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WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: June 14, 2011

SUBJECT: EPTC: Human Health Risk Assessment for Proposed Uses on Grass Grown for Seed.

PC Code: 041401
Decision No.:
Petition No.:
Risk Assessment Type: Single Chemical/Aggregate
TXR No.: None
MRID No.: None

DP Barcode: D371022
Registration No.:
Regulatory Action: Section 3 Registration
Case No.: None

CAS No.: 759-94-4
40 CFR:

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The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Gowan Company has requested the establishment of a regionally restricted, permanent registration of the active ingredient (ai) EPTC for use on grasses grown for seed production. The Registration Division (RD) of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed use of EPTC on grass grown for seed. HED has evaluated the toxicity and exposure

databases for the active ingredient, EPTC, and has conducted a human health risk assessment in support of the proposed use. An analysis of the exposures and risk estimates resulting from the currently registered uses of EPTC has also been included because significant changes have been made to the EPTC hazard assessment since the last EPTC assessment was completed by the Health Effects Division (Paula Deschamp, DP 244982, 4/7/99).

HED has examined the toxicology, residue chemistry, and exposure databases for EPTC. Based on the revised hazard assessment, HED has determined that there are potential occupational dermal risk estimates of concern for mixer/loaders from the previously registered uses of EPTC, specifically at higher application rates (i.e., over 6 lbs ai/A). There are also potential risk estimates of concern for workers entering fields treated with EPTC for the requested use on grass grown for seed as well as for the previously registered uses of EPTC. **Prior to RD granting the requested use, HED recommends that:**

1) **The proper dermal personal protective equipment (PPE) is placed on the labels to protect mixer/loaders.**
2) **The proper REIs are put in place on the labels to protect postapplication workers when EPTC is used as a post-emergent application.**

A summary of the findings and an assessment of human health risk resulting from the proposed use for EPTC are provided in this document. The HED team members contributing to this risk assessment include Monica Hawkins (occupational/residential assessments), Yvonne Barnes (residue chemistry and dietary assessment), Judy Facey (hazard evaluation), and Charles Smith (risk assessment). James K. Wolf, Environmental Scientist, Environmental Risk Branch III (ERB3), Environmental Fate and Effects Division (EFED), provided the drinking water exposure assessment.

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1.0 Executive Summary

The Gowan Company has requested the establishment of a regionally restricted, permanent registration of the active ingredient (ai) EPTC for use on grasses grown for seed production. This document contains the human health exposure and risk assessment for the requested use. An analysis of the exposures and risk estimates from the currently registered uses of EPTC has also been included because significant changes have been made to the EPTC hazard assessment since the last EPTC assessment was completed by the Health Effects Division (Paula Deschamp, DP 244982, 4/7/99).

Use Profile: EPTC (s-ethyl dipropylthiocarbamate) is a thiocarbamate herbicide used to control the growth of germinating annual weeds, especially grasses. EPTC is also currently registered for use on alfalfa, almonds, ladino clover, beans, citrus nursery stock and young field plantings, cotton, potatoes, safflower, idle and fallow ground, sugar beets, sunflower, sweet potatoes, tomatoes, and walnuts. Formulated products include emulsifiable concentrate (EC) liquids containing up to 87.8% EPTC active ingredient and granular (G) formulations containing up to 20% EPTC active ingredient. The currently registered labels allow EPTC to be applied as a single annual, pre-emergence or early post-emergence application and is usually incorporated into the soil immediately after application to prevent volatilization.

Hazard Assessment: EPTC, as well as other thiocarbamates, have toxic effects on the central and peripheral nervous systems. EPTC toxicological studies showed an increased incidence and severity of neuronal necrosis/degeneration in both the central and peripheral nervous systems of both rats and dogs. EPTC also consistently produced cardiomyopathy and neuronal cell necrosis in studies of varying length of treatment and in different species throughout the toxicity database for EPTC. Cholinesterase (ChE) inhibition was also seen in a number of toxicology studies, however, no consistent pattern was witnessed across studies with respect to ChE inhibition between different species, length of treatment, or the type of ChE enzyme measured.

Metabolism studies in the rat indicate that EPTC is extensively absorbed, metabolized and excreted through the urine (~81 and 88% of the administered dose for males and females within 24 hours, respectively). The feces and expired air were minor excretion routes. Absorption was estimated to be 86.7- 97.5% of the administered dose for the two sexes. Absorbed EPTC was widely distributed, with the greatest amount of radioactivity per mg organ found in the blood, kidneys, liver, and spleen after 24 hours.

Quantification of dermal risks was performed using data obtained from two oral rat studies (a Chronic/Carcinogenicity study and a 2-Generation Reproduction study) because a route specific dermal toxicity study was not submitted. The LOAELs from these studies were 25 and 10 mg/kg/day, respectively based on decreased body weight, increased incidences of myocardial and neuromuscular lesions, and cardiomyopathy. A NOAEL of 5 mg/kg/day was established. A target MOE of 100 is considered adequate for adults and children (10X for interspecies extrapolation and a 10X for intraspecies variability). Based on two dermal absorption studies in the rat which utilized a charcoal impregnated filter to capture vapors lost from the skin, absorption of EPTC was determined to be 5% at 10 hours.

Quantification of inhalation risks was performed using data obtained from a 90-day rat inhalation study. The BMDL10 from the study was 1.90 mg/kg/day based on decreased brain cholinesterase inhibition in males, decreased food consumption, and increased incidence of cardiomyopathy. The BMD10 was 3.75 mg/kg/day. The Reference Concentration (RfC) methodology was used to calculate human equivalent concentrations (HEC) for use in the occupational and residential assessments. A target MOE of 30 is considered adequate for adults and children (3X interspecies extrapolation and a 10X for intraspecies variability). Since the toxicological effects are not the same for the dermal and inhalation PoDs, the dermal and inhalation risks to handlers need not be combined for this assessment.

Evidence of increased qualitative and quantitative susceptibility of the offspring was only observed in the developmental neurotoxicity rat study. Specifically, a marginal decrease in absolute (not relative) pup brain weight (4-6%) was observed in only one sex (male pups) and at only one time point (PND 63). This marginal effect, had no dose-response, was not seen after perfusion, and had no corresponding necrosis. Therefore this effect was considered marginal at best and not robust. Furthermore, neither the rat or rabbit developmental studies nor the rat reproduction studies identified any teratogenic effects.

EPTC is classified as "Not Likely to be Carcinogenic to Humans." This is supported by lack of a carcinogenic effect in long-term studies and no genetic component in reproduction and developmental studies. There is no concern for mutagenicity and clastogenicity based on a genotoxicity panel that included *in vivo* and *in vitro* assays.

The acute toxicity profile of EPTC consists of low toxicity via the oral and dermal routes of exposure (Category III) and moderately high toxicity via the inhalation route (Category II). EPTC is not a severe eye irritant (Category III) or skin irritant (Category IV) and it is not a dermal sensitizer.

Dietary Exposure (food/water): The residue chemistry data and environmental fate data are adequate to assess human exposure. The acute and chronic dietary food exposure assessments are conservative in nature. The assessment is based on reliable data and will not underestimate exposure/risk.

Acute: A highly refined acute dietary risk analysis was conducted with the DEEM-FCID™ model incorporating field trial data, processing factors where available, percent of crop treated, and surface water distributions to form a conservative evaluation of acute dietary exposure for EPTC. The Mississsippi corn (MS) drinking water scenario was used as it resulted in the highest estimated drinking water concentrations (EDWCs). At the 99.9th percentile of exposure, none of the acute analyses yielded risk estimates that exceeded HED's level of concern (>100% of the aPAD) for the population subgroups. For food and drinking water, acute aggregate dietary risk was calculated to be 5.69% of the aPAD for the general population. For the subgroup with the highest calculated exposure, all infants (< 1 year old), acute aggregate dietary risk occupied 19% of the aPAD.

Chronic: A refined chronic dietary risk analysis was conducted with the DEEM-FCID™ model incorporating tolerance-level residues, processing factors where available, and percent of crop treated data to form a conservative evaluation of chronic dietary exposure for EPTC. All chronic analyses yielded risk estimates below 100% of the cPAD threshold level of concern for each

population subgroup. For food and drinking water, the chronic aggregate dietary risk was calculated at 2.2% of the cPAD for the general U.S. population. For the subgroup with the highest calculated exposure, all infants <1 year old and children 1-2 years old, chronic aggregate dietary risk occupied 4.7% of the cPAD.

Residential Exposure: There are currently no registered residential uses associated with EPTC as all of these uses have been voluntarily cancelled; therefore, a residential/non-occupational exposure assessment is not required. However, an EPTC bystander volatilization inhalation exposure assessment was performed that including both acute and short-/intermediate-term exposure scenarios. The results of these assessments indicate that some of the application site air concentrations result in acute and/or short- and intermediate-term risks of concern (MOEs < 30 for adults and children); however, this preliminary bystander inhalation assessment should be considered in context with the data limitations and considerations discussed in more detail in this document.

Aggregate Risk: There are currently no registered residential uses for EPTC; therefore, the ETPC aggregate risk assessment includes only dietary exposure (food and water).

Occupational Exposure/Risk:
Agricultural Handlers: Occupational short- and intermediate-term dermal and inhalation exposures are expected from EPTC handler activities associated with the proposed agricultural uses. The short- and intermediate-term dermal risks for all handler scenarios do not exceed HED's level of concern (MOEs > 100) at some level of PPE. The short- and intermediate-term inhalation risks for all handler scenarios do not exceed HED's level of concern (MOEs > 30) at some level of PPE.

Agricultural Post-application: The results indicate that occupational postapplication risks, as calculated per HED default values, exceed HED's level of concern (MOE < 100) on day zero after application for some crop and postapplication task combinations. All current EPTC labels have an REI of 12 hours based on the acute toxicity of EPTC. Most of the expected uses of EPTC are pre-plant or at plant, therefore there is minimal foliar contact, but there are some post-plant emergence uses on the current EPTC labels. HED's assessment should be considered conservative because the dermal exposure studies were conducted with more mature foliage plants.

Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment was not performed for EPTC at this time.

Review of Human Research: This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies (listed in Appendix A) have been determined to require a review of their ethical conduct and all of the studies utilized in this assessment have received the appropriate review.

2.0 HED Recommendations

HED has examined the toxicology, residue chemistry, and exposure databases for EPTC. Based on the revised hazard assessment, HED has determined that there are potential occupational dermal risk estimates of concern for mixer/loaders from the previously registered uses of EPTC, specifically at

higher application rates (i.e., over 6 lbs ai/A). There are also potential risk estimates of concern for workers entering fields treated with EPTC for the requested use on grass grown for seed as well as for the previously registered uses of EPTC. **Prior to RD granting the requested use, HED recommends that:**

1) **The proper dermal personal protective equipment (PPE) is placed on the labels to protect mixer/loaders.**
2) **The proper REIs are put in place on the labels to protect postapplication workers when EPTC is used as a post-emergent application.**

2.1 Data Deficiencies/Conditions of Registration

The following data are required as a condition of registration:

TOXICOLOGY

870.7800 Immunotoxicity
The immunotoxicity study in rats and/or mice is required to fulfill the current Section 158 data requirements.

870.3200 21/28 Day Dermal Study
The 21/28 day dermal study in rats is required to fulfill the current Section 158 data requirements.

The following data should be submitted with future uses:

RESIDUE CHEMISTRY

860.1360 Confined Accumulation in Rotational Crops
The 1984 EPTC rotational crop study (MRID 0015245) does not meet current test guideline requirements. No new rotational crop study needs to be performed if crop rotation is limited to only those crops already listed on labels of registered products containing EPTC. If the registrant wishes to expand the list of crops that may be rotated after EPTC, a new confined rotational crop study must be conducted in accordance to current test guidelines.

860.1340 Residue Analytical Methods
The 1998 residue chemistry chapter produced for the EPTC Reregistration Eligibility Decision (RED) required radiovalidation for the existing enforcement method for EPTC residues and for the proposed enforcement method for the hydroxy metabolites. Radiovalidation data for the EPTC method have not been submitted and these data remain outstanding. Radiovalidation data for the method for the hydroxy metabolites have been submitted and are undergoing an Agency method validation.

860.1650 Submittal of analytical reference standards
Currently the National Pesticide Repository has only the parent (EPTC) in stock and the following metabolites must be submitted: (1) EPTC S-ethyl 2-hydroxypropyl(propyl); (2)

EPTC sulfoxide, (3) EPTC, S-(2-hydroxy ethyl) dipropyl-, and (4) EPTC, S-ethyl 2-hydroxypropyl (propyl)-.

The required sample should be submitted to the following address:

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350
(Note that the mail will be returned if the extended zip code is not used.)

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate enforcement method is available for EPTC and its hydroxy metabolites. Samples were analyzed for EPTC and three hydroxy metabolites (R248722, R248723, and R245255). Residues of EPTC were determined using Stauffer Method Number RRC 84-58, "Determination of SC-1029 (EPTC, R-29148 and R-33865) Residues in Corn Grain and Silage by Gas Chromatography," dated September 27, 1984, and Morse Labs modifications to the method dated February 18, 2009. Residues of EPTC hydroxy metabolites were determined using Zeneca Ag Products, Report No. RR 96-089B, "EPTC: Determination of the EPTC Hydroxy Metabolites and Their Conjugates in Crops by Gas Chromatography," dated October 14, 1996 and Morse Labs modifications to the method dated June 09, 2008 and March 17, 2009. Residues of EPTC and its hydroxy metabolites were quantitated as equivalents of EPTC (parent compound). The methods were evaluated both prior to sample analysis and concurrently with sample analysis. Based on the lowest level of method validation (LLMV), the limit of quantitation (LOQ) was 0.05 ppm for EPTC and 0.01 ppm for the hydroxy metabolites. The limit of detection (LOD) was defined as 1/3 of LOQ. The methods were adequate for data collection based on acceptable concurrent method recoveries (MRID 47867601).

The 1998 Residue Chemistry Chapter for produced for the EPTC Reregistration Eligibility Decision (RED) required radiovalidation for the existing enforcement method for EPTC residues and for the proposed enforcement method for the hydroxy metabolites. Radiovalidation data for the EPTC method have not been submitted and these data remain outstanding. Radiovalidation data for the method for the hydroxy metabolites have been submitted and are undergoing an Agency method validation.

2.2.2 International Harmonization

There are no established or proposed Codex MRLs for EPTC residues; accordingly, there are no issues of compatibility with respect to current U.S. tolerances and Codex MRLs. (Barcode: D234927 dated 10/01/2010).

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2.2.3 Recommended Tolerances

Tolerances are currently established for residues of the herbicide EPTC, including its metabolites and degradates on a number of commodities. Compliance with the tolerance levels is to be determined by measuring only the sum of EPTC (carbamothioic acid, dipropyl-, S-ethyl ester) and its hydroxy metabolites (N-2-hydroxypropyl EPTC, N-3-hydroxypropyl EPTC, and 2-hydroxyethyl EPTC), calculated as the stoichiometric equivalent of EPTC, in or on the commodity.

The tolerances proposed by the petitioner in the current petition are listed below in Table 2.2.3, along with HED's recommended tolerance levels. The OCED MRL tolerance spreadsheet recommends a tolerance of 0.60 ppm for forage and 0.50 ppm for hay. These tolerance level recommendations are higher than the levels proposed by the petitioner. The petitioner must submit a revised Section F reflecting the revised tolerances and commodity definitions presented in Table 2.2.3.

Table 2.2.3: Proposed Tolerance Summary for EPTC

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Grass, forage	0.2	0.6	*Grass, grown for seed, forage*
Grass, hay	0.1	0.5	*Grass, grown for seed, hay*

2.3 Label Recommendations

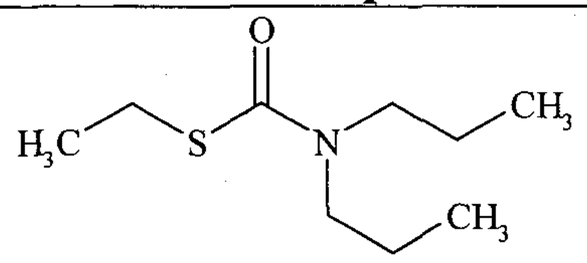
2.3.1 Recommendations from Occupational Assessment

There are a number of uses that result in short- and intermediate-term occupational handler dermal and inhalation risk estimates of concern at the personal protective equipment (PPE) currently required on the EPTC labels. This includes the proposed use on grass grown for seed. The required PPE for EPTC should be revisited. There are also potential risk estimates of concern for workers entering fields treated with EPTC for the requested use on grass grown for seed as well as for the previously registered uses of EPTC. The required REIs for EPTC should be revisited.

3.0 Ingredient Profile

EPTC is a thiocarbamate herbicide used to control the growth of germinating annual weeds, especially grasses.

3.1 Structure and Nomenclature

Table 3.1: Test Compound Nomenclature	
Chemical Structure	
Common Name	EPTC
IUPAC name	s-ethyl N, N-dipropylcarbamothioate
CAS Name	s-ethyl dipropylthiocarbamate
CAS Registry Number	759-94-4
Chemical Class	Thiocarbamate herbicide

3.2 Physical/Chemical Characteristics

Table 3.2: Physical and Chemical Properties		
Parameter	**Value**	**Reference**
Molecular Weight	189.32 g/mol.	42120801
Melting point/range	137-138 °C	
pH at 25°C (PAI) (TGAI)	6.2 7.4	
Density (PAI) (TGAI)	0.9633 g/mL 0.9639 g/mL	
Water solubility (25°C)	0.0344 g/100mL	
Solvent solubility (20°C to 25°C)	Visually miscible in Acetone, Hexane, Methanol, 1-octanol, Toluene, Acetonitrile, Dichloromethane, Ethyl Acetate	
Vapor pressure (25°C)	0.024 mm Hg	
Dissociation constant, pKa	Not Applicable	
Octanol/water partition coefficient, (25°C)	3.34 log K_{OW}	
UV/visible absorption spectrum	Not Available	Not Available

3.3 Summary of Existing/Proposed Uses

EPTC is a thiocarbamate herbicide used to control the growth of germinating annual weeds, especially grasses. Gowan Company has requested the establishment of a regionally restricted, permanent registration of the active ingredient EPTC for use on grasses grown for seed production (See Table 3.3). EPTC is also registered for use on several agricultural, tree, and orchard crops. EPTC has a number of currently registered products for use on alfalfa, almonds, ladino clover, beans, citrus nursery stock and young field plantings, cotton, potatoes, safflower, idle and fallow ground, sugar beets, sunflower, sweet potatoes, tomatoes, and walnuts among others. Formulated products include emulsifiable concentrate (EC) liquids containing up to 87.8% EPTC active ingredient and granular (G) formulations containing up to 20% EPTC active ingredient. The application rates range from 3.0 to 6.0 lb ai/A for the granular formulations and from 1.96 to 7.91 lb ai/A for the liquid formulations. The label allows for EPTC to be applied as a single annual, pre-

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emergence or early post-emergence application and is usually incorporated into the soil immediately after application to prevent volatilization.

Table 3.3 Summary of Directions for Use of EPTC on Grass

Commodity	Trade Name (EPA Reg. No.)	Application Timing, Type, and Equipment	Maximum Application Rate (lb ai/A)	Maximum Number Applications per Season	Maximum Seasonal Application Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Grass grown for seed – New Plantings	Eptam® 7-E Selective Herbicide (10163-283)	Broadcast pre-plant incorporated or post plant, pre-emergence	3.5	Not reported	Not reported	Not reported	Min. spray volume: 10 GPA. For pre-plant incorporated, apply 3 to 4 weeks prior to carbon-seeding planting of perennial ryegrass in a September to November timing.
Grass grown for seed – established stands		Broadcast post-emergence	4.4	Not reported	Not reported	Not reported	Min. spray volume: 10 GPA. Apply in fall prior to emergence of annual bluegrass.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The toxicology database for the active ingredient, EPTC [S-ethyl dipropylthiocarbamate], is considered adequate for risk assessment in support of the proposed regionally restricted, permanent registration on grasses grown for seed production. Since the completion of the Reregistration Eligibility Document (RED, 10/30/1999), the Registrant completed and submitted a DNT study (2004). The toxicity database (including the DNT study) was reviewed by the Health Effects Division and endpoints based on current policies and practices were updated. Based on the revised December 2009, Part 158 requirements an immunotoxicity study and a 21/28 day dermal study are required.

Data from the following studies were used to evaluate the hazard potential of EPTC:

- Acute: acute oral; rat; acute dermal, rat; acute inhalation, rat; acute eye irritation, rabbit; acute dermal irritation, rabbit; and dermal sensitization, guinea pig.
- Subchronic: 13-week oral, rat; 13-week inhalation, rat and 13-week oral, dog
- Chronic: two 52-week oral, dog; 78 –week oral/ carcinogenicity, mouse; and two 2-year oral /carcinogenicity, rat.
- Neurotoxicity: 14- day acute neurotoxicity, rat; subchronic neurotoxicity, rat and developmental neurotoxicity, rat
- Reproduction/developmental: developmental toxicity, rabbit; developmental toxicity/one-

generation reproduction, rat and two-generation reproduction, rat.
- Other: 8 genotoxicity screens, 1 metabolism study, rat and 2 dermal absorption studies, rat.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

No differences in the excretion profile based on gender or radiolabel position were observed in a rat metabolism study. EPTC was rapidly absorbed and excreted: the urine of males and females contained 81% and 88% of the administered radiolabel, respectively, within 24 hours. The feces and expired air were minor excretion routes, each containing ≤ 3.2% of the radioactivity over 96 hours. Absorption was estimated to be 86.7- 97.5% of the administered dose for the two sexes. Absorbed EPTC was widely distributed, with the greatest amount of radioactivity per mg organ found in the blood, kidneys, liver, and spleen after 24 hours. Radioactivity declined significantly with time in all tissues except blood and spleen, which retained 72-80% of their 24-hour radioactivity after 7 days. Only 1.2% of the given radioactivity was in all the tissues after 7 days, indicating that there was no significant bioaccumulation.

4.2.1 Dermal Absorption

Dermal absorption studies (rats) with EPTC indicate that it rapidly evaporates (volatilize) from application site. This is consistent with findings for other thiocarbamates. In both studies, protective, non-occluding devices/covers were attached to the rats to isolate the dose area. Because of the volatility of EPTC, a charcoal- impregnated matrix was incorporated into the device/covers to capture EPTC vapors. The conditions under which the dermal studies were conducted are considered to be conservative relative to typical use patterns for EPTC. In one dermal absorption study (MRID 41686201), the total amount of EPTC absorbed was between 1- 2.5% over an order of magnitude dose spread after 1 hour of exposure. After 10 hours of exposure dermal absorption was 3-5% while after 24 hours the absorbed dose was ≈ 3-9%. The dose-duration of the exposure did not appear to produce a discernable pattern of absorption. In a second dermal absorption study (MRID 43712502) with a dose of 29μg/cm^2, most of the material either evaporated before the application site was covered or was trapped in the charcoal filter (≈86% of applied dose). The remainder of the radioactivity was recovered as follows: 3% was in the skin wash, 1.4% remained at the application site, and 5.8% was absorbed. Based on the results from both dermal absorption rat studies which utilized a charcoal impregnated filter to capture vapors lost from the skin, a conservative dermal absorption factor of 5% at 10 hours was determined for 2.73 mg/29 cm^2.

4.3 Toxicological Effects

EPTC is an S-alkylthiocarbamate which consistently produced cardiomyopathy and neuronal cell necrosis in studies of varying length of treatment and in different species throughout the toxicity database. Cardiotoxicity was observed in subchronic and long-term studies, and in general, the severity and incidence of the lesion increased with increasing dose of EPTC. In 90-day feeding and inhalation studies and in two chronic feeding/oncogenicity studies, all in the adult rat, histopathological evaluation revealed myocardial degeneration. Myocardial degeneration in adult rats was also observed in two separate two-generation reproduction studies. In two chronic dog studies, degenerative changes in the cardiac muscle were observed when EPTC was administered in a capsule, but not when administered (at comparable doses) in the diet. In both of the dog studies,

electrocardiograms were taken, but only one high- dose male in the capsule study had changes which were described as "potentially' treatment- related.

EPTC, as well as other thiocarbamates (molinate, cycloate, pebulate, vernolate and butylate), have toxic effects on the central and peripheral nervous systems. With EPTC, there was an increased incidence and severity of neuronal necrosis/degeneration in both the central and peripheral nervous systems of rats and dogs. In the neurotoxicity studies in rats, dose- related increases in the incidence of neuronal necrosis were observed in the brains after acute and subchronic exposure to EPTC. The DNT study revealed decreased brain weight in the rat pups, but not in the parent rats. In both of the combined chronic toxicity/oncogenicity studies in the rat and in the chronic (capsule) study in the dog, treatment-related neuromuscular lesions were observed. In all of these studies hindquarter weakness with corresponding histopathology findings of atrophy and degeneration of the skeletal muscle were observed. In the dog study, the lesions were described as Wallerian-type degeneration in the spinal cords and various peripheral nerves.

EPTC is also a reversible inhibitor of cholinesterase (ChE). Toxicology studies with EPTC did not show any consistent pattern of ChE inhibition between different species, length of treatment, or the type of ChE enzyme measured. In some studies brain ChE activity was inhibited without any effect on either plasma or erythrocyte ChE activities. In other studies, erythrocyte ChE was inhibited with no inhibition of either plasma or brain ChE. As a class of compounds, thiocarbamates do not produce consistent inhibition profiles of ChE. A study with rats measured the inhibition of ChE by cycloate, butylate, pebulate or vemolate at doses at or near the acute median lethal doses (MRID 43925901). While vemolate, pebulate and cycloate inhibited plasma, erythrocyte and brain ChE to varying degrees, butylate inhibited plasma ChE only, and EPTC inhibited only erythrocyte and brain ChE but not plasma ChE.

EPTC has moderate acute toxicity via the oral and dermal routes of exposure. It is slightly irritating to the eye; a weak skin sensitizer under the condition of the guinea pig maximum test; and highly toxic via the inhalation route.

EPTC is classified as "Not Likely to be Carcinogenic to Humans." This is supported by lack of a carcinogenic effect in long-term studies and no genetic component in reproduction and developmental studies. There is no concern for mutagenicity and clastogenicity based on a genotoxicity panel that included *in vivo* and *in vitro* assays.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

Based on the hazard and exposure data, and current OPP policies, the EPTC risk assessment team has recommended that the FQPA Safety Factor be reduced to 1X because there is an adequate toxicity database for EPTC and exposure data are unlikely to underestimate potential exposures. Although there is evidence of susceptibility noted in the rat developmental neurotoxicity study (decrease in absolute pup brain weights (4-6%) in male pups only on PND 63 at all dose levels), the risk assessment points of departure were established using the most sensitive and robust endpoint (cardiomyopathy). In addition, the decrease in absolute pup brain weight (4-6%) demonstrated a flat dose response, was only observed in one sex (males) at one time-point (PND 63) with no corresponding necrosis noted and no difference noted in the brain weight after perfusion. In addition,

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there is no evidence of susceptibility following *in utero* and/or postnatal exposure in the developmental toxicity studies in rats or rabbits, and in the 2-generation rat reproduction study. Therefore, there are no residual uncertainties concerning pre- and postnatal toxicity and no neurotoxicity concerns. The acute and chronic dietary (food and drinking water) exposure assessments are conservative. The dietary and residential assessments are based on reliable exposure and toxicity data and will likely not underestimate exposure/risk. Based on these data and conclusions, the FQPA Safety Factor can be reduced to 1X.

4.4.1 Completeness of the Toxicology Database

As mentioned in Section 4.1., the toxicology database is lacking an immunotoxicity study (OPPTS 870.7800) which is a new data requirement under 40 CFR Part 158.500 for registration of a pesticide (food and non-food uses). Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or sub-chronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity. Consequently, the immunotoxicity study is required to detect and more fully characterize the potential immunotoxic effects of EPTC.

EPA has evaluated the available toxicity data for EPTC and determined that an additional database uncertainty factor is not needed to account for potential immunotoxicity. The reasons follow:

- EPTC does not belong to a class of chemicals that would be expected to be immunosuppressive. Therefore, the Agency does not believe that conducting a functional immunotoxicity study will result in a lower POD than the currently used POD for the overall risk assessment, and therefore, a database uncertainty factor (UF_{DB}) is not needed to account for the lack of this study.
- Throughout the toxicity database there were no findings suggesting that the immune system is affected by EPTC exposure (including the absence of changes in spleen or thymus weights or blood cell counts).

However, an immunotoxicity study in rats and/or mice (OPPTS 870.7800) is required as part of the new 40 CFR §158 Guidelines and shall be a condition of registration.

The 21/28 day dermal study (OPPTS 870.3200) required under 40 CFR Part 158.500 for registration of a pesticide (food uses) has also not been fulfilled to date.

4.4.2 Evidence of Neurotoxicity

EPTC is a thiocarbamate herbicide used to control the growth of germinating annual weeds, especially grasses. EPTC as well as other thiocarbamates have toxic effects on the central and peripheral nervous systems. Neuronal necrosis/ degeneration were observed in both the central and peripheral nervous systems of both rats and dogs after acute and subchronic exposure. Treatment related neuromuscular lesions were also observed in chronic rat and dog studies. In all of these studies hindquarter weakness was noted, and at necropsy evaluation atrophy and degeneration of the skeletal muscle was observed. In the dog study, the lesions were described as Wallerain-type degeneration in the spinal cords and various peripheral nerves.

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4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Evidence of increased qualitative and quantitative susceptibility of the offspring was only observed in the recent developmental neurotoxicity rat study. Specifically, a marginal decrease in absolute (not relative) pup brain weight (4-6%) was observed in only one sex (male pups) and at only one time point (PND 63). Furthermore, this marginal effect, had no dose-response, was not seen after perfusion, and had no corresponding necrosis. Therefore this effect was considered marginal at best and not robust. Furthermore, neither the rat or rabbit developmental studies nor the rat reproduction studies identified any teratogenic effects.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. Since the dietary and non-dietary exposure estimates were based on several conservative assumptions, HED does not believe that the exposure estimates are underestimated.

The acute and chronic dietary assessments conducted with DEEM-FCID were refined analyses. The assessment utilized tolerance level residues for all crops. In addition, default processing factors were assumed for all commodities. One hundred percent crop treated was assumed for all commodities. The DEEM analysis also assumed that all drinking water will contain EPTC at the highest chronic estimated drinking water concentration (EDWC) levels modeled by EFED for ground water or surface water. For these reasons it can be concluded that the DEEM-FCID analysis does not underestimate risk from chronic exposure to EPTC.
Similarly, HED does not believe that the non-dietary occupational and residential exposure are underestimated because they are also based on conservative assumptions including maximum application rates, labeled PPE, and standard values for unit exposures, acreage treated/amount handled.

