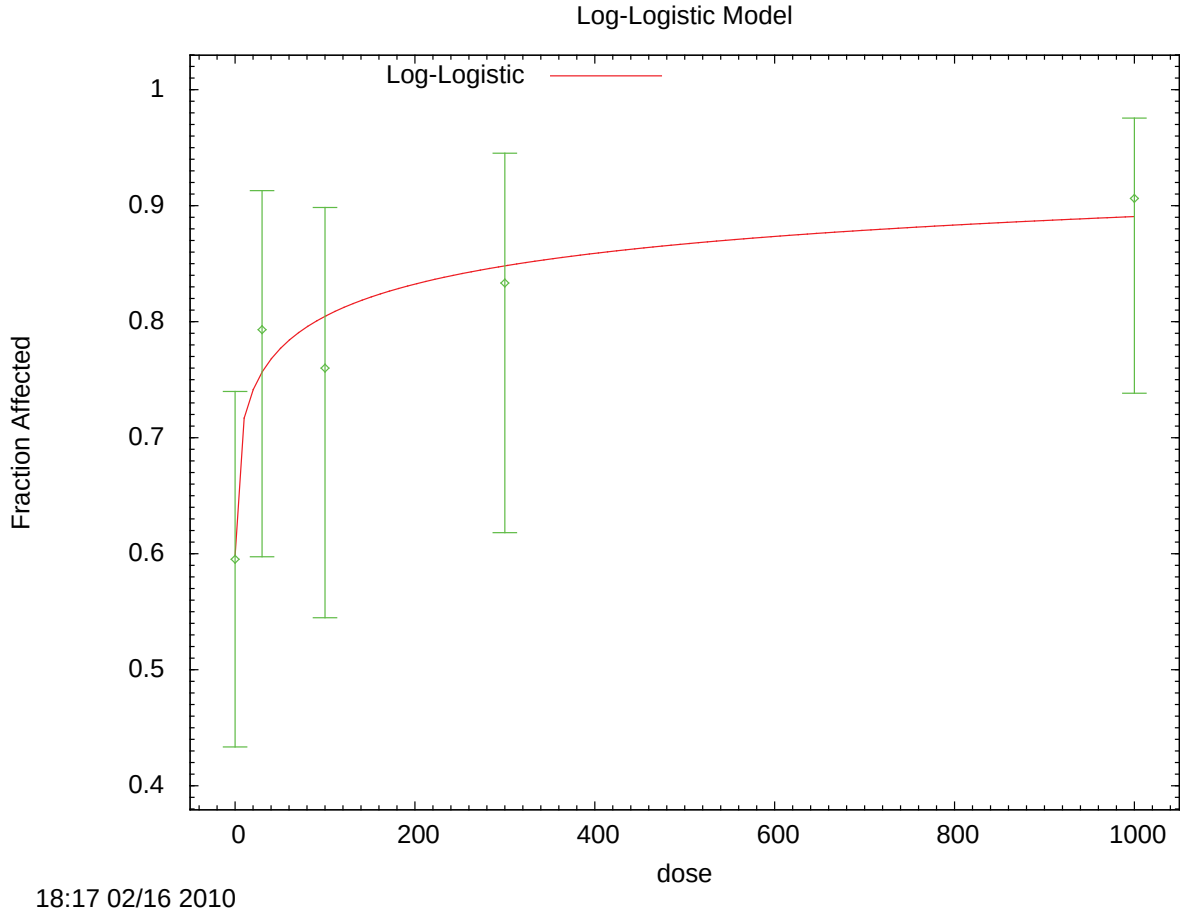
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.371315

           Benchmark dose computation failed.  Lower limit includes zero.
```

G.3.34.5. ***Figure for Additional Model Presented: Log-Logistic, Unrestricted***



G.3.35. Murray et al. (1979): Fertility in F2 Generation

G.3.35.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	0	N/A	61.729	7.016E+00	1.698E+00	
Logistic	1	0.072	60.497	4.007E+00	2.836E+00	
Log-logistic	0	N/A	61.729	7.902E+00	1.584E+00	
Multistage, 1-degree	1	0.053	61.644	2.380E+00	1.320E+00	
Multistage, 2-degree[a]	**1**	**0.094**	**59.935**	**4.548E+00**	**1.635E+00**	
Probit	1	0.070	60.613	3.707E+00	2.615E+00	
Weibull	0	N/A	61.729	8.115E+00	1.698E+00	
Log-probit, unrestricted	0	N/A	61.729	6.373E+00	1.503E+00	unrestricted (slope = 2.306)

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.35.2. *Output for Selected Model: Multistage, 2-Degree*

Murray et al. (1979): Fertility in F2 Generation

```
 ========================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\1\Murray_1979_fert_index_f2_Multi2_1.(d)
        Gnuplot Plotting File:  C:\1\Murray_1979_fert_index_f2_Multi2_1.plt
                                          Tue Feb 16 20:08:06 2010
 ========================================================================

 Table 1 but expressed as number of dams who do not produce offspring
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values
Background = 0.0624181
Beta(1) = 0
Beta(2) = 0.00532688

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(1)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(2)
Background	1	-0.44
Beta(2)	-0.44	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0772201	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.00509404	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-25.8194	3			
Fitted model	-27.9673	2	4.29584	1	0.03821
Reduced model	-34.0009	1	16.363	2	0.0002798

AIC: 59.9347

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual

0.0000	0.0772	2.471	4.000	32	1.013
1.0000	0.0819	1.638	0.000	20	-1.336
10.0000	0.4455	8.911	9.000	20	0.040

Chi^2 = 2.81 d.f. = 1 P-value = 0.0936

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

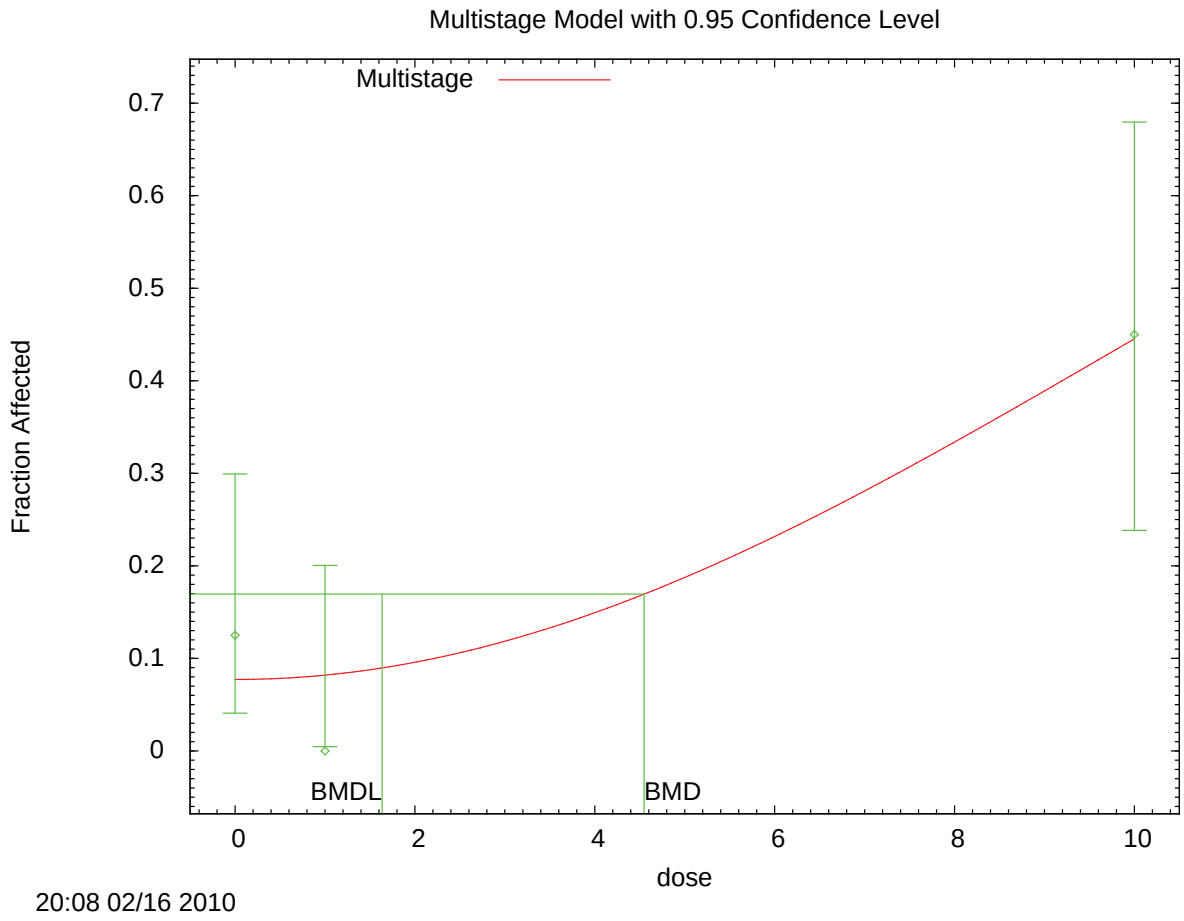
BMD = 4.54787

BMDL = 1.63487

BMDU = 6.79105

Taken together, (1.63487, 6.79105) is a 90 % two-sided confidence interval for the BMD

G.3.35.3. *Figure for Selected Model: Multistage, 2-Degree*



G.3.36. National Toxicology Program (1982): Toxic Hepatitis, Male Mice

G.3.36.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	1	0.026	113.097	1.552E+01	5.155E+00	
Logistic	2	0.093	110.712	1.769E+01	1.383E+01	
Log-logistic	1	0.027	113.093	1.499E+01	6.628E+00	
Log-probit	1	0.027	113.111	1.360E+01	7.237E+00	
Multistage, 3-degree[a]	**1**	**0.028**	**112.555**	**1.488E+01**	**4.676E+00**	
Probit	2	0.088	110.696	1.564E+01	1.261E+01	
Weibull	1	0.026	113.056	1.619E+01	4.903E+00	

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.36.2. *Output for Selected Model: Multistage, 3-Degree*

National Toxicology Program (1982): Toxic Hepatitis, Male Mice

```
 ======================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\1\37_NTP_1982_ToxHep_Multi3_1.(d)
        Gnuplot Plotting File:  C:\1\37_NTP_1982_ToxHep_Multi3_1.plt
                                          Tue Feb 16 18:17:51 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0525767
                        Beta(1) =   0.00243254
                        Beta(2) =            0
                        Beta(3) = 5.29052e-006


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(1)      Beta(3)

Background            1        -0.69         0.66
```

Beta(1)	-0.69	1	-0.98
Beta(3)	0.66	-0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0383474	*	*	*
Beta(1)	0.00605732	*	*	*
Beta(2)	0	*	*	*
Beta(3)	4.60855e-006	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-51.0633	4			
Fitted model	-53.2776	3	4.42854	1	0.03534
Reduced model	-121.743	1	141.358	3	<.0001

AIC: 112.555

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0383	2.799	1.000	73	-1.097
1.4000	0.0465	2.278	5.000	49	1.847
7.1000	0.0803	3.937	3.000	49	-0.492
71.0000	0.8798	43.990	44.000	50	0.004

Chi^2 = 4.86 d.f. = 1 P-value = 0.0275

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

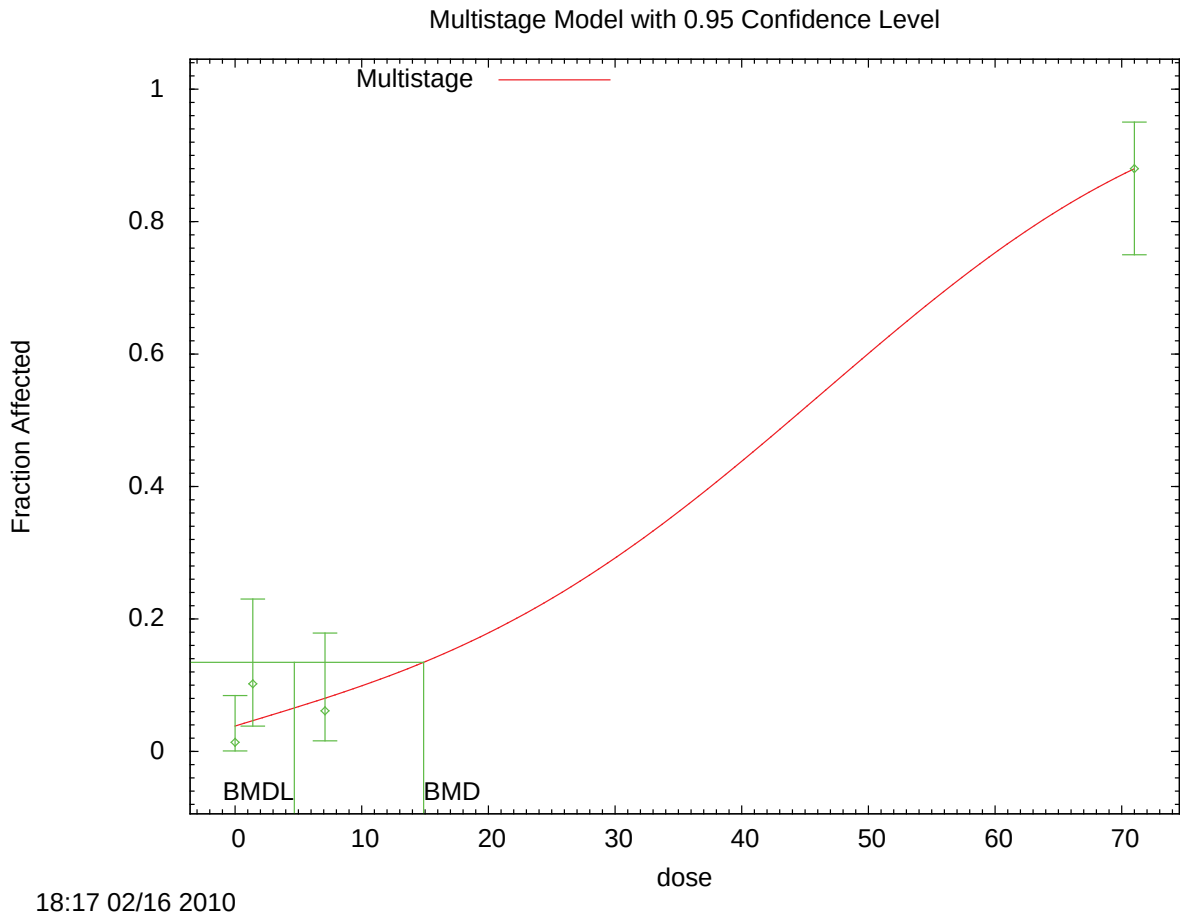
BMD = 14.8848

```
            BMDL =        4.67636

            BMDU =        28.8293

Taken together, (4.67636, 28.8293) is a 90     % two-sided confidence
interval for the BMD
```

G.3.36.3. *Figure for Selected Model: Multistage, 3-Degree*



G.3.37. National Toxicology Program (2006): Alveolar Metaplasia

G.3.37.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	4	<0.001	340.127	2.240E+00	1.791E+00	power bound hit (power = 1)
Logistic	4	<0.001	358.346	4.997E+00	4.149E+00	
Log-logistic[a]	**4**	**0.409**	**312.970**	**6.644E−01**	**5.041E−01**	**slope bound hit (slope = 1)**
Log-probit	4	<0.001	340.296	3.291E+00	2.517E+00	slope bound hit (slope = 1)
Multistage, 5-degree	4	<0.001	340.127	2.240E+00	1.791E+00	final ß = 0
Probit	4	<0.001	362.181	5.656E+00	4.810E+00	
Weibull	4	<0.001	340.127	2.240E+00	1.791E+00	power bound hit (power = 1)
Gamma, unrestricted	3	0.407	314.135	2.211E−02	8.081E−04	unrestricted (power = 0.297)
Log-logistic, unrestricted[b]	3	0.739	312.487	3.062E−01	7.972E−02	unrestricted (slope = 0.785)
Log-probit, unrestricted	3	0.727	312.543	3.316E−01	8.968E−02	unrestricted (slope = 0.471)
Weibull, unrestricted	3	0.586	313.176	9.000E−02	1.341E−02	unrestricted (power = 0.465)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.37.2. *Output for Selected Model: Log-Logistic*

National Toxicology Program (2006): Alveolar Metaplasia

```
 ========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\40_NTP_2006_AlvMeta_LogLogistic_1.(d)
        Gnuplot Plotting File:  C:\1\40_NTP_2006_AlvMeta_LogLogistic_1.plt
                                          Tue Feb 16 18:19:30 2010
 ========================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

```
   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =    0.0377358
                      intercept =     -2.03745
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1         -0.4

 intercept         -0.4            1



                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background        0.0448753            *                *
*
      intercept         -1.78837            *                *
*
          slope                1            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -152.615         6
   Fitted model        -154.485         2        3.7393      4
0.4424
  Reduced model        -216.802         1       128.374      5         <.0001
```

AIC: 312.97

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0449	2.378	2.000	53	-0.251
2.1400	0.2966	16.017	19.000	54	0.889
7.1400	0.5647	29.928	33.000	53	0.851
15.7000	0.7366	38.301	35.000	52	-1.039
32.9000	0.8531	45.214	45.000	53	-0.083
71.4000	0.9262	48.162	46.000	52	-1.147

Chi^2 = 3.98 d.f. = 4 P-value = 0.4088

Benchmark Dose Computation

Specified effect = 0.1

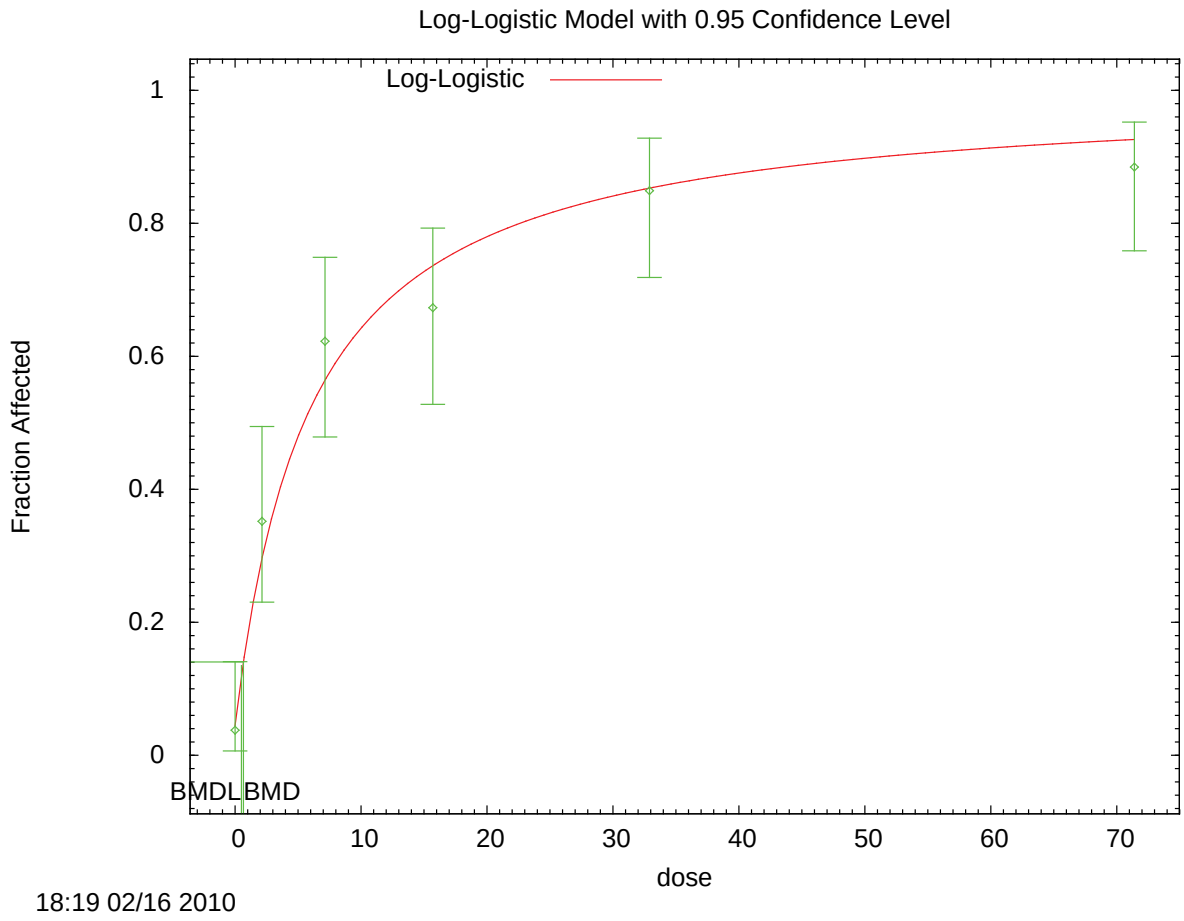
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.664411

BMDL = 0.504109

G.3.37.3. *Figure for Selected Model: Log-Logistic*



G.3.37.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

National Toxicology Program (2006): Alveolar Metaplasia

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\40_NTP_2006_AlvMeta_LogLogistic_U_1.(d)
        Gnuplot Plotting File:  C:\1\40_NTP_2006_AlvMeta_LogLogistic_U_1.plt
                                          Tue Feb 16 18:19:31 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
```

Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.0377358
intercept = -1.26694
slope = 0.784484

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.24	0.11
intercept	-0.24	1	-0.9
slope	0.11	-0.9	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0375286	*	*	*
intercept	-1.26811	*	*	*
slope	0.785033	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-152.615	6			
Fitted model	-153.244	3	1.2566	3	0.7395
Reduced model	-216.802	1	128.374	5	<.0001

AIC: 312.487

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0375	1.989	2.000	53	0.008
2.1400	0.3631	19.609	19.000	54	-0.172
7.1400	0.5845	30.980	33.000	53	0.563
15.7000	0.7205	37.468	35.000	52	-0.763
32.9000	0.8207	43.498	45.000	53	0.538
71.4000	0.8934	46.455	46.000	52	-0.204

Chi^2 = 1.26 d.f. = 3 P-value = 0.7388

Benchmark Dose Computation

Specified effect = 0.1

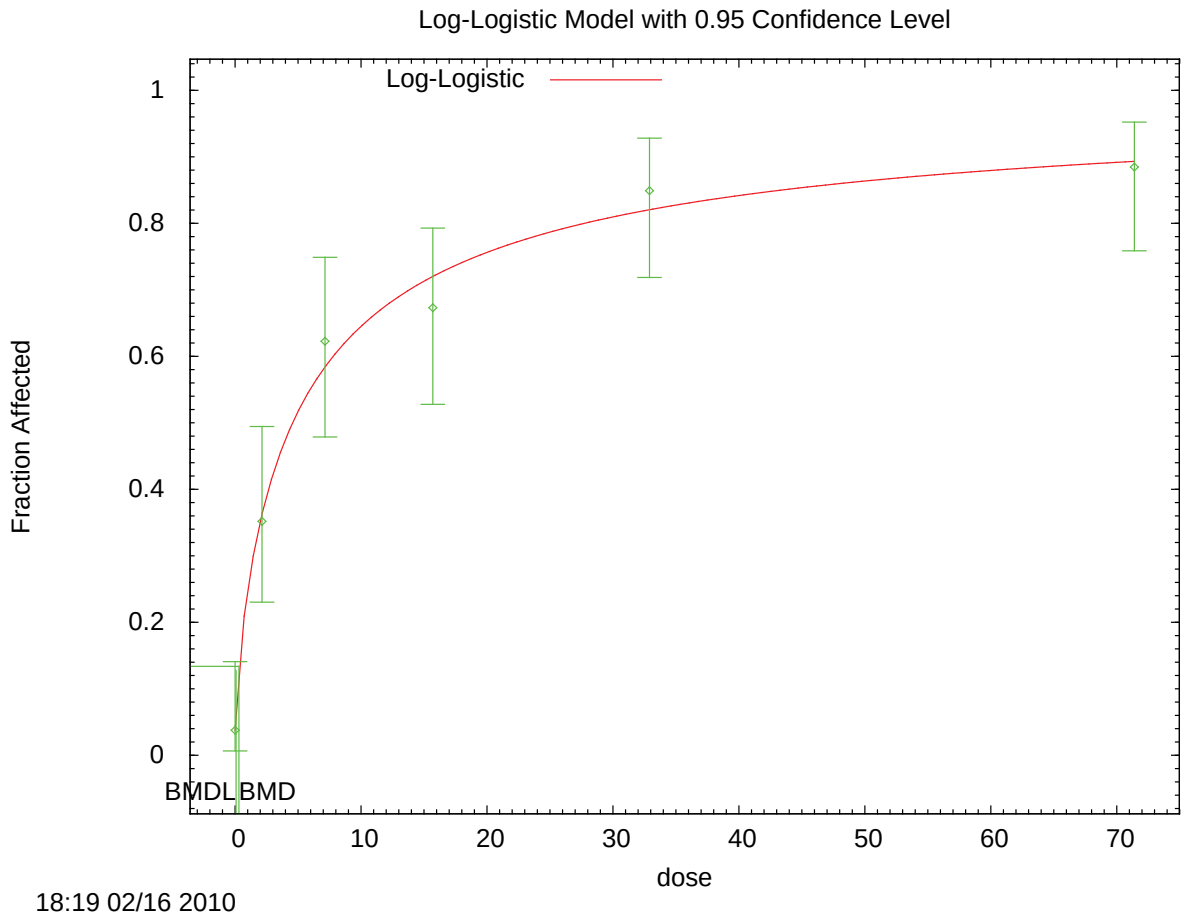
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.306194

BMDL = 0.0797223

G.3.37.5. ***Figure for Additional Model Presented: Log-Logistic, Unrestricted***



G.3.38. National Toxicology Program (2006): Eosinophilic Focus, Liver

G.3.38.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	4	0.367	330.457	5.676E+00	4.532E+00	power bound hit (power = 1)
Logistic	4	0.167	333.343	1.258E+01	1.071E+01	
Log-logistic	3	0.117	334.148	4.727E+00	2.867E+00	
Log-probit	4	0.084	334.683	1.078E+01	8.514E+00	
Multistage, 5-degree	3	0.313	331.771	6.568E+00	4.666E+00	
Probit[a]	**4**	**0.187**	**332.962**	**1.196E+01**	**1.031E+01**	
Weibull	4	0.367	330.457	5.675E+00	4.532E+00	power bound hit (power = 1)
Log-probit, unrestricted	3	0.087	334.849	4.750E+00	1.757E+00	unrestricted (slope = 0.643)

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.38.2. *Output for Selected Model: Probit*

National Toxicology Program (2006): Eosinophilic Focus, Liver

```
 ======================================================================
        Probit Model. (Version: 3.1;  Date: 05/16/2008)
        Input Data File: C:\1\45_NTP_2006_LivEosFoc_Probit_1.(d)
        Gnuplot Plotting File:  C:\1\45_NTP_2006_LivEosFoc_Probit_1.plt
                                          Tue Feb 16 18:25:56 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = CumNorm(Intercept+Slope*Dose),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                    Default Initial (and Specified) Parameter Values
```

```
background =            0   Specified
 intercept =     -1.11935
     slope =    0.0279665
```

Asymptotic Correlation Matrix of Parameter Estimates

```
( *** The model parameter(s)  -background
      have been estimated at a boundary point, or have been
specified by the user,
      and do not appear in the correlation matrix )
```

	intercept	slope
intercept	1	-0.69
slope	-0.69	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
intercept	-1.06148	0.109177	-1.27546	-0.847497
slope	0.0269279	0.00327788	0.0205034	0.0333525

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-161.07	6			
Fitted model	-164.481	2	6.8221	4	0.1456
Reduced model	-202.816	1	83.4925	5	<.0001

AIC: 332.962

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1442	7.645	3.000	53	-1.816
2.1400	0.1577	8.517	8.000	54	-0.193
7.1400	0.1924	10.195	14.000	53	1.326
15.7000	0.2615	13.860	17.000	53	0.982
32.9000	0.4303	22.807	22.000	53	-0.224
71.4000	0.8054	42.688	42.000	53	-0.239

Chi^2 = 6.16 d.f. = 4 P-value = 0.1873

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        11.9584

            BMDL =        10.3075
```

G.3.38.3. *Figure for Selected Model: Probit*

G.3.39. National Toxicology Program (2006): Fatty Change Diffuse, Liver

G.3.39.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	4	0.668	252.294	4.224E+00	3.166E+00	
Logistic	4	0.005	269.825	1.092E+01	9.292E+00	
Log-logistic	4	0.292	255.082	4.697E+00	3.153E+00	
Log-probit	4	0.118	257.548	6.236E+00	5.204E+00	slope bound hit (slope = 1)
Multistage, 5-degree	4	0.808	251.545	4.021E+00	3.250E+00	
Probit	4	0.005	269.430	1.052E+01	9.068E+00	
Weibull[a]	**4**	**0.679**	**252.218**	**4.252E+00**	**3.174E+00**	
Log-probit, unrestricted	4	0.282	255.258	4.581E+00	3.193E+00	unrestricted (slope = 0.824)

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.39.2. *Output for Selected Model: Weibull*

National Toxicology Program (2006): Fatty Change Diffuse, Liver

```
 ========================================================================
        Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
        Input Data File: C:\1\47_NTP_2006_LivFatDiff_Weibull_1.(d)
        Gnuplot Plotting File:  C:\1\47_NTP_2006_LivFatDiff_Weibull_1.plt
                                          Tue Feb 16 18:26:57 2010
 ========================================================================

 NTP_liver_fatty_change_diffuse
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]


   Dependent variable = DichEff
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial (and Specified) Parameter Values
                     Background =   0.00925926
                          Slope =   0.00962604
                          Power =      1.28042
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Slope	Power
Slope	1	-0.97
Power	-0.97	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Slope	0.0223474	0.00951041	0.0037073	0.0409874
Power	1.07133	0.122134	0.831952	1.31071

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-122.992	6			
Fitted model	-124.109	2	2.23388	4	0.6928
Reduced model	-204.846	1	163.708	5	<.0001

