B

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

005006

FEB 21 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Telone II Risk Assessment

FROM: Bernice Fisher, Statistician *Bernice Fisher*
SMSS, Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Henry Jacoby, PM 21
Registration Division (TS-767C)

THRU: Bertram Litt, Statistical Team Leader *Bertram Litt*
SMSS, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Reto Engler, Ph.D. *Reto Engler*
Chief, Mission Support Staff
Toxicology Branch/HED (TS-769C)

Summary

The results from the two chronic studies, on mice and on rats indicate that increasing doses of Telone is associated with increasing tumor rates in both species of both sexes. It appears that male rats are the most sensitive in that, increasing doses of the chemical significantly produces increasing numbers of forestomach or liver or adrenal or thyroid tumors. The potency estimate, Q_1^*, based on these data in terms of human equivalence is 1.75×10^{-1} (mg/kg/day)[B_1].

Background

Two oncogenicity studies, each lasting two years, in B6C3F1 mice and F344lN rats dosed by gavage with Telone II (Technical grade, 1,3-Dichloropropene - Caswell No. 542-75-6, containing 1.0% Epichlorohydrin as a stabilizer) were conducted by the National Toxicology Program, Research Triangle Park, N.C.

The design of these studies are presented in the attached "Special Report, Risk Assessment of Telone II by Brian Cook and Thomas L. Christison of Dynamac, EPA 68-02-4225, Task 1-13, January 1986 (pages 3-4).

Qualitative Review

Survival analysis by Dynamac (see page 5 of Dynamac's Report) revealed no significant differences in the comparison of the controls and the treated group of rats in either sex.

Modifications were made by Dynamac, of the denominators of the male mice in order to reflect deaths prior to 12 weeks before the first tumors of interest were diagnosed. In male mice, 25 out of the 39 that died in the control group, occurred within the first year of the study, thus any conclusions based on statistical comparisons are considerably weakened unless adjusted for survival.

In female mice there was a significant decrease ($p < .05$) in survival in the high dose of Telone as compared with the controls.

Significant* ($p =. 04$) increases in urinary tumors occurred with increasing doses of Telone in the male mice. In females, forestomach, lung and urinary baldder tumors displayed significantly ($p = .009$, $p = .011$ and $p < .0001$ respectively) increasing trends with increasing treatment doses (see Table 5a - Dynamac's report). Since the females have significant number of tumors in three out of four sites, all tumor bearing animals were combined in order to obtain a global interpretation of Telone's effect. These combined data indicated that the number of tumor bearing animals, regardless of tumor site, increased significantly ($p < .0001$) with increasing doses of Telone (see Table 5, Dynamac's report).

In male rats the tumors in forestomach and in the liver increased significantly ($p < .0001$ and $p < .006$ respectively) with increasing doses of Telone. Again the total number of tumor bearing animals increased significantly ($p < .001$) with increasing doses of Telone in this group.

---

* Table 5 and 6 in the Dynamac report lists the X^2 results based upon the Cochran-Armitage Linear Trend test for mice and rats. In addition the report shows the associated p values for a two-sided test for the X^2 with one Degree of Freedom. However in the evaluation of a Hypothesis that is concerned with a trend that is associated with increasing tumor rates and increasing doses of Telone, it is appropriate to use only half the p value listed in Dynamac's report in order to determine the significance of the associations. The reason being that X^2 with one Degree of Freedom is equivalent to the square of a normal distribution and since the Cochran-Armitage Null Hypothesis in testing this linear trend only declares that the slope is greater than zero, it is expedient to use a one-sided p value in order to determine the statistical significance of the test.

In female rats, the forestomach and the endocrine system's tumors also increased significantly ($p = .001$ and $p = .025$ respectively) with increasing Telone doses (see Table 6, Dynamac's report).

Dose-Response Associations

The Maximum Likelihood Estimator (MLE) of doses of Telone in fitting five models (Probit, Logit, Weibull, Gamma and Multistage) to each set of tumor data related to the given sites and for selected combined sites are shown in Dynamac's Tables 10 and 11. The 95 per cent lower confidence limits of these MLE Doses are also presented by Dynamac in Tables 10 and 11.

The results of the multistage model computed by Dynamac (see Table 7, Dynamac report) were used to estimate the potency of Telone in experimental animals (Q_1^*), using the aforementioned tumors in various sites and also for combined tumor bearing animals in selected groups of mice and rats, in both sexes (see Table 1 for details).

In addition, since there was a survival problem in both male and female mice, a time to death tumor factor was added to the Multistage model by use of Crump's Weibull 82 program.

The data used in the estimation was based upon tumor-bearing mice with one or more of the following tumors: for mouse, males - liver, lung, forestomach, thyroid and/or urinary bladder; for females - any of the preceeding and/or adrenal. The potency estimate, Q_1^* of 1.9×10^{-2} in males and 2.6×10^{-2} for females based on these data did not alter the magnitudes previously obtained from Dynamac's summary data (see Table 2 for details).

The review of the potency estimates, indicates that male rats with either forestomach, liver, adrenal, or thyroid tumors were the most sensitive. Thus increasing doses of Telone has an oncogenic effect in the male rats. The estimated potency, Q_1^* is 3.3×10^{-2} $(mg/kg/day)^{-1}$.

This potency of Telone is converted to human equivalence by means of a) Lehman's Tables* which convert the diet of a rat - 20 ppm to rat - 1 mg/kg/day and then b) the conversion of rat mg/kg/day to human equivalence by use of the Mantel-Schneiderman's formula**

of $\left(\frac{\text{Human Weight}}{\text{Rat Weight}}\right)^{1/3}$

for surface area correction is $\underline{Q_{1\,H}^* = 1.75 \times 10^{-1}}$.

---

* Lehman, 1959, Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, Assoc. of Drug Officials of the U.S.

