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

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FEB - 5 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: TELONE* II Soil Fumigant: 2-Year Inhalation Chronic Toxicity-Oncogenicity Study in Mice - EPA Accession No. 403123-00; Toxicology Branch Proj. No. 7-0985; Caswell No. 324A

FROM: Alan C. Levy, Ph.D. Alan C. Levy Feb. 1, 1988
Toxicologist, Review Section V
Toxicology Branch/HED (TS-769C)

TO: Lois Rossi - PM # 21
Registration Division (TS-767C)

THRU: Quang Q. Bui, Ph.D., D.A.B.T. Quang Q. Bui 2/2/88
Acting Section Head, Review Section V for 2/5/88

and

Theodore M. Farber, Ph.D., D.A.B.T.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant: Dow Chemical Company

Action Requested: Review the 2-year mouse inhalation toxicity-oncogenicity study with TELONE II Soil Fumigant.

Recommendation: The study is considered to be Minimum Data.

A positive oncogenic effect (bronchioloalveolar adenomas) was observed in males at 60 ppm (HDT) but not in either of the lower-dose males (5 or 20 ppm) or at any of the doses in females.

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Primary Reviewer: Alan C. Levy, Ph.D.
Review Section V/HED (TS-769C)

Secondary Reviewer: Quang Q. Bui, Ph.D., D.A.B.T.
Acting Section Head, Review Section V

I. Study Type: Oncogenicity Study
(Guideline § 83-2)

Study Title: TELONE* II Soil Fumigant: 2-year Inhalation Chronic Toxicity-Oncogenicity Study in Mice

EPA Identification Numbers:

EPA Identification: 464-511
EPA Accession: 403123-00
EPA Record: 202023
Caswell: 324A
Tox. Branch Project: 7-0985

Sponsor: Dow Chemical USA
Midland, MI 08640

Testing Laboratory: Mammalian and Environmental Toxicology Research Laboratory
Health and Environmental Sciences, U.S.A.
Dow Chemical U.S.A.
Midland, MI 48674

Study Number: M-003993-009

Study Date: July 13, 1987

Study Authors: W. T. Stott, Ph.D., K. A. Johnson, D.V.M., Ph.D., L. L. Calhoun, B.S., S. K. Weiss, H.T. (ASCP), and L. E. Frauson, B.S., M.T. (ASCP)

Test Material: ·PRODUCT IMPURITY INFO. NOT INCLUDED

Name: TELONE * II soil fumigant ·INERT INGREDIENT INFORMATION IS NOT INCLUDED

Chemical Composition (at start of study): 1,3-dichloropropene, 92.1% (cis 49.5% and trans 42.6%); [redacted]

Stabilizer: [redacted]

Lot No.: TB831213-4

Description: Stable pale yellow liquid at room temperature.

Molecular Weight: 111

Specific Gravity: 1.2

Boiling Point: 104°C (cis); 112°C (trans)

Vapor Pressure: 28 mm Hg (25°C)

Saturated Atmosphere: 37,000 ppm (25°C)

II. Materials and Methods

B6C3F1 mice, 5-6 weeks of age, were obtained from Charles River Breeding Laboratories, Portage, MI. After an acclimation period of 20 days, the animals were weighed and randomly assigned (on the basis of body weights) to exposure groups consisting of 70 mice/sex. Ten mice/sex/group were randomly assigned to 6- and 12-month exposure periods with the remaining 50/sex/group assigned to the 24-month exposure period. Mice were housed one per cage. Food and water were supplied ad libitum except that food was not provided during the inhalation exposure periods.

Exposures were conducted in 14 cubic meter (8x8x8 feet) live-in chambers. [A figure of the inhalation chamber was included in the report.] The airflow was approximately 2500 liters/minute (10 air changes/hour). Minimum and maximum temperatures and relative humidity were recorded during exposures.

Mice were exposed 6 hours/day, 5 days/week for a total of 510 days of exposure in the 2-year period. The animals were exposed to the following:

Table 1

AMOUNT OF TELONE II TO WHICH MICE WERE EXPOSED

Target Concentration (ppm)	Vapors of TELONE II (mg/m^3)	Concentration of DCP[a] (ppm)	(mg/m^3)
0	0	0	0
5	22.7	4.6	20.9
20	90.8	18.4	83.6
60	272.4	55.2	251

a = dichlorpropene; TELONE II soil fumigant is 92% DCP.

These data were extracted from the text of the report (Materials and Methods, Exposures).

Vapor generation analysis was described in detail (see Materials and Methods section of the report which is appended).

Mice were observed at least once/day and changes in appearance recorded. All animals were examined for palpable masses during the randomization period, at 6 and 12 months, and at approximately monthly intervals thereafter. [Palpable mass data from only those animals designated for 2 years of exposure were described in the report.] Body weights were recorded prior to the start of the study, weekly for the first 13 weeks, and at approximately 4 week intervals thereafter. [Body weights from only those mice designated for 2 years of exposure were included in the report.] Food consumption was not reported as having been measured.

