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

9/6/85

004645

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of chronic, sub-chronic, and teratology studies with Telone II.
EPA Reg. No. 464-511
Accession No. 255013 Caswell No. 324 A

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

FROM: Quang Q. Bui, Ph.D. Quang Q Bui 8/27/85
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THROUGH: Laurence D. Chitlik, D.A.B.T. W. Tellus, for 8-28-85
Section Head, Section V
Toxicology Branch/HED (TS-769C)

and

Theodore M. Farber, Ph.D. 9/6/85
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant:

Dow Chemical Company
Midland, Michigan 48640

Action Requested

Review of sub-chronic, chronic, and teratology studies with Telone II (Data call in).

RECOMMENDATION

In this action, seven studies were submitted. Recommendation for each study is as follows:

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1. Subchronic inhalation study in rats, rabbits, guinea pigs, and dogs. Dow Chemical Company # NBT 3.4-61-3 and 4, final report 2/16/73:
   Test Material: Telone II (1,3-dichloropropene 99%
   epichlorohydrin 1%)
   Core Classification: Supplementary Data.
   This study cannot be upgraded due to:
   a. Inadequate number of animals/dose level
   b. Inadequate number of dose levels used (only 2 dose levels)
   c. Lack of clinical chemistry data

2. Inhalation teratology study in Fischer-344 rats. Dow Chemical Company #HET M-003993-006, final report 10/31/83 :
   Test Material: Telone II (1,3-dichloropropene 90.1%
   epichlorohydrin 1.0%)
   Core Classification: Supplementary Data
   All the reported findings could neither be confirmed nor verified since only a tabulated summary of all findings was reported. This study will be re-evaluated if supporting individual maternal data (clinical observations, necropsy, body weight, food consumption, reproduction) and individual fetal data (weight, sex, and anomalies) are submitted for review.

3. Inhalation teratology study in New Zealand white rabbits. Dow Chemical Company #HET M-003993-006, final report 10/31/83:
   Test Material: Telone II (1,3-dichloropropene 90.1%
   epichlorohydrin 1.0%)
   Core Classification: Supplementary Data
   All the reported findings could neither be confirmed nor verified since only a tabulated summary of all findings was reported. This study will be re-evaluated if supporting individual maternal data (clinical observations, necropsy, body weight, food consumption, reproduction) and individual fetal data (weight, sex, and anomalies) are submitted for review.

4. Sub-chronic inhalation and reproduction in rats. Shell Toxicology Lab. (Tunstall, England) # TLGR.80.023, final report 4/23/80:
   Test Material: Technical D-D epichloronydrin free
   [mixture of 1,3-dichloropropene (53.7%)] [redacted]

   a. Inhalation section: Core Classification: Supplementary Data (*)

      This section may potentially be upgraded if organ/body weight ratios and food consumption data are provided by the registrant

   b. Reproduction section: remains classified as Supplementary Data (*)

      This section was previously reviewed by G. Burin (memo of 6/16/82) However, re-calculation of the pre-implantation loss in the low dose group is requested.

(*) This study cannot fulfill the regulatory requirements for Telone II since Technical D-D contains only 53.7% of cis- and trans-1,3-dichloropropene whereas Telone II includes 92% of cis- and trans-dichloropropene.

PRODUCT IMPURITY INFORMATION IS NOT INCLUDED

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5. Carcinogenesis study in rats. National Toxicology Program #NTP TR 269, NTP-83-22, NIH Publication #84-2525, 8/1984 (Board draft):

Test Material: Telone II (1,3-dichloropropene 89%
epichlorohydrin 1%)
Oncogenicity Core Classification: Minimum Data

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.

Chronic Toxicity Core Classification: Supplementary Data

This chronic section of the study cannot be upgraded since:
a. Only two dosage levels were used
b. Animals were gavaged only for 3 times a week
c. Lack of ophthalmologic examinations and urinalysis
d. Lack of food consumption data

6. Carcinogenesis study in mice. National Toxicology Program #NTP TR 269, NTP-83-22, NIH Publication #84-2525, 8/1984 (Board draft).
Test Material: Telone II (1,3-dichloropropne 89%
epichlorohydrin 1%)
Core Classification: 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/day, three days a week for 104 weeks).