AIC: 252.218

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	53	0.000
2.1400	0.0492	2.659	2.000	54	-0.414
7.1400	0.1677	8.889	12.000	53	1.144
15.7000	0.3475	18.420	17.000	53	-0.409
32.9000	0.6107	32.365	30.000	53	-0.666
71.4000	0.8851	46.909	48.000	53	0.470

```
 Chi^2 = 2.31      d.f. = 4        P-value = 0.6785

   Benchmark Dose Computation

Specified effect =            0.1

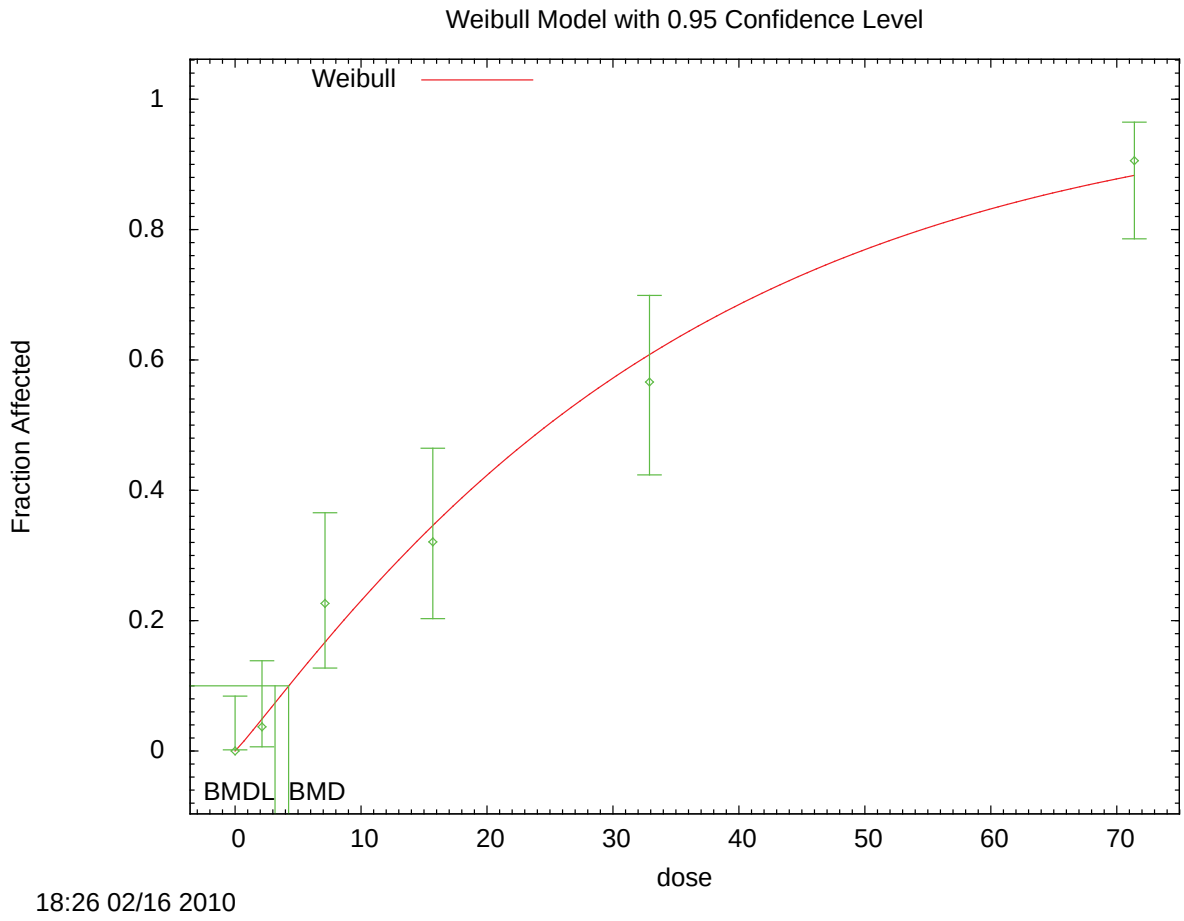
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        4.25219

            BMDL =       3.17375
```

G.3.39.3. *Figure for Selected Model: Weibull*



G.3.40. National Toxicology Program (2006): Gingival Hyperplasia, Squamous, 2 Years

G.3.40.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	4	0.012	318.867	2.295E+01	1.417E+01	power bound hit (power = 1)
Logistic	4	0.008	320.908	3.594E+01	2.564E+01	
Log-logistic[a]	**4**	**0.015**	**317.969**	**1.838E+01**	**1.044E+01**	**slope bound hit (slope = 1)**
Log-probit	4	0.003	323.633	4.313E+01	2.794E+01	slope bound hit (slope = 1)
Multistage, 5-degree	4	0.012	318.867	2.295E+01	1.417E+01	final ß = 0
Probit	4	0.008	320.687	3.436E+01	2.425E+01	
Weibull	4	0.012	318.867	2.295E+01	1.417E+01	power bound hit (power = 1)
Gamma, unrestricted	3	0.651	307.529	2.480E−01	5.096E−09	unrestricted (power = 0.199)
Log-logistic, unrestricted[b]	3	0.675	307.416	3.710E−01	1.505E−07	unrestricted (slope = 0.265)
Log-probit, unrestricted	3	0.688	307.354	4.688E−01	8.851E−07	unrestricted (slope = 0.156)
Weibull, unrestricted	3	0.663	307.471	3.076E−01	3.210E−08	unrestricted (power = 0.23)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.40.2. *Output for Selected Model: Log-Logistic*

National Toxicology Program (2006): Gingival Hyperplasia, Squamous, 2 Years

```
 ========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\42_NTP_2006_GingHypSq_LogLogistic_1.(d)
        Gnuplot Plotting File:  C:\1\42_NTP_2006_GingHypSq_LogLogistic_1.plt
                                          Tue Feb 16 18:20:29 2010
 ========================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

```
   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =    0.0188679
                      intercept =      -4.5509
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.71

 intercept        -0.71            1



                                 Parameter Estimates

                                                                 95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background         0.117717            *                *
*
      intercept         -5.10866            *                *
*
          slope                1            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -149.95         6
   Fitted model        -156.985         2       14.0696      4
0.007076
  Reduced model        -162.631         1       25.3627      5
0.0001186
```

AIC: 317.969

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1177	6.239	1.000	53	-2.233
2.1400	0.1290	6.965	7.000	54	0.014
7.1400	0.1542	8.174	14.000	53	2.216
15.7000	0.1942	10.292	13.000	53	0.940
32.9000	0.2641	13.995	15.000	53	0.313
71.4000	0.3837	20.335	16.000	53	-1.225

Chi^2 = 12.38 d.f. = 4 P-value = 0.0147

Benchmark Dose Computation

Specified effect = 0.1

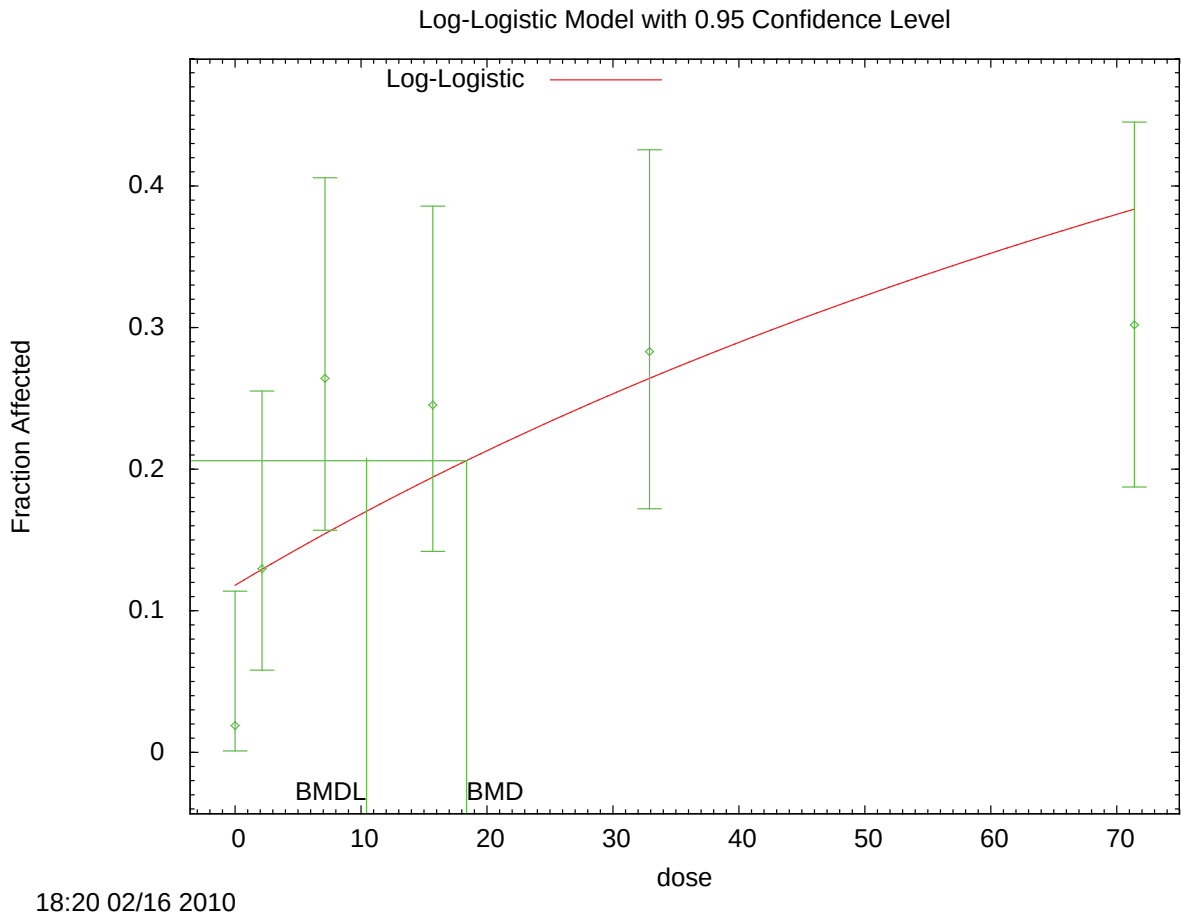
Risk Type = Extra risk

Confidence level = 0.95

BMD = 18.3832

BMDL = 10.4359

G.3.40.3. *Figure for Selected Model: Log-Logistic*



G.3.40.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

National Toxicology Program (2006): Gingival Hyperplasia, Squamous, 2 Years

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\42_NTP_2006_GingHypSq_LogLogistic_U_1.(d)
        Gnuplot Plotting File:
C:\1\42_NTP_2006_GingHypSq_LogLogistic_U_1.plt
                                          Tue Feb 16 18:20:29 2010
 ======================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]
```

```
Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



User has chosen the log transformed model


                Default Initial Parameter Values
                   background =    0.0188679
                    intercept =     -2.04571
                        slope =     0.299277


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1         -0.3         0.12

 intercept         -0.3            1        -0.91

     slope         0.12        -0.91            1



                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background        0.0185126            *                *
*
      intercept         -1.93464            *                *
*
          slope         0.264795            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -149.95         6
   Fitted model        -150.708         3        1.5163      3
0.6785
```

```
  Reduced model        -162.631         1       25.3627      5
0.0001186

           AIC:         307.416


                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.0185         0.981     1.000          53        0.019
    2.1400     0.1659         8.959     7.000          54       -0.717
    7.1400     0.2105        11.155    14.000          53        0.959
   15.7000     0.2447        12.972    13.000          53        0.009
   32.9000     0.2806        14.873    15.000          53        0.039
   71.4000     0.3219        17.059    16.000          53       -0.311

 Chi^2 = 1.53      d.f. = 3        P-value = 0.6750


   Benchmark Dose Computation

Specified effect =            0.1

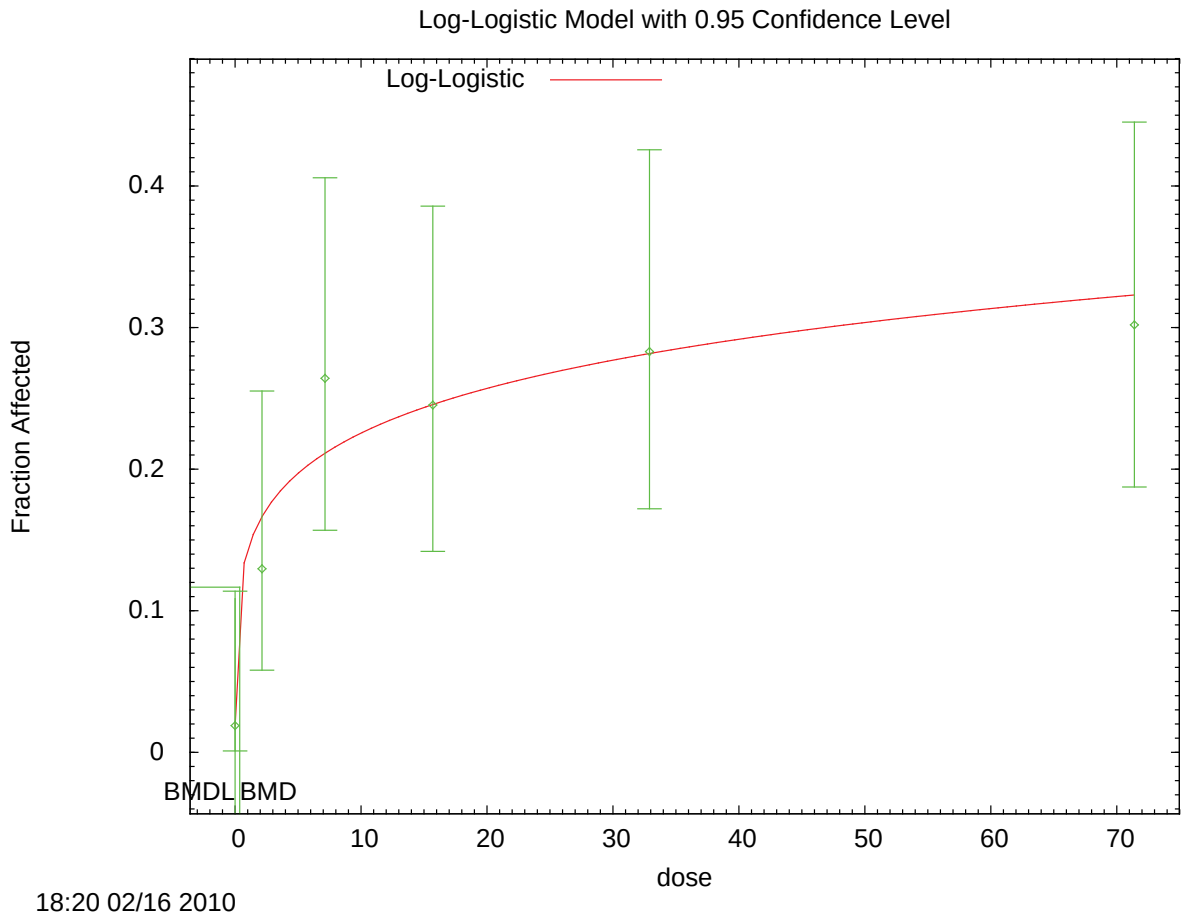
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.370958

            BMDL =   1.50494e-007
```

G.3.40.5. ***Figure for Additional Model Presented: Log-Logistic, Unrestricted***



G.3.41. National Toxicology Program (2006): Hepatocyte Hypertrophy, 2 Years

G.3.41.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	4	<0.001	290.365	1.647E+00	1.340E+00	power bound hit (power = 1)
Logistic	4	<0.001	310.492	4.315E+00	3.650E+00	
Log-logistic	5	0.010	278.082	6.978E−01	5.454E−01	slope bound hit (slope = 1)
Log-probit	4	<0.001	297.168	2.930E+00	2.267E+00	slope bound hit (slope = 1)
Multistage, 5-degree[a]	**4**	**<0.001**	**290.365**	**1.647E+00**	**1.340E+00**	**final ß = 0**
Probit	4	<0.001	313.841	4.564E+00	3.923E+00	
Weibull	4	<0.001	290.365	1.647E+00	1.340E+00	power bound hit (power = 1)
Gamma, unrestricted	4	0.029	275.042	error	error	unrestricted (power = 0.478)
Log-logistic, unrestricted	4	0.005	280.068	6.672E−01	2.939E−01	unrestricted (slope = 0.984)
Log-probit, unrestricted	4	0.006	279.204	7.167E−01	3.322E−01	unrestricted (slope = 0.594)
Weibull, unrestricted	4	0.019	275.967	3.709E−01	1.315E−01	unrestricted (power = 0.64)

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.41.2. *Output for Selected Model: Multistage, 5-Degree*

National Toxicology Program (2006): Hepatocyte Hypertrophy, 2 Years

```
 ========================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\1\43_NTP_2006_HepHyper_Multi5_1.(d)
        Gnuplot Plotting File:  C:\1\43_NTP_2006_HepHyper_Multi5_1.plt
                                          Tue Feb 16 18:21:00 2010
 ========================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                  -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-
beta5*dose^5)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose
```

```
 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 6
 Total number of specified parameters = 0
 Degree of polynomial = 5


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.232262
                        Beta(1) =     0.045074
                        Beta(2) =            0
                        Beta(3) =            0
                        Beta(4) =            0
                        Beta(5) = 2.59945e-010


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(2)    -Beta(3)    -Beta(4)
-Beta(5)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(1)

Background            1        -0.64

   Beta(1)        -0.64            1



                                  Parameter Estimates

                                                                  95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background        0.0541647            *                *
*
        Beta(1)        0.0639585            *                *
*
        Beta(2)                0            *                *
*
        Beta(3)                0            *                *
*
        Beta(4)                0            *                *
*
        Beta(5)                0            *                *
*
```

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-129.986	6			
Fitted model	-143.183	2	26.3932	4	2.6361629e-005
Reduced model	-219.97	1	179.968	5	<.0001

AIC: 290.365

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0542	2.871	0.000	53	-1.742
2.1400	0.1752	9.458	19.000	54	3.416
7.1400	0.4009	21.248	19.000	53	-0.630
15.7000	0.6535	34.635	42.000	53	2.126
32.9000	0.8847	46.887	41.000	53	-2.532
71.4000	0.9902	52.479	52.000	53	-0.667

Chi^2 = 26.48 d.f. = 4 P-value = 0.0000

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

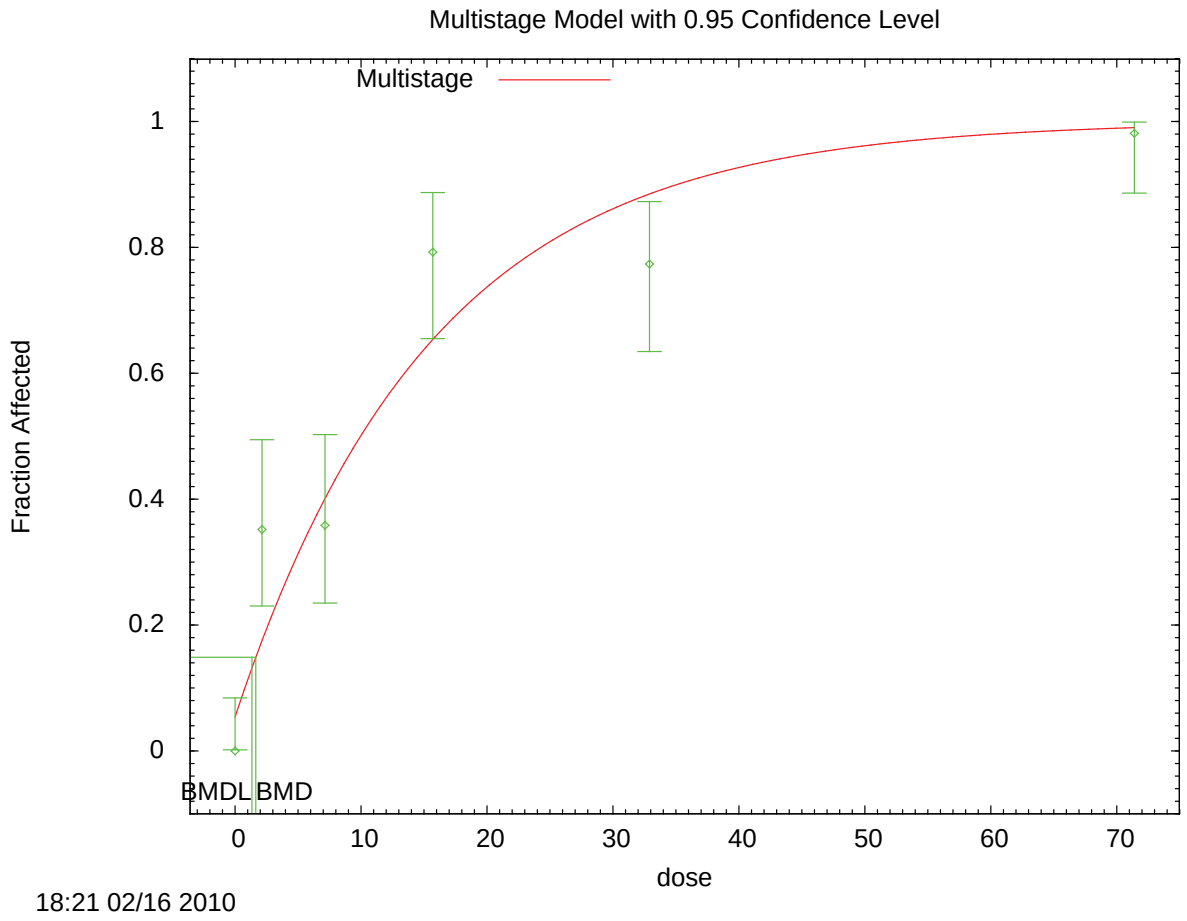
BMD = 1.64733

BMDL = 1.34007

BMDU = 2.0581

Taken together, (1.34007, 2.0581) is a 90 % two-sided confidence interval for the BMD

G.3.41.3. *Figure for Selected Model: Multistage, 5-Degree*



G.3.42. National Toxicology Program (2006): Necrosis, Liver

G.3.42.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Logistic	4	0.397	238.314	3.484E+01	2.842E+01	negative intercept (intercept = −2.601)
Log-logistic	4	0.810	235.265	1.791E+01	1.194E+01	slope bound hit (slope = 1)
Log-probit	4	0.290	239.107	3.205E+01	2.382E+01	slope bound hit (slope = 1)
Multistage, 5-degree	4	0.763	235.581	2.019E+01	1.419E+01	final ß = 0
Probit	4	0.445	237.888	3.266E+01	2.637E+01	
Weibull	4	0.763	235.581	2.019E+01	1.419E+01	power bound hit (power = 1)
Gamma, unrestricted	3	0.869	236.344	1.114E+01	3.487E+00	unrestricted (power = 0.599)
Log-logistic, unrestricted	3	0.833	236.483	1.112E+01	3.581E+00	unrestricted (slope = 0.695)
Log-probit, unrestricted[a]	**3**	**0.768**	**236.742**	**1.061E+01**	**3.498E+00**	**unrestricted (slope = 0.367)**
Weibull, unrestricted	3	0.856	236.393	1.117E+01	3.554E+00	unrestricted (power = 0.64)

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.42.2. *Output for Selected Model: Log-Probit, Unrestricted*

National Toxicology Program (2006): Necrosis, Liver

```
 ======================================================================
        Probit Model. (Version: 3.1;  Date: 05/16/2008)
        Input Data File: C:\1\50_NTP_2006_LivNec_LogProbit_U_1.(d)
        Gnuplot Plotting File:  C:\1\50_NTP_2006_LivNec_LogProbit_U_1.plt
                                          Tue Feb 16 18:34:31 2010
 ======================================================================

 NTP_liver_necrosis
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
```

Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0.0188679
intercept = -1.98094
slope = 0.316942

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.69	0.59
intercept	-0.69	1	-0.97
slope	0.59	-0.97	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0228339	0.0230818	-0.0224057	0.0680734
intercept	-2.14844	0.527256	-3.18184	-1.11503
slope	0.367034	0.139055	0.0944904	0.639577

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-114.813	6			
Fitted model	-115.371	3	1.1157	3	0.7733
Reduced model	-127.98	1	26.3331	5	<.0001

AIC: 236.742

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0228	1.210	1.000	53	-0.193

2.1400	0.0529	2.858	4.000	54	0.694
7.1400	0.0979	5.187	4.000	53	-0.549
15.7000	0.1475	7.819	8.000	53	0.070
32.9000	0.2116	11.215	10.000	53	-0.409
71.4000	0.2968	15.729	17.000	53	0.382

Chi^2 = 1.14 d.f. = 3 P-value = 0.7678

Benchmark Dose Computation

Specified effect = 0.1

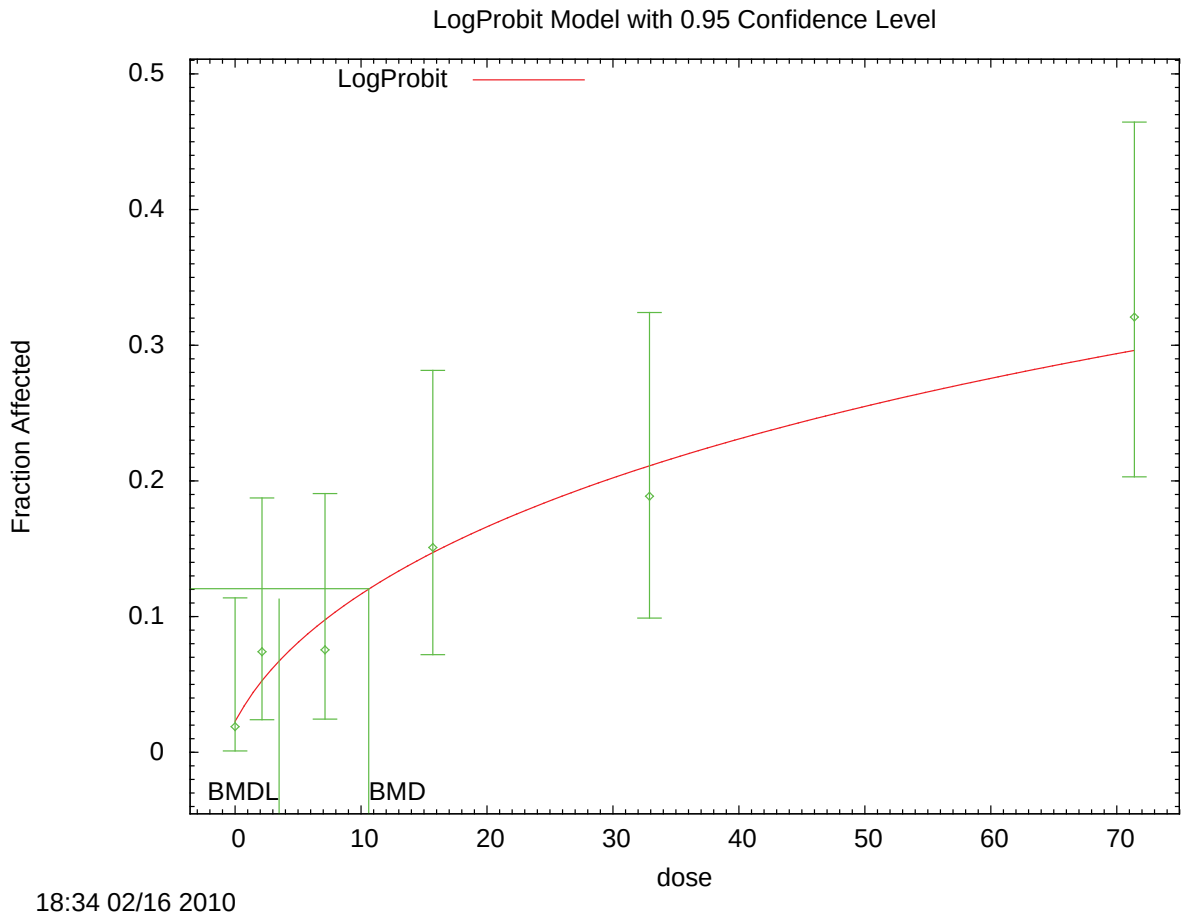
Risk Type = Extra risk

Confidence level = 0.95

BMD = 10.6107

BMDL = 3.49791

G.3.42.3. *Figure for Selected Model: Log-Probit, Unrestricted*



G.3.43. National Toxicology Program (2006): Oval Cell Hyperplasia

G.3.43.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	3	0.072	199.446	8.970E+00	5.499E+00	
Logistic	4	0.069	199.875	9.792E+00	8.245E+00	
Log-logistic	3	0.039	202.012	9.708E+00	7.247E+00	
Log-probit	3	0.068	200.421	9.968E+00	7.758E+00	
Multistage, 5-degree	2	0.066	198.641	5.424E+00	3.514E+00	
Probit[a]	**4**	**0.112**	**198.166**	**9.103E+00**	**7.701E+00**	
Weibull[b]	3	0.075	198.690	7.712E+00	4.692E+00	

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.43.2. *Output for Selected Model: Probit*

National Toxicology Program (2006): Oval Cell Hyperplasia

```
 ========================================================================
        Probit Model. (Version: 3.1;  Date: 05/16/2008)
        Input Data File: C:\1\53_NTP_2006_OvalHyper_Probit_1.(d)
        Gnuplot Plotting File:  C:\1\53_NTP_2006_OvalHyper_Probit_1.plt
                                          Tue Feb 16 19:51:52 2010
 ========================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = CumNorm(Intercept+Slope*Dose),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial (and Specified) Parameter Values
                     background =            0   Specified
                      intercept =     -1.92612
                          slope =    0.0670004
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-0.8
slope	-0.8	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
intercept	-1.82129	0.16954	-2.15359	-1.489
slope	0.0767832	0.00835175	0.060414	0.0931523

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-92.4898	6			
Fitted model	-97.0832	2	9.18683	4	0.0566
Reduced model	-210.191	1	235.402	5	<.0001

AIC: 198.166

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0343	1.817	0.000	53	-1.372
2.1400	0.0488	2.633	4.000	54	0.864
7.1400	0.1015	5.379	3.000	53	-1.082
15.7000	0.2690	14.258	20.000	53	1.779
32.9000	0.7596	40.256	38.000	53	-0.725
71.4000	0.9999	52.993	53.000	53	0.082

Chi^2 = 7.50 d.f. = 4 P-value = 0.1119

Benchmark Dose Computation