** Mantel and Schneiderman - J. Cancer Research, June 1975, pg. 1385

Risk Characterization

No data have been provided to characterize risk from Telone. Because the TOX Branch Peer Review Group assigned Telone a weight-of-the-evidence rating of [B_1] a hypothetical example of how to show Telone Risk levels is given. Suppose there is a daily lifetime exposure of .001 mg/kg/day, then Exposure x Q_1^* = risk for Telone (.001 x 1.75 x 10^{-4} [B_1]) and should be shown as 2 x 10^{-4} [B_1].

Attachment

cc:
Quang Bui, Ph.D.

Table 1 - Estimates of Telone II Carcinogenic Potency (Q_1^*) for Experimental Animals, Mice and Rats - mg/kg/day (Based on Dynamac's Report - Tables 10 and 11)

	Mice		Rats	
Tumors	Males	Females	Males	Females
Adrenal or Thyroid			1.4×10^{-2}	5.0×10^{-3}
Forestomach		2.5×10^{-3}	5.0×10^{-3}	5.0×10^{-3}
Liver		5.0×10^{-3}	1.0×10^{-2}	
Lung	1.25×10^{-2}	5.0×10^{-3}		
Urinary Bladder	1.7×10^{-3}	1.25×10^{-2}		
Combined Tumors Adrenal or Thyroid or Forestomach or Liver			3.3×10^{-2}	
Forestomach or Liver			2.5×10^{-2}	
Forestomach or Liver or Lung or Urinary Bladder		2.5×10^{-2}		
Liver or Lung		1.0×10^{-2}		

005006

Table 2 - Estimates Telone II Carcinogenic Potency (Q_1^*) for Experimental Mice mg/kg/day (Based on results of the Weibull 82 Program)

All Tumors in Week No.	Q_1^* for Males	Q_1^* for Females
70	5.7×10^{-3}	1.03×10^{-2}
90	1.18×10^{-2}	1.78×10^{-2}
104	1.80×10^{-2}	2.44×10^{-2}
106	1.90×10^{-2}	
107		2.60×10^{-2}

cc:
Quang Bui

005006

EPA: 68-02-4225
DYNAMAC No. 1-13
February 12, 1986

DRAFT

DATA EVALUATION RECORD

SPECIAL REPORT

Risk Assessment of Telone II

STUDY IDENTIFICATION: Telone II.--Two year gavage study in mice and rats. National Toxicology Program, Research Triangle Park, NC. NTP Project NTPTR269, NIH Publication No. 85-2525, May 1985.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: Ira Cecil Felkner

Date: 2-12-86

DRAFT

7

DRAFT

1. CHEMICAL: Telone II, Technical grade 1,3-Dichloropropene

2. TEST MATERIAL: Technical grade, 1,3-Dichloropropene [CAS No. 542-75-6] containing 1.0% Epichlorohydrin as a stabilizer.

3. STUDY/ACTION TYPE: Two oncogenicity studies in B6C3F1 mice and F344/N rats dosed by gavage for two years.

4. STUDY IDENTIFICATION: Telone II.--Two year gavage study in mice and rats. National Toxicology Program, Research Triangle Park, NC. NTP Project NTPTR269, NIH Publication No. 85-2525, May 1985.

5. REVIEWED BY:

Thomas L. Christison Principal Reviewer Dynamac Corporation	Signature: Thomas L. Christison Date: 2-12-86
Brion Cook, M.S. Independent Reviewer Dynamac Corporation	Signature: I. Cecil Felkner for Date: 2-12-86

6. APPROVED BY:

I. Cecil Felkner, Ph.D. Technical Quality Control Dynamac Corporation	Signature: I. Cecil Felkner Date: 2-12-86
Bertram Litt EPA Reviewer	Signature: ____________ Date: ____________

I. INTRODUCTION

This document describes the procedures and calculations used to quantify human carcinogenic risk due to exposure to the pesticide Telone II. Two lifetime rodent carcinogenicity studies were available for this risk assessment in which B6C3F1 mice and F344/N rats were dosed by gavage with Telone II. The dose-response incidences of various tumor types from these studies were used to predict human exposure levels corresponding to selected levels of human risk. Various low-dose extrapolation models were fitted to these data to estimate the probability of cancer as a function of dose. Estimates corresponding to extra risks of 1×10^{-4} and 1×10^{-6} as well as lower 95% confidence bounds on these doses are presented.

This report is divided into three sections: 1) a description of the carcinogenicity studies, 2) a characterization of the dose-response relationship, and 3) the low-dose extrapolation.

II. DESCRIPTION OF STUDIES

Two chronic carcinogenicity studies were conducted on Telone II (NTP, 1985). The studies were conducted in mice and rats by NTP.

Results in rats have shown increased incidences of squamous cell papillomas and carcinomas in the forestomach of both sexes and neoplastic nodules of the liver in the males.

Results in female mice showed increased incidences of squamous cell papillomas and carcinomas in the forestomach and alveolar/bronchiolar adenomas in the lungs. Male mice exhibited increased incidences of transitional cell carcinomas of the urinary bladder.

Telone II technical-grade 1,3-Dichloropropene [CAS No. 542-75-6] containing 1.0% epichlorohydrin as a stabilizer was administered to mice and rats by gavage for a period of 24 months in each lifetime carcinogenicity study.

Groups of 50 male and 50 female B6C3F1 mice received doses of 0, 50, or 100 mg/kg by gavage three times per week for 104 weeks. Groups of 52 male and 52 female F344/N rats received gavage doses at 0, 25 or 50 mg/kg three times per week for 104 weeks. Ancillary studies with an additional 25 rats per each sex were conducted in which five male and five female rats from each dose group were killed after receiving Telone® for 9, 16, 21, 24, or 27 months by gavage at 0, 25 or 50 mg/kg.

For the purposes of this risk assessment, estimates will be presented for each species and sex separately with the number of animals examined adjusted downward to exclude early deaths.

Tables 1-2 show the dose-response incidence data for various tumor types for the two studies.

Tables 3-4 show the rates of tumor development by sex for mice and rats with the weekly intervals collapsed to show monotonic increases in tumor development.

