BD-1604
TXR-4908

1/30/86

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of toxicology data of Telone II
EPA No. 464-511
EPA Accession No. 259101
Caswell No. 324A

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

FROM: Quang Q. Bui, Ph.D. Quang Q. Bui 1/22/86
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Laurence D. Chitlik, D.A.B.T. W. Peters for L. Chitlik 1-23-86
Section Head, Section V
Toxicology Branch/HED (TS-769C) 1/30/86

and

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

Registrant:
Dow Chemical Co.,
Midland, Michigan

Action Requested:

Review of 2 sub-chronic inhalation, 1 inhalation pharmacokinetic, 4 dermal sensitization, 2 mutagenicity, and 2 carcinogenic studies with Telone II.

RECOMMENDATION

(see individual study review for a detail discussion of the findings)

1. 13-week inhalation study in rats and mice, Dow Chemical Co., 11/30/84,
Core Classification: Supplementary Data

2. Inhalation pharmacokinetics in rats, Dow Chemical Co., 8/1/85,
Core Classification: Supplementary Data

1 of 40

INERT INGREDIENT INFORMATION IS NOT INCLUDED

004903

3. Dermal sensitization with [redacted] in guinea pigs.
   Dow Chemical Co., 9/27/83
   Core Classification: Supplementary Data

4. Dermal sensitization with Telone II in guinea pigs.
   Dow Chemical Co., 9/27/83
   Core Classification: Supplementary Data

5. Dermal sensitization with [redacted] in guinea pigs.
   Dow Chemical Co., 11/17/83
   Core Classification: Supplementary Data

6. Dermal sensitization with [redacted] in guinea pigs.
   Dow Chemical Co., 11/23/83
   Core Classification: Supplementary Data

7. Unscheduled DNA synthesis in rat hepatocytes with Telone II.
   Dow Chemical Co., April 85.
   Core Classification: Not acceptable in its present format

8. Mouse bone marrow micronucleus test with Telone II.
   Lake Jackson Research Center, May 85.
   Core Classification: Equivocal results
   Not acceptable for registration purposes

9. Carcinogenesis study, NTP TR-269, May 85.
   a. Rat study:
      Core Classification: Minimum Data - oncogenicity
      Supplementary Data - chronic toxicity
   b. Mouse study:
      Core Classification: Supplementary Data - oncogenicity
      Not applicable - chronic toxicity

STUDY REVIEW No. 1

Chemical: Telone II, 1,3-dichloropropene
Test Material: A mixture of cis- and trans-1,3-dichloropropene, 90.9% and epichlorohydrin, 1.2%.
Study/Action Type: Sub-chronic inhalation

STUDY IDENTIFICATION:

"Telone II soil fumigant: A 13-week inhalation study in rats and mice"

Testing Facility: Dow Chemical Co.,
Final Report No.: N/A
Final Report Date: 11/30/84
Study authors: W.T. Stott et al.,
EPA Accession No.: 259101

CONCLUSIONS AND RECOMMENDATION

Under the conditions of both the rat and mouse 90-day inhalation studies, a systemic NOEL may be tentatively established at 10 ppm for Telone II in both species. Exposure to 90 or 150 ppm resulted in significant body weight reductions in both species. Significant alterations in relative and absolute weights of several organs were associated with these two highest dosage levels in both species. Rats exposed to 30, 90, or 150 ppm also exhibited compound-related histopathologic changes in the nasal turbinates. Similar histopathologic changes were also observed in mice exposed to either 90 or 150 ppm. Additionally, aggregation of mononuclear cells in the submucosa of the urinary bladder was noted in female mice in the 30, 90, and 150 ppm groups. However, both rat and mouse 90-day inhalation studies are classified as Core Supplementary Data due to the following:

1. All findings in the report are tabulated and presented as means ± S.D. with no individual data to substantiate the reported results.
2. Clinical measurements of calcium, potassium, sodium, phosphorus, chloride, and glucose were not performed.
3. Data on lung weights were not presented.

004903

13-WEEK INHALATION IN RATS

A. PROCEDURES:

Dose levels: 0, 10, 30, 90, or 150 ppm (0, 45.4, 136, 409, and 681 mg/m^3)
6 hours/day, 5 days/week for 13 weeks
Species used: Fischer 344 rats
10 animals per sex per dose

A copy of the procedures used is appended. In general, the protocol employed follows the 1982 FIFRA Guidelines and hence is acceptable. However, the following comments are noted:

1. Clinical chemistry measurements of calcium, chloride, potassium, sodium, phosphorus, and glucose were not performed.
2. Lung weight was not presented.
3. All findings are tabulated and presented as means ± S.D. with no individual data to substantiate the reported results.

B. RESULTS

1. Analytical Determinations

The authors indicated that the concentration of 1,3-dichloropropene was measured analytically 2 to 3 times per hour by infrared spectometer. The mean values of the analytical concentrations were within the acceptable range of the target concentrations as cepicted in the following table.

Target Conc. (ppm)	Analytical Concentration (a)	Coef.of variation (b)
	Analytical Concentration	
0		
10	10.3 ± 0.6	5.8%
30	30.3 ± 1.0	3.3%
90	89.9 ± 3.2	3.6%
150	150.7 ± 0.9	0.6%

(a) Values are mean ± S.D. of daily time-weighted average (TWA) values for n = 66 days
(b) is the S.D. of daily TWA measurements divided by the mean (x 100)

2. Clinical Observations

No deaths occurred during this investigation. Roughened and wet-looking coats were the main clinical signs observed in females at the highest dosage level.

3. Body Weights

Body weights were recorded weekly throughout the entire study and are summarized in the next table. After 3 exposures, the body weights of both males and females in the two highest dose groups (90 and 150 ppm) were significantly decreased as compared to the controls and remained statistically different until study termination. The body weights and body weight gains of the 10 and 30 ppm groups were comparable to the controls.

Body Weights (grams)

	Control		10 ppm		30 ppm		90 ppm		150 ppm	
	M	F	M	F	M	F	M	F	M	F
Day -1	176	132	180	132	177	131	176	131	176	131
Day 3	192	139	.195	138	190	139	181*	132*	174*	127*
Day 46	272	165	280	168	272	163	249*	156*	228*	144*
Day 88	308	175	321	175	310	171	282*	164*	248*	144*
BW Gain °	132	43	141	43	133	40	107*	34*	72*	13*
% of control°			+6.4	0.0	+0.4	-8.8	-19.4*	-22.4*	-45.6*	-71.4*

(*) Significantly different from controls, P < 0.05
(°) Calculated by this reviewer

4. Organ Weights

The absolute and relative (ratio of organ/terminal body weight) weights of several organs collected at terminal sacrificed are tabulated as follows.