4.5 Toxicity Endpoint and Point of Departure Selections

The details for selecting toxicity endpoints and points of departure are presented in Appendix **B2**. An acute reference dose for the general population (including Females age 13-49 population subgroup) was established based on neuronal cell necrosis in the brain of male rats in an acute neurotoxicity study. The chronic reference dose, along with the intermediate- and short-term incidental oral and dermal endpoints were based on decreased body weight/ body weight gain and cardiomyopathy from the combined chronic/carcinogenicity and 2- generation reproduction studies in rats. This endpoint was selected after an evaluation of the totality of the data for EPTC integrating the observations of neurotoxic signs (*e.g.*, neuronal necrosis, decreases in brain weight, and ChE inhibition,) along with neuromuscular lesions and cardiomyopathy. Cardiotoxicity was observed in subchronic and long-term studies in adult animals, and, in general, the severity and incidence of the lesion increased with increasing dose of EPTC. Also following exposure to EPTC, there was an increased incidence and severity of neuronal necrosis/ degeneration in both the central and peripheral nervous systems of both rats and dogs. As for the slight decrease pup brain weights observed in the DNT, this effect was considered marginal at best and not robust. The Agency considers these observations to be part of a larger suite of effects reflecting alterations in the nervous

system. Furthermore, the cardiomyopathy endpoint chosen for the points of departure are protective of the NOAELs/LOAELs where neurotoxic signs were observed throughout the database, including the decrease absolute pup brain weight (males) noted in the developmental neurotoxicity rat study. Intermediate- and short-term inhalation endpoints were based on a subchronic inhalation rat study in which brain ChE inhibition was the most sensitive endpoint. Since a NOAEL for brain ChE was not established in the study, a benchmark dose analysis ($BMDL_{10}$) was conducted to determine a point of departure (PoD).

4.5.1 Dose-Response Assessment

Among the species tested, cardiomyopathy and neuronal cell necrosis were observed in studies of varying length of treatment. Cardiotoxicity was observed in subchronic and long-term studies in adult animals, and, in general, the severity and incidence of the lesion increased with increasing dose of EPTC. In 90-day feeding and inhalation studies and in two chronic feeding/ oncogenicity studies, all in rats, histopathological evaluation revealed myocardial degeneration. Myocardial degeneration was also observed in adult rats in two separate two- generation reproduction studies. In two chronic dog studies, degenerative changes in the cardiac muscle were observed when EPTC was administered in a capsule, but not when administered (at comparable doses) in the diet. In both of the dog studies, electrocardiograms were taken, but only one high-dose male in the capsule study had changes which were described as "potentially" treatment- related.

EPTC has toxic effects on the central and peripheral nervous systems. For example, there was an increased incidence and severity of neuronal necrosis/degeneration in both the central and peripheral nervous systems of both rats and dogs. In the acute and subchronic neurotoxicity studies in the rat a dose-related increase was observed in the incidence of neuronal necrosis in the brain. In the developmental neurotoxicity rat study, a marginal decrease in pup brain (absolute) weight (4-6%) was observed only in males at one time point (PND 63). This marginal decrease in absolute brain weight, however, had no dose response, was not observed after perfusion, and occurred without corresponding necrosis. In both of the combined chronic toxicity/oncogenicity rat studies and in the chronic (capsule) dog study, treatment-related neuromuscular lesions were observed. In all of these studies hindquarter weakness with corresponding histopathology findings of atrophy and degeneration of the skeletal muscle were observed.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

Exposures (dermal, oral and inhalation) can be combined if the toxicological effects are the same. Decreased body weight/ body weight gain and cardiomyopathy were the endpoint of concern for the chronic dietary, short-term/intermediate-term incidental oral and dermal scenarios for risk assessment; brain ChE inhibition, however, was the endpoint of concern for the intermediate- and short-term inhalation scenarios. Therefore, the inhalation route of exposure should not be combined with the other routes of exposure to estimate aggregate risk since a common endpoint was not observed.

4.5.3 Cancer Classification and Risk Assessment Recommendation

EPTC is classified as "Not likely to be Carcinogenic to Humans." This is based on the lack of carcinogenic potential noted in the available studies. There is no concern for mutagenicity and clastogenicity.

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4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1: Summary of Toxicological Doses and Endpoints for EPTC Residential and Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty Factors	RfD Level of Concern	Study and Toxicological Effects
Acute (all populations)	**Males** LOAEL= 200 mg/kg/day	UF_A = 10X UF_H = 10X UF_L = 10X FQPA = 1X	aRfD = 0.2 mg/kg/day aPAD = 0.2 mg/kg/day	**Acute Neurotoxicity study – Rats (MRID 46039701, 43297401)** NOAEL = not established in **males**; 200 mg/kg/day in **females**. LOAEL = 200 mg/kg/day **in males** based on neuronal cell necrosis in the brain. LOAEL = 1000 mg/kg/day **in females** based on clinical signs (lacrimation, salivation, hypoactivity, upward curvature of the spine) death, and neuronal cell necrosis in the brain.
Chronic (all populations)	NOAEL= 5 mg/kg/day	UF_A = 10X UF_H = 10X FQPA = 1X	cRfD = 0.05 mg/kg/day cPAD = 0.05 mg/kg/day	**Chronic/ Carcinogenicity and 2-Generation Reproduction – Rats (MRID 00145004, 00145311, 00161597)** **Chronic/ Carcinogenicity study** **NOAEL= 5 mg/kg/day** **LOAEL = 25 mg/kg/day** based on decreased body weight and increased incidences of myocardial and neuromuscular lesions. **2- Generation Reproduction study** **Parental NOAEL = 2.5 mg/kg/day Parental LOAEL = 10 mg/kg/day** based on decreased body weight/ body weight gain and cardiomyopathy. **Dev. NOAEL** = 10 mg/kg/day. **Dev. LOAEL** = 40mg/kg/day, based on decreased mean pup weight during lactation days 4 to 21. **Repro. NOAEL** = 40 mg/kg/day. **Repro. LOAEL** > 40 mg/kg/day.
Incidental Oral- Children (short- and intermediate-term)	NOAEL= 5 mg/kg/day	UF_A = 10X UF_H = 10X FQPA = 1X	MOE = 100	**Chronic/ Carcinogenicity and 2-Generation Reproduction – Rats (MRID 00145004, 00145311, 00161597)** **Chronic/ Carcinogenicity study** **NOAEL= 5 mg/kg/day** **LOAEL = 25 mg/kg/day** based on decreased body weight and increased incidences of myocardial and neuromuscular lesions. **2- Generation Reproduction study** **Parental NOAEL = 2.5 mg/kg/day Parental LOAEL = 10 mg/kg/day** based on decreased body weight/ body weight gain and cardiomyopathy. **Dev. NOAEL** = 10 mg/kg/day. **Dev. LOAEL** = 40mg/kg/day, based on decreased mean pup weight during lactation days 4 to 21. **Repro. NOAEL** = 40 mg/kg/day. **Repro. LOAEL** > 40 mg/kg/day.

Table 4.5.4.1: Summary of Toxicological Doses and Endpoints for EPTC Residential and Occupational Human Health Risk Assessments.

Dermal (short- and intermediate-term)	NOAEL= 5 mg/kg/day Dermal absorption factor = 5%.	UF_A = 10X UF_H = 10X FQPA = 1X	MOE = 100 adult	**Chronic/ Carcinogenicity and 2-Generation Reproduction – Rats (MRID 00145004, 00145311, 00161597)** **Chronic/ Carcinogenicity study** **NOAEL= 5 mg/kg/day** **LOAEL = 25 mg/kg/day** based on decreased body weight and increased incidences of myocardial and neuromuscular lesions. **2- Generation Reproduction study** **Parental NOAEL = 2.5 mg/kg/day Parental LOAEL = 10 mg/kg/day** based on decreased body weight/ body weight gain and cardiomyopathy. **Dev. NOAEL** = 10 mg/kg/day. **Dev. LOAEL** = 40mg/kg/day, based on decreased mean pup weight during lactation days 4 to 21. **Repro. NOAEL** = 40 mg/kg/day. **Repro. LOAEL** > 40 mg/kg/day.
Inhalation Acute	$BMDL_{10}$ = 1.90 mg/m^3 **Bystanders** HEC = 0.32 mg/kg; 1.22 mg/m^3 **Occupational** HEC= 0.95 mg/kg; 3.65 mg/m^3	UF_A = 3X UF_H = 10X FQPA = 1X	MOE = 30 Adult (female workers) MOE = 30 children	**90 day Inhalation toxicity study- Rat (MRID 00154784)** BMD_{10} = 3.75 mg/m^3 $BMDL_{10}$ = 1.90 mg/m^3 based on brain cholinesterase inhibition in males; decreased food consumption at the mid and high dose and increased prothrobin time in females at the mid and high dose.
Inhalation (short- and intermediate-term)	$BMDL_{10}$ = 1.90 mg/m^3 **Bystanders** HEC = 0.227 mg/kg; 0.87 mg/m^3 **Occupational** HEC= 0.68 mg/kg; 2.61 mg/m^3	UF_A = 3X UF_H = 10X FQPA = 1X	MOE = 30 Adult (female workers) MOE = 30 children	**90 day Inhalation toxicity study- Rat (MRID 00154784)** BMD_{10} = 3.75 mg/m^3 $BMDL_{10}$ = 1.90 mg/m^3 based on brain cholinesterase inhibition in males; decreased food at the mid and high dose and increased prothrobin time in females at the mid and high dose.
Cancer (oral , dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the lack of carcinogenic potential noted in the available studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key date (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable. HEC= human equivalent concentration.

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Table 4.5.4.2. BMD Modeling Results of Rat Brain Cholinesterase Data from EPTC Inhalation Study (MRID 00154784)

Sex/age	Time (weeks)	BMD Results (mg/m^3)	
		BMD_{10}	$BMDL_{10}$
Adult Male	9	no adequate fit	no adequate fit
Adult Male	13	3.75	1.90
Adult Female	9	181.6	81.2
Adult Female	13	25.5	10.5

The full BMD modeling analysis is reported in Appendix **B.5**.

4.6 Endocrine Disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA is issuing test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

EPTC is among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. The Agency will review the EDSP Tier 1 data and any "other scientifically relevant information" submitted in response to test orders. Based on this review the Agency will determine the need for additional testing. For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

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5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

Plant Metabolism Studies

The qualitative nature of EPTC residues in plants is adequately understood based on metabolism studies conducted in three dissimilar crops (corn, potatoes, and pinto beans). In plants, EPTC is metabolized to a variety of products via several different metabolic pathways discussed in Section 5.1.3 below. Tolerances for EPTC residues in or on plants represent the presence of EPTC and its hydroxylated metabolites (free or conjugated). The available data show that the ratio of residues of toxicological concern (i.e., sum of EPTC and hydroxylated metabolites) to EPTC (i.e., parent only) varies from 1.5:1 (potatoes) to 13.2:1 (bean vines).

Animal Metabolism Studies

The qualitative nature of EPTC in animals is adequately understood, based on feeding studies conducted in lactating goats and laying hens. Only a single EPTC residue of toxicological concern is found in goats (EPTC-cysteine conjugate) or hens (intact EPTC) fed highly exaggerated doses of EPTC and in either case the residue is formed only in low concentrations. Therefore, HED has concluded that residues of EPTC in animal commodities represent a Category 3 situation under 40 CFR §180.6(a) (i.e., situations in which it is not possible to establish with certainty whether finite residues will be incurred under reasonable worst-case exposure scenarios, but there is no reasonable expectation of the occurrence of finite residues in animal commodities). As a result, tolerances for residues of EPTC in animal commodities need not be established.

5.1.2 Summary of Environmental Degradation

The major dissipation processes for EPTC are volatilization, runoff, and leaching. Abiotic hydrolysis and photodegradation are not significant degradation pathways for EPTC. Volatilization of EPTC from soil and water and the metabolism of EPTC in soil appear to be the two most important dissipation pathways. Since the major degradation pathways of EPTC appear to be volatilization and metabolism, it may be more persistent in soil substrata with low microbial activity, or in ground water and deep surface water. The primary environmental (soil and water) transformation/degradation products are EPTC sulfoxide (ESO) and dipropylamine (a synonym is Di-n-propylamine).

The Henry's Law constant is greater than 2×10^{-5} m^3-atm/g-mol, suggesting that volatilization can be important in all waters (Thomas, 1981). EPTC must be incorporated into the soil via mechanical means or via irrigation to reduce losses from the soil through volatilization. The aerobic soil metabolism half-lives ($T_{1/2}$) ranged 36 to 75 days and the DT_{50} ranged from 10 to 37 days (USEPA, 1999). These half-lives include losses from volatilization (CO_2 from metabolism of EPTC and the

vaporization of EPTC). In aerobic soil studies neither dipropylamine nor EPTC sulfoxide appear to accumulate. The overall results of these mechanisms of dissipation appear to indicate that EPTC has low to moderate persistence in the environment. EPTC can be classified as having medium mobility (K_{oc} 136 to 264 mL/g-carbon) while EPTC sulfoxide is classified as having a high mobility (K_{oc} 13 to 67 mL/g-carbon).

5.1.3 Comparison of Metabolic Pathways

In plants, EPTC is metabolized to a variety of products via several different metabolic pathways. The major metabolic pathway of EPTC involves initial oxidation of the sulfur atom to a sulfoxide, which is oxidized further to a sulfone. The sulfone metabolite is then conjugated with glutathione via glutathione-S-transferase. The resultant glutathione conjugate is sequentially metabolized to cysteine-; N-malonyl cysteine-; S-lactic acid-; and O-malonyl-S-lactic acid- conjugates.

The second metabolic pathway of EPTC is hydroxylation of the alkyl substituents. Hydroxylation of EPTC occurs to a lesser extent than the pathway involving sulfoxide formation and glutathione conjugation. Hydroxylation takes place on each of the alkyl moieties of EPTC, yielding: N-(2-hydroxy) propyl-; N-(3-hydroxy)propyl-; and S-(2hydroxy) ethyl-metabolites. The C-OH moiety of the latter substance is oxidized further to S-carboxymethvl EPTC. The -OH moiety of the hydroxylated metabolites can become conjugated and foremother adducts. Hence, in plants, the hydroxylated metabolites may exist in their free or conjugated form.

The third metabolic pathway of EPTC is N-dealkylation to dipropylamine and propylamine. However, this pathway is considered minor with respect to the other two metabolic pathways mentioned in the preceding paragraphs.

5.1.4 Residues of Concern Summary and Rationale

The Agency previously concluded in the 1999 RED that the residues of concern for risk assessment purposes for EPTC include the parent and its hydroxylated metabolites (free or conjugated). Due to structural similarity, the parent and its hydroxylated metabolites are assumed to have comparable toxicity.

The available data show that the ratio of residues of toxicological concern (i.e., sum of EPTC and hydroxylated metabolites) to EPTC (i.e., parent only) varies from 1.5:1 (potatoes) to 13.2:1 (bean vines). Based on this data, HED used a conservative 15x to estimate the concentration of residues of concern when assessing the dietary risks posed by EPTC. This factor was selected to cover the high-end of the range of metabolite ratios.

5.2 Food Residue Profile

Processed Food and Feed

The Agency does not require residue data for any processed commodities associated with grass (seed crops). Therefore, data requirements for processed food and feed are not relevant to this tolerance petition.

Processing studies for the currently registered EPTC uses are also adequate. Studies were submitted for the magnitude of the residue in processed commodities for the following crops: corn, field; cottonseed (safflower, flaxseed); sugar beet; potatoes; sunflower; and, tomatoes. The data from these studies indicate that residues of EPTC and its hydroxylated metabolites do not concentrate in the processed fractions of these crops, except sugar beet molasses (4x concentration factor) and potato granules (1.4x).

Storage Stability

Freezer storage stability data are available which demonstrate that residues of EPTC *per se* are stable under frozen storage conditions for up to 3 years in/on alfalfa hay, almond nutmeats, and wheat grain and straw; up to 2 years in/on peppers, potatoes, and soybeans; up to 1 year in/on apples and oranges; and up to 4 months in/on com grain (D245000; S. DeVito; 09/25/1998); and up to 19 months in/on sugar beet tops (D301921; D. Wilbur; 01/23/2007). In addition, residues of R248722, R245255, and R248723 have been shown to be stable at -18° ± 5°C for 39 months in cornstarch, corn oil, and tomato pomace. Those residues were also stable at -20°±5°C for a duration of 36 months in corn grain, corn forage, corn fodder, tomatoes, alfalfa forage, and sugar beets and for 24 months in sunflower seeds (D287731; M. Sahafeyan; 04/24/2003).

Meat, Milk, Poultry, and Eggs

The Agency has determined that no animal feeding studies are needed to determine secondary transfer of EPTC residues of concern in milk, eggs, and edible tissues. Any EPTC residues of concern in animal commodities resulting from transfer of EPTC in the feedstuffs are expected to be non-detectable. This rationale is based upon the exaggerated dosing levels used in the animal metabolism studies compared to the maximum theoretical dietary burden of EPTC for ruminants and poultry, and the low levels of residues of toxicological concern present in animal commodities following the exaggerated dosing levels.

Rotational Crops

A confined rotational crop study performed by the Stauffer Chemical Company was submitted to the Agency in 1984. In its review of the study (January 11, 1985), EPA concluded that EPTC is unlikely to accumulate in crops grown from soils treated one-year earlier with EPTC, and that the study results meet EPA Guidelines Registering Pesticides Requirements (1983) (Sec. 165-1). This study does not meet current test guideline requirements (Confined Accumulation in Rotational Crops, OPPTS 860.1850, August 1996). However, no new rotational crop study needs to be

performed if crop rotation is limited to only those crops already listed on labels of registered products containing EPTC. If the registrant wishes to expand the list of crops that may be rotated after EPTC, a new confined rotational crop study must be conducted in accordance to current test guidelines.

Crop Field Trials

For the purposes of this petition, Gowan Company has submitted field trial data for EPTC in/on perennial ryegrass. A total of three field trials were conducted in NAFTA growing regions Zone 11 (1 trial, WA) and Zone 12 (2 trials, OR). One treated plot and one untreated control plot were established at each trial site. For each trial, one foliar broadcast application of Eptam® 7-E Selective Herbicide (an emulsifiable concentrate formulation of EPTC containing 87.8% EPTC) was made to ryegrass at an application rate of 6.12 lbs ai/A. The spray volume was 15-18 gallons per acre (140-168 L/ha). Surfactants were not used in the spray mixtures. Perennial ryegrass forage and hay raw agricultural commodity (RAC) samples were cut 30±1 days after application. Forage samples were collected immediately; hay samples were allowed to dry in the field for 6-8 days or placed into forced air forage dryers to reduce the moisture content to 10-20%.

The submitted residue data for grasses are adequate. The residue data for grasses were entered into the Agency's tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP to determine appropriate tolerance levels. The tolerance spreadsheet recommends a tolerance of 0.50 ppm (instead of the proposed 0.2 ppm) for residues in/on grass forage and 0.35 ppm (instead of the proposed 0.1ppm) in/on grass hay. Thus, HED recommends a tolerance of 0.50 ppm in/on grass forage and 0.35 ppm in/on grass hay for residues of EPTC and its hydroxyl metabolites (N-2-hydroxypropyl EPTC, N-3-hydroxypropyl EPTC, and 2-hydroxyethyl EPTC) based on the residue data from grass (seed crop). **Note:** These tolerance level recommendations are higher than the levels proposed by the petitioner.

Table 5.2: Summary of Residue Data from Crop Field Trials with EPTC – Grass grown for Seed

Commodity	Total Application Rate (lb a.i./A) [kg a.i./ha]	PHI (days)	Residue Levels[1] (ppm)						
			n	Min.	Max.	HAFT[2]	Median	Mean	Std. Dev.
EPTC									
Ryegrass - Forage	6.11-6.33 [6.85-7.09]	29-30	6	<0.050	<0.050	<0.050	<0.050	<0.050	NA
Ryegrass - Hay			6	<0.050	<0.050	<0.050	<0.050	<0.050	NA
N-2-hydroxypropyl EPTC									
Ryegrass - Forage	6.11-6.33 [6.85-7.09]	29-30	6	0.016	0.073	0.061	0.039	0.040	0.021
Ryegrass - Hay			6	<0.010	0.059	0.046	0.034	0.034	0.020
N-3-hydroxypropyl EPTC									
Ryegrass - Forage	6.11-6.33 [6.85-7.09]	29-30	6	<0.010	0.039	0.035	0.013	0.019	0.013
Ryegrass - Hay			6	<0.010	0.016	0.013	0.010	0.011	0.002
2-hydroxyethyl EPTC									
Ryegrass - Forage	6.11-6.33 [6.85-7.09]	29-30	6	<0.010	0.012	0.011	0.010	0.011	0.001
Ryegrass - Hay			6	<0.010	<0.010	<0.010	<0.010	<0.010	NA
Total Residue									
Ryegrass - Forage	6.11-6.33 [6.85-7.09]	29-30	6	0.086	0.290	0.231	0.180	0.175	0.077
Ryegrass - Hay			6	0.080	0.224	0.170	0.148	0.152	0.053

[1] For calculations of median, mean, and standard deviation, the LLMV was used for any results reported as <LLMV
[2] HAFT = highest-average field trial.

Residue data from crop field trials for the currently registered EPTC uses are also adequate. These studies depict combined residues of EPTC and its three hydroxylated metabolites. Residues of EPTC and its three hydroxylated metabolites were nondetectable (<0.05 ppm) in the majority of samples of raw and processed commodities from the submitted field trials.

5.3 Water Residue Profile

The most recent drinking water assessment for EPTC was prepared by the Environmental Fate and Effects Division (EFED) in 2010 (D371028; J. Wolf; 6/9/10). The application rates for the proposed grass grown for seed use range from 1.75 to 3.5 lbs a.i./A for pre-emergent use and from 3.0625 to 4.375 lbs a.i./A for post-emergent use. The proposed seasonal maximum application rate for the grasses grown for seed use is 4.375 lbs a.i./A/season. The proposed application rates for grasses grown for seed are lower than the maximum application rate assessed in a 2008 EFED drinking water memo D339490; J. Wolf; 1/10/08). This assessment included maximum rates ranging from 3.1 lbs a.i./A on sunflower to 7.9 lbs a.i./A on potatoes, with a seasonal maximum of 6.2 and 12.2 lbs a.i./A for sunflowers and potatoes, respectively.

(EDWCs) should be determined for EPTC, EPTC sulfoxide, and EPTC sulfone. The EPTC transformation product, EPTC sulfoxide (ESO) was not detected in several environmental fate studies submitted by the registrant and is not expected to form at significant levels in the environment. However, EPTC may also be transformed (via oxidation) to EPTC sulfoxide and EPTC sulfone during water disinfection. Therefore, as a first approximation of potential degradation product concentrations, it is assumed that 100% conversion of EPTC to the EPTC sulfoxide and EPTC sulfone. Concentrations of EPTC sulfoxide and EPTC sulfone were estimated from the EPTC concentration using molecular weight ratios of 1.084 (205.31/189.32) for EPTC sulfoxide and 1.169 (221.31/189.32) for EPTC sulfone. It is important to recognize that since EPTC sulfoxide is a precursor to EPTC sulfone, the EDWCs need to be considered separately and not cumulatively.

The EDWCs were estimated with the current version of exposure models (PRZM, EXAMS, and SCI-GROW). Table 5.3.1.1 below lists the EDWCs for EPTC from the proposed use of grasses grown for seed (reflecting the proposed use area of Idaho, Oregon, and Washington).

Table 5.3.1.1: EDWCs for EPTC/EPTC Sulfoxide/EPTC Sulfone from the Maximum Application Rate for the Proposed Use on Grasses Grown for Seed

Surface Water			
Exposure Endpoint	**EPTC[1]**	**EPTC sulfoxide[2]**	**EPTC sulfone[3]**
Peak (µg/L)	126.05	136.64	147.35
Chronic (µg/L)	8.13	8.81	9.50
30 year average (µg/L)	4.38	4.75	5.12
Ground Water			
Acute/chronic	1.02	4.35[2,4]	4.69[3,4]

[1] For surface water: one application at 4.375 lb a.i./A using PRZM/EXAMS

[2] EPTC concentration x 1.084 = ESO concentration

[3] EPTC concentration x 1.169 = EPTC sulfone concentration

[4] For ground water: one application at 4.375 lb a.i./A using SCI-GROW, Koc for ESO

The EDWCs from the 2008 drinking water assessment are listed in Table 5.3.1.2 below (D339490; J. Wolf; 1/10/08). Because the EDWCs are higher for the currently registered uses of EPTC, EFED recommends that the EDWCs from the previous assessment be used in this assessment.

Table 5.3.1.2: Tier II EDWCs (adjusted by PCA)) for EPTC/EPTC sulfoxide (ESO)

Scenario	Analyte	1-in-10 year EDWC		
		Peak	Annual	Overall
		µg/L		
Fallow/Idle				
IL Corn	EPTC	133.6	10.3	5.5
	ESO	148.1	10.1	4.6
MS Corn	EPTC	258.6	17.8	9.7
	ESO	243.3	15.6	8.2
MS Cotton	EPTC	259.4	19.6	9.1
	ESO	286.1	18.4	7.5
OR Sweet Corn	EPTC	81.2	6.9	3.4
	ESO	114.8	9.8	4.2
MS Soybean	EPTC	179.2	16.7	7.0
	ESO	199.9	16.1	5.8
Potatoes				
ID Potato	EPTC	28.3	4.0	3.1
	ESO	28.6	3.4	2.5
ME Potato	EPTC	113.7	12.5	7.2
	ESO	160.2	12.7	6.3
Sunflowers				
KS Sorghum	EPTC	112.3	9.5	6.6
	ESO	100.7	8.3	5.1
ND Wheat	EPTC	64.7	6.9	3.8
	ESO	68.8	6.9	3.8

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

HED previously concluded in the 1999 RED that the residues of concern for risk assessment purposes for EPTC include the parent and its hydroxylated metabolites (free or conjugated). Due to structural similarity, the parent and its hydroxylated metabolites are assumed to have comparable toxicity. HED has concluded that for purposes of assessing the risks posed by EPTC, the concentration of any marker compound residues will be multiplied by 15 to estimate the concentration of residues of concern.

DEEM-FCID™ Version 7.81 default processing factors were assumed for the requested crop use and all existing crop use with the exception of sugar beet molasses (4x concentration factor) and potato granules (1.4x). The residue file created using the DEEM [tm] software for these dietary exposure analyses reflects these processing factors. The highest EDWCs for EPTC resulted from the MS corn and MS cotton scenarios.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The EPTC acute and chronic dietary risk assessments used the most recent Screening Level Usage Analysis (SLUA), dated 17-November-2010.

5.4.3 Acute Dietary Risk Assessment

A highly refined acute dietary risk analysis was conducted with the DEEM-FCID™ model to form an evaluation of acute dietary exposure for EPTC. The analysis incorporated field trial data, processing factors where available, percent of crop treated, and surface water distributions. The surface water distributions were included to attempt to refine the EDWCs because drinking water is a risk driver for EPTC. A number of scenarios (e.g., food + water) were evaluated to give risk managers a better picture of the EPTC acute dietary risks. Specific details for the evaluated scenarios are discussed below. An overview summarizing the results of the acute dietary assessments with the population subgroup having the highest exposure noted in bold is presented in Table 5.4.6.1.

Acute dietary exposure estimates from food and drinking water do not exceed HED's level of concern (>100% aPAD) at the 99.9th percentile of exposure for all population subgroups. The Mississippi corn water scenario represents a location that generally has greater rainfall which drives off-site transport and this resulted in the highest EPTC EDWC. Dietary exposure to EPTC using the MS corn application at the 99.9th percentile from food and drinking water is 5.69% of the aPAD for the U.S. population and 19.69% of the aPAD for all infants (<1 year old), the most highly exposed population subgroup.

5.4.4 Chronic Dietary Risk Assessment

A refined analysis was performed with the DEEM-FCID™ model for the chronic dietary exposure assessment. The analysis incorporated tolerance level residue values for commodities on which EPTC is used including the appropriate processing data when available or default processing factors to form a conservative evaluation. Percent of crop treated data were also used based on the most current screening level usage analysis.

The results of this analysis indicate that all chronic analyses yielded risk estimates below 100% of the cPAD threshold level of concern for each population subgroup. For food and drinking water, the chronic aggregate dietary risk was calculated at 2.2% of the cPAD for the general U.S. population. Chronic aggregate dietary risk occupied 4.7% of the cPAD for the subgroups with the highest calculated exposure, all infants <1 year old and children 1-2 years old. An overview summarizing the results of the chronic dietary assessments with the population subgroup having the highest exposure noted in bold is presented in Table 5.4.6.2.

5.4.5 Cancer Dietary Risk Assessment

EPTC is classified as "Not Likely to be Carcinogenic to Humans", therefore, a cancer dietary exposure assessment was not conducted.

5.4.6 Dietary Summary Tables

Table 5.4.6.1: Results of Acute Dietary Exposure and Risk Estimates for EPTC (99.9th Percentile of Exposure)

Population Subgroup	DEEM-FCID™ (food and water)	
	Exposure (mg/kg/day)	% aPAD*
U.S. Population	0.011385	5.7
All infants (< 1 yr)	**0.039390**	**19**
Children 1-2 yrs	0.017340	8.7
Children 3-5 yrs	0.015564	7.8
Children 6-12 yrs	0.010806	5.4
Youth 13-19 yrs	0.008775	4.4
Adults 20-49 yrs	0.010291	5.2
Adults 50+ yrs	0.009608	4.8
Females 13-49 yrs	0.010313	5.2

* % PADs are reported to 2 significant figures.
aPAD = 0.20 mg/kg/day
The values for the highest population for each type of risk assessment are in **bold** text.

Table 5.4.6.2: Results of Chronic Dietary Exposure and Risk Estimates for EPTC

Population Subgroup	DEEM-FCID™ (food and water)	
	Exposure (mg/kg/day)	%cPAD*
U.S. Population	0.001115	2.2
All infants (< 1 yr)	**0.002337**	**4.7**
Children 1-2 yrs	**0.002348**	**4.7**
Children 3-5 yrs	0.002031	4.1
Children 6-12 yrs	0.001373	2.7
Youth 13-19 yrs	0.000970	1.9
Adults 20-49 yrs	0.000949	1.9
Adults 50+ yrs	0.000968	1.9
Females 13-49 yrs	0.000919	1.8

* % PADs are reported to 2 significant figures.
CPAD = 0.050 mg/kg/day
The values for the highest population for each type of risk assessment are in **bold** text.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are currently no registered residential uses associated with EPTC as all of these uses have been voluntarily cancelled; therefore, a residential/non-occupational exposure assessment is not required. However, HED has performed an inhalation bystander exposure and risk assessment for EPTC which is presented below in Section 6.1.

6.1 Residential Bystander Postapplication Inhalation Exposure

Recently, the Agency has begun exploring the development of an approach for assessing inhalation exposure resulting from the field volatilization of conventional pesticides. The Agency has sought expert advice and input on these issues from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel in December 2009. More information on pesticide volatilization can be found on the Agency's website at http://www.epa.gov/opp00001/about/intheworks/volatilization.htm.