Tables 5-6 show the Cochran-Armitage Trend test components; Chi-square for the departure from linear trend and the the linear trend goodness-of-fit tests and the associated p-values.

Linear trends in the dose-response relationships were displayed in the male rat forestomach (squamous cell papilloma or carcinoma) and liver (neoplastic nodules or carcinoma); in the datasets of the combined liver and forestomach and in the combined forestomach, liver, adrenal (pheochromocytoma) and thyroid (follicular cell adenoma or carcinoma).

Female rats showed linear trends in the dose-response relationship of the forestomach (squamous cell papilloma or carcinoma).

Data from the Chi-square goodness-of-fit tests showed that there were statistically significant differences between the observed and linearly predicted proportions in the male rat datasets of the stomach (squamous cell papilloma or carcinoma), and the combined adrenal (pheochromocytoma) and thyroid (follicular cell adenoma or carcinoma).

None of the female rat datasets showed statistical differences between the observed and linearly predicted proportions, using the Chi-square goodness-of-fit test.

There were no departures from linear trend exhibited in the male mouse lung (alveolar/bronchiolar adenoma or carcinoma) and the urinary bladder (transitional cell carcinoma) datasets. The lung dataset showed a statistically significant difference between the observed and linearly predicted proportions using the Chi-square goodness-of-fit test.

Female mouse data showed statistical departures from the dose-response linear trend in the forestomach (squamous cell pailloma or carcinoma), lung (alveolar/bronchiolar adenoma or carcinoma), urinary bladder (transitional cell carcinoma) datasets; the combined lung and liver (hepatocellular adenoma or carcinoma) and the combined lung, liver, forestomach and urinary bladder datasets. In the female mouse datasets, there were no statistical differences between the observed and linearly predicted proportions using the Chi-square goodness-of-fit test.

These data are used to estimate cancer risk using various low-dose extrapolation models.

Survival analyses were conducted for each species and sex group by NTP. In rats, there were no significant differences in survival between the control group and treated groups of either sex. In addition, the incidence of tumors described in this report were almost all found either at terminal sacrifice or during the last 3 months of the study. Exceptions were one male rat in the high dose in which a tumor of the adrenals was found at week 89 and two female rats in the mid-dose group which exhibited a fore-stomach tumor at week 87 and a liver tumor at week 91. No additional information would be gained by weighing the data with time to tumor development.

In mice, death of 39 male mice in the control group were attributed to suppurative inflammation of the heart. Twenty-five of these animals died between week 46 and 51. Thirteen low-dose animals and 5 high-dose animals were also diagnosed with myocarditis. Survival in the control animals was significantly ($p<0.05$) different than that of the two dosage groups. This may effect the low dose extrapolation involving tumor sites in male mice.

In female mice, the high-dose group showed significantly ($p<0.05$) different survival than the control group. Most tumors of interest were found at terminal sacrifice or during the last 3 months of the study. Exceptions are two animals in the high-dose group; one female mouse died at week 70 with a lung tumor and one died at week 75 with a lung tumor and a liver tumor.

III. LOW-DOSE EXTRAPOLATION

Various low-dose extrapolation models were fit to the dose-response incidence data presented in Tables 7-8 after appropriate conversions of the experimental dose concentrations in mg/kg for the test animals. Since the animals in both studies were dosed 3 days per week, the concentrations were multiplied by 3/7 to obtain the average daily dosage in mg/kg/day. Table 9 presents the average daily doses in mg/kg/day used in this assessment.

As no environmental doses were available, doses and associated lower 95% confidence bounds were estimated for levels of extra risk of 1×10^{-4} and 1×10^{-6} for the multistage probit, logit, Weibull and Gamma multi-hit models.

Estimates were calculated using a software program called ANALYSIX developed under contract to the US EPA Office of Toxic Substances. This program unifies the output of the GLOBAL83 multistage model of Howe and Crump and the RISK81 models of Krewski and Kovar. Estimates for each species were calculated for each sex group. These data are presented in Tables 10-11.

REFERENCES

ANALYSIX, Battelle Memorial Laboratories, unpublished documentation.

Armitage, P., (1955) Tests for Linear Trend in Proportions and Frequencies, Biometrics 11:375.

Howe, R. B. and Crump, K. S. GLOBAL83, unpublished documentation.

Kovar, J. and Krewski, D. RISK81. A Computer Program for Low Dose Extrapolation of Quantal Response Toxicity Data, April 1981, unpublished.

Memorandum - Request for Risk Assessment for Telone II.

National Toxicology Program, Toxicology and Carcinogenesis Studies of Telone II in P344/N Rats and $B6C3F_1$ Mice, U.S. Department of Health and Human Services, Technical Report Series No. 269, 1985.

TABLE 1. Incidences of Selected Tumors in Mice Dosed by Gavage with Telone II for 2 Years by Sex (NTP, 1984)

		Dose Levels (mg/kg)		
		0	50	100
MALES				
Forestomach	Squamous Cell Papilloma	0/22	2/40	3/47
Lung	Alveolar/Bronchiolar Adenoma	1/22	11/40	9/47
	Alveolar/Bronchiolar Adenoma or Carcinoma	1/22	13/40	12/47
Urinary Bladder	Transitional Cell Carcinoma	0/22	0/40	2/47
FEMALES				
Forestomach	Squamous Cell Papilloma	0/50	1/50	2/44
	Squamous Cell Papilloma or Carcinoma	0/50	1/50	4/44
Lung	Alveolar/Bronchiolar Adenoma	0/50	3/50	8/44
	Alveolar/Bronchiolar Adenoma or Carcinoma	2/50	4/50	8/44
Urinary Bladder	Transitional Cell Carcinoma	0/50	8/50	21/42
Liver	Hepatocellular Adenoma	0/50	5/50	3/44
	Hepatocullular Adenoma or Carcinoma	1/50	8/50	3/44
Lung -and/or- Liver	Alveolar/Bronchiolar Adenoma or Carcinoma -and/or- Hepatocellular Adenoma or Carcinoma	3/50	10/50	10/44
Lung -and/or- Liver -and/or- Forestomach -and/or- Urinary Bladder	Alveolar/Bronchiolar Adenoma or Carcinoma -and/or- Hepatocellular Adenoma or Carcinoma -and/or- Squamous Cell Papilloma or Carcinoma -and/or- Transitional Cell Carcinoma	3/50	18/50	27/44