ORGAN WEIGHTS (Grams)

Groups (ppm)	Brain		Heart		Kidney		Liver		Testes/Ovary	
	Abs	Rel	Abs	Rel	Abs	Rel	Abs	Rel	Abs	Rel
MALES										
0	1.88	0.66	0.83	0.29	2.05	0.71	7.32	2.55	3.07	1.07
10	1.93	0.65	0.87	0.29	2.10	0.70	7.77	2.59	3.23	1.08
30	1.92	0.67	0.85	0.29	2.07	0.72	7.41	2.57	3.19	1.11
90	1.91	0.73*	0.82	0.31*	1.99	0.76*	7.12*	2.71*	3.17	1.21*
150	1.83*	0.79*	0.75*	0.32*	1.87*	0.80*	6.61*	2.84*	3.08	1.32*
FEMALES										
0	1.72	1.07	0.55	0.34	1.26	0.78	4.25	2.63	0.19	0.12
10	1.70	1.04	0.54	0.34	1.26	0.78	4.28	2.64	0.19	0.12
30	1.70	1.08	0.53	0.34	1.24	0.78	4.13	2.62	0.18	0.12
90	1.70	1.11	0.53	0.35	1.29	0.85*	4.15	2.72	0.19	0.12
150	1.62*	1.22*	0.49*	0.37*	1.20*	0.90*	3.65*	2.74	0.14*	0.10

(*) Significantly different from controls, P < 0.05
Abs. = absolute weight Rel. = Relative weight

In animals of the 150 ppm dosage level, significant decreases in the absolute weight of the brain, heart, kidney, and liver were found with corresponding significant increases in relative weights. In the males, significant decreases in absolute liver weights and significant increases in the relative weights of the heart, brain kidney, liver, and testes were also noted in the 90 ppm group. These findings may have resulted from the significant decreases in terminal body weights observed in these two highest dose groups. No alterations in either absolute or relative organ weights were noted in animals of the 10 and 30 ppm dosage levels.

6. Hematology

Findings of interest are summarized in the next table:

Hematology Data

	Control		10 ppm		30 ppm		90 ppm		150 ppm	
	M	F	M	F	M	F	M	F	M	F
RBC (10^6/mm^3)	8.7	7.9	8.7	8.1	8.8	8.2*	8.7	8.2*	8.9	8.6*
WBC (10^3/mm^3)	5.5	5.4	5.3	5.9	6.2	5.8	7.0*	6.4	6.6	6.4
Platelets (10^3/mm^3)	723	727	735	731	741	733	765	725	690	646*

(*) Significantly different from controls, $P < 0.05$

Trend increases in WBC count were noted in both treated males and females, however, statistically significant differences were found only for 90 ppm males. Significant increases in RBC count were noted in females dosed with 30, 90, or 150 ppm but not in males. Platelet count was decreased in both 150 ppm males and females but a significant difference was detected only for females.

7. Urinalysis

Compound-related effects were not evident from the data submitted.

8. Clinical Chemistry

The next table summarizes the clinical chemistry data at necropsy.

Clinical Chemistry Data

	Control		10 ppm		30 ppm		90 ppm		150 ppm	
	M	F	M	F	M	F	M	F	M	F
BUN (mg/dl)	16	18	14	17	14	16*	14	20	14	31
AP (mU/ml)	63	52	62	55	64	53	64	59	67	66*
TP (g/dl)	5.8	5.6	5.7	5.4	5.6	5.4	5.6	5.2*	5.4*	4.9*
Alb (g/dl)	3.6	3.5	3.5	3.3	3.4	3.3	3.5	3.2*	3.5	3.2*
Glo (g/dl)	2.2	2.1	2.2	2.1	2.2	2.0	2.1	2.0	2.0*	1.7*

(*) Significantly different from controls, $P < 0.05$

[BUN = blood urea nitrogen; AP = alkaline phosphatase; TP = total protein; Alb = albumin; Glo = Globulin]

Significant decreases in total protein were found in 150 ppm males and 90 and 150 ppm females. The globulin levels were also significantly decreased in both males and females of the 150 ppm dosage level. Although the male albumin levels were not significantly different from controls, significant decreases in albumin were found for 90 and 150 ppm females. Increases in alkaline phosphatase were noted in animals of the 150 ppm dosage level with statistically significant difference found in females.

9. Gross Pathologic Observations

Gross pathologic observations were made on all animals. The submitted data did not reveal any evidence of a compound-related effect.

10. Histopathology

Compound-related effects were not found in any tissue examined except for the nasal turbinates and the mesenteric tissues.

Histopathologic Observations

	Control		10 ppm		30 ppm		90 ppm		150 ppm	
	M	F	M	F	M	F	M	F	M	F
NASAL TURBINATES										
Degeneration, olfactory epithelium	0	0	0	0	0	0	0	1	10	10
Hyperplasia, respiratory epithelium	0	0	0	0	2	0	10	10	10	10
MESENTERIC TISSUE										
Atrophy, adipose tissue	0	1	-	-	-	-	-	-	1	7

Degeneration of the olfactory epithelium was observed in all animals exposed to 150 ppm and in 1/10 females of the 90 ppm group and hyperplasia of the respiratory epithelium was noted in all animals exposed to either 90 or 150 ppm and in 2 males in the 30 ppm group. The findings in the nasal turbinates are highly suggestive of a compound-related effect.

13-WEEK INHALATION IN MICE

Dose levels: 0, 10, 30, 90, or 150 ppm (0, 45.4, 136, 409, and 681 mg/m^3)
6 hours/day, 5 days/week for 13 weeks

Species used: B6C3F1 mice (Charles River, Portage, MI.)
10 animals/sex/dose

The protocol used was similar to that of the rat study. Therefore, comments on the rat study procedures also apply to this mouse inhalation study.

1. Clinical Observations and Mortality

Three mice died during this investigation: one female each in the control and 90 ppm group on day 3 and one 150 ppm female on day 35. The investigators indicated the cause of death for both the control and 90 ppm females as "handling trauma" and that of the 150 ppm female as "undetermined". The investigators also stated that a "strong mercaptan odor" was associated with the coats of mice exposed to either 90 or 150 ppm Telone II.

2. Body Weights

The table below summarizes the body weights and body weight gains of all groups:

Body Weight Data (grams)

	Control		10 ppm		30 ppm		90 ppm		150 ppm	
	M	F	M	F	M	F	M	F	M	F
Days -1	24.6	18.9	25.1	18.8	24.3	19.2	24.9	19.0	24.0	18.4
Days 3	24.7	19.8	25.4	19.6	24.4	19.4	25.2	19.0	24.1	18.4
Days 45	28.8	23.8	29.0	23.5	28.7	24.3	27.4	21.9*	25.2*	24.0
Days 87	30.5	25.5	31.3	25.8	30.5	25.9	29.5	24.7	26.7*	23.0*
BW gain †	5.9	6.6	6.2	7.0	6.2	6.7	4.6	5.7	2.7*	4.6
% of control †			+5.0	+6.0	+5.0	+1.5	-22.0	-13.6	-54.0*	-30.3*

(*) Significantly different from controls, $P < 0.05$
(†) Calculated by this reviewer

Animals in the 90 and 150 ppm groups weighed and gained less than controls with statistically significant differences found at the 150 ppm dosage level terminally. Males and females of the 10 and 30 ppm dosage levels had comparable body weights and weight gains as controls.

