BB-1604
TXR-6531

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

006531

DEC 21 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: TELONE II* Soil Fumigant: 2-Year Inhalation Chronic Toxicity-Oncogenicity Study in Rats - EPA Accession No. 403122-01; Toxicology Branch Proj. No. 7-0986; Caswell No. 324A.

FROM: Alan C. Levy, Ph.D.
Toxicologist, Review Section V
Toxicology Branch/HED (TS-769C)
Alan C. Levy 12/18/87

TO: Bruce Kapner - PM # 70
Registration Division (TS-767C)

THRU: Quang Q. Bui, Ph.D., D.A.B.T.
Acting Section Head, Review Section V
Quang Q Bui 12/18/87

and

Theodore M. Farber, Ph.D., D.A.B.T.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)
12/21/87

Registrant: Dow Chemical Company

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

Recommendations: There was no oncogenicity observed in this study after exposure to any of the concentrations examined (5, 20 and 60 ppm).

The Systemic Toxicity No Observed Effect Level (NOEL) is 20 ppm. The Systemic Toxicity Lowest Observed Effect Level (LOEL) 60 ppm (highest dose tested - HDT). This HDT caused histopathological changes in nasal tissue as well as the suggestion of a decrease in body weight gain during the first year of the study.

The study is Classified as Core Minimum.

The Toxicology Branch recommends that, because of the effec of inhalation exposure of TELONE II on nasal tissue, appropriate protection be required for handlers of this chemical.

1 of 26

006531

006531

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: Chronic Toxicity/Oncogenicity Study
(Guideline § 83-1 and 83-2)

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

EPA Identification Numbers:

EPA Identification: 464-511
EPA Accession: 403122-01
EPA Record: 202050
Caswell: 324A
Tox. Branch Project: 7-0986

Sponsor: Dow Chemical USA
Midland, MI 48640

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-003993-009R

Study Date: July 13, 1987

Study Authors: L. G. Lomax, D.V.M., Ph.D., L. L. Calhoun, B.S., W. T. Stott, Ph.D., D.A.B.T. and L. E. Frauson, B.S., M.T. (ASCP)

Recommendation: There was no oncogenicity observed in this study after exposure to any of the concentrations examined (5, 20 and 60 ppm).

The Systemic Toxicity No Observed Effect Level (NOEL) is 20 ppm. The Systemic Toxicity Lowest Observed Effect Level (LOEL) is 60 ppm (highest dose tested - HDT). This HDT caused histopathological changes in nasal tissue as well as the suggestion of a decrease in body weight gain during the first year of the study.

The study is Classified as Core Minimum.

The Toxicology Branch recommends that, because of the effect of inhalation exposure of TELONE II on nasal tissue, appropriate protection be required for handlers of this chemical.

006531

006531

Test Material: PRODUCT IMPURITY INFORMATION NOT INCLUDED

Name: TELONE II soil fumigant

Chemical Composition (at start of study): 1,3-dichloropropene, 92.1% [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)

Solubility: Miscible with most organic solvents.

006531

II. Materials and Methods

Fischer 344 rats, 6-8 weeks of age, were obtained from Charles River Breeding Laboratories, Portage, MI. After an acclimation period of at least 7 days, the animals were randomly assigned to exposure level groups consisting of 70 rats/sex. Ten rats/sex/group were randomly assigned to the 6- and 12-month interim sacrifice groups with the remaining 50/sex/group assigned to the 24-month exposure period. 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.

Rats were exposed 6 hours/day, 5 days/week (excluding holidays) for a total of 509 days of exposure in the 2-year period. The animals were exposed to the following:

Table 1

AMOUNT OF TELONE II TO WHICH RATS 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	20.3
20	90.8	18.4	83.6
60	272.4	55.2	250.6

a = dichloropropene; 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).

Animals were observed after each exposure period and changes in appearance were recorded. All rats were examined for palpable masses during the randomization procedure, 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 rats designated for 2 years of exposure were included in the report.] Food

comsumption was not reported as having been measured.