Blood samples for hematology and clinical chemistry determinations were obtained from 20 mice/sex/group by posterior orbital sinus puncture under methoxyflurane anesthesia at the time of necropsy (no urinalyses were conducted). Hematology parameters were: erythrocyte count (RBC), hemoglobin concentration (HGB), hematocrit (HCT), RBC indices (mean corpuscular volume - MCV, mean corpuscular hemoglobin - MCH, and mean corpuscular hemoglobin concentration - MCHC), platelet count (PLAT), leukocyte counts (WBC) and differential leukocyte counts (only on mice from 0 and 60 ppm groups). No differential counts were performed on animals from the low (5 ppm) or mid-dose (20 ppm) groups because of the lack of treatment related effects in the high-dose (60 ppm) group.

Clinical chemistry parameters were: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), urea nitrogen (UN), glucose (GLUC), total protein (TP), albumin (ALB) and globulin (GLOB).

After 2 years of exposure all survivors were necropsied (not fasted prior to sacrifice). The animals were weighed, anesthetized with methoxyflurane and their tracheas exposed and clamped prior to decapitation. The eyes were examined by a microscopic slide technique with fluorescent illumination. About 50 tissues were removed and preserved in neutral phosphate-buffered 10% formalin. Urinary bladders and lungs were distended with formalin. Nasal cavities were flushed with formalin via the pharyngeal duct to ensure rapid fixation of the nasal mucosa. The following organs were weighed: brain, heart, kidneys, liver and testes. Data were presented as absolute (grams) and relative (grams/100 grams of final body weight) weights. Final body or organ weights were not obtained nor were detailed eye examinations conducted on animals found dead.

Detailed descriptions of statistical analyses employed were described.

A Quality Assurance statement was included.

A copy of the Materials and Methods section from the report is appended.

There are no comments regarding the Materials and Methods section.

III. Results

Exposure Chamber Concentrations and Conditions: The mean daily time weighted average (TWA) analytical concentration was essentially the same as the intended target concentration for each exposure chamber (Table 2). There was also resonable agreement between the mean daily TWA analytical concentrations and the mean daily nominal concentrations, indicating that test material losses were minimal in the vapor generation and exposure systems. Average daily chamber temperatures and relative humidities ranged from 23-25°C and 50-52%, respectively (Table 2).

Table 2

EXPOSURE CONCENTRATIONS AND CHAMBER CONDITIONS - TWO YEAR INHALATION MOUSE STUDY WITH TELONE II

Targ. Conc. ppm	Analytical Concentration			Nominal Concentration		Temp.[c] (°C)		Relative Humidity[c]
	Analyt. Conc.[a] (ppm)	Coeff. of Var.[b]	Range of Values (ppm)	Nominal Conc. (ppm)	Range of Values (ppm)	Max.	Min.	%
0	-	-	-	-	-	24±1	23±1	52±9
5	5.0±0.2	4.0%	3.6-5.9	5.3±0.4	3.7-7.1	25±1	23±1	50±8
20	20.1±0.5	2.5%	17.6-21.6	19.5±0.9	15.0-23.2	25±1	24±1	51±9
60	60.1±0.9	1.5%	51.5-63.7	58.5±1.7	47.0-65.1	25±1	24±1	52±9

a = Numbers are Mean ± S.D. daily time-weighted average (TWA) values for N = 510 days of exposure.
b = Coefficient of variation is the standard deviation of daily TWA measurements divided by the mean (x 100).
c = Mean ± S.D. of daily measurements taken while exposure was in progress.

These data are reproduced from Table 5, page 50, of the report.

Tables 3 and 4 show the assay of 1,3-Dichloropropene and the distribution of TELONE II within the exposure chambers:

Table 3

ASSAY OF 1,3-DICHLOROPROPENE (LOT # TB831213-4)[a]

Date of Assay	Cis Isomer (Wt %)	Trans Isomer (Wt %)	Total (Wt %)
January 9, 1984	49.5±0.4	42.6±0.2	92.1
October 2, 1984	49.4±0.4	42.2±0.2	91.6
February 4, 1985	49.4±0.4	42.5±0.2	91.9
June 10, 1985	49.2±0.4	42.3±0.2	91.5
December 20, 1985	49.3±0.3	43.3±0.2	92.6

a = Data obtained using gas chromatographic analysis of test material.
These data are reproduced from Table 1, page 46, of the report.