3. Organ Weights

The absolute heart and liver weights were decreased in males exposed to 90 and 150 ppm. Absolute brain, kidney, and thymus weights were significantly decreased in 150 ppm males. These changes correlated with significant decreases in relative heart and liver weights in 90 and 150 ppm males, and in relative kidney and brain weights in 150 ppm males.

In females, the absolute brain, heart, liver, and thymus weights were significantly decreased at the 150 ppm dosage level. Significant decreases in relative liver and thymus weights and a significant increase in relative kidney weights was also

associated with this dosage level. Significant decreases in both relative and absolute thymus weights were also noted at the 90 ppm dosage level.

ORGAN WEIGHTS (grams)

	Brain		Heart		Kidney		Liver		Thymus	
	Abs	Rel	Abs	Rel	Abs	Rel	Abs	Rel	Abs	Rel
MALES										
0 ppm	0.47	1.61	0.15	0.51	0.47	1.62	1.67	5.76	0.04	0.12
10 ppm	0.46	1.58	0.14	0.48	0.49	1.67	1.66	5.63	0.04	0.14
30 ppm	0.46	1.56	0.14	0.48	0.48	1.63	1.60	5.40	0.04	0.14
90 ppm	0.45	1.60	0.13*	0.46*	0.45	1.58	1.43*	5.04*	0.03	0.10
150 ppm	0.44*	1.72*	0.11*	0.44*	0.39*	1.51*	1.27*	4.94*	0.03*	0.10
FEMALES										
0 ppm	0.47	1.86	0.11	0.45	0.33	1.30	1.43	5.67	0.05	0.21
10 ppm	0.46	1.83	0.11	0.45	0.33	1.32	1.39	5.57	0.05	0.19
30 ppm	0.46	1.86	0.12	0.46	0.33	1.32	1.37	5.48	0.05	0.18
90 ppm	0.45	1.85	0.11	0.45	0.35	1.43*	1.31	5.39	0.04*	0.17*
150 ppm	0.43*	1.88	0.10*	0.44	0.32	1.42*	1.15*	5.07*	0.03*	0.14*

(*) Significantly different from controls, $P < 0.05$
Abs. = absolute weight Rel.= relative weight (organ/body weight)

4. Clinical Chemistry

Statistically significant decreases in BUN levels were found in males exposed to 90 and 150 ppm but not in treated females. Both males and females exposed to 150 ppm also had significantly increases in SGPT levels. All other clinical chemistry determinations were not biologically significantly different from controls.

5. Hematology Data

Significant increases in platelet count were noted in all treated males, including the lowest dose level used (10 ppm). The platelet counts (expressed as $10^3/mm^3$) for the 0, 10, 30, 90, and 150 ppm were, respectively, 1053, 1210, 1165, 1193, and 1332. However, biologically significant differences in platelet count were not found in treated females being 1007, 1067, 1045, 1048, and 1024 (expressed as $10^3/mm^3$) for the 0, 10, 30, 90, and 150 ppm groups, respectively.

A slight decrease in RBC (X $10^6/mm^3$) was noted in both treated males and females but a statistical difference was not attained. The RBC counts for the 0, 10, 30, 90, and 150 ppm were, respectively, 9.53, 9.14, 9.35, 9.33, and 9.26 for males, and 9.36, 9.46, 9.22, 9.26, and 9.01 for female mice.

6. Gross Pathologic Observations

Gross pathologic observations did not reveal any evidence of a compound-related effect except for the decreased thymus size noted in 9 males of the 150 ppm dosage level.

004903

7. Histopathologic Observations

Histopathologic results of interest are summarized in the next table:

HISTOPATHOLOGIC OBSERVATIONS

	Control		10 ppm		30 ppm		90 ppm		150 ppm	
	M	F	M	F	M	F	M	F	M	F
No. TISSUES EXAMINED										
	9	9	10	10	10	10	10	9	10	9
URINARY BLADDER										
Aggregation of mononuclear (predominantly lymphoid) cells, submucosa	2	2	1	3	0	9	2	6	0	4
Moderate hyperplasia, epithelial cells	0	0	0	0	0	0	0	7	0	6
NASAL TURBINATES										
Degeneration, Olfactory epithelium	0	0	0	0	0	0	10	9	10	9
Hyperplasia, Respiratory epithelium	0	0	0	0	0	0	10	9	10	9
Metaplasia, Olfactory epithelium, multifocal, slight	0	0	0	0	0	0	0	0	10	6

(Data extracted from Table 23 of the final report)

Aggregation of mononuclear cells in the urinary bladder was observed mostly in females of the 30, 90, and 150 ppm. Moderate hyperplasia of the epithelial cells of the urinary bladder was also noted in 90 and 150 ppm females. Compound-related effects were noted in the nasal turbinates in all animals exposed to either 90 or 150 ppm.

DISCUSSION

Under the conditions of the rat study, significant decreases in body weights were observed in animals exposed to either 90 or 150 ppm Telone II. Significant alterations in the relative and absolute weights of several organs were also associated with these two highest dose levels. In females, a significant increase in RBC was noted in animals of the 30, 90, and 150 ppm groups. However, a similar polycythemic effect was not found for males. The total protein and globulin levels were also significantly decreased in both males and females of the 150 ppm dosage level. Compound-related histopathologic findings were evidenced by the findings of epithelial degeneration and hyperplasia in the nasal turbinates observed in animals exposed to 30, 90, or 150 ppm.

In the mouse study, body weight reductions were also noted at the 90 and 150 ppm dosage levels. Significant changes in absolute and relative weights of several organs were also associated with these two highest dosage levels. Significant decreases in platelets count were found in males at all dosage levels tested; however, similar findings were not observed in any of the treated females. Although an apparent polycythemic effect was noted in female rats, consistent effects were not found in female mice. Histopathologic changes in the nasal turbinates were found in mice exposed to 90 or 150 ppm. Additionally, aggregation of mononuclear cells in the submucosa of the urinary bladder was noted in females exposed to 30, 90, or 150 ppm.