The Agency has developed a preliminary bystander volatilization inhalation exposure assessment for EPTC utilizing the currently available inhalation toxicity and air monitoring data. There are two available EPTC air monitoring studies. These include:

- One application site study conducted in Merced County, CA by the California Air Resource Board (CARB), and
- Two ambient air studies
    - one conducted in Lompoc, CA by the California Department of Pesticide Regulation (CDPR); and
    - one conducted in Imperial County, CA by CARB

Application site air monitoring refers to the collection of air samples around the edges of a treated field during and after a pesticide application. Samples are generally collected for short intervals (e.g., < 8 hours), for at least the first day or two after application with subsequent samples increasing in duration. In comparison, ambient air monitoring is typically focused on characterizing the airborne pesticide levels within a localized airshed or community structure of some definition (e.g., city, township, or municipality). Samples are generally taken for 24 consecutive hours and collected at the same site over an extended period of time (e.g., several weeks or months). In contrast to application site air monitoring, information on the precise timing and location of pesticide applications are rarely collected in ambient air monitoring studies. However, this does not mean that an application did not occur near an ambient sampler during the monitoring period

The EPTC bystander volatilization inhalation exposure assessment compares the maximum air concentration detected in each of the monitoring studies to the acute HEC for residential bystanders. This comparison was done to represent a potential resident who lives next to a treated field and may be exposed to the peak concentration of EPTC volatilizing off the field over a 24-hour period. In addition, the arithmetic mean EPTC air concentration from each study was compared to the short-/intermediate-term HEC for residential bystanders. This comparison was done to represent a potential seasonal exposure. Table 5.1 provides EPTC volatilization MOE calculations for each site. None of the ambient air concentrations results in acute or short-/intermediate-term risk estimates of concern (MOEs > 30 for adults and for children). Some of the application site air concentrations

result in acute and/or short-/intermediate-term risk estimates of concern (MOEs < 30 for adults and for children); however, this preliminary bystander inhalation assessment should be considered in context with the data limitations and considerations discussed below.

Table 6.1: EPTC Residential Bystander Postapplication Inhalation Exposures and Risks For EPTC

Study	Year of Study	Sampler/Site Location	Number of samples	Duration of samples	Duration of sampling period	Maximum Air Concentration (ng/m^3)	Arithmetic Mean Air Concentration (ng/m^3)	Acute MOEs[a]	Short-term MOEs[b]
Application Site Data									
Merced County (CARB)	1997	East	Each site included 7 samples (including background sample)	Ranged from 1-hour to 24-hour samples; taken pre-application up to 3 days post-application	3 days	11,442	4,389	11	20
		North				2,476	728	49	130
		South				11,650	4,098	10	21
		West				8,404	1,642	14	53
Ambient Air Data									
Lompoc, CA (CalDPR)[c]	2000	Northwest	40	24-hour	2 months	1.23	0.35	99,000	250,000
		West	40			3.6	0.41	34,000	210,000
		Southwest	40			4.6	0.57	26,000	150,000
		Central	40			6.5	0.42	19,000	210,000
Imperial County, CA (CARB)	1997	Meadows Union School	24	24-hour	1.5 months	242	75	500	1,200
		Agricultural Commissioner's Office	24			120	17	1,000	5,100
		Imperial High School	24			110	34	1,100	2,600
		ARB Ambient Monitoring Station	24			53	24	2,300	3,600
		Imperial County Fire Department	24			204	53	590	1,600

a. Acute MOE = Acute HEC (121,000 ng/m^3) / Study maximum air concentration (ng/m^3). LOC = 30 for adults and for children

b. Short-term MOE = Short-term HEC (87,000 ng/m^3) / Study arithmethic mean air concentration (ng/m^3). LOC = 300 for adults and for children

c. 4 samples reported quantifiable air concentrations, 4 samples reported trace air concentrations, and all other samples were reported as non-detects. For non-detects, assumed 1/2 Method Detection Limit (MDL) of 0.61 ng/m^3. For trace concentrations, assumed concentration halfway between MDL and Estimated Quantitation Limit (1.23 ng/m^3).

Some of the limitations and considerations that have been identified that should be considered in the interpretation of these results include:

- The application site study from Merced County, CA appears to have been performed at a typical application rate (5.74 lb ai/A) and using typical application equipment (groundboom

with immediate soil incorporation). The study did not collect the soil parameters (e.g., soil moisture, organic matter, soil temperature, etc.) of the treated field and these parameters can have a significant impact on the volatilization of pesticides from treated soils (Smith and Dawson; D306857; 06/09/08). The study also did not collect enough air monitoring or meteorological data to be able to calculate EPTC flux rates that could be used in a probabilistic air model such as the Probabilistic Exposure and Risk Model for Fumigants (PERFUM). EPTC is highly volatile ($3.4x10^{-2}$ mmHg at 20 °C) and based on the available application site data, appears to volatilize significantly off the field in the first day or two after application. Based on this volatilization pattern, an EPTC field flux study that allows for estimation of EPTC flux rates from a treated field would provide significant refinement of the bystander inhalation risk assessment.

- Acute MOEs were estimated using a toxicological endpoint selected from a 90-day inhalation rat inhalation toxicity study. This should be considered a very conservative use of this data. The effects observed in this study varied from portal of entry effects (nasal histopathology) to cholinesterase inhibition and increased incidence of cardiomyopathy. However, it is currently unknown if any of these effects would occur following a single, acute exposure. Based on the volatilization pattern of EPTC and the fact that EPTC is a category II acute inhalation toxicant, an acute inhalation study that examines for portal of entry and systemic effects would provide significant refinement of this acute bystander inhalation assessment.

- Most of the data utilized in this preliminary assessment are 24-hour air samples. When this data is used, an assumption is made that an individual is exposed to the same air concentration for 24-hours every day. However, this is not always the case as real world time-activity data indicate that many parts of the population move from site to site on a daily basis (e.g., go to work and back).

- This assessment is only representative of outdoor concentrations (i.e., the exposure and risk estimates assume an individual is outdoors and standing near the field the whole time). It does not take into account potential effects of air conditioning systems and similar air filtration systems which could potentially reduce air concentrations of EPTC indoors. The Agency believes that indoor concentrations will be at worst equivalent to outdoor concentrations and may potentially be lower.

- All of the data used for this analysis have been generated in California; however, EPTC is used in many regions throughout the country. Therefore, the results based on the limited available air monitoring data were used to represent the rest of the country due to a lack of adequate information for any other region. It is unclear what potential impacts this extrapolation might have on the risk assessment. Factors such as meteorology and cultural practices may impact the overall amounts of EPTC that volatilize from a treated field as well as the rate at which it volatilizes.

- As part of the December 2009 SAP, the Agency presented their analysis of several models that could be used as screening tools to predict the air concentration and volatilization flux based on intrinsic properties and transport behaviors of pesticides. These models would allow the Agency to better represent the potential volatilization of semi-volatile pesticides

across various regions of the country and thus would provide refinement to this assessment over using straight air monitoring data. The SAP provided a number of comments regarding the Agency's model analysis, including the recommendation to evaluate some additional models. The Agency is currently in the process of evaluating the SAP's comments. As appropriate, the Agency will revise the modeling approach presented to the SAP for determining the rate of volatilization (flux) for semi-volatile pesticides and for estimating air concentrations of applied pesticides in the atmosphere under varying environmental conditions. After any policies or procedures are put into place, the Agency may revisit the EPTC residential bystander exposure and risk assessment.

- At this point in time, HED is not including the residential bystander estimated exposure in the EPTC human health risk assessment aggregate due to the data limitations and conservative assumptions surrounding this preliminary assessment.

6.2 Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial applications, but, to a lesser extent, could also be a potential source of exposure from ground applications; both of which are employed for applying EPTC. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices, and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast, and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

7.0 Aggregate Exposure/Risk Characterization

Aggregate risk assessments evaluate the combined risk from dietary exposure (food and water) and any non-occupational (residential) uses. However, there are currently no registered residential uses for EPTC; therefore the ETPC aggregate risk assessment includes only dietary exposure (food and water). Sections 5.4.3 and 5.4.4 discuss the acute and chronic dietary (food and water) exposure assessments.

8.0 Cumulative Exposure/Risk Characterization

The Food Quality Protection Act (FQPA) requires the Agency to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. The Agency determined that there was insufficient evidence to suggest EPTC shares a common mechanism of toxicity with other chemical substances (thiocarbamates). At a September 2001 meeting, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) supported the Agency's determination

(Common Mechanism of Action of Thiocarbamates and Dithiocarbamates, the FIFRA SAP meeting, September 7, 2001).

9.0 Occupational Exposure/Risk Characterization

9.1 Short- and Intermediate-Term Handler Risk

EPTC liquid formulations may be applied using aerial, chemigation, and ground equipment. EPTC granular formulations may be applied using aerial and ground equipment. The application methods, maximum application rates, and use sites are summarized in Table 9.1.1. There is potential for exposure to EPTC during mixing, loading, and applying activities. Handler exposure is expected to be short- or intermediate-term based on information provided on the proposed label.

The quantitative exposure and risk assessment developed for occupational handlers is based on the following exposure scenarios:

<u>Mixing/Loading</u>
1) emulsifiable concentrate (EC) formulations to support aerial application;
2) emulsifiable concentrate (EC) formulations to support chemigation application;
3) emulsifiable concentrate (EC) formulations to support groundboom application;
4) granular (G) formulations to support aerial application;
5) granular (G) formulations to support tractor drawn spreader application;

<u>Applying</u>
6) sprays with aerial equipment;
7) sprays with groundboom equipment;
8) granular with aerial equipment;
9) granular with tractor drawn spreader equipment;

<u>Flaggers</u>
10) flagging for aerial spray application; and
11) flagging for aerial granular application.

No chemical-specific handler exposure data were submitted in support of this regionally restricted, permanent registration. To assess handler exposures for regulatory actions when chemical-specific monitoring data are not available, HED relies on the most scientifically-reliable surrogate data currently available from various sources such as the Pesticide Handler Exposure Database (PHED), the Agricultural Handler Exposure Task Force (AHETF), and the Outdoor Residential Exposure Task Force (ORETF). Some of this data, such as the industry task force data, is compensatory, subject to the data protection provisions of FIFRA. HED policy on use of surrogate data is described in more detail on the Agency's website (http://www.epa.gov/pesticides/science/handler-exposure-data.html). Scenario-specific surrogate exposure data, including their sources, are presented in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (http://www.epa.gov/pesticides/science/handler-exposure-table.pdf).

Table 9.1.1: Use Pattern for EPTC			
Crop	**Treatment Type/Target of Application**	**Application Equipment**	**Maximum Application Rate (lb ai/A)**
EPTAM 7-E Selective Herbicide, EPA Reg. No. 10163-283, EC with 87.8% a.i.			
Potatoes	Soil-Directed Spray	Aerial, Chemigation, or Groundboom	7.91
Sweet Potatoes			7.42
Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground, Pine Seedling Nurseries			6.16
Grass Seed			4.375
Alfalfa, Birdsfoot, Trefoil, Clovers, Lespedeza, Beans (green or dry), Sunflower			3.92
Alfalfa,(established stands), Almonds, Ladino Clover (established stands), Safflower, Sugar Beets, Tomatoes, Walnuts			3.08
Cotton			1.96
Eptam 20-G Granules, EPA Reg. No. 10163-281, G with 20% a.i.			
Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground	Soil-Directed	Aerial or Tractor Drawn Spreader	6
Sugar beets, Sunflower			4
Alfalfa (established stands), Alfalfa, Birdsfoot, Trefoil, Clovers, Lespedeza, Beans (green or dry), Conifer Nursery Stock and Young Field Plantings, Corn, Potatoes (Irish), Safflower			3

To determine the short- and intermediate-term dermal risks, daily dermal exposures (assuming 5% absorption) were compared to the NOAEL of 5 mg/kg/day based on two rat studies (i.e., a Chronic/Carcinogenicity study and a 2-Generation Reproduction study). A target MOE of 100 is considered adequate for adults (10X for interspecies extrapolation and a 10X for intraspecies variability).

To determine the short- and intermediate-term inhalation risks, daily inhalation exposures (assuming 100% absorption) were compared to the occupational HEC of 0.68 mg/kg/day based on a 90-day inhalation toxicity study in rats. A target MOE of 30 is considered adequate for adults (3X interspecies extrapolation and a 10X for intraspecies variability).

Summaries of the dermal and inhalation risk estimates for occupational handlers are included in Tables 9.1.2 and 9.1.3, respectively. The short- and intermediate-term dermal risks for all handler scenarios do not exceed HED's level of concern (MOEs > 100) at some level of PPE. The short- and intermediate-term inhalation risks for all handler scenarios do not exceed HED's level of concern (MOEs > 30) at some level of PPE.

Table 9.1.2: Short- and Intermediate-Term Occupational Handler Dermal Doses and Risks for EPTC

Exposure Scenario	Crop or Target	Application Rate (lb ai/A) [a]	Area Treated Daily (Acres) [b]	Dermal Dose [c] (mg/kg/day)			Margin of Exposure [d] (Target MOE = 100)		
				PPE-G	PPE-G, DL	Eng Cont	PPE-G	PPE-G, DL	Eng Cont
Mixer/Loader									
Mixing/Loading Liquids for Aerial Applications (1)	Potatoes	7.91	350	0.074	0.058	0.017	67	150	290
	Sweet Potatoes	7.42	350	0.07	0.054	0.016	72	160	310
	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground, Pine Seedling Nurseries	6.16	350	0.058	0.045	0.013	86	190	380
	Grass Grown for Seed	4.375	350	0.041	0.032	0.0094	120	270	530
	Alfalfa, Birdsfoot Trefoil, Clovers, Lespedeza, Beans (Green or Dry), Sunflower	3.92	350	0.037	0.029	0.0084	140	300	590
	Alfalfa (Established stands), Almonds, Ladino Clover (established stands), Safflower, Sugar Beets, Tomatoes, Walnuts	3.08	350	0.029	0.022	0.0066	170	380	760
	Cotton	1.96	350	0.018	0.014	0.0042	270	600	1200
Mixing/Loading Liquids for Chemigation Applications (2)	Potatoes	7.91	350	0.074	0.058	0.017	67	150	290
	Sweet Potatoes	7.42	350	0.07	0.053	0.016	72	160	310
	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground, Pine Seedling Nurseries	6.16	350	0.058	0.045	0.013	86	190	380
	Grass Grown for Seed	4.375	350	0.041	0.032	0.0094	120	270	530
	Alfalfa, Birdsfoot Trefoil, Clovers, Lespedeza, Beans (Green or Dry), Sunflower	3.92	350	0.037	0.029	0.0084	140	300	590
	Alfalfa (Established stands), Almonds, Ladino Clover (established stands), Safflower, Sugar Beets, Tomatoes, Walnuts	3.08	350	0.029	0.022	0.0066	170	380	760
	Cotton	1.96	350	0.018	0.014	0.0042	270	600	1200

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Table 9.1.2: Short- and Intermediate-Term Occupational Handler Dermal Doses and Risks for EPTC

Exposure Scenario	Crop or Target	Application Rate (lb ai/A) [a]	Area Treated Daily (Acres) [b]	Dermal Dose [c] (mg/kg/day)			Margin of Exposure [d] (Target MOE = 100)		
				PPE-G	PPE-G, DL	Eng Cont	PPE-G	PPE-G, DL	Eng Cont
Mixing/Loading Liquids for Groundboom Applications (3)	Potatoes	7.91	80	0.017	0.013	0.0039	290	650	1300
	Sweet Potatoes	7.42	80	0.016	0.012	0.0036	310	690	1400
	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground, Pine Seedling Nurseries	6.16	80	0.013	0.010	0.003	380	840	1700
	Grass Grown for Seed	4.375	80	0.0094	0.0073	0.0022	530	1200	2300
	Alfalfa, Birdsfoot Trefoil, Clovers; Lespedeza, Beans (Green or Dry), Sunflower	3.92	80	0.0084	0.0065	0.0019	590	1300	2600
	Alfalfa (Established stands), Almonds, Ladino Clover (established stands), Safflower, Sugar Beets, Tomatoes, Walnuts	3.08	80	0.0066	0.0051	0.0015	760	1700	3300
	Cotton	1.96	80	0.0042	0.0033	0.00096	1200	2600	5200
Loading Granulars for Aerial Applications (4)	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground	6	350	0.01	0.0051	0.00026	480	980	20000
	Sugar Beets, sunflower	4	350	0.0069	0.0034	0.00017	720	1500	29000
	Alfalfa (established stands), Alfalfa, Birdsfoot, Trefoil, Clovers, Lespedeza, Beans (green or dry), Conifer Nursery Stock and Young Field Plantings, Corn, Potatoes (Irish), Safflower	3	350	0.0052	0.0026	0.00013	970	2000	39000
Loading Granulars for Tractor Drawn Spreader Applications (5)	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground	6	80	0.0024	0.0012	0.000058	2100	4300	86000
	Sugar Beets, sunflower	4	80	0.0016	0.00078	0.000039	3200	6400	130000
	Alfalfa (established stands), Alfalfa, Birdsfoot, Trefoil, Clovers, Lespedeza, Beans (green or dry), Conifer Nursery Stock and Young Field Plantings, Corn, Potatoes (Irish), Safflower	3	80	0.0012	0.00058	0.000029	4200	8600	170000

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Table 9.1.2: Short- and Intermediate-Term Occupational Handler Dermal Doses and Risks for EPTC

Exposure Scenario	Crop or Target	Application Rate (lb ai/A) [a]	Area Treated Daily (Acres) [b]	Dermal Dose [c] (mg/kg/day)			Margin of Exposure [d] (Target MOE = 100)		
				PPE-G	PPE-G, DL	Eng Cont	PPE-G	PPE-G, DL	Eng Cont
Applicator									
Applying Sprays via Aerial Equipment (6)	Potatoes	7.91	350	N/A	N/A	0.0099	N/A	N/A	510
	Sweet Potatoes	7.42	350	N/A	N/A	0.0093	N/A	N/A	540
	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground, Pine Seedling Nurseries	6.16	350	N/A	N/A	0.0077	N/A	N/A	650
	Grass Grown for Seed	4.375	350	N/A	N/A	0.0055	N/A	N/A	910
	Alfalfa, Birdsfoot Trefoil, Clovers, Lespedeza, Beans (Green or Dry), Sunflower	3.92	350	N/A	N/A	0.0049	N/A	N/A	1000
	Alfalfa (Established stands), Almonds, Ladino Clover (established stands), Safflower, Sugar Beets, Tomatoes, Walnuts	3.08	350	N/A	N/A	0.0039	N/A	N/A	1300
	Cotton	1.96	350	N/A	N/A	0.0025	N/A	N/A	2000
Applying Sprays via Groundboom Equipment (7)	Potatoes	7.91	80	0.0073	0.0057	0.0023	690	880	2200
	Sweet Potatoes	7.42	80	0.0068	0.0053	0.0021	730	940	2300
	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground, Pine Seedling Nurseries	6.16	80	0.0057	0.0044	0.0018	880	1100	2800
	Grass Grown for Seed	4.375	80	0.004	0.0032	0.0013	1200	1600	3900
	Alfalfa, Birdsfoot Trefoil, Clovers, Lespedeza, Beans (Green or Dry), Sunflower	3.92	80	0.0036	0.0028	0.0011	1400	1800	4400
	Alfalfa (Established stands), Almonds, Ladino Clover (established stands), Safflower, Sugar Beets, Tomatoes, Walnuts	3.08	80	0.0028	0.0022	0.00088	1800	2300	5600
	Cotton	1.96	80	0.0018	0.0014	0.00056	2800	3500	8800

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Table 9.1.2: Short- and Intermediate-Term Occupational Handler Dermal Doses and Risks for EPTC

Exposure Scenario	Crop or Target	Application Rate (lb ai/A) [a]	Area Treated Daily (Acres) [b]	Dermal Dose [c] (mg/kg/day)			Margin of Exposure [d] (Target MOE = 100)		
				PPE-G	PPE-G, DL	Eng Cont	PPE-G	PPE-G, DL	Eng Cont
Applying Granulars via Aerial Equipment (8)	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground	6	350	N/A	N/A	0.0026	N/A	N/A	2000
	Sugar Beets, sunflower	4	350	N/A	N/A	0.0017	N/A	N/A	2900
	Alfalfa (established stands), Alfalfa, Birdsfoot, Trefoil, Clovers, Lespedeza, Beans (green or dry), Conifer Nursery Stock and Young Field Plantings, Corn, Potatoes (Irish), Safflower	3	350	N/A	N/A	0.0013	N/A	N/A	3900
Applying Granulars via Tractor Drawn Spreader (9)	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground	6	80	0.0025	0.0014	0.00072	2000	3500	6900
	Sugar Beets, sunflower	4	80	0.0016	0.00096	0.00048	3000	5200	10000
	Alfalfa (established stands), Alfalfa, Birdsfoot, Trefoil, Clovers, Lespedeza, Beans (green or dry), Conifer Nursery Stock and Young Field Plantings, Corn, Potatoes (Irish), Safflower	3	80	0.0012	0.00072	0.00036	4100	6900	14000
Flagger									
Flagging for Aerial Sprays Applications (10)	Potatoes	7.91	350	0.022 [e]	0.02	0.00044	230 [e]	250	11000
	Sweet Potatoes	7.42	350	0.02 [e]	0.019	0.00041	250 [e]	270	12000
	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground, Pine Seedling Nurseries	6.16	350	0.017 [e]	0.015	0.00034	300 [e]	320	15000
	Grass Grown for Seed	4.375	350	0.012 [e]	0.011	0.00024	420 [e]	460	21000
	Alfalfa, Birdsfoot Trefoil, Clovers, Lespedeza, Beans (Green or Dry), Sunflower	3.92	350	0.011 [e]	0.0098	0.00022	460 [e]	510	23000
	Alfalfa (Established stands), Almonds, Ladino Clover (established stands), Safflower, Sugar Beets, Tomatoes, Walnuts	3.08	350	0.0085 [e]	0.0077	0.00017	590 [e]	650	30000
	Cotton	1.96	350	0.0054 [e]	0.0049	0.00011	930 [e]	1000	46000

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Table 9.1.2: Short- and Intermediate-Term Occupational Handler Dermal Doses and Risks for EPTC

Exposure Scenario	Crop or Target	Application Rate (lb ai/A) [a]	Area Treated Daily (Acres) [b]	Dermal Dose [c] (mg/kg/day)			Margin of Exposure [d] (Target MOE = 100)		
				PPE-G	PPE-G, DL	Eng Cont	PPE-G	PPE-G, DL	Eng Cont
Flagging for Aerial Granular Applications (11)	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground	6	350	0.0042 [e]	0.0024	0.000084	1200 [e]	2100	60000
	Sugar Beets, sunflower	4	350	0.0028 [e]	0.0016	0.000056	1800 [e]	3100	89000
	Alfalfa (established stands), Alfalfa, Birdsfoot, Trefoil, Clovers, Lespedeza, Beans (green or dry), Conifer Nursery Stock and Young Field Plantings, Corn, Potatoes (Irish), Safflower	3	350	0.0021 [e]	0.0012	0.000042	2400 [e]	4200	120000

N/A = Not applicable

a Application Rates based on maximum use rates on EPTC labels.

b Exposure Science Advisory Council Policy No. 9.1.

c Short- and Intermediate-Term Dermal Dose (mg/kg/day) = daily unit exposure (mg/lb ai) x application rate (lb ai/acre) x acres treated / body weight (70 kg).

d Short- and Intermediate-Term Dermal MOE = NOAEL (mg/kg/day) / dermal daily dose (mg/kg/day). LOC = 100

e Dermal dose and MOEs represent use of baseline (no glove) data as glove data is not available.

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Table 9.1.3: Short- and Intermediate-Term Occupational Handler Inhalation Exposures and Risks for EPTC

Exposure Scenario	Crop or Target	Application Rate (lb ai/A) [a]	Area Treated Daily (Acres) [b]	Inhalation Dose [c] (mg/kg/day)				Margin of Exposure [d] (Target MOE = 30)			
				Baseline	Dust-Mist Respirator	Organic Vapor Respirator	Eng Cont	Baseline	Dust-Mist Respirator	Organic Vapor Respirator	Eng Cont
Mixer/Loader											
Mixing/Loading Liquids for Aerial Applications (1)	Potatoes	7.91	350	0.0087	0.0016	0.00079	0.0033	79	430	860	210
	Sweet Potatoes	7.42	350	0.0081	0.0015	0.00074	0.0031	84	460	920	220
	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground, Pine Seedling Nurseries	6.16	350	0.0067	0.0012	0.00062	0.0026	100	550	1100	270
	Grass Grown for Seed	4.375	350	0.0048	0.00088	0.00044	0.0018	140	780	1600	370
	Alfalfa, Birdsfoot Trefoil, Clovers, Lespedeza, Beans (Green or Dry), Sunflower	3.92	350	0.0043	0.00078	0.00039	0.0016	160	870	1700	420
	Alfalfa (Established stands), Almonds, Ladino Clover (established stands), Safflower, Sugar Beets, Tomatoes, Walnuts	3.08	350	0.0034	0.00062	0.00031	0.0013	200	1100	2200	530
	Cotton	1.96	350	0.0021	0.00039	0.0002	0.00081	320	1700	3500	840
Mixing/Loading Liquids for Chemigation Applications (2)	Potatoes	7.91	350	0.0087	0.0016	0.00079	0.0033	79	430	860	210
	Sweet Potatoes	7.42	350	0.0081	0.0015	0.00074	0.0031	84	460	920	220
	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground, Pine Seedling Nurseries	6.16	350	0.0067	0.0012	0.00062	0.0026	100	550	1100	270
	Grass Grown for Seed	4.375	350	0.0048	0.00088	0.00044	0.0018	140	780	1600	370
	Alfalfa, Birdsfoot Trefoil, Clovers, Lespedeza, Beans (Green or Dry), Sunflower	3.92	350	0.0043	0.00078	0.00039	0.0016	160	870	1700	420
	Alfalfa (Established stands), Almonds, Ladino Clover (established stands), Safflower, Sugar Beets, Tomatoes, Walnuts	3.08	350	0.0034	0.00062	0.00031	0.0013	200	1100	2200	530
	Cotton	1.96	350	0.0021	0.00039	0.0002	0.00081	320	1700	3500	840

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Table 9.1.3: Short- and Intermediate-Term Occupational Handler Inhalation Exposures and Risks for EPTC

Exposure Scenario	Crop or Target	Application Rate (lb ai/A) [a]	Area Treated Daily (Acres) [b]	Inhalation Dose [c] (mg/kg/day)				Margin of Exposure [d] (Target MOE = 30)			
				Baseline	Dust-Mist Respirator	Organic Vapor Respirator	Eng Cont	Baseline	Dust-Mist Respirator	Organic Vapor Respirator	Eng Cont
Mixing/Loading Liquids for Groundboom Applications (3)	Potatoes	7.91	80	0.002	0.00036	0.00018	0.00075	340	1900	3800	910
	Sweet Potatoes	7.42	80	0.0019	0.00034	0.00017	0.0007	370	2000	4000	970
	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground, Pine Seedling Nurseries	6.16	80	0.0015	0.00028	0.00014	0.00058	440	2400	4800	1200
	Grass Grown for Seed	4.375	80	0.0011	0.0002	0.001	0.00042	620	3400	6800	1600
	Alfalfa, Birdsfoot Trefoil, Clovers, Lespedeza, Beans (Green or Dry), Sunflower	3.92	80	0.00098	0.00018	0.00009	0.00037	690	3800	7600	1800
	Alfalfa (Established stands), Almonds, Ladino Clover (established stands), Safflower, Sugar Beets, Tomatoes, Walnuts	3.08	80	0.00077	0.00014	0.00007	0.00029	880	4800	9700	2300
	Cotton	1.96	80	0.00049	0.00009	0.000015	0.00019	1400	7600	15000	3700
Loading Granulars for Aerial Applications (4)	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground	6	350	0.051	0.01	0.0051	0.001	13	67	130	670
	Sugar Beets, sunflower	4	350	0.034	0.0068	0.0034	0.00068	20	100	200	1000
	Alfalfa (established stands), Alfalfa, Birdsfoot, Trefoil, Clovers, Lespedeza, Beans (green or dry), Conifer Nursery Stock and Young Field Plantings, Corn, Potatoes (Irish), Safflower	3	350	0.026	0.0051	0.0026	0.00051	27	130	270	1300
Loading Granulars for Tractor Drawn Spreader Applications (5)	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground	6	80	0.012	0.0023	0.0012	0.00023	58	290	580	2900
	Sugar Beets, sunflower	4	80	0.0078	0.0016	0.00078	0.00016	88	440	880	4400
	Alfalfa (established stands), Alfalfa, Birdsfoot, Trefoil, Clovers, Lespedeza, Beans (green or dry), Conifer Nursery Stock and Young Field Plantings, Corn, Potatoes (Irish), Safflower	3	80	0.0058	0.0012	0.00058	0.00012	120	580	1200	5800

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Table 9.1.3: Short- and Intermediate-Term Occupational Handler Inhalation Exposures and Risks for EPTC

Exposure Scenario	Crop or Target	Application Rate (lb ai/A) [a]	Area Treated Daily (Acres) [b]	Inhalation Dose [c] (mg/kg/day)				Margin of Exposure [d] (Target MOE = 30)			
				Baseline	Dust-Mist Respirator	Organic Vapor Respirator	Eng Cont	Baseline	Dust-Mist Respirator	Organic Vapor Respirator	Eng Cont
Applicator											
Applying Sprays via Aerial Equipment (6)	Potatoes	7.91	350	N/A	N/A	N/A	0.0027	N/A	N/A	N/A	250
	Sweet Potatoes	7.42	350	N/A	N/A	N/A	0.0025	N/A	N/A	N/A	270
	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground, Pine Seedling Nurseries	6.16	350	N/A	N/A	N/A	0.0021	N/A	N/A	N/A	320
	Grass Grown for Seed	4.375	350	N/A	N/A	N/A	0.0015	N/A	N/A	N/A	460
	Alfalfa, Birdsfoot Trefoil, Clovers, Lespedeza, Beans (Green or Dry), Sunflower	3.92	350	N/A	N/A	N/A	0.0013	N/A	N/A	N/A	510
	Alfalfa (Established stands), Almonds, Ladino Clover (established stands), Safflower, Sugar Beets, Tomatoes, Walnuts	3.08	350	N/A	N/A	N/A	0.001	N/A	N/A	N/A	650
	Cotton	1.96	350	N/A	N/A	N/A	0.00067	N/A	N/A	N/A	1000
Applying Sprays via Groundboom Equipment (7)	Potatoes	7.91	80	0.0031	0.00063	0.00027	0.00039	220	1100	2500	1700
	Sweet Potatoes	7.42	80	0.0029	0.00059	0.00025	0.00036	240	1100	2700	1900
	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground, Pine Seedling Nurseries	6.16	80	0.0024	0.00049	0.00021	0.0003	280	1400	3200	2200
	Grass Grown for Seed	4.375	80	0.0017	0.00035	0.00015	0.00022	400	1900	4500	3200
	Alfalfa, Birdsfoot Trefoil, Clovers, Lespedeza, Beans (Green or Dry), Sunflower	3.92	80	0.0015	0.00031	0.00013	0.00019	450	2200	5100	3500
	Alfalfa (Established stands), Almonds, Ladino Clover (established stands), Safflower, Sugar Beets, Tomatoes, Walnuts	3.08	80	0.0012	0.00025	0.00011	0.00015	570	2800	6400	4500
	Cotton	1.96	80	0.00076	0.00016	0.000067	0.000096	890	4300	10000	7100