TABLE 2. Incidences of Selected Tumors in Rats Dosed by Savage with Telone II for 2 Years by Sex (NTP, 1984)

		Dose Levels (mg/kg)		
		0	25	50
MALES				
Forestomach	Squamous Cell Papilloma	1/74	1/72	13/75
	Squamous Cell Papilloma or Carcinoma	1/74	1/72	17/75
Liver	Neoplastic Nodules	1/74	6/71	8/75
	Neoplastic Nodules or Carcinoma	1/74	6/71	9/75
Forestomach Liver	Squamous Cell Papilloma or Carcinoma -and/or- Neoplastic Nodules or Carcinoma	2/49	7/47	19/50
Adrenal Thyroid	Pheochromocytoma -and/or- Follicular Cell Adenoma or Carcinoma	2/49	10/47	7/50
Forestomach Liver Adrenal Thyroid	Squamous Cell Papilloma or Carcinoma -and/or- Neoplastic Nodules or Carcinoma -and/or- Pheochromocytoma -and/or- Follicular Cell Adenoma or Carcinoma	4/49	14/47	23/50
FEMALES				
Forestomach	Squamous Cell Papilloma or Carcinoma	0/72	2/73	8/77
Thyroid	Follicular Cell Adenoma	0/72	1/73	3/77
	Follicular Cell Adenoma or Carcinoma	0/72	2/73	4/77

TABLE 3a. Tumor Incidences for Male Mice Dosed by Gavage with Telone II for 2 Years

Tissue - Tumor Type	Week	Treatment Level (mg/kg) 0	50	100
Stomach - Squamous Cell papilloma	<42.1	0	0	0
	42.1- 63.0	0	0	1
	63.1- 84.0	0	0	1
	84.1-105.0	0	2	1
Lung - Alveolar/Bronchiolar Adenoma	<64.6	0	0	0
	64.6- 86.0	0	1	0
	86.1-107.5	1	10	9
Lung - Alveolar/Bronchiolar Adenoma or Carcinoma	<64.6	0	0	0
	64.6- 86.0	0	1	0
	86.1-107.5	1	12	12
Urinary Bladder - Transitional Cell Carcinoma	<75.1	0	0	0
	75.1- 90.0	0	0	1
	90.1-105.0	0	0	1

TABLE 3b. Tumor Incidences for Female Mice Dosed by Gavage with Telone II for 2 Years

Tissue - Tumor Type	Week	Treatment Level (mg/kg) 0	50	100
Stomach - Squamous Cell Papilloma	<104.1	0	0	0
	104.1-108.0	0	1	2
Stomach - Squamous Cell Papilloma or Carcinoma	<91.1	0	0	0
	91.1-104.0	0	0	1
	104.1-108.0	0	1	3
Lung - Alveolar/Bronchiolar Adenoma	<66.1	0	0	0
	66.1- 88.0	0	0	1
	88.1-108.0	0	3	7
Lung - Alveolar/Bronchiolar Adenoma or Carcinoma	<66.1	0	0	0
	66.1- 88.0	0	0	1
	88.1-108.0	2	4	7
Urinary Bladder - Transitional Cell Carcinoma	<68.1	0	0	0
	68.1- 85.0	0	0	1
	85.1-102.0	0	1	1
	102.1-108.0	0	7	19
Liver - Hepatocellular Adenoma	<72.1	0	0	0
	72.1- 90.0	0	0	1
	90.1-108.0	0	5	2
Liver - Hepatocellular Adenoma or Carcinoma	<72.1	0	0	0
	72.1- 90.0	0	0	1
	90.1-108.0	1	8	2
Liver - Hepatocellular Adenoma or Carcinoma and/or Lung - Alveolar/Bronchiolar Adenoma or Carcinoma	<54.1	0	0	0
	54.1- 72.0	0	0	1
	72.1- 90.0	0	0	1
	90.1-108.0	3	10	8
Liver - Hepatocellular Adenoma or Carcinoma and/or Lung - Alveolar/Bronchiolar Adenoma or Carcinoma and/or Stomach - Squamous Cell Papilloma or Carcinoma and/or Urinary - Transitional Cell Carcinoma	<64.1	0	0	0
	64.1- 80.0	0	0	2
	80.1- 96.0	0	0	2
	96.1-108.0	3	18	23

005006

TABLE 4a. Tumor Incidences for Male Rats Dosed by Gavage with Telone II for 2 Years

Tissue - Tumor Type	Week	Treatment Level (mg/kg) 0	25	50
Stomach - Squamous Cell Papilloma	<80.1	0	0	0
	80.1- 96.0	0	0	3
	96.1-108.0	1	1	10
Stomach - Squamous Cell Papilloma or Carcinoma	<80.1	0	0	0
	80.1- 96.0	0	0	3
	96.1-108.0	1	1	14
Liver - Neoplastic Nodules	<104.1	0	0	0
	104.1-108.0	1	6	8
Liver - Neoplastic Nodules or Carcinoma	<91.1	0	0	0
	91.1-104.0	0	0	1
	104.1-108.0	1	6	8
Liver - Neoplastic Nodules or Carcinoma and/or Stomach - Squamous Cell Papilloma or Carcinoma	<91.1	0	0	0
	91.1-104.0	0	1	2
	104.1-108.0	2	6	17
Adrenal - Pheochromocytoma and/or Thyroid - Follicular Cell Adenoma or Carcinoma	<78.1	0	0	0
	78.1- 91.0	0	0	1
	91.1-104.0	0	1	3
	104.1-108.0	2	9	3
Liver - Neoplastic Nodules or Carcinoma and/or Stomach - Squamous Cell Papilloma or Carcinoma and/or Adrenal - Pheochromocytoma and/or Thyroid - Follicular Cell Adenoma or Carcinoma	<78.1	0	0	0
	78.1- 91.0	0	0	1
	91.1-104.0	0	1	3
	104.1-108.0	4	13	19