```
Specified effect =            0.1

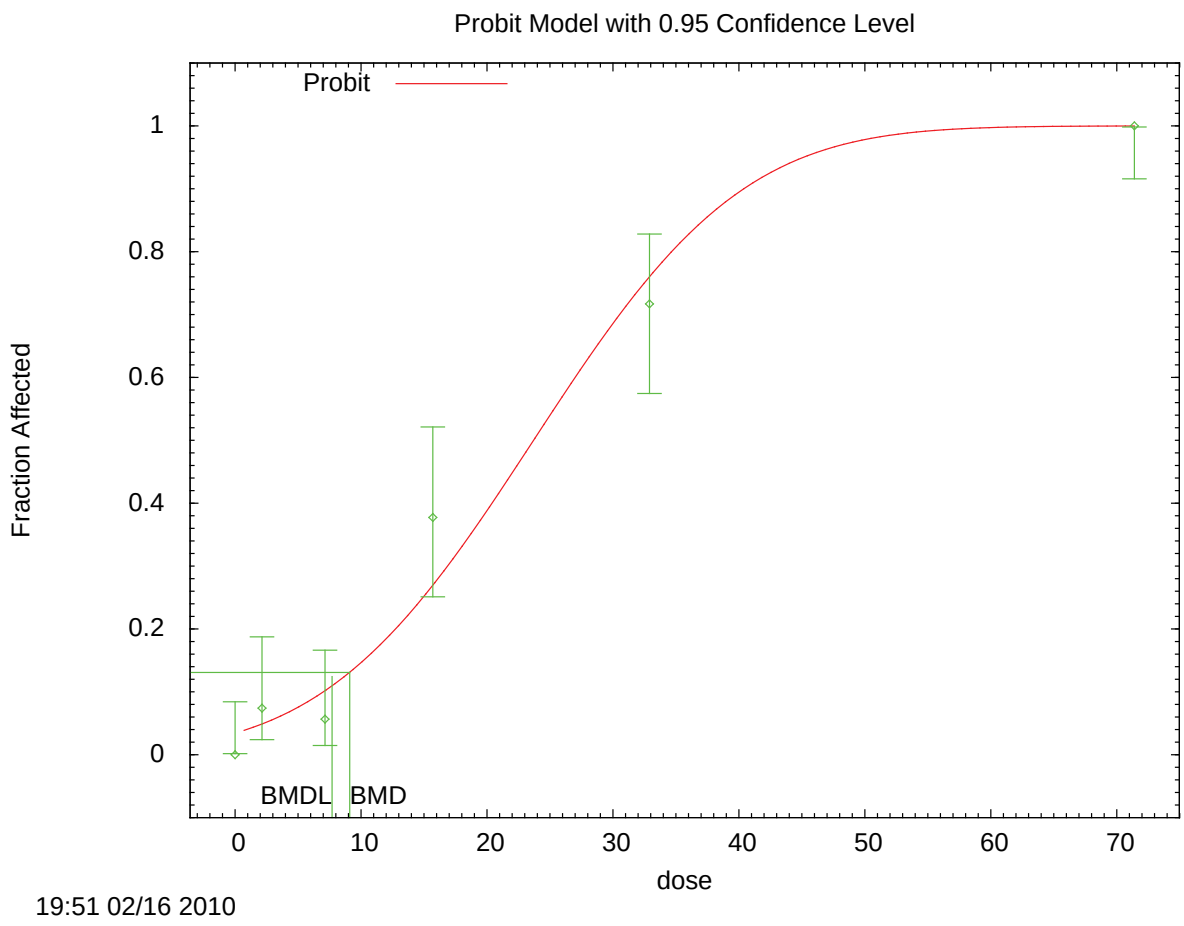
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         9.1026

            BMDL =         7.7011
```

G.3.43.3. *Figure for Selected Model: Probit*



G.3.43.4. *Output for Additional Model Presented: Weibull*

National Toxicology Program (2006): Oval Cell Hyperplasia

```
 ======================================================================
        Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
        Input Data File: C:\1\53_NTP_2006_OvalHyper_Weibull_1.(d)
        Gnuplot Plotting File:  C:\1\53_NTP_2006_OvalHyper_Weibull_1.plt
                                          Tue Feb 16 19:51:53 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]


   Dependent variable = DichEff
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                   Default Initial (and Specified) Parameter Values
                      Background =   0.00925926
                           Slope =    0.0044452
                           Power =      1.63009


            Asymptotic Correlation Matrix of Parameter Estimates

              Background        Slope        Power

Background            1        -0.63         0.61

     Slope        -0.63            1        -0.99

     Power         0.61        -0.99            1



                                  Parameter Estimates

                                                                  95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
```

```
     Background         0.021258        0.0198428          -0.0176332
0.0601492
          Slope        0.0028715       0.00303327          -0.0030736
0.0088166
          Power          1.76359         0.309457             1.15706
2.37011
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-92.4898	6			
Fitted model	-96.3448	3	7.70998	3	0.0524
Reduced model	-210.191	1	235.402	5	<.0001

AIC: 198.69

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0213	1.127	0.000	53	-1.073
2.1400	0.0320	1.725	4.000	54	1.760
7.1400	0.1073	5.685	3.000	53	-1.192
15.7000	0.3234	17.138	20.000	53	0.840
32.9000	0.7490	39.698	38.000	53	-0.538
71.4000	0.9953	52.750	53.000	53	0.501

Chi^2 = 6.92 d.f. = 3 P-value = 0.0746

Benchmark Dose Computation

Specified effect = 0.1

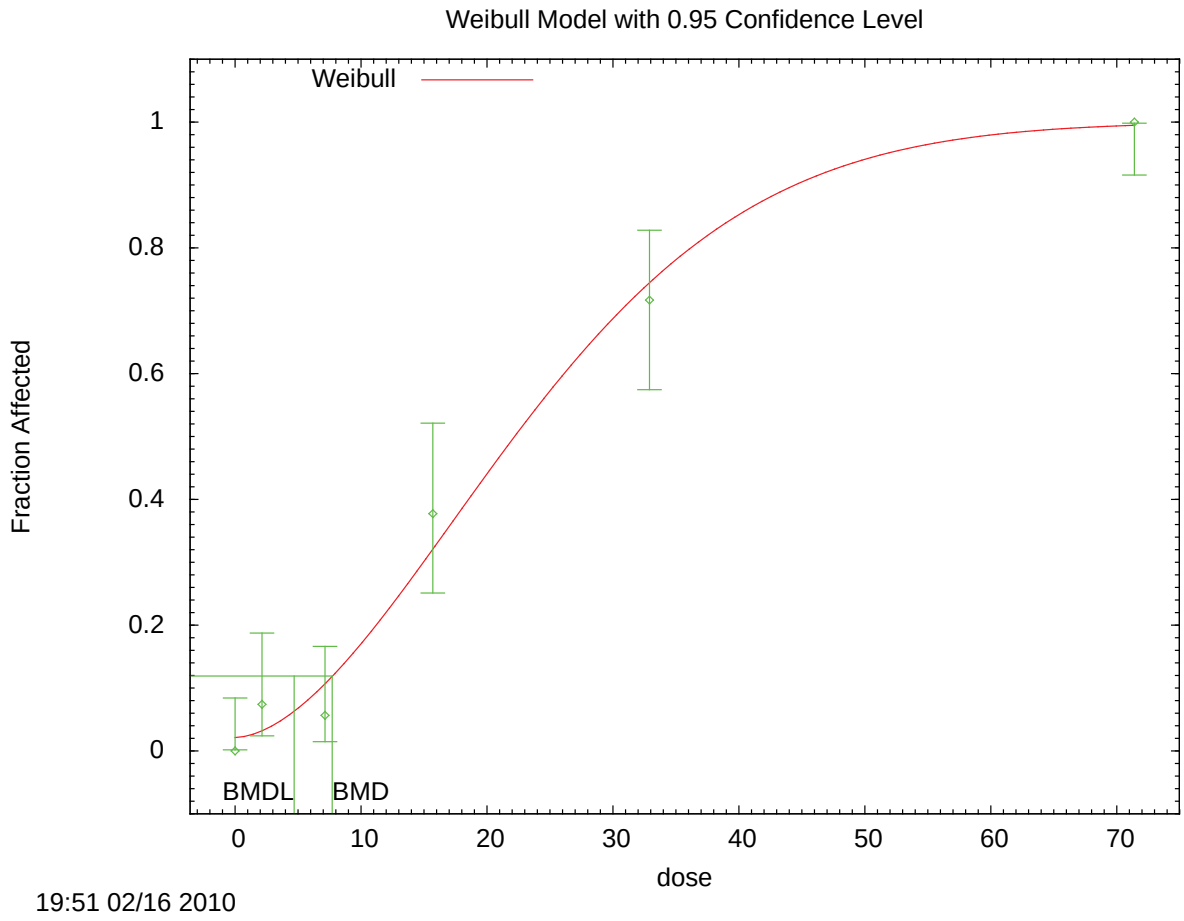
Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.71171

BMDL = 4.69152

G.3.43.5. *Figure for Additional Model Presented: Weibull*



G.3.44. National Toxicology Program (2006): Pigmentation, Liver

G.3.44.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	3	0.385	197.655	1.547E+00	8.055E−01	
Logistic	4	<0.001	203.517	2.259E+00	1.872E+00	
Log-logistic	3	0.978	195.600	2.212E+00	1.452E+00	
Log-probit[a]	**3**	**0.980**	**195.450**	**2.072E+00**	**1.399E+00**	
Multistage, 5-degree	3	0.210	199.850	9.396E−01	7.079E−01	final ß = 0
Probit	4	<0.001	210.309	2.259E+00	1.916E+00	
Weibull	3	0.290	198.489	1.280E+00	7.518E−01	

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.44.2. *Output for Selected Model: Log-Probit*

National Toxicology Program (2006): Pigmentation, Liver

```
 ====================================================================
        Probit Model. (Version: 3.1;  Date: 05/16/2008)
        Input Data File: C:\1\54_NTP_2006_Pigment_LogProbit_1.(d)
        Gnuplot Plotting File:  C:\1\54_NTP_2006_Pigment_LogProbit_1.plt
                                          Tue Feb 16 19:52:19 2010
 ====================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                   Default Initial (and Specified) Parameter Values
                      background =    0.0754717
                       intercept =     -1.91144
                           slope =      1.07385


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.45         0.35

 intercept        -0.45            1        -0.94

     slope         0.35        -0.94            1


                                   Parameter Estimates
```

95.0% Wald Confidence Interval

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
background	0.0735956	0.0343284	0.00631316	0.140878
intercept	-2.19294	0.400053	-2.97703	-1.40885
slope	1.25068	0.169731	0.918012	1.58335

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-94.6177	6			
Fitted model	-94.7248	3	0.214232	3	0.9753
Reduced model	-210.717	1	232.198	5	<.0001

AIC: 195.45

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0736	3.901	4.000	53	0.052
2.1400	0.1729	9.338	9.000	54	-0.122
7.1400	0.6338	33.591	34.000	53	0.117
15.7000	0.9023	47.822	48.000	53	0.082
32.9000	0.9863	52.275	52.000	53	-0.325
71.4000	0.9992	52.959	53.000	53	0.202

Chi^2 = 0.18 d.f. = 3 P-value = 0.9801

Benchmark Dose Computation

Specified effect = 0.1

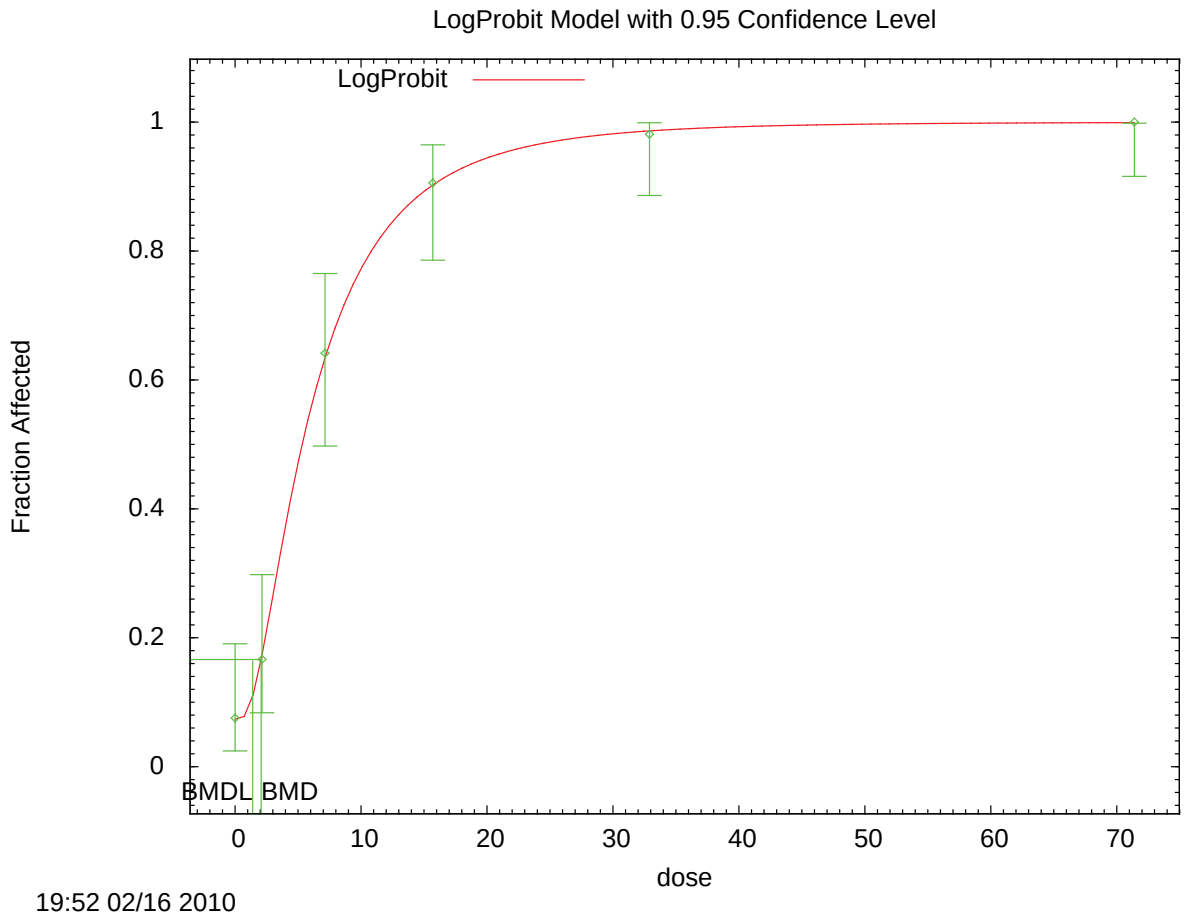
Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.07241

BMDL = 1.39932

G.3.44.3. *Figure for Selected Model: Log-Probit*



G.3.45. National Toxicology Program (2006): Toxic Hepatopathy

G.3.45.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	4	0.772	185.634	4.668E+00	3.317E+00	
Logistic	4	0.012	198.445	7.070E+00	5.925E+00	
Log-logistic	3	0.362	190.061	5.676E+00	4.040E+00	
Log-probit	3	0.378	189.858	6.061E+00	4.079E+00	
Multistage, 5-degree[a]	**4**	**0.577**	**186.521**	**4.163E+00**	**2.701E+00**	**final ß = 0**
Probit	4	0.019	197.159	6.784E+00	5.712E+00	
Weibull	4	0.745	185.657	4.454E+00	3.159E+00	

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.45.2. *Output for Selected Model: Multistage, 5-Degree*

National Toxicology Program (2006): Toxic Hepatopathy

```
 ======================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\1\55_NTP_2006_ToxHepa_Multi5_1.(d)
        Gnuplot Plotting File:  C:\1\55_NTP_2006_ToxHepa_Multi5_1.plt
                                          Tue Feb 16 19:52:49 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                  -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-
beta5*dose^5)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 6
 Total number of specified parameters = 0
 Degree of polynomial = 5


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                   Default Initial Parameter Values
                      Background =            0
                         Beta(1) =            0
                         Beta(2) =            0
                         Beta(3) =            0
                         Beta(4) =            0
                         Beta(5) = 5.40983e+010


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(3)    -Beta(4)
-Beta(5)
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )
```

	Beta(1)	Beta(2)
Beta(1)	1	-0.91
Beta(2)	-0.91	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.019656	*	*	*
Beta(2)	0.00135796	*	*	*
Beta(3)	0	*	*	*
Beta(4)	0	*	*	*
Beta(5)	0	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-89.8076	6			
Fitted model	-91.2606	2	2.90597	4	0.5737
Reduced model	-218.207	1	256.799	5	<.0001

AIC: 186.521

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	53	0.000
2.1400	0.0471	2.545	2.000	54	-0.350
7.1400	0.1891	10.021	8.000	53	-0.709
15.7000	0.4745	25.146	30.000	53	1.335
32.9000	0.8796	46.616	45.000	53	-0.682
71.4000	0.9998	52.987	53.000	53	0.113

Chi^2 = 2.89 d.f. = 4 P-value = 0.5771

Benchmark Dose Computation

```
Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

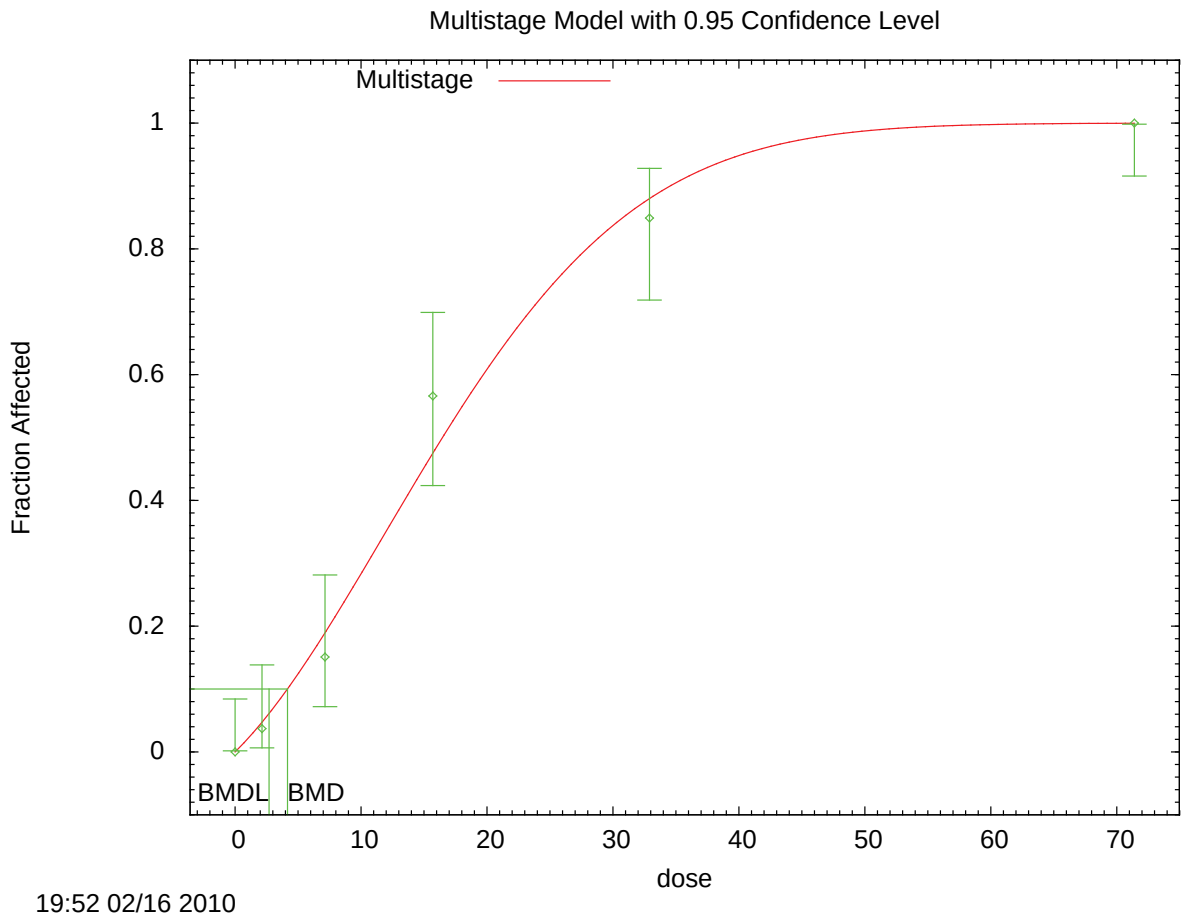
             BMD =        4.16294

            BMDL =        2.70063

            BMDU =        6.00186

Taken together, (2.70063, 6.00186) is a 90     % two-sided confidence
interval for the BMD
```

G.3.45.3. *Figure for Selected Model: Multistage, 5-Degree*



G.3.46. Ohsako et al. (2001): Ano-Genital Length, PND 120

G.3.46.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	0.019	171.804	5.650E+02	3.785E+02	
Exponential (M3)	3	0.019	171.804	5.650E+02	3.785E+02	power hit bound (*d* = 1)
Exponential (M4)	2	0.117	168.204	2.854E+01	1.054E+01	
Exponential (M5)	1	0.049	169.789	2.948E+01	1.135E+01	
Hill[b]	**2**	**0.148**	**167.727**	**3.722E+01**	**9.752E+00**	***n* lower bound hit (*n* = 1)**
Linear	3	0.018	171.954	5.852E+02	4.047E+02	
Polynomial, 4-degree	3	0.018	171.954	5.852E+02	4.047E+02	
Power	3	0.018	171.954	5.852E+02	4.047E+02	power bound hit (power = 1)
Hill, unrestricted[c]	1	0.055	169.600	5.101E+01	3.066E+00	unrestricted (*n* = 0.502)
Power, unrestricted	2	0.151	167.689	6.200E+01	2.291E+00	unrestricted (power = 0.252)

[a] Constant variance model selected (*p* = 0.165).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.46.2. *Output for Selected Model: Hill*

Ohsako et al. (2001): Ano-Genital Length, PND 120

```
 ========================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\56_Ohsako_2001_Anogen_HillCV_1.(d)
        Gnuplot Plotting File:  C:\1\56_Ohsako_2001_Anogen_HillCV_1.plt
                                          Tue Feb 16 19:53:25 2010
 ========================================================================

 Figure 7
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	7.27386	
rho =	0	Specified
intercept =	28.905	
v =	-5.1065	
n =	1.40226	
k =	33.9669	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	-2.2e-009	-2.4e-008	-7.2e-009
intercept	-2.2e-009	1	-0.66	-0.5
v	-2.4e-008	-0.66	1	-0.11
k	-7.2e-009	-0.5	-0.11	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	7.08444	1.3634	4.41223	9.75666
intercept	28.9809	0.745637	27.5195	30.4423
v	-4.79692	0.983318	-6.72418	-2.86965
n	1	NA		
k	29.8628	24.4463	-18.0511	77.7767

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

0	12	28.9	29	3.13	2.66	-0.0988
12.5	10	27.9	27.6	2.5	2.66	0.442
50	10	25.2	26	3.21	2.66	-0.963
200	10	26	24.8	2.85	2.66	1.42
800	12	23.8	24.4	1.56	2.66	-0.726

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-77.952340	6	167.904680
A2	-74.703868	10	169.407736
A3	-77.952340	6	167.904680
fitted	-79.863340	4	167.726680
R	-89.824703	2	183.649405

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	30.2417	8	0.0001916
Test 2	6.49694	4	0.165
Test 3	6.49694	4	0.165
Test 4	3.822	2	0.1479

```
The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

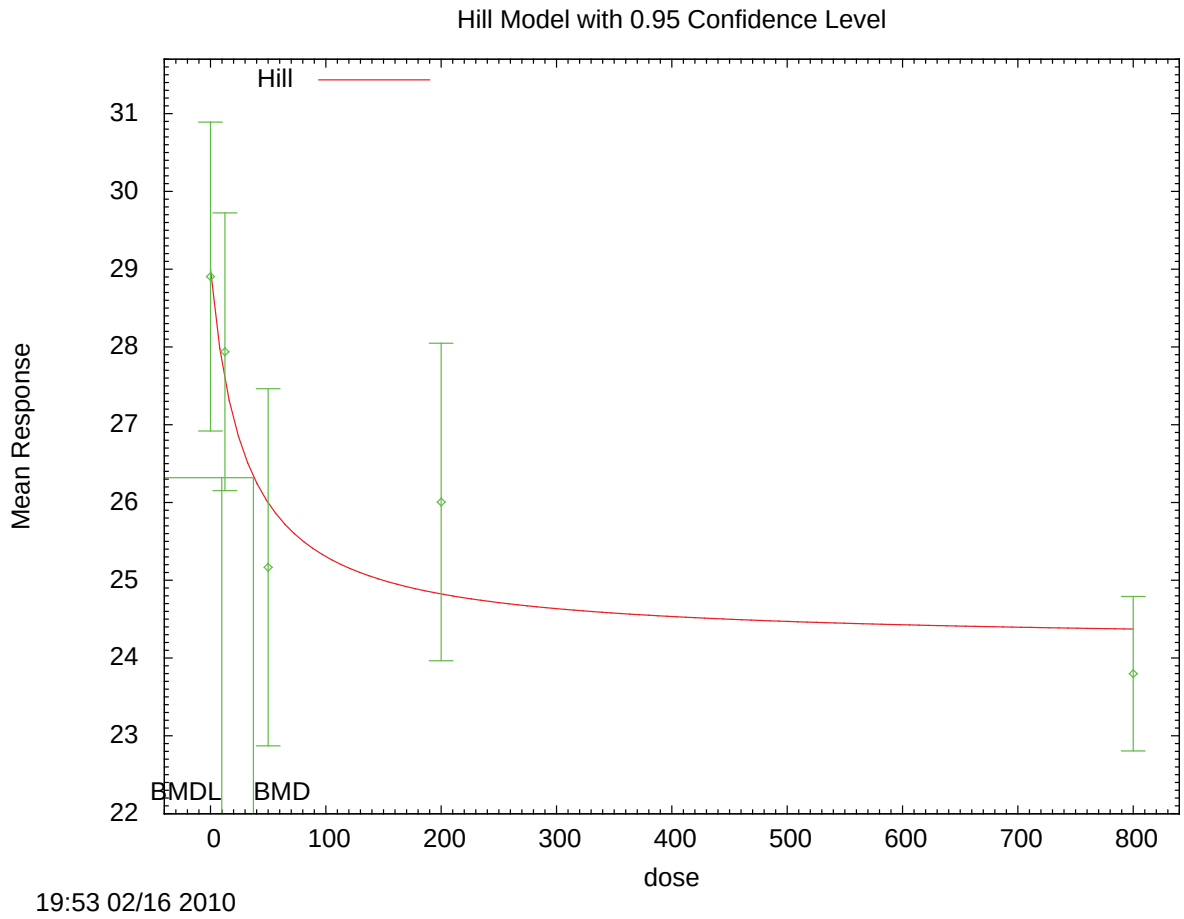
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =        37.2249