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Table 9.1.3: Short- and Intermediate-Term Occupational Handler Inhalation Exposures and Risks for EPTC

Exposure Scenario	Crop or Target	Application Rate (lb ai/A) [a]	Area Treated Daily (Acres) [b]	Inhalation Dose [c] (mg/kg/day)				Margin of Exposure [d] (Target MOE = 30)			
				Baseline	Dust-Mist Respirator	Organic Vapor Respirator	Eng Cont	Baseline	Dust-Mist Respirator	Organic Vapor Respirator	Eng Cont
Applying Granulars via Aerial Equipment (8)	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground	6	350	N/A	N/A	N/A	0.039	N/A	N/A	N/A	17
	Sugar Beets, sunflower	4	350	N/A	N/A	N/A	0.026	N/A	N/A	N/A	26
	Alfalfa (established stands), Alfalfa, Birdsfoot, Trefoil, Clovers, Lespedeza, Beans (green or dry), Conifer Nursery Stock and Young Field Plantings, Corn, Potatoes (Irish), Safflower	3	350	N/A	N/A	N/A	0.02	N/A	N/A	N/A	35
Applying Granulars via Tractor Drawn Spreader (9)	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground	6	80	0.0082	0.0016	0.00082	0.0015	83	410	830	450
	Sugar Beets, sunflower	4	80	0.0055	0.0011	0.00055	0.001	120	620	1200	680
	Alfalfa (established stands), Alfalfa, Birdsfoot, Trefoil, Clovers, Lespedeza, Beans (green or dry), Conifer Nursery Stock and Young Field Plantings, Corn, Potatoes (Irish), Safflower	3	80	0.0041	0.00082	0.00041	0.00075	170	830	1700	900
Flagger											
Flagging for Aerial Sprays Applications (10)	Potatoes	7.91	350	0.014	0.0028	0.0014	0.00028	49	250	490	2500
	Sweet Potatoes	7.42	350	0.013	0.0026	0.0013	0.00026	52	260	520	2600
	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground, Pine Seedling Nurseries	6.16	350	0.011	0.0022	0.0011	0.00022	63	320	630	3200
	Grass Grown for Seed	4.375	350	0.0077	0.0015	0.00077	0.00015	89	440	890	4400
	Alfalfa, Birdsfoot Trefoil, Clovers, Lespedeza, Beans (Green or Dry), Sunflower	3.92	350	0.0069	0.0014	0.00069	0.00014	99	500	990	5000
	Alfalfa (Established stands), Almonds, Ladino Clover (established stands), Safflower, Sugar Beets, Tomatoes, Walnuts	3.08	350	0.0054	0.0011	0.00054	0.00011	130	630	1300	6300
	Cotton	1.96	350	0.0034	0.00069	0.00034	0.000069	200	990	2000	9900

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Table 9.1.3: Short- and Intermediate-Term Occupational Handler Inhalation Exposures and Risks for EPTC

Exposure Scenario	Crop or Target	Application Rate (lb ai/A) [a]	Area Treated Daily (Acres) [b]	Inhalation Dose [c] (mg/kg/day)				Margin of Exposure [d] (Target MOE = 30)			
				Baseline	Dust-Mist Respirator	Organic Vapor Respirator	Eng Cont	Baseline	Dust-Mist Respirator	Organic Vapor Respirator	Eng Cont
Flagging for Aerial Granular Applications (11)	Citrus Nursery Stock and Young Field Plantings, Idle and Fallow Ground	6	350	0	0.0009	0.00045	0.00009	150	760	1500	7600
	Sugar Beets, sunflower	4	350	0	0.0006	0.0003	0.00006	230	1100	2300	11000
	Alfalfa (established stands), Alfalfa, Birdsfoot, Trefoil, Clovers, Lespedeza, Beans (green or dry), Conifer Nursery Stock and Young Field Plantings, Corn, Potatoes (Irish), Safflower	3	350	0	0.00045	0.00023	0.000045	300	1500	3000	15000

N/A = Not applicable

a Application Rates based on maximum use rates on EPTC labels.

b Exposure Science Advisory Council Policy No. 9.1.

c Short- and Intermediate-Term Inhalation Dose (mg/kg/day) = unit exposure (mg/lb ai) x application rate (lb ai/acre) x acres treated / body weight (70 kg).

d Short- and Intermediate-Term Inhalation MOE = NOAEL (mg/kg/day) / inhalation daily dose (mg/kg/day). LOC = 30

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9.2 Short- and Intermediate-Term Post-Application Risk

HED uses the term "postapplication" to describe exposures to individuals that occur as a result of being in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). HED believes that there are distinct job functions or tasks related to the kinds of activities that occur in previously treated areas. Job requirements (e.g., the kinds of jobs necessary to cultivate a crop), the nature of the crop or target that was treated, and how the chemical residues degrade in the environment can cause exposure levels to differ over time and each of these factors has been considered in this assessment.

9.2.1 Occupational Dermal Postapplication

EPTC labels indicate that applications may be made using aerial, chemigation, and ground spray applications. EPTC is mostly applied as a single annual, pre-emergent or early post-emergent herbicide and is usually incorporated into the soil immediately after application to prevent volatilization. HED has estimated postapplication risks for the proposed uses of EPTC to reflect early postemergent use of the herbicide.

The use of personal protective equipment or other types of equipment to reduce exposures for postapplication workers is not considered a viable alternative for the regulatory process. This is described in some detail in the Agency's Worker Protection Standard (40CFR170). As such, an administrative approach is used by the Agency to reduce the risks by assigning a restricted entry interval (REI). Postapplication risk levels are generally calculated in the risk assessment process on a chemical-, crop-, and activity-specific basis. To establish REIs, the Agency considers postapplication risks on varying days after application.

Since no postapplication data were submitted in support of this registration action, dermal exposures during postapplication activities were estimated using dermal transfer coefficients from the Science Advisory Council for Exposure Policy Number 3 (http://www.epa.gov/pesticides/science/exposac_policy3.pdf), summarized in Table 9.2.1 below.

To determine the short- and intermediate-term dermal risks, daily dermal exposures (assuming 5% absorption) were compared to the NOAEL of 5 mg/kg/day based on two rat studies (i.e., a Chronic/Carcinogenicity study and a 2-Generation Reproduction study). A target MOE of 100 is considered adequate for adults (10X for interspecies extrapolation and a 10X for intraspecies variability).

To determine the short- and intermediate-term inhalation risks, daily inhalation exposures (assuming 100% absorption) were compared to the occupational HEC of 0.68 mg/kg/day based on a 90-day inhalation toxicity study in rats. A target MOE of 30 is considered adequate for adults (3X interspecies extrapolation and a 10X for intraspecies variability).

Summaries of the dermal risk estimates for occupational postapplication workers are included in Table 9.2.1. The results indicate that occupational postapplication risks, as calculated per HED default values, exceed HED's level of concern (MOE < 100) on day zero after application for some crop and postapplication task combinations.

Table 9.2.1: Short- and Intermediate-Term Occupational Postapplication Dermal Exposures and Risks for EPTC

Crop Grouping	Crop	Exposure Potential	Application Rate [a] (lb ai/ acre)	Transfer Coefficient (cm^2/hr)	Activities	MOE at Day Zero	Day Acceptable MOE
Field/Row Crop (Low/Medium)	Potatoes	Low	7.91	210 1900	Scouting Irrigation	230 26	-- 13 days
Field/Row Crop (Low/Medium)	Sweet Potatoes	Low	7.42	210 1900	Scouting Irrigation	250 28	-- 13 days
Field/Row Crop (Low/Medium)	Grasses grown for seed	Low	4.375	1100 1900	Scouting Irrigation	81 47	2 days 8 days
Field/Row Crop (Low/Medium)	Alfalfa, beans (green or dry)	Low	3.92	1100 1900	Scouting Irrigation	91 52	1 day 7 days
Field/Row Crop (Low/Medium)	Sunflower	Low	3.92	90	Scouting	1100	--
Field/Row Crop (Low/Medium)	Ladino Clover	Low	3.08	1100 1900	Scouting Irrigation	120 67	-- 4 days
Field/Row Crop (Low/Medium)	Sugar Beets	Low	3.08	210	Scouting	600	--

a Application Rates based on maximum use rates on EPTC labels.

Restricted-Entry Interval (REI)

All current EPTC labels have an REI of 12 hours based on the acute toxicity of EPTC. Most of the uses of EPTC are pre-plant or at plant, therefore there is minimal foliar contact, but there are some post-plant emergence uses on the current EPTC labels. HED has produced a post-application assessment to cover the early post-emergent uses with less mature plants that are closer to the ground. These assessments should be considered conservative because the dermal TC studies were conducted with more mature foliage plants. However, RD should ensure the proper REIs are put in place on the labels to reflect the potential postapplication risks from using EPTC as a post-emergent application.

9.2.2 Occupational Inhalation Postapplication

Based on the Agency's current practices, a quantitative occupational postapplication inhalation exposure assessment was not performed for EPTC at this time. However, there are multiple potential sources of postapplication inhalation exposure to individuals performing postapplication activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the

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SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report as well as available postapplication inhalation exposure data generated by the Agricultural Reentry Task Force and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate occupational postapplication inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational postapplication inhalation exposure assessment for EPTC.

10.0 Environmental Justice Considerations

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

11.0 References

Drinking Water Assessment for Section 3 New Uses (fallow/idle), additional Regions (sunflowers) and Modifications (adding post-emergent application to sunflowers, reducing PHI on potatoes, and increasing the post-plant pre-emergence rate on potatoes) to Existing Label (Reg. No. 10163-283) for the herbicide EPTAM 7-E (EPTC). D339490; James Wolf; January 10, 2008.

EPTC. Residue Chemistry Chapter for the Reregistration Eligibility Document. D245000; S. DeVito; September 25, 1998.

EPTC (S-Ethyl dipropylthiocarbamate): HED Risk Assessment for the Reregistration Eligibility Decision (RED) Document. D244982; Paula A. Deschamp; April 7, 1999.

EPTC. Storage Stability. D287731; M. Sahafeyan; April 24, 2003.

EPTC (S-ethyl dipropylthiocarbamate). Storage Stability Data for EPTC in/on Sugar Beet Tops, Submitted in Response to Deficiencies Noted in the 1999 EPTC Reregistration Eligibility Decision (RED). D301921; Donald Wilbur; January 23, 2007.

EPTC: Response to Comments pertaining to Residue Chemistry Data Requirements. D234927; P. Yvonne Barnes; October 1, 2009.

EPTC: (Carbamothioic acid, dipropyl-, S-ethyl ester) Acute and Chronic Aggregate Dietary (Food and Drinking Water,) Exposure and Risk Assessment[s] for Tolerance Petition for EPTC in Forage and Hay of Grass Grown for Seed. D390096; Yvonne Barnes; June 9, 2011.

EPTC: Occupational and Residential Exposure Assessment for Proposed Section 3 Registration for use on Grasses Grown for Seed Production. D390097; Monica Hawkins; June 9, 2011.

Thomas, R.G., 1981. Chapter 15, Volatilization from water. IN W.J. Lyman et al. Research and Development for Estimating Physicochemical Properties of Organic Compounds of Environmental Concerns. Contract. 17-78-C-8073.Arthur D. Little, Inc. Cambridge, MA

Tier II Drinking Water Exposure Assessment for EPTC in Support of New Use Tolerance Petition for Grasses Grown for Seed. D371208; James Wolf; June 9, 2010.

USEPA. 1999. EPTC. Reregistration Eligibility Decision (RED) EPA 738-R-99-006. U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances. Office of Pesticide Programs. Washington, DC

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Appendix A: Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal and inhalation exposure. Many such studies, involving exposure to many different pesticides, comprise generic pesticide exposure databases such as the Pesticide Handlers Exposure Database (PHED), the Agricultural Handlers Exposure Task Force (AHETF) Database, and the Agricultural Reentry Task Force (ARTF) Database. EPA has reviewed all the studies supporting these multi-pesticide generic exposure databases, and has found no clear and convincing evidence that the conduct of any of them was either fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time the research was conducted. All applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied, and there is no regulatory barrier to continued reliance on these studies.

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Appendix B: Toxicology Assessment

B.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for EPTC are shown in the table below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21/28-Day Dermal	yes	**no**
870.3250	90-Day Dermal	no	--
870.3465	90-Day Inhalation	no	yes
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5550	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	--
870.6100b	90-Day Neurotoxicity (hen)	no	--
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90-Day Neuro. Screening Battery (rat)	yes	yes
870.6300	Develop. Neuro	yes	yes
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	--
870.7800	Immunotoxicity	yes	**no**
Special Studies for Ocular Effects			
	Acute Oral (rat)	no	--
	Subchronic Oral (rat)	no	--
	Six-month Oral (dog)	no	--

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B.2. Toxicity Profiles

Table B.2.1. Acute Toxicity Profile for EPTC

Guideline No.	Study Type	MRID	Results	Toxicity Category
870.1100	Acute oral- rat	00157868	♂LD_{50} = 1465 (1290-1663) mg/kg ♀ LD_{50} = 1712 (1324-2214) mg/kg Combined LD_{50} = 1599 (1294-1976) mg/kg	III
870.1200	Acute dermal- rabbit	00157869	♂LD_{50} > 2000 mg/kg ♀ LD_{50} > 2000 mg/kg	III
870.1300	Acute inhalation - rat	00157870	Combined LC_{50} = 1.39 (0.97-2.00) mg/L	II
870.2400	Primary eye irritation- rabbit	00157871	PIS (24 hrs) = 2.2 Reversed within 3 days	III
870.2500	Primary Dermal irritation- rabbit	00157872	PII = 1.4	IV
870.2600	Skin sensitization- guinea pig	00157873	Very slight sensitizer	N/A
870.2600	Skin sensitization- guinea pig	41709201	Weak sensitizer (Magnusson-Kligman)	N/A

Table B.2.2. EPTC: Subchronic, Chronic and Other Toxicity Profile

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100	90-Day oral toxicity (rat)	00144651 (1983) Acceptable/guideline M: 0, 18, 36, 72, 120 mg/kg/day F: 0, 3, 15, 72, 120 mg/kg/day	Systemic NOAEL = 18 mg/kg/day ♂, 3 mg/kg/day ♀ Systemic LOAEL = 36 mg/kg/day ♂, 15 mg/kg/day ♀, based on decreased body weight and body weight gain and increased incidence of cardiomyopathy. ChE NOAEL = 120 mg/kg/day ♂, 72 mg/kg/day ♀ ChE LOAEL = not est. in ♂, 120 mg/kg/day ♀ based on 14% inhibition of plasma ChE in females
870.3150	90-Day oral toxicity (dog)	00150327 (1985) Acceptable/guideline 0, 200, 600, 1800 ppm 0, 5, 15, 45 mg/kg/day	Systemic NOAEL = 15mg/kg/day ♂, 45 mg/kg/day ♀ Systemic LOAEL = 45 mg/kg/day ♂, not est. in ♀ based on excess salivation and decreased body weight gain in males ChE NOAEL = 15 mg/kg/day ♂, 45 mg/kg/day ♀ ChE LOAEL = 45 mg/kg/day ♂, not est. in ♀ based on 25% decreased in plasma ChE in males
870.	90-Day Inhalation toxicity (rat)	00154784 (1985) Acceptable/guideline 0, 8.3, 58, 290 mg/m^3 MMAD= 2.8 µm BMD_{10}= 3.75 $BMDL_{10}$= 1.90	BMD_{10}= 3.75 $BMDL_{10}$= 1.90 based on brain cholinesterase inhibition in males; decreased food consumption in males at mid and high doses, and increased prothrombin time in females at mid and high doses..
870.3700a	Prenatal developmental in (rat)	00138919 (1983) Acceptable/guideline F: 0, 30, 100, 300 mg/kg/day	**Maternal** NOAEL = 100 mg/kg/day LOAEL = 300 mg/kg/day based on lethality, decreased body weight gain, corrected body weight gain, and food consumption. **Developmental** NOAEL = 100 mg/kg/day. LOAEL= 300 mg/kg/day based on decreased fetal body weight, decreased litter size, increased resorptions, increased incidence of omphalocle and increased incidence of unossified sternebrae.

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Table B.2.2. EPTC: Subchronic, Chronic and Other Toxicity Profile

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700b	Prenatal developmental in (rabbit)	40442302 (1987) Acceptable/guideline F: 0, 5, 40, 300 mg/kg/day	**Maternal** NOAEL = 40 mg/kg/day LOAEL = 300 mg/kg/day based on decreased body weight, food consumption, mortality and clinical signs **Developmental** NOAEL = 40 mg/kg/day LOAEL = 300 mg/kg/day based on reduced fetal body weight. **Maternal** ChE NOAEL was not established. **Maternal** ChE LOAEL ≤ 5 mg/kg/day based on inhibition of serum ChE by 10%.
870.3800	Reproduction and fertility effects (rat)	0012128 (1982), 40420408 (1987) Acceptable/guideline 0, 40, 200, 1000 ppm 0, 2, 10, 50 mg/kg/day	**Parental/Systemic** NOAEL = 10 mg/kg/day LOAEL = 50 mg/kg/day based on degenerative cardiomyopathy in males and females and renal tubule degenerative in females **Reproductive** NOAEL = 50 mg/kg/day LOAEL > HDT. **Offspring** NOAEL = 10 mg/kg/day LOAEL = 50mg/kg/day based on decreased pup weight during postnatal day 14 to 21.
870.3800	Reproduction and fertility effects (rat)	00161597 (1986) Acceptable/guideline 0, 50, 200, 800 ppm 0, 2.5, 10, 40 mg/kg/day	**Parental/Systemic** NOAEL = 2.5 mg/kg/day LOAEL = 10 mg/kg/day based on decreased body weight/ body weight gain and cardiomyopathy. **Reproductive** NOAEL = 40 mg/kg/day LOAEL > HDT. **Offspring** NOAEL = 10 mg/kg/day LOAEL = 40mg/kg/day based on decreased mean pup weight during lactation days 4 to 21.
870.4100b	Chronic toxicity oral (dog)	00161595 (1986) Unacceptable/guideline 0, 200, 600, 1800 ppm M: 0, 5.6, 17.3, 48.5 mg/kg/day F: 0, 6.1, 17.4, 54.7 mg/kg/day	NOAEL = 48.5 mg/kg/day ♂, 54.7 mg/kg/day ♀. LOAEL was not established.

Table B.2.2. EPTC: Subchronic, Chronic and Other Toxicity Profile

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.4100b	Chronic toxicity capsule (dog)	40442301 (1987) Acceptable/guideline 0, 1, 8, 60 mg/kg/day	Systemic NOAEL = 8 mg/kg/day Systemic LOAEL = 60 mg/kg/day based on decreased body weight gain in males and peripheral/ central nervous system degeneration and skeletal/ cardiac muscle degeneration in males and females. ChE NOAEL = 8 mg/kg/day ChE LOAEL = 60 mg/kg/day based on ChE inhibition (decreased plasma ChE by 32 and 42% in males and 23 to 26% in females
870.4200	Carcinogenicity (mouse)	00161596 (1985) Acceptable/ guideline 0, 200, 600, 1800 ppm 0, 30, 90, 270 mg/kg/day	NOAEL = 90 mg/kg/day LOAEL = 270 mg/kg/day based on decreased body weight and food consumption.
870.4300	Chronic/ Carcinogenicity (rat)	40215001 (1987) Acceptable/guideline carcinogenicity part 0, 9, 18, 36, 72 mg/kg/day Unacceptable/ guideline Chronic portion because systemic toxicity was not established.	NOAEL = not est. LOAEL = 9 mg/kg/day based on decreased body weights, body weight gain, and increased incidence of degenerative cardiomyopathy.
870.4300	Chronic/ Carcinogenicity (rat)	00145004; 00145311 (1983) Acceptable/guideline M: 0, 5.01, 25, 125.8 mg/kg/day F: 0, 4.97, 24.8, 124.8 mg/kg/day	NOAEL = 5 mg/kg/day LOAEL = 25 mg/kg/day based on decreased body weight and increased incidences of myocardial and neuromuscular lesions.
870.5100	Bacterial Reverse Mutation	00152451 (1978) Acceptable/ guideline	Negative with/ without S9 activation at 10- 500 µg/plate
870.5100	Bacterial Reverse Mutation	00152452 (1977) Acceptable/ guideline	Negative with / without 59 activation at 0.001 - 5.0 µL/plate
870.5300	In vitro Mouse Lymphoma assay	00152454 (1984) Acceptable/ guideline	Negative without S9 activation at 0.0125-0.15 µL/mL, and slightly mutagenic effect with S9 activation at 0.005 -0.06 µL/mL.
870.5300	In vitro Mouse Lymphoma assay	00161602 (1986) Acceptable/ guideline	Negative without S9 activation Positive with S9 activation

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Table B.2.2. EPTC: Subchronic, Chronic and Other Toxicity Profile

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.5375	In vitro Chinese Hamster Ovary (CHO) Chromosome Aberration	00161601 (1985) Acceptable/ guideline	Negative with/without S9 activation
870.5375	Mouse Lymphoma Chromosomal Aberration Assay	00152455 (1984) Acceptable/ guideline	Negative without S9 activation at 0.0125-0.15 µL/mL and with S9 activation at 0.005-0.06 µL /mL
870.5395	Mammalian Erythrocyte Micronucleus	00142895 1984) Acceptable/ guideline	Negative at MTD (55% lethality)
870.5395	Drosophila melanogaster Sex-linked Recessive Lethal Mutations	00153248 (1985) Acceptable/ guideline	Negative for inducing sex-linked recessive lethals
870.5395	Bacillus subtilis Rec-Assay	00152451 (1978) Acceptable/ guideline	Negative without S9 activation at 1 to 100% (v/v), with 59 activation not evaluated.
870.5550	Unscheduled DNA Synthesis in Mammalian Cultured Cells	00161600 (1986) Acceptable/ guideline	Negative
870.6200a	Acute neurotoxicity screening battery	43039701, 43297401 (1994) Acceptable/ guideline 0, 200, 1000, 2000 mg/kg/day	NOAEL = not est. ♂, 200 mg/kg/day ♀ LOAEL = 200 mg/kg/day ♂, 1000 mg/kg/day ♀ based on neuronal cell necrosis in the brain in males and clinical signs, death, and neuronal cell necrosis in the brain in females.
870.6200b	Subchronic neurotoxicity screening battery	43230901 (1994) Acceptable/guideline 0, 500, 1000, 2500 ppm M: 0, 7.9, 39.4, 193 mg/kg/day F: 0, 8.8, 43.5, 205 mg/kg/day	NOAEL = 7.9 mg/kg/day ♂, 8.8 mg/kg/day ♀ LOAEL = 39 mg/kg/day ♂, 44 mg/kg/day ♀ based on decreased body weight gain and relative brain weight in females and neuronal necrosis in the brain in males and females.
870.6300	Developmental Neurotoxicity	46319101 (2004) Acceptable/guideline 0, 100, 300, 1000 ppm 0, 7.6, 21.9 and 67.2 mg/kg/day	Maternal NOAEL= 21.9 mg/kg/day Maternal LOAEL = 67.2 mg/kg based on clinical signs (piloerection, hunched posture, sides pinched in) decreased body weight, body weight gain, and food consumption and increased incidence of whole losses. Dev. /Offspring NOAEL = not established. Dev. /Off spring LOAEL = 7.6 mg/kg/day based on decreases in absolute brain weights in male pups only on PND.

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Table B.2.2. EPTC: Subchronic, Chronic and Other Toxicity Profile

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485	Metabolism (rat)	00142896 (1979) Acceptable/guideline 121-150 mg/kg	Eptam was rapidly absorbed and excreted: the urine of males and females contained 81 and 88% of the administered radiolabel, respectively, within 24 hours. The feces and expired air were minor excretion routes, each containing ≤ 3.2% of the radioactivity over 96 hours. Absorption was estimated to be 86.7-97.5% of the administered dose for the two sexes. The mass balance accounting for the 1, 3, and 7 day experiments was acceptable: radioactivity from the expired air, urine, feces, and cage wash accounted for 90.1, 99.6, and 88.8% of the given dose, respectively (for males and females combined; there were no notable gender-related differences). Absorbed Eptam was widely distributed, with the greatest amount of radioactivity per mg organ found in the blood, kidneys, liver, and spleen after 24 hours. Radioactivity declined significantly with time in all tissues except blood and spleen, which retained 72-80% of their 24-hour radioactivity after 7 days. Only 1.2% of the given radioactivity was in all the tissues after 7 days, however, indicating that there was no significant bioaccumulation.

B.3 Hazard Identification and Endpoint Selection

B.3.1 Acute Reference Dose (aRfD) – All Population

Study Selected: Acute Neurotoxicity Study– Rat
MRID No: 46039701, 43297401
Executive Summary: See Appendix B, Guideline 870.6200a
Dose and Endpoint for Risk Assessment: LOAEL = 200mg/kg/day based on neuronal cell necrosis in the brain.
Uncertainty Factor: 1000X [10X interspecies extrapolation, 10X intraspecies variability; UF_L = 10X for use of LOAEL; lack of NOAEL in the critical study] FQPA SF = 1X.
Comments about Study/Endpoint/ Uncertainty Factor: This study is appropriate for acute dietary risk assessment since the affects were observed following a single exposure to EPTC. The endpoint selected (neuronal cell necrosis in the brain) is also appropriate since this neuropathological effect has been observed in several other studies (subchronic neurotoxicity study in rats, chronic feeding study in rat, and one-year oral (capsule) study in the dog). Since a NOAEL was not established for males and the LOAEL was used, an additional modifying factor of 10X was used in deriving the acute RfD.

B.3.2 Chronic Reference Dose (cRfD)

Study Selected: Combined Chronic/ Carcinogenicity and 2-Generation Reproduction Studies– Rat
MRID No: 00145004, 00145311, 00161597
Executive Summary: See Appendix B, Guideline 870.4300 & 870.3800
Dose and Endpoint for Risk Assessment: NOAEL = 5 mg/kg/day based on decreased body weight/ body weight gain and cardiomyopathy and neuromuscular lesions.
Uncertainty Factor: 100X [10X interspecies extrapolation, 10X intraspecies variability,] FQPA SF = 1X.
Comments about Study/Endpoint/ Uncertainty Factor: The route and duration of exposure are appropriate for selection of the chronic dietary endpoint based on the most sensitive endpoints observed in the database. The concern of degenerative cardiomyopathy is supported by the same endpoint observed in the combined 2- year chronic toxicity/ carcinogenicity study (MRID 40215001). In that study, increased incidence of degenerative cardiomyopathy was seen at that lowest dose tested (9 mg/kg/day); a NOAEL was not achieved. Furthermore, myocardial lesions were observed at the LOAEL in the subchronic feeding study in the rat (MRID 0014651) and at the mid and high doses in the subchronic inhalation study in the rat (MRID 00154784). Additionally, the NOAEL selected (5 mg/kg/day) is also protective of the effects seen in pups (decrease brain weight) on PND 63 in the DNT study.

B.3.3 Incidental Oral Exposure (Short- and Intermediate Term)

Study Selected: Combined Chronic/ Carcinogenicity and 2-Generation Reproduction Studies– Rat

MRID No: 00145004, 00145311, 00161597

Executive Summary: See Appendix B, Guideline 870.4300 & 870.3800

Dose and Endpoint for Risk Assessment: NOAEL = 5 mg/kg/day based on decreased body weight/ body weight gain, cardiomyopathy and neuromuscular lesions.

Uncertainty Factor: LOC for MOE = 100 [10X interspecies extrapolation, 10X] FQPA SF = 1X.

Comments about Study/Endpoint/ Uncertainty Factor: A chronic/ carcinogenicity study in rats (MRID 00145004, 00145311; parental NOAEL/LOAEL = 5/25mg/kg/day) and a 2-generation study in rats (MRID 00161597; parental NOAEL/LOAEL = 2.5/10 mg/kg/day) serve as co-critical studies since similar effects were seen in both rat studies (decreased body weight/ body weight gain, cardiomyopathy and neuromuscular lesions). Similar effects were noted in a combined 2- year chronic toxicity/ carcinogenicity study (MRID 40215001). Myocardial lesions were also observed at the LOAEL in the subchronic feeding study in the rat (MRID 0014651) and at the mid and high dose in the subchronic inhalation study in the rat (MRID 00154784). Additionally, the NOAEL selected (5 mg/kg/day) is also protective of the effects seen in pups (decrease brain weight) on PND 63 in the DNT study.

B.3.4 Dermal Exposure (Short- and Intermediate Term)

Study Selected: Combined Chronic/ Carcinogenicity and 2-Generation Reproduction Studies– Rat

MRID No: 00145004, 00145311, 00161597

Executive Summary: See Appendix B, Guideline 870.4300 & 870.3800

Dose and Endpoint for Risk Assessment: NOAEL = 5 mg/kg/day based on decreased body weight/ body weight gain, cardiomyopathy and neuromuscular lesions.

Uncertainty Factor: LOC for MOE = 100 [10X interspecies extrapolation, 10X intraspecies variability] FQPA SF = 1X.

Comments about Study/Endpoint/ Uncertainty Factor: A dermal study is currently not available to assess dermal effects for EPTC. Therefore, an oral chronic/ carcinogenicity study in rats (MRID 00145004, 00145311; parental NOAEL/LOAEL = 5/25mg/kg/day) and a 2-generation study in rats (MRID 00161597; parental NOAEL/LOAEL = 2.5/10 mg/kg/day) serve as co-critical studies since similar effects were seen in both rat studies (decreased body weight/ body weight gain, cardiomyopathy and neuromuscular lesions). A dermal Absorption factor of 5% was derived from both of the available dermal absorption studies.

B.3.5 Inhalation Exposure (Short- and Intermediate Term)

Study Selected: 90- Day inhalation – Rat

MRID No: 0015784

Executive Summary: See Appendix B, Guideline 870.3465

Dose and Endpoint for Risk Assessment: BMD_{10} = 3.75 mg/m^3; $BMDL_{10}$ = 1.90 mg/m^3 based on decreased brain ChE inhibition in males; decreases food consumption (males and females at mid and high doses and increased prothrombin time in females at mid and high

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doses. **Bystanders;** HEC = 0.227 mg/kg; 0.87 mg/m^3; 0.00087 mg/L; **Occupational** HEC= 0.68 mg/kg; 2.61 mg/m^3; 0.0026 mg/L

Uncertainty Factor: ***Children***: 30X [3X interspecies extrapolation,10X intraspecies variability]. FQPA SF = 1X.

Adult: 30X [3X interspecies extrapolation and 10X intraspecies variability]. FQPA SF = 1X.

Comments about Study/Endpoint/ Uncertainty Factor: The 2009 Field Volatilization SAP suggested that the Agency use route specific inhalation studies instead of relying on oral studies in risk assessment. The oral studies may be less conservative than route specific studies. For EPTC, an inhalation study is available and did evaluate the most sensitive endpoint (cardiomyopathy). In additional, since a NOAEL was not established in the study, a benchmark dose analysis ($BMDL_{10}$) was conducted to determine a point of departure (PoD). It should be noted that port of entry effects were not evaluated in this inhalation study.