TABLE 4b. Tumor Incidences for Female Rats Dosed by Gavage with Telone II for 2 Years

		Treatment Level (mg/kg)		
Tissue - Tumor Type	Week	0	25	50
Stomach - Squamous Cell Papilloma or Carcinoma	<80.1	0	0	0
	80.1- 96.0	0	1	0
	96.1-108.0	0	1	8
Thyroid - Follicular Cell Adenoma	<91.1	0	0	0
	91.1-104.0	0	0	1
	104.1-108.0	0	1	2
Thyroid - Follicular Cell Adenoma or Carcinoma	<91.1	0	0	0
	91.1-104.0	0	0	1
	104.1-108.0	0	2	3

005006

TABLE 5a. Cochran-Armitage Chi-Square Tests for Trend Linearity and Departure and Associated P-values on Tumor Incidences in Mice by Sex

Tissue	Tumor Type(s)	Sex	Dosage Level (mg/kg)	Average Daily Dose (mg/kg/day)	Number: Re-sponding	Number: Exam-ined	Cochran-Armitage Trend Test: Linear Trend Goodness-of-Fit: Chi^2	Linear Trend Goodness-of-Fit: P-Value	Departure from Linear Trend: Chi^2	Departure from Linear Trend: P-Value
Lung	Alveolar/Bronchiolar Adenoma or Carcinoma	Male	0	0.0	1	22	2.208	0.137	4.027	0.045**
			50	21.4	13	40				
			100	42.9	12	47				
Urinary Bladder	Transition Cell Carcinoma		0	0.0	0	22	3.041	0.081	1.014	0.314
			50	21.4	0	40				
			100	42.9	2	47				
Forestomach	Squamous Cell Papilloma or Carcinoma	Female	0	0.0	0	50	5.636	0.018*	0.630	0.427
			50	21.4	1	50				
			100	42.9	4	44				
Lung	Alveolar/Bronchiolar Adenoma or Carcinoma		0	0.0	2	50	5.267	0.022*	0.355	0.551
			50	21.4	4	50				
			100	42.9	8	44				
Urinary Bladder	Transitional Cell Carcinoma		0	0.0	0	50	34.432	<0.0001*	1.610	0.204
			50	21.4	8	50				
			100	42.9	21	42				
Liver	Hepatocellular Adenoma or Carcinoma		0	0.0	1	50				
			50	21.4	8	50				
			100	42.9	3	44				

DRAFT

*Statistical difference between observed and linearly predicted proportions.

**Indicates departure from linear trend.

005306

TABLE 5b. Cochran-Armitage Chi-Square Tests for Trend Linearity and Departure and Associated P-values on Tumor Incidences in Mice by Sex

Tissue	Tumor Type(s)	Sex	Dosage Level (mg/kg)	Average Daily Dose (mg/kg/day)	Number Re-sponding	Number Exam-ined	Cochran-Armitage Trend Test: Linear Trend Goodness-of-Fit Chi^2	Linear Trend Goodness-of-Fit P-Value	Departure from Linear Trend Chi^2	Departure from Linear Trend P-Value
Lung	Alveolar/Bronchiolar Adenoma or Carcinoma	Female	0	0.0	3	50	5.034	0.025*	0.771	0.380
			50	21.4	10	50				
-and/or-			100	42.9	10	44				
Liver	Hepatocellular Adenoma or Carcinoma									
Lung	Alveolar/Bronchiolar Adenoma or Carcinoma		0	0.0	3	50	32.448	<0.0001*	0.079	0.779
			50	21.4	18	50				
-and/or-			100	42.9	27	44				
Liver	Hepatocellular Adenoma or Carcinoma									
-and/or-										
Forestomach	Squamous Cell Papilloma or Carcinoma									
-and/or-										
Urinary Bladder	Transitional Cell Carcinoma									

*Statistical difference between observed and linearly predicted proportions.

**Indicates departure from linear trend.

DRAFT

0050υ6

TABLE 6. Cochran-Armitage Chi-Square Tests for Trend Linearity and Departure and Associated P-values on Tumor Incidences in Rats by Sex

Tissue	Tumor Type(s)	Sex	Dosage Level (mg/kg)	Average Daily Dose (mg/kg/day)	Number Re-sponding	Number Exam-ined	Cochran-Armitage Trend Test: Linear Trend Goodness-of-Fit Chi^2	Linear Trend Goodness-of-Fit P-Value	Departure from Linear Trend Chi^2	Departure from Linear Trend P-Value
Forestomach	Squamous Cell Papilloma or Carcinoma	Male	0	0.0	1	74	21.631	<0.0001*	6.967	0.008**
			25	10.7	1	72				
			50	21.4	17	75				
Liver	Neoplastic Nodules or Carcinomas		0	0.0	1	74	6.254	0.012*	0.225	0.636
			25	10.7	6	71				
			50	21.4	9	75				
Forestomach -and/or- Liver	Squamous Cell Papilloma; Neoplastic Nodules or Carcinomas		0	0.0	2	49	18.412	<0.0001*	0.777	0.378
			25	10.7	7	47				
			50	21.4	19	50				
Adrenal -and/or- Thyroid	Pheochromocytoma; Follicular Cell Adenoma or Carcinoma		0	0.0	2	49	2.116	0.146	4.215	0.040**
			25	10.7	10	47				
			50	21.4	7	50				
Forestomach -and/or- Liver -and/or- Adrenal -and/or- Thyroid	Squamous Cell Papilloma; Neoplastic Nodules or Carcinomas; Pheochromocytoma; Follicular Cell Adenoma or Carcinoma		0	0.0	4	49	17.527	<0.0001*	0.116	0.734
			25	10.7	14	47				
			50	21.4	23	50				
Forestomach	Squamous Cell Papilloma or Carcinoma	Female	0	0.0	0	72	9.438	0.002*	0.686	0.407
			25	10.7	2	73				
			50	21.4	8	77				
Thyroid	Follicular Cell Adenoma or Carcinoma		0	0.0	0	72	3.815	0.051	0.004	0.951
			25	10.7	2	73				
			50	21.4	4	77				

DRAFT

*Statistical difference between observed and linearly predicted proportions.