(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)

7. Carcinogenesis study in mice. Van Duuren et al., 1979. Article published in JNCI, Vol. 63, No. 6, pp. 1433-1439:
Test Material: cis 1,3-dichloropropene
Core Classification: Supplementary Data

(Published article not intended for regulatory purposes. This study cannot be upgraded).

(*) Neoplasms not found in studies using epichlorohyrin only (see individual study review)

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STUDY REVIEW

Chemical: Telone II; 1,3-Dichloropropene
Test Material: Technical Telone II : 99% 1,3-dichloropropene
1% epichlorohydrin
Study/Action Type: Sub-chronic inhalation study

STUDY IDENTIFICATION:

"The toxicity of 1,3-dichloropropene vapor as determined by repeated exposure of laboratory animals"

Testing Facility: The Dow Chemical Company
Final Report No.: NBT 3.4-61-3 & 4
Final Report Date: 2/16/73
Study Authors: T.R. Torkelson, T.Z. Wujkowski, and F. Oyen
EPA Accession No.: 255013

Study Reviewed by: Quang Q. Bui, Ph.D.
Section V, Toxicology Branch
Hazard Evaluation Division

Review Approved by: Laurence D. Chitlik, D.A.B.T.
Section Head, Section V
Toxicology Branch/HED

CONCLUSIONS:

The investigators reported that exposure to Telone II vapor at 2.8 and 3.0 ppm for 6 months may result in "reversible slight cloudy swelling of the renal tubular epithelium" in male rats. However, reported summary findings were not supported by actual individual data. Clinical observations, histopathologic findings, body weight data, hematologic values, and necropsy data are presently not available to substantiate the reported summary findings.

The limited number of dogs (2/dose level) and rabbits (3/dose level) precluded a meaningful assessment of the data in these species.

The human sensory test was not scientifically sound since analytical determination of 1,3-dichloropropene in the chambers was not conducted and hematologic, clinical and physiologic parameters were not measured.

RECOMMENDATION:

It is recommended that this study be classified as Core Supplementary Data. A systemic NOEL could not be determined from this study in the absence of supporting data. This study cannot be upgraded due to several deficiencies listed as follows:

a. Inadequate number of animals (dogs and rabbits)
b. Inadequate dosage levels (only two dose levels were used)
c. Lack of clinical chemistry data
d. Lack of hematological values for rabbits, guinea pigs
e. Lack of supporting data

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PROCEDURES

Material: A mixture of:

Cis 1,3-dichloropropene	46%
Trans 1,3-dichloropropene	53%
Epichlorohydrin	1%

Dosage levels: 1 and 3 ppm
Route of administration: Inhalation (vapor)
Species used: Rats, rabbits, guinea pigs, and dogs.

This study was designed to investigate the effects of repeated exposure to Telone II on rats, guinea pigs, dogs, and rabbits.

Groups of 12 male and 12 female rats, 12 male and 12 female guinea pigs, 3 male and 3 female rabbits, and 2 dogs were exposed to 1 or 3 ppm of Telone II for 7 hours/day, 5 days/week for 6 months (125 to 130 exposures). All animals were sacrificed at the end of the investigation.

Groups of 12 male and 12 female rats were also exposed to the aforementioned conditions but were kept without subsequent exposure for 3 months after the last exposure. These groups were designated as "recovery groups".

In addition to the animals exposed for 7 hours/day, groups of 5 male rats each were also exposed to 3 ppm for either 1/2, 1, 2, or 4 hours/day, 5 day/week for 6 months.

A human sensory test was also conducted with 10 volunteers exposed to 1 and 3 ppm for 1 to 3 minutes. Following each exposure, each subject independently gave a verbal report of his reaction.