            BMDL =       9.75249
```

G.3.46.3. *Figure for Selected Model: Hill*



G.3.46.4. *Output for Additional Model Presented: Hill, Unrestricted*

Ohsako et al. (2001): Ano-Genital Length, PND 120

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\56_Ohsako_2001_Anogen_HillCV_U_1.(d)
        Gnuplot Plotting File:  C:\1\56_Ohsako_2001_Anogen_HillCV_U_1.plt
                                          Tue Feb 16 19:53:26 2010
 ======================================================================

 Figure 7
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
```

```
rho is set to 0
Power parameter is not restricted
A constant variance model is fit

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                         alpha =      7.27386
                           rho =            0   Specified
                     intercept =       28.905
                             v =      -5.1065
                             n =      1.40226
                             k =      33.9669


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha    intercept            v            n            k

     alpha            1     2.1e-009    -1.8e-008    -1.7e-008     1.6e-008

 intercept     2.1e-009            1        0.012       0.0075        -0.13

         v    -1.8e-008        0.012            1         0.98        -0.99

         n    -1.7e-008       0.0075         0.98            1        -0.97

         k     1.6e-008        -0.13        -0.99        -0.97            1


                                 Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          7.06785          1.36021             4.40189
9.73381
      intercept          28.9608         0.755363             27.4803
30.4413
              v         -6.94236          12.2514            -30.9547
17.07
              n         0.501942         0.915162            -1.29174
2.29563
```

```
              k          131.957           1071.9            -1968.92
2232.84


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0    12       28.9           29         3.13         2.66        -0.0727
 12.5    10       27.9         27.3          2.5         2.66           0.72
   50    10       25.2         26.3         3.21         2.66          -1.37
  200    10         26         25.1         2.85         2.66           1.04
  800    12       23.8           24         1.56         2.66         -0.287


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -77.952340            6     167.904680
             A2          -74.703868           10     169.407736
             A3          -77.952340            6     167.904680
         fitted          -79.800035            5     169.600070
              R          -89.824703            2     183.649405


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	30.2417	8	0.0001916
Test 2	6.49694	4	0.165
Test 3	6.49694	4	0.165
Test 4	3.69539	1	0.05456

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

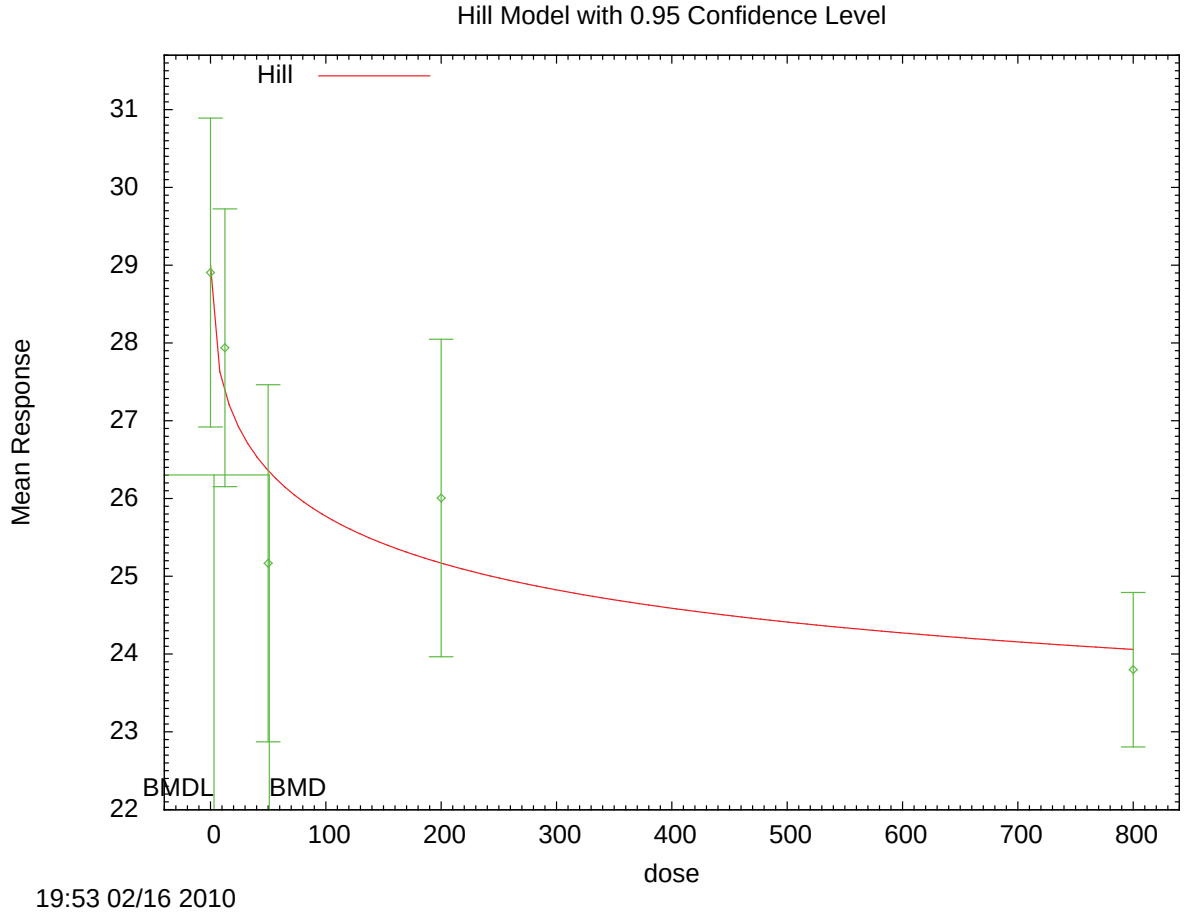
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 51.0107

BMDL = 3.06631

G.3.46.5. ***Figure for Additional Model Presented: Hill, Unrestricted***



G.3.47. Sewall et al. (1995): T4 In Serum

G.3.47.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	0.424	205.966	5.762E+01	3.783E+01	
Exponential (M3)	3	0.424	205.966	5.762E+01	3.783E+01	power hit bound (*d* = 1)
Exponential (M5)	2	0.611	206.152	2.523E+01	8.442E+00	power hit bound (*d* = 1)
Hill[b]	**2**	**0.702**	**205.875**	**2.071E+01**	**5.164E+00**	***n* lower bound hit (*n* = 1)**
Linear	3	0.332	206.584	6.788E+01	4.858E+01	
Polynomial, 4-degree	3	0.332	206.584	6.788E+01	4.858E+01	
Power	3	0.332	206.584	6.788E+01	4.858E+01	power bound hit (power = 1)
Hill, unrestricted[c]	1	0.844	207.205	1.657E+01	1.903E+00	unrestricted (*n* = 0.427)
Power, unrestricted	2	0.983	205.200	1.658E+01	1.820E+00	unrestricted (power = 0.403)

[a] Constant variance model selected (*p* = 0.4078).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.47.2. *Output for Selected Model: Hill*

Sewall et al. (1995): T4 In Serum

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\58_Sewall_1995_T4_HillCV_1.(d)
        Gnuplot Plotting File:  C:\1\58_Sewall_1995_T4_HillCV_1.plt
                                          Tue Feb 16 19:54:30 2010
 ======================================================================

 Figure 1, Saline noninitiated
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	33.0913	
rho =	0	Specified
intercept =	30.6979	
v =	-12.2937	
n =	0.695384	
k =	24.6674	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	1.2e-008	4.1e-008	-2.4e-008
intercept	1.2e-008	1	0.14	-0.66
v	4.1e-008	0.14	1	-0.76
k	-2.4e-008	-0.66	-0.76	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	29.8807	6.29941	17.5341	42.2274
intercept	29.9609	1.64749	26.7319	33.1899
v	-14.2338	4.35645	-22.7723	-5.69537
n	1	NA		
k	33.2198	37.0852	-39.4658	105.905

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

0	9	30.7	30	4.66	5.47	0.404
3.5	9	27.9	28.6	7.17	5.47	-0.399
10.7	9	25.9	26.5	6.81	5.47	-0.328
35	9	23.6	22.7	5.38	5.47	0.493
125	9	18.4	18.7	4.12	5.47	-0.171

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-98.583448	6	209.166896
A2	-96.590204	10	213.180407
A3	-98.583448	6	209.166896
fitted	-98.937315	4	205.874631
R	-109.013252	2	222.026503

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	24.8461	8	0.001651
Test 2	3.98649	4	0.4078
Test 3	3.98649	4	0.4078
Test 4	0.707735	2	0.702

```
The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

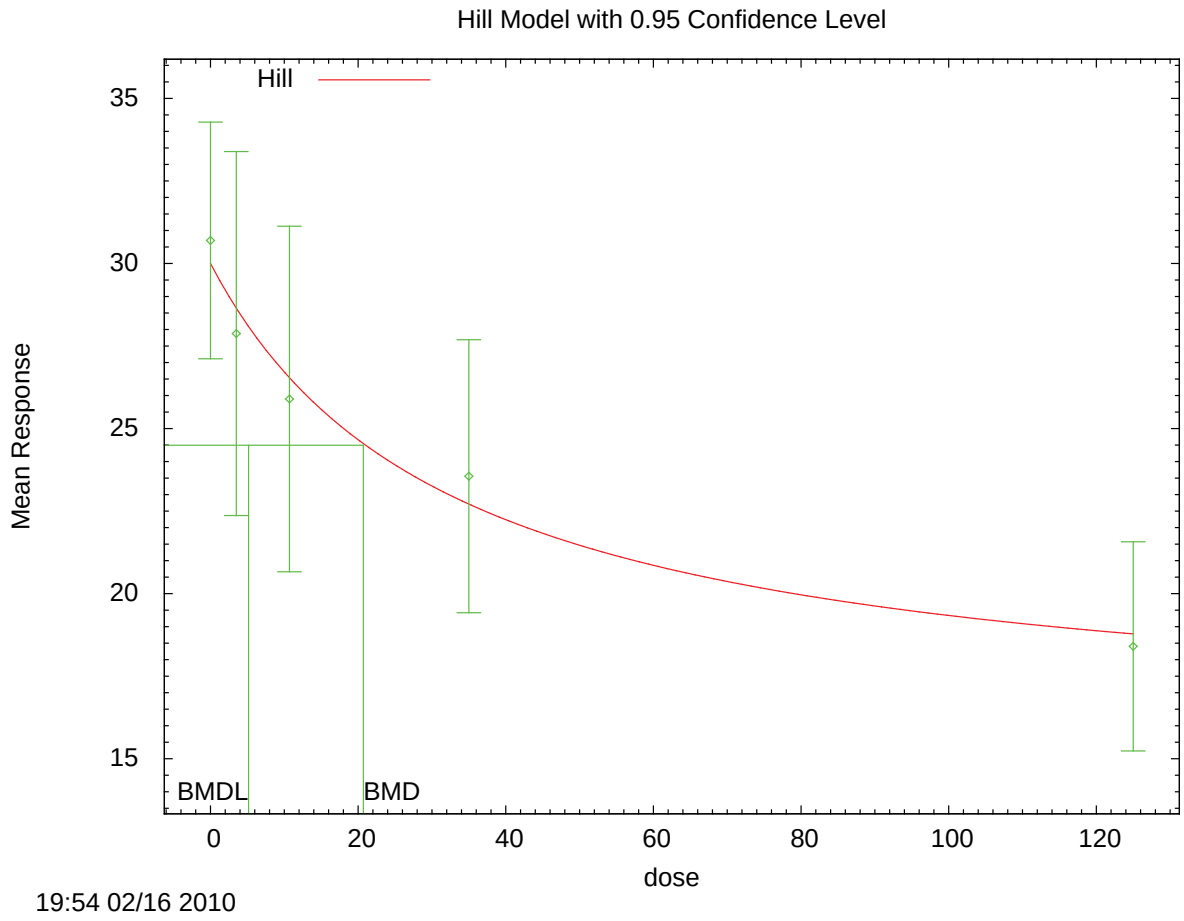
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =        20.7117

            BMDL =       5.16405
```

G.3.47.3. *Figure for Selected Model: Hill*



G.3.47.4. *Output for Additional Model Presented: Hill, Unrestricted*

Sewall et al. (1995): T4 In Serum

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\58_Sewall_1995_T4_HillCV_U_1.(d)
        Gnuplot Plotting File:  C:\1\58_Sewall_1995_T4_HillCV_U_1.plt
                                          Tue Feb 16 19:54:31 2010
 ======================================================================

 Figure 1, Saline noninitiated
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
```

```
rho is set to 0
Power parameter is not restricted
A constant variance model is fit

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                         alpha =      33.0913
                           rho =            0   Specified
                     intercept =      30.6979
                             v =     -12.2937
                             n =     0.695384
                             k =      24.6674


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha    intercept            v            n            k

     alpha            1      -0.0004       0.0059       0.0048      -0.0059

 intercept      -0.0004            1       -0.026        -0.44         0.07

         v       0.0059       -0.026            1         0.77           -1

         n       0.0048        -0.44         0.77            1        -0.82

         k      -0.0059         0.07           -1        -0.82            1


                                  Parameter Estimates

                                                                 95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          29.4396          6.20653             17.2751
41.6042
      intercept          30.6757          1.77521             27.1963
34.155
              v         -141.324           1202.4            -2497.98
2215.33
              n         0.426599         0.262207          -0.0873175
0.940515
```

```
              k            31487           770429       -1.47853e+006
1.5415e+006


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0     9       30.7         30.7         4.66         5.43         0.0123
  3.5     9       27.9         27.8         7.17         5.43         0.0279
 10.7     9       25.9         26.1         6.81         5.43         -0.137
   35     9       23.6         23.3         5.38         5.43          0.132
  125     9       18.4         18.5         4.12         5.43        -0.0354


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -98.583448            6     209.166896
             A2          -96.590204           10     213.180407
             A3          -98.583448            6     209.166896
         fitted          -98.602701            5     207.205403
              R         -109.013252            2     222.026503


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	24.8461	8	0.001651
Test 2	3.98649	4	0.4078
Test 3	3.98649	4	0.4078
Test 4	0.0385071	1	0.8444

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

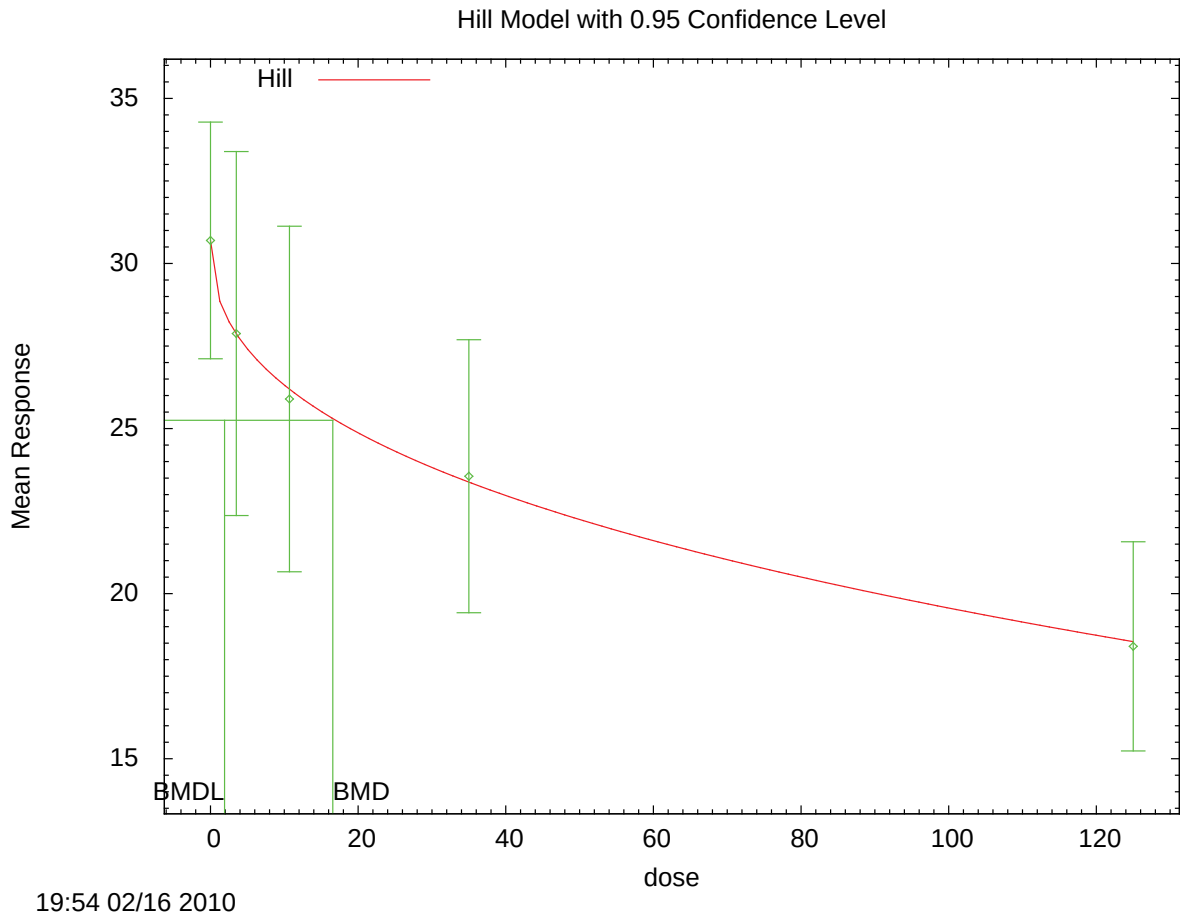
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 16.5689

BMDL = 1.90347

G.3.47.5. *Figure for Additional Model Presented: Hill, Unrestricted*



G.3.48. Shi et al. (2007): Estradiol 17B, PE9

G.3.48.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	0.001	395.701	1.729E+01	8.956E+00	
Exponential (M3)	3	0.001	395.701	1.729E+01	8.956E+00	power hit bound (*d* = 1)
Exponential (M4)[a]	**2**	**0.494**	**383.635**	**5.559E−01**	**2.236E−01**	
Exponential (M5)	2	0.494	383.635	5.559E−01	2.236E−01	power hit bound (*d* = 1)
Hill	2	0.773	382.743	4.434E−01	error	*n* lower bound hit (*n* = 1)
Linear	3	0.001	397.484	2.243E+01	1.523E+01	
Polynomial, 4-degree	3	0.001	397.484	2.243E+01	1.523E+01	
Power	3	0.001	397.484	2.243E+01	1.523E+01	power bound hit (power = 1)
Hill, unrestricted	1	0.874	384.251	3.998E−01	error	unrestricted (*n* = 0.616)
Power, unrestricted	2	0.506	383.589	3.409E−01	5.002E−03	unrestricted (power = 0.155)

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.48.2. *Output for Selected Model: Exponential (M4)*

Shi et al. (2007): Estradiol 17B, PE9

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\59_Shi_2007_Estradiol_Exp_1.(d)
        Gnuplot Plotting File:
                                            Tue Feb 16 19:55:06 2010
 ======================================================================

 Figure 4 PE9 only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	2.65881
rho	0.913414
a	108
b	0.136287
c	0.340136
d	1

Parameter Estimates

Variable	Model 4
lnalpha	1.81331
rho	1.12126
a	100.526
b	1.53823
c	0.431796
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	102.9	41.41
0.143	10	86.19	19.58
0.714	10	63.33	29.36
7.14	10	48.1	18.82
28.6	10	38.57	22.59

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	100.5	32.83	0.2245
0.143	89.25	30.71	-0.3147
0.714	62.45	25.14	0.1108
7.14	43.41	20.5	0.723
28.6	43.41	20.5	-0.7458

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-188.3615	6	388.7231
A2	-183.667	10	387.3339
A3	-186.1132	7	386.2263
R	-203.3606	2	410.7211
4	-186.8176	5	383.6352

Additive constant for all log-likelihoods = -45.95. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	39.39	8	< 0.0001
Test 2	9.389	4	0.05208
Test 3	4.892	3	0.1798
Test 6a	1.409	2	0.4944

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

```
  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

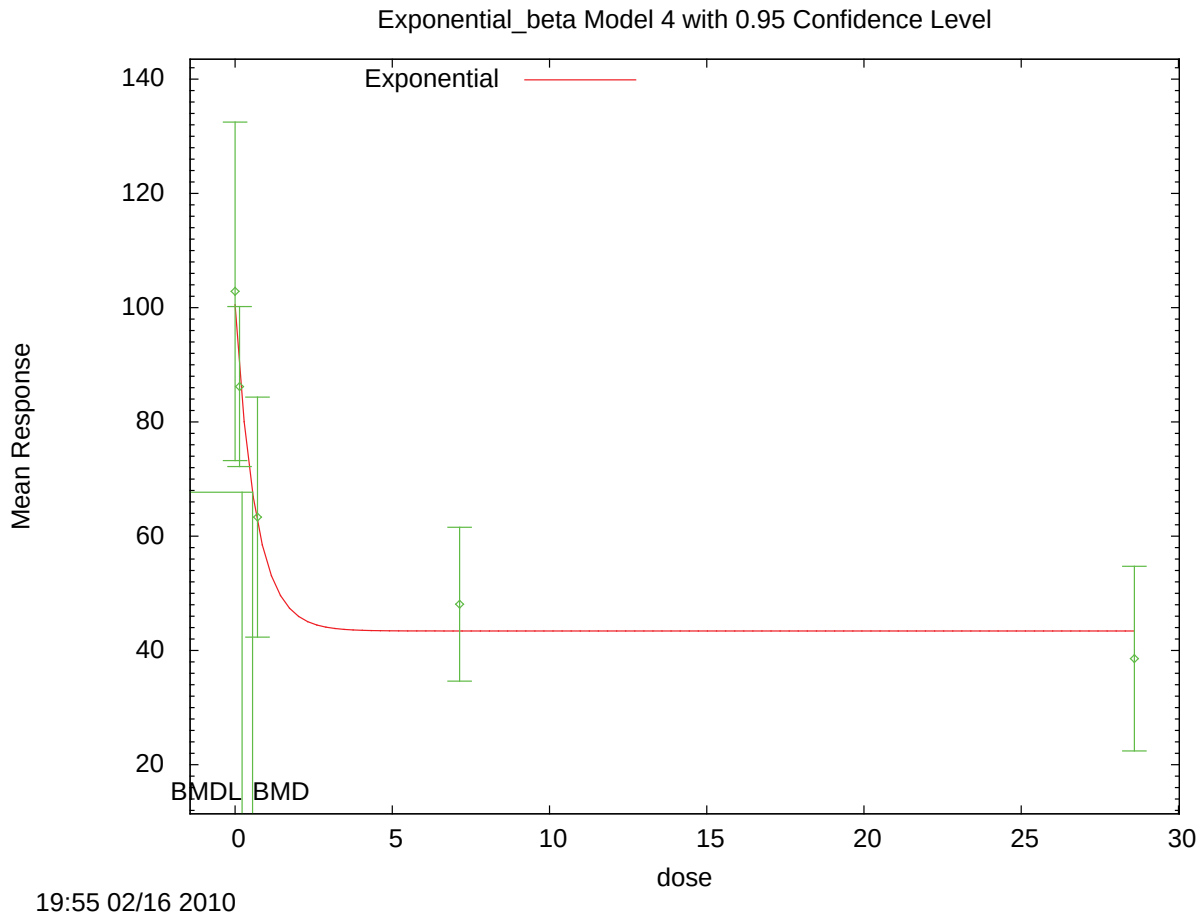
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =     0.555948

              BMDL =     0.223612
```

G.3.48.3. *Figure for Selected Model: Exponential (M4)*



G.3.49. Smialowicz et al. (2008): PFC per 10^6 Cells

G.3.49.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	0.048	903.586	8.234E+01	4.833E+01	
Exponential (M3)	3	0.048	903.586	8.234E+01	4.833E+01	power hit bound (*d* = 1)
Exponential (M4)	2	0.019	905.578	8.032E+01	6.220E+00	
Exponential (M5)	2	0.019	905.578	8.032E+01	6.220E+00	power hit bound (*d* = 1)
Hill	2	0.026	904.975	1.617E+01	2.214E+00	*n* lower bound hit (*n* = 1)
Linear	3	0.016	905.992	1.450E+02	1.102E+02	
Polynomial, 4-degree	2	<0.0001	1,198.471	1.375E+03	3.331E+01	
Power[a]	3	0.016	905.992	1.450E+02	1.102E+02	power bound hit (power = 1)
Hill, unrestricted	1	0.183	901.442	8.297E+00	4.172E−01	unrestricted (*n* = 0.266)
Power, unrestricted[b]	**2**	**0.446**	**899.282**	**7.676E+00**	**4.087E−01**	**unrestricted (power = 0.249)**

[a] Alternate model, BMDS output also presented in this appendix.
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.49.2. *Output for Selected Model: Power, Unrestricted*

Smialowicz et al. (2008): PFC per 10^6 Cells

```
 ====================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\60_Smial_2008_PFCcells_PwrCV_U_1.(d)
        Gnuplot Plotting File:  C:\1\60_Smial_2008_PFCcells_PwrCV_U_1.plt
                                          Tue Feb 16 19:55:53 2010
 ====================================================================

 Anti Response to SRBCs, PFC per 10to6 cells, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is not restricted
   A constant variance model is fit

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	232385	
rho =	0	Specified
control =	1491	
slope =	-384.362	
power =	0.215085	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	control	slope	power
alpha	1	-1.5e-009	-8.2e-009	-1.1e-008
control	-1.5e-009	1	-0.79	-0.65
slope	-8.2e-009	-0.79	1	0.96
power	-1.1e-008	-0.65	0.96	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	220294	38061.1	145696	294893
control	1470.38	124.07	1227.21	1713.55
slope	-282.777	145.113	-567.193	1.64025
power	0.248621	0.0856348	0.0807799	0.416462

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	15	1.49e+003	1.47e+003	716	469	0.17
1.07	14	1.13e+003	1.18e+003	171	469	-0.429
10.7	15	945	961	516	469	-0.129
107	15	677	567	465	469	0.91
321	8	161	283	117	469	-0.735

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-444.832859	6	901.665718
A2	-425.402825	10	870.805651
A3	-444.832859	6	901.665718
fitted	-445.641102	4	899.282205
R	-463.753685	2	931.507371

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	76.7017	8	<.0001
Test 2	38.8601	4	<.0001
Test 3	38.8601	4	<.0001
Test 4	1.61649	2	0.4456

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a different variance model

```
The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =             1

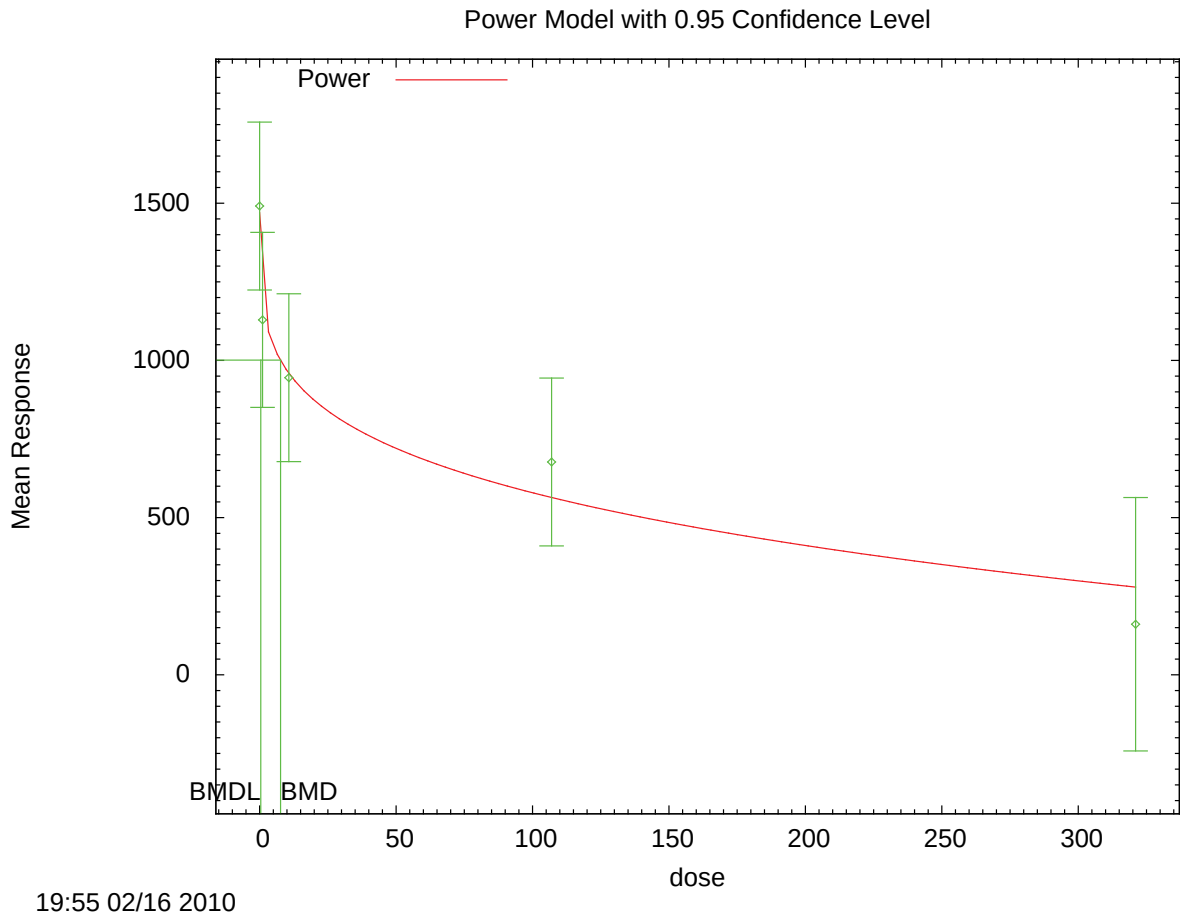
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 7.67564


            BMDL = 0.408661
```