Table 4

DISTRIBUTION OF TELONE II VAPOR WITHIN EXPOSURE CHAMBERS[a]

	Target Concentrations					
	10 ppm		30 ppm		90 ppm	
	Concen. ppm	% Dev. from Ref.	Concen. ppm	% Dev. from Ref.	Concen. ppm	% Dev. from Ref.
Reference Line[c]						
Mean	12.3	-	30.0	-	86.7	-
S.D.	0.5	-	0.0	-	0.3	-
N =	4	-	2	-	3	-
Distribution Area[d]						
A	11.0	10.6	30.0	0.0	86.5	0.2
B	13.0	5.4	30.0	0.0	85.5	1.4
C	-	-	30.0	0.0	88.5	2.1
D	12.5	1.6	30.0	0.0	87.0	0.3
E	13.8	12.2	30.0	0.0	85.0	2.0
F	11.0	10.6	30.0	0.0	86.5	0.2
G	11.5	6.5	30.0	0.0	83.0	4.3
H	11.5	6.5	-	-	-	-
Mean	12.0	7.7	30.0	0.0	86.0	1.5
S.D.	1.1	3.7	0.0	0.0	1.7	1.5
N =	7	7	7	7	7	7

- = Not applicable. Dev. = Deviation Ref. = Reference
a = Distribution checks were conducted without animals prior to start of study using target concentrations of 10, 30 or 90 ppm; study exposure concentrations of 5, 20 or 60 ppm were subsequently selected.
b = % deviation = (reference - distribution) x 100/reference
c = The sampling line through which daily analytical concentrations were measured.
d = Additional sampling lines placed throughout the animals' breathing zone. A, B, C, etc., represent general areas within a chamber.
These data are reproduced from Table 2, page 47, of the report.

In-Life Observations and Survival: No clinical signs observed in exposed animals were considered attributable to TELONE II administration.

There was no decrease in survival from control values in any of the treated groups (Table 5): control, 5, 20 and 60 ppm percent of survival after two years were 90, 88, 90 and 94% for males and 84, 88, 96 and 80% for females, respectively.

Table 5

SURVIVAL OF MALE AND FEMALE MICE RECEIVING TELONE II BY INHALATION FOR TWO YEARS

Males				Females			
Control	5 ppm	20 ppm	60 ppm	Control	5 ppm	20 ppm	60 ppm
Day- %	Day- %	Day- %	Day- %	Day- %	Day- %	Day- %	Day- %
1-100	1-100	1-100	1-100	1-100	1-100	1-100	1-100
25- 98	547- 98	346- 98	558- 98	591- 98	163- 98	389- 98	18- 98
670- 96	626- 96	680- 96	588- 96	624- 96	489- 96	557- 96	490- 96
693- 94	670- 94	681- 94	646- 94	625- 94	516- 94		606- 94
730- 92	690- 92	687- 92		633- 92	625- 92		625- 92
738- 90	694- 90	694- 90		645- 90	738- 88		694- 90
	736- 88			667- 88			715- 88
				668- 86			719- 86
				693- 84			724- 84
							734- 82
							735- 80
2 years							
90	88	90	94	84	88	96	80

Note: Data are for 50 animals/group scheduled for the 24-month portion of the study.

There were no statistically identified differences from control survival pattern by Gehan Wilcoxon procedures, Alpha = 0.05.

These data are reproduced from Table 6, page 51, of the report.

Diagnoses of palpable masses were based on histopathology and there were no apparent increases in the incidence of these masses due to TELONE II exposure.

Body Weights: There was a statistically significant decrease in body weight gain in 60 ppm males (3-9%) and females (2-11%) during the last approximately 19-20 months of the study. [See Table 6.]

Table 6

BODY WEIGHTS OF MICE RECEIVING TELONE II BY INHALATION FOR TWO YEARS

Days on Test	Males				Females			
	0 ppm	5 ppm	20 ppm	60 ppm	0 ppm	5 ppm	20 ppm	60 ppm
-6	18.0	18.1	18.5	18.5	16.3	15.7	15.4*	16.2
-2	21.8	21.7	22.3	21.8	19.0	19.1	18.8	19.0
7	24.4	24.2	23.9	23.0*	21.0	20.8	20.3*	19.7*
34	26.7	26.4	27.7*	26.6	22.8	2[illegible]4	23.8*	23.5*
62	28.5	28.6	29.1	27.6*	24.6	24.6	24.6	24.6
90	28.9	29.0	28.8	28.3	25.3	25.4	25.6	24.8
118	29.6	29.8	29.5	29.0	26.3	26.4	26.3	25.7
174	31.6	31.8	31.4	29.8*	28.1	27.6	27.6	26.8*
230	32.1	32.6	31.6	30.8*	28.7	28.6	28.5	27.8*
286	31.3	31.7	31.0	29.7*	28.7	28.3	28.0	27.1*
342	32.0	32.5	31.2	29.7*	29.3	28.6	28.5*	27.1*
398	31.5	32.3	31.3	30.2*	28.9	29.3	28.7	28.1*
454	32.0	33.0*	32.0	29.8*	29.4	29.7	28.5*	27.6*
510	32.9	33.0	31.9*	30.3*	29.6	30.0	29.3	27.7†
566	33.1	33.7	33.0	30.6*	30.0	30.2	29.5	28.4*
622	33.0	33.1	32.5	30.0*	30.7	30.4	30.0	27.2†
678	30.9	31.7	30.3	28.6*	29.5	30.1	28.4	27.1*
734	30.7	31.3	30.8	28.6*	29.6	30.0	29.1	26.8*

* = Statistically different from control mean by Dunnett's Test, alpha = 0.05.

† = Statistically different from control mean by Wilcoxon's Test, alpha = 0.05.

Note: All weighing intervals below dotted line are 8 weeks.