Table B.3.5.1 HEC Array for Non-Occupational (Bystander) Risk Assessment

Relevant Study		LOAEL (BMD_{10}) mg/L	NOAEL ($BMDL_{10}$) mg/L	Da	Dh	Wa	Wh	RDDR	HEC (mg/L)	inter	intra	UF
Acute Exposure												
90-days inhalation rat (0015784)	Systemic	3.75	1.90	6	24	1	1	2.564	0.00122	3	10	1
	[redacted]											
Short-& Intermediate-Term Exposure												
90-days inhalation rat (0015784)	Systemic	3.75	1.90	6	24	5	7	2.564	0.00087	3	10	1
	[redacted]											

Table B.3.5.2 HEC Array for Occupational Risk Assessment

Relevant Study		LOAEL (BMD_{10}) mg/L	NOAEL ($BMDL_{10}$) mg/L	Da	Dh	Wa	Wh	RDDR	HEC (mg/L)	inter	intra	UF
Acute Exposure												
90-days inhalation rat (0015784)	Systemic	3.75	1.90	6	8	1	1	2.564	0.00365	3	10	1
	[redacted]											
Short-& Intermediate-Term Exposure												
90-days inhalation rat (0015784)	Systemic	3.75	1.90	6	8	5	5	2.564	0.00261	3	10	1
	[redacted]											

The HECs (based on the systemic effect of ChE inhibition and resulting $BMDL_{10}$ value from the inhalation study a Route-to- Route Extrapolation (inhalation or oral) displayed above were extrapolated from mg/L to mg/kg by the following equations:

dose (systemic HEC value) mg/L x A x CF (L/hr/kg) x D (hours) x AF = mg/kg;

Bystander: (0.0087 mg/L) x 1 x 43.5 x 6 x 1 = 0.227 mg/kg;
Occupational: (0.00261 mg/L) x 1 x 43.5 x 6 x 1 = 0.68 mg/kg

Where:

A absorption: ratio of deposition and absorption in respiratory tract compared to absorption by the oral route.
CF Conversion Factor: A L/hr/kg factor which accounts for respiratory volume and body weight for a given species and strain (Table 1 of guidance document).
D Duration: Duration of daily animal or human exposure (hours).
AF Activity Factor: Animal default is 1.

When conducting inhalation risk assessments, the magnitude of the UFs applied is dependent on the methodology used to calculate risk. For studies in this risk assessment with inhalation animal data, UFs are based on the RfC methodology developed by the Office of Research and Development (ORD) for the derivation of inhalation reference concentration s (RfCs) and human equivalent concentrations (HECs) for use in margin of exposure (MOE) calculations. Since the RfC methodology takes into consideration the pharmacokinetic (PK) differences but not pharmacodynamic (PD) differences, the UF for interspecies extrapolation may be reduced to 3X (to account for the PD differences) while the UF for intraspecies variation is retained at 10X[1]. Thus, the UF when using the RfC methodology is customarily 30X.
Based on current EPTC Labels, HEC believes exposures can be acute (less than 24 hours), short-term (1-30 days), or intermediate-term (1 month- 6 months) in duration while long-term exposures are not anticipated for EPTC based on proposed labeled uses.
For the acute, short-term s and intermediate-term scenarios, inhalation data from the 90- day inhalation rodent study was most appropriate for determining HECs. In the RfC methodology, different HECs may be calculated for the same experimental NOAEL due to:

1. Different algorithms are used to derive HECs for systemic versus port-of-entry effects. Typically, HECs are calculated separately for systemic versus port-of-entry effect. For EPTC, port-of-entry irritation was not observed and therefore, only systemic HECs were derived.
2. Time adjustments are traditionally needed for non-occupational (bystander) versus occupational exposure scenarios. Traditionally, HECs for non-occupational exposure are based on the number of hours an individual may be at home. Therefore, the most conservative estimate of hours spent at home would be 24 hours/day and 7 days/week. In comparison, the average work week for an occupational worker is 8

[1] A 3X UF for interspecies extrapolation is retained to account for the PD differences between animals and humans which are not accounted for in the RfC methodology.

hours/day and 5 days/week. The HEC array table reflects the time adjustment in the calculations.

B.4 Executive Summaries

B.4.1 Subchronic Toxicity

870.3100 90- Day Oral Toxicity – Rat

In this subchronic toxicity study (MRID No.: 00144651), CD-Crl:CD (SD)BR rats (20/sex/dose) were fed diets containing EPTC (98.4%) at 0, 18/3, 36/15, 72, or 120 mg/kg/day, When it became apparent to the study director that a NOAEL for body weight may not be achieved after six weeks of treatment, the two lowest doses were reduced to 3 and 15 mg/kg for the remainder of the study (weeks 7 to 13).

No treatment-related deaths or clinical signs were observed during the study. Mean body weights at week 6 (just prior to dose reduction) were significantly reduced at 18, 36, 72, and 120 mg/kg/day in males (8, 11, 13, and 17%, respectively) and females (7, 10, 10, and 9%, respectively). At week 13, statistically significant decreases in body weights were observed at 15, 72, and 120 mg/kg/day in males (10, 15, and 19%, respectively) and females (9, 11, and 13%, respectively). For weeks 0 to 6, body weights gains were significantly decreased at 8, 36, 72, and 120 mg/kg/day by 13, 17, 20, and 29%, respectively, in males and by 16, 25, 25, and 23%, respectively, in females. Following the reduction in dose at week 7 through the remainder of the study, body weight gains were statistically significantly decreased from control values only at 72 mg/kg/day (20%, males; 14%, females) and 120 mg/kg/day (17%, males; 24%, females). Overall (weeks 1 to 13) body weight gains were statistically significantly decreased from control values at 36/15, 72, and 120 mg/kg/day in males (13, 21, and 26%, respectively) and females (11, 12, and 12%, respectively). Food consumption was consistently decreased in males at 36 mg/kg/day (through week 6) and males and females treated at 72 and 120 mg/kg/day for the entire study. Food consumption was decreased in males at 36, 72, and 120 mg/kg/day during the first 6 weeks of treatment, but not after the reduction in dose at week 7. At week 13, clinical pathology results showed treatment-related changes in clinical chemistry parameters; hematology findings were not affected by treatment. Blood urea nitrogen concentrations were significantly increased over control values at 72mg/kg/day (135%, males; 148%, females) and 120 mg/kg/day (136%, males; 153%, females). Blood glucose concentrations were significantly decreased in females at 72 mg/kg/day (88% of control) and 120 mg/kg/day (77% of control). Aspartate aminotransferase (AST) activity was greater than control values at 72 mg/kg/day (207%, males; 149%, females) and 120 mg/kg/day (237%, males; 196%, females). Brain cholinesterase (ChE) activity was also significantly decreased by 14% in high- dose females. Plasma, blood and brain ChE activities in low-, mid-, and high-dose males and low- and mid-dose females were comparable to control values.

Necropsy evaluations revealed treatment-related changes in organ weights. Absolute hearts weights were significantly ($p \leq 0.05$) decreased in males treated at 36/15 mg/kg/day (1.36 g) and 120 mg/kg/day (1.34 g) compared to the control value (1.47 g). Relative heart weights (as % of terminal body weight) in males were significantly ($p \leq 0.05$) increased at 72 mg/kg/day (0.33%) and 120 mg/kg/day (0.34%) compared to the control value (0.30%). Organ weights of males treated at 18/3 mg/kg/day and all treated females groups were comparable to control values.
Histopathological evaluation revealed a dose-related increase in the incidence and severity of chronic myocardial inflammation. The inflamation was described as focal to multifocal degeneration

with infiltrating mononuclear cells, fibroplasia and occasional fatty changes. While no myocardial inflammation was noted in control males, treatment-related findings were observed in males dosed at 18/3 mg/kg/day (1/19, slight), 36/15 mg/kg/day (5/20, slight; 1/20, minimal), 72 mg/kg/day (5/20, slight; 5/20., minimal), and 120 mg/kg/day (1/20, slight; 6/20, minimal; 9/20, marked; and 4/20, severe). For females no myocardial inflammation was observed in control and low-dose groups, while increases were noted at 36/15 mg/kg/day (2/20, slight), 72 mg/kg/day (3/20, slight; 10/20, minimal; 2/20 marked) and 120 mg/kg/day (4/20, slight; 2/20, minimal; 3/20 marked).

Based on the results of this study (decreased body weight and body weight gain and increased incidence of cardiomyopathy), the LOAEL was established at 15 mg/kg/day in males and females. The NOAEL was established at 3 mg/kg/day in males and females.

The cholinesterase LOAEL was established at 120 mg/kg/day based of 14% inhibition of plasma ChE in females find not established in males. The NOAEL was established at 72 mg/kg/day in females and 120 mg/kg/day in males.

This study is acceptable (guideline), and satisfies requirements (82-1) for a subchronic toxicity study in the rat.

870.3150 90- Day Oral Toxicity – Dog

In this subchronic study (MRID No.: 00150327), dogs (6/sex/dose) were fed diets containing EPIC (98.4%) at 0,200,600, or 1800 ppm (equivalent to approximately 0, 5, 15 or 45 mg/kg/day) for three months.

Except for consistently excessive salivation in one high-dose male, no other clinical signs considered to be treatment-related were observed in any of the test animals throughout the study.
Mean body weights of high-dose males were consistently lower than control values throughout the study and were attributed to emaciation (of unknown cause) in two animals. One low-dose male was also emaciated during the 13 weeks of treatment, but its weight loss did not significantly skew the mean value for the group. Transient decrease in food consumption was observed in high-dose males and females on day 1, and was attributed to initial palatability of the test diet. During the remainder of the study, food consumption of high-dose females increased to control levels, while that of the males remained slightly reduced.

Except for hypertrophy and prolapse of the third lid of the right eye of one mid-dose male (considered a common lesion in Beagles), no ocular abnormalities attributable to treatment were recorded.

Treatment-related changes were observed in some of the clinical chemistry, but not hematology, parameters. Blood urea nitrogen (BUN) levels were increased in the two high-dose emaciated males. Mean plasma ChE activity of high-dose males was slightly, but significantly, decreased (about 25% of control value) at week 7 and at termination. Plasma, blood and brain ChE activities of other males and female treatment groups were comparable to control values.
No gross, organ weight, or histopathological changes were found in EPTC-treated animals.
The LOAEL for systemic toxicity was established at 1800 ppm (45 mg/kg/day) based on excess salivation and decreased body weight in males; the LOAEL was not established in females. The

NOAEL was established at 600 ppm (15 mg/kg/day) in males and 1800 ppm (45 mg/kg/day) in females.

Based on decreased plasma ChE activity (25%) in males, the LOAEL for ChE inhibition was established at 1800 ppm (45 mg/kg/day); the LOAEL was not established in females. The NOAEL was established at 600 ppm (15 mg/kg/day) in males and 1800 ppm (45 mg/kg/day) in females.

This study is acceptable (guideline) and fulfills requirements [§82-1(b)] for a subchronic toxicity study in the dog.

870.3465 90- Day Inhalation Toxicity – Rat

In this subchronic inhalation study (MRID No.: 00154784), Sprague-Dawley rats (24/sex/dose, 7 to 8 weeks old) were exposed in a whole body chamber to aerosolized (particle size, MMADar = 2.8 µm) EPTC (98.6%) at concentrations of 0, 8.3, 58 or 290mg/m^3, six hr/day, 5 days/week, for 13 weeks. Interim sacrifices were carried out after 3 weeks and between 9 and 10 weeks on 6 animals /sex/dose/time period and at 14 weeks on 12 animals/sex/dose.

With the exception of one low-dose male, which died of undetermined causes during week 5, all remaining animals survived to terminal sacrifice. Clinical signs were observed at all dose levels, but occurred sooner and increased incidence in mid- and high-dose animals. These clinical signs consisted of ocular irritation, chromodacyorrhea, and alopecia.

Food consumption was significantly lower in mid- and high-dose animals, however, mean body weights were not affected by treatment.

Clinical pathology results, showed treatment-related changes in clinical chemistry and clotting time parameters. At the high-dose level, AST activity was significantly increased by 153% in females. At 7 weeks, brain ChE was inhibited in high-dose males (15%) and in females (13%). At study termination, brain ChE activity was decreased in low- mid- and high-dose males (13%, 20%, and 18%, respectively) and mid- and high-dose females (16% and 20%, respectively). Clotting abnormalities were observed in mid- and high-dose females (increased prothrombin time) arid high-dose males (increased partial thromboplastin and stypven times).

Histopathology revealed increased incidence of cardiomyopathy in all (24/24) high-dose males and females. Any treatment-related effect is confounded by increased incidence in control males (17/24) and females (18/24), as compared to low- dose (7/23, males; 14/24, females), and mid-dose (20/24, males; 14/24, females) animals.

For neurotoxicity, a BMD analysis based on the brain ChE data support a BDM10 of 3.75 mg/m3 and BMDL10 of 1.90 mg/m3 with (clinical signs, decreased food consumption, and increased prothrombin time in females at the mid and high doses).
This study is acceptable (guideline) and satisfies requirements (82-4) for a subchronic inhalation study in the rat.

B.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study- Rat

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In this developmental toxicity study (MRID No.: 00138919), female COBS CD rats (25/dose) were gavaged with EPTC (assumed 100%) at doses of 0 (vehicle, corn oil), 30, 100, or 300 mg/kg/day on gestation days (GD) 6 through 15.

No deaths occurred in the control, low- or mid-dose groups, while in the high-dose group, 14 deaths occurred between GD 11 and 17 (one of these deaths was attributed to dosing error). Of the treatment-related deaths; high incidences of "metrorrhagia", severe internal hemorrhage, or cardiorespiratory arrest were observed at necropsy evaluation. Clinical signs were observed on GD 7 in all high-dose animals and consisted of wet, matted, stained urogenital region and red matter in the facial area and/or various other body surfaces. No treatment-related clinical signs were observed in low- or mid-dose animals.

Body weights and body weight gains were adversely affected in the high-dose group. Mean body weights were decreased by 12% on GD 16 and 17% on GD 20 when compared to control values. During GD 6 to 16 high-dose animals lost an average of 17 g, compared to a gain of 34 g by control animals. During the entire gestation period, body weight gain by high-dose animals was 39% lower than the control. Adjusted mean body weight (total maternal body weight - gravid uterine weight) was also significantly deceased in the high-dose group (13.6 g vs. 33.8 for control). Food consumption by high-dose animals was markedly decreased during GD 6 to 9(43%), GD 9to 12 (23%), and GD 12 to 16 (43%).

The high incidence of maternal deaths in the high-dose group resulted in only six litters with viable fetuses surviving to scheduled sacrifice; litter sizes of 22, 19, and 21 were obtained in the control, low- and mid-dose groups, respectively. Post-implantation loss per litter for control, low-, mid-, and high-dose females was 0.5, 0.6, 1.2, and 2.1, respectively. The high number of losses in the mid- and high-dose groups was attributed a reduction in the number of viable fetuses in the mid- and high-dose groups. The reduction was due to complete (early) litter resorption in one high-dose female and one mid-dose female with total (early) litter resorptions and one with several early resorptions. Reproductive data available from post-mortem examination of high-dose animals which died on study showed early and late resorptions to be 3.4 and 1.2 per dam, respectively, the number of corpora lutea to be 11.1 per dam, and the number of normal implants to be 7.3 per dam. Mean fetal body weight of high-dose liners was significantly reduced (2.8 g vs 3.4 g for control). In control, low-, mid- and high dose groups, the percent of malformed fetuses was 0%, 0.4% (omphalocele). 0.4% (absent arteriosus and abnormal great vessels), and 2.6% (omphalocele), respectively and the percent of litters with malformed fetuses was 0%. 5.3%, 4.8%, and 33.3% ($p \leq 0.05$). Historical control values for the percent of litters and percent of fetuses with omphalocele were 0 to 4.5% and 0.0% to 0.3%, respectively. A significant number of high-dose litters had fetuses with unossified sternebrae Nos. 1, 2, 3, and/or 4.

Based on the results of this study (lethality, decreased body weight, body weight gain, corrected body weight gain, and food consumption), the LOAEL for maternal toxicity was established at 300 mg/kg/day; the NOAEL was established at 100 mg/kg/day.

Based on the results of this study (decreased fetal body weight, decreased litter size, increased resorptions, increased incidence of omphalocle and increased incidence of unossified stenebrae), the

LOAEL for developmental toxicity was established at 300 mg/kg/day; the NOAEL was established at 100 mg/kg/day.

This study is classified as acceptable (guideline) and satisfies requirements (§83-3a) for a developmental toxicity study in the rat.

870.3700b Prenatal Developmental Toxicity Study- Rabbit

In this developmental toxicity study (MRID No.: 40442302), pregnant New Zealand White rabbits (16/dose and 18/high-dose) were dose with EPTC (97.6%) at nominal doses of 0 (vehicle, corn oil), 5, 40, or 300 mg/kg/day (achieved doses: 0, 10.3, 75.8, or 568 mg/kg/day, respectively) from GD 7 through 19.

Treatment-related clinical findings were limited to high-dose animals, and consisted of loose stools (9/18), hematuria (4/18), salivation (1/18), stained nose or lip (2/18), wet fur coat (3/18), loss of appetite/anorexia (12/18). Two high-dose animals died on GD 20, while one control doe died on GD 23. All pregnant surviving animals had live fetuses, and no animals aborted.

Mean body weights and corrected body weights of treated animals were comparable to control values. Mean body weight gain by high-dose animals were significantly reduced on GDs13 and 19. The decreases in body weight were attributed to six adversely affected animals in this dose group which had extended periods of little or no food consumption during GD 13 through 20.
Serum and erythrocyte ChE activities were statistically significantly (all $p \leq 0.05$) decreased in all treatment groups. Serum ChE activity was inhibited by 10%, 18% and 56% in the low-, mid-, and high-dose groups, respectively, and erythrocyte ChE, by 14% and 70% in the mid-dose and high-dose groups, respectively.

At termination of the study, organ weights (absolute and relative) and necropsy findings of treated animals were comparable to control values. The two high-dose animals which died on study had gross changes which would suggest bleeding within the reproductive tract (both of these animals had hairballs).

Changes in intrauterine finding were generally limited to high-dose animals. At the high- dose level, mean fetal body weight was significantly decreased by 13% (35.3 g vs. 40.3 g for control, $p \leq 0.05$). The percent of malformed fetuses (7.4% vs. 2.4% for control) and affected implants (13.1% vs. 5.0% for control) were increased in high-dose animals. In the mid- and high-dose groups, the percent of post-implantation losses (7.2% and 6.2%, respectively) was greater than that of the controls (2.8%). However, none of the values were significantly different from the concurrent control values and none were outside of the historical control ranges of 2% to 19% for percent postimplantation loss, 1.4% to 18.1% for percent of malformed fetuses, and 4.6% to 25.4% for percent of affected fetuses. Despite the findings for individual litters, no statistically significant increases in external, visceral, and skeletal anomalies were observed in any of the treatment groups. Litters of three of the adversely affected animals in the high-dose had two fetuses with extremely convoluted retinas, blood-filled eye sockets and/or vitreous bodies; one fetus with forefoot overflexion and cleft palate; and one with malformed centra of the thoracic vertebrae. The fetal effects were considered to be secondary to the marked maternal toxicity at the high-dose.

Based on the results of the study (inhibition of serum ChE by 10%), the LOAEL for maternal ChE inhibition was established at 5 mg/kg/day, the NOAEL was not established.
Based on the results of the study (decreased body weight and food consumption, mortality and clinical signs), the LOAEL for maternal systemic toxicity was established at 300 mg/kg/day, the NOAEL was established at 40 mg/kg/day.

Based on the results of this study (reduced fetal body weights), the LOAEL for developmental toxicity was established at 300 mg/kg/day, the NOAEL was established at 40 mg/kg/day.
This study is acceptable (guideline) and satisfies requirements [§83-3(b)] for a developmental toxicity in the rabbit.

B.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects- Rat

In this two-generation, two-litter reproduction study (MRID Nos.: 0012128, 40420408) 6 to 8 week old weanling Sprague Dawley Cr1 CD SD) BR rats (IS/dose, males; 30/dose, females) were administered EPTC (98.6%) at dietary levels of 0, 40, 200, or 1000 ppm (calculated doses: 0, 2, 10, or 50 mg/kg/day).

No adverse, treatment-related clinical findings were observed during the study. Mean body weights were statistically significantly ($p \leq 0.05$) decreased in high-dose F_0 females (8 to 13%) and F_1 males (16%) and females (13%); the body weights of F_1 males were not affected by treatment. For F_0 females (F_{1b} litter) mean body weights were decreased by about 9% during gestation and 10 to 14% during lactation. For F_1 females (F_{1b} litter) mean body weights were decreased by about 11 to 12% during gestation and 11 to 14% during lactation. Terminal body weights were significantly decreased in F_0 males (7%) and females (10%) and F_1 males (18%) and females (15%). In addition to the observed decreases in body weights, food consumption was also decreased.

No treatment-related effects were noted in any of the reproductive and survivability indices parameters of parental for either mating or generation. Pup survival indices for the treatment groups were comparable to controls values. Mean body weights of F_{1a}, F_{1b} and F_{2a} high-dose pups were statistically significantly decreased lactation days 14 and 21. Terminal body weights were also significantly decreased in both the F_{1a} (males, 15%; females, 18%) and F_{1b} (males, 10%; females, 9%) weanlings. Non-significant decreases in terminal body weights were observed in F_{2b} males and females weanlings. No treatment-related changes were noted in any of the developmental landmarks. Although differences in absolute and relative organ weights were observed in high-dose animals, in most cases, the changes did not appear to be treatment-related and may be a reflection of decreased body weights. Further, abnormal histopathological findings were present in the liver.

Necropsy findings of adult animals revealed treatment-related toxicity. Histological evaluation of the hearts revealed a highly significant ($p \leq 0.1$) increase in the incidence of myocardial degeneration in F_0 females and F_1, males and females; this lesion was present in treated F_0 males, but the incidence (12/15 to 13/15) was not significantly different from that of the control (8/15). The severity of the lesion increased from minimal to slight with increasing dose. For F_0 females in the control, low-, mid- and high-dose groups, the incidence of degeneration was 6/30, 7/30, 11/30 and 26/30, respectively. For control, low-, mid- and high- dose F_1 animals the incidences were 5/15, 11/15, 8/15, and IS/IS, respectively, in males and 8/30, 8/30, 5/30, and 25/30, respectively, in females.

Other histological effects included degeneration, with calcification, of the kidney epithelial tubules. This effect was observed in high-dose (low- and mid-dose kidneys were not evaluated) F_0 males (5/15 *vs* none in control, $p \leq 0.01$) and control, low-, mid-, and high-dose females (11/30, 19/30, 18/30 and 22/30, $p \leq 0.01$).

The LOAEL for parental systemic toxicity was established at 1000 ppm (50 mg/kg/day), based on degenerative cardiomyopathy in males and females and renal tubule degeneration in females; the NOAEL was established at 200 ppm (10 mg/kg/day).

The LOAEL for reproductive toxicity was not established (> 1000 ppm, > 50mg/kg/day); the NOAEL was established at 1000 ppm (50 mg/kg/day).

The LOAEL for developmental toxicity was established at 1000 ppm (50 mg/kg/day) based on decreased pup weight during postnatal day 14 to 21; the NOAEL was established at 200 ppm (10 mg/kg/day).

This study is acceptable (guideline) and satisfies requirements (§83-4) for a two-generation reproduction study in the rat.

870.3800 Reproduction and Fertility Effects- Rat

In this two-generation, two litter reproduction study (MMD No.: 00161597) EPTC (98.4%) was administered to weanling (no age given) Crl:CD(SD)Br rats (30/sex/dose) at dietary levels of 0, 50, 200. or 800 ppm (calculated doses: 0, 2.5, 10, or 40 mg/kg/day).

There were no treatment-related clinical findings. Morality occurred sporadically in all dose groups and was not suggestive of any treatment-related effect; further, post-mortem examination of these animals indicated that the deaths were incidental.

At the high-dose level, body weights during the pre-mating period were statistically significantly ($p \leq 0.05$) decreased in F_0 males (7 to 12%. weeks 8 to 23) and females (9%, weeks 8 to 12) and in F_1 males (13 to 20%, weeks 0 to 23) and females (7 to 12%, weeks 0 to 12). During GD 0 to 20, the body weights of F_0 females were decreased by 6 to 9% and of F_1 females, by 11 to 13%. During lactation, body weights of F_0 females were decreased by 11% only on day 0, while that of F_1 females was decreased by 9 to 14% throughout the lactation period. Food consumption was significantly reduced during pretreatment high-dose F_0 males and low-, mid- and high dose F_1 males. Food consumption was reduced in high-dose F_1 females with sporadic decreased noted at the low- and mid-dose levels. During the first week of gestation, food consumption was decreased only in high-dose F_1 females.

Evaluation of clinical pathology parameters did not reveal any treatment-related changes; brain, plasma, and erythrocyte ChE activities of treated animals were comparable to control values. Post-mortem observations and gross necropsy findings of adult animals did not suggest any parental toxicity. Histological findings of F_0 tissues revealed only incidental findings. However, after weaning of the F_{2a} litters, the incidence of degenerative cardiomyopathy for F_1 adult was 4/25, 3/25, 15/25 and 25/25 for control, low-, mid- and high-dose males, respectively and 1/25, 0/25, 5/25 and

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25/25 control, low-, mid- and high-dose females, respectively. The hearts were not examined in the F_0 animals.

Mean bodyweights of F_{1a} and F_{1b} high-dose pups were statistically significantly ($p \leq 0.05$) in males (9 to 21%, weeks 0 to 21) and females (16 to 25%, weeks 4 to 21). No other treatment- related differences were noted in any of the other reproductive parameters.

The parental systemic LOAEL was established at 200 ppm (10 mg/kg/day) in males and females, based on decreased body weight/body weight gain and cardiomyopathy, the NOAEL was established at 50 ppm (2.5 mg/kg/day).

The LOAEL for developmental toxicity was established at 800 ppm (40 mg/kg/day) based on decreased mean pup weight during lactation days 4 to 21. The NOAEL was established at 200 ppm (10 mg/kg/day).

The LOAEL for reproductive toxicity was not established (> 40 mg/kg/day). The NOAEL was established at 800 ppm (40 mg/kg/day).

This study is classified as acceptable (guideline) and satisfies requirements (§83-4) for a two-generation reproduction study in the rat.

B.4.4 Chronic Toxicity

870.4100b Chronic Toxicity – Dog

In this chronic toxicity study (MRID No.: 00161595), Beagle dogs (6/sex/dose) were fed diets containing 0,200, 600, or 1800 ppm (equivalent to 0, 5.6, 17.3, or 48.5 mg/kg/day in males and 0, 6.1, 17.4 or 54.7 mg/kg/day in females) EPTC (98.4%) for one-year.

Clinical evaluations did not reveal any overt signs of toxicity, however, little or no feces was observed in mid- and high-dose males (2/6 and 3/6, respectively) and females (1/6 and 3/6, respectively) during the first week of testing. No treatment-related changes were observed in either the electrocardiographs (EKG), ophthalmological, or neurological evaluations.

Statistically significant decreases in mean body weights were observed only in mid-dose males (10 to 12% of control); females were unaffected. Since no dose-response relationship existed, the effects were not considered to be treatment-related. Food consumption of treated animals was comparable to control values.

No treatment-related changes were observed in hematology, clinical chemistry or urinalysis results. Although sporadic statistically significant differences in clinical chemistry parameters were observed, none were considered biologically significant. ChE activities were unaffected by treatment.

At terminal sacrifice, no toxicologically significant changes in the incidence of gross and histopathological lesions were observed. In high-dose animals, absolute and relative testicular and left thyroid gland weights were decreased in males, and absolute and relative pituitary weights in

females. Since these tissues did not show any histopathological changes, the differences in weights were considered unrelated to treatment.

The LOAEL for this study was not established; the NOAEL was established at 1800 ppm (48.5 mg/kg/day, males; 54.7 mg/kg/day, females).

This study is unacceptable (guideline), and does not satisfy requirements [§83-1(b)] for a chronic toxicity study in the dog (LOAEL for study not achieved).

870.4100b Chronic Toxicity – Dog

In this chronic toxicity study (MRID No.: 40442301), Beagle dogs were dosed (capsule) at 0, 1, 8 or 60 mg/kg/day EPTC (97.6%) for one-year. Five animals /sex were assigned to control and high-dose groups, while 4 animals/sex were assigned to the low- and mid-dose groups.

One high-dose male showed signs of anorexia, ataxia, dull fur coat, muscle fasciculations, reduced activity, stiff gait in the hind limbs, and weakness in the front limbs before being sacrificed in extremis on day 84. All other animals survived to terminal sacrifice with minimal clinical signs in mid- and high-dose animals. Erythema of the ears was observed in mid- and high-dose males (3/4 and 3/5, respectively) and dull fur coat in high-dose males (2/5) and females (1/5) and mid-dose females (1/4). Stiff gait in the hindlimbs was observed in 2/5 high- dose females. Despite the effects observed during the clinical exams, no abnormalities were noted during the neurological examinations. One high-dose male had changes in the EKG which were described as "potentially treatment-related.

Body weights and food consumption of treated animals were comparable to control values throughout the study. Compared to the body weight gain of 1 .7 kg for control males, high-dose males gained only 0.1 kg during the entire 52-week study.

Clinical pathological examinations revealed some treatment-related changes in both the hematological and clinical chemistry parameters. Hemoglobin concentration, hematocrit, and erythrocyte count were reduced slightly, but significantly. in high-dose males. Alkaline phosphatase activities were increased in males (1.5 to 2.5-fold higher than controls) and females (1.4 to 2.6-fold higher than controls). Significant increases were noted in serum cholesterol levels of high-dose females, while BUN levels were decreased in high-dose males (significant) and females (non-significant). At the high-dose level, serum ChE activity was inhibited by 32 to 42% in males (entire study) and 23 to 26% in females (months I and 12 only). No treatment- related decreases were noted in brain and erythrocyte ChE activities.

Treatment-related necropsy findings were limited to high-dose animals. Increased relative (females) and absolute (males) liver weights were observed in high-dose animals, but, the lack of supporting histopathological findings suggests that the effects were adaptive, rather than treatment-related. Gross findings of the high dose male which was sacrificed revealed muscle atrophy; gross findings of other treated animals were similar to controls.

Histopathological evaluation of high-dose males and females, revealed Wallerian-type degeneration (described as swelling and/or degeneration of axons and/or myelin sheaths, plus the presence of

lipid-laden macrophages and/or proliferating Schwann cells) in the spinal cords (all levels) and various peripheral nerves (seiatic, sacral, and tibial nerves). The male which was sacrificed early showed widespread and very severe degenerative lesions in peripheral nerves as well as at all levels of the spinal cord, extending into the brain stem as well as the brain itself (cerebellar peduncles). Degenerative changes in the skeletal and cardiac muscle were also observed. Other possible treatment-related effects included mild thymic atrophy was observed two high-dose males, one mid-dose male and one low-dose female and mild bile stasis in the livers of high-dose males (4/5 vs. 1/5 for control). Additionally, small foci of alveolar fibrosis, accompanied by chronic inflammation, were found in the lungs of high-dose males (2/5), and all treated females (1/5, low-dose; 3/4, mid-dose; 2/5, high-dose vs. 1/5 for control).