G.3.49.3. *Figure for Selected Model: Power, Unrestricted*



G.3.49.4. *Output for Additional Model Presented: Power*

Smialowicz et al. (2008): PFC per 10^6 Cells

```
 ====================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\60_Smial_2008_PFCcells_PwrCV_1.(d)
        Gnuplot Plotting File:  C:\1\60_Smial_2008_PFCcells_PwrCV_1.plt
                                          Tue Feb 16 19:55:53 2010
 ====================================================================

 Anti Response to SRBCs, PFC per 10to6 cells, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
```

```
rho is set to 0
The power is restricted to be greater than or equal to 1
A constant variance model is fit

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                         alpha =       232385
                           rho =            0   Specified
                       control =         1491
                         slope =     -2925.99
                         power =    -0.136613


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -power
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                  alpha      control        slope

     alpha            1     3.6e-009    -1.2e-008

   control     3.6e-009            1        -0.53

     slope    -1.2e-008        -0.53            1



                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha           250878          43345.1              165923
335833
        control          1176.24          72.2586             1034.61
1317.86
          slope         -3.45384         0.592114            -4.61436
-2.29332
          power                1               NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	15	1.49e+003	1.18e+003	716	501	2.43
1.07	14	1.13e+003	1.17e+003	171	501	-0.325
10.7	15	945	1.14e+003	516	501	-1.5
107	15	677	807	465	501	-1
321	8	161	67.6	117	501	0.528

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-444.832859	6	901.665718
A2	-425.402825	10	870.805651
A3	-444.832859	6	901.665718
fitted	-449.996183	3	905.992366
R	-463.753685	2	931.507371

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	76.7017	8	<.0001

Test 2	38.8601	4	<.0001
Test 3	38.8601	4	<.0001
Test 4	10.3266	3	0.01598

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a different variance model

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

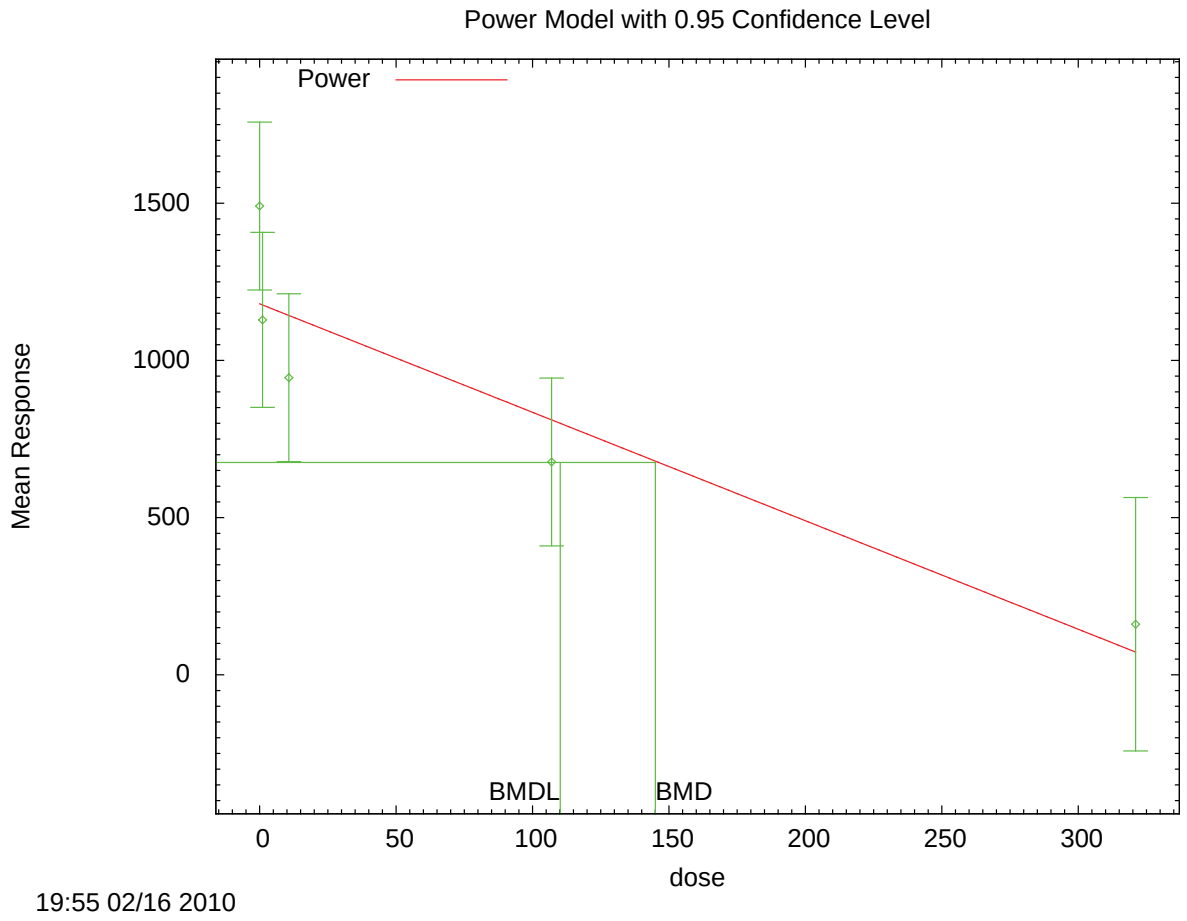
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 145.02

BMDL = 110.161

G.3.49.5. *Figure for Additional Model Presented: Power*



G.3.50. Smialowicz et al. (2008): PFC per Spleen

G.3.50.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	0.133	377.395	1.320E+02	8.431E+01	
Exponential (M3)	3	0.133	377.395	1.320E+02	8.431E+01	power hit bound (*d* = 1)
Exponential (M4)	3	0.133	377.395	1.320E+02	8.184E+01	
Exponential (M5)	2	0.061	379.395	1.320E+02	8.184E+01	power hit bound (*d* = 1)
Hill	2	0.069	379.150	1.401E+02	error	*n* lower bound hit (*n* = 1)
Linear	3	0.044	379.895	2.151E+02	1.704E+02	
Polynomial, 4-degree	3	0.044	379.895	2.151E+02	1.704E+02	
Power[a]	3	0.044	379.895	2.151E+02	1.704E+02	power bound hit (power = 1)
Hill, unrestricted	2	<0.0001	441.885	7.545E−23	error	unrestricted (*n* = 0.038)
Power, unrestricted[b]	**2**	**0.230**	**376.738**	**9.374E+01**	**2.088E+01**	**unrestricted (power = 0.418)**

[a] Alternate model, BMDS output also presented in this appendix.
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.50.2. *Output for Selected Model: Power, Unrestricted*

Smialowicz et al. (2008): PFC per Spleen

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\61_Smial_2008_PFCspleen_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\61_Smial_2008_PFCspleen_Pwr_U_1.plt
                                          Tue Feb 16 19:56:26 2010
 ======================================================================

 Anti Response to SRBCs - PFC x 10 to the 4 per spleen, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                    Default Initial Parameter Values
```

```
lalpha =      4.76607
   rho =            0
control =         27.8
  slope =     -7.21601
  power =     0.213905
```

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.98	0.25	-0.27	-0.23
rho	-0.98	1	-0.31	0.28	0.23
control	0.25	-0.31	1	-0.81	-0.74
slope	-0.27	0.28	-0.81	1	0.99
power	-0.23	0.23	-0.74	0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	0.747155	1.0244	-1.26063	2.75494
rho	1.36972	0.357098	0.66982	2.06962
control	25.1733	2.93169	19.4273	30.9193
slope	-1.98465	1.82113	-5.554	1.5847
power	0.417867	0.141932	0.139686	0.696048

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	15	27.8	25.2	13.4	13.2	0.769
1.07	14	21	23.1	13.6	12.5	-0.639
10.7	15	17.6	19.8	9.4	11.2	-0.768
107	15	12.6	11.2	8.7	7.59	0.721
321	8	3	3.04	3.1	3.11	-0.0353

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-190.565019	6	393.130038
A2	-181.476284	10	382.952569
A3	-181.900030	7	377.800059
fitted	-183.369059	5	376.738118
R	-204.636496	2	413.272993

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.3204	8	<.0001
Test 2	18.1775	4	0.001139
Test 3	0.84749	3	0.8381
Test 4	2.93806	2	0.2301

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems

to adequately describe the data

```
                Benchmark Dose Computation

Specified effect =             1

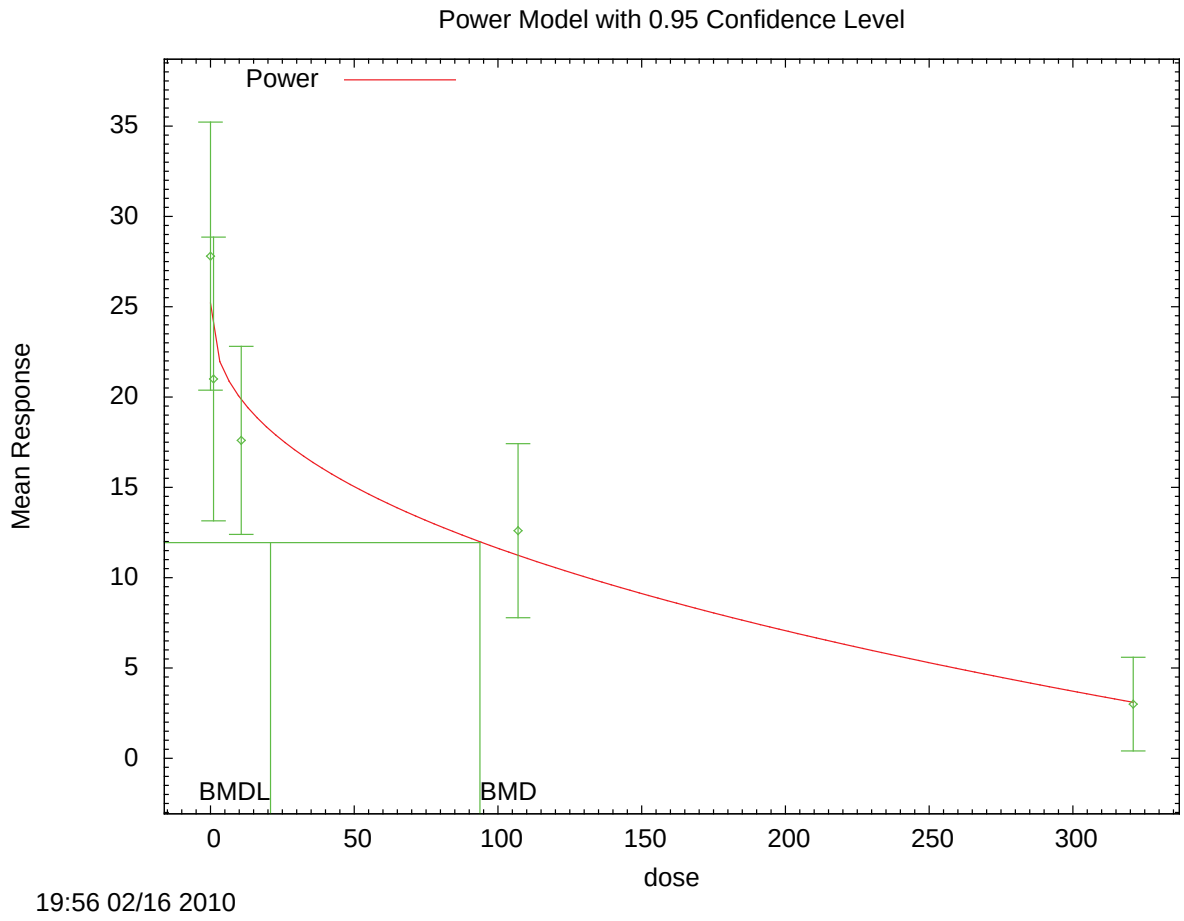
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD = 93.7416


             BMDL = 20.8758
```

G.3.50.3. *Figure for Selected Model: Power, Unrestricted*



G.3.50.4. *Output for Additional Model Presented: Power*

Smialowicz et al. (2008): PFC per Spleen

```
 ====================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\61_Smial_2008_PFCspleen_Pwr_1.(d)
        Gnuplot Plotting File:  C:\1\61_Smial_2008_PFCspleen_Pwr_1.plt
                                          Tue Feb 16 19:56:25 2010
 ====================================================================

 Anti Response to SRBCs - PFC x 10 to the 4 per spleen, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
```

```
The power is restricted to be greater than or equal to 1
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                        lalpha =      4.76607
                           rho =            0
                       control =         27.8
                         slope =     -54.5244
                         power =    -0.136501


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -power
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                 lalpha          rho      control        slope

    lalpha            1        -0.98         0.16        -0.48

       rho        -0.98            1        -0.25         0.54

   control         0.16        -0.25            1        -0.88

     slope        -0.48         0.54        -0.88            1


                                 Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         0.474614          1.09569             -1.6729
2.62213
            rho          1.48709         0.385029            0.732449
2.24173
        control          21.3571          1.69233             18.0402
24.674
          slope       -0.0574184       0.00632057          -0.0698064
-0.0450303
          power                1               NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	15	27.8	21.4	13.4	12.3	2.02
1.07	14	21	21.3	13.6	12.3	-0.0898
10.7	15	17.6	20.7	9.4	12.1	-1.01
107	15	12.6	15.2	8.7	9.6	-1.05
321	8	3	2.93	3.1	2.82	0.0745

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-190.565019	6	393.130038
A2	-181.476284	10	382.952569
A3	-181.900030	7	377.800059
fitted	-185.947278	4	379.894555
R	-204.636496	2	413.272993

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.3204	8	<.0001
Test 2	18.1775	4	0.001139
Test 3	0.84749	3	0.8381
Test 4	8.0945	3	0.0441

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

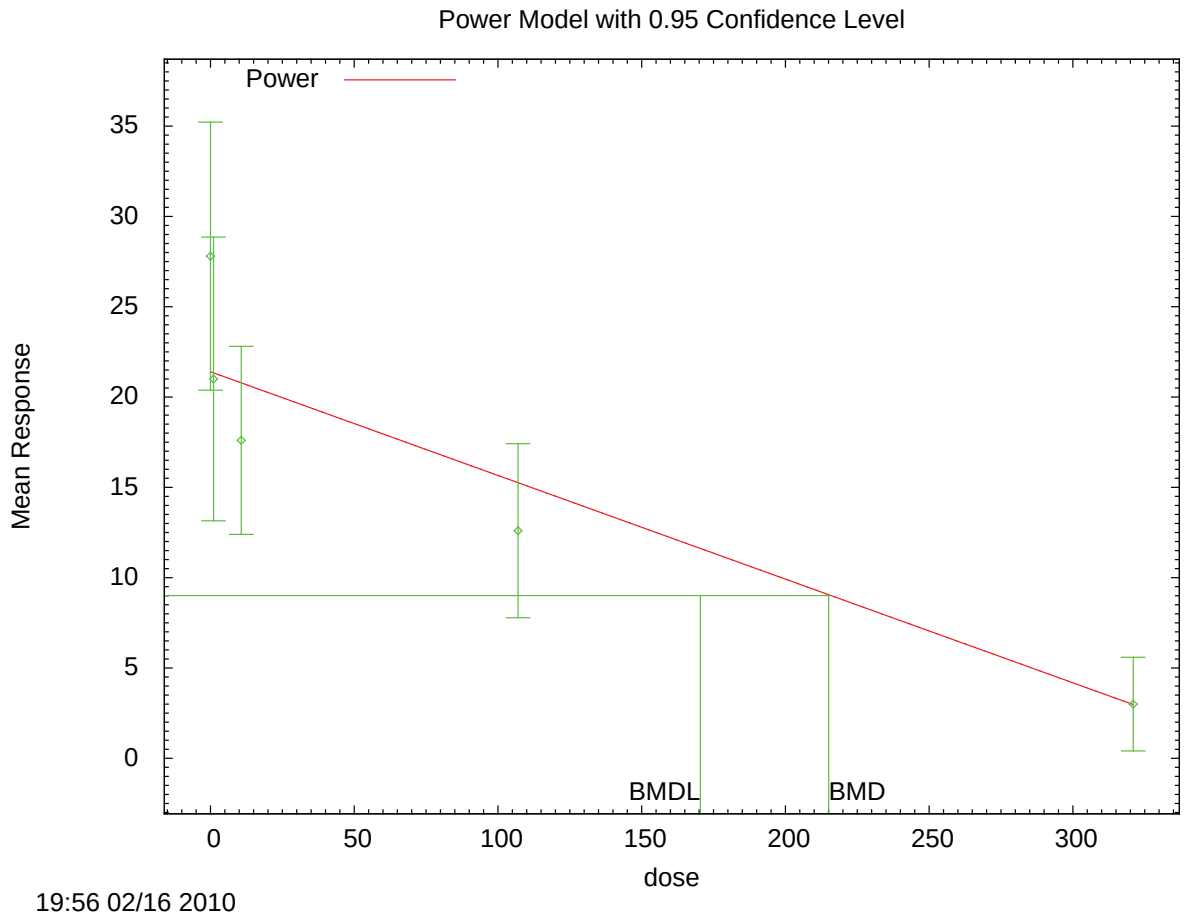
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 215.073

BMDL = 170.412

G.3.50.5. *Figure for Additional Model Presented: Power*



G.3.51. Smith et al. (1976): Cleft Palate in Pups

G.3.51.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	3	0.4203	69.78	6.184E+02	2.205E+02	
Logistic	4	0.5057	68.90	9.754E+02	7.256E+02	
Log-logistic [a]	**3**	**0.4194**	**69.82**	**6.816E+02**	**1.842E+02**	
Log-probit	3	0.4132	69.89	7.341E+02	3.927E+02	
Multistage, 5th degree	3	0.4528	69.43	4.829E+02	2.277E+02	
Probit	4	0.5721	68.33	8.688E+02	6.580E+02	
Weibull	3	0.43	69.68	5.908E+02	2.223E+02	
Gamma, unrestricted	3	0.4203	69.78	6.184E+02	1.227E+02	
Log-logistic, unrestricted	3	0.4194	69.82	6.816E+02	1.705E+02	
Log-probit, unrestricted	3	0.4133	69.89	7.341E+02	1.767E+02	
Weibull, unrestricted	3	0.43	69.68	5.908E+02	1.432E+02	

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.51.2. *Output for Selected Model: Log-Logistic*

```
=====================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File:
C:\USEPA\BMDS21\1a\76_Smith_1976_cleft_palate_LogLogistic_1.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\1a\76_Smith_1976_cleft_palate_LogLogistic_1.plt
                                          Thu Sep 01 12:46:35 2011
 ====================================================================

 Table 3 cleft palate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model
```

Default Initial Parameter Values
background = 0
intercept = -7.91888
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.18	0.17
intercept	-0.18	1	-1
slope	0.17	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0262471	*	*	*
intercept	-15.6136	*	*	*
slope	2.05633	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-29.9486	6			
Fitted model	-31.9094	3	3.92153	3	0.2701
Reduced model	-52.2767	1	44.6562	5	<.0001

AIC: 69.8188

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0262	0.892	0.000	34	-0.957
1.0000	0.0262	1.076	2.000	41	0.903
10.0000	0.0263	0.499	0.000	19	-0.716
100.0000	0.0283	0.482	1.000	17	0.758
1000.0000	0.2175	4.132	4.000	19	-0.074
3000.0000	0.7085	9.918	10.000	14	0.048

```
 Chi^2 = 2.83      d.f. = 3        P-value = 0.4194

   Benchmark Dose Computation

Specified effect =            0.1

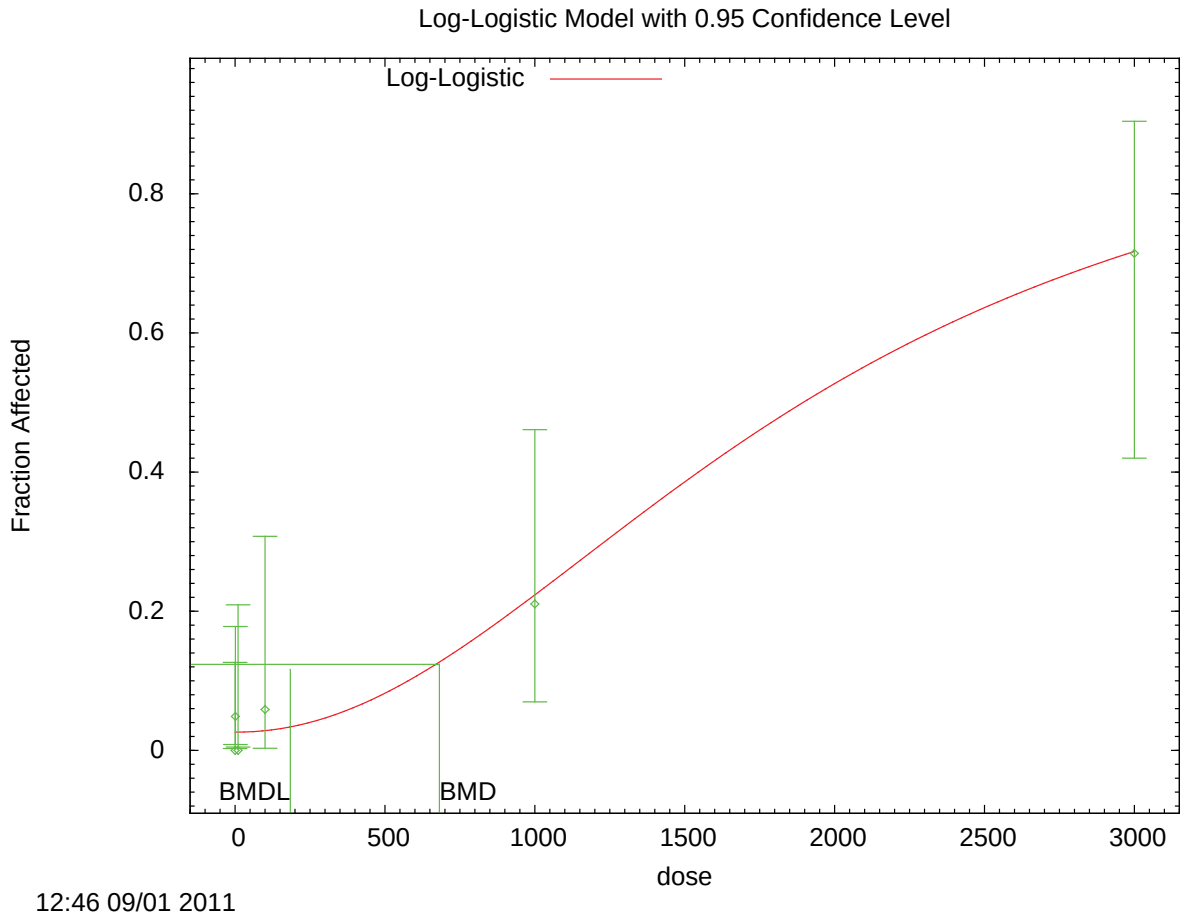
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        681.581

            BMDL =        184.164
```

G.3.51.3. *Figure for Selected Model: Log-Logistic*



G.3.52. Sparschu et al. (1971): Fetal Body Weight, Male

G.3.52.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	0.0001	-246.49	6.665E+02	4.188E+02	
Exponential (M3)	3	0.0001	-246.49	6.665E+02	4.188E+02	
Exponential (M4)	2	0.0002	-247.97	5.744E+02	3.197E+02	
Exponential (M5)[b]	**1**	**<0.0001**	**-246.36**	**5.459E+02**	**1.296E+02**	
Hill	1	<0.0001	-246.90	5.105E+02	error	
Linear	3	<0.0001	-245.45	7.248E+02	4.607E+02	
Polynomial, 3-degree	3	<0.0001	-245.45	7.248E+02	4.607E+02	
Power	3	<0.0001	-245.45	7.248E+02	4.607E+02	
Hill, unrestricted	1	<0.0001	-246.90	5.105E+02	error	
Power, unrestricted	2	<0.0001	-245.65	6.812E+02	3.949E+02	

[a] Modeled variance model presented ($p < 0.0001$) ; variance not appropriately captured (*p*-test 3 = 0.008).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.52.2. *Output for Selected Model: Exponential (M5)*

```
=====================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File:
C:\USEPA\BMDS21\1a\74_Sparschu_1971_pup_bw_male_Exp_1.(d)
        Gnuplot Plotting File:
                                            Thu Sep 01 12:56:10 2011
 ====================================================================

 Table 4 males
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 5
```

Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 5
lnalpha	-4.28192
rho	1.66816
a	4.347
b	0.000395512
c	0.312859
d	1

Parameter Estimates

Variable	Model 5
lnalpha	16.7441
rho	-13.5393
a	4.04428
b	0.00167144
c	0.859252
d	1.18216

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	117	4.03	0.37
30	55	4.14	0.26
125	66	3.85	0.35
500	39	3.86	0.61
2000	3	2.72	0.25

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	4.044	0.3372	-0.458
30	4.028	0.3465	2.398
125	3.962	0.3878	-2.336
500	3.729	0.5845	1.404
2000	3.484	0.9255	-1.43

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	126.4055	6	-240.8109
A2	145.7666	10	-271.5331
A3	137.4206	7	-260.8413
R	101.5293	2	-199.0587
5	129.1813	6	-246.3626

Additive constant for all log-likelihoods = -257.3. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 7a: Does Model 5 fit the data? (A3 vs 5)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	88.47	8	< 0.0001
Test 2	38.72	4	< 0.0001
Test 3	16.69	3	0.0008177
Test 7a	16.48	1	< 0.0001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

```
The p-value for Test 3 is less than .1.  You may want to
consider a different variance model.

The p-value for Test 7a is less than .1.  Model 5 may not adequately
describe the data; you may want to consider another model.


Benchmark Dose Computations:

Specified Effect = 1.000000

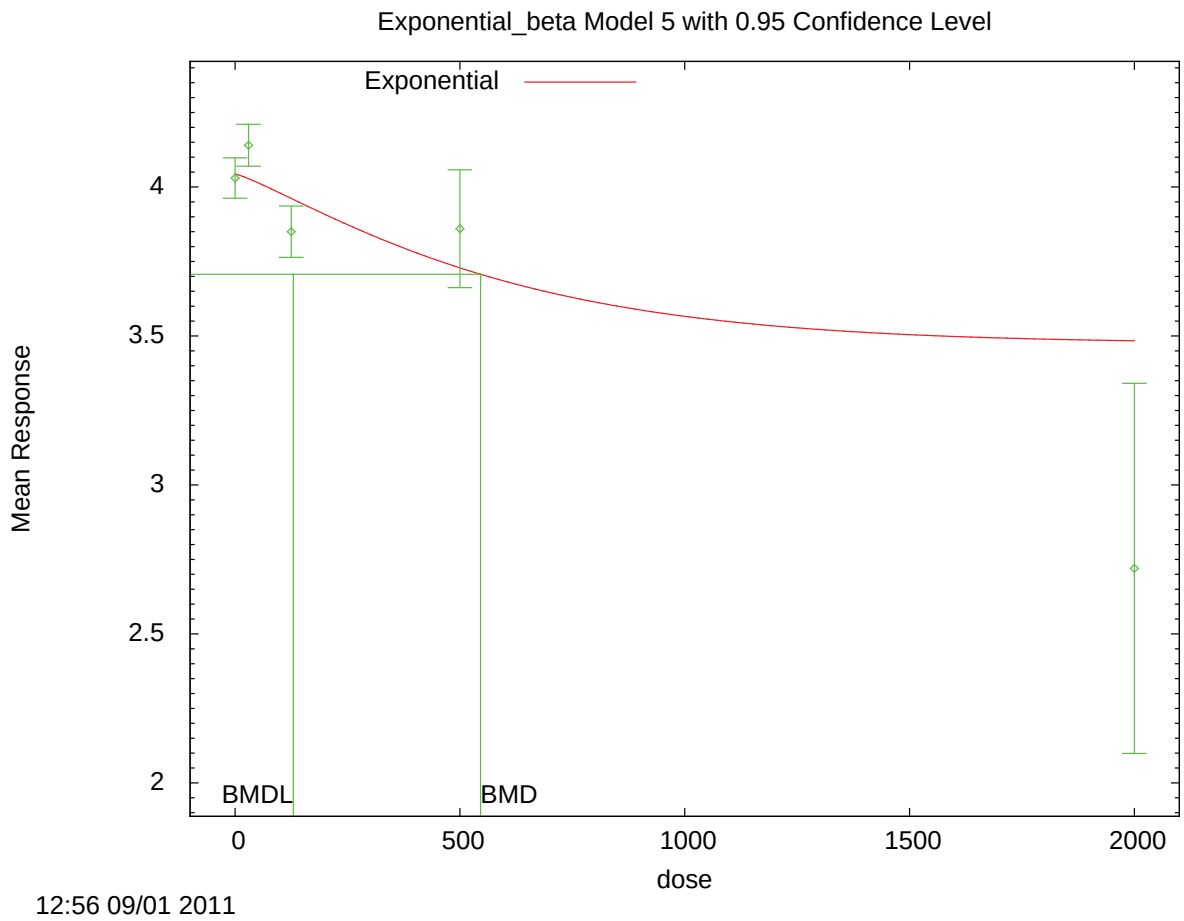
       Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

             BMD =      545.876

            BMDL =      129.551
```

G.3.52.3. *Figure for Selected Model: Exponential (M5)*



G.3.53. Sparschu et al. (1971): Fetal Body Weight, Female

G.3.53.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2) [b]	**3**	**0.0278**	**-229.517**	**1.033E+03**	**6.479E+02**	
Exponential (M3)	3	0.0278	-229.517	1.033E+03	6.479E+02	
Exponential (M4)	2	0.0147	-228.188	1.057E+03	5.759E+02	
Exponential (M5)	2	0.0147	-228.188	1.057E+03	5.759E+02	
Hill	2	0.0151	-228.244	1.073E+03	5.800E+02	
Linear	3	0.0245	-229.239	1.050E+03	6.749E+02	
Polynomial, 3-degree	3	0.0245	-229.239	1.050E+03	6.749E+02	
Power	2	0.0025	-224.657	1.860E+03	5.877E+02	
Hill, unrestricted	1	0.0038	-226.278	1.073E+03	5.828E+02	
Power, unrestricted	2	0.0146	-228.180	1.077E+03	6.192E+02	

[a] Modeled variance model presented (p = 0.001); variance not appropriately captured (p-test 3 = 0.005).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.53.2. *Output for Selected Model: Exponential (M2)*

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File:
C:\USEPA\BMDS21\1a\75_Sparschu_1971_pup_bw_male_Exp_1.(d)
        Gnuplot Plotting File:
                                            Thu Sep 01 13:43:52 2011
 ======================================================================

 Table 4 females
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 5
```

Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 2
lnalpha	-7.22746
rho	4.02075
a	3.75712
b	0.000140769
c	0
d	1

Parameter Estimates

Variable	Model 2
lnalpha	10.6901
rho	-9.26779
a	3.89584
b	0.000100525
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	129	3.89	0.39
30	60	3.98	0.35
125	58	3.71	0.37
500	54	3.78	0.54
2000	4	2.69	0.19

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	3.896	0.3842	-0.1727
30	3.884	0.3896	1.907
125	3.847	0.4072	-2.566
500	3.705	0.4849	1.139
2000	3.186	0.9753	-1.018

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	123.0729	6	-234.1458
A2	132.131	10	-244.262
A3	123.3163	7	-232.6326
R	100.5646	2	-197.1292
2	118.7583	4	-229.5166

Additive constant for all log-likelihoods = -280.3. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	63.13	8	< 0.0001
Test 2	18.12	4	0.001171
Test 3	17.63	3	0.0005244
Test 4	9.116	3	0.02779