These data are extracted from Tables 9 (pages 58-60) and 10 (pages 61-63) of the report.

Clinical Pathology Determinations: The statistically significant differences in hematology parameters were decreases in erythrocyte counts and hematocrit values in high-dose (60 ppm) males only. Because of the relatively small differences in these two parameters (about one standard deviation from the mean - 20 mice/mean value), no indication of a statistically significant decrease in the mean hemoglobin value and no decreases in any of these three indices in females, it is felt that the differences were due to normal biological variations in these measurements. [See Table 7.]

Clinical chemistry values which were statistically different from control values were: increases in urea nitrogen and alkaline phosphatase as well as a decrease in globulin in high-dose (60 ppm) males. There was also a non-statistically significant increase in alkaline phosphatase in high-dose females (less than one standard deviation from the mean control value). All of the above differences are considered to be within normal biological variations, with the possible exception of serum urea nitrogen. It should be noted that not only was this a relatively small increase (one standard deviation from the control mean), but there was no apparent increase in females). [See Table 7.]

Terminal Sacrifice Body and Organ Weights: There was a statistically significant (grams) decrease in mean high-dose (60 ppm) male final body weights (control = 28.9 $\pm$1.7 S.D.; high dose = 27.6 $\pm$ 1.4 - a decrease of 4.5%). For high-dose females, there was a non-statistically significant decrease in gain of 4.4% (control = 27.5 $\pm$ 2.4; high dose = 26.3 $\pm$ 2.3). [See Table 8.]

Mean absolute (grams) and/or relative (grams/100 grams of final body weight) weights of heart, kidney and liver from high-dose (60 ppm) males were 10-15% lower than the control means (statistically significant). A 3% (statistically significant) increase in relative high-dose brain weights was also observed in males. In females, statistically significant (7-8%) decreases were observed in mean absolute brain and heart weights of high-dose (60 ppm) animals. The relatively small differences of the organ weights between high-dose and control mice, with the absence of observed histopathological changes, suggests that these values are the result of a decrease in body weight gain and/or normal biological variation.

Gross Pathology: Assessment of a tumorigenic response was based upon histopathological findings rather than gross observations. [See Table 9.]

Table 7

MEAN HEMATOLOGY AND CLINICAL CHEMISTRY VALUES FOR MICE RECEIVING TELONE II BY INHALATION FOR TWO YEARS (data from two year interval)

Parameter	ppm	Males 0	Males 5	Males 20	Males 60	Females 0	Females 5	Females 20	Females 60
HEMATOLOGY									
RBC (x 10^6/mm^3)		9.31	9.16	9.04	8.79†	8.33	9.18	8.85	8.79
HGB (G/DL)		16.3	16.3	16.1	15.8	15.0	16.4	16.2	16.0
HCT (%)		37.5	36.8	36.7	35.8*	34.3	37.4	36.0	35.3
MCV (Microns^3)		40	41	41	41	42	41	41	40
MCH (Micro Microg)		17.6	17.9	17.9	17.9	18.1	17.9	18.3	18.2
MCHC (%)		43.5	44.2	44.0	44.1	43.5	44.0	44.9	45.3
PLAT (x 10^3/mm^3)		1967	2005	2020	1893	1079	1079[d]	986[f]	1099
WBC (x 10^3/mm^3)		3.7	5.7[b]	3.3	3.4	3.9[c]	3.2[e]	2.9[g]	3.6
SEG WBC (%)		39	-[a]	-	39	34	-	-	33[h]
LYMPH (%)		56	-	-	58	62	-	-	63[i]
CLINICAL CHEMISTRY									
UREA NIT.	(mg/dl)	22	24	22	26*	22	19	20	21
ALT	(Mu/ml)	52[j]	90[l]	38[p]	44	37[s]	37	29	43[w]
ALK. PHOS	(Mu/ml)	48	51[m]	51[q]	53†	160	156[t]	197[v]	216
AST	(Mu/ml)	60[k]	130[n]	57[r]	58	62	64[u]	53	66
GLUCOSE	(mg/dl)	184	176[o]	182	179	151	156	166	160
TP	(g/dl)	5.0	5.0	5.0	4.7	5.1	5.1	4.8	5.0
ALBUMIN	(g/dl)	2.5	2.4	2.5	2.5	2.6	2.7	2.6	2.7
GLOBULIN	(g/dl)	2.6	2.7	2.5	2.3†	2.5	2.5	2.2	2.3

* = Statistically different from control mean by Dunnett's Test, Alpha = 0.05.

† = Statistically different from control mean by Wilcoxon's Test, Alpha = 0.05.

NOTE: Values are means of 20/sex/group.

RBC = Red Blood Cells; HGB = Hemoglobin; HCT = Hematocrit; MCV = Mean Corpuscular Volume; MCH = Mean Corpuscular Hemoglobin; MCHC = Mean Corpuscular Hemoglobin Concentration; PLAT = Platelets; WBC = White Blood Cells; SEG = Segmented; LYMPH = Lymphocytes; NIT = Nitrogen; ALT = Alanine Aminotransferase; ALK. PHOS = Alkaline Phosphatase; AST = Aspartate Aminotransferase; TP = Total Protein.