The following comments are noted relative to the study experimental method:

1. Only two dose levels were used; At least three dosage levels should be used.
2. The number of rabbits and dogs tested per dosage level was inadequate for statistical analysis.
3. Hematological determinations were conducted only in rats and dogs.
4. Blood chemistry and urinalysis were not performed in all species used.
5. Although the recovery groups were initiated with 12 male and 12 female rats, the data presented for the sham control and 3 ppm males were averaged from 2 and 3 animals, respectively. The authors indicated that 9 males exposed to 3 ppm "were used in another experiment". Their statement could not be verified. Therefore, the recovery groups (although an ancillary portion of this study) would not be useful for assessment of reversibility of reported effects.

RESULTS

Rats exposed to 1 or 3 ppm for 7 hours/day, 5 day/week for 6 months

The only effect reported was cloudy swelling of the renal tubular epithelium in male rats exposed to 3 ppm. The 1 ppm group had similar body weight, clinical signs, hematological values, and histopathologic observations as the sham control group.

Rats exposed to 1 or 3 ppm for 7 hours/day, 5 day/week for 6 months and allowed 3 months of recovery

The investigators reported that the cloudy swelling of the renal tubular epithelium observed in males exposed to 3 ppm and sacrificed promptly was not present in males of the recovery groups.

Rats exposed to 3 ppm for 0.5, 1, 2, and 4 hours/day, 5 day/week for 6 months

The investigators reported an analytical concentration of 2.8 ppm of 1,3-Dichloropropene. They also indicated that the only effect observed was slight cloudy swelling of the renal tubular epithelium in male rats exposed 4 hours/day. No effects were found in the 0.5, 1, and 2 hours/day exposure groups.

Dogs, guinea pigs, and rabbits exposed to 1 or 3 ppm for 7 hours/day, 5 day/week for 6 months

No noticeable adverse effects were noted in these species with respect to body weight, clinical signs, necropsy and histopathologic observations.

Human sensory tests

Human subjects reported "fatiguing of the sense of smell" after a few minutes and the effect after exposure to 1 ppm was fainter than that of the 3 ppm.

DISCUSSION AND CONCLUSIONS

In this study, only a summary of findings was reported. No histopathologic observation data, body weight gain data, clinical observations, individual hematologic values, and necropsy data were appended to the final report. Therefore, the reported summary findings were not supported by actual individual data. The authors indicated that analytical determinations of the chamber concentrations were performed periodically. However, their statement could not be supported due to the absence of supporting data.

Furthermore, the number of dogs (2/dose level) and rabbits (3/dose level) used was inappropriate and precluded more meaningful assessment. The data reported for male rats in the control and 3 ppm recovery groups were inadequate (2 and 3 males, respectively) for statistical analysis.

The histopathologic reported findings of "cloudy and swelling of the renal tubular epithelium" were unsupported. The number of males affected and the severity of the findings could not be determined in the absence of histopathologic data.

The human sensory test was not scientifically sound since the concentration of 1,3 dichloropropene in the inhalation chamber was not measured. No clinical, hematologic, or physiologic data were collected from the volunteers.

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STUDY REVIEW

Chemical: Telone II; 1,3-dichloropropene
Test Material: Technical Telone II, Lot No. 29
Cis 1,3 dichloropropene 47.7%
Trans 1,3 dichloropropene 42.4%
epichlorohydrin 1.0%
Study/Action Type: Teratology Study

STUDY IDENTIFICATION:

"Inhalation teratology study in Fischer 344 rats and New Zealand white rabbits"

Testing Facility: Dow Chemical Company
Final Report No.: HET M-003993-006
Final Report Date: 10/31/83
Study Authors: J.A. John, P.M. Kloes, L.L. Calhoun, and J.T. Young
EPA Accession No.: 255013