These data collectively suggest that a systemic NOEL may be established at 10 ppm for Telone II in both mouse and rat 90-day inhalation studies. However, both studies are classified as Core Supplementary Data due to the following:

1. All findings are tabulated and presented as means $\pm$ S.D. with no individual data to substantiate the reported results.
2. Clinical measurements were not performed for calcium, potassium, glucose, chlorine, sodium, and phosphorus.
3. Data on lung weights, the major organ of concern in an inhalation study, were not submitted.

1,3-DICHLOROPROPENE

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Pages 12 through 15 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.

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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.

004903

STUDY REVIEW No. 2

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

Chemical: Telone II; 1,3-dichloropropene
Test Material: 1,3-dichloropropene, Lot No. AGR 204046 containing: 49.3% cis isomer, 42.8% trans isomer, [redacted] (unspecified), and no added stabilizing agents
Study/Action Type: Pharmacokinetics - Inhalation

STUDY IDENTIFICATION

"Inhalation pharmacokinetics of Technical grade 1,3-dichloropropene in rats"

Testing Facility: Dow Chemical Co.,
Final Report No.: N/A
Final Report Date: 8/1/85
Study Authors: Stott W.T. and Kastl P.E.
EPA Accession No.: 259101

CONCLUSIONS AND RECOMMENDATION

The submitted data indicated that the absorption of 1,3-dichloropropene (DCP) vapor occurred primarily in the lung (50% of total inhaled) with a smaller amount (11-16%) by the nasal mucosa. The elimination of DCP was dose-dependent and bi-phasic. The first phase of elimination was rapid (2-40 minutes half life) followed by a slower eliminating phase (30-40 minutes half life).

It is recommended that this study be classified as Core Supplementary Data. The final report was submitted as a publication format with no individual data to substantiate the reported findings. Furthermore, the exact number of samples used to calculate each mean value was unknown and necessary information to confirm the rates of absorption, tissue non-protein sulfhydryl (NPSH) levels, blood levels of cis- and trans-DCP, and half-lives were not available. It should be noted that this study cannot be used as a substitute for the Agency requirement of a metabolism study.

I. PROCEDURES

Dose Levels: 30, 90, 300, or 900 ppm (136, 409, 1362, or 4086 mg/m^3) for 3 hours
Species Used: Male Fischer-344 rats
(Charles River Lab., Kinston, N.Y.)

This investigation was undertaken to:

1. Quantify the uptake of inhaled 1,3-dichloropropene (DCP) and elimination of DCP from the blood.
2. Determine the site of absorption within the respiratory tract
3. Investigate whether changes in DCP uptake are due to changes in respiration and/or saturation of DCP metabolism.

II. RESULTS

A. Vapor Uptake Measurements

The vapor concentration of DCP in the test atmosphere entering and leaving the "head only" chamber was analyzed at hourly intervals by chromatography. Quantification of vapors was performed by comparison with appropriate standards. The study authors mentioned the following formula to measure the vapor uptake:

$$\text{Uptake of vapors (mol/min)} = \frac{(b - a)(c)}{d}$$

a = mol chemical/mol effluent gas
b = mol chemical/mol test atmosphere entering the chamber
c = liters/min flow rate through the chamber
d = 24.45 liter/mol

The results of vapor uptake measurements are tabulated as follows:

Uptake of Vapors of DCP by Head-Only Exposed Male Rats

Exposure (ppm)	Vapor Uptake (nmol/min) †	Normalized Vapor Uptake (Uptake/Exposure)
30	144 ± 14	4.8
90	307 ± 13	3.4
300	880 ± 83	2.9
900	1810 ± 76	2.0

(†) Mean ± S.D. for 3-6 animals/group. Measurements for individual rats after 1, 2, and 3 hours of exposure were averaged and these average values for the individual animals were in turn used to calculate the mean ± S.D.

As illustrated in the above table, the rate of vapor uptake increased with exposure concentration being, respectively, 144, 307, 880 and 1,810 nmol/min for the 30, 90, 300, and 900 exposure levels. However, normalized vapor uptake did not increase proportionately with the exposure level as demonstrated by a decrease in the ratio of uptake/exposure.

B. Site of Absorption

To identify the primary site of absorption within the respiratory tract, groups of rats were anesthetized with pentobarbital and the upper respiratory tract (URT) and lower respiratory tract (LRT) were isolated and the absorption of DCP vapors at 90 or 150 ppm was studied. The absorption of DCP vapors by pentobarbital anesthetized intact rats was also determined for comparative purposes.

The investigators mentioned two equations to calculate the rate of uptake:

$$U = (Inh)\ (f\ URT)$$
$$P = (Inh - U)\ (f\ LRT)$$

URT = upper respiratory tract; LRT = lower respiratory tract
U = mol/min absorbed by URT; Inh = mol/min inhaled by animal;
f = fraction of total vapors entering the URT or LRT absorbed
P = mol/min absorved by LRT

A comparison of the uptake of DCP vapors by the anesthetized intact animal, isolated URT, and isolated LRT is given in the next table:

(nmol/min)	EXPOSURE LEVEL 90 ppm (a)	% (b)	150 ppm (a)	% (b)
Lower Respiratory Tract	111 ± 12.0	50	161 ± 24.6	48
Upper Respiratory Tract	60.5 ± 15.9	16	72.4 ± 13.6	11
Nose-Only Anesthetized Intact Rats	102 ± 23.4	51	161 ± 14.5	48

(a) Mean ± S.D. for 3-4 animals
(b) Percentage of vapors available for absorption at a respiratory minute volume (RMV) = 53 ml/min (LRT and nose only exposed rats) or ventilation rate of 105 ml/min (URT) which were absorbed.

According to the data submitted, nose-only exposed anesthetized rats and the isolated LRT of rats absorbed approximately 50% of inhaled vapors. However, the isolated URT of rats absorbed only 16 and 11% for the 90 and 150 ppm dosage levels, respectively. The authors used these data and applied to the two equations listed above and reported that "the LRT was estimated to absorb approximately 73% and 79% of the total vapors absorbed by an anesthetized rat inhaling 90 or 150 ppm DCP, respectively". The authors stated that the sum of URT and LRT vapor uptake at 90 and 150 ppm exposure levels were 117 nmol/min and 182 nmol/min, respectively.

C. Respiratory Physiologic Measurements

The respiratory rate, tidal volume, and respiratory minute volume were calculated in animals exposed to 30, 90, 300, or 900 ppm DCP for 3 hours. In animals exposed to 300 and 900 ppm, both respiratory rate and respiratory minute volume apparently were decreased. Since the results were presented as bar graphs and expressed as % of pre-exposure levels, they could neither be confirmed nor verified by this reviewer.

D. Cis- and Trans-DCP Blood Levels

Blood samples were drawn at hourly intervals during the exposure period and up to 2 hours post-exposure. The cis- and trans-isomers were determined by gas chromatography-mass spectrometry and the half-life for each isomer was calculated.