Blood samples for hematology and clinical chemistry evaluations were obtained from 20 rats/sex/group and were collected at the time of necropsy. Hematology parameters (posterior orbital sinus puncture) were: erythrocyte count (RBC), hemoglobin (HGB), hematocrit (HCT), RBC indices (mean corpuscular volume - MCV, mean corpuscular hemoglobin - MCH, and mean corpuscular hemoglobin concentration - MCHC), platelet count (PLAT), leukocyte (WBC) count and differential leukocyte counts (only on rats 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), glucose, total protein (TP), albumin (ALB) and globulin (GLOB). Blood was collected from the severed cervical vessels of rats at necropsy.

Urinary parameters (urine collected a week prior to necropsy) were: protein, glucose, bilirubin, blood, urobilinogen, pH and specific gravity.

After 2 years of exposure, rats were fasted prior to necropsy. 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 or sacrificed moribund.

Detailed descriptions of statistical analyses employed were described.

A Quality Assurance statement was included.

Blood electrolytes were not reported in this study. FIFRA Guideline § 83-1 (Chronic Toxicity) suggest Calcium, Phosphorus, Chloride, Sodium and Potassium. Because there was no evidence of histopathological changes which might be related to electrolyte alterations, this reviewer does not feel that a repeat of this study to examine these electrolyte parameters would add significant scientific information. There are no other comments regarding the Materials and Methods section.

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

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 reasonable 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 was reproduced from page 39 of the report.]

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

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 were 46, 56, 60 and 56% for males and 60, 52, 76 and 72% for females.

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

Body Weights: There was a statistically significant ($p<0.05$) decrease in mean body weights of males exposed to 60 ppm from days 13-425 (difference was approximately 5%), but weights were similar to controls for the remainder of the study. Males at 20 ppm had statistically significicant decreases (about 3%) from controls at 5 of 36 weighing intervals. Females exposed to 60 ppm had mean body weights approximately 5% less than the control value from days 6-327 with values similar to controls throughout the remainder of the study. [See Table 6.]

Clinical Pathology Determinations: There were no statistically significant differences from controls regarding any hematological parameters in males or females. The only statistical differences for clinical chemistry determinations were for 60 ppm female total protein (decrease of 6.3%) and albumin (decrease of 5.9%); these differences were not considered to be of toxicological significance. [See table 7.] Urinary parameters of TELONE II exposed rats did not appear to be different from controls.

As noted in Table 7, there were instances where individual hematology/clinical chemistry values were statistically (according to the report) and/or considered by the reviewer, outside of "acceptable" ranges and therefore, additional means have been calculated and presented in Table 7 by the reviewer.]

Table 2

EXPOSURE CONCENTRATIONS AND CHAMBER CONDITIONS - TWO YEAR INHALATION RAT 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±	52±9
5	5.0±0.2	4.0%	3.6-5.6	5.3±.4	3.7-7.1	24±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	23±1	51±8
60	60.1±0.9	1.5%	51.5±63.7	58.4±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 = 509 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 exposured in progress.
- = Not applicable.
These data are reproduced from Table 4 of the report.

006531

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 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	5.7	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 of the report.

Table 5

SURVIVAL OF MALE AND FEMALE RATS 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
274- 98	136- 98	490- 98	357- 98	465- 98	486- 98	287- 98	212- 98
434- 96	476- 96	515- 96	401- 96	525- 96	544- 96	289- 96	365- 96
534- 94	561- 94	560- 94	471- 94	584- 94	571- 94	499- 94	501- 94
547- 92	570- 92	575- 92	535- 92	597- 92	574- 92	519- 92	524- 92
550- 90	577- 90	612- 90	536- 90	639- 90	584- 90	536- 90	531- 90
597- 88	585- 88	613- 88	570- 88	640- 88	592- 88	599- 88	554- 88
606- 86	592- 86	620- 86	603- 86	668- 86	604- 86	681- 86	583- 86
614- 84	602- 84	633- 84	648- 84	689- 84	610- 84	688- 82	585- 84
632- 82	611- 82	638- 82	658- 82	697- 82	613- 82	721- 80	665- 82
634- 80	626- 80	644- 80	661- 78	703- 80	624- 80	732- 78	672- 80
638- 78	637- 76	653- 78	665- 76	704- 78	651- 78	735- 76	693- 78
662- 76	641- 74	678- 76	666- 74	716- 74	665- 76		708- 76
672- 74	679- 70	681- 74	668- 72	718- 70	678- 74		714- 74
673- 72	689- 68	693- 68	675- 70	719- 68	690- 72		720- 72
675- 70	693- 66	696- 66	679- 66	724- 64	696- 70		
679- 68	700- 64	703- 66	683- 64	729- 62	697- 68		
687- 66	708- 62	708- 64	693- 62	735- 60	700- 66		
689- 62	714- 58	716- 62	701- 60		702- 64		
697- 60	731- 56	731- 60	735- 56		710- 62		
700- 58					714- 60		
702- 56					717- 58		
716- 54					718- 56		
718- 50					722- 54		
722- 48					736- 52		
728- 46							
2 years							
46	56	60	56	60	52	76	72