**Indicates a departure from linear trend.

TABLE 7a. Chi-square Goodness-of-Fit and Associated P-Values for Various Models.

MALE MICE

Tissue / Tumor Type	Additive Background Models				Multistage Models	
	Probit	Logit	Weibull	Gamma	Two Stages	One Hit
LUNG -- Alveolar/Bronchiolar Adenoma or Carcinoma	n/a 0.0000	n/a 0.0000	n/a 0.0000	3.194 0.0000	4.4089 0.1103	4.4089 0.1103
URINARY BLADDER -- Transitional Cell Carcinoma	Not available -- Only one dose level with a positive response.					

Additive Background Models calculated with 0 degrees of freedom.

Multistage Models calculated with 2 degrees of freedom.

TABLE 7b. Chi-square Goodness-of-Fit and Associated P-Values for Various Models.

FEMALE MICE

Tissue / Tumor Type	Additive Background Models				Multistage Models	
	Probit	Logit	Weibull	Gamma	Two Stages	One Hit
FORESTOMACH -- Squamous Cell	0.000	0.000	0.000	0.001	0.0206	0.8236
Papilloma or Carcinoma	0.0000	0.0000	0.0000	0.0000	0.9897	0.7321
LUNG -- Alveolar/Bronchiolar	0.064	0.031	0.023	0.083	0.0000	0.3932
Adenoma or Carcinoma	0.0000	0.0000	0.0000	0.0000	1.0000	0.8215
URINARY -- Transitional Cell	0.000	0.000	0.000	0.001	0.0000	2.7822
BLADDER Carcinoma	0.0000	0.0000	0.0000	0.0000	1.0000	0.2488
LIVER -- Hepatocellular	0.586	0.614	0.605	4.502	3.1578	3.1578
Adenoma or Carcinoma	0.0000	0.0000	0.0000	0.0000	0.2062	0.2062
LIVER -- Hepatocellular	0.000	0.000	0.000	0.493	0.6308	0.6308
Adenoma or Carcinoma	0.0000	0.0000	0.0000	0.0000	0.7295	0.7295
- and/or -						
LUNG -- Alveolar/Bronchiolar						
Adenoma or Carcinoma						
LUNG -- Alveolar/Bronchiolar	0.000	0.000	0.000	0.016	0.0000	0.1569
Adenoma or Carcinoma	0.0000	0.0000	0.0000	0.0000	1.0000	0.9199
- and/or -						
LIVER -- Hepatocellular						
Adenoma or Carcinoma						
- and/or -						
FORESTOMACH -- Squamous Cell						
Papilloma or Carcinoma						
- and/or -						
URINARY -- Transitional Cell						
BLADDER Carcinoma						

Additive Background Models calculated with 0 degrees of freedom.

Multistage Models calculated with 2 degrees of freedom.

005006

TABLE 8a. Chi-square Goodness-of-Fit and Associated P-Values for Various Models.

MALE RATS

Tissue / Tumor Type	Additive Background Models				Multistage Models	
	Probit	Logit	Weibull	Gamma	Two Stages	One Hit
FORESTOMACH Squamous Cell Papilloma or Carcinoma	3.472 0.0000	2.539 0.0000	2.776 0.0000	3.972 0.0000	3.3562 0.1867	7.4535 0.0240
LIVER -- Neoplastic Nodules and/or Carcinoma	0.000 0.0000	0.000 0.0000	0.000 0.0000	0.135 0.0000	0.1848 0.9117	0.1848 0.9117
FORESTOMACH -- Squamous Cell Papilloma or Carcinoma - and/or - LIVER -- Neoplastic Nodules or Carcinoma	0.014 0.0000	0.000 0.0000	0.000 0.0000	0.057 0.0000	0.0000 1.0000	1.2223 0.5427
ADRENAL -- Pheochromocytoma - and/or - THYROID - Follicular Cell Adenoma or Carcinoma	n/a 0.0000	n/a 0.0000	n/a 0.0000	2.645 0.0000	4.0952 0.1290	4.0952 0.1290
FORESTOMACH -- Squamous Cell Papilloma or Carcinoma - and/or - LIVER -- Neoplastic Nodules or Carcinoma - and/or - ADRENAL -- Pheochromocytoma - and/or - THYROID - Follicular Cell Adenoma or Carcinoma	0.000 0.0000	0.000 0.0000	0.000 0.0000	0.222 0.0000	0.0006 0.9997	0.0006 0.9997

DRAFT

Additive Background Models calculated with 0 degrees of freedom.

Multistage Models calculated with 2 degrees of freedom.

TABLE 8b. Chi-square Goodness-of-Fit and Associated P-Values for Various Models.

FEMALE RATS

Tissue / Tumor Type	Additive Background Models				Multistage Models	
	Probit	Logit	Weibull	Gamma	Two Stages	One Hit
FORESTOMACH Squamous Cell	0.000	0.000	0.000	0.005	0.0000	0.7717
Papilloma or Carcinoma	0.0000	0.0000	0.0000	0.0000	1.0000	0.6799
THYROID Follicular Cell	0.000	0.000	0.000	0.038	0.0022	0.0022
Adenoma or Carcinoma	0.0000	0.0000	0.0000	0.0000	0.9989	0.9989

Additive Background Models calculated with 0 degrees of freedom.

Multistage Models calculated with 2 degrees of freedom.

DRA

TABLE 9. Average Daily Doses[a] in mg/kg/day by Sex for Mice and Rats Dosed by Gavage with Telone II for 2 Years

	Nominal Dose (mg/kg)			
	0	25	50	100
MICE				
Males	0.000	n/a	21.40	42.90
Females	0.000	n/a	21.40	42.90
RATS				
Males	0.000	10.70	21.40	n/a
Females	0.000	10.70	21.40	n/a

[a] Animals were fed three times per week at the nominal dose. Average daily doses were calculated by multiplying nominal dose by 3/7.