Two graphs were submitted representing the time-response curves of cis- and trans-DCP. From these two graphs, the blood levels of both cis- and trans-DCP were both dose- and time-dependent, peaked at 3 hours after exposure, and then declined upon termination of exposure. The maximum blood concentration of cis-DCP reached approximately 1.0 and 15.0 ug/ml for rats exposed to, respectively, 300 and 900 ppm. Maximum blood concentration of approximately 2 and 20 ug/ml trans-DCP were found in rats exposed to, respectively, 300 and 900 ppm.

The authors stated that the elimination of both isomers was biphasic and dose-dependent. A rapid initial elimination phase (2-40 min. half-life) was followed by a slower elimination phase (30-40 min. half-life). However, the limited data presented in these two graphs would not allow this reviewer to confirm the findings.

E. Tissue Non-Protein Sulfhydryl (NPSH) Level Determinations

Groups of 3 rats each were exposed, head only, to either 0 or 90 ppm DCP for 3 hours. All animals were sacrificed immediately after the exposure period. The liver, lung, and kidneys were removed, weighed, and the tissue levels of NPSH determined.

A graph was submitted representing the levels of NPSH in these organs. The authors reported a 31% and 41% reduction in kidney and liver NPSH levels, respectively, as compared to controls. No alterations in lung NPSH levels were found by the investigators.

III. DISCUSSION

From the submitted data, it may be shown that absorption of DCP vapors occurred primarily in the lung (50% of total inhaled) with a smaller amount (11-16%) by the nasal mucosa. Following absorption, the elimination of DCP was dose-dependent and bi-phasic. The first phase of elimination was rapid (2-40 min half life) followed by a slower elimination (30-40 min half life). Exposure to 90 ppm DCP also resulted in decreases in non-protein sulfhydryl levels in the kidneys and liver but not in the lung. In head-only exposed rats, the uptake of DCP vapors did not increase proportionately with increasing exposure concentration due to an exposure-level-related decrease in the respiratory ventilatory frequency. Dose-dependent decreases in respiratory minute volume were also apparent from the data submitted.

It should be noted, however, that this study was submitted in a publication format. Therefore, (1) individual data were not available to substantiate the findings, (2) the exact number of samples used to calculate each mean value was unknown, (3) necessary information to confirm the rates of absorption, tissue NPSH levels, blood levels of cis- and trans-DCP, and half-lives was not reported.

This study is classified as Core Supplementary Data. Furthermore, it should be noted that this study cannot be used as a substitute for the Agency required metabolism study.

004903

STUDY REVIEW No. 3

Chemical: [redacted]

Study/Action Type: Dermal Sensitization Study

STUDY IDENTIFICATION:

[redacted] Skin sensitization potential in the guinea pig"

Testing Facility: Dow Chemical Co.,
Study Authors: Rao, K.S. and Young, J.T.
Final Report No.: N/A
Final Report Date: 9/27/83
EPA Accession No.: 259101

CONCLUSIONS AND RECOMMENDATION

Under the conditions of this study, [redacted] as a 10% Dowanol DPM/Tween 80 (9:1) solution did not induce any signs of dermal sensitization in the guinea pigs. However, it is recommended that this study be classified as Core Supplementary Data due to the following:

1. Individual animal data are not available to substantiate the reported findings.
2. Initial and terminal body weights, as required by the 1982 FIFRA Guidelines, were not reported.
3. All data should be summarized in a tabular form showing at each observation period the skin reaction (grading values) of each individual animal (including positive control animals).

004903

PROCEDURES

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Groups of 10 guinea pigs each were exposed to either [redacted] or DER 331 epoxy resin as a 10% solution in Dowanol DPM/Tween 80. The DER 331 epoxy resin exposed animals served as positive controls. The investigators indicated that the study was carried out following a modification of the method of Maguire (1973). A copy of the procedures used is attached. The following comments are noted:

1. Individual animal data were not submitted with this report to confirm the reported findings.
2. Initial and terminal body weights were not presented.
3. The grading system used and the skin reactions for each individual animal at each observation period (24 and 48 hours) were not reported.

RESULTS

The study authors indicated that application of DER 331 epoxy resin resulted in signs of dermal sensitization (slight to moderate) in the positive control animals (8/10). None of the 10 guinea pigs exposed dermally to [redacted] exhibited signs of dermal sensitization. The investigators concluded that [redacted] was not a skin sensitizing agent.

The investigators' conclusions could not be confirmed in the absence of individual data.

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Page 22 is not included in this copy.

Pages _____ through _____ 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.

004903

STUDY REVIEW No. 4

Chemical: Telone II, 1,3-dichloropropene
Test Material: Telone II, Lot TB-830504-15 (unknown purity)
Study/Action Type: Dermal Sensitization

STUDY IDENTIFICATION

"Telone II: Skin sensitization potential in the guinea pig"

Testing Facility: Dow Chemical Co.,
Final Report No.: N/A
Final Report Date: 9/27/83
Study Authors: Rao, K.S. and Young, J.T.
EPA Accession No.: 259101

CONCLUSIONS AND RECOMMENDATION

The investigators concluded that Telone II as a 10% solution in Dowanol DPM/ Tween 80 possessed some potential to induce human skin sensitization. However, it is recommended that this study be classified as Core Supplementary Data due to the following:

1. Individual animal data are not available.
2. Initial and terminal body weights, as required by the 1982 FIFRA Guidelines, were not reported.
3. All data should be summarized in a tabular form showing at each observation period the skin reaction (grading values) of each individual animal (including positive control animals).
4. Purity of Telone II was not stated.

PROCEDURES

Groups of 10 guinea pigs each were exposed to either Telone II (unknown purity) or DER 331 epoxy resin as a 10% solution in Dowanol DPM/Tween 80. DER 331 epoxy resin exposed animals served as positive controls. The investigators stated that this study was conducted according to a modification of the method of Maguire (1973). A copy of the procedures used is attached with Study Review # 3. The following comments are noted:

1. Individual animal data were not submitted to substantiate the reported findings.
2. Initial and terminal body weights were not presented.
3. The grading system used and the skin reactions for each individual animal at each observation period (24 and 48 hours) were not reported.

RESULTS

The investigators stated that in animals exposed dermally to Telone II (as a 10% solution in Dowanol DPM/Tween 80), 3/10 exhibited slight to moderate redness, indicating sensitization. Positive sensitization response was also observed in 4/10 animals treated with the epoxy resin. The authors concluded that Telone II should be considered as a dermal sensitizing agent.

However, in the absence of supporting individual animal data, the reported findings could not be confirmed or verified.