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 Tables 5 and 6 of the report.

Table 6

BODY WEIGHTS OF RATS 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
-1	150.0	151.8	153.3	148.8	108.3	107.9	107.6	107.4
6	179.4	180.3	182.7	172.4	126.1	125.5	126.6	121.0*
34	255.3	259.3	255.4	246.2*	162.3	163.5	163.8	155.5*
62	295.5	292.6	291.7	283.3*	181.9	179.6	182.0	174.1*
90	321.4	322.6	316.6	307.6*	193.6	194.2	191.8	184.7*
117	344.1	342.4	334.9*	325.6*	201.6	202.0	199.8	193.1*
173	371.2	372.0	364.8	355.8*	211.9	212.1	210.2	204.6*
229	401.7	400.6	387.1*	382.8*	222.3	221.4	222.5	214.7*
285	421.6	418.4	405.2†	399.6†	231.3	231.8	228.2	224.7*
341	420.7	419.3	413.0	406.5†	236.0	238.4	236.0	232.4
397	428.9	425.3	417.8	410.6†	248.5	252.3	250.1	248.2
453	432.7	434.2	430.8	422.6	259.2	262.3	262.9	259.9
509	430.3	434.0	428.0	424.0	269.8	271.5	272.4	267.2
565	431.9	436.3	430.1	424.7	274.9	269.7	286.2*	275.9
621	432.3	431.5	425.2	418.3	280.2	277.3	287.6	281.7
677	404.8	403.4	402.1	396.6	280.0	278.9	284.7	281.9
733	413.5	396.5	391.2	389.8	282.5	286.9	281.0	288.9

* = 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 and 10 of the report.

Table 7

MEAN HEMATOLOGY AND CLINICAL CHEMISTRY VALUES FOR RATS 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)		7.34	7.53	7.40	7.70	7.35	6.85	6.98	7.22
HGB (G/DL)		15.0	15.3	15.2	15.9	15.9	15.2	15.3	15.6
HCT (%)		39.1	40.5	39.7	41.4	40.3	38.5	38.8	39.6
MCV (Microns^3)		53	56	56	55	55	57	57	55
MCH (Micro Microg)		20.4	21.1	21.8	21.0	22.1	22.5	22.9	21.7
MCHC (%)		38.3	37.9	38.8	38.3	39.7	39.5	39.8	39.4
PLAT (x 10^3/mm^3)		946	910	920	846	769	740	695	802
WBC (x 10^3/mm^3)		4.5	16.6[a]	7.3	7.7	3.6	5.7	6.3	3.3
SEG WBC (%)		34	-[b]	-	41	32	-	-	39
LYMPH (%)		63	-	-	56	65	-	-	59
CLINICAL CHEMISTRY									
UREA NIT.	(mg/dl)	22	24	21	20	16	16	14	15
ALT	(Mu/ml)	46	72[c]	54	54	45	43	51	39
ALK. PHOS	(Mu/ml)	65	65	73	68	37	45	45	45[h]
AST	(Mu/ml)	108	190[d]	163[e]	129[f]	102	112	152[g]	92
GLUCOSE	(mg/ml)	142	141	140	144	140	152	143	146
TP	(g/dl)	5.8	5.9	5.6	5.6	6.3	6.0	6.1	5.9*
ALBUMIN	(g/dl)	2.8	2.8	2.6	2.7	3.4	3.3	3.3	3.2*
GLOBULIN	(g/dl)	3.0	3.1	3.0	2.9	2.9	2.7	2.9	2.7

* = Statistically different from control mean by Dunnett's Test, Alpha = 0.05.
NOTE: Values are means of 20/sex/group.