TABLE 10a. Estimates of Dose and Lower Bounds on Dose Associated with Specified Excess Risks by Tumor Site Based on Telone II NTP Bioassay Tumor Incidence in Mice

	Extra Risk			
	10^{-4}		10^{-6}	
	MLE	Lower 95% CB	MLE	Lower 95% CB
MALES				
<u>Lung</u>				
Alveolar/Bronchiolar Adenoma and/or Carcinoma				
<u>Model</u>				
Additive Probit	0	0	0	0
Additive Logit	0	0	0	0
Additive Weibull	0	0	0	0
Additive Gamma	4×10^{-3}	7×10^{-4}	4×10^{-5}	7×10^{-6}
Multistage	1×10^{-2}	8×10^{-3}	1×10^{-4}	8×10^{-5}
<u>Urinary Bladder</u>				
Transitional Cell Carcinoma				
<u>Model</u>				
Additive Probit				
Additive Logit	Not available -- Model would not converge.			
Additive Weibull				
Additive Gamma				
Multistage	2×10^{-0}	6×10^{-2}	2×10^{-1}	6×10^{-4}

DRAFT

005006

TABLE 10b. Estimates of Dose and Lower Bounds on Dose Associated with Specified Excess Risks by Tumor Site Based on Telone II NCI Bioassay Tumor Incidence in Mice

	Extra Risk			
	10^{-4}		10^{-6}	
	MLE	Lower 95% CB	MLE	Lower 95% CB
FEMALES				
<u>Lung</u>				
Alveolar/Bronchiolar Adenoma or Carcinoma				
<u>Model</u>				
Additive Probit	2×10^{-0}	8×10^{-4}	7×10^{-1}	6×10^{-5}
Additive Logit	6×10^{-1}	1×10^{-1}	4×10^{-2}	1×10^{-3}
Additive Weibull	5×10^{-1}	9×10^{-2}	3×10^{-2}	2×10^{-3}
Additive Gamma	7×10^{-1}	8×10^{-2}	6×10^{-2}	8×10^{-4}
Multistage	9×10^{-2}	2×10^{-2}	9×10^{-4}	2×10^{-4}
<u>Urinary Bladder</u>				
Transitional Cell Carcinoma				
<u>Model</u>				
Additive Probit	3×10^{-0}	2×10^{-3}	1×10^{-0}	3×10^{-4}
Additive Logit	9×10^{-1}	1×10^{-2}	1×10^{-1}	2×10^{-4}
Additive Weibull	5×10^{-1}	5×10^{-2}	5×10^{-2}	5×10^{-4}
Additive Gamma	7×10^{-1}	5×10^{-2}	2×10^{-2}	4×10^{-4}
Multistage	3×10^{-1}	8×10^{-3}	6×10^{-3}	8×10^{-5}
<u>Liver</u>				
Hepatocellular adenoma or Carcinoma				
<u>Model</u>				
Additive Probit	Not available -- Model would not converge.			
Additive Logit				
Additive Weibull				
Additive Gamma				
Multistage	4×10^{-2}	2×10^{-2}	4×10^{-4}	2×10^{-4}

DRAFT

TABLE 10b. Estimates of Dose and Lower Bounds on Dose Associated with Specified Excess Risks by Tumor Site Based on Telone II NCI Bioassay Tumor Incidence in Mice (cont.)

	Extra Risk			
	10^{-4}		10^{-6}	
	MLE	Lower 95% CB	MLE	Lower 95% CB
FEMALES				
<u>Liver</u>				
Hepatocellular Adenoma or Carcinoma				
-and/or-				
<u>Lung</u>				
Alveolar/Bronchiolar Adenoma or Carcinoma				
-and/or-				
<u>Forestomach</u>				
Squamous Cell Papilloma or Carcinoma				
-and/or-				
<u>Urinary Bladder</u>				
Transitional Cell Carcinoma				
<u>Model</u>				
Additive Probit	1×10^{-2}	5×10^{-3}	1×10^{-4}	5×10^{-5}
Additive Logit	1×10^{-2}	5×10^{-3}	1×10^{-4}	5×10^{-5}
Additive Weibull	8×10^{-3}	3×10^{-3}	8×10^{-5}	3×10^{-5}
Additive Gamma	9×10^{-3}	5×10^{-3}	9×10^{-5}	5×10^{-5}
Multistage	7×10^{-3}	4×10^{-3}	7×10^{-5}	4×10^{-5}

005036

TABLE 10b. Estimates of Dose and Lower Bounds on Dose Associated with Specified Excess Risks by Tumor Site Based on Telone II NCI Bioassay Tumor Incidence in Mice (cont.)

	Extra Risk			
	10^{-4}		10^{-6}	
	MLE	Lower 95% CB	MLE	Lower 95% CB
FEMALES				
<u>Lung</u>				
Alveolar/Bronchiolar Adenoma or Carcinoma				
-and/or				
<u>Liver</u>				
Hepatocellular Adenoma or Carcinoma				
<u>Model</u>				
Additive Probit	7×10^{-4}	3×10^{-5}	7×10^{-6}	3×10^{-7}
Additive Logit	5×10^{-4}	2×10^{-5}	5×10^{-6}	2×10^{-7}
Additive Weibull	4×10^{-4}	1×10^{-5}	$4 \times 10^{-}$[illegible]	[illegible] 10^{-7}
Additive Gamma	2×10^{-2}	4×10^{-3}	2×10^{-4}	[illegible] 10^{-5}
Multistage	2×10^{-2}	1×10^{-2}	2×10^{-4}	[illegible] x 10^{-4}
<u>Forestomach</u>				
Squamous Cell Papilloma or Carcinoma				
<u>Model</u>				
Additive Probit	9×10^{-1}	1×10^{-3}	1×10^{-1}	2×10^{-5}
Additive Logit	3×10^{-1}	2×10^{-10}	6×10^{-3}	8×10^{-14}
Additive Weibull	3×10^{-1}	1×10^{-10}	6×10^{-3}	6×10^{-14}
Additive Gamma	3×10^{-1}	2×10^{-2}	3×10^{-3}	2×10^{-4}
Multistage	1×10^{-1}	4×10^{-2}	1×10^{-3}	4×10^{-4}