004903

STUDY REVIEW No. 5

Chemical: [redacted]

Study/Action Type: Dermal sensitization

STUDY IDENTIFICATION

[redacted] Skin sensitization potential in the guinea pig"

Testing Facility: Dow Chemical Co.
Final Report No.: N/A
Final Report Date: 11/17/83
Study Authors: Rao, K.S. and Young J.T.
EPA Accession No.: 259101

CONCLUSIONS AND RECOMMENDATION

[redacted] The investigators indicated that application of undiluted [redacted] to guinea pigs did not result in dermal sensitization. However, the study authors' conclusion could not be substantiated in the absence of supporting data. It is recommended that this study be classified as Core Supplementary Data due to the following:

1. Individual animal data are not available
2. Initial and terminal body weights, as required by the 1982 FIFRA guidelines, were not reported.
3. All data should be summarized in a tabular form showing at each observation period the skin reaction (grading values) of each individual animal (including positive control animals).

004903

PROCEDURES

This dermal sensitization study was conducted according to a modified method of Maguire (1973). A copy of the procedures used is attached with Review Study #3. Groups of 10 guinea pigs each were exposed dermally to either [redacted] or DER 331 epoxy resin as a 10% solution in Dowanol DPM/Tween 80. Epoxy resin treated animals served as positive controls.

The following comments are noted:

1. Individual animal data were not submitted with this final report.
2. Initial and terminal body weights, as required by the 1982 FIFRA Guidelines, were not presented.
3. All data should be summarized in a tabular form showing at each observation period the skin reaction (grading values) of each individual animal (including positive control animals).

RESULTS

The investigators indicated that application of DER 331 epoxy resin resulted in dermal sensitization in 7/10 guinea pigs. None of the 10 guinea pigs exposed to [redacted] exhibited signs of dermal sensitization. The authors conclud[redacted] that [redacted] was not considered as a potential human dermal sensitizing agent.

However, the authors' conclusions could not be confirmed or verified in the absence of individual animal data.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

004903

STUDY REVIEW No. 6

Chemical: [redacted]

Study/Action Type: Dermal sensitization

STUDY IDENTIFICATION

[redacted] Skin sensitization potential in the guinea pig"

Testing Facility: Dow Chemical Co.,
Final Report No.: N/A
Final Report Date: 11/23/85
Study Authors: Rao, K.S. and Young, J.T.
EPA Accession No.: 259101

CONCLUSIONS AND RECOMMENDATION

Under the conditions of this study, the investigators stated that application of undiluted [redacted] to guinea pigs did not result in dermal sensitization. However, it is recommended that this study be classified as Core Supplementary Data due to the following:

1. Individual animal data are not available to substantiate the reported findings.
2. Initial and terminal body weights, as required by the 1982 FIFRA Guidelines, were not presented.
3. All data should be summarized in a tabular form showing at each observation period the skin reaction (grading values) of each individual animal (including positive control animals).

PROCEDURES

A copy of the procedures used is attached to Study Review No. 3. This study was conducted following a modified method of Maguire (1973). Groups of 10 guinea pigs each were exposed dermally to either undiluted [redacted] of DER 331 epoxy resin as a 10% solution in Dowanol DPM/Tween 80. Epoxy resin exposed animals served as positive controls. The following comments are noted:

1. Individual animal data were not submitted with this final report.
2. Initial and terminal body weights, as required by the 1982 FIFRA Guidelines, were not presented.
3. All data should be summarized in a tabular form showing at each observation period the skin reaction (grading values) of each individual animal (including positive control animals).

RESULTS

The investigators indicated that application of undiluted [redacted] did not result in dermal sensitization. However, 7/10 guinea pigs exposed to DER 331 epoxy resin exhibited signs of dermal sensitization. The authors concluded that [redacted] was not considered as a dermal sensitizing agent.

However, the investigators' conclusions could not be confirmed or verified in the absence of supporting animal data.

004903

STUDY REVIEW No. 7

Chemical: Telone II; 1,3-dichloropropene (92.4% purity)
Test Material: 1,3-dichloropropene, a mixture of
cis-1,3 dichloropropene 49.5%
trans-1,3 dichloropropene 42.6%
Study/Action Type: Mutagenicity

STUDY IDENTIFICATION

"Evaluation of Telone II® in the rat hepatocyte unscheduled DNA synthesis assay"

Testing Facility: Dow Chemical Co.,
Final Report No.: N/A
Final Report Date: 4/85
Study Author: Mehrlala, A.L.
EPA Accession No. 259101

CONCLUSIONS AND RECOMMENDATION

The study author stated that, under the conditions of this study, Telone II did not induce unscheduled DNA synthesis in rat hepatocytes. Toxicity to the hepatocytes, as evidenced by detachment of the cells and/or granular appearance, was observed at dose levels of $1x10^{-4}$ M/liter and greater.

However, this study is inconclusive due to the following:

1. Net grain counts were calculated only from 15 cells each in two coverslips. Counts from 50 cells would be more desirable.
2. Individual data were not submitted to substantiate the reported findings.
3. Survival measurement at 2 and 24 hours after treatment was not reported and/or monitored.
4. Preliminary cytotoxicity data were not appended to support the dose level selection.
5. Percent of nuclei with 6 or more grain counts and percent of nuclei with 20 or more grain counts were not reported.

PROCEDURES

Test Material:	1,3-dichloropropene (92.4% purity) in DMSO
Dose Levels:	$3x10^{-3}$, $1x10^{-3}$, $3x10^{-4}$, $1x10^{-4}$, $3x10^{-5}$, $1x10^{-5}$, $3x10^{-6}$, and $1x10^{-6}$ M.
Positive controls:	2-acetylaminofluorene in DMSO at concentrations of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7} M.
Species:	Male Fischer-344 rats (Charles River Lab., Wilmington, MA.)

A copy of the procedures used is appended. The investigators indicated that this study was conducted following a modified method of Williams et al. (1977). The following comments are noted:

1. Preliminary cytotoxicity data were not presented to support the dosage levels selected.
2. All findings were compiled in one table and presented as means ± S.D. The mean of net grain counts reported for each dosage level apparently was the mean net nuclear grain counts determined from 2 slides within each treatment group. Individual mean net grain counts calculated from 15 cells in each slide was not reported. Therefore, all reported findings could not be confirmed or verified.
3. Two slides were used for each dosage level. Three slides should have been used for nuclear counting in each treatment group.
4. Survival measurement for each dosage level by performing viable cell counts at 2 and 24 hours after treatment was not reported and/or monitored.
5. The percentage of nuclei with six or more grains and the percentage of nuclei with 20 or more grains were not reported.

RESULTS

In the first assay, test chemical toxicity (as indicated by detachment of cells from the coverslip and/or granular appearance) was observed at all dosage levels tested except at the two lowest concentrations: $3x10^{-6}$ and $1x10^{-6}$. The authors indicated that due to high cytoplasmic grain counts observed in the first assay, a second assay was initiated using the same dosage levels.