FOOTNOTES FOR TABLE 7

a = - = No data available.
b = One mouse value of 15.6; mean without this value is 5.2.
c = Two mouse values of 1.0 and 11.2; mean without these values is 3.7.
d = Two mouse values of 460 and 390; mean without these values is 1151.
e = Three mouse values of 1.8, 1.4 & 1.6; mean without these values is 3.1.
f = One mouse value of 278; mean without this value is 1023.
g = One mouse value of 0.8; mean without this value is 3.0.
h = One mouse value of 66; mean without this value is 31.
i = One mouse value of 30; mean without this value is 64.
j = One mouse value of 257; mean without this value is 36.
k = One mouse value of 174; mean without this value is 54.
l = One mouse value of 1150; mean without this value is 35.
m = One mouse value of 176; mean without this value is 46.
n = One mouse value of 1635; mean without this vlue is 51.
o = One mouse value of 80; mean without this value is 181.
p = Two mouse values of 153 and 112; mean without these values is 26.
q = One mouse value of 126; mean without this value is 47.
r = One mouse value of 159; mean without this value is 52.
s = One mouse value of 111; mean without this value is 33.
t = Three mouse values of 401, 350 & 22; mean without these values is 138.
u = Two mouse values of 149 and 186; mean without these values is 52.
v = Two mouse values of 414 and 66; mean without these values is 192.
w = One mouse value of 153; mean without this value is 37.

These data are extracted from Tables 11-14 (pages 64-67) of Volume 1 of the report and Tables 8-11 of the Appendix, Volume 1.

Table 8

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ORGAN AND ORGAN/BODY WEIGHTS OF MICE GIVEN TELONE II BY INHALATION FOR TWO YEARS

Exposure Conc. ppm	Final Body Wt. (g)	Brain		Heart		Kidneys		Liver		Testes	
		g	g/100[a]	g	g/100	g	g/100	g	g/100	g	g/100
MALES											
0 (45)§	28.9[b]	0.464	1.609	0.159	0.550	0.599	2.072	1.530[d]	5.291[e]	0.202	0.701
	1.7[c]	0.018	0.086	0.013	0.035	0.059	0.156	0.521	1.828	0.014	0.057
5 (44)	29.6	0.466	1.584	0.159	0.539	0.636†	2.151	1.560[f]	5.284[g]	0.203	0.690
	2.0	0.017	0.109	0.013	0.036	0.071	0.192	0.429	1.470	0.020	0.074
20 (45)	28.8	0.465	1.616	0.153	0.530	0.580	2.012	1.519[h]	5.242[i]	0.204	0.709
	1.8	0.016	0.082	0.014	0.039	0.057	0.138	0.603	1.921	0.016	0.064
60 (47)	27.6*	0.457	1.662*	0.137*	0.497*	0.507†	1.841†	1.357†	4.933	0.201	0.730
	1.4	0.018	0.091	0.014	0.042	0.042	0.104	0.310	1.144	0.014	0.058
FEMALES											
0 (42)	27.5	0.476	1.743	0.135	0.491	0.419	1.526	1.383	4.996	-	-
	2.4	0.019	0.130	0.019	0.057	0.046	0.115	0.360	0.954	-	-
5 (44)	27.9	0.480	1.726	0.137	0.491	0.430	1.544	1.437	5.143	-	-
	1.9	0.019	0.129	0.013	0.045	0.031	0.118	0.236	0.710	-	-
20 (48)	27.6	0.470	1.713	0.131	0.477	0.416	1.510	1.481[j]	5.324[k]	-	-
	2.3	0.018	0.127	0.016	0.044	0.041	0.112	0.450	1.280	-	-
60 (40)	26.3	0.464*	1.774	0.124†	0.471	0.409	1.554	1.374	5.197	-	-
	2.3	0.015	0.143	0.011	0.033	0.045	0.124	0.410	1.400	-	-

* = Statistically different from control mean by Dunnett's Test, Alpha = 0.05.
† = Statistically different from control mean by Wilcoxon's Test, Alpha = 0.05.
§ = Number of mice at terminal sacrifice (50/sex/group started).

a = Grams of tissue/100 grams of final body weight.
b = Group Mean.
c = Standard Deviation.
d = Two mouse values of 3.734 and 3.225; mean without these values is 1.439.
e = Two mouse values of 13.881 and 10.859; mean without these values is 4.962.
f = Two mouse values of 3.125 and 3.048; mean without these values is 1.485.
g = One mouse value of 11.405; mean without this value is 5.142.
h = Three mouse values of 3.419, 3.278 & 3.791; mean without these values is 1.378.
i = Three mouse values of 11.996, 10.574 & 11.959; mean without these values is 4.795.
j = One mouse value of 3.568; mean without this value is 1.436.
k = One mouse value of 11.473; mean without this value is 5.193.

These data are extracted from Tables 15 and 16 (pages 68 and 69) of the report and Volume I of the Appendix.