DRAFT

005006

TABLE 11a. Estimates of Dose and Lower Bounds on Dose Associated with Specified Excess Risks by Tumor Site Based on Telone II NCI Bioassay Tumor Incidence in Rats

	Extra Risk			
	10^{-4}		10^{-6}	
	MLE	Lower 95% CB	MLE	Lower 95% CB
MALES				
Forestomach				
Squamous Cell Papilloma or Carcinoma				
Model				
Additive Probit	1×10^{-1}	4×10^{-2}	1×10^{-3}	4×10^{-4}
Additive Logit	1×10^{-1}	5×10^{-2}	1×10^{-3}	5×10^{-4}
Additive Weibull	1×10^{-1}	5×10^{-2}	1×10^{-3}	5×10^{-4}
Additive Gamma	8×10^{-2}	3×10^{-2}	8×10^{-4}	3×10^{-4}
Multistage	5×10^{-1}	2×10^{-2}	5×10^{-2}	2×10^{-4}
Liver				
Neoplastic Nodules or Carcinomas				
Model				
Additive Probit	7×10^{-3}	9×10^{-4}	7×10^{-5}	9×10^{-6}
Additive Logit	5×10^{-3}	6×10^{-4}	5×10^{-5}	6×10^{-6}
Additive Weibull	5×10^{-3}	6×10^{-4}	5×10^{-5}	6×10^{-6}
Additive Gamma	2×10^{-2}	3×10^{-3}	2×10^{-4}	3×10^{-5}
Multistage	2×10^{-2}	1×10^{-2}	2×10^{-4}	1×10^{-4}
Forestomach				
Squamous Cell Papilloma or Carcinoma				
-and/or-				
Liver				
Neoplastic Nodules or Carcinoma				
Model				
Additive Probit	2×10^{-2}	8×10^{-3}	2×10^{-4}	8×10^{-5}
Additive Logit	2×10^{-2}	9×10^{-3}	2×10^{-4}	9×10^{-5}
Additive Weibull	2×10^{-2}	8×10^{-3}	2×10^{-4}	8×10^{-5}
Additive Gamma	1×10^{-2}	9×10^{-3}	1×10^{-4}	9×10^{-5}
Multistage	5×10^{-2}	4×10^{-3}	5×10^{-4}	4×10^{-5}

DRAFT

005036

TABLE 11a. Estimates of Dose and Lower Bounds on Dose Associated with Specified Excess Risks by Tumor Site Based on Telone II NCI Bioassay Tumor Incidence in Rats (cont.)

	Extra Risk			
	10^{-4}		10^{-6}	
	MLE	Lower 95% CB	MLE	Lower 95% CB
MALES				
Adrenal				
Pheochromocytoma				
-and/or-				
Thyroid				
Follicular Cell Adenoma or Carcinoma				
Model				
Additive Probit	0	0	0	0
Additive Logit	0	0	0	0
Additive Weibull	0	0	0	0
Additive Gamma	4×10^{-3}	5×10^{-4}	4×10^{-5}	5×10^{-6}
Multistage	1×10^{-2}	7×10^{-3}	1×10^{-4}	7×10^{-5}
Forestomach				
Squamous Cell Papilloma or Carcinoma				
-and/or-				
Liver				
Neoplastic Nodules or Carcinoma				
-and/or-				
Adrenal				
Pheochromocytoma				
-and/or-				
Thyroid				
Follicular Cell Adenoma or Carcinoma				
Model				
Additive Probit	5×10^{-3}	2×10^{-4}	5×10^{-5}	2×10^{-5}
Additive Logit	5×10^{-3}	2×10^{-4}	5×10^{-5}	2×10^{-5}
Additive Weibull	4×10^{-3}	1×10^{-4}	4×10^{-5}	1×10^{-5}
Additive Gamma	7×10^{-3}	3×10^{-4}	7×10^{-5}	3×10^{-5}
Multistage	4×10^{-3}	3×10^{-3}	4×10^{-5}	3×10^{-5}

DRAFT

005036

TABLE 11b. Estimates of Dose and Lower Bounds on Dose Associated with Specified Excess Risks by Tumor Site Based on Telone II NCI Bioassay Tumor Incidence in Rats

	Extra Risk			
	10^{-4}		10^{-6}	
	MLE	Lower 95% CB	MLE	Lower 95% CB
FEMALES				
Forestomach Squamous Cell Papilloma or Carcinoma				
Model				
Additive Probit	2×10^{-0}	1×10^{-3}	2×10^{-1}	9×10^{-5}
Additive Logit	7×10^{-1}	6×10^{-2}	7×10^{-2}	6×10^{-4}
Additive Weibull	6×10^{-1}	8×10^{-2}	6×10^{-2}	9×10^{-4}
Additive Gamma	4×10^{-1}	5×10^{-2}	6×10^{-3}	4×10^{-4}
Multistage	5×10^{-1}	2×10^{-2}	1×10^{-2}	2×10^{-4}
Thyroid Follicular Cell Adenoma or Carcinoma				
Model				
Additive Probit	2×10^{-1}	3×10^{-4}	1×10^{-2}	2×10^{-6}
Additive Logit	3×10^{-2}	7×10^{-12}	2×10^{-4}	5×10^{-16}
Additive Weibull	3×10^{-2}	4×10^{-12}	2×10^{-4}	2×10^{-16}
Additive Gamma	3×10^{-3}	2×10^{-8}	4×10^{-6}	2×10^{-11}
Multistage	4×10^{-2}	2×10^{-2}	4×10^{-4}	2×10^{-4}

DRAFT