Based on the results of this study (decreased body weight gain in males and peripheral/central nervous system degeneration and skeletal/cardiac muscle degeneration in males and females), the LOAEL of this study was established at 60 mg/kg/day. The NOAEL was established at 8 mg/kg/day. The LOAEL for ChE inhibition (decreased plasma ChE by 32 to 42% in males and 23 to 26% in females) was established at 60 mg/kg/day. The NOAEL for ChE inhibition was established at 8 mg/kg/day.

This study is acceptable (guideline) and satisfies requirements [§83- 1(b)] for a chronic toxicity study in the dog.

B.4.5 Carcinogenicity

870.4200a Carcinogenicity Study- Rat

Combined Chronic Toxicity/Oncogenicity study in the Rat: In this combined chronic toxicity and oncogenicity study (MRID Nos.: 00145004. 00145311), Charles River CD rats were fed diets containing sufficient EPTC (purity not given) to yield doses of 0 (basal diet), 5, 25, or 125 mg/kg/day (achieved doses: 0, 5.01, 25.0, or 125.8 mg/kg/day in males and 4.97, 24.8, or 124.8 mg/kg/day in females) for either 52 weeks (interim sacrifice, 10 animals/sex/dose) or 104 weeks (50 animals/sex/dose). The amount of EPTC in the diets was varied to achieve the desired dose levels. Treatment-related clinical signs were observed primarily in high-dose animals. After 85 to 95 weeks of treatment, females, followed shortly thereafter by males, exhibited hindquarter weakness (inability to assume an upright stance). Of the high-dose males in the main study, only 15/50 survived to terminal sacrifice; males in the low- and mid-dose groups and all female test groups had survival rates comparable to their control values. Other clinical observations in high- dose males included an increased incidence of cataracts (13/23 vs. 2/28 for controls) and discolored urine. Dose-related decreases in mean body weights were observed in both males and females. For the low-, mid- and high-dose groups, body weights (compared to concurrent control values) were decreased by 7, 15 and 36%, respectively, in males and 10, 16, and 40%, respectively, in females. Parallel decreases were also noted in mean feed consumption.

Clinical pathological evaluation revealed changes in some clinical chemistry and hematology parameters. High-dose males showed clotting abnormalities (increased activated partial thromboplastin and prothrombin times) at all of the evaluation times. BUN and AST were increased in high-dose males and females. Erythrocyte ChE activities were significantly decreased in high-dose males and females; no treatment related changes in brain or plasma ChE activities were seen.

Histopathological examination revealed treatment-related myocardial and neuromuscular lesions. The myocardial lesions were described as atrophied, chronic myocarditis, endocarditis, fibrosis, perica.rdial chronic inflammation, mineralization, pigmentation, and thrombosis. At the high-dose level, myocardial lesions correlated with increased AST activities. The overall (unscheduled plus scheduled deaths) incidence of all cardiac lesions for the entire study in the control, low-, mid- and high-dose groups was 24/60(40%), 18/60 (30%), 26/60 (43%) and 3 8/60 (63%) for males, respectively, and 8/60(13%), 8/60(13%), 7/60(12%), and 39/60(65%) for females, respectively. Neuromuscular lesions were described as degeneration/atrophy of fore- and hind-limb skeletal, increased incidence of axonal degeneration in the peripheral (sciatic and tibial nerves) and central (lumbar spine) nervous systems. Mid- and high-dose groups which died during the second year of the study and those at terminal sacrifice had high incidences of neuromuscular lesions. For mid-dose animals and high-dose animals, atrophy- and degeneration of muscle adjacent to sciatic nerve in males [3 1/47 (66%) and 37/39(95%), respectively, vs. 1/46 (2%) for control] and females [13/50(26%) and 34/43 (79%), respectively, vs. 0/47(0%) for control]; similar effects were noted in the biceps muscle of mid- and high-dose males and females. Atrophy and degeneration was observed in the sciatic nerves of mid- and high-dose males [37/46(80%) and 33/38 (87%), respectively, vs. 10/44 (2 1%) for control] and mid- and high-dose females [3 1/38 (82%) and 38/43 (88%), respectively, vs. 7/46(15%) for control]. Similar effects were noted in the tibial nerve of mid- and high-dose males and females. Axonal degeneration was noted in the lumbar spinal cords of mid- and high-dose males [40/47 (85%) and 25/38 (66%). respectively, vs. 21/47(45%) for control] and mid- and high-dose females [38/50 (76%) and 35/48 (73%), respectively, vs. 8/47 (17%) for control]. A lower incidence of axonal degeneration was noted in the sacral spinal cords of mid- and high-dose males [5/41 (12%) and 7/38 (18%), respectively, vs. 0/46(0%) for control] and mid- and high-dose females [3/47(6%) and 9/40(23%), respectively, vs. 0/39(0%) for control]. The incidence of axonal degeneration in the thoracic spinal cords of treated animals were similar to control values. There was no evidence that EPTC increased the incidences of neoplastic lesions.

Based on the results of this study (decreased body weight and increased incidences of myocardial and neuromuscular lesions), the LOAEL was established at 25 mg/kg/day in males and females. The NOAEL was established at 5 mg/kg/day.

This study is acceptable (guideline), and satisfies requirements (83-l and §83-2) for a combined chronic toxicity/oncogenicity study in the rat.

870.4200a Carcinogenicity Study- Rat

In a combined chronic toxicity/oncogenicity study (MRID No.: 40215001), EPTC (98.4%) was administered to 90 Crl:CD(SD)BR rats/sex/dose in diet at dose levels of 0,9, 18, 36, or 72 mg/kg/day for 104 weeks. Ten animals/sex/dose were sacrificed at 6, 12, and 18 months for interim evaluations. Mortality was unaffected by treatment. Systemic toxicity was characterized by changes in body weight, body weight gain, and food consumption, and neuromuscular and heart effects. When body weights of the treated groups were compared with controls, 9 and 18 mg/kg/day males weighed up to 9% less, 32 mg/kg/day males weighed up to 22% less, and 72 mg/kg/day males weighed up to 40% less, while 18 mg/kg/day females weighed up to 21% less, 36 mg/kg/day females weighed 28% less, and 72 mg/kg/day females weighed up to 40% less. Although not generally statistically significant, body weights were decreased in 9 mg/kg/day females during the second year (up to -13% less). Overall body weight gains were depressed ($p \leq 0.05$) by 28% and 41% in 36 and 72 mg/kg/day males,

respectively, and by 12%, 27%, 36%, and 55% in 9, 18, 36, and 72 mg/kg/day females, respectively. Food consumption was significantly ($p \leq 0.05$) decreased in 36 and 72 mg/kg/day males and females throughout most of the study. In addition, food efficiency was decreased in 36 and 72 mg/kg/day males (-20, -28%) and in all treated female groups (-11, -26, -30, -48%) as compared with controls. Other systemic signs of toxicity were generally present and statistically significant ($p \leq 0.05$) in main study males fed at least 18 mg/kg/day and in females fed at least 36 mg/kg/day. Neuromuscular effects were manifested by a general dose-related increase in hindquarter muscle syndrome and skeletal muscle atrophy, degeneration and necrosis, and steatosis. Changes observed in the sciatic nerve included cholesterol clefts, mineralization of blood vessels, and decreased myelin staining with increased interaxonal space. Cardiotoxicity was indicated by an increased incidence of microscopic lesions, including degenerative cardiomyopathy, fibrosis, mononuclear cell infiltration, and cartilaginous metaplasia of the endocardium. The appearance of cardiomyopathy was accelerated in a dose-related manner in treated animals as compared with controls. The incidence of cardiomyopathy was statistically increased ($p \leq 0.05$) in all treated males at 12 and 18 months, in 12-month interim females fed at least 18 mg/kg/day, and in all 18-month interim females. By the 24-month evaluation, low-dose males and 9 and 18 mg/kg/day females no longer had a significantly increased incidence of cardiomyopathy as compared with controls.

A LOAEL of 9 mg/kg/day was established in male and female rats based on decreased body weights and bodyweight gains and an accelerated appearance of cardiomyopathy in males, and decreased body weights, body weight gains, and food efficiency and an accelerated appearance of cardiomyopathy in females. A NOAEL could not be established for males or females.

Because a NOAEL for systemic toxicity was not established, this study is classified as unacceptable (guideline) and does not satisfy guideline requirement for a chronic toxicity study in rats (§83-1). The LOAEL was established at 9 mg/kg/day based on increased incidence of degenerative cardiomyopathy.

The carcinogenicity portion of this study is acceptable (guideline) and fulfills requirements for a carcinogenicity study in the rat. At the doses tested, there was not a treatment-related increase in tumor incidences when compared to controls. Dosing was considered adequate based on observed treatment-related toxicity.

870.4200b Carcinogenicity Toxicity- Mouse

Oncogenicity Study in the Mouse: In this study, CRL:CD-1(IRC)BR mice (60/sex/dose) were fed diets containing EPTC (98.5%) at concentrations of 0, 200, 600 or 1800 ppm (approximately 0, 30, 90, or 270 mg/kg/day in males and females) for 78 weeks. An interim sacrifice at week 52 was performed on an additional 5 animals/sex/dose.

No treatment-related clinical signs were observed during the study. Mortality of treated animals was comparable to control values.

At the high-dose level, consistent and statistically significant ($p \leq 0.05$) decreases in body weights of 3 to 13% in males and 10 to 13% in females. At the mid-dose level, females showed a slight (3 to 6%), but statistically significant ($p \leq 0.05$) decreases in body weights at most measurement intervals up to week 68; body weights of mid-dose males were comparable to control values. Food

consumption was significantly ($p \leq 0.05$) decreased by 13.6 to 42% in high- dose females up to week 20; at later time points, sporadic decreases were observed.

No treatment-related differences were noted in any of the hematological parameters evaluated. Clinical chemistry and urinalysis were not performed.

Pathological evaluation did not reveal any treatment-related macroscopic effects; the Jesions were not considered unusual in type, frequency, or severity. The incidences of non neoplastic microscopic lesions were similar between control and treated mice.

There was no evidence of carcinogenicity attributed to EPTC. The tumor profiles of treated animals were comparable to control values. Malignant neoplasms, benign tumors, and other histopathological lesions generally occurred to the same extent in the control and dose animals. The doses used in this study were adequate to assess the oncogenic potential of EPTC.

Based on the results of this study (decreased body weight and food consumption), the LOAEL was established at 1800 ppm (270 mg/kg/day). The NOAEL was established at 600 ppm (90 mg/kg/day).

This study is acceptable (guideline) and satisfies requirements (§83-2) for an oncogenicity study in the mouse.

B.4.6 Mutagenicity Studies

870.5100 Salmonella tvphimurium Gene Mutation / Eseherichia coli Reverse Gene Mutation Assays:

In one study (MMD No.: 00152451), EPTC (97.2%) was evaluated for mutagenic potential in the reverse mutation test (Ames assay), with and without S9 activation using Salmonella typhimurim (TA 1535, TA1537, TA1538, TA98 and TA100) and *Escherichia coli* (WP2 *hcr* (*uvr*A)). EPTC was tested to the limit of cytotoxicity or solubility. EPTC did not induce a mutagenic response in the Ames assay with or without 89 activation at doses from 10 to 5000 µg/plate. Positive control materials for all tester strains induced large numbers of revertants over the solvent control, confirming the sensitivity of the assay.

This study is acceptable (guideline) and satisfies §84-4 requirements for a gene mutation assay.

870.5100 Salmonella tvphimurium Gene Mutation / Eseherichia coli Reverse Gene Mutation Assays:

In another gene mutation assay (MRID No.: 00152452) EPTC (purity not given) was evaluated for mutagenic potential in the reverse mutation test (Ames assay), with and without S9 activation using Salmonella typhimurim (TA1535, TA1537, TA1538, TA98 and TA100).

In this assay, EPTC (0.001 - 5.0 µL/plate) was not mutagenic with or without S9 activation. Positive control materials for all tester strains induced large numbers of revertants over the solvent control, confirming the sensitivity of the assay.

This study is acceptable (guideline) and satisfies §84-4 requirements for a gene mutation assay.

870.5300 In vitro mouse lymphoma assay

In one mouse lymphoma assay (MMD No.: 00152454), EPTC (98.6%) was evaluated for mutagenic potential in L5 I 78Y (TK+/-) mouse lymphoma cells with and without metabolic (S9) activation. EPTC, over a dose range of 0.006 to 3.0µg/mL, showed dose-related cytotoxicity at dose levels greater than or equal to 0.023 µg/mL with and without S9 activation. In the mutagenicity assay, EPTC was evaluated over a dose range of 0.0125 to 0.1500µg/mL without S9 activation and, 0.005 to 0.06µg/mL with S9 activation. Under conditions of this assay, EPTC induced a slight mutagenic effect at a concentration of 0.05 and 0.06 µg/mL in duplicate with metabolic activation, but was negative over a dose range of 0.0125 to 0.15 µg/mL in the nonactivated system.

This study is acceptable (guideline) and satisfies §84-4 requirements for a gene mutation assay

870.5300 In vitro mouse lymphoma assay

In another mouse lymphoma assay, (MRID No.: 00 61602), EPTC (98.5%) was evaluated in a mouse lymphoma cell metagenesis assay (TK+/- +TK-/-) with or without metabolic (S9) activation. In the absence of S9 activation, EPTC was negative up to cytotoxic concentrations (250 µg/mL) did not increase the number of mutant colonies over the solvent control value (average mutant frequency of $80/10^6$ cells). With S9 activation, EPTC was positive at all concentrations tested (42 to 250 µg/mL).

This study is acceptable (guideline) and satisfies §84-4 requirements for a gene mutation assay.

870.5300 3) Drosophila melanogaster Sex-Linked Recessive Lethal Mutations

In this published article (MRID 00153248), the mutagenic potential 53 compounds, including EPTC (99%) was evaluated in *Drosophila*. EPTC was administered for 3 days to Canton-S males either in the diet at 150 ppm or intra-abdominally at 1250 ppm. The doses were selected to produce 30% mortality. Individual flies were mated 3, 5, and 7 days after dosing to mutant (*Basc)* females. Based on the results of the study, EPIC was negative for inducing sex-linked recessive lethals. The frequency of lethals in the progeny from EPTC-fed males was 7/5531(0.13%) and from injected flies, 7/5048 (0.14%).

This study is acceptable (guideline) and satisfies §84-4 requirements for a gene mutation assay.

870.5375 In vitro Chinese Hamster Ovary (CHO) Cell Chromosome Aberration Assay

In this study (MRID 00161601), EPTC (% purity not stated) was evaluated for inducing chromosome aberrations in *CHO* cells treated at a doses of 30, 60, 90, 120, 150 or 200 µg/mL without metabolic activation (S9) and 15,30, 75, 150, 225 or 300 µg/mL with S9 activation. In the absence of S9 activation, no dividing cells were observed at EPTC doses of 150 and 200 µg/mL and 20% reduction (non-significant) in monolayer confluency, combined with observable deceases in mitosis, at 90 and 120 µg/mL. At doses of 30 to 60µg/mL no significant increases in chromosomally aberrant cells over controls were found. The positive control, MMC, induced large increases in aberrant cells (26%), the number of aberrations per cell (>0.32 vs. 0.03 for controls), and multiple aberrant cells (4.0% vs. 0.5%).

In the presence of S9 activation, EPTC at 225 and 300µg/mL were lethal. At 150µg/mL there was moderate reduction in confluency (25%), and slightly reduced number of observable mitotic cells. There was no significant increase in chromosome aberrations at 15, 30, 75 or 150µg/mL (2.5%, 1.0%, 1% and 4%, respectively). Positive controls treated with CP resulted in 36% of the cells with aberrations overall, at a rate of 0.48 aberrations per cell, and 8.0% with more than one aberration. From the results of this assay, EPTC was negative for the induction of chromosome aberrations in CHO cells with or without S9 activation.

This study is acceptable (guideline) and satisfies 84-4 requirements for a chromosomal aberration assay.

870.5375 Mouse Lymphoma Chromosomal Aberration Assay

In this study (MRID No.:00152455) the mutagenic potential of EPTC (98.6%) was evaluated in a chromosomal aberration assay in mouse lymphoma cells. EPTC concentrations ranged from 0.0125 to 0.15µg/mL without metabolic (S9) activation and 0.005 to 0.06 µg/mL with S9 activation. EPTC was cytotoxic above concentrations of 0.023µg/mL or higher with and without S9 activation. EPTC did not induce a dose-related statistically significant increase in chromosomal aberrations compared to the concurrent solvent control. Therefore, EPTC was not considered clastogenic in mouse lymphoma cells L5178Y over dose ranges of 0.0125 to 0.15 µg/mL without S9 activation or 0.005 to 0.06 µg/mL with S9 activation.

This study is acceptable (guideline) and satisfies §84-4 requirements for a gene mutation assay.

870.5550 Mouse Micronucleus Assay

In this study (MRID No.: 00142895), the mutagenic potential of EPTC (98.6%) was evaluated in a bone marrow micronucleus assay in the mouse. Male and female mice were orally gavaged with EPTC at doses of 0 (corn oil), 250, 500, or 1000 mg/kg in one trial and at doses of 0, 1000, 1200, or 1400 mg/kg in another. Animals were sacrificed 24, 48, and 72 hours after dosing: Positive control mice were treated with cyclophosphamide.
There were no significant increases in micronuclei at any dose or sacrifice time in either sex. No increase in induction of micronuclei with EPTC, administered at toxic levels (reduction in survival by 45%).

This study is acceptable (guideline), and satisfies §84-4 requirements for a mutagenicity study.

870.5550 *Bacillus subtilis* Rec-Assay

In this study (MRID No.: 00152451), EPTC (97.2%) was evaluated for its ability to induce DNA repair using strains HA17 and M45 of *Bacillus subtilis* without metabolic (S9) activation. EPTC did not induce DNA damage in *B. subtilis rec*M45 strain at concentrations from 1 to 100% (v/v) without S9 activation.

This study is acceptable (guideline) and satisfied §84-4 requirements for other genotoxic effects.

870.5550 Unscheduled DNA Synthesis (UDS) Assay

In this study (MRID No.: 00161600), EPTC (98.5%) was evaluated in a primary DNA damage/repair assay in isolated primary rat hepatocytes. The hepatocytes were exposed to graded concentrations of EPTC (0.1 to 5000µg/mL, preliminary assay; 3 to 500µg/mL, replicate assay) together with 10 µCi/mL ^{3}H-thymidine for 19 to 21 hr at 37°C. The cells were washed, swelled in hypotonic saline, fixed, and prepared for autoradiographic grain counts. 2-AAF (2-acetylaminofluorene) was used as a positive control.

EPTC was cytotoxic at concentrations of 250µg/mL and above; precipitation was noted at 1000 and 5000 µg/mL. In contrast to the positive UDS response in the majority of cells treated with 2-AAF, test plates were negative at all useful concentrations of EPTC up to the nontoxic level of 100 µg/mL, registering negative NG values in the few cells with any grains (not different from the negative controls).

This study in acceptable (guideline), and satisfies §84-4 requirements for other genotoxic effects.

870.7485 Metabolism

In a metabolism study (MRID 00142896), Long-Evans rats (6/sex) were given 121-150 mg/kg [propyl-1-^{14}C] Eptam (98% a.i.; lot/batch no. not given) by oral intubation. Their excretion pattern was determined for 1, 3, or 7 days, when they were sacrificed and tissue samples (100-250 mg) were collected and frozen. The tissues were subsequently combusted and radioanalyzed (for $^{14}CO_2$,) to determine Eptam distribution. *In vitro* studies with mouse post-mitochondrial supernatant were conducted to elucidate the Eptam metabolic pathway.

Eptam was rapidly absorbed and excreted: the urine of males and females contained 81 and 88% of the administered radiolabel, respectively, within 24 hours. The feces and expired air were minor excretion routes, each containing ≤ 3.2% of the radioactivity over 96 hours. Absorption was estimated to be 86.7-97.5% of the administered dose for the two sexes. The mass balance accounting for the 1, 3, and 7-day experiments was acceptable: radioactivity from the expired air, urine, feces, and cage wash accounted for 90.1, 99.6, and 88.8% of the given dose, respectively (for males and females combined; there were no notable gender-related differences). Absorbed Eptam was widely distributed, with the greatest amount of radioactivity per mg organ found in the blood, kidneys, liver, and spleen after 24 hours. Radioactivity declined significantly with time in all tissues except blood and spleen, which retained 72-80% of their 24-hour radioactivity after 7 days. Only 1.2% of the given radioactivity was in all the tissues after 7 days, however, indicating that there was no significant bioaccumulation.

The *in vitro* studies with Eptam and mouse post-mitochondrial supernatant showed that NADPH was required for Eptam metabolism, implicating the involvement of mixed function oxidases. Three metabolites tentatively identified by TLC were dipropyl amine, the Eptam sulfoxide, and the OSH conjugate. Exogenous GSH substantially increased the formation of the GSH conjugate from both Eptam and Eptam sulfoxide.

This metabolism study is classified as acceptable (guideline) and fulfills Tier 1 data requirements for a metabolism study in the rat (OPPTS 870-7485).

B.4.7 Neurotoxicity Studies

870.6100a Acute Delayed Neurotoxicity Study in the Hen

In this acute delayed neurotoxicity study (MRID No.: 00150325), hens (10/dose) were dosed with EPTC (98.4%) at 4674 mg/kg (LD_{50}) and observed for 2l days. Surviving hens were redosed with EPTC and observed for an additional 21 days. Negative (corn oil) and positive (TOCP, 500 mg/kg) control groups were included in the study.

No EPTC-treated hens lost weight, became subdued and/or unsteady. All surviving hens recovered by day 7. At termination of the study, no histopathological evidence of neurotoxicity was observed in the EPTC-treated hens. All TOCP-treated hens, however, exhibited ataxia, which became progressively worse over time. Neuropathological evaluation of the TOCP-treated hens had significant neurological degeneration in one or more spinal cord levels, as well as peripheral nerves.

This study is classified as acceptable (guideline), and satisfies requirements (8l-7) for an acute delayed neurotoxicity study in hen.

870.6200a Acute Neurotoxicity Study in the Rat

In this acute neurotoxicity study (MRID No.:43039701, 43297401), Alpk:APfSD rats (10/sex/dose, 34 to 36 days old) were treated orally with EPTC (98.4%) at doses of 0 (vehicle only, 100% corn oil), 200. 1000, or 2000 mg/kg. Clinical observations were made at least once daily, while body weights, Functional Observational Battery (FOB) and motor activity were evaluated at prestudy (day -1), at the peak time of effect (5 hr post-dosing) and on days 8 and 15. At study termination, five animals/sex/dose were perfusion fixed for neurohistopathological evaluation.

Four animals died or were euthanized within two days post-dosing; two high-dose males were found dead on day 2, and one female each from the mid-dose and high-dose groups were sacrificed in extremis on days 1 and 2, respectively.

Body weights were reduced in mid- and high-dose males on day 8 (6 and 16%, respectively) and day 15 (2% and 9%, respectively). Body weights of high-dose females were significantly lower (4%) than control values on day 8, but were slightly higher than control values by day 15. Food consumption was reduced during the first week treatment in mid- and high-dose males (14% and 35%, respectively, $p \leq 0.01$).

Neurobehavioral evaluations (FOB and motor activity) revealed treatment-related effects at the peak time-of-effect (1to 5 hr post-dosing) with decreasing incidence on subsequent days. Clinical signs were observed in mid- and high-dose animals at the peak time-of-effect (lacrimation, salivation, hypoactivity, upward curvature of the spine, and reduced foot withdrawal reflex). Some animals continued to show clinical signs on day 2; animals were, in general, symptom free on days 4 or 5. Decreased motor activity was observed in males and female at the mid- and/or high-dose levels. For the first five minutes post-dosing, mid- and high-dose males and high-dose females showed significantly lower motor activity; overall motor activity was similar to control values.
Brain measurements at terminal sacrifice revealed statistically significant decreases in weight of mid- and high-dose males (5.5 and 6.5%, respectively) and females (2.7 and 3.3%, respectively) compared to control values. The brain length of high-dose males was reduced by 3%.

Neuropathological evaluations revealed neuronal necrosis in pyriform/entorhinal cortex of the cerebrum or the ventral/caudal portion of the dentate gyrus or both in the brains of low-(males: 2/5, minimal; 0/5, females), mid- (males: 1/5, minimal, 3/5, slight, 1/5, moderate; females: 3/5, slight, 2/5, moderate) and high- (males: 5/5, marked; females: 2/5, moderate, 3/5. marked) dose animals.

Based on the results of this study, the LOAEL was established at 200 mg/kg in males (neuronal cell necrosis in the brain) and 1000 mg/kg in females (clinical signs, death, and neuronal cell necrosis in the brain). The NOAEL was not established in males and established at 200 mg/kg in females.

This study is acceptable (guideline), and satisfies requirements (81-7(b) for an acute neurotoxicity study in the rat.

870.6200b Subchronic Neurotoxicity Study in the Rat

In this subchronic neurotoxicity study (MRID No.: 43230901), Alpk:APfSO rats (12/sex/dose, approximately 6 weeks old) were fed diets containing EPTC (98.4%) at 0 (basal diet), 500, 1000, or 2500 ppm (0, 7.9, 39.4, or 193 mg/kg/day, males; 0, 8.8, 43.5, or 205 mg/kg/day, females) for 13 weeks. Clinical observations were made at least once daily, while body weights and food consumption were determined on a weekly basis. Functional Observational Battery (FOB) and motor activity were evaluated at study weeks 1, 5, 9, and 14. At study termination, six animals/sex/dose were perfusion fixed for neurohistopathological evaluation.

One high-dose male was found dead on day 3; the cause of death could not be determined; all other animals survived to terminal sacrifice Urine incontinence was observed in 5/12 high-dose females; no other treatment-related clinical signs were observed.

Mean body weights were statistically significantly ($p \leq 0.05$) lower in mid- and high-dose females and high-dose males, the differences were, however, not biologically significant (5 to 7%). Body weight gains were decreased in mid-dose males (7%, NS) and females (13%, $p \leq 0.05$) and high-dose males (10%, $p \leq 0.05$) and females (17%, $p \leq 0.05$). Food consumption was significantly lower in high-dose males (8 to 14%) and females (10 to 18%). Food utilization did not show any consistent treatment-related effects.

At the high-dose, FOB results showed significantly decreased landing foot splay in females and increases in time to tail flick in males. No other consistent treatment-related findings were observed. At study termination, significant differences were noted in the brain measurements of mid- and high-dose animals. Relative (to body weight) brain weights were significantly decreased in .mid- and high-dose females (4.0 and 9.6%, respectively) and high-dose males (2.3%). Relative brain width of high-dose females was decreased (4.1%). For males, no treatment-related differences were noted brain widths and lengths, either absolute or corrected for body weights.

Neuropathological evaluation of the brains revealed treatment-related increases in the incidence of neuronal necrosis (all graded as minimal) in mid- and high-dose males (2/6 and 4/6, respectively), compared to 1/6 control (and low-dose) males. Necrosis was also noted in mid- and high-dose females (1/6 and 5/6, respectively), while no lesions were observed in control and low- dose females.

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Based on the results of this study (decreased body weight gain and relative brain weight in females and neuronal necrosis in the brain in males and females), the LOAEL was established at 500 ppm (39 mg/kg/day, males; 44mg/kg/day, females). The NOAEL was established at 100 ppm (7.9 mg/kg/day, males; 8.8 mg/kg/day, females).

This study is acceptable (guideline) and satisfies the requirements (82-5(b)) for a subchronic neurotoxicity study in the rat.

B.5 Bench Mark Dose Analysis for EPTC 00154784 Inhalation Study

B.5.1 EPTC 00154784 Inhalation 82-7 adult brain Female 9 week

Exponential
Constant variance
10 bmr

```
================================================================
        Exponential Model. (Version: 1.7;  Date: 12/10/2009)
        Input Data File: C:/Usepa/BMDS212/Data/exp_Actualruns_Setting.(d)
        Gnuplot Plotting File:
                                              Fri Sep 10 10:32:49 2010
================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

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            Model 3            Model 4            Model 5
     --------            -------            -------            -------            -------
     lnalpha             3.16431            3.16431            3.16431            3.16431
         rho(S)                   0                  0                  0                  0
51.975
           b        0.000594231        0.000594231         0.00153859         0.00153859
           c                 --                 --           0.390572           0.390572
           d                 --                  1                 --                  1

     (S) = Specified
```

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Parameter Estimates by Model

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	3.26609	3.20656	3.26609	3.20656
rho	0	0	0	0
a	48.6981	48.2667	48.6981	48.2667
b	0.000580176	0.00295984	0.000580176	0.00291765
c	--	--	0	0
d	--	11.4877	--	10.5007

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	6	46.7	6.02
8.3	6	48.6	2.65
58	6	49.5	4.53
290	6	40.6	7.06

Estimated Values of Interest

Model	Dose	Est Mean	Est Std	Scaled Residual
2	0	48.7	5.119	-0.956
	8.3	48.46	5.119	0.06499
	58	47.09	5.119	1.155
	290	41.16	5.119	-0.2664
3	0	48.27	4.969	-0.7722
	8.3	48.27	4.969	0.1643
	58	48.27	4.969	0.6079
	290	40.6	4.969	1.507e-007
4	0	48.7	5.119	-0.956
	8.3	48.46	5.119	0.06499
	58	47.09	5.119	1.155
	290	41.16	5.119	-0.2664
5	0	48.27	4.969	-0.7722
	8.3	48.27	4.969	0.1643
	58	48.27	4.969	0.6079
	290	40.6	4.969	-6.208e-008

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	-49.97171	5	109.9434
A2	-47.22102	8	110.442
A3	-49.97171	5	109.9434
R	-54.90681	2	113.8136
2	-51.19307	3	108.3861
3	-50.47874	4	108.9575
4	-51.19307	3	108.3861
5	-50.47874	4	108.9575

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)

Test 5a: Does Model 3 fit the data? (A3 vs 3)
Test 5b: Is Model 3 better than Model 2? (3 vs. 2)

Test 6a: Does Model 4 fit the data? (A3 vs 4)
Test 6b: Is Model 4 better than Model 2? (4 vs. 2)

Test 7a: Does Model 5 fit the data? (A3 vs 5)
Test 7b: Is Model 5 better than Model 3? (5 vs. 3)
Test 7c: Is Model 5 better than Model 4? (5 vs. 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	15.37	6	0.01756
Test 2	5.501	3	0.1386
Test 3	5.501	3	0.1386
Test 4	2.443	2	0.2948
Test 5a	1.014	1	0.3139
Test 5b	1.429	1	0.232
Test 6a	2.443	2	0.2948
Test 6b	0	0	N/A
Test 7a	1.014	1	0.3139
Test 7b	-1.821e-007	0	N/A
Test 7c	1.429	1	0.232

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.

The p-value for Test 5a is greater than .1. Model 3 seems

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to adequately describe the data.

The p-value for Test 5b is greater than .05. Model 3 does not seem to fit the data better than Model 2.
The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Degrees of freedom for Test 6b are less than or equal to 0.
The Chi-Square test for fit is not valid.

The p-value for Test 7a is greater than .1. Model 5 seems to adequately describe the data.

Degrees of freedom for Test 7b are less than or equal to 0.
The Chi-Square test for fit is not valid.