Table 9

GROSS OBSERVATIONS OF MASS/NODULE

LUNGS

	males				females			
ppm	0	5	20	60	0	5	20	60
Mass/nodule-probably metastatic tumor, multifocal:	0	1	0	0	1	0	0	0
Mass/nodule:	5	3	8	13	2	3	3	2
Mass/nodule (two):	0	0	1	1	0	0	0	0
TOTAL:	5	4	9	14	3	3	3	2

NOTE: 50 mice/sex/group examined.
Data from Table 17, page 75 of the report.

LACRIMAL GLAND

	males				females			
ppm	0	5	20	60	0	5	20	60
No. of Mice Examined	50	47	44	47	48	48	49	49
Mass/Nodule:	0	3	6	2	2	2	1	1
Mass/Nodule (two):	0	0	0	1	0	0	0	0
TOTAL:	0	3	6	3	2	2	1	1

NOTE: 50 mice/sex/group examined.
Data from Table 17, page 73, of the report.

UTERUS

ppm	0	5	20	60
Mass/nodule	1	5	4	8

NOTE: 50 mice/sex/group examined.
Data from Table 17, page 81, of the report.

Using a dissecting stereomicroscope, examination of the urinary bladders revealed the following:

	Males				Females			
ppm	0	5	20	60	0	5	20	60
No. of Mice Examined	50	50	50	50	50	50	50	49*
Focus dark (hemorrhage) serosa, focal	1	0	0	0	0	0	0	0
Roughened, irregular and opaque surface								
Slight	0	1	0	2	3	4	7	14
Moderate	0	0	0	3	0	1	11	14
Marked	0	0	0	1	0	0	2	2
Mass or Nodule	0	1	0	0	0	0	1	0

* = One bladder not examined by dissecting microscope, but prepared for histopathology.
[Data reproduced from Table 18, page 82, of the report.]

Histopathology - Nonneoplastic: Microscopic examination of tissues revealed statistically identified increases in treatment related effects in the urinary bladder and nasal mucosa in both sexes, nonglandular portion of the stomach and kidmneys in males and the livers of females exposed to 20 ppm or 60 ppm or both.

Table 9

STATISTICALLY IDENTIFIED INCREASES IN MICROSCOPICALLY OBSERVED TREATMENT RELATED EFFECTS IN MICE HAVING RECEIVED TELONE II BY INHALATION FOR TWO YEARS

	Males				Females			
Tissue — ppm	0	5	20	60	0	5	20	60
URINARY BLADDER								
Number examined	47	48	48	47	47	46	48	45
Hyperplasia (simple), mucosa:								
very slight	4	7	7	16	1	3	13	5
slight	0	0	3	18	0	1	6	18
moderate	0	0	0	2	0	0	0	19
Hyperplasia-nodular, mucosa:								
slight	0	0	1	0	0	0	0	0
moderate	0	0	0	1	0	0	2	2
NASAL MUCOSA								
Number examined	50	50	50	50	50	50	50	50
Respiratory Epithelium: Hypertrophy and hyperplasia, respiratory mucosa bilateral								
very slight	5	1	4	38	4	4	28	39
slight	0	0	0	10	0	0	0	10
Olfactory Epithelium: Degeneration, olfactory epithelium bilateral								
very slight	1	0	1	32	0	0	1	29
slight	0	0	0	16	0	0	0	16
NONGLANDULAR PORTION OF THE STOMACH								
Number examined	50	50	50	50	50	9	4	50
Hyperplasia, often accompanied by chronic inflammation, focal or multifocal	0	3	1	8	0	0	0	2

[The above data are extracted from pages 21 and 23 of the report. Photomicrographs depicting examples of nonneoplastic lesions were included on pages 37-44 of the report.]

URINARY BLADDER - Almost all high-dose (60 ppm) males and females showed an increase in hyperplasia of the transitional epithelium with a lesser number being effected at 20 ppm. Females appeared to have more severe changes than males. [The report stated that since the mucosa undergoes autolytic change and sloughing fairly rapidly, no diagnoses of hyperplasia were made for any mice dying spontaneously.] In females exposed to 20 or 60 ppm, there appeared to be a decrease in lymphoid aggregates but increased inflammation of the mucosa.

NASAL MUCOSA - There were hypertrophy and hyperplasia of the respiratory epithelium and degeneration of the olfactory epithelium in almost all 60 ppm males and females. Hyperplasia of the respiratory epithelium was also observed in a majority of females at 20 ppm. Both types of nasal lesions involved approximately 10% or less of the epithelium and were considered by the study pathologist to be of minimal severity. Respiratory and olfactory epithelium lesions occurred bilaterally. The nasal turbinate bone and septum were primarily involved.

NONGLANDULAR STOMACH - Hyperplasia was statistically identified in 60 ppm males only.

KIDNEY AND LIVER - Decreased vacuolation of kidney tubular epithelial cells was noted in high-dose (60 ppm) males (29/50 vs. 9/50 controls) and liver cells in females (24/50 vs. 10/50 controls). Renal and hepatic changes were observed in males after 6 and 12 months exposure with decreased organ weights. [No data included in this 2-year report.] In the 2-year study, kidney weights were decreased and there was a slight elevation of serum urea nitrogen in high-dose males.