CONCLUSIONS

Under the conditions of the rat teratology study, maternal toxicity was demonstrated at all dosage levels tested (maternal NOEL < 20 ppm, lowest dose tested) as evidenced by significant decreases in body weight gain (days 6-20) and food consumption during the dosing period (days 6-15). However, the significance of this finding could not be accurately interpreted due to the absence of initial body weight and body weight gain data from days 0-6 of gestation. The authors indicated that rats exposed to Telone II by inhalation during the period of organogenesis did not exhibit any compound-related evidence of teratogenicity up to and including a dosage level of 120 ppm/day. Signs of fetotoxicity were demonstrated at the highest dose level (120 ppm) as demonstrated by an increase in delayed ossification of the vertebral centra. However, since only a tabulated summary of all findings was reported, all the reported findings could neither be confirmed nor verified. Furthermore, clinical observation data, maternal necropsy data, individual body weight and food consumption data were not available.

Evidence of teratogenic effects was not apparent in the rabbit study. However, litter and fetal incidences of all findings could not be calculated in the absence of individual litter data. Signs of maternal toxicity were found at 60 and 120 ppm as evidenced by decreased maternal weight gain during the dosing period (days 6-18). However, no initial body weight data and body weight gain prior to the dosing period (days 0-6) were available. In addition, all maternal and fetal findings were summarized and reported as means. No supporting individual data, necropsy data, and fetal data were attached with this final report. Consequently, all these findings could neither be verified nor confirmed. The maternal NOEL is tentatively determined to be 20 ppm (lowest dose tested).

RECOMMENDATION

It is recommended that this teratogenic investigation in rats and rabbits be classified as Core Supplementary Data since only a summarized form of the data was reported. Developmental toxicity NOELs for rats and rabbits could not be determined.

PROCEDURES

Dosage levels: 0, 20, 60, or 120 ppm
(equivalent to 0, 0.091, 0.272, and 0.545 mg/L)
Inhalation exposure for 6 hours/day
Duration of exposure: days 6-15 of gestation for rats
days 6-18 of gestation for rabbits

A copy of the procedures used is appended. The following comments are noted:

1. Only a summary of findings was submitted for review. All values were reported as mean ± S.D. In the absence of individual data, the reported findings could neither be confirmed nor verified.
2. Only a summary of the analytical and nominal concentrations, temperature, and humidity of the exposure chamber was available. Individual measurements must be submitted to confirm the reported concentrations.
3. Body weight data were not recorded from days 0-6 of gestation for either rats or rabbits.
4. Rabbits were described as "artificially inseminated". However, the artificial insemination procedure was not described in detail (buck number, volume of semen used to inseminate, HCG injection, sperm count,....).
5. Rats were sacrificed on day 21 of gestation instead of day 20 of gestation as usually performed in a teratology study.
6. Necropsy and clinical observation data for both species were not available.

RAT-TERATOLOGY STUDY

Maternal Toxicity

No deaths occurred among the control and treated groups. The authors indicated that no "consistent treatment related effects on general appearance or demeanor" were noted. However, their statement cannot be verified in the absence of clinical observation data.

Maternal body weight

As indicated earlier, body weights were not recorded prior to the dosing period. Consequently, randomization, weight and age variability among all groups could not be verified and the weight gain throughout gestation (days 0-21) could not be calculated. The maternal body weigh gain on gestational days 6-20 is presented as follows:

Body Weight Gain (in grams)	Control	20 ppm	60 ppm	120 ppm
# of animals	27	25	20	24
Days 6-15 (a)	27	21	14*	7*
Days 16-20	40	38	41	46*
Days 6-20	66	59*	55*	48*

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

During the dosing period (days 6-15), body weight reductions were noted in all groups, attaining significant differences at the 60 and 120 ppm dosage levels. Statistical differences in body weight gains were observed in all treated groups, including the lowest dosage level, from gestational days 6-20.

Food Consumption

The food consumption of all treated groups was found to be significantly different from control values during the dosing period (days 6-15).

Gross Necropsy Observations

The absolute liver weights of all treated groups were reported by the authors as significantly different from controls. However, no differences in relative liver weights were found. Recalculation of these findings was not possible due to the absence of individual data.