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

```
The p-value for Test 3 is less than .1.  You may want to
consider a different variance model.

The p-value for Test 4 is less than .1.  Model 2 may not adequately
describe the data; you may want to consider another model.


Benchmark Dose Computations:

Specified Effect = 1.000000

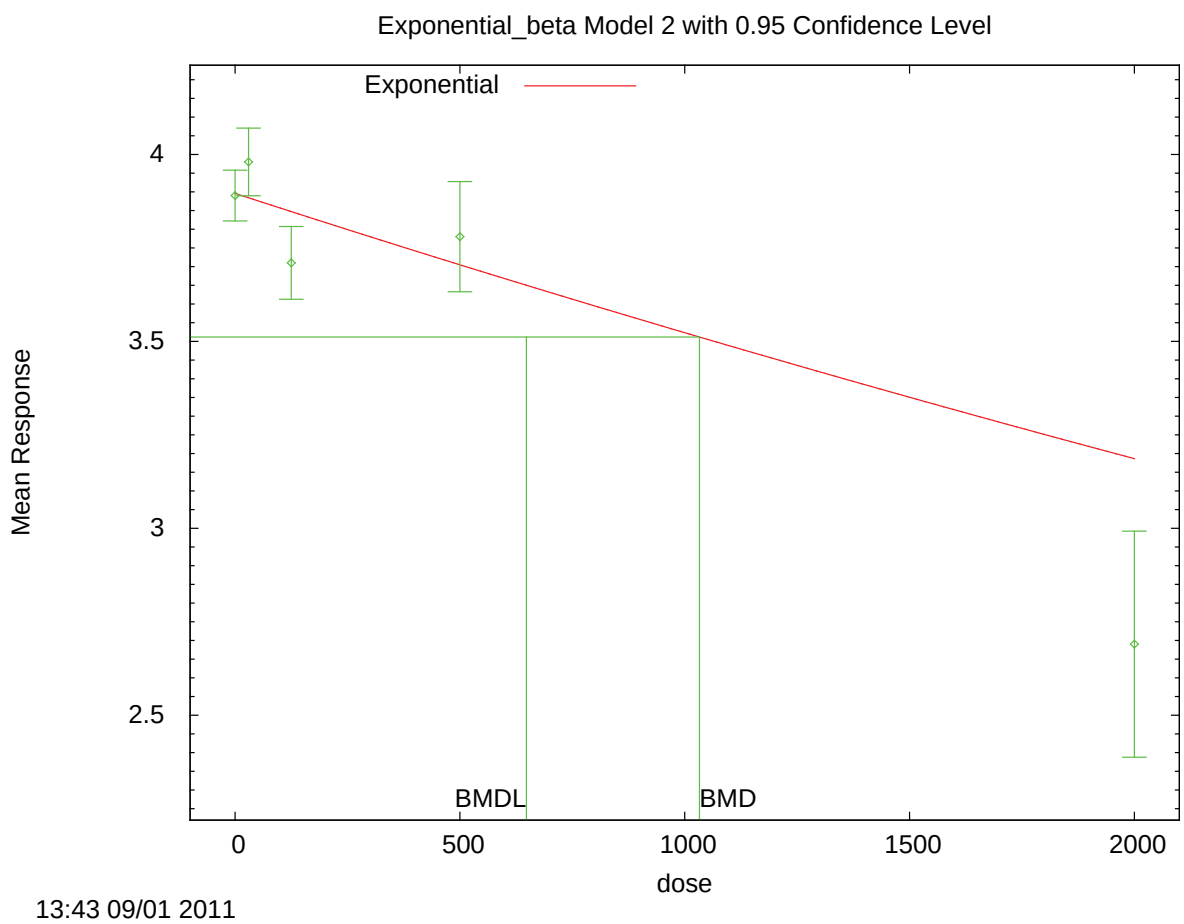
       Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

             BMD =      1032.78

            BMDL =      647.855
```

G.3.53.3. *Figure for Selected Model: Exponential (M2)*



G.3.54. Toth et al. (1979): Amyloidosis

G.3.54.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	2	0.022	150.666	2.296E+02	1.460E+02	power bound hit (power = 1)
Logistic	2	0.013	152.187	4.088E+02	3.125E+02	
Log-logistic[a]	**2**	**0.028**	**149.984**	**1.759E+02**	**9.729E+01**	**slope bound hit (slope = 1)**
Log-probit	2	0.007	153.479	4.402E+02	2.965E+02	slope bound hit (slope = 1)
Multistage, 3-degree	2	0.022	150.666	2.296E+02	1.460E+02	final ß = 0
Probit	2	0.014	152.040	3.846E+02	2.911E+02	
Weibull	2	0.022	150.666	2.296E+02	1.460E+02	power bound hit (power = 1)
Gamma, unrestricted	2	0.917	140.208	7.687E−01	7.637E−04	unrestricted (power = 0.187)
Log-logistic, unrestricted[b]	2	0.847	140.370	8.465E−01	1.565E−03	unrestricted (slope = 0.238)
Log-probit, unrestricted	2	0.811	140.458	8.545E−01	2.334E−03	unrestricted (slope = 0.135)
Weibull, unrestricted	2	0.882	140.287	8.179E−01	1.140E−03	unrestricted (power = 0.212)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.54.2. *Output for Selected Model: Log-Logistic*

Toth et al. (1979): Amyloidosis

```
 ========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\62_Toth_1979_Amy1yr_LogLogistic_1.(d)
        Gnuplot Plotting File:  C:\1\62_Toth_1979_Amy1yr_LogLogistic_1.plt
                                          Tue Feb 16 19:56:59 2010
 ========================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =            0
                     intercept =     -6.90711
                         slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.47

 intercept        -0.47            1



                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background        0.0848984            *                *
*
      intercept         -7.36716            *                *
*
          slope                1            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -68.017         4
   Fitted model        -72.9918         2        9.9496      2
0.00691
  Reduced model        -82.0119         1         27.99      3         <.0001

           AIC:         149.984
```

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0849	3.226	0.000	38	-1.878
1.0000	0.0855	3.761	5.000	44	0.668
100.0000	0.1393	6.128	10.000	44	1.686
1000.0000	0.4392	18.884	17.000	43	-0.579

Chi^2 = 7.15 d.f. = 2 P-value = 0.0280

Benchmark Dose Computation

Specified effect = 0.1

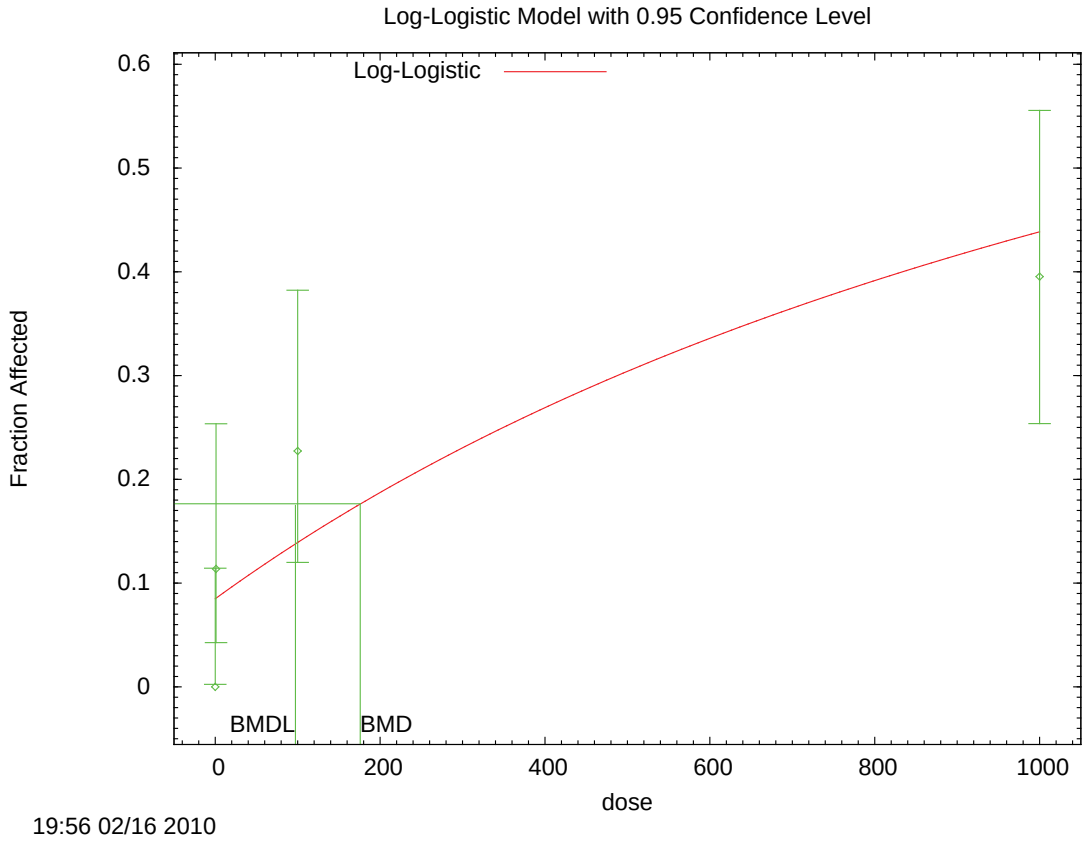
Risk Type = Extra risk

Confidence level = 0.95

BMD = 175.903

BMDL = 97.2899

G.3.54.3. *Figure for Selected Model: Log-Logistic*



G.3.54.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Toth et al. (1979): Amyloidosis

```
 ======================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\62_Toth_1979_Amy1yr_LogLogistic_U_1.(d)
        Gnuplot Plotting File:  C:\1\62_Toth_1979_Amy1yr_LogLogistic_U_1.plt
                                          Tue Feb 16 19:57:00 2010
 ======================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted
```

```
   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =            0
                      intercept =     -2.10894
                          slope =     0.227921


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

              intercept        slope

 intercept            1        -0.89

     slope        -0.89            1



                                 Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background                0            *                *
*
      intercept         -2.15753            *                *
*
          slope         0.238304            *                *
*

* - Indicates that this value is not calculated.



                       Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -68.017         4
   Fitted model        -68.1848         2       0.33571      2
0.8455
  Reduced model        -82.0119         1         27.99      3         <.0001
```

AIC: 140.37

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	38	0.000
1.0000	0.1036	4.560	5.000	44	0.218
100.0000	0.2573	11.321	10.000	44	-0.456
1000.0000	0.3749	16.119	17.000	43	0.277

Chi^2 = 0.33 d.f. = 2 P-value = 0.8471

Benchmark Dose Computation

Specified effect = 0.1

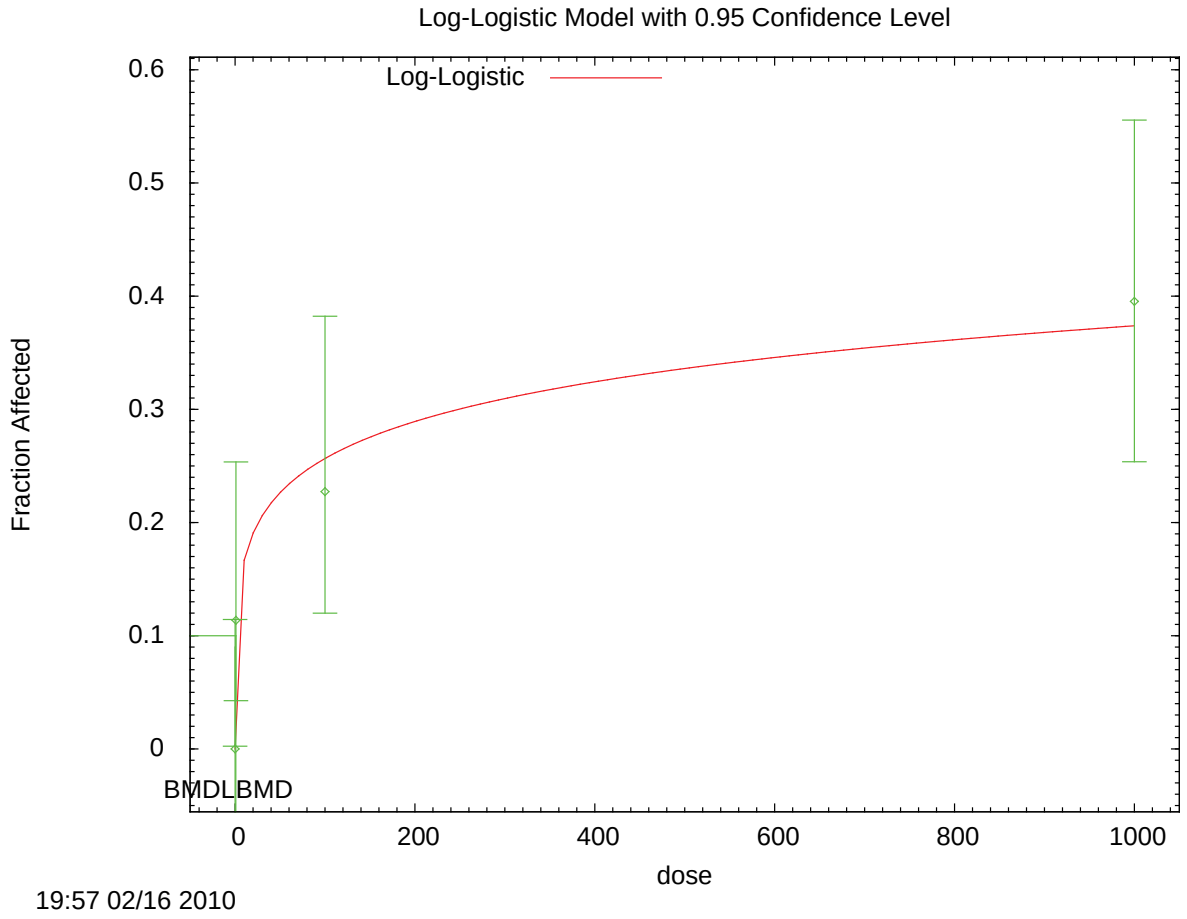
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.846547

BMDL = 0.00156534

G.3.54.5. ***Figure for Additional Model Presented: Log-Logistic, Unrestricted***



G.3.55. Toth et al. (1979): Skin Lesions

G.3.55.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	2	0.009	159.223	1.181E+02	8.308E+01	power bound hit (power = 1)
Logistic[a]	**2**	**0.002**	**162.974**	**2.709E+02**	**2.147E+02**	
Log-logistic	2	0.029	156.567	6.750E+01	4.057E+01	slope bound hit (slope = 1)
Log-probit	2	0.001	164.598	2.446E+02	1.626E+02	slope bound hit (slope = 1)
Multistage, 3-degree	2	0.009	159.223	1.181E+02	8.308E+01	final ß = 0
Probit	2	0.003	162.684	2.522E+02	2.015E+02	
Weibull	2	0.009	159.223	1.181E+02	8.308E+01	power bound hit (power = 1)
Gamma, unrestricted	2	0.882	147.287	error	error	unrestricted (power = 0.251)
Log-logistic, unrestricted[b]	2	0.630	147.969	1.137E+00	5.477E−02	unrestricted (slope = 0.351)
Log-probit, unrestricted	2	0.558	148.218	1.096E+00	6.847E−02	unrestricted (slope = 0.202)
Weibull, unrestricted	2	0.762	147.581	1.077E+00	4.080E−02	unrestricted (power = 0.3)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.55.2. *Output for Selected Model: Logistic*

Toth et al. (1979): Skin Lesions

```
 ========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\63_Toth_1979_SkinLes_Logistic_1.(d)
        Gnuplot Plotting File:  C:\1\63_Toth_1979_SkinLes_Logistic_1.plt
                                             Tue Feb 16 19:57:29 2010
 ========================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the probability function is:

    P[response] = 1/[1+EXP(-intercept-slope*dose)]


    Dependent variable = DichEff
    Independent variable = Dose
    Slope parameter is not restricted

    Total number of observations = 4
```

Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

background =	0	Specified
intercept =	-2.53484	
slope =	0.00299511	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-0.67
slope	-0.67	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
intercept	-1.91768	0.26892	-2.44475	-1.39061
slope	0.00230499	0.000419329	0.00148312	0.00312686

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-71.5177	4			
Fitted model	-79.487	2	15.9387	2	0.0003459
Reduced model	-95.8498	1	48.6642	3	<.0001

AIC: 162.974

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1281	4.869	0.000	38	-2.363

```
    1.0000      0.1284          5.649      5.000           44        -0.292
  100.0000      0.1561          6.870     13.000           44         2.546
 1000.0000      0.5956         25.612     25.000           43        -0.190

 Chi^2 = 12.19     d.f. = 2        P-value = 0.0023


   Benchmark Dose Computation

Specified effect =            0.1

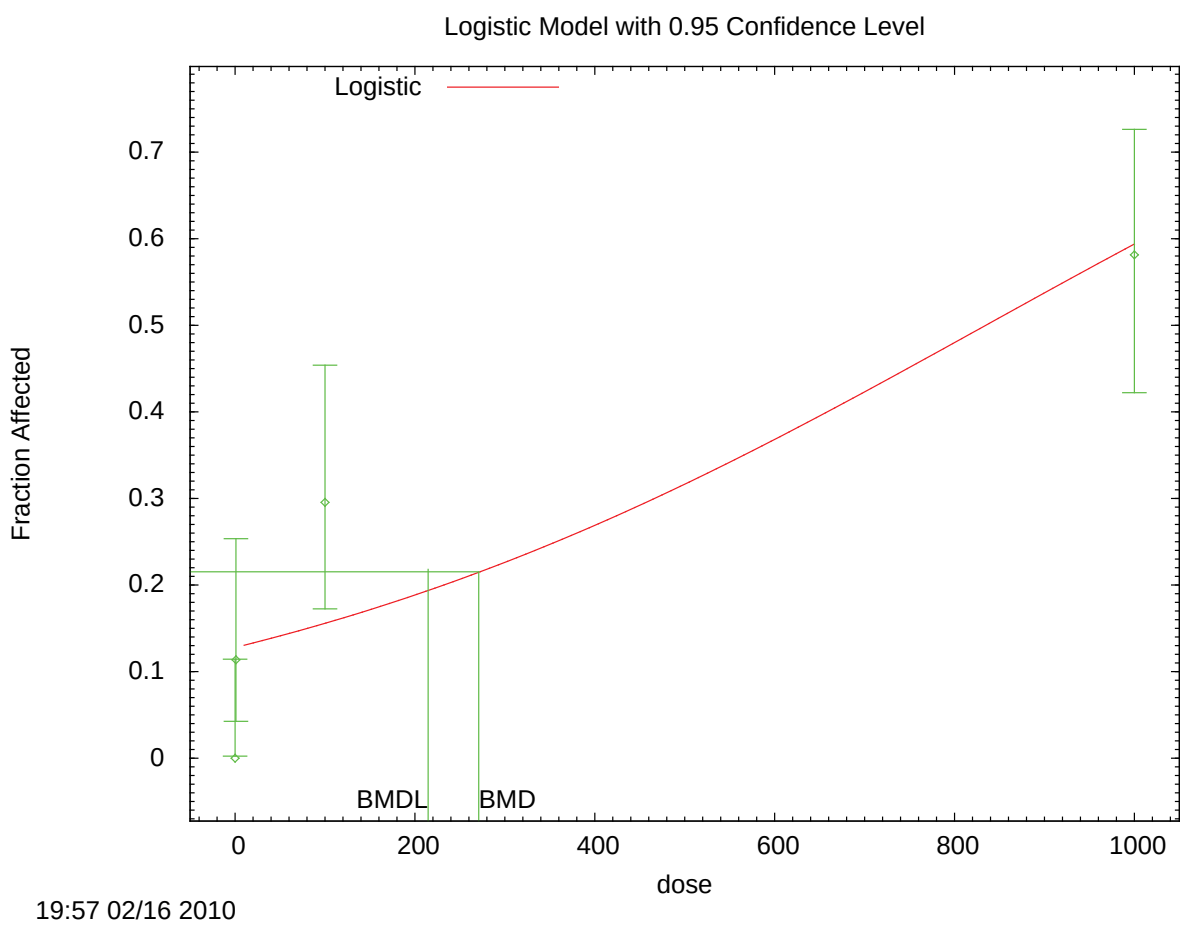
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        270.917

            BMDL =         214.66
```

G.3.55.3. *Figure for Selected Model: Logistic*



G.3.55.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Toth et al. (1979): Skin Lesions

```
 ====================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\63_Toth_1979_SkinLes_LogLogistic_U_1.(d)
        Gnuplot Plotting File:  C:\1\63_Toth_1979_SkinLes_LogLogistic_U_1.plt
                                          Tue Feb 16 20:01:56 2010
 ====================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                   Default Initial Parameter Values
                      background =            0
                       intercept =     -2.14055
                           slope =     0.332409


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

              intercept        slope

 intercept            1         -0.9

     slope         -0.9            1
```

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	*	*	*
intercept	-2.24241	*	*	*
slope	0.350932	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-71.5177	4			
Fitted model	-71.9844	2	0.93345	2	0.6271
Reduced model	-95.8498	1	48.6642	3	<.0001

AIC: 147.969

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	38	0.000
1.0000	0.0960	4.224	5.000	44	0.397
100.0000	0.3483	15.327	13.000	44	-0.736
1000.0000	0.5453	23.448	25.000	43	0.475

Chi^2 = 0.93 d.f. = 2 P-value = 0.6295

Benchmark Dose Computation

Specified effect = 0.1

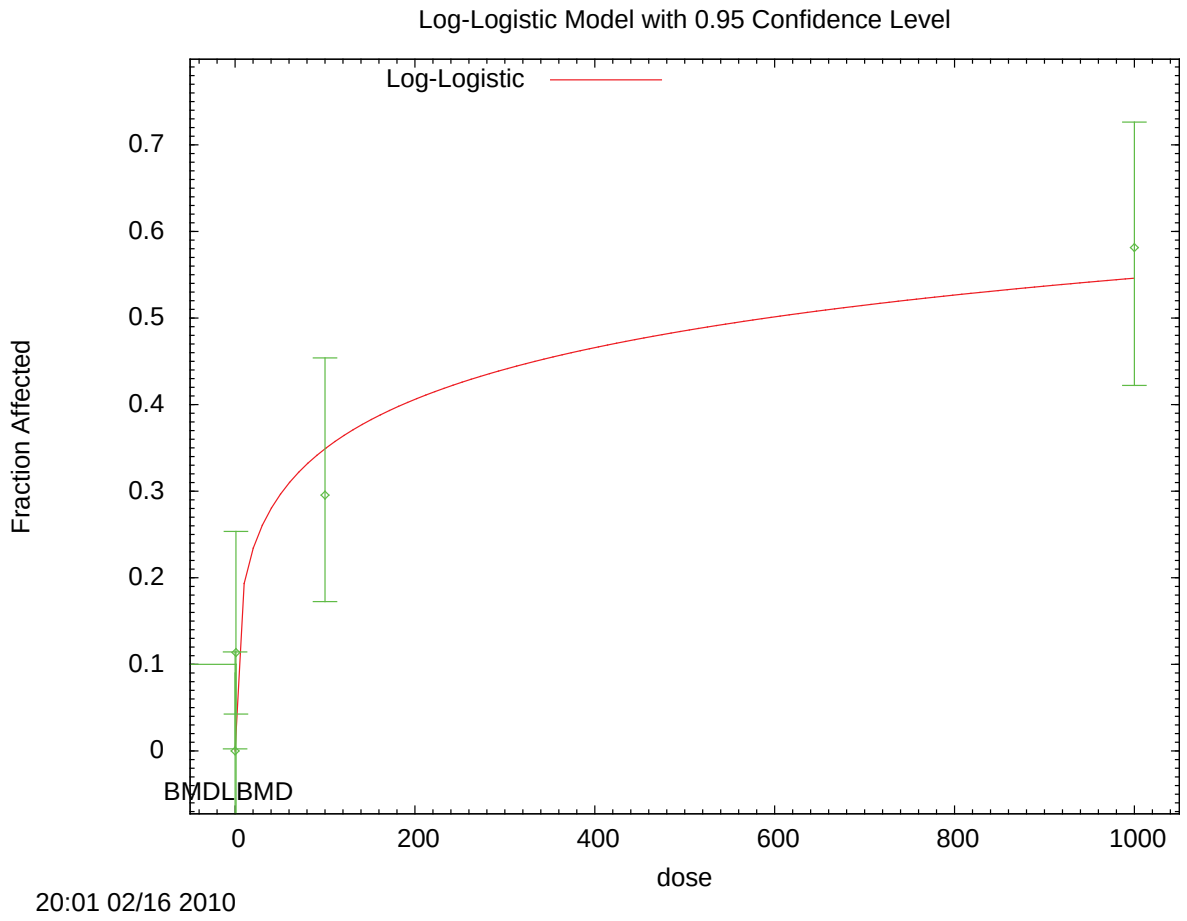
Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.1374

BMDL = 0.0547689

G.3.55.5. ***Figure for Additional Model Presented: Log-Logistic, Unrestricted***



G.3.56. van Birgelen et al. (1995): Hepatic Retinol

G.3.56.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	4	<0.0001	164.340	2.912E+02	error	
Exponential (M3)	4	<0.0001	164.340	2.912E+02	error	power hit bound (*d* = 1)
Exponential (M4)[a]	**3**	**<0.0001**	**148.052**	**1.151E+02**	**7.098E+01**	
Exponential (M5)	3	<0.0001	148.052	1.151E+02	7.098E+01	power hit bound (*d* = 1)
Hill	3	0.044	128.757	1.314E+01	error	*n* lower bound hit (*n* = 1)
Linear	4	<0.0001	178.734	7.815E+02	5.997E+02	
Polynomial, 5-degree	0	N/A	283.606	2.481E+03	error	
Power	4	<0.0001	178.734	7.815E+02	5.997E+02	power bound hit (power = 1)
Hill, unrestricted	2	0.269	125.273	5.561E+00	error	unrestricted (*n* = 0.571)
Power, unrestricted[b]	3	0.025	129.990	4.205E−01	8.504E−03	unrestricted (power = 0.118)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.56.2. *Output for Selected Model: Exponential (M4)*

van Birgelen et al. (1995): Hepatic Retinol

```
 ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\65_VanB_1995a_HepRet_Exp_1.(d)
        Gnuplot Plotting File:
                                            Tue Feb 16 20:03:05 2010
 ======================================================================

 Tbl3, hepatic retinol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	-1.16065
rho	1.53688
a	15.645
b	0.00625117
c	0.0365247
d	1

Parameter Estimates

Variable	Model 4
lnalpha	-0.882225
rho	1.82707
a	10.5294
b	0.00720346
c	0.0688661
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	14.9	8.768
14	8	8.4	3.394
26	8	8.2	2.263
47	8	5.1	0.8485
320	8	2.2	0.8485
1024	8	0.6	0.5657

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	10.53	5.526	2.237
14	9.589	5.073	-0.6628
26	8.855	4.717	-0.3926
47	7.714	4.159	-1.778
320	1.703	1.046	1.343

1024	0.7313	0.4833	-0.7681

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-87.1567	7	188.3134
A2	-47.28742	12	118.5748
A3	-55.32422	8	126.6484
R	-109.967	2	223.934
4	-69.02619	5	148.0524

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	125.4	10	< 0.0001
Test 2	79.74	5	< 0.0001
Test 3	16.07	4	0.002922
Test 6a	27.4	3	< 0.0001

The p-value for Test 1 is less than .05. There appears to be a

```
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is less than .1.  You may want to
  consider a different variance model.

  The p-value for Test 6a is less than .1.  Model 4 may not adequately
  describe the data; you may want to consider another model.