Histopathology - Neoplastic: The incidence of benign and malignant neoplasms is presented in Tables 10 and 11. There was an increase in bronchioloalveolar adenomas (benign) in 60 ppm males - 22/50 (44%) vs.9/50 (18%) in controls. [The laboratory indicated the historical range of these lesions for the 7 previous chronic studies to be 7-32%, including 20% in another 2-year inhalation study.] The tumors replaced the normal lung parenchyma and compressed the adjacent tissue. The only malignant lung neoplasms (at least 2 in a sex of the category) were osteogenic sarcomas (secondary) in 2 control females. [Photomicrographs of benign lung tumors were included on page 45 of the report.]

Benign Lacrimal Gland Tumors -

Males	ppm	0	5	20	60
		1/50	6/50	10/50	5/50
	%	2	12	20	10

There was no statistical identification. Historical range was 2-16% with an average of 11%.

No histopathological data from the 6- or 12-month interim sacrifices were included in this report.

Table 10

BENIGN TUMORS IN MICE ADMINISTERED TELONE II BY INHALATION FOR TWO YEARS
(Tumors appearing in at least two mice in any group)

	Male				Female			
ppm	0	5	20	60	0	5	20	60
Liver	50[a]	50	50	50	50	50	50	50
adenoma, hepatocellular, primary	13	14	8	11	8	6	7	9
adenoma, hepatocellular, primary (two)	2	3	3	0	1	0	1	0
adenoma, hepatocellular, primary (three)	0	0	2	0	0	0	0	0
Lungs	50	50	50	50	50	50	50	50
adenoma, bronchioloalveolar, primary	9	6	11	20	3	3	4	3
adenoma, bronchioloalveolar, primary (two)	0	0	2	2	0	0	1	0
adenoma, bronchioloalveolar, primary (three)	0	0	0	0	1	0	0	0
Ovaries	-	-	-	-	49	50	50	49
hemangioma, primary					3	1	2	0
Pituitary	50	48	49	48	49	48	49	48
adenoma, anterior (pars distalis), primary	0	0	0	1	6	16	11	7
Spleen	50	50	50	50	50	50	50	50
hemangioma, primary	0	0	1	0	0	0	2	2
Stomach	50	50	50	50	50	9	4	50
squamous papilloma, nonglandular mucosa, primary	0	3	2	0	3	2	0	3
Uterus	-	-	-	-	50	50	50	50
endometrial stromal polyp, primary					2	4	1	4
endometrial stromal polyp, primary (two)					1	0	0	0
leiomyoma, muscularis, primary					0	2	1	0

a = Number of animals from which tissue was examined.

- = Not applicable/not examined.

Data extracted from Table 20 (pages 114-121) as well as Volumes 2 and 3 of the Appendix.

Table 11

MALIGNANT TUMORS IN MICE ADMINISTERED TELONE II BY INHALATION FOR TWO YEARS
(Tumors appearing in at least two mice in any group)

	Male				Female			
ppm	0	5	20	60	0	5	20	60
Bone	50[a]	6	5	50	50	6	3	50
osteogenic sarcoma, primary, metastasis	0	0	0	0	2	0	0	0
Liver	50	50	50	50	50	50	50	50
carcinoma, hepatocellular, primary, no metastasis	11	5	3	3	1	1	0	1
Lungs	50	50	50	50	50	50	50	50
osteogenic sarcoma, secondary	0	0	0	0	2	0	0	0
Mammary Gland	-	-	-	-	50	50	50	50
adenocarcinoma, primary, no metastasis					2	0	0	1
Mesenteric Lymph Node	49	50	48	48	48	49	47	48
lymphosarcoma, primary, metastatic	2	2	2	0	3	11	5	6
Multiple Organs	b	b	b	b	b	b	b	b
histiocytic sarcoma (spleen), secondary	0	2	0	-	5	0	1	0
lymphosarcoma (mesenteric lymph node), secondary, no metastasis	2	1	2	-	3	10	2	6
Pituitary	50	48	49	48	49	48	49	48
adenocarcinoma, anterior (pars distalis), no metas.	0	0	0	0	1	1	3	0
Preputial	13	13	12	6	-	-	-	-
squamous cell carcinoma, primary, no metastasis	0	2	0	0				
Skeletal Muscle	50	6	5	50	50	6	3	50
hemangiosarcoma, primary, no metastasis	0	0	0	0	0	0	2	0
Small Intestine	50	8	6	50	50	8	6	50
lymphosarcoma, (mesenteric lymph node), secondary	0	1	0	0	0	0	2	0
Spleen	50	50	50	50	50	50	50	50
histiocytic sarcoma, primary, metastasis	0	2	0	0	5	0	1	0
Urinary Bladder	50	50	50	50	50	50	50	50
carcinoma, primary, no metastasis	0	0	0	0	0	0	2	0

a = Number of animals from which tissue was examined.
b = Number of tissues examined not given in report.
- = Not applicable/not examined.