RBC = Red Blood Cells; HBG = 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

a = One rat value of 235.6; mean without this value is 5.1.
b = - = No data available.
c = One rat value of 790; mean without this value is 32.
d = One rat value of 2125; mean without this value is 88.
e = Three rat values of 875, 425 and 290; mean without the three values is 98.
f = One rat value of 703; mean without this value is 98.
g = Two rat values of 446 and 900; mean without these two values is 95.
h = One rat value of 223; mean without this value is 36.

These data are extracted from Tables 11-14 of Volume 1 and Tables 8-11 of the Appendix, Volume 2.

Terminal Sacrifice Body and Organ Weights: Although the final mean male body weights of all treated groups were less than the control mean, these differences were not statistically significant (no more than 5.1% less than control). There were essentially no differences in female groups. [See Table 8.]

The only organ weight that was statistically different from the control mean was the absolute (grams) weight of the brain in the 60 ppm female group (this mean group decrease of 1.5% is not considered to be of biological significance). [See Table 8.]

[As noted in Table 8, there were instances where individual organ weights were considered to be outside of "acceptable" ranges and therefore, additional means have been calculated and presented in Table 8 by the reviewer.]

Gross Pathology: There were no gross pathological observations that indicated any exposure-related effects.

Histopathology: The following data (reproduced from page 19 of the report) indicate statistically identified exposure-related effects on nasal tissues of rats in the 60 ppm group (no apparent nasal histopathological findings in the lower doses of 20 or 5 ppm). These differences concerned the thickness of olfactory epithelium, erosions of olfactory epithelium and submucosal fibrosis. [The report included five photomicrographs of H & E stained nasal tissue.] Other observed inflammatory, degenerative, and/or hyperplastic microscopic changes occurred in portions of the respiratory epithelium from some rats in all groups (including control).

STATISTICALLY IDENTIFIED MICROSCOPIC CHANGES IN NASAL TISSUES AND ANATOMIC LEVEL OF OCCURRENCE IN RATS EXPOSED TO 60 PPM TELONE II SOIL FUMIGANT FOR 2 YEARS

Microscopic change	Overall Incidence	Number affected / Number examined	Anatomic Level[a] 1	2	3	4
MALES (60 ppm)						
Decreased thickness olfactory epithelium	20/50 (40%)		0	17	15	10
Erosions of olfactory epithelium	15/50 (30%)		0	12	14	10
Submucosal fibrosis	6/50 (12%)		0	4	5	6
FEMALES (60 ppm)						
Decreased thickness olfactory epithelium	15/49 (31%)		0	12	8	5
Erosion of olfactory epithelium	6/49 (12%)		0	5	4	4
Submucosal fibrosis	2/49[b] (4%)		0	0	1	1

a=Any given animal may have 1 or more levels affected. Level 1 = most anterior, obtained just posterior to the incisor teeth; Level 2 = obtained at the incisive papilla; Level 3 = obtained at level of second palatal ridge; Level 4 = most posterior, obtained at level of first upper molar teeth.

b=Not statistically identified.

Table 8

006531

ORGAN AND ORGAN/BODY WEIGHTS OF RATS 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 (23)[†]	377.0[b]	2.059	0.551	1.114	0.297	3.114	0.833	11.449	3.054	5.285[d]	1.415[e]
	39.4[c]	.044	0.052	0.083	0.024	0.297	0.110	1.310	0.368	2.028	0.557
5 (28)	363.7	2.078	0.579	1.134	0.315	3.198	0.887	12.120	3.353	5.549[f]	1.508[g]
	40.3	0.052	0.070	0.108	0.043	0.388	0.126	2.169	0.611	2.207	0.540
20 (30)	357.8	2.051	0.579	1.111	0.314	3.148[h]	0.889[i]	1.524	3.244	5.376	1.487
	41.1	0.055	0.056	0.095	0.040	0.456	0.163	1.947	0.576	2.160	0.536
60 (28)	365.1	2.048	0.564	1.088	0.299	3.178	0.872	12.215[j]	3.330[k]	5.621[l]	1.568[m]
	32.3	0.044	0.043	0.068	0.024	0.312	0.072	2.756	0.566	2.514	0.736
FEMALES											
0 (30)	261.6	1.869	0.720	0.891	0.343	2.120	0.815	7.796	2.985	-	-
	25.3	0.044	0.064	0.057	0.029	0.253	0.102	1.241	0.418	-	-
5 (26)	262.9	1.871	0.719	0.882	0.338	2.412[n]	0.933[o]	7.800	2.977	-	-
	28.9	0.037	0.067	0.053	0.028	1.498	0.632	1.092	0.372	-	-
20 (38)	262.3	1.875	0.719	0.889	0.342	2.187	0.837	7.990	3.057	-	-
	20.9	0.048	0.066	0.069	0.044	0.217	0.086	1.257	0.490	-	-
60 (36)	265.8	1.841*	0.702	0.894	0.340	2.194	0.837	7.768	2.946	-	-
	35.8	0.048	0.077	0.083	0.042	0.231	0.134	1.079	0.425	-	-