Benchmark Dose Computations:

  Specified Effect = 1.000000

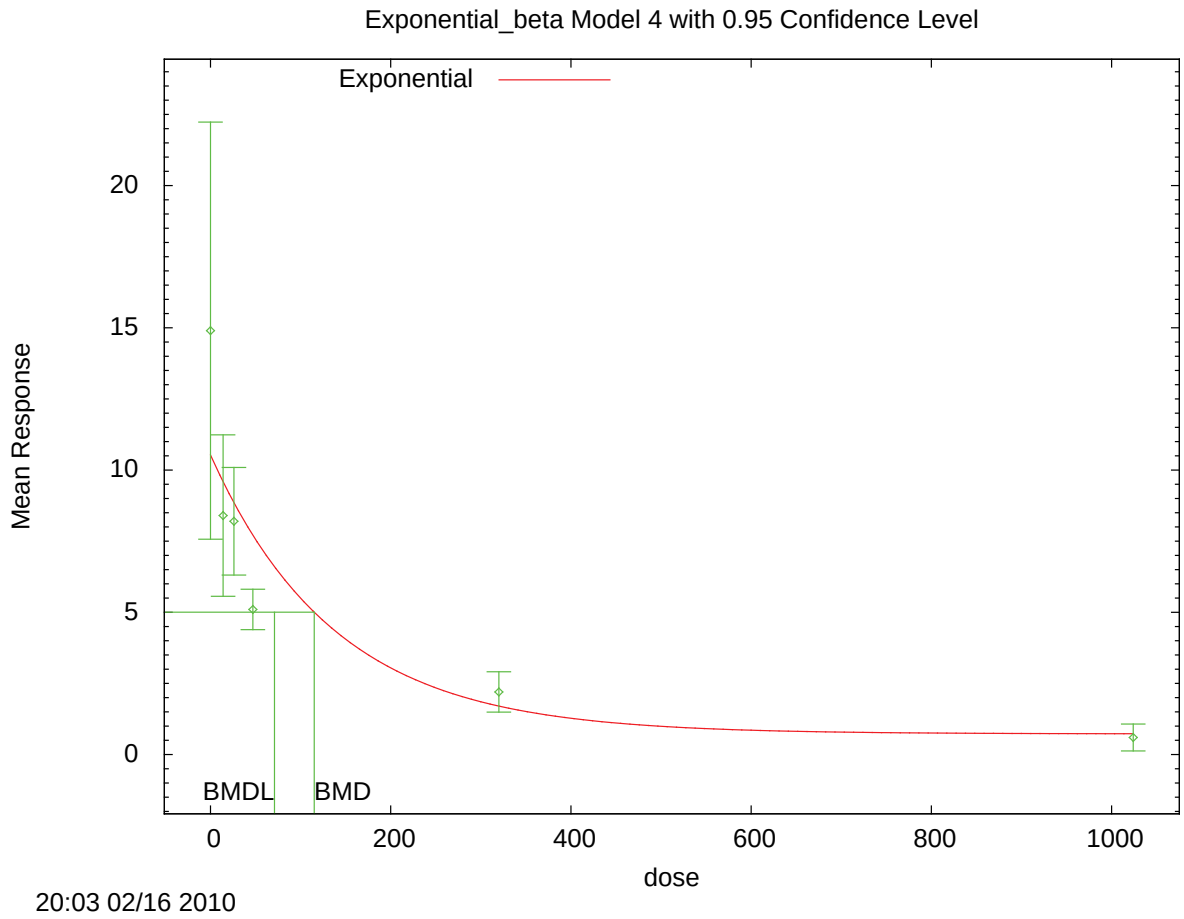
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      115.128

              BMDL =       70.981
```

G.3.56.3. *Figure for Selected Model: Exponential (M4)*



G.3.56.4. *Output for Additional Model Presented: Power, Unrestricted*

van Birgelen et al. (1995): Hepatic Retinol

```
 ======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\65_VanB_1995a_HepRet_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\65_VanB_1995a_HepRet_Pwr_U_1.plt
                                          Tue Feb 16 20:03:11 2010
 ======================================================================

 Tbl3, hepatic retinol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
```

```
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                Default Initial Parameter Values
                        lalpha =      2.76506
                           rho =            0
                       control =         14.9
                         slope =     -3.78637
                         power =     0.191713


         Asymptotic Correlation Matrix of Parameter Estimates

               lalpha          rho      control        slope        power

    lalpha            1         -0.8       -0.047        0.042        0.065

       rho         -0.8            1       -0.085      -0.0029        -0.11

   control       -0.047       -0.085            1        -0.95        -0.81

     slope        0.042      -0.0029        -0.95            1         0.96

     power        0.065        -0.11        -0.81         0.96            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         -1.02622         0.389164            -1.78897
-0.263475
            rho          1.68421         0.199212             1.29376
2.07466
        control          16.9577          2.21133             12.6235
21.2918
          slope         -7.19097          1.99708            -11.1052
-3.27676
          power         0.117935        0.0225396           0.0737578
0.162111


     Table of Data and Estimated Values of Interest
```

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	14.9	17	8.77	6.49	-0.896
14	8	8.4	7.14	3.39	3.13	1.14
26	8	8.2	6.4	2.26	2.86	1.78
47	8	5.1	5.63	0.849	2.57	-0.588
320	8	2.2	2.76	0.849	1.41	-1.12
1024	8	0.6	0.672	0.566	0.428	-0.475

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-87.156698	7	188.313395
A2	-47.287416	12	118.574833
A3	-55.324218	8	126.648436
fitted	-59.994980	5	129.989960
R	-109.967018	2	223.934036

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	125.359	10	<.0001
Test 2	79.7386	5	<.0001

Test 3	16.0736	4	0.002922
Test 4	9.34152	3	0.02508

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is less than .1. You may want to consider a different variance model

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

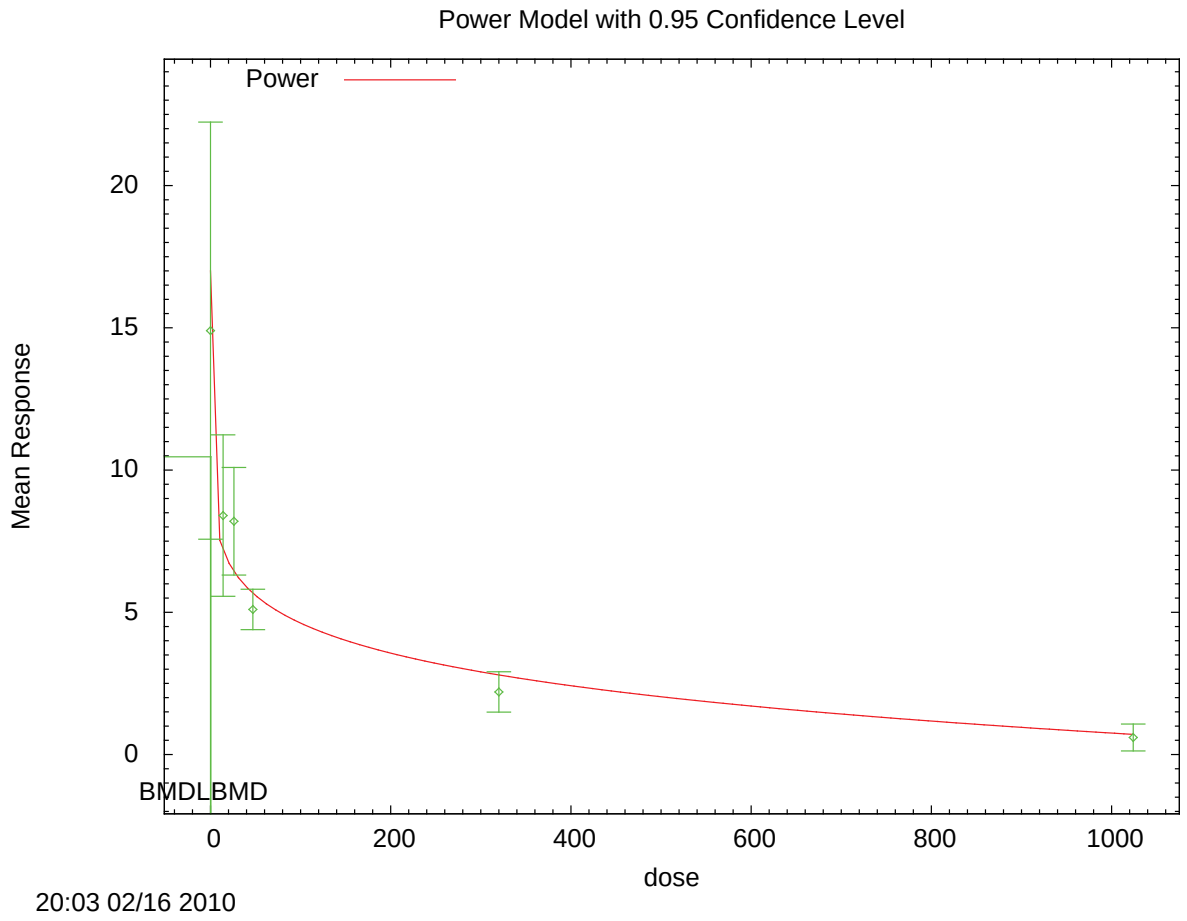
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.420475

BMDL = 0.00850422

G.3.56.5. ***Figure for Additional Model Presented: Power, Unrestricted***



G.3.57. van Birgelen et al. (1995): Hepatic Retinol Palmitate

G.3.57.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	4	<0.0001	467.446	error	error	
Exponential (M3)	4	<0.0001	467.446	error	error	power hit bound (*d* = 1)
Exponential (M4)	3	<0.0001	454.087	error	error	
Exponential (M5)	3	<0.0001	454.087	error	error	power hit bound (*d* = 1)
Hill	3	<0.0001	563.579	error	error	
Linear[a]	**4**	**<0.0001**	**488.446**	**1.420E+03**	**9.889E+02**	
Polynomial, 5-degree	0	N/A	573.977	error	error	
Power	4	<0.0001	488.446	1.420E+03	9.889E+02	power bound hit (power = 1)
Hill, unrestricted	3	<0.0001	522.322	2.418E−12	2.418E−12	unrestricted (*n* = 0.452)
Power, unrestricted[b]	3	0.348	408.062	3.765E−02	1.208E−05	unrestricted (power = 0.054)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.57.2. *Output for Selected Model: Linear*

van Birgelen et al. (1995): Hepatic Retinol Palmitate

```
 ======================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\66_VanB_1995a_HepRetPalm_Linear_1.(d)
        Gnuplot Plotting File:  C:\1\66_VanB_1995a_HepRetPalm_Linear_1.plt
                                            Tue Feb 16 20:03:46 2010
 ======================================================================

 Tbl3, hepatic retinol palmitate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                           lalpha =      9.57332
```

```
                    rho =            0
                beta_0 =      177.506
                beta_1 =    -0.204775
```

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.95	-0.017	0.022
rho	-0.95	1	0.00019	-0.0048
beta_0	-0.017	0.00019	1	-1
beta_1	0.022	-0.0048	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-0.723216	0.638291	-1.97424	0.527811
rho	2.26615	0.140196	1.99137	2.54093
beta_0	150.535	31.5457	88.7064	212.363
beta_1	-0.143931	0.0308317	-0.20436	-0.0835018

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	472	151	272	204	4.45
14	8	94	149	67.9	201	-0.766
26	8	107	147	76.4	199	-0.567
47	8	74	144	39.6	194	-1.02
320	8	22	104	22.6	135	-1.73
1024	8	3	3.15	2.83	2.56	-0.166

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
```

```
Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-250.554817	7	515.109634
A2	-196.755746	12	417.511491
A3	-197.383174	8	410.766347
fitted	-240.223107	4	488.446215
R	-276.789644	2	557.579287

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	160.068	10	<.0001
Test 2	107.598	5	<.0001
Test 3	1.25486	4	0.869
Test 4	85.6799	4	<.0001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

```
Specified effect =             1

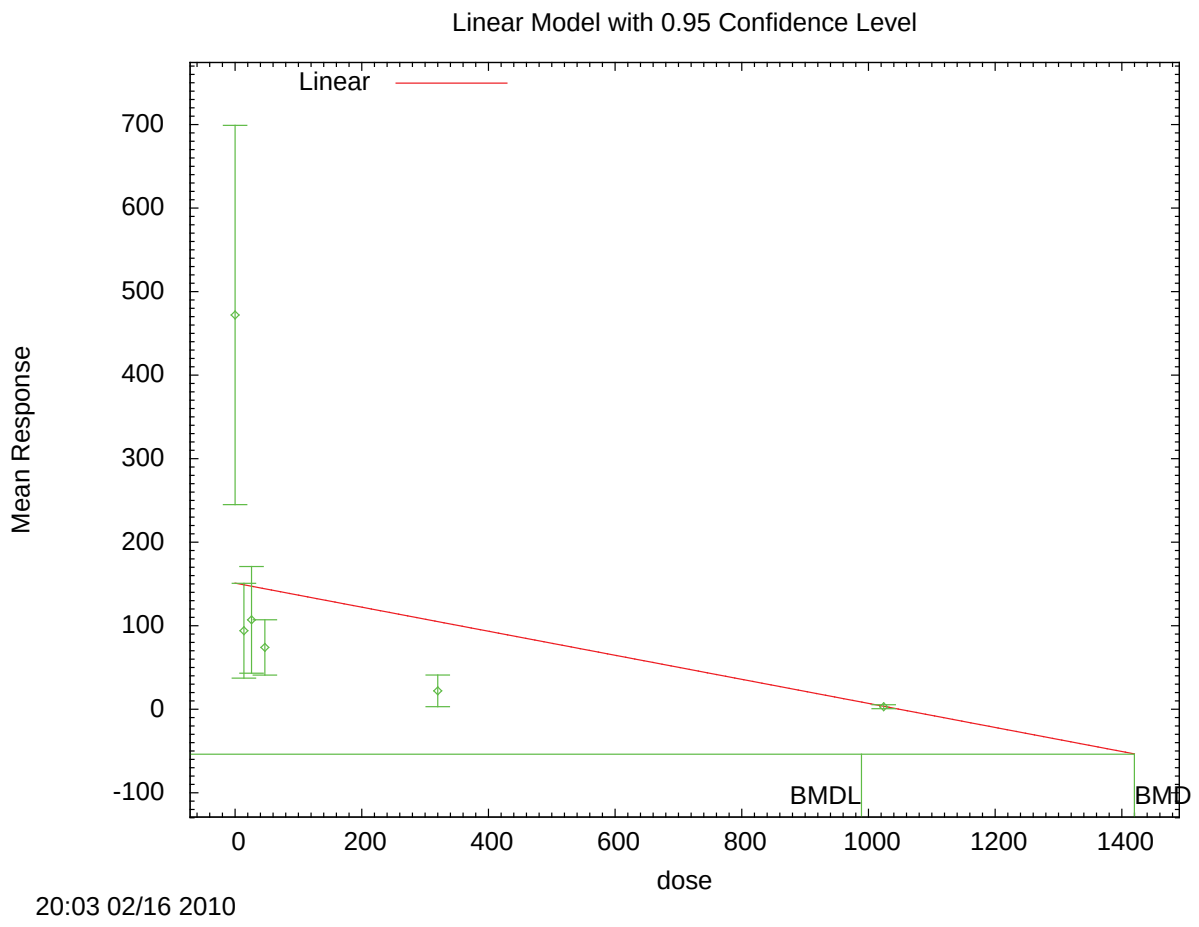
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        1419.81


            BMDL =        988.945
```

G.3.57.3. *Figure for Selected Model: Linear*



G.3.57.4. *Output for Additional Model Presented: Power, Unrestricted*

van Birgelen et al. (1995): Hepatic Retinol Palmitate

```
 ====================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\66_VanB_1995a_HepRetPalm_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\66_VanB_1995a_HepRetPalm_Pwr_U_1.plt
                                          Tue Feb 16 20:03:50 2010
 ====================================================================

 Tbl3, hepatic retinol palmitate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                         lalpha =      9.57332
                            rho =            0
                        control =          472
                          slope =     -315.054
                          power =    0.0586881


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho      control        slope        power

    lalpha            1        -0.95         0.29        -0.31         -0.3

       rho        -0.95            1         -0.4         0.39         0.29

   control         0.29         -0.4            1        -0.98        -0.82

     slope        -0.31         0.39        -0.98            1         0.91

     power         -0.3         0.29        -0.82         0.91            1
```

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	0.0734958	0.849559	-1.59161	1.7386
rho	1.80632	0.194602	1.42491	2.18774
control	465.497	86.914	295.149	635.845
slope	-318.06	82.4127	-479.586	-156.534
power	0.0540573	0.0117709	0.0309869	0.0771278

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	472	465	272	266	0.069
14	8	94	98.7	67.9	65.6	-0.201
26	8	107	86.2	76.4	58.1	1.01
47	8	74	73.8	39.6	50.5	0.0086
320	8	22	31.1	22.6	23.1	-1.11
1024	8	3	2.86	2.83	2.68	0.145

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-250.554817	7	515.109634

A2	-196.755746	12	417.511491
A3	-197.383174	8	410.766347
fitted	-199.031154	5	408.062307
R	-276.789644	2	557.579287

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	160.068	10	<.0001
Test 2	107.598	5	<.0001
Test 3	1.25486	4	0.869
Test 4	3.29596	3	0.3482

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

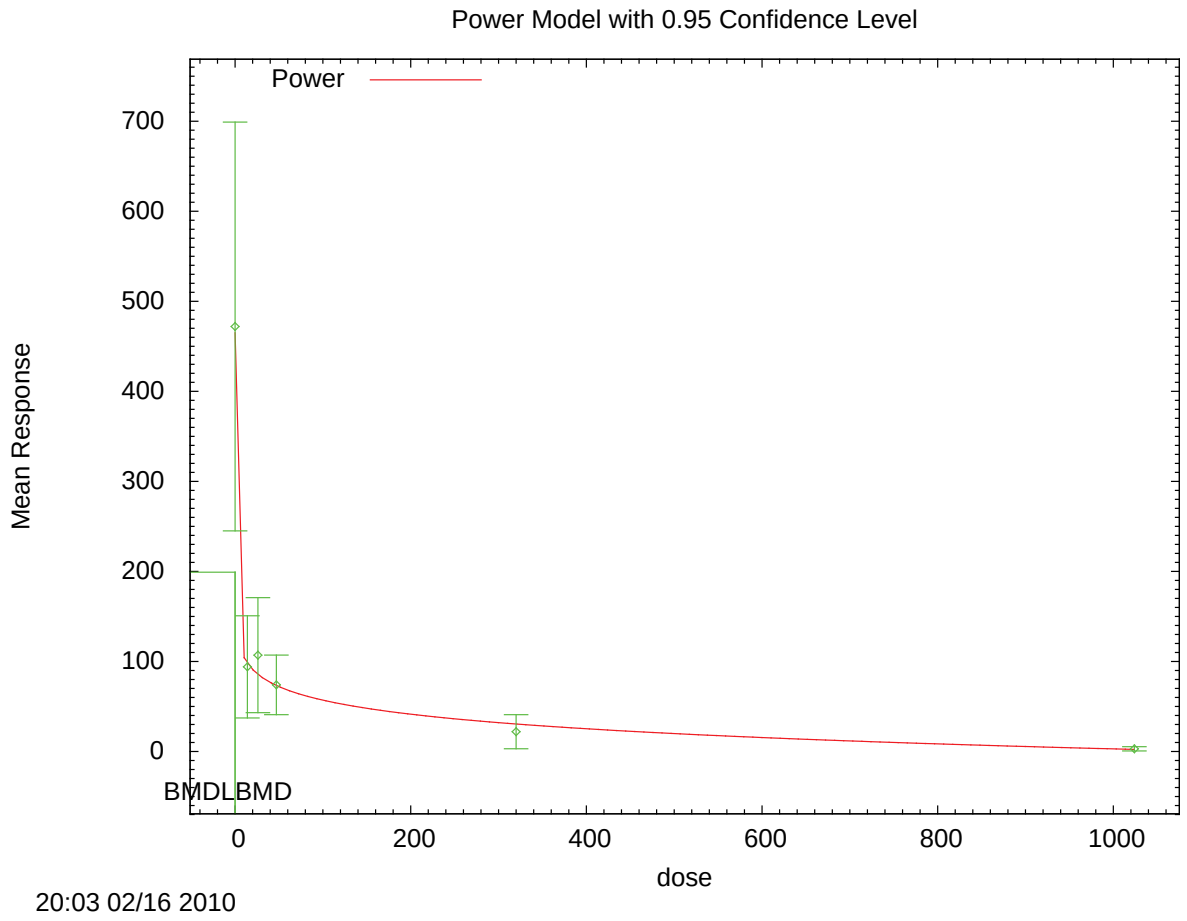
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.0376489

BMDL = 1.20769e-005

G.3.57.5. ***Figure for Additional Model Presented: Power, Unrestricted***



G.3.58. White et al. (1986): CH50

G.3.58.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	5	0.001	391.472	4.480E+02	2.844E+02	
Exponential (M3)	5	0.001	391.472	4.480E+02	2.844E+02	power hit bound (*d* = 1)
Exponential (M4)	4	0.001	392.128	3.126E+02	1.140E+02	
Exponential (M5)	4	0.001	392.128	3.126E+02	1.140E+02	power hit bound (*d* = 1)
Hill[a]	**4**	**0.001**	**391.223**	**2.042E+02**	**3.585E+01**	***n* lower bound hit (*n* = 1)**
Linear	5	<0.0001	396.430	8.065E+02	5.899E+02	
Polynomial, 6-degree	3	<0.0001	643.059	9.600E+02	error	
Power	5	<0.0001	396.430	8.065E+02	5.899E+02	power bound hit (power = 1)
Hill, unrestricted[b]	3	0.058	381.943	9.677E−01	1.900E−01	unrestricted (*n* = 0.211)
Power, unrestricted	4	0.131	379.574	7.186E−01	1.157E−02	unrestricted (power = 0.188)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.58.2. *Output for Selected Model: Hill*

White et al. (1986): CH50

```
 ======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\71_White_1986_CH50_Hill_1.(d)
        Gnuplot Plotting File:  C:\1\71_White_1986_CH50_Hill_1.plt
                                            Tue Feb 16 20:06:45 2010
 ======================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 7
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                           lalpha =      5.60999
```

```
                    rho =            0
              intercept =           91
                      v =          -74
                      n =    0.0969998
                      k =           10
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-0.99	0.19	0.13	-0.22
rho	-0.99	1	-0.2	-0.14	0.23
intercept	0.19	-0.2	1	0.33	-0.7
v	0.13	-0.14	0.33	1	-0.86
k	-0.22	0.23	-0.7	-0.86	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	4.34761	1.59601	1.21948	7.47574
rho	0.381496	0.413764	-0.429467	1.19246
intercept	71.6585	5.38454	61.105	82.212
v	-62.7464	14.9646	-92.0765	-33.4163
n	1	NA		
k	441.016	460.151	-460.864	1342.9

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

0	8	91	71.7	14.1	19.9	2.75
10	8	54	70.3	8.49	19.8	-2.33
50	8	63	65.3	11.3	19.5	-0.329
100	8	56	60.1	25.5	19.2	-0.598
500	8	41	38.3	17	17.6	0.43
1000	8	32	28.1	17	16.6	0.661
2000	8	17	20.2	17	15.6	-0.589

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-181.340979	8	378.681959
A2	-175.820265	14	379.640529
A3	-181.238690	9	380.477380
fitted	-190.611743	5	391.223485
R	-212.367055	2	428.734109

Explanation of Tests

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	73.0936	12	<.0001
Test 2	11.0414	6	0.0871
Test 3	10.8369	5	0.05471

```
   Test 4              18.7461          4       0.0008815

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =             1

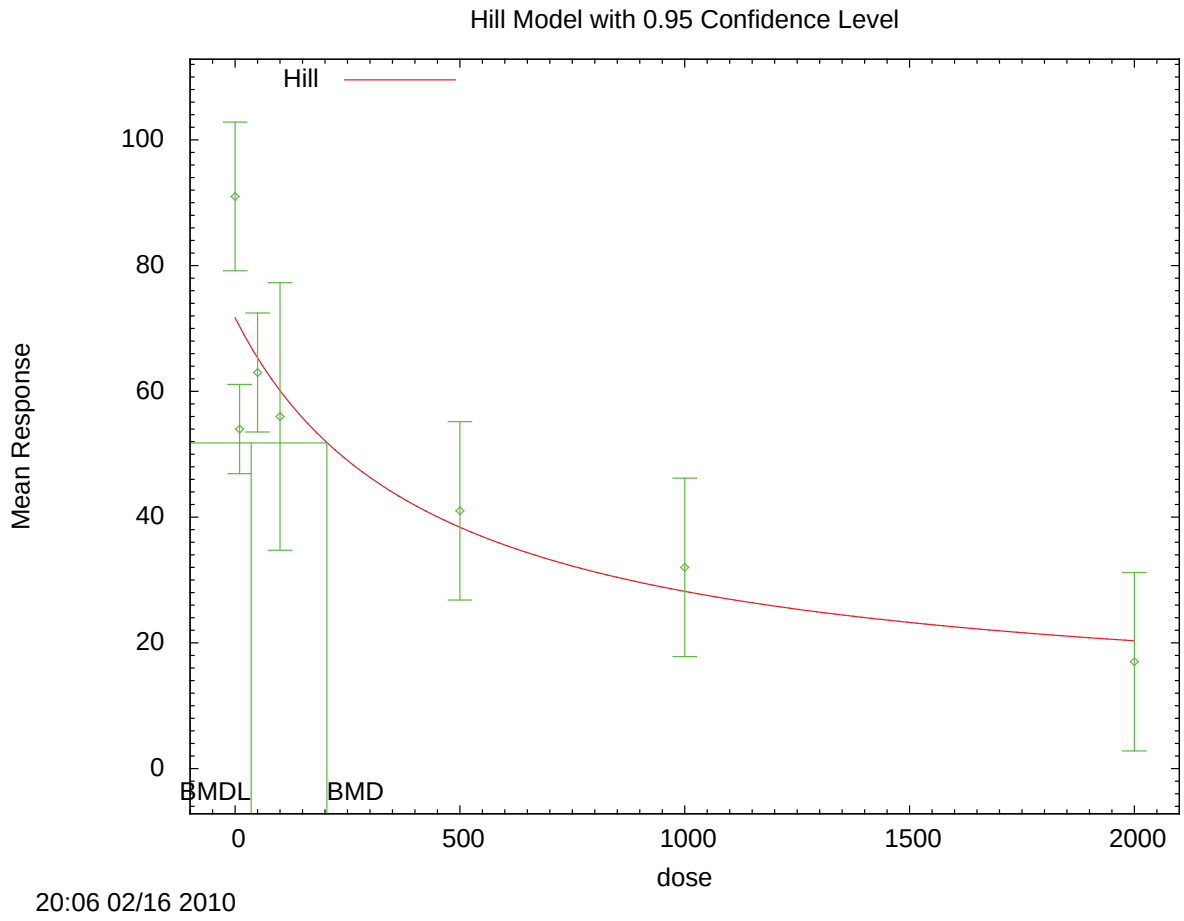
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =        204.214

            BMDL =       35.8504
```

G.3.58.3. *Figure for Selected Model: Hill*



G.3.58.4. *Output for Additional Model Presented: Hill, Unrestricted*

White et al. (1986): CH50

```
=====================================================================
       Hill Model. (Version: 2.14;  Date: 06/26/2008)
       Input Data File: C:\1\71_White_1986_CH50_Hill_U_1.(d)
       Gnuplot Plotting File:  C:\1\71_White_1986_CH50_Hill_U_1.plt
                                          Tue Feb 16 20:06:46 2010
=====================================================================

[insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function is:

  Y[dose] = intercept + v*dose^n/(k^n + dose^n)


  Dependent variable = Mean
  Independent variable = Dose
```

```
Power parameter is not restricted
The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

Total number of dose groups = 7
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                Default Initial Parameter Values
                       lalpha =      5.60999
                          rho =            0
                    intercept =           91
                            v =          -74
                            n =    0.0969998
                            k =           10


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n
k

    lalpha            1           -1         0.17         0.22        -0.42
-0.022

       rho           -1            1        -0.17        -0.22         0.42
0.019

 intercept         0.17        -0.17            1         0.16        -0.58
0.0069

         v         0.22        -0.22         0.16            1       -0.048
-0.91

         n        -0.42         0.42        -0.58       -0.048            1
-0.35

         k       -0.022        0.019       0.0069        -0.91        -0.35
1


                                 Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha          6.62767          2.14235             2.42875
10.8266
            rho        -0.266376         0.555274            -1.35469
0.821941
      intercept           89.579          5.61106             78.5815
100.576
```

```
              v         -458.615          402.837            -1248.16
330.93
              n         0.210614        0.0503369            0.111956
0.309273
              k     9.00638e+006     4.61231e+007       -8.13933e+007
9.94061e+007
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	91	89.6	14.1	15.1	0.266
10	8	54	65.4	8.49	15.8	-2.04
50	8	63	56.3	11.3	16.1	1.18
100	8	56	51.5	25.5	16.3	0.777
500	8	41	37.9	17	16.9	0.516
1000	8	32	30.8	17	17.4	0.191
2000	8	17	22.9	17	18.1	-0.927

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-181.340979	8	378.681959
A2	-175.820265	14	379.640529
A3	-181.238690	9	380.477380
fitted	-184.971691	6	381.943382
R	-212.367055	2	428.734109

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?