The p-value for Test 7c is greater than .05. Model 5 does not seem to fit the data better than Model 4.

Benchmark Dose Computations:

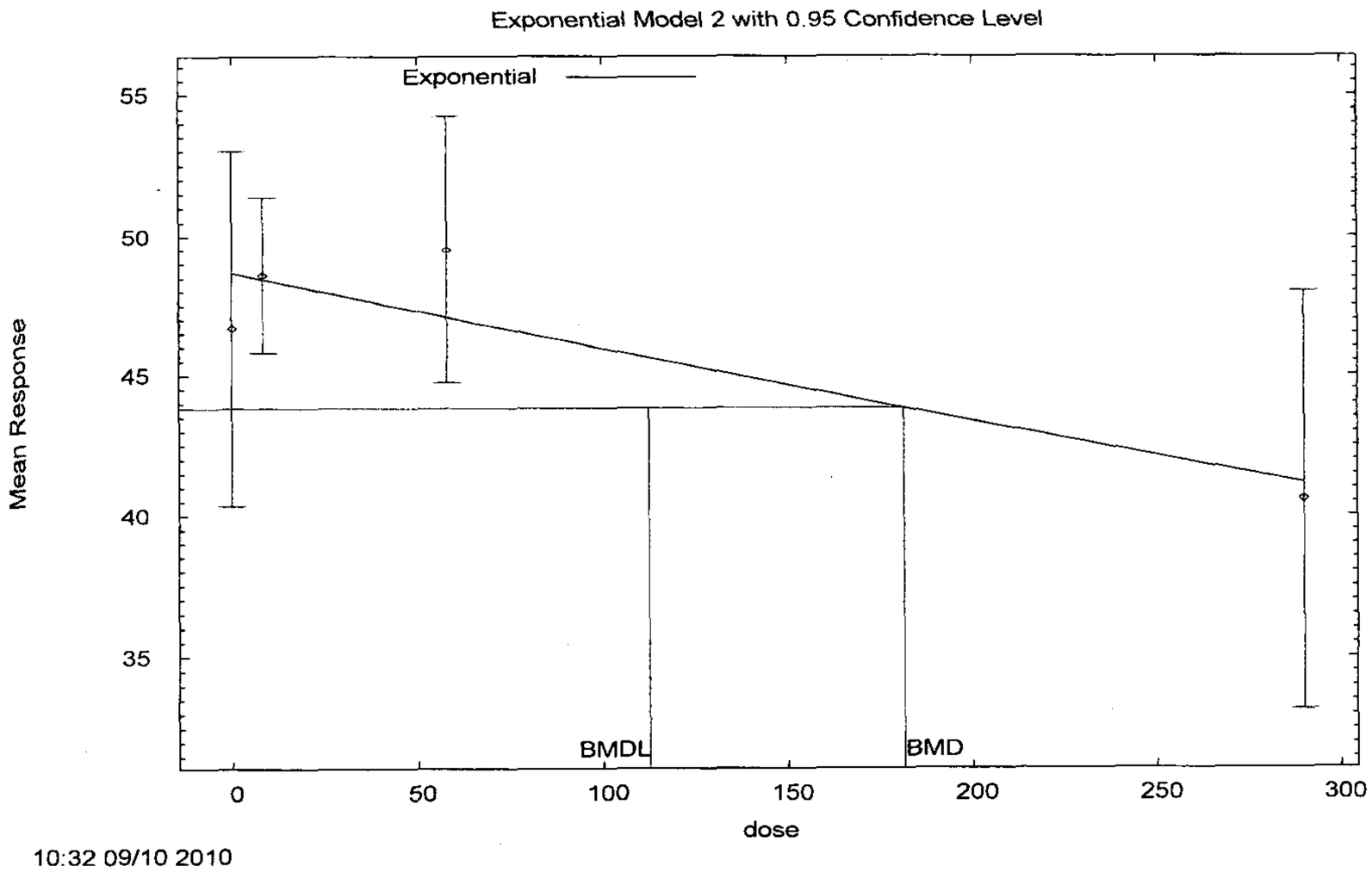
Specified Effect = 0.100000

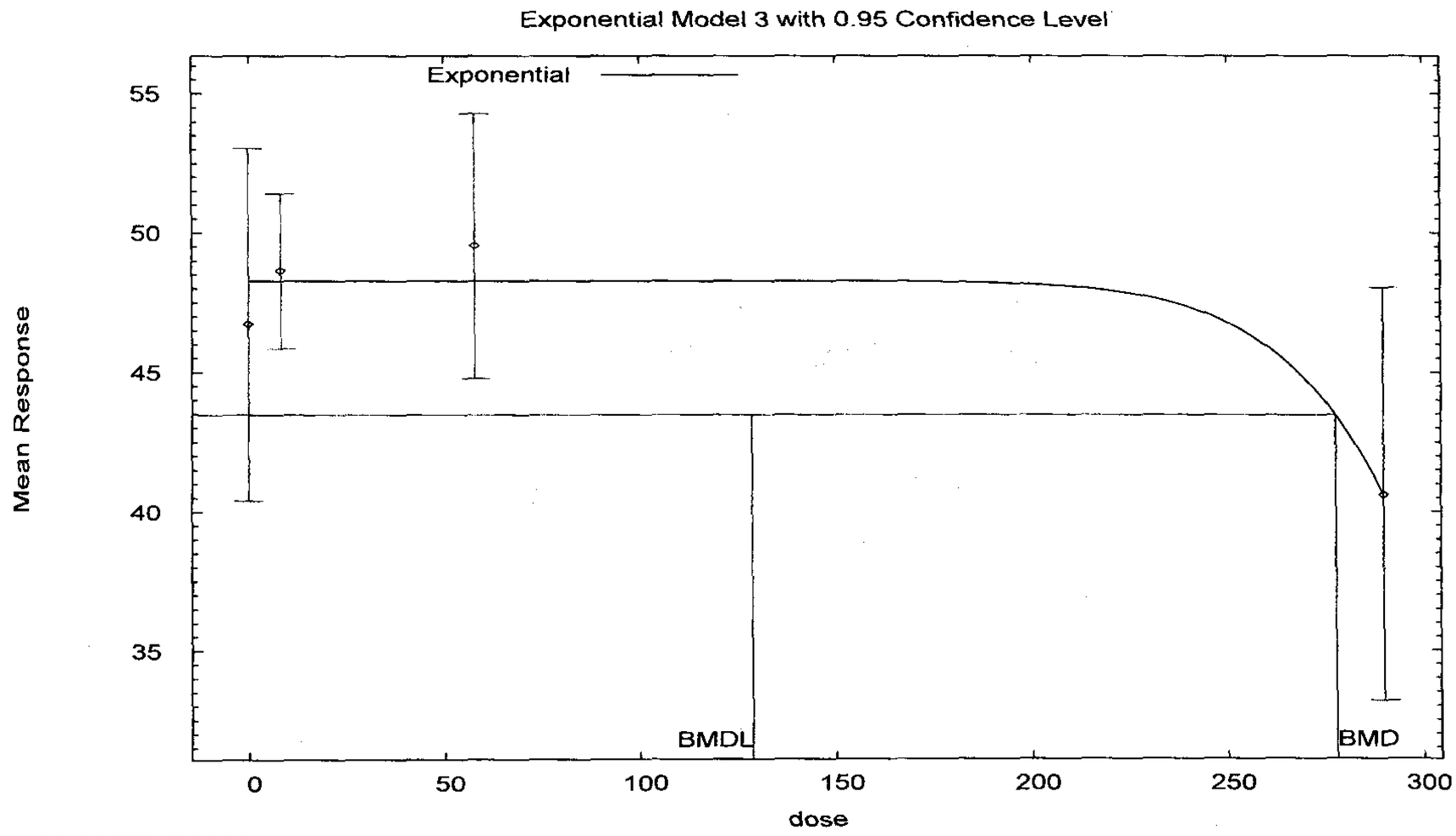
Risk Type = Relative deviation

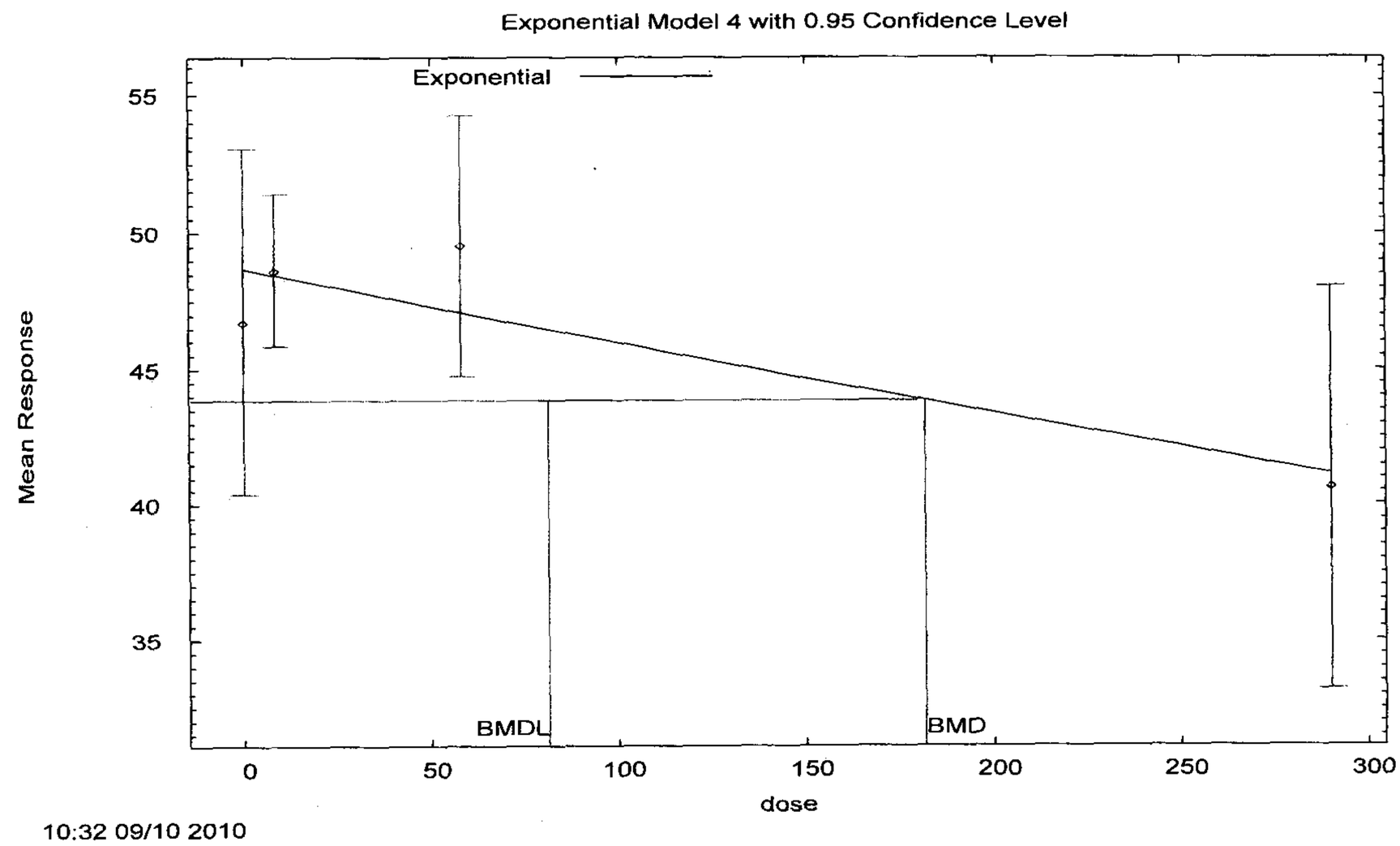
Confidence Level = 0.950000

BMD and BMDL by Model

Model	BMD	BMDL
2	181.601	112.543
3	277.751	128.666
4	181.601	81.2392
5	276.627	60.5932




Exponential Model 3 with 0.95 Confidence Level
Exponential
Mean Response
55
50
45
40
35
BMDL
BMD
0
50
100
150
200
250
300
dose
10:32 09/10 2010


Exponential Model 4 with 0.95 Confidence Level
Exponential
Mean Response
55
50
45
40
35
BMDL
BMD
0
50
100
150
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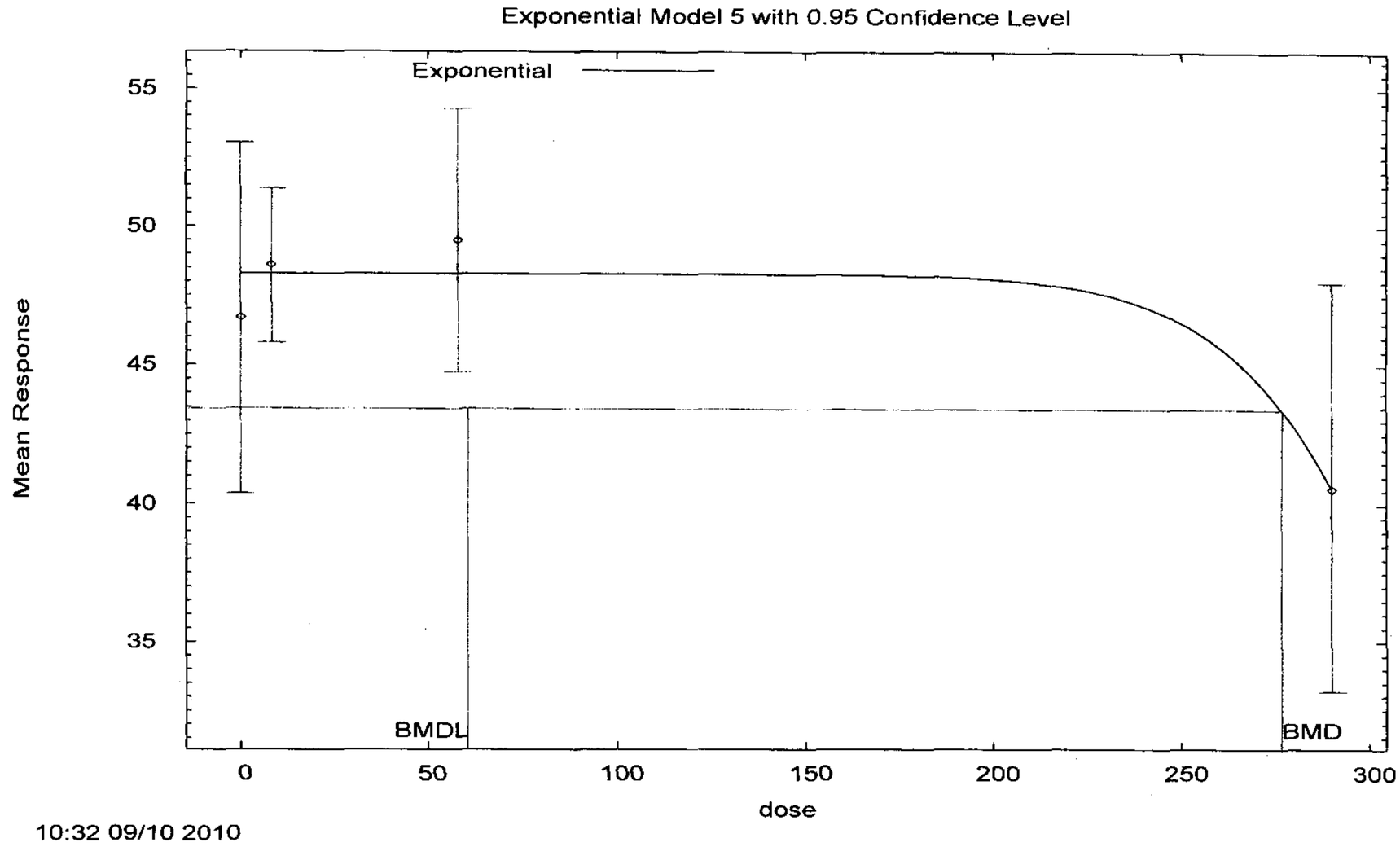
250
300
dose
10:32 09/10 2010