* = Statistically different from control mean by Dunnett's Test, Alpha = 0.05.
a = Grams of tissue/100 grams of final body weight.
b = Group Mean.
c = Standard Deviation.
d = One rat value of 11.626; mean without this value is 4.996.
e = One rat value of 3.032; mean without this value is 1.341.
f = One rat value of 10.246; mean without this value is 5.375.
g = One rat value of 2.690; mean without this value is 1.464.
h = One rat value of 4.905; mean without this value is 3.088.
i = One rat value of 1.570; mean without this value is 0.866.
j = One rat value of 21.127; mean without this value is 11.884.
k = One rat value of 4.302; mean without this value is 3.293.
l = Two rat values of 0.633 and 12.794; mean without these values is 5.332.
m = Two rat values of 0.129 and 3.976; mean without these values is 1.475.
n = One rat value of 9.726; mean without this value is 2.119.
o = One rat value of 4.009; mean without this value is 0.810.

† = Number of rats at terminal sacrifice (50/sex/group started).

These data are extracted from Tables 17 and 18 of the report.

Statistically identified, but considered of no toxicological significance, were microscopic changes in the heart, kidneys, liver and tongue. In 60 ppm males, chronic myocardial inflammation was decreased. Bilateral diffuse severe glomerulonephropathy was decreased in females exposed to 5 or 20 ppm. Five ppm males had an increase in periportal fibrosis (all grades of severity combined) and foci of altered cells (moderate) in the liver (no difference when all categories of severity of foci were combined). [The authors of the report considered periportal fibrosis to be an aging change in Fischer 344 rats.] Other liver changes were increased focal infarcts in 20 ppm males, decreased diffuse sinusoidal congestion in 60 ppm females and increased hepatocellular necrosis in 5 ppm females. There was a decrease in multifocal mineralization of blood vessels in the tongue of 60 ppm females. [The authors of the report state that this change occurs sporadically in untreated Fischer 344 rats.]

There were no statistically significant differences between treated and control groups in either benign or malignant neoplasms. Tables 9 (benign) and 10 (malignant) indicate the numbers of tumors reported. These tables (generated by the reviewer) include tumors which had been observed in at least two rats/sex/group (when only one animal of a sex/group had a described histopathological neoplasm, it was not included in these tables).

IV. Discussion

There was no effect of exposure to TELONE II on the survival of males or females. Slight (approximately 5% in 60 ppm males and females as well as 3% in 20 ppm males) decreases in body weight gain were observed (statistically significant, $p<0.05$) generally only during the first year of the study. Absolute (grams) or relative (grams/100 grams body weight) organ weights of treated male or female rats did not appear to be different from respective control values (significant female brain weight considered to be within normal biological limits).

No toxicological significance was attributed to the slightly (approximately 6%) decreased mean total protein and albumin concentrations in 60 ppm females only. The authors of the report state that there was also a slight decrease in these values in 60 ppm females at the 6-month interim sacrifice but not at the sacrifice performed at 12 months. [The interim 6- and 12-month sacrifice data were not included in the 2-year report.] This reviewer feels that these decreases are not of toxicological significance because of the relatively small mean decrease from controls, the animal-to-animal variation, the authors' statement of a slight decrease at the 6-month but not 12-month sacrifice, no apparent progression in severity (6-, 12- or 24-month intervals) and no microscopic indication of liver or kidney damage.