In the second assay, test chemical toxicity was demonstrated at the $1x10^{-4}$, $3x10^{-4}$, $1x10^{-3}$, and $3x10^{-3}$ dose levels. Test chemical toxicity was evidenced by detachment of cells from the coverslip and/or granular appearance. The authors also indicated that the high cytoplamic grain count observed previously in the initial assay was not present in the second assay. From the data submitted, the mean of net nuclear grains observed in the negative control was 1.4 ± 3.2 S.D. Compared to these negative control values, Telone II apparently did not induce unscheduled DNA synthesis. However, in the positive control slides (2-acetylaminofluorene), positive results were obtained at the $1x10^{-4}$, $1x10^{-5}$, and $1x10^{-6}$ concentrations.

RAT HEPATOCYTE UNSCHEDULED DNA SYNTHESIS

	Concentration moles/liter	Net Nuclear Grains[a] (Mean + Standard Deviation)	
		1st Assay	2nd assay
Negative Control (DMSO 0.1%)	0	-3.8 + 3.6	1.4 + 3.2
Telone II			
	$3x10^{-3}$	(b)	-0.7 + 0.9[c]
	$1x10^{-3}$	-1.0 + 1.0[c]	0.5 + 3.8[c]
	$3x10^{-4}$	-3.5 + 3.7[c]	-1.2 + 2.2[c]
	$1x10^{-4}$	-7.4 + 7.3[c]	-2.9 + 3.5[c]
	$3x10^{-5}$	-12.1 + 8.1[c]	-2.8 + 2.3
	$1x10^{-5}$	-5.4 + 4.3[c]	-3.0 + 3.0
	$3x10^{-6}$	-3.5 + 2.8	-4.1 + 3.6
	$1x10^{-6}$	-3.1 + 3.0	-2.4 + 2.7
2-acetylaminofluorene			
	$1x10^{-4}$	78.1 + 27.1[c]*	80.1 + 17.2[c]*
	$1x10^{-5}$	56.6 + 13.3[c]*	86.5 + 22.1[c]*
	$1x10^{-6}$	56.3 + 20.8[c]*	54.6 + 12.8*
	$1x10^{-7}$	6.4 + 5.1*	4.8 + 3.7

(a) Net nuclear grains = Nuclear grains - Background cytoplasm grains
(b) No. cells remaining for evaluation - Test chemical toxicity
(c) Test chemical toxicity observed
(*) Positive response: 6 or more net nuclear grains and statistical significance ($p < 0.05$).
DMSO: dimethylsulfoxide

DISCUSSION

The investigators stated that, under the conditions of this assay, Telone II did not induce unscheduled DNA synthesis in rat hepatocytes at levels between $1x10^{-5}$ and $1x10^{-4}$. Toxicity was apparent at $1x10^{-4}$ and greater concentrations. However, it is recommended that the results obtained from this study be considered as inconclusive due to reporting deficiencies as mentioned on the previous page (see section on "Procedures").

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Pages 32 through 34 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.

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____ 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.

STUDY REVIEW No. 8

Chemical: Telone II
Test Material: 1,3-dichloropropene, a mixture of
cis-1,3 dichloropropene 49.5%
trans-1,3 dichloropropene 42.6%
Lot No. T2231213-4
Study/Action Type: Mutagenicity

STUDY IDENTIFICATION

"Evaluation of Telone II® soil fumigant in the mouse bone marrow micronucleus test"

Testing Facility: Lake Jackson Research Center, Texas
Final Report No.: N/A
Final Report Date: 5/85
Study Authors: Gollapudi, B.B. et al.,
EPA Accession No.: 259101

CONCLUSIONS AND RECOMMENDATIONS

Under the conditions of this study, the investigators concluded that Telone II was not clastogenic in the mouse bone marrow micronucleus assay. The activity of the positive control, cyclophosphamide, indicated that the test assay used was sensitive. Although the highest dose used (300 mg/kg; approximately 60% of the LD50) resulted in 3/10 deaths in the treated males, this dosage level still could not be considered as the maximum tolerated dose for the target organ in this assay (bone marrow): decreased erythropoietic activity was not observed at any dose level used, including the highest dose (300 mg/kg).

It thus appears that the mouse bone marrow micronucleus test is not appropriate for investigating the clastogenic potential of Telone II.

004903

PROCEDURES

Highlights of the procedures used are as follows:

1. The test animals used were CD-1 (ICR) BR mice of both sexes (Charles River, Wilmington, MA.) and had been acclimated to laboratory conditions for two weeks. All animals had access to food and water ad libitum.
2. The test compound was reported as 92.1% (cis-isomer, 49.5% and trans-isomer, 42.6%) and dissolved in corn oil.
3. The test material was administered singly by gavage (0.5 ml/35 g mouse) to groups of 10 animals per sex each at 38, 115, or 380 mg/kg. The authors stated that the highest dose was about 60% of the LD50 in mice (640 mg/kg).
4. The positive control group received cyclophosphamide at 120 mg/kg of body weight. Corn oil treated animals served as negative controls.
5. Bone marrow smears were prepared at 24 and 48 hours after treatment. Positive control smears were prepared only at 24 hours after treatment.
6. Analysis of smear was conducted according to the method of Schmid (1976). The number of micronucleated polychromatic erythrocytes (MN-PCE) was recorded in 1,000 erythrocytes per animal. The number of micronucleated normochromatic erythrocytes (MN-NCE) in the optical field of 1,000 polychromatic erythrocytes was also counted. The ratio of polychromatic erythrocytes (PCE) to total erythrocytes (PCE + NCE) was also determined by counting a total number of approximately 200 erythrocytes.

RESULTS

The investigators indicated that one male in the 380 mg/kg-24 hour sacrifice and two males in the 380 mg/kg-48 hour sacrifice died prior to sacrifice. The cause of death was not mentioned but, apparently, was compound-related. No deaths were recorded in treated females.

Data on the frequencies of micronucleated polychromatic erythrocytes (MN-PCE) in the bone marrow of male and female mice treated with Telone II or cyclophosphamide are presented in the next two tables.

FREQUENCIES OF MN-PCE IN MALE MICE

	24-hour sacrifice				48-hour sacrifice			
	N	# PCE Examined	MN-PCE[a]	% PCE	N	# PCE Examined	MN-PCE	% PCE
Corn oil	5	5000	1.0 ± 1.0	56.8	5	5000	1.2 ± 0.4	57.3
Telone II (38mg/kg)	5	5000	1.6 ± 1.5	56.8	5	5000	0.6 ± 0.9	61.5
Telone II (115 mg/kg)	5	5000	1.4 ± 1.1	55.1	5	5000	0.6 ± 0.9	61.6
Telone II (380 mg/kg)	4	4000	1.8 ± 1.5	60.3	2	2000	1.5 ± 2.1	52.0
Cyclophosphamide (120 mg/kg)	5	5000	47 ± 11*	34.1	No data			

(*) Significantly different from negative controls, $p < 0.05$

(a) Micronucleated polychromatic erythrocytes : Means ± S.D.