B.5.2 EPTC 00154784 Inhalation 82-7 adult brain Female 13 week

Exponential
Constant variance
Bmr 10

```
================================================================
        Exponential Model. (Version: 1.7;  Date: 12/10/2009)
        Input Data File: C:/Usepa/BMDS212/Data/exp_Actualruns_Setting.(d)
        Gnuplot Plotting File:
                                          Fri Sep 10 10:44:32 2010
================================================================
 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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	Model 3	Model 4	Model 5
lnalpha	3.72883	3.72883	3.72883	3.72883
rho(S)	0	0	0	0
a	38.3498	38.3498	49.14	49.14
b	0.000768227	0.000768227	0.0081606	0.0081606
c	--	--	0.695777	0.695777
d	--	1	--	1

(S) = Specified

Parameter Estimates by Model

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	3.89334	3.89334	3.77582	3.73961
rho	0	0	0	0
a	44.2353	44.2353	46.443	45.85
b	0.000815618	0.000815618	0.0218827	0.0182244
c	--	--	0.765939	0.782988
d	--	1	--	9.67295

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	12	44.9	5.84
8.3	12	46.8	9.7
58	12	37.7	6.21
290	12	35.9	3.86

Estimated Values of Interest

Model	Dose	Est Mean	Est Std	Scaled Residual
2	0	44.24	7.005	0.3287
	8.3	43.94	7.005	1.416
	58	42.19	7.005	-2.221
	290	34.92	7.005	0.4857
3	0	44.24	7.005	0.3287
	8.3	43.94	7.005	1.416
	58	42.19	7.005	-2.221
	290	34.92	7.005	0.4857

4	0	46.44	6.606	-0.8092
	8.3	44.64	6.606	1.134
	58	38.63	6.606	-0.4865
	290	35.59	6.606	0.1617
5	0	45.85	6.487	-0.5073
	8.3	45.85	6.487	0.5073
	58	37.7	6.487	1.42e-007
	290	35.9	6.487	-2.984e-007

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	-113.4919	5	236.9837
A2	-108.4759	8	232.9519
A3	-113.4919	5	236.9837
R	-123.4208	2	250.8416
2	-117.4402	3	240.8804
3	-117.4402	3	240.8804
4	-114.6198	4	237.2396
5	-113.7506	5	237.5012

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 4: Does Model 2 fit the data? (A3 vs. 2)

Test 5a: Does Model 3 fit the data? (A3 vs 3)
Test 5b: Is Model 3 better than Model 2? (3 vs. 2)

Test 6a: Does Model 4 fit the data? (A3 vs 4)
Test 6b: Is Model 4 better than Model 2? (4 vs. 2)

Test 7a: Does Model 5 fit the data? (A3 vs 5)
Test 7b: Is Model 5 better than Model 3? (5 vs. 3)
Test 7c: Is Model 5 better than Model 4? (5 vs. 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	29.89	6	< 0.0001
Test 2	10.03	3	0.0183
Test 3	10.03	3	0.0183
Test 4	7.897	2	0.01929
Test 5a	7.897	2	0.01929
Test 5b	-3.979e-013	0	N/A
Test 6a	2.256	1	0.1331
Test 6b	5.641	1	0.01755
Test 7a	0.5175	0	N/A
Test 7b	7.379	2	0.02498
Test 7c	1.738	1	0.1873

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. Model 2 may not adequately describe the data; you may want to consider another model.

The p-value for Test 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model.

Degrees of freedom for Test 5b are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

The p-value for Test 6b is less than .05. Model 4 appears to fit the data better than Model 2.

Degrees of freedom for Test 7a are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 7b is less than .05. Model 5 appears to fit the data better than Model 3.

The p-value for Test 7c is greater than .05. Model 5 does not seem to fit the data better than Model 4.

Benchmark Dose Computations:

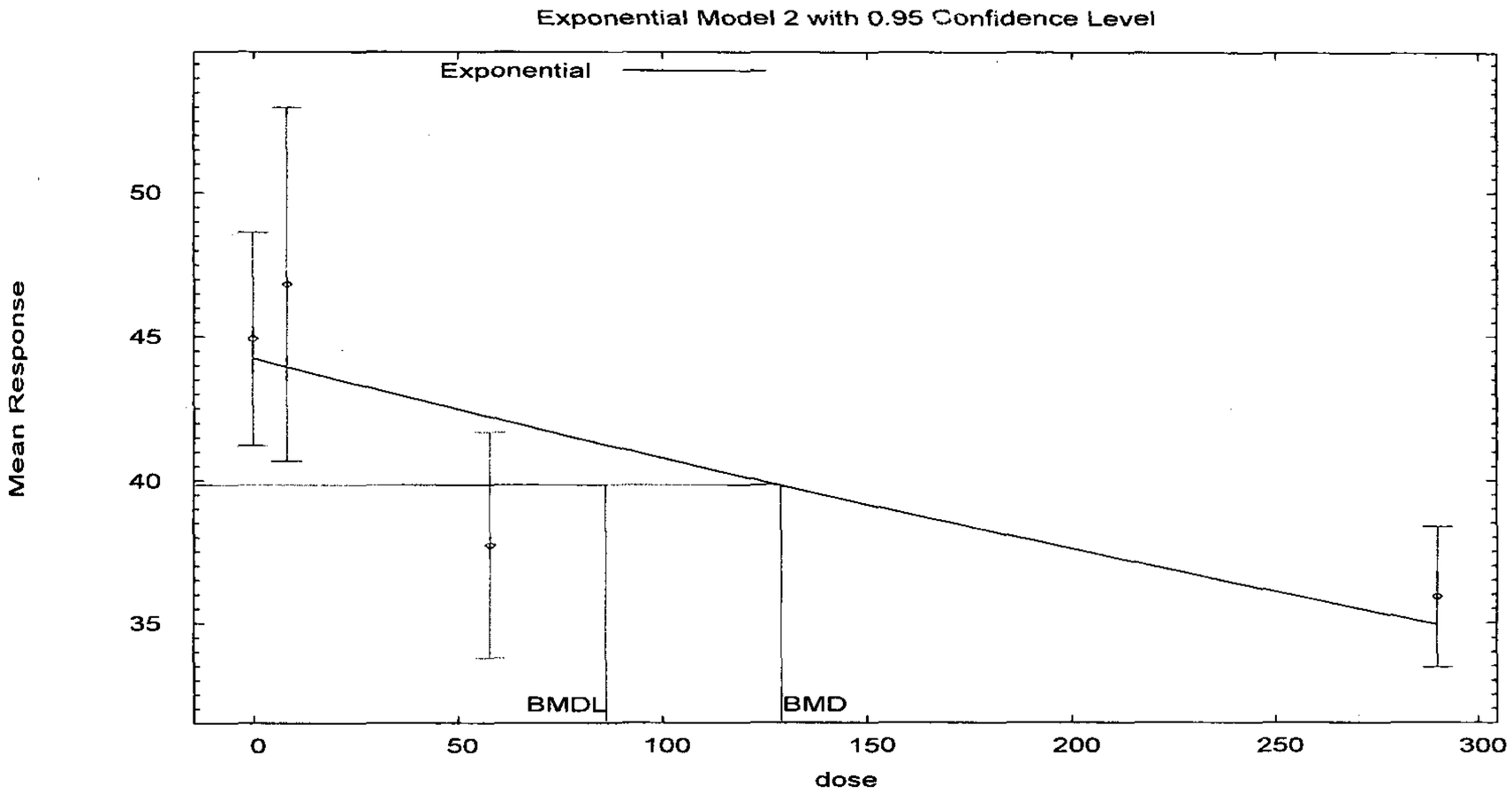
Specified Effect = 0.100000

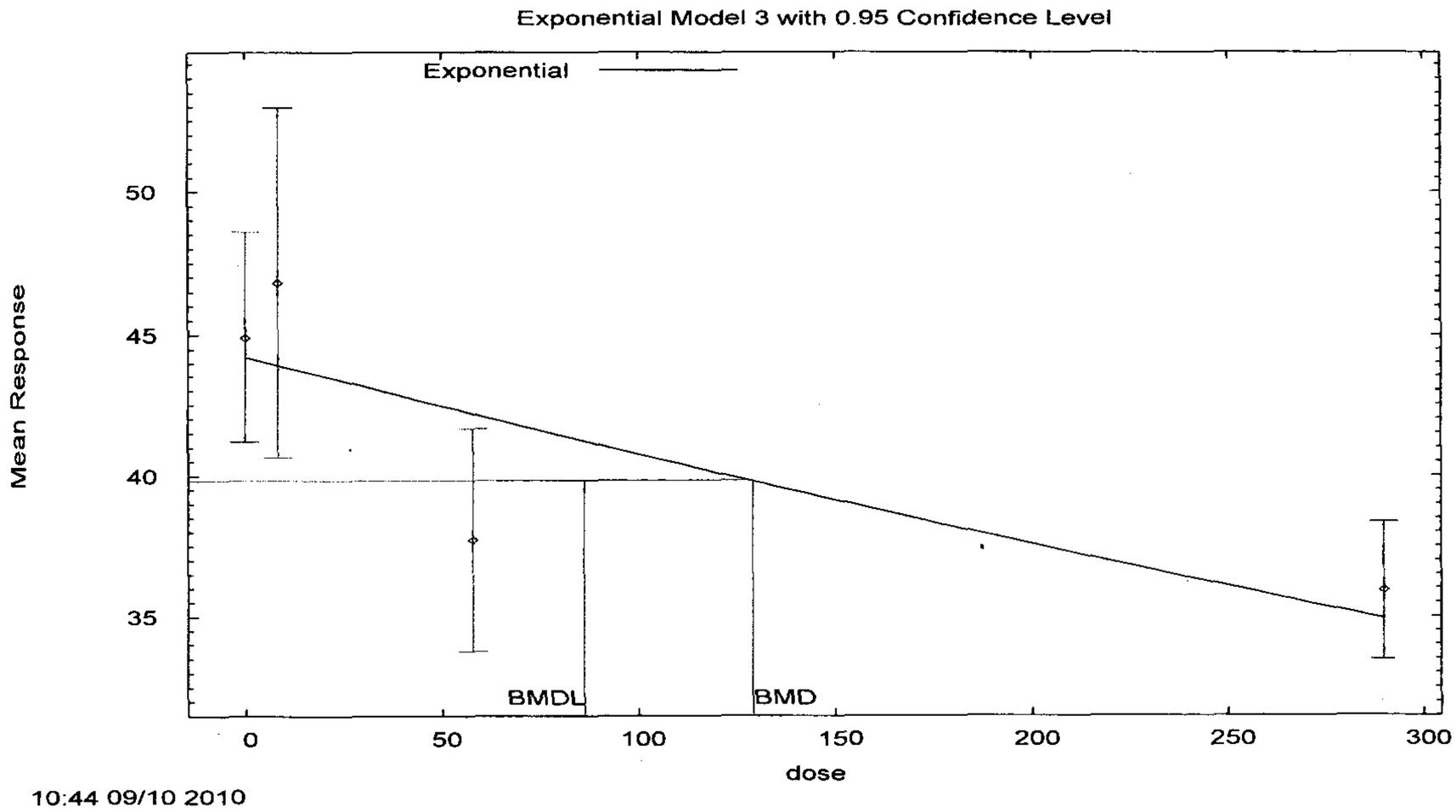
Risk Type = Relative deviation

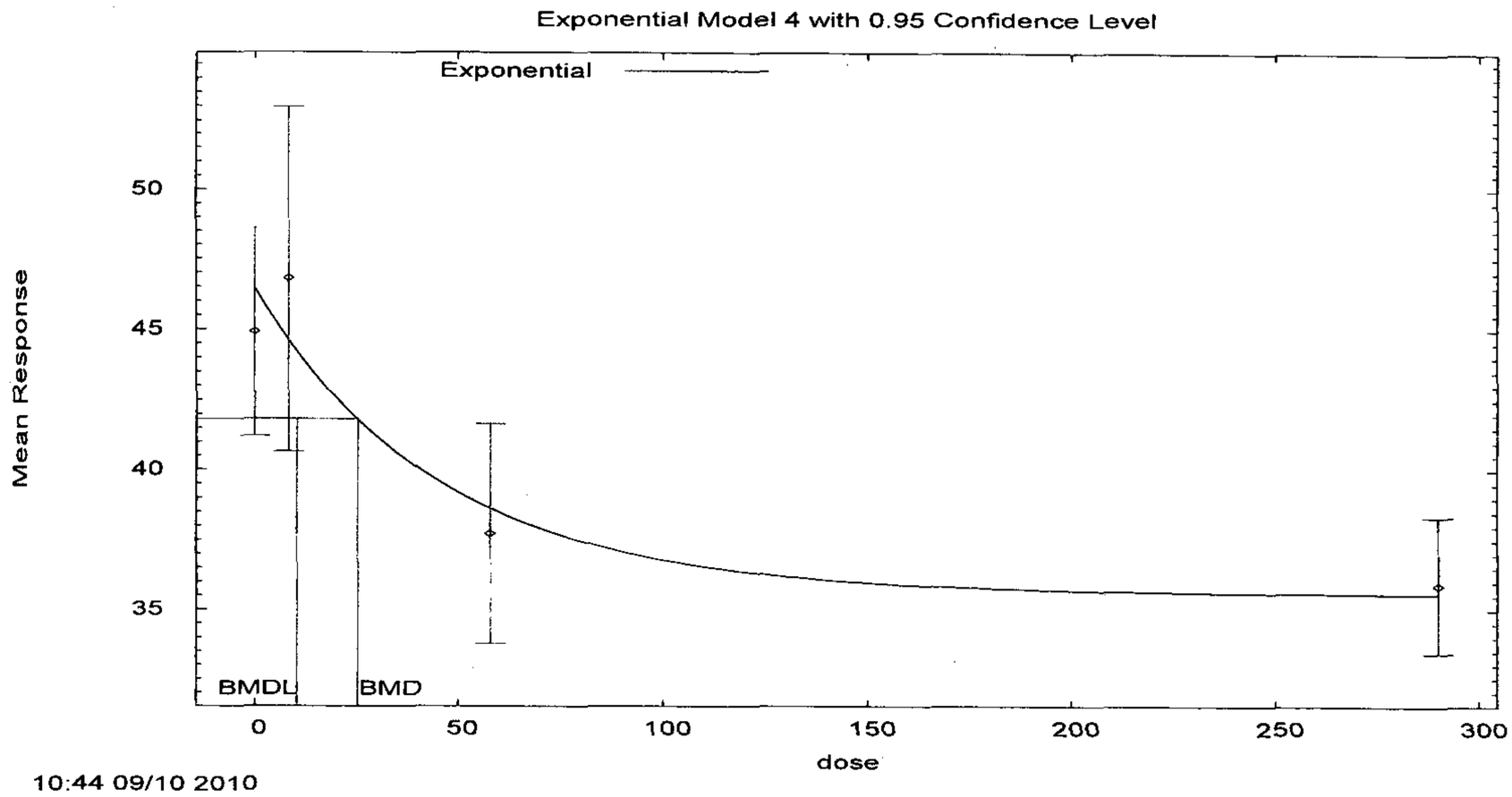
Confidence Level = 0.950000

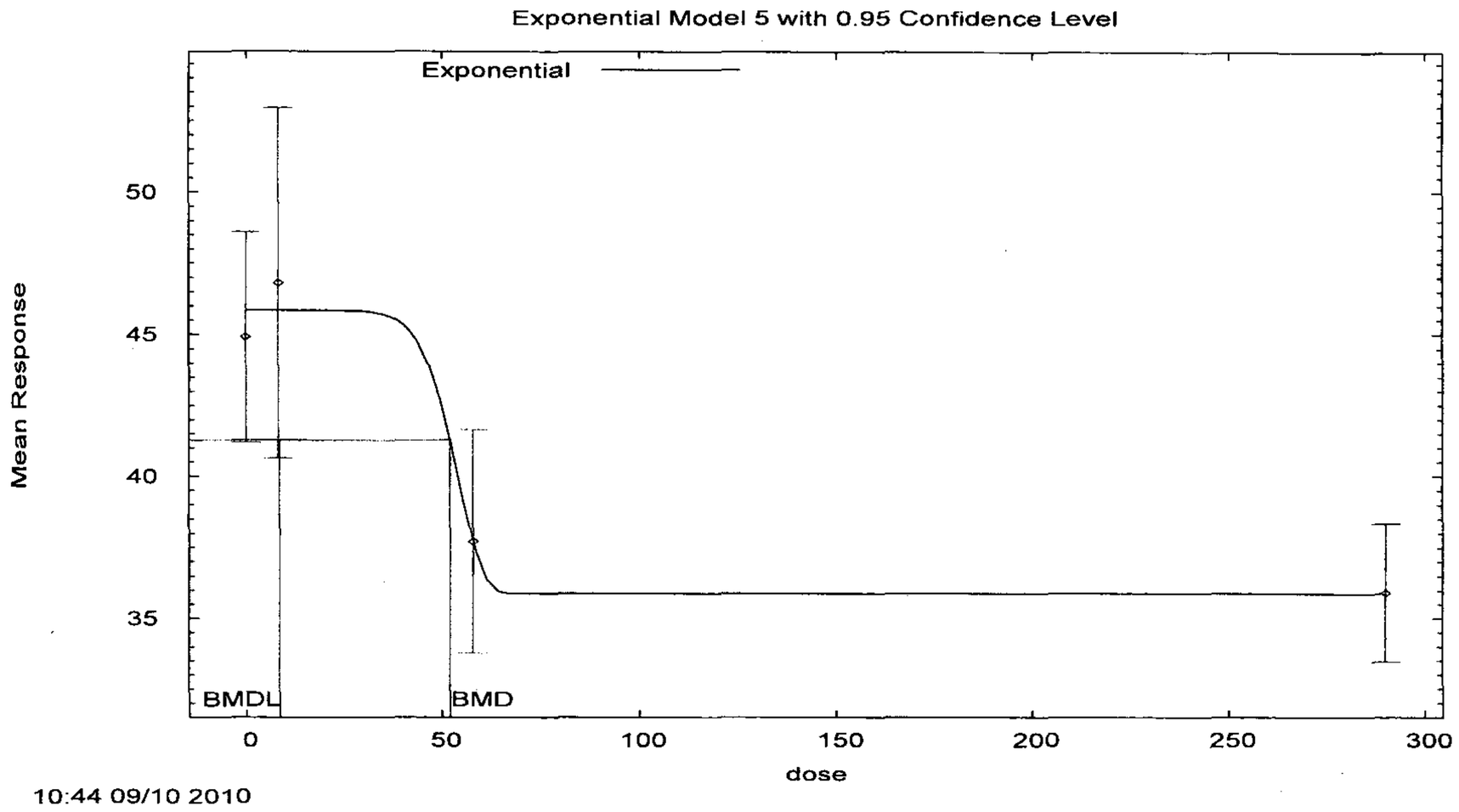
BMD and BMDL by Model

Model	BMD	BMDL
2	129.179	86.2451
3	129.179	86.2451
4	25.467	10.4775
5	52.2053	8.65791









B.5.3 EPTC 00154784 Inhalation 82-7 adult brain Male 13 week

Exponential
model variance
10 bmr

Exponential Model. (Version: 1.7; Date: 12/10/2009)
Input Data File: C:/Usepa/BMDS212/Data/exp_Actualruns_Setting.(d)
Gnuplot Plotting File:

Fri Sep 10 10:25:04 2010

BMDS Model Run

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	Model 3	Model 4	Model 5
lnalpha	-28.954	-28.954	-28.954	-28.954
rho	8.62526	8.62526	8.62526	8.62526
a	35.1396	35.1396	43.785	43.785
b	0.000362296	0.000362296	0.0065991	0.0065991
c	--	--	0.728669	0.728669
d	--	1	--	1

Parameter Estimates by Model

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	-61.9287	-61.9287	-29.0258	-29.0256
rho	18	18	8.65829	8.65823
a	37.368	37.368	42.0658	42.0657
b	0.0003122	0.0003122	0.199924	0.177614
c	--	--	0.810395	0.810396
d	--	1	--	1.3047

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	12	41.7	5.9
8.3	12	36.1	1.63
58	12	33.5	2.57

290 12 34.4 2.32

Estimated Values of Interest

Model	Dose	Est Mean	Est Std	Scaled Residual
2	0	37.37	5.068	2.961
	8.3	37.27	4.951	-0.8195
	58	36.7	4.306	-2.572
	290	34.13	2.244	0.4115
3	0	37.37	5.068	2.961
	8.3	37.27	4.951	-0.8195
	58	36.7	4.306	-2.572
	290	34.13	2.244	0.4115
4	0	42.07	5.338	-0.2374
	8.3	35.61	2.594	0.6579
	58	34.09	2.148	-0.9513
	290	34.09	2.148	0.5001
5	0	42.07	5.338	-0.2373
	8.3	35.61	2.594	0.6577
	58	34.09	2.148	-0.9512
	290	34.09	2.148	0.5001

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	-82.26579	5	174.5316
A2	-70.49979	8	156.9996
A3	-73.57558	6	159.1512
R	-97.61108	2	199.2222
2	-89.89092	4	187.7818
3	-89.89092	4	187.7818
4	-73.88733	5	157.7747
5	-73.88726	6	159.7745

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 4: Does Model 2 fit the data? (A3 vs. 2)

Test 5a: Does Model 3 fit the data? (A3 vs 3)
Test 5b: Is Model 3 better than Model 2? (3 vs. 2)

Test 6a: Does Model 4 fit the data? (A3 vs 4)
Test 6b: Is Model 4 better than Model 2? (4 vs. 2)

Test 7a: Does Model 5 fit the data? (A3 vs 5)
Test 7b: Is Model 5 better than Model 3? (5 vs. 3)
Test 7c: Is Model 5 better than Model 4? (5 vs. 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	54.22	6	< 0.0001
Test 2	23.53	3	< 0.0001
Test 3	6.152	2	0.04615
Test 4	32.63	2	< 0.0001
Test 5a	32.63	2	< 0.0001
Test 5b	2.842e-013	0	N/A
Test 6a	0.6235	1	0.4298
Test 6b	32.01	1	< 0.0001
Test 7a	0.6234	0	N/A
Test 7b	32.01	2	< 0.0001
Test 7c	0.0001386	1	0.9906

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.

The p-value for Test 5a is less than .1. Model 3 may not adequately describe the data; you may want to consider another model.

Degrees of freedom for Test 5b are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

The p-value for Test 6b is less than .05. Model 4 appears to fit the data better than Model 2.

Degrees of freedom for Test 7a are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 7b is less than .05. Model 5 appears to fit the data better than Model 3.

The p-value for Test 7c is greater than .05. Model 5 does

not seem to fit the data better than Model 4.

Benchmark Dose Computations:

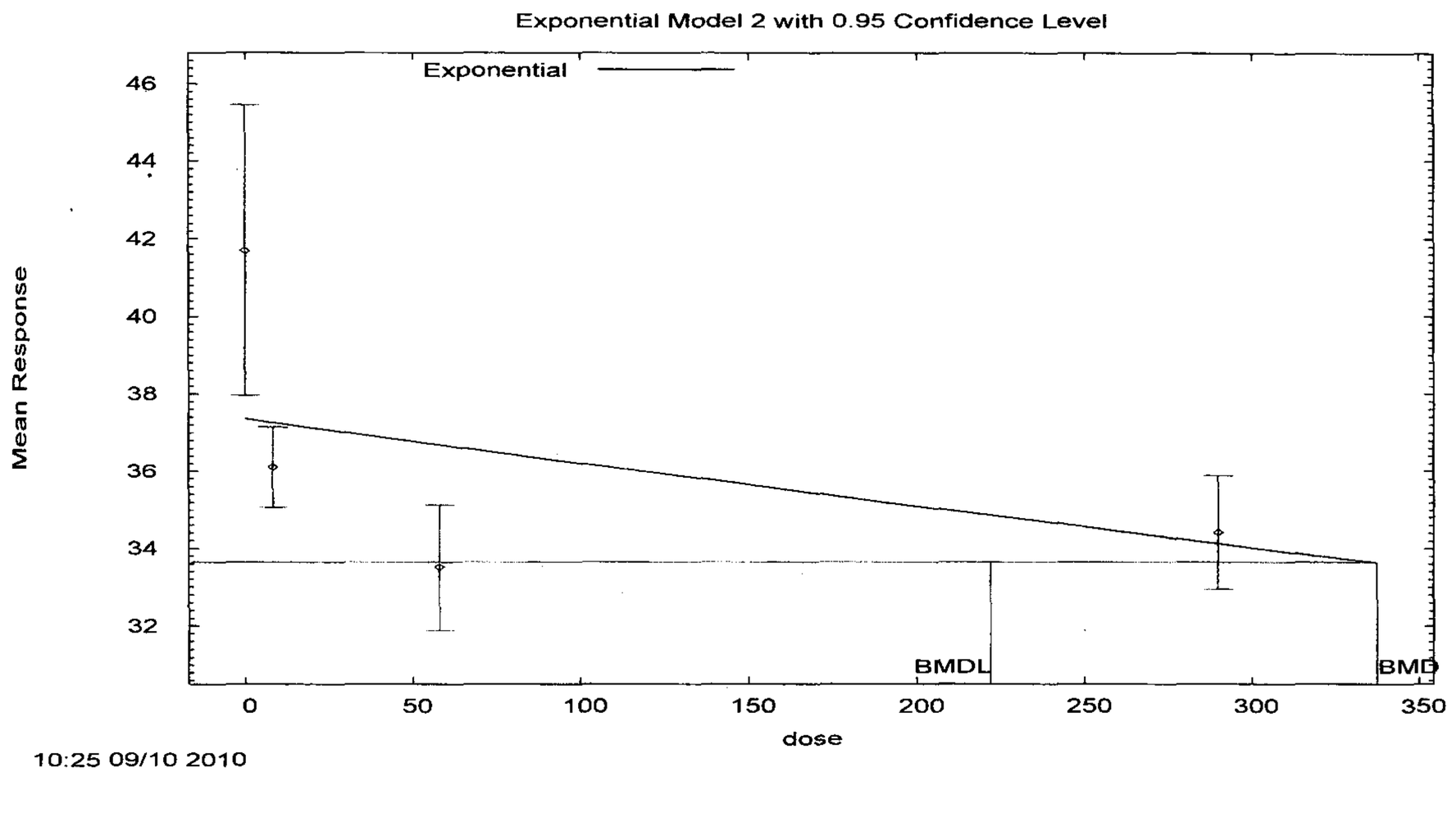
Specified Effect = 0.100000

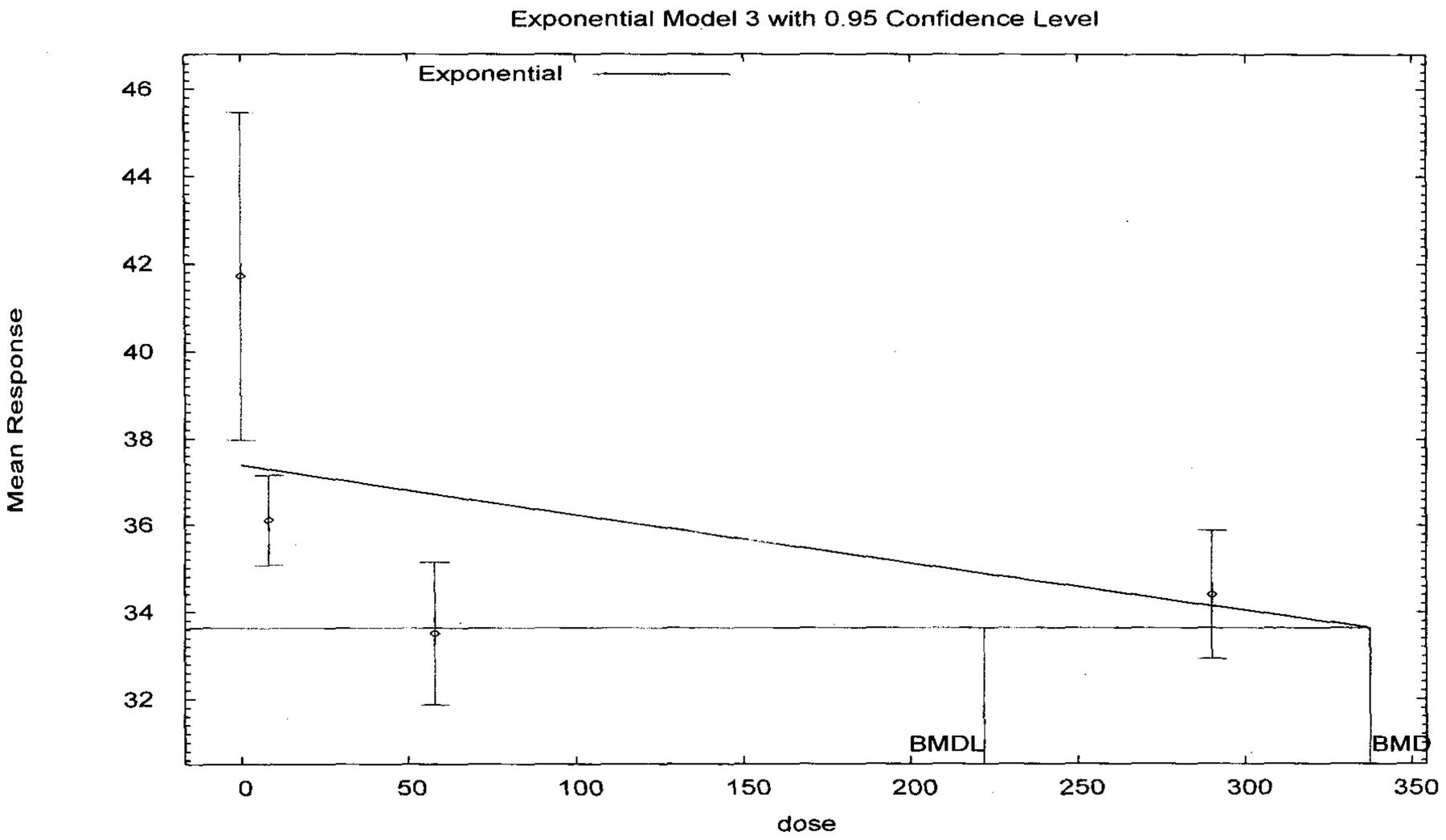
Risk Type = Relative deviation

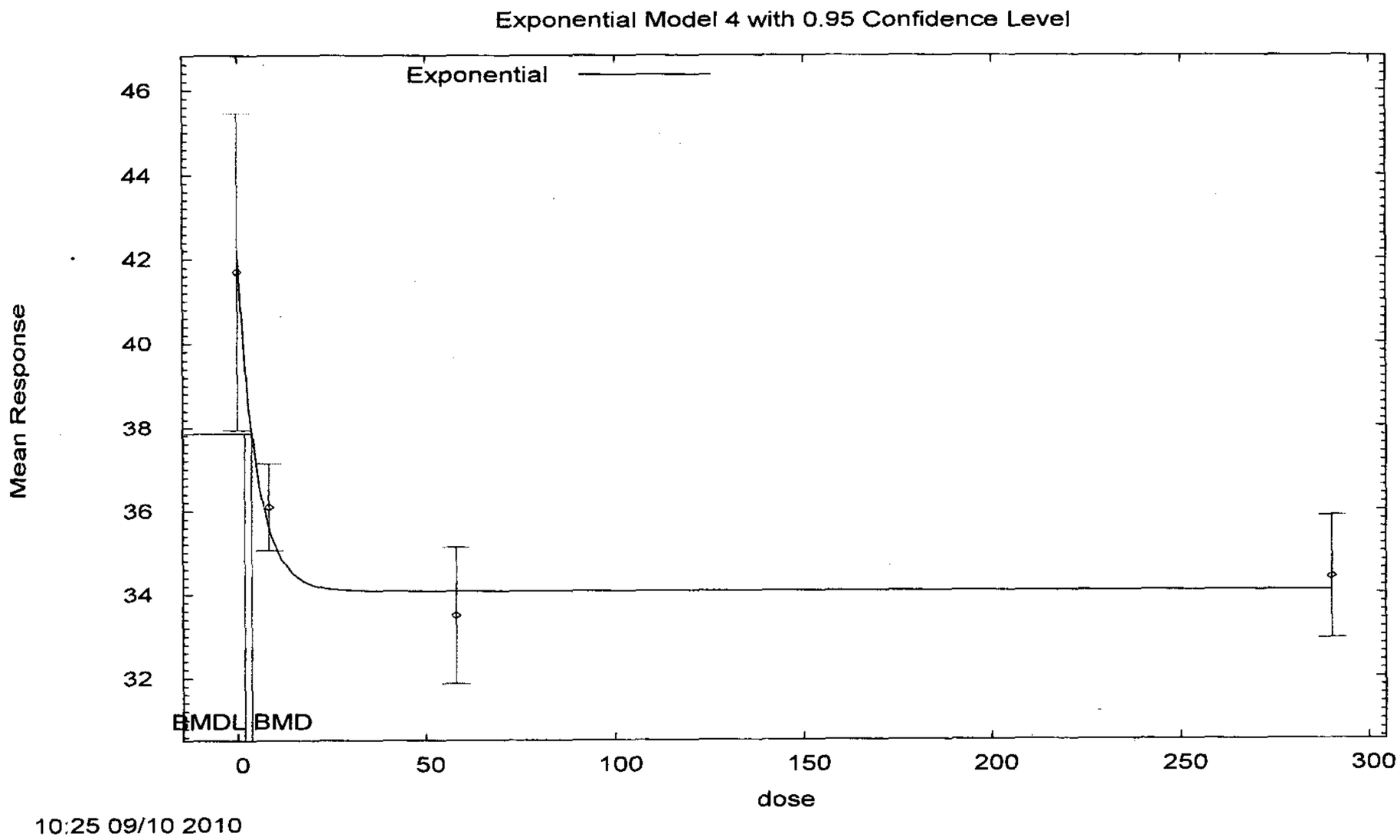
Confidence Level = 0.950000

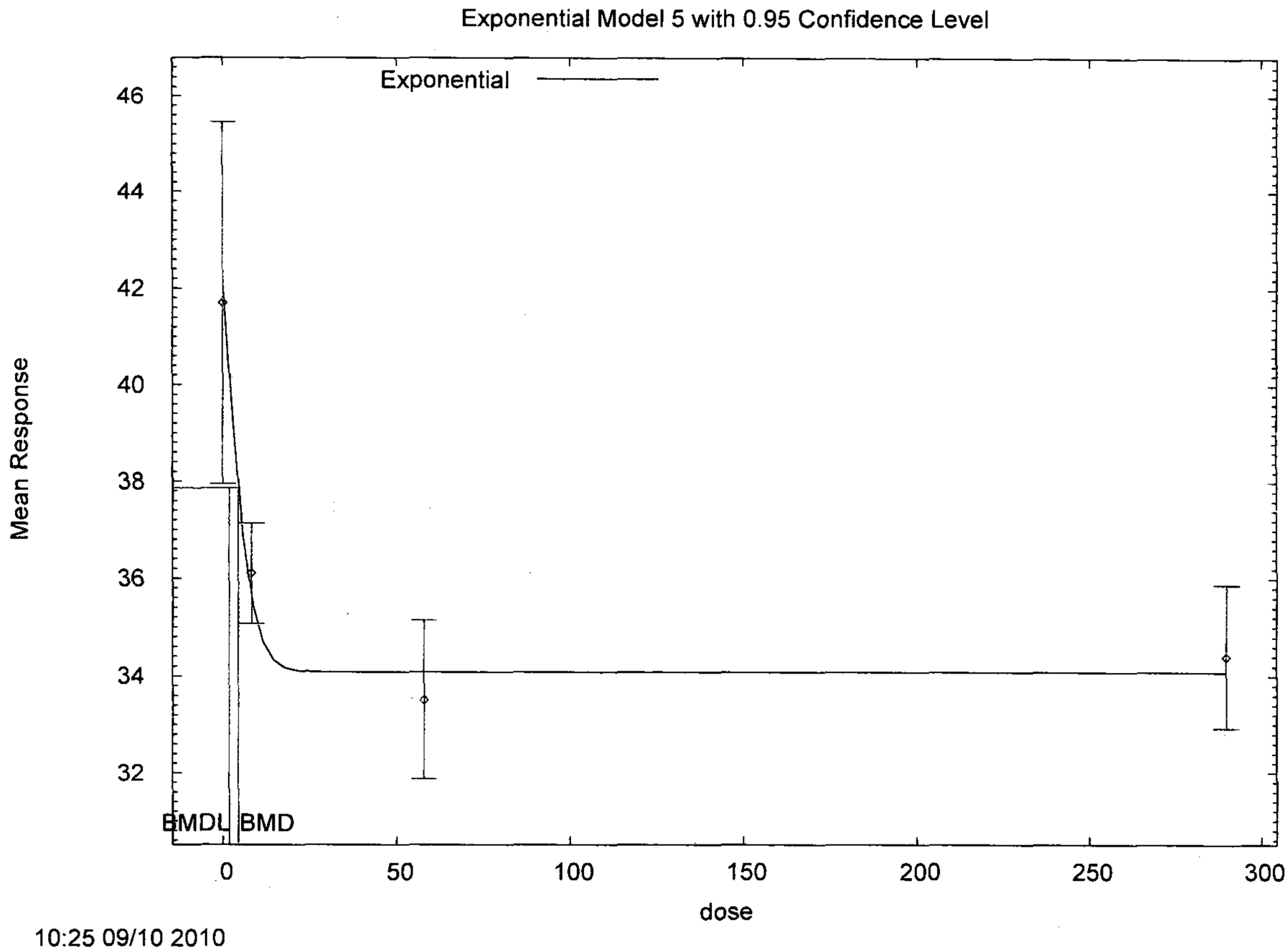
BMD and BMDL by Model

Model	BMD	BMDL
2	337.478	221.922
3	337.478	221.922
4	3.74909	1.89772
5	4.51394	1.89776




Exponential Model 3 with 0.95 Confidence Level
Exponential
Mean Response
46
44
42
40
38
36
34
32
BMDL
BMD
0
50
100
150
200
250
300
350
dose
10:25 09/10 2010


Exponential Model 4 with 0.95 Confidence Level
Exponential
Mean Response
46
44
42
40
38
36
34
32
BMDL
BMD
0
50
100
150
200
250
300
dose
10:25 09/10 2010



B.6 HEC Inhalation Calculations

METHODOLOGIES FOR INHALATION RISK CALCULATIONS

The RfC methodology applies a dosimetric adjustment that takes into consideration not only the differences in ventilation rate (MV) but also the physicochemical properties of the inhaled compound, the type of toxicity observed (*e.g.* systemic vs. port of entry) and the pharmacokinetic (PK) **but not pharmacodynamic** (PD) differences between animals and humans. Based on the RfC guidance (1994), the methodology for RfCs derivation is an estimate of the quantitative dose-response assessment of chronic non-cancer toxicity for individual inhaled chemicals and includes dosimetric adjustment to account for the species-specific relationships of exposure concentration to deposited/delivered dose. This adjustment is influenced by the physicochemical properties of the inhaled compound as well as the type of toxicity observed (*e.g.* systemic vs. port of entry), and takes into consideration the PK differences between animals and humans. Though the RfC methodology was developed to estimate toxicity of inhaled chemicals over a lifetime, it can be used for other inhalation exposures (*e.g.* acute and short-term exposures) since the dosimetric adjustment incorporates mechanistic determinants of disposition that can be applied to shorter duration of exposures provided the assumptions underlying the methodology are still valid. These assumptions, in turn, vary depending on the type of toxicity observed and will be discussed later on in this document. Thus the derivation of a HEC for inhaled gases is described by the following equation:

$$HEC = POD_{study} * \frac{D \text{ animal exposure (hrs / day)}}{D \text{ human exposure (hrs / day)}} * \frac{W \text{ animal exposure (days / wk)}}{W \text{ human exposure (days / wk)}} * RGDR$$

Where:

POD_{study}: Point of departure identified in the critical toxicology study
$D_{animal\ exposure}$: Duration of animal exposure (hrs/day; days/wk)
$D_{anticipated\ exposure}$: Anticipated human duration of exposure (hrs/day; days/wk)
RGDR: Regional Gas Dose Ratio

For gases eliciting both port of entry and systemic effects, calculations to estimate the inhalation risk to humans are dependent on the regional gas dose ratio (RGDR). In the case of systemic effects, the RGDR is defined as the ratio of the blood:gas partition coefficient of the chemical for the test species to humans ($H_{b/g\ animal}/H_{b/g\ human}$). When this ratio is unknown or when the $H_{b/g\ animal} > H_{b/g\ human}$ a default value of 1.0 is used as the RGDR. This default is based on the observation that for chemicals where partition coefficient data are available in both rats and humans the RGDR value has usually been comparable or slightly higher than 1. Thus, the use of an RGDR of 1 results in a protective calculation of the inhalation risk. Some of the key assumptions fundamental to the use of the RfC methodology to derive a HEC based on systemic effects include:

1) all the concentrations of inhaled gas within the animal's body are periodic with respect to time (*i.e.* periodic steady state - the concentration *vs* time profile is the same for every week). Periodicity must be attained for at least 90% of the exposure.
2) in the respiratory tract, the air, tissue, capillary blood concentration are in equilibrium with respect to each other.
3) systemically, the blood and tissue concentrations are in equilibrium with respect to each other.

In the case of chloropicrin, the physicochemical properties and metabolism data for the compound indicate that these conditions (*i.e.* periodicity and equilibrium between different compartments) will be achieved in a very short period of time. Under these conditions, therefore, the use of the RfC methodology to estimate acute inhalation risk is appropriate.

When the critical toxic effect in a study occurs in the respiratory tract (*i.e* port of entry effects), the RGDR is not related to the blood:gas partition coefficient of the compound but rather the ratio of the minute volume (MV) to the surface area (SA) of the affected region. In these instances, attaining periodicity or equilibrium between the compartments is not critical (since the effect is a function of the direct interaction between the inhaled compound and the affected region in the respiratory tract) and the RGDR may be calculated using the following equation:

$$RGDR = \frac{MV_{animal} / SA_{animal}}{MV_{human} / SA_{human}}$$

Where:

MV_{animal}: Minute volume for the test species (varies depending on body weight)
SA_{animal}: Surface area of the affected region in animals
MV_{human}: Minute volume for humans (default value is 13.8 l/min)
SA_{human}: Surface area of the affected region in humans

The MV_{animal} is calculated using the allometric scaling provided in USEPA (1988a). The equation for calculation of the MV_{animal} is:

$$\ln MV_{animal} = b_0 + b_1 \ln(BW)$$

Where:
ln MV_{animal} : natural logarithm of the minute volume
b_0 : species specific intercept used in the algorithm to calculate minute volumes based on body weight
b_1: species specific coefficient used in the algorithm to calculate minute volumes based on body weight
ln BW: natural logarithm of the body weight (expressed in kg)

The values for the species-specific parameters used to calculate the MV_{animal} based on body weight and the values for the surface areas of various regions of the respiratory tract (extrathoracic, thoracic, and pulmonary) are provided in the EPA document "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" (1994).

Calculations used to estimate the inhalation risk to humans from aerosols are dependent not on the RGDR as for gases, but on the regional deposited dose ratio (RDDR). Inhalation studies using aerosols characterize particulate exposure by defining the particulate diameter (mass median aerodynamic diameter [MMAD]) and the geometric standard deviation (σ_g), which is then used to determine the RDDR. The RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal (A) to the predicted inhalation particulate exposure concentration for a human (H) that would be associated with the same dose delivered to the rth region or target tissue.

$$RDDR_r = \frac{(RDD_r/\text{Normalizing Factor})_A}{(RDD_r/\text{Normalizing Factor})_H}$$

As with calculations for gases, the r regions and potential target tissues are the three respiratory regions (ET, TB, PU). The RDDR is easily calculated by using a software program designed specifically for computing the RDDR from the MMAD and σ_g defined from an aerosol inhalation study. The values for the species-specific parameters used to calculate the RDDR are provided in

the EPA document "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry."

The magnitude of the UFs applied is dependent on the methodology used to calculate risk. The RfC methodology takes into consideration the PK differences **but not the PD differences**. Consequently, the UF for interspecies extrapolation may be reduced to 3X (to account for the PD differences) while the UF for intraspecies variation is retained at 10X. Thus, the UF when using the RfC methodology is customarily 30X.

B.6.1 Acute and Short Term Exposure OCCUPATIONAL

INHALATION HEC	EPTC			
NOAEL	[redacted]	mg/m3	BMDL10	
# of exposed hrs		hrs		
RDDR				
Acute (day)	1.00	(1 a/ 1h)		
24 hrs	8	hrs	[redacted]	
Total UF	[redacted]	Kids		
		(5 a/		
Short Term (days)	0.714	7h)		
MRID	154784			
[redacted]	3.6537	mg/m3	[redacted]	inhalation
[redacted]	2.60874	mg/m3	[redacted]	inhalation

Route-to-route Extrapolation Method:	[redacted]	mg/kg	short term
Inhalation to oral		mg/kg	acuteterm

Mg/L x A x CF (l/hr/kg) x D (hrs) x AF = mg/kg

0.00261 mg/l x 1 x 43.5 x 6 x 1	short term
0.00365 mg/l x1 x 43.5 x 6 x 1	acute term

B.6.2 Acute and Short- Term Exposure **BYSTANDERS**

INHALATION HEC	EPTC		
NOAEL	[redacted]	mg/m3	BMDL10
# of exposed hrs		hrs	
RDDR			
Acute (day)	1.00	(1 a/ 1h)	
24 hrs	24	hrs	[redacted]
Total UF	[redacted]	Kids	
		(5 a/	
Short Term (days)	0.714	7h)	
MRID	154784		
[redacted]	1.2179	mg/m3	[redacted] inhalation
	0.86958	mg/m3	[redacted] inhalation

Route-to-route Extrapolation Method:	[redacted]	mg/kg short term
Inhalation to oral		mg/kg acute term

Mg/L x A x CF (l/hr/kg) x D (hrs) x AF = mg/kg

0.00087 mg/l x 1 x 43.5 x 6 x 1	short term
0.00122 mg/l x 1x 43.5 x 6 x 1	acute term

13544

R192656

Chemical Name: Carbamothioic acid, dipropyl-, S-ethyl ester

PC Code: 041401
HED File Code: 14000 Risk Reviews
Memo Date: 6/14/2011
File ID: 00000000
Accession #: 000-00-0137

HED Records Reference Center
6/16/2011