Reproductive Data

The following table summarizes the data collected at C-section

	Control	20 ppm	60 ppm	120 ppm
# bred	30	30	30	30
# pregnant	28	25	21	24
Pregnancy Index (%)	93	83	70*	80
# litters	27	25	21	24
$\bar{X}$ corpora lutea	11	11	11	11
$\bar{X}$ implantations	10	11	10	10
$\bar{X}$ fetuses/litter	10	10	9	9
$\bar{X}$ resorptions/litter	0.3	0.6	0.5	0.5
Postimplantation loss (%)	3	6	6	5
# fetuses	264	245	186	221
Fetal weight (g)	4.4	4.3	4.4	4.4
Crown-rump length (mm)	43.4	44.9	44.0	44.0

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

The pregnancy index of all treated groups was lower than that of control but significant difference was found only at the 60 ppm dosage level. The investigators indicated that a pregnancy index of 70-83% observed in the treated groups was comparable to historical control values. However, historical control data were not attached with this report for confirmation.

No significant differences relative to the mean numbers of corpora lutea, implantations, resorptions, and litter size were noted among the control and treated groups. However, individual data are not available to confirm the reported findings.

No differences with respect to fetal weight and fetal crown-rump length were found between the treated and control groups.

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Malformations and Variations

The authors reported the following findings:

	Control	20 ppm	60 ppm	120 ppm
External examination				
# fetuses (litters) examined	264(27)	245(25)	186(20)	221(24)
Microphthalmia	1(1)*	0(0)	0(0)	1(1)
Soft tissue examination				
# fetuses (litters) examined	138(27)	129(25)	98(20)	119(24)
Dilated ureter	1(1)	0(0)	0(0)	0(0)
Dilated renal pelvis	1(1)	0(0)	0(0)	0(0)
Dilated lateral ventricle of brain	1(1)	1(1)	1(1)	0(0)
Testicular agenesis unilateral	0(0)	1(1)	0(0)	0(0)
Coarctation of aorta	0(0)	0(0)	0(0)	1(1)
Skeletal observations				
# fetuses (litters) examined	264(27)	245(25)	186(20)	221(24)
Vertebral centra, delayed ossification	8(6)	8(7)	10(7)	14(12)

(*): fetus (litter) incidence

From the data reported, no apparent compound and dose-related increases in fetal and litter malformations were noted. The incidences of external and soft-tissues malformations were very similar among the control and treated groups. Isolated cases of coarctation of the aorta and microphthalmia were found in the 120 ppm dosage group; dilated lateral ventricle of the brain in the 60 ppm groups; and unilateral testicular agenesis and dilated lateral ventricle of the brain in the 20 ppm group.

The incidences of skeletal variations were similar between the control and treated groups except for a slight increase in delayed ossification of the vertebral centra which was noted in the treated groups. Litter percentages of 22, 28, 35, and 50% for this finding were found in the control, 20, 60, and 120 ppm, respectively.

RABBIT TERATOLOGY STUDY

Maternal mortality and observations

Three does died during this investigation, one each in the control, 60, and 120 ppm groups. Necropsy data were not available to determine the cause of death. The authors stated that "no effects on general appearance or demeanor" were observed. However, their statement could not be confirmed in the absence of clinical observation data.

Pregnancy indices of 86, 72, 68, and 88% were obtained for the control, 20, 60, and 120 ppm groups, respectively. These values are within acceptable ranges for artificially inseminated rabbits.

Maternal body weights

Data on body weight gain are tabulated as follows:

Body Weight Gain (grams)	Control	20 ppm	60 ppm	120 ppm
Number of dams	24	18	17	21
Days 6-18(a)	213	168	83*	66*
Days 19-28	103	110	137	242*
Days 6-29	319	278	218	309

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

During the dosing period (days 6-18), compound-related effects were found with respect to body weight gain data. The 20, 60, and 120 ppm groups gained respectively 79, 39, and 31% of their concurrent controls.