The olfactory region of the nasal cavity appeared to be the target tissue as determined by histopathological examination. Males and females having been exposed to 60 ppm (no evidence reported at lower concentrations of 20 or 5 ppm) showed decreased thickness and

Table 9

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

	Male				Female			
ppm	0	5	20	60	0	5	20	60
Adrenal	50[a]	49	50	50	50	50	50	50
pheochromocytoma, primary	8	4	8	2	0	1	4	0
Liver	50	50	50	50	50	50	50	50
adenoma, hepatocellular, primary	3	3	3	0	1	0	1	1
Mammary Gland	50	29	24	50	50	35	25	50
adenoma, acini, primary	1	0	0	0	1	0	1	2
fibroadenoma, acini, primary	3	4	4	2	12	12	11	12
Oral Tissues	50	25	22	50	50	24	18	49
squamous papilloma, hard palate, primary	2	1	3	0	0	0	2	1
Ovaries	-	-	-	-	50	50	50	50
granulosa-theca cell tumor, primary					0	1	2	0
Pancreas	50	50	50	50	50	50	50	50
adenoma, islets, primary	9	8	4	2	1	1	2	0
Pituitary	49	49	50	50	48	47	47	47
adenoma, anterior (pars distalis), primary	14	18	17	19	26	22	17	23
Preputial/Clitoral Gland	6	9	8	6	1	2	2	0
adenoma, primary	3	1	1	1	0	0	1	-
Skin and Subcutaneous	50	27	30	50	50	25	15	50
inverted papilloma, dermis, primary	0	0	2	1	0	0	0	0
papilloma, epidermis, primary	0	2	3	1	2	1	1	1
fibroma, subcutaneous, primary	3	3	2	5	1	0	2	3
Testes	50	50	50	50	-	-	-	-
Leydig cell tumor, primary	13	6	6	7				
Leydig cell tumor, primary (two)	32	40	38	32				
Thyroid	50	50	50	50	49	50	50	50
parafollicular cell adenoma, primary	6	6	7	5	3	4	1	5
Tongue	50	23	19	50	50	25	13	50
squamous papilloma, primary	0	0	0	0	0	1	2	0
Uterus	-	-	-	-	50	50	50	50
endometrial stromal polyp, lumen, primary					16	14	11	12
endometrial stromal polyp, lumen, primary (two)					0	2	1	1

a = Number of animals from which tissue was examined.
- = Not applicable/not examined.

Data extracted from Tables 20 and 22 of the report as well as Volumes 2 and 3 of the Appendix.

Table 10

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

	Male				Female			
ppm	0	5	20	60	0	5	20	60
Adrenal	50[a]	49	50	50	50	50	50	50
pheochromocytoma, primary	0	0	0	2	0	0	0	0
Auditory Sebaceous Gland	0	2	3	0	1	1	0	0
carcinoma, primary	-	2	3	-	0	1	-	-
Brain	50	26	22	50	50	27	18	50
carcinoma (pituitary), secondary	2	0	0	0	1	0	0	0
Mammary Gland	50	29	24	50	50	35	25	50
adenocarcinoma, acini, primary	0	0	0	0	3	1	0	2
Multiple Organs	b	b	b	b	b	b	b	b
mesothelioma (testes), secondary	5	1	2	0	0	0	0	0
leukemia (large granular lymphocyte), secondary [Fischer rat]	16	16	16	14	7	14	12	8
Pituitary	49	49	50	50	48	47	47	47
carcinoma, pars distalis, primary, metastisis	2	0	0	0	1	0	0	0
Small Intestine	50	23	23	50	50	24	12	50
adenocarcinoma, primary	0	0	0	2	0	0	0	0
Spleen	50	50	50	50	50	50	50	50
leukemia (large granular lymphocyte), primary [Fischer rat]	16	16	16	15	7	14	12	8
Testes	50	50	50	50	-	-	-	-
mesothelioma, tunic, primary, metastisis	5	1	2	0				
Thyroid	50	50	50	50	49	50	50	50
adenocarcinoma, parafollicular cell, primary, metastisis	0	0	0	0	0	2	0	0
Uterus	-	-	-	-	50	50	50	50
stromal cell sarcoma, primary, metastisis					0	2	0	0
Vagina	-	-	-	-	50	24	12	50
stromal cell carcinoma (uterus), secondary					0	2	0	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 Tables 20 and 22 of the report as well as Volumes 2 and 3 of the Appendix.