FREQUENCIES OF MN-PCE IN FEMALE MICE

	24-hour sacrifice				48-hour sacrifice			
	N	# PCE Examined	MN-PCE	% PCE	N	# PCE Examined	MN-PCE	% PCE
Corn oil	5	5000	1.4 ± 0.9	63.8	5	5000	0.2 ± 0.4	61.5
Telone II (33 mg/kg)	5	5000	0.6 ± 0.8	64.1	5	5000	0.6 ± 0.5	64.2
Telone II (115 mg/kg)	5	5000	0.8 ± 0.8	62.7	5	5000	0.2 ± 0.4	63.3
Telone II (330 mg/kg)	5	5000	0.8 ± 1.3	62.1	5	5000	1.6 ± 1.5	41.4
Cyclophosphamide (120 mg/kg)	5	5000	46 ± 14*	49.0	No data			

(*) Significantly different from negative controls, $p < 0.05$

DISCUSSION

There was no increase in the incidence of polychromatic erythrocytes with micronuclei in either male or female mice treated with 33, 115, or 330 mg/kg at any sampling period up to 48 hours. However, the positive control (cyclophosphamide) produced a significant increase in MN-PCE at the 24-hour interval as compared to negative control values.

The highest dose used (330 mg/kg; approximately 60% of the LD50) resulted in death of 3 males: 1 in the 24-hour sacrifice group and 2 in the 48-hour sacrifice group. It can be assumed that a maximum tolerated dose relative to systemic toxicity had been utilized by the investigators. However, this dosage level (330 mg/kg) apparently did not produce any toxicity to the primary target organ of this assay, i.e. bone marrow, as evidenced by no changes in the erythropoietic system at all dosage levels tested. Therefore, the mouse bone marrow micronucleus assay apparently was not appropriate for determining the clastogenic potential of Telone II. It should also be noted that in this investigation, the ratio of PCE to total erythrocytes (PCE + NCE) was determined by examining approximately 200 erythrocytes. It would have been more desirable to determine this ratio by counting 1000 erythrocytes.

The study authors concluded that Telone II was not clastogenic in the mouse bone marrow micronucleus assay. However, in the absence of confirming target organ (bone marrow) toxicity, the reported data are considered as equivocal.

004903

STUDY REVIEW # 9

Chemical: Telone II, 1,3-dichloropropene
Test Material: Technical Grade containing:
89% cis and trans-1,3-dichloropropene
2.5% 1,2-dichloropropane
[redacted]
1.0% epichlorohydrin
Study/Action Type: Carcinogenicity

STUDY IDENTIFICATION:

"Toxicology and Carcinogenesis studies of Telone II® in F 344/N rats and B6C3F1 mice (gavage studies)"

Testing Facility: Frederick Cancer Research Center
Sponsored by: National Toxicology Program
Research Triangle Park, N.C. 27709
Final Report Date: May 1985
Final Report No.: NTP TR 269
NIH Publication No. 85-2525 NTP 83-22

BACKGROUND INFORMATION

The carcinogenesis potential of Telone II in rats and mice was previously submitted to the Agency as a "board draft" (NIH Publication #84-2525) by the registrant under Accession No. 255013. Both studies were reviewed by the Agency (Q. Bui's memo of 9/6/85 to H. Jacoby) with the following core classification:

1. Carcinogenesis study in rats:
   Oncogenicity Core Classification: Minimum Data
   Chronicity Core Classification: Supplementary Data
2. Carcinogenesis study in mice:
   Oncogenicity Core Classification: Supplementary Data
   Chronicity Core Classification: Not Applicable
   (The study was not designed to investigate the systemic toxicity of Telone II in mice. Hematology, clinical chemistry, ophthalmologic examination, urinalysis, and food consumption were not measured).

In this current action (Accession No. 259101), final reports of both investigations were submitted for review.

DISCUSSION

1. Carcinogenesis study in F344/N rats

All data from both the main and ancillary rat final reports were compared to those of the board drafts. It is concluded that all data in the final reports are identical to those of the board drafts previously reviewed by the Agency except for the following:

Forestomach, basal cell or epithelial hyperplasia

	Control	25 mg/kg	50 mg/kg
A. MALES			
Board draft			
Main Study	1/52	3/52	9/52
Overall Rates (†)	2/77	11/77	27/77
Final Report			
Main Study	2/52	5/52	13/52
Overall Rates	3/77	13/77	31/77
B. FEMALES			
Board draft			
Main Study	0/52	0/52	12/52
Overall Rates	0/75	5/77	31/77
Final Report			
Main Study	1/52	0/52	16/52
Overall Rates	1/75	5/77	35/77

(†) Pooled results from the 2-year and the ancillary studies

2. Carcinogenesis study in B6C3F1 mice

A comparison of the data presented in the "board draft" and the final report revealed no differences between the two documents.

DISCUSSION AND RECOMMENDATION

The differences between data of the board draft and final report for forestomach non-neoplastic findings noted in both male and female rats does not alter the conclusions originally drawn from this study (see Q. Rui's memo of 9/6/85 to H. Jacoby).

Based upon the finalized findings, it is recommended that:

1. Carcinogenesis study in rats, NTP TR-269, May 1985, remain classified as:

a) Core Minimum Data for oncogenicity
Positive oncogenic effect (forestomach papillomas/carcinomas, neoplastic nodules in liver of males, and forestomach papillomas in females) at 25 and 50 mg/kg/day, 3 days/week for 104 weeks.

b) Core Supplementary Data for chronic toxicity
The chronic section of the study cannot be upgraded since:

- Only two dosage levels were used
- Animals were gavaged only 3 times a week
- Lack of ophthalmologic examinations and urinalysis
- Lack of food consumption data

2. Carcinogenesis study in mice, NTP TR-269, May 1985, remains classified as:

a. Core Supplementary Data for oncogenicity
Excessive mortality in control males and lack of randomization at study initiation limit the utility of this study. However, positive oncogenic findings (forestomach carcinomas/papillomas, urinary bladder transitional cell carcinomas, and alveolar/bronchiolar adenomas) were noted in both sexes (doses tested = 50 and 100 mg/kg, 3 days/week for 104 weeks)

b. Chronic toxicity: Not applicable
The study was not designed to investigate the systemic toxicity of Telone II in mice. Hematology, clinical chemistry, ophthalmologic examination, urinalysis, and food consumption were not measured.