From days 6-29 of gestation, although the treated groups gained slightly less than their controls, no statistical significances were attained.

Reproductive data at necropsy

	Control	20 ppm	60 ppm	120 ppm
# of litters	24	18	17	21
$\bar{X}$ corpora lutea/dam	10	10	10	10
$\bar{X}$ implantations/dam	9	8	8	8
Preimplantation loss (%)	10	16	17	18
$\bar{X}$ fetuses/dam	8	8	7	8
$\bar{X}$ resorptions/litter	0.8	0.6	0.8	0.7
Litter totally resorbed	0	0	1	0
# fetuses	201	137	121	159
$\bar{X}$ fetal weight (grams)	37.1	37.6	36.7	36.1
$\bar{X}$ crown-rump length (mm)	96.9	95.6	96.2	94.9

No significant differences in the mean numbers of corpora lutea and implantation sites were noted among the groups. A slight increase in pre-implantation loss was observed in the treated groups as compared to control values but statistical significance was not obtained.

The mean litter size was similar among the groups. Only one litter of the 60 ppm had all of its fetuses resorbed.

No statistically significant differences in fetal weight and fetal crown-rump length were found between the control and treated groups.

Fetal Observations

The investigators reported the following findings:

	Control	20 ppm	60 ppm	120 ppm
External Observations				
# fetuses (litters) examined	201(24)	137(18)	121(16)	159(21)
Forelimb flexure	1(1)	0(0)	0(0)	2(2)†
Omphalocele	0(0)	1(1)	0(0)	0(0)
Microphthalmia	0(0)	0(0)	0(0)	1(1)†
Exencephaly	0(0)	1(1)*	0(0)	0(0)
Soft Tissue Observations				
# fetuses (litters) examined	109(24)	76(18)	65(16)	88(21)
Hydrocephaly	0(0)	0(0)	0(0)	1(1)†
Diffuse corneal cloudiness	0(0)	0(0)	0(0)	1(1)†
Patent ductus arteriosus	0(0)	0(0)	1(1)	0(0)
Ventricular septal defect	0(0)	0(0)	1(1)††	0(0)
Enlarged aorta	0(0)	0(0)	1(1)††	0(0)
Coarctation of aorta	0(0)	0(0)	0(0)	1(1)†
Retroesophageal rt. subclavian artery	0(0)	0(0)	0(0)	1(1)†
Undescended testes	0(0)	1(1)*	0(0)	0(0)
Convoluted ureter	2(2)	0(0)	1(1)	3(3)
Skeletal Observations				
# fetuses (litters) examined	138(23)	130(18)	105(16)	153(20)
Hyoid, crooked	0(0)	1(1)	0(0)	0(0)
Misaligned centra, vert.	0(0)	0(0)	0(0)	1(1)
Ribs, calloused	0(0)	2(2)	0(0)	0(0)
Sternebrae fused	1(1)	0(0)	1(1)	0(0)

(*) A single fetus exhibited exencephaly and undescended testes
(†) Observations found in a single fetus
(††) A single fetus exhibited ventricular septal defect and enlarged aorta

From the reported findings, apparently no compound-related increases in either litter or fetal incidences of malformations were noted in the Telone-treated animals. Findings of microphthalmia, forelimb flexure, hydrocephaly, coartation of aorta, and diffuse corneal cloudiness were noted in a single fetus of the 120 ppm group.

Further, no evidences of increased skeletal variations were observed in the treated groups.

DISCUSSION AND CONCLUSIONS

1. Rat Study

Maternal toxicity was demonstrated in all treated groups as evidenced by decreased maternal weight gain (days 6-15) and food consumption during the dosing period (days 6-15 of gestation). However, the lack of body weight data from days 0-6 precluded an accurate assessment of the body weight gain data.