erosions of the epithelium as well as minimal submucosal fibrosis. These differences from lower doses or control animals suggest that there was irritation by the TELONE II vapors at the highest concentration tested. [The authors of the report stated that these microscopic changes were not observed at any exposure concentration at the 6- and 12-month interim sacrifices. They concluded that, "Possible explanations ((reviewer commen : not finding the effect at 6 or 12 months)) include the small sample sizes (10 rats/sex/exposure concentration) of the interim sacrifices, lack of detection of subtle nasal changes by light microscopy or the changes were manifest only after prolonged exposure (i.e., greater than one year) at the concentrations used."]

As a possible explanation for the olfactory changes by the authors of the report, the following paragraph is reproduced from page 23 of the report:

"The inhalation pharmacokinetics of DCP in rats may help explain the moderate prevalence of olfactory microscopic toxic changes following chronic exposure. The most prevalent microscopic change (decreased thickness of olfactory epithelium) in the nasal cavity of rats exposed to 60 ppm had a 40% incidence in males and 31% incidence in females. Stott and Kastl (1986) have demonstrated a 16% depression in respiratory frequency in rats exposed to 90 ppm DCP for 3 hours and a 26% depression in rats exposed to 300 ppm. The 26% depression of respriatory frequency correlated with a 38% decrease in the uptake of DCP vapors. Additionally, these authors have shown that the mucosa of the nasal cavity absorbs about 20 to 30% of inhaled DCP vapors while most of the remainder is absorbed by the lungs. These results suggest that both the respiratory physiologic response to DCP vapors and the relatively low absorption capability of the nasal mucosa for DCP could conceivably limit the uptake of material."

[Stott, W.T. and Kastl, P.E. (1986). Inhalation Pharmacokinetics of Technical Grade 1,3-Dichloropropene in Rats. Toxicol. Appl. Pharmacol. 85:332-341.]

This 2-year exposure of TELONE II by inhalation did not appear to cause any increases in tumor incidence (no statistically significant identification). The report stated that a National Toxicology Program sponsored oral gavage study demonstrated an increased incidence of forestomach and liver neoplasms in rats administered 25 or 50 mg/kg/day. The contrasting results (gavage versus inhalation) indicate that there could be a difference due to route of administration. In a gavage study the entire amount of material is administrated at one time (bolus) compared with the inhalation route which was for a 6 hour/day period. Additional differences might be the dose (60 ppm inhalation versus 25 or 50 mg/kg/day by gavage) and/or dosing regimen (number of days/week - possibly 7 for gavage versus 5 for inhalation).

The Maximum Tolerated Dose (MTD) was 60 ppm. The highest dose tested (60 ppm) caused histopathological changes in nasal tissue as well as an approximate 5% decrease in body weight gain in both sexes during the first year of the study but not in the second year.

In the gavage study noted above, forestomach neoplasms were reported after administration of 25 or 50 mg/kg/day. Regarding the current inhalation study, there were no observed neoplasms, one papilloma (control female), 3 instances of focal nonglandular mucosa hyperplasia (one 60 ppm male and two 5 ppm females) and 3 instances of multifocal nonglandular mucosa hyperplasia (two 5 ppm and one 60 ppm females).

Recommendation:

There was no oncogenicity observed in this study after exposure to any of the concentrations examined (5, 20 and 60 ppm).

The Systemic Toxicity No Observed Effect Level (NOEL) is 20 ppm. The Systemic Toxicity Lowest Observed Effect Level (LOEL) is 60 ppm (highest dose tested - HDT). This HDT caused histopathological changes in nasal tissue as well as the suggestion of a decrease in body weight gain during the first year of the study.

The study is Classified as Core Minimum.

The Toxicology Branch recommends that, because of the effect of inhalation exposure of TELONE II on nasal tissue, appropriate protection be required for handlers of this chemical.

1,3-DICHLOROPROPENE

Page_____ is not included in this copy.

Pages 19 through 26 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.