```
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              73.0936         12          <.0001
   Test 2              11.0414          6          0.0871
   Test 3              10.8369          5         0.05471
   Test 4                7.466          3         0.05844

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =             1

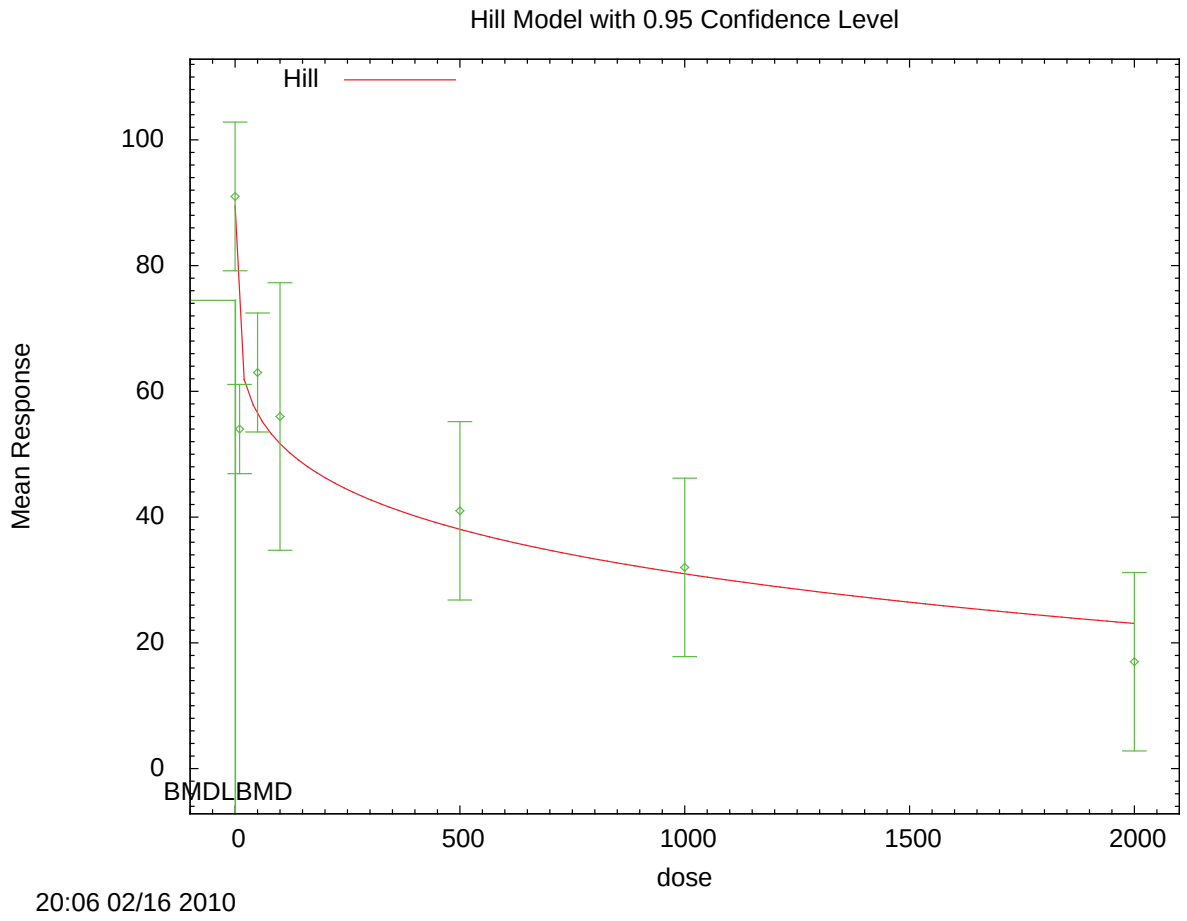
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =       0.967689

            BMDL =      0.189992
```

G.3.58.5. *Figure for Additional Model Presented: Hill, Unrestricted*



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APPENDIX H

Endpoints Excluded From Reference Dose Derivation Based on Toxicological Relevance

January 2012

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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APPENDIX H. ENDPOINTS EXCLUDED FROM REFERENCE DOSE DERIVATION BASED ON TOXICOLOGICAL RELEVANCE

The National Academy of Sciences committee commented on the low dose model predictions and the need to discuss the biological significance of the noncancer health effects modeled in the 2003 Reassessment. In selecting point of departure (POD) candidates from the animal bioassays for derivation of the reference dose (RfD), U.S. Environmental Protection Agency (EPA) had to consider the toxicological relevance of the identified endpoint(s) from any given study. Often endpoints/effects may be sensitive, but lack general toxicological significance due to not being clearly adverse (defined in the Integrated Risk Information System glossary as a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge), being an adaptive response, or not being clearly linked to downstream functional or pathological alterations. It is standard EPA RfD derivation policy not to base a reference value on endpoints that are not adverse or not obvious precursors to an adverse effect. For select studies, a rationale for lack of toxicological relevance of particular endpoints reported is listed here. These endpoints were not considered for derivation of the RfD.

H.1. BURLESON ET AL. (1996)

Burleson et al. (1996) analyzed the effect of a 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on viral host resistance following a single gavage dose of TCDD by measuring mortality mediated by influenza virus challenge in B6C3F$_1$ female mice. The study authors found that TCDD at ≥10 ng/kg-day increased influenza-induced mortality. The experimental design calls for a 30% mortality in untreated animals (15% was achieved); mortality, itself, is not a direct result of TCDD exposure. None of the other immunologically-relevant measures were affected by TCDD treatment in this study, and no other effects were reported. The interpretation of these results with respect to humans is problematic. Furthermore, the findings were not reproduced by Nohara et al. (2002) using the same experimental design (see Section 2.4.2 and Table 2-4). Therefore, this endpoint is not considered relevant as a POD candidate.

H.2. DEVITO ET AL. (1994)

Devito et al. (1994) assessed the activity of CYP1A1 and CYP1A2, the amount of phosphorylation of phosphotyrosyl proteins (pp32, pp34, and pp38), and the levels of estrogen receptor in the liver, uterus, lung and skin tissue of female $B6C3F_1$ mice administered TCDD for 5 days a week for 13 weeks. The authors hypothesized that these measurements may be sensitive biomarkers for exposure to TCDD. Body weights were also recorded weekly. Induction of CY1A1 and CYP1A2, as well as increased phosphorylated forms of pp32, pp34, and pp38 were sensitive indicators of TCDD exposure, with statistically significant changes seen at 1.07 ng/kg-day. 7-ethoxyresorufin-O-deethylase (EROD) activity in the ling, skin, and liver was also observed with significant increases at this dose. However, the authors did not find a change in rat body or terminal organ weights, nor did they note any pathology in the animals at this dose level. The role of cytochrome P450s (CYPs) and phosphorylated pp32, pp34, and pp38 in TCDD-mediated toxicity is unknown, and changes in the activity or function of these proteins are not considered adverse. Therefore, these endpoints are not considered suitable as PODs.

H.3. HASSOUN ET AL. (2003; 2002; 2000; 1998)

In multiple studies by Hassoun et al. (2003; 2002; 2000; 1998), various indicators of oxidative stress were measured in hepatic and brain tissue of female $B6C3F_1$ mice and Sprague-Dawley rats following 13 or 30 weeks of TCDD gavage dosing (5 days a week). Biomarkers for oxidative stress included production superoxide anion, lipid peroxidation, and DNA single-strand breaks. The authors report a statistically significant effect on several oxidative stress markers as a result of TCDD exposure, the lowest dose producing an effect being 0.32 ng/kg-day (1998). In this study, all oxidative stress markers were significantly affected, but no other indicators of brain pathology were assessed. Thus, it is impracticable to link the markers of oxidative stress to a toxicological outcome in the brain, and this study and its endpoints are not considered relevant POD candidates.

H.4. HONG ET AL. (1989)

Hong et al. (1989) studied the immunotoxicity of TCDD in female adult rhesus monkeys administered 0.12 or 0.67 ng/kg-day TCDD in feed for 4 years. Additionally, offspring from exposed mothers were examined. In adult monkeys, an increased number of T lymphocytes

were observed in the 0.67 ng/kg-day dose group, but there was not a proportional increase in each of the T cells subsets. Macrophage depletion in the 0.12, and 0.67 ng/kg-day groups resulted in the absence of amplification in a mixed lymphocyte response assay, compared to a fivefold amplification in control monkeys. In the offspring, there was an immune hyperresponsiveness to tetanus toxoid immunization which correlated with TCDD tissue levels. Although a thorough immunological investigation, in the absence of any relevant immunotoxicity endpoints or functional decrements of immune function following TCDD exposure, there are no suitable endpoints for consideration as candidate PODs in this study.

H.5. KITCHIN AND WOODS (1979)

Kitchin and Woods (1979) administered female Sprague-Dawley rats a single gavage dose of TCDD and measured CYP levels and benzo[*a*]pyrene hydroxylase (BPH) activity as a marker of hepatic microsomal cytochrome P448-mediated enzyme activity. They found a statistically significant increase in BPH at doses ≥2 ng/kg and a significant increase in cytochrome P450 levels at doses ≥600 ng/kg. Aryl hydrocarbon hydrolase and EROD were both significantly increased 3 months after exposure; however the elevation did not maintain statistical significance at 6 months. No other indicators of hepatic effects were analyzed. CYP induction alone is not considered a significant toxicologically adverse effect given that CYPs are induced as a means of hepatic processing of xenobiotic agents. Additionally, the role of CYP induction in hepatotoxicity and carcinogenicity of TCDD is unknown, and CYP induction is not considered a relevant POD without obvious pathological significance.

H.6. LATCHOUMYCANDANE ET AL. (2003)

Latchoumycandane et al. (2003) examined the induction of oxidative stress in epididymal sperm of male Wistar rats. The activities of antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GRX), and glutathione peroxidase (GPX), as well as the oxidative stress indicators hydrogen peroxide (H_2O_2) and lipid peroxidation (LPX) were measured in epididymal sperm, caput epididymis, corpus epididymis, and cauda epididymis following gavage dosing of 0, 100, 1,000, and 10,000 ng/kg-day TCDD for 4 consecutive days. No significant changes in epididymal sperm counts were evident at any dose tested compared to control. SOD, CAT, GRX, and GPX activities were significantly decreased at doses

≥1,000 ng/kg-day in epididymal sperm. H_2O_2 and LPX were significantly increased at all doses tested. SOD, CAT, GRX, and GPX activities were significantly decreased only at the highest dose in the caput epididymis and corpus epididymis, but were significantly decreased at all doses tested in the cauda epididymis. Conversely, H_2O_2 and LPX were significantly increased only at the highest dose in the caput epididymis and corpus epididymis, but were significantly increased at all doses tested in the cauda epididymis. Although several oxidative stress indicators were significantly changed in this study, sperm count was not altered, and no other indices of sperm function were assessed; it is unfeasible to link the markers of oxidative stress to a TCDD-induced toxicological outcome. Therefore, these endpoints are not considered relevant as POD candidates.

H.7. LUCIER ET AL. (1986)

Because TCDD had been detected in the soil of contaminated locations, determining the bioavailability of TCDD from ingested soil may be important to the calculation of safe exposure levels. Lucier et al. (1986) fed adult female Sprague-Dawley rats TCDD contaminated soil or gave them TCDD in corn oil at various doses and compared the effects of TCDD on biochemical parameters from liver tissue. They found that equivalent doses of TCDD in corn oil and soil produced similar increases in hepatic aryl hydrocarbon hydroxylase activity (AHH) and uridine diphosphate (UDP) glucuronyltransferase activity. They determined that AHH was statistically induced 1.8-fold at 15 ng/kg in corn oil and 40 ng/kg in soil. Cytochrome P450 was significantly increased at higher doses. No clinical signs of acute toxicity or changes in body weight were observed. The association between AHH activity and TCDD-mediated hepatotoxicity is unknown and no adverse endpoints were measured. Thus, this endpoint is not suitable as a POD candidate.

H.8. MALLY AND CHIPMAN (2002)

Mally and Chipman (2002) evaluated the effect of TCDD on gap junctions, hypothesizing that as a nongenotoxic carcinogen, TCDD may induce tumor formation by disturbing tissue homeostasis. Female F344 rats were dosed with TCDD by oral gavage for either 3 consecutive days or 2 days a week for 28 days. Gap junction connexin (Cx) plaque expression and hepatocyte proliferation was measured. The study authors report a decrease in

Cx32 plaque number and area in the liver of rats exposed to 0.7 ng/kg-day and higher, however they did not find an associated increase in hepatocyte proliferation. No clinical signs of toxicity were observed, and histological examination of the liver revealed no abnormalities. In the absence of additional indicators of hepatotoxicity, a decrease in Cx32 plaque formation is not clearly linked to TCDD-mediated hepatotoxicity or hepatocarcinogenicity, nor is it considered an adverse effect. This endpoint is not considered a toxicologically relevant POD.

H.9. SEWALL ET AL. (1993)

Sewall et al. (1993) investigated alterations in the epidermal growth factor receptor (EGFR) pathway in a two-stage initiation promotion model of TCDD hepatic cancer. EGFR signaling has been implicated in the altered cell growth induction by tumor promoters. Female Sprague-Dawley rats were administered TCDD biweekly by oral gavage for 30 weeks following initiation by a single dose of diethylnitrosamine (DEN). A group also received TCDD without prior DEN initiation. Livers were harvested and fixed from sacrificed animals and sections tested for EGFR binding, autophosphorylation, immunolocalization, and hepatic cell proliferation. The authors report a significant dose-dependent decrease in plasma membrane EGFR maximum binding capacity in TCDD-exposed rats beginning at 3.5 ng/kg-day. However, at this same dose, the authors note a statistically significant decrease in cell proliferation (as measured by DNA replication labeling), with increases in proliferation only occurring at higher doses (125 ng/kg-day). No other indicators of hepatic toxicity or tumorigenicity were assessed. The role of EGFR in TCDD-mediated hepatotoxicity and hepatocarcinogenicity is unknown, and as such, this endpoint cannot be unequivocally linked to TCDD-induced hepatic effects nor labeled as adverse. Thus, it is not suitable as a POD candidate.

H.10. SLEZAK ET AL. (2000)

Slezak et al. (2000) studied the impact of subchronic TCDD exposure on oxidative stress in various organs of $B6C3F_1$ female mice. The oxidative stress indicators superoxide anion (SA), lipid peroxidation (measured through formation of thiobarbituric acid reactive substances [TBARS] in tissue homogenates), ascorbic acid (AA), and total glutathione (GSH) were measured in liver, lung, kidney, and spleen following gavage dosing for 13 weeks (5 days a week). Tissue TCDD concentrations also were measured. Significant TCDD-induced changes

in the liver included decreased SA and GSH at 0.15 ng/kg-day, increased GSH at 0.45 ng/kg-day, increased SA and AA at 15 and 150 ng/kg-day, and increased GSH and TBARS at 150 ng/kg-day. Unlike the liver, there was no significant increase in SA in the lung, but SA was significantly decreased at 0.45, 15, and 150 ng/kg-day. Lung GSH and AA were decreased at 0.15 ng/kg-day, while AA was increased at 15 and 150 ng/kg-day. In the kidney, SA was increased at 15 and 150 ng/kg-day. Renal GSH, like the liver and the lung, was decreased at 0.15 ng/kg-day with this trend continuing at 0.45 and 1.5 ng/kg-day, and AA levels were lower at all doses except 1.5 ng/kg-day. In the spleen, SA was unchanged, GSH was increased at 150 ng/kg-day, and AA was decreased at 0.15, 1.5, and 150 ng/kg-day. Although several oxidative stress indicators were significantly changed in this study, no other indices of liver, lung, kidney, or spleen pathology were measured, and it is unfeasible to link the markers of oxidative stress to a TCDD-induced toxicological outcome in the organs assessed. Therefore, these endpoints are not considered relevant as POD candidates.

H.11. SUGITA-KONISHI ET AL. (2003)

Sugita-Konishi et al. (2003) investigated the change in host resistance of mice offspring lactationally exposed to TCDD. Pregnant C57BL/6NCji mice were administered TCDD via drinking water from parturition to weaning of the offspring (17 days). One group of offspring was then infected with *Listeria monocytogenes* and blood and spleen samples were collected various time points post infection. Uninfected, TCDD exposed offspring were weighed and their spleens and thymuses removed for assay of cellular content and protein expression. TCDD exposure caused a statistically-significant decrease in relative spleen weight and a statistically-significant increase in thymic CD4+ cells in the high-dose group (11.3 ng/kg-day). Offspring infected with *Listeria* following TCDD exposure exhibited a statistically significant increase in serum tumor necrosis factor alpha 2 days after infection in both sexes in the low- (1.14 ng/kg-day) and high-dose groups. The authors conclude that exposure to TCDD disrupted the host resistance of the offspring at the lowest dose tested, despite the primary immune parameters being unaffected. Without an obvious association between TCDD and immune function, however, this endpoint is not suitable for identification of a lowest-observed-adverse-effect level (LOAEL). Thus, the LOAEL for this study is 11.3 ng/kg-day, and the no-observed-adverse-effect level is 1.14 ng/kg-day.

H.12. TRITSCHER ET AL. (1992)

Tritscher et al. (1992) performed an initiation-promotion study in female Sprague-Dawley rats. Rats were initiated with an i.p. injection of DEN or saline, followed 2 weeks later by promotion with biweekly administration of TCDD via gavage for 30 weeks. Hepatic cytochrome P450 levels (CYP1A1 and CYP1A2) and EROD activity were quantified, and immunohistochemical detection of CYP1A1 and CYP1A2 in liver was also conducted. Liver TCDD concentrations were also analyzed. A dose-response trend for increased liver CYP1A1 and CYP1A2 protein was observed in initiated and noninitiated rats as assessed by microsomal quanitification and immunihistochemical staining. A strong relationship between liver TCDD concentration and CYP1A1 and CYP1A2 protein levels and EROD activity was also observed in DEN/TCDD-treated rats. CYP induction alone is not considered a significant toxicologically adverse effect given that CYPs are induced as a means of hepatic processing of xenobiotic agents. Additionally, the role of CYP induction in the hepatotoxicity and carcinogenicity of TCDD is unknown, and CYP induction is not considered a relevant POD without obvious pathological significance.

H.13. VANDEN HEUVEL ET AL. (1994)

Vanden Heuvel et al. (1994) analyzed changes in hepatic messenger ribonucleic acid (mRNA) following a single administration of TCDD to female Sprague-Dawley rats by oral gavage. Four days after treatment, animals were sacrificed and livers were excised. Using reverse transcriptase-polymerase chain reaction on hepatic ribonucleic acid, they compared levels of “dioxin responsive” mRNA’s (CYP1A1, UDP-glucuronosyltransferase I, plasminogen activator inhibitor 2, and transforming growth factor α) at various doses of TCDD and at control (baseline) levels. They determined that CYP1A1 elicited the most sensitive response to TCDD, with a statistically significant increase (threefold) in mRNA from rat livers exposed to 1 ng/kg-day TCDD. Induction of CYP1A1 expression is not considered an adverse effect, as the role of CYP1A1 in TCDD-mediated carcinogenicity is unsettled. Therefore, in the absence of other indicators of hepatoxicity, increases in liver CYP1A1 cannot be considered toxicologically relevant for a POD candidate.

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APPENDIX I

Literature Search Terms

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National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

CONTENTS—Appendix I: Literature Search Terms

APPENDIX I. LITERATURE SEARCH TERMS I-1
I.1. REFERENCES I-10

APPENDIX I. LITERATURE SEARCH TERMS

The U.S. Environmental Protection Agency (EPA) has developed a literature database of peer reviewed studies on 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) toxicity, including in vivo mammalian dose response studies and epidemiologic studies for use in quantitative TCDD dose-response assessment and supporting qualitative discussions. An initial literature search for studies published since the 2003 Reassessment was conducted by the U.S. Department of Energy's Argonne National Laboratory (ANL) through an Interagency Agreement with EPA. ANL used the online National Library of Medicine database (PubMed) and identified studies published between the year 2000 and October 31, 2008.

EPA published the initial literature search results in the Federal Register on November 24, 2008 (U.S. EPA, 2008) and invited the public to review the list and submit additional peer reviewed in vivo mammalian dose response studies for TCDD, including epidemiologic studies that were absent from the list (U.S. EPA, 2008). Submissions were accepted by the EPA through an electronic docket, email and hand delivery, and were evaluated for use in TCDD dose-response assessment.

This appendix contains the search terms utilized by ANL in conducting the literature search.

LITERATURE SEARCH TERMS

1746-01-6
2,3,7,8-TCDD; TCDD
dioxin
absorbed, absorbed dose
absorbed, absorption
accident
acetylcholine
acetylcholinesterase
acute
acute myocardial infarction
adenocarcinoma
adenoma
adipose
administered
administered, administered dose
adrenal
adrenal (gland, cortex)
adverse
age
agent orange
agonist
Ah, aryl hydrocarbon, Ah receptor
AhR, arylhydrocarbon receptor
alveolar
alveolar duct
alveoli
AMI
anamnestic response
anemia
animal, animal stud
antibody
antigen
antigen presenting cell

antigenic
aorta
apoptosis
arcuate nucleus
area under curve
artery
atheromatous plaque
atria
atrioventricular
atrioventricular fistula
atrioventricular node
atrioventricular opening
atrioventricular valve
atrium
atrophy
AUC, area under the curve
autoimmune
B cell
B-cell
beagle
behavior
behavioral
behavioral abnormalities
benchmark (see BMC, BMD, others)
benign
bicuspid
bicuspid valve
bile
bile, biliary
bile, biliary
biliary
binding
bioaccumulation

bioavailability, bioavailable
bioavailable, bioavailability
biochem, biochemical
biological half-life
biotransformation
blind
blood
blood cells
blood concentration
blood pressure
blood, blood concentration
BMC, benchmark concentration
BMD, benchmark dose
BMDL
BMR, benchmark response
body burden
body weight
bolus
bone
bowel
brain
brain aromatase
brain stem
brain tissue
brain tissues
brainstem
breast milk
breast milk, lactation, milk
bronchi
bronchial
bronchial tree
bronchiole
CA, cancer, carcino, carcinogen

LITERATURE SEARCH TERMS (continued)

cancer
carcinogen
carcinogenesis
carcinogenic
carcinoma
cardiac
cardiac arrest
cardiac cycle
cardiac notch
cardio
cardio (myopathy), cardiovascular, CV
cardiogenic
cardiogenic plate
cardiomyopathy
cardiovascular
cardiovascular disease
case report
CD4
CD8
cell, cell line, cell proliferation
cell-mediated immune response
central nervous system
cerebellar
cerebral
cerebrum
chloracne
cholesterol
chordae tendineae
chronic
chronic lymphocytic leukemia
chronic obstructive pulmonary disease
cirrhosis
cirrhotic
cleft

clinical
cognition
cognitive
cognitive abnormalities
cohort
colitis
colon
compartment
concentration, peak
conjugate
contaminant, contamination, contaminated
control
COPD
COPD, chronic obstructive pulm disease
coplanar, coplanar PCB(s)
cornea
corneal
coronary
cortical
cortical asymmetry
cortical cells
cortical thickness
count
critical
culture, tissue culture
cuspid
cutaneous
CV
CVD
CVD (CV), cardiovascular disease
CYP, cytochrome P450
cytochrome, CYP (1A1, 1A2)
cytokine
dam

deficit
defoliant
degeneration
delayed-type hypersensitivity reaction
dendrite
dendritic
dentition
depot
depot
dermal
dermal, dermis, transdermal
dermal, transdermal, skin
dermis
developing
developmental
developmental, developmental effect
diabetes
diabetic
dialysis
diaphragm
diastole
diet, dietary
dietary, ingestion
differentiation, cell differentiation
diffusion, permeability
disease
disposition
distribute, distributed, distribution
DLC, dioxin-like compound
dog
dorsal raphe nuclei
dose response, dose-response
dose, dose metric, dose-dependent
dose, dose-dependent

LITERATURE SEARCH TERMS (continued)

dose-dependent
duodenum
dysplasia
ED, effective dose
edema
effect, effect level
eliminate, eliminated, elimination
embryo
embryo, embryotox(ic), embryonic
embryonic
embryotoxic
endo, endocrine, endocrine disrupt(or/ion)
endocarditis
endocrine
endocrine disrupter
endocrine disrupting
endocrine disruption
endocrine disruptor
endocrinology
endometrial
endometriosis
endometriosis
enterohepatic
enzyme
epidemiol, epidemiologic
epidermal
epidermis
equilibrium
ER
EROD
EROD, ethoxyresorufin-o-deethylase
estrogen
estrogen receptor
estrogen, ER, estrogen receptor

ethoxyresorufin-O-deethylase
excrete(d), excretion
excrete, excreted, excretion
eye
fat
fat, fatty
fate
fatty
fecal
fecal, feces
feces
fecundity (2 spellings?)
FEL, frank effect, frank effect level
female
fertility
fetal
fetal, feto, fetotox, fetotoxic, fetus
fetotoxic
fetus
FEV
fish
foci
food consumption
forced expiratory volume
forebrain
fraction
fraction, ratio
function
furan, furans
gastritis
gastrointestinal
gastrointestinal, GI, gut
gastrointestine
gastrointestine, gastrointestinal, GI, gut

gavage
gavage, bolus
GD
gender
genotox, genotoxicity
genotoxic
genotoxicity
gerbil
gestation
gestation, gestational, gestational day, GD
gestational
gestational day
GI
glia
glial cells
glomerular
glomerulus
glucagon
gonadotropin
granule neuroblast
gravid
growth hormone
gut
haematology
haematopoiesis
haemopoeisis
haemopoeitic
half-life, half life, half-lives
half-life, half-lives
hamster
hamster (Syrian golden)
HDL
HDL, high-density lipoprotein
health

LITERATURE SEARCH TERMS (continued)

heart
heart attack
heart disease
heart murmur
hematology
hematopoiesis
hemoglobin
hemopoeisis
hemopoeisis, hematopoiesis / poeitic
hemopoeitic
hemorragic
hemorrhage
hemorrhage, hemorragic
hemotoxin
hepatic
hepatic enzyme
hepatic, hepato(cyte), hepatotox(ic)(ity)
hepatic, liver
hepatocyte
hepatoma
hepatotoxicity
hepatoxic
herbicide
high blood pressure
high density lipoprotein
high-density lipoprotein
hippocampus
histologic, histopathologic, histopath
Hodgkins (2 spellings)
hormone, hormone
hospital
human
human, human stud
humoral immune response

hydronephrosis
hydroxylate(ion)
hyperglycemia
hyperglycemia, hypoglycemia
hyperglycemic
hyperplasia
hyperplasia, hypertrophy
hypersensitivity reaction
hypersensitized
hypertension
hypertrophy
hypertrophys
hypoglycemia
hypoglycemic
hypotension
hypothalamus
hypothalamus-preoptic area
IL
IL 5, interleukin 5
ileitis
ileum
immune
immune regulation
immune response
immune suppression
immune system
immune, immuno, immunological
immunocompromised
immunoglobulin
immunologic
immunological
immunology
immunosuppression
immunosuppressive

immunotox, immunotoxicity
immunotoxic
immunotoxicity
implantation
impurity, impurities, impure
in vitro, in vivo
individual
induce(d), inducible, induction
induce(d), inducible, induction, induc
infant
infection
infertility
inflammation
inflammatory
inflammatory lesion
inflammatory, inflammation
influenza
ingestion
inhal, inhalation
inhibition
injection
instillation
instillation, tracheal instillation
insulin
interleukin
intermediate
intermediate, reactive intermediate
intestinal
intestine
intraperitoneal, ip
intravenous, iv
involuntary muscle
IP, intraperitoneal
islets of Langerhorn

LITERATURE SEARCH TERMS (continued)

IV, intravenous
jaw
jejunum
keratitis, keratitic, keratin(ized), kerat
kidney
kinetic
Kupffer
lactat(ion), lactate, lactational
lactation
lactational
large intestine
LC, lethal concentration
LD, lethal dose
LDL
LDL, low-density lipoprotein
lesion
lethality
leukemia
leukemia, leukemic
leukemic
lipid
lipophilic
lipophilic, lipophilicity
lipophilicity
liver
liver enzyme
LOAEL, LOEL
lobes
low blood pressure
low density lipoprotein
low-density lipoprotein
low-dose
lung
lymph node

lymph, lymphatic
lymphocyte
lymphoid
lymphoid organs
lymphoma
macaque
macrophage
major histocompatibility complex
male
malignancy
malignant
malignant, malignancy
mammal
mammary
mammary gland
mammary, mammary gland
man
mandible
marker
mating behavior
mechanism, mechanistic (see MOA)
median raphe nuclei
men
metabolic
metabolism, metabolite, metabolize
metabolite
metaplasia
methoxyresorufin-O-deethylase
MHC
MI
mice (several strains)
microsome, microsomal
mink
mitral

mitral regurgitation
mitral valve
MOA, mode (mechanism) of action
model
molar
monkey (rhesus)
mortality
motor development
mouse (incl. Swiss)
MR
MROD
Mrp, multidrug resistance-assoc protein
mucosa
mucosa, mucosal, oral mucosa
mucosal
muscosa
muscosal
muta, mutagen, mutation
mutagen
mutation
myeloid leukemia
myocardial
myocardial infarction
myocardium
myocyte
nasal
nasal (turbinates)
nasal turbinates
natural killer
neocortical
neonatal
neoplasia
neoplasm
neoplasm, neoplast, neoplastic, neoplasia

LITERATURE SEARCH TERMS (continued)

neoplastic
nephron
nerve
nerve conductance
nerve conduction
nerves
neural
neural activity
neuro, neurologic
neuroblast
neuroblastoma
neurochemical
neurodevelopment
neurological
neuropathy
neuropeptides
neuropsychological
neurotox, neurotoxic, neurotoxicity
neurotoxic
neurotoxicity
neurotransmitters
neurotrophic factor
neutrophil
NK
NOAEL, NOEL
nonca, noncancer, noncarcinogenic
non-Hodgkins lymphoma (4 spellings)
NTS
nuclear receptor
nucleus of solitary tract
occupational
ocular
olfactory bulb
oncogen

oncogene
oncogenic
optic
oral
oral mucosa
organ
osteo
osteoblast
osteosarcoma
ovary
palate
palate, palat
pancreas
pancreatic
pancreatitis
papillary muscle
papilloma
paraventricular nucleus
parent
parenteral
partition, partitionong
pathol, pathology
pathway
patient
PB, physiol, physiologically based
PBPK
PCB, polychlorinated biphenyl
PD, pharmacodynamic
peak
peak, peak dose
people
percent
pericardium
perinatal

peripheral nervous system
peripheral neuropathy
person
pesticide
physiological
pig, guinea pig (Hartley)
pituitary
pituitary hormone
PK, pharmacokinetic
plasma
PND
PND, postnatal day
POD, point of departure
polymorphism, polymorph
polyneuropathy
POP, persistent organic pollutant
population
porphyrin, porphyria
postnatal
postnatal day
potency, potent
pregnancy
pregnant
pregnant, pregnancy
prenatal
preoptic area
primate
product, production
profile
progesterone
proliferation
promotion, promoter, promote, promoting
public
pulmonary

LITERATURE SEARCH TERMS (continued)

pulmonary artery
pulmonary edema
pulmonary embolism
pulmonary epithelium
pulmonary valve
pulmonary vein
pulmonary, transpulmonary
pup
pup survival
rabbit
rat (several strains)
rate
rate, time, time-dependent
ratio, fraction
reactive (intermediate)
reactive oxygen species
receptor, receptor mediated
red blood cells
regenerate, regeneration, regen
regeneration
renal
repro, reproductive, reprotox
reproduction
reproductive
reprotoxic
respiration
respiratory
respiratory, respired air
respired air
response
retina
retinal
rhabdomyosarcoma
risk, risk analysis, risk assessment

rodent
ROS
sarcoma
SCC
SCC, squamous cell carcinoma
sensitive, sensitivity
sequestration
serum
sex
sex ratio
sheep red blood cells
short term
sight
signal, signaling
skeletal
skeleton
skin
skin
small intestine
smooth muscle
soft tissue sarcoma
somatic sensory cortex
species
sperm
sperm abnormality
sperm count
spleen
sprayed area
squamous cell carcinoma
SRBC
SRBC, sheep red blood cell
steady state
stomach
storage, stored

strain
subacute
subchronic
subcutaneous, sc
substantia negra
superior vena cava
superoxide anion
superoxide dismutase
suprachiasmatic nucleus
susceptible, susceptibility
synapse
synaptic
system
systole
T cell
T3
T4
T-cell
TD, toxicodynamics
teeth
TEF, toxic equivalency factor
TEQ, toxic equivalent
teratogen
teratogen, teratogenic(ity)
teratogenic
teratogenicity
testes
testes, testicular, testic
testicular
testosterone
TG
TG, triglyceride
TH
TH, thyroid hormone

LITERATURE SEARCH TERMS (continued)

threshold	TSH, thyroid stimulating hormone	white blood cells
thymi	tubular	women
thymic atrophy	tubule	worker
thymocyte	tumor	
thymus	tumor, tumorigenic	
thymus involution	tumorigenic	
thymus, thymic, thym	turbinates	
thyroid	uncertainty	
thyroid function	urinary, urine	
thyroid hormone	urine, urinary	
thyroid stimulating hormone	uterine	
thyroid, thyroid function	uterus	
thyroxine	uterus, uterine	
thyroxine, T4; T3, triiodothyronine	variability	
time	vascular	
time, time-dependent	vascular disease	
time, time-weighted	vehicle	
tissue	vein	
tissue, target tissue	ventricle	
TK, toxicokinetics	ventricular	
tooth	ventromedial hypothalamus	
toxic, toxicity, toxico, toxicological	vision	
trachea	visual cognition	
transcutaneous	visual motion	
transdermal	visual, visual acuity	
transduction	vital capacity	
transformation	vitamin A	
transpire(d) air	vitamin D	
transpulmonary	vulnerable	
tricuspid	vulnerable plaque	
tricuspid valve	wasting syndrome	
triglyceride	WBC	
triiodothyronine	weight	
TSH	white blood cell	

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