No significant variations in reproductive data collected at necropsy and in fetal weight and crown-rump length were noted. However, all the data presented were summarized, rounded-off, and averaged as the mean ± S.D. In the absence of individual data, the mean values reported could neither be verified nor confirmed.

No compound-related increases in the incidences of litter and fetus with malformations were apparent from the final report. A fetotoxic effect apparently was noted in the 120 ppm group as characterized by a significant increase in "delayed ossification of vertebral centra". However, the incidences of litter and fetus with malformations or variations could not be calculated in the absence of individual litter data. A developmental toxicity NOEL could not be determined at the present time.

This study may potentially be upgraded if additional individual maternal and fetal data are submitted by the registrant for evaluation.

2. Rabbit Study

A dose-response decrease in maternal weight gain was noted in the treated animals during the dosing period (days 6-18). However, the absence of initial body weight and body weight data prior to the dosing period (days 0-6) precluded an assessment of body weight gain data throughout gestation.

Three animals were found dead in this study: One each in the control, 60, and 120 ppm group. No necropsy data were available to determine the cause of death. Clinical observation data were also not appended with this report.

No significant differences in maternal reproductive data, litter and fetal incidences of variations and malformations, and fetal weight and crown length were found among the control and treated groups. However, all these data were reported as means ± S.D. without any supporting individual data.

In a rabbit teratology study, it is the usual practice to conduct both visceral and skeletal examinations on all fetuses. However, in this study fetal visceral examination was performed only in approximately 55% of fetuses in each group (see table on page 12). Furthermore, it appears that not all fetuses were processed for skeletal staining and/or observation. For example, 121 fetuses of the 60 ppm group were observed externally but only 105 fetuses were examined for skeletal findings. From the table on page 12, apparently, 3, 7, 16, and 6 fetuses of the 0, 20, 60, and 120 ppm groups, respectively were not examined skeletally. The registrant is requested to provide clarification relative to these issues.

A developmental toxicity NOEL could not be determined at the present time. However, this study may potentially be upgraded if additional individual maternal and fetal data are submitted by the registrant for evaluation.

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Pages 14 through 19 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.

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STUDY REVIEW

Chemical: D-D soil fumigant
Test Material: Technical D-D (98% minimum purity)

[redacted]

Study/Action Type: Subchronic inhalation and Reproduction

STUDY IDENTIFICATION

"A 10-week inhalation study of mating behaviour, fertility, and toxicity in male and female rats"

Testing Facility: Shell Toxicology Lab. (Tunstall), England
Final Report No.: TLGR.80.023
Report Date: 4/23/80
Study Director: D.G. Clark
EPA Accession No.: 255013

Study Reviewed by: Quang Q. Bui, Ph.D.
Section V, Toxicology Branch
Hazard Evaluation Division

Review Approved by: Laurence D. Chitlik, D.A.B.T.
Head, Section V
Toxicology Branch/HED

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

BACKGROUND INFORMATION

This study consists of two sections: subchronic inhalation and reproduction. The reproductive section of this study was adequately evaluated by G. Burin (memo of 6/16/82) who classified it as Core Supplementary Data. No effects on reproduction were indicated at the highest dose tested (443 mg/m^3).

In this action, the subchronic inhalation section is evaluated and, hence, serves as an addendum to G. Burin's memo of 6/16/82.

CONCLUSION/RECOMMENDATION

Exposure to a concentration of 443 mg/m^3 (expressed as the sum of the two isomers of 1,3-dichloropropene and 1,2-dichloropropane) was associated with significant decreases in body weight gain in both male and female rats. Significant increases in kidney and liver weights were also found in both males and females of the highest dose tested (443 mg/m^3). However, histopathologic examinations did not reveal any changes which could account for these findings.

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It should be noted that in this study the investigators expressed all exposure levels as the sum of the two isomers of 1,3-dichloropropene and 1,2-dichloropropane. The dosage levels as expressed in this study are thus misleading since Technical D-D was used in this investigation and not the two isomers of 1,3-dichloropropene plus 1,2-dichloropropane. In addition to these ingredients, Technical D-D also consists of [redacted] Therefore, the effects observed in this study should not solely be limited to the two isomers of 1,3-dichloropropene and 1,2-dichloropropane, which together constitute only 79% w/w of Technical D-D. This reviewer believes that all dosage levels used in this study must be rectified to correctly represent Technical D-D concentrations.