These data were extracted from Table 20 (pages 114-121) of the report as well as Volumes 2 and 3 of the Appendix.

IV. Discussion

Exposure to TELONE II by inhalation for two years did not have any effect on survival (at least 80% in each group). There was a statistically significant decrease in body weight gain in 60 ppm males (3-9%) and females (2-11%). Mean absolute and/or relative weights of the heart, kidney and liver from 60 ppm males were significantly below control means (10-15%). Relative 60 ppm male brain weights were increased (3%, statistically significant). In 60 ppm females, there was a decrease in absolute brain and heart weights of 7-8%. The relatively small differences between treated and control organ weights are felt to be due to a decrease in body weight gain and/or normal biological variation. Even though there were statistically significant differences in some hematology and clinical chemistry parameters, the lack of corroborating findings indicated that these differences were most likely due to biological variations.

Urinary bladder effects were noted in both sexes at 20 and 60 ppm. The report indicated that hyperplasia of the bladder epithelium had been observed in female mice exposed to 90 and 150 ppm by inhalation for 13 weeks as well as mostly in females exposed to 60 ppm vapors for 6 and 12 months (the interim sacrifice portions of this 2-year study). These data, plus the observation that males were less severely affected than females in the present study (Table 9 - at 60 ppm "very slight" or "slight" simple hyperplasia: males = 34, females = 23; "moderate": males = 2, females = 19), indicated the progression of this lesion with increasing exposure duration and an apparent sex difference in sensitivity. In a 1985 2-year oral gavage NTP study, hyperplasia of the transitional epithelium of the urinary bladder was described in female mice.

Hypertrophy and hyperplasia of the nasal respiratory mucosa (very slight/slight) were observed in most 60 ppm mice of both sexes and in 20 ppm females. Degeneration of olfactory epithelium (very slight/slight) was noted in most 60 ppm mice of both sexes. No lesions of the epithelium were said to have been reported after 6 months exposure, with only a few animals affected after 12 months duration. The degenerative changes were observed in a 13-week inhalation study at 90 and 150 ppm. Hyperplastic changes of respiratory epithelium also occurred in the 13-week study. In the 2-year exposure study, the pathologist indicated that, "... even the most severe of these nasal mucosal lesions still involved less than approximately 10% of the respective epithelium present and only those areas of the mucosa having the most contact with inhaled air were affected."

Hyperplasia of the epithelial lining of the nonglandular portion of the stomach was observed in 60 ppm males (0,5,20,60 ppm - males: 0,3,1,8; females: 0,0,0,2). The authors indicated that the lesion was a result of ingestion of TELONE II which was absorbed in respiratory tract secretions and subsequently swallowed, as well as during grooming. A similar effect (including a tumorigenic response), but at a higher incidence, was reported in a 1985 NTP oral gavage study (no neoplastic response was noted in the 2-year inhalation study).

The only tumorigenic response was an increased incidence in benign lung tumors (bronchioloalveolar adenomas) in 60 ppm males only (22/50 vs. 9/50 controls). This response was also observed in female mice at 50 ppm (6%) or 100 ppm (16%) in the 1985 NTP oral gavage study (no male data due to excessive early control mortality).

The authors also commented on the "differences" between the oral gavage and current inhalation studies. The stabilizer in the formulation of TELONE II was different. In addition, calculations indicated that 60 ppm for 6 hours/day x 5 days/week in the 2-year inhalation study was estimated to be 2-3 times higher than the high dose administered 3 times/week in the NTP oral gavage study. Although the total amount of TELONE II received by the mice was greater in the inhalation study, it should be pointed out that in the oral gavage study, the material was administered as a "bolus" as well as directly into the gastrointestinal tract.

V. Conclusions

The stabilizer in the TELONE II formulation administered in the oral gavage NTP study was epichlorohydrin. In the 2-year mouse inhalation study, the stabilizer was [redacted]. The observation of bronchioloalveolar adenomas in both studies indicates that it is unlikely that one of the stabilizers was the cause of the tumors.

The survival rate of both male (88-94%) and female (80-96%) B6C3F1 mice in this study is excellent. Experience with historical control values for this strain of mouse dosed via various routes has been that survival is considerably less than the data here indicate.

The maximum mean body weight values, particularly of the males, appears to be somewhat less than would have been expected for B6C3F1 mice. The highest mean value was 34.3 grams for males (594 days weighing, 5 ppm) and 31.2 grams for females (594 days weighing, control). In addition, no individual male appears to weigh as much as 40 grams. One might expect the male means to be in the 40-50 gram range at some time during the study, with some individuals weighing at least 50 grams. As no food consumption data were included in the report (no food available during the period of TELONE II exposure), it is not possible to correlate food intake with body weight.

VI. Recommendation

The study is considered to be Minimum Data. A Positive oncogenic effect (bronchioloalveolar adenomas) was observed in males at 60 ppm (HDT) but not in either of the lower-dose males (5 or 20 ppm) or at any of the doses in females.

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