Also, the two isomers of 1,3-dichloropropene (cis and trans) together constitute only 53.7% w/w of Technical D-D. Therefore, the results obtained from this study could not be used as a valid substitution for a subchronic inhalation study for the registration of Telone II (92% 1,3-dichloropropene).

Under the conditions of this study, it is recommended that:

1. The sub-chronic inhalation section be classified as Core Supplementary Data. Food consumption and organ/body weight ratios were not measured. Further, individual organ weight data are available but are illegible and, hence, could not be confirmed by this reviewer.

2. The reproduction section remains classified as Core Supplementary Data. The registrant is requested to provide explanation and re-calculation of the pre-implantation loss for the low dose group.

Values for pre-implantation loss are of doubtful meaning. This reviewer noted that female #2136 (mated with male #131 of the low dose group, week 3) was described with 31 corpora lutea and 1 implantation site (page 142). This number was used by the investigators to calculate different indices for males of the low dose group at week 3. To this reviewer, it is highly unlikely that 31 corpora lutea may be found in one animal with only one implantation and these erroneous values may account for the unreasonably high incidence of pre-implantation loss reported for the low dose group at week 3 (24.9%).

PRODUCT IMPURITY INFORMATION IS NOT INCLUDED

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PROCEDURES

1. Test Material:

The test material used was "Technical D-D epichlorohydrin free" with a 99.8% minimum purity. The soil fumigant D-D is a mixture of

*1,3 Dichloropropene cis	28.1 % w/w
*1,3 Dichloropropene trans	25.6 % w/w
[redacted]	

(*) active ingredient of Telone

2. Dosage levels:

In this study, the investigators expressed the dose levels as the sum total of the two isomers of 1,3-dichloropropene (DCP) plus [redacted] Analytical analyses of the test atmospheres were conducted daily and yielded the following exposure levels: 0, 64, 145, and 443 mg/m^3 equivalent to 0, 14, 32, and 96 ppm, respectively. Analytical concentrations of 0, 41, 97, and 293 mg/m^3 were obtained when the dosage levels were expressed as the sum of the two isomers of 1,3-DCP only.

3. Group Organization:

A copy of the procedures used is appended. In general, this study was divided into 3 sub-groups:

a. Sub-group I: 10 males and 9 females/dose — Males and females were exposed to D-D for 6 hours/day, 5 days/week for 10 weeks (animals were not exposed during two public holidays that occurred during the experiment: 5/7 and 5/28/79). All animals were sacrificed after 10 weeks of exposure with necropsy and histopathologic examinations performed.

b. Sub-group II: 20 males/dose — Reproductive capabilities of males were assessed after 2, 4, 7, and 10 weeks of exposure (6 hours/day, 5 days/week) with virgin untreated females. All males were sacrificed 5 weeks post-exposure.

c. Sub-group III: 15 females/dose — Reproductive capabilities of females were assessed after 10 weeks of exposure (6 hours/day; 5 days/week) with unexposed males. All females were sacrificed 7 weeks post-exposure

Total number of animals used per dose level: 30 males and 24 females

Reviewer's note: In this action, only the subchronic inhalation section (sub-group I) is evaluated. Data from sub-group II and III were evaluated in G. Burin's memo of 6/16/82.

PRODUCT IMPURITY INFORMATION IS NOT INCLUDED

Clinical Observations

No compound-related effects were noted by the investigators.

Mortality

One male (#96) of the 145 mg/m^3 group died after 3 weeks of exposure and one male (#93) of the same group was removed from the experiment on week 6 due to "severe bites on the feet and testes".

Body weight

The body weight gain data are presented as follows:

Table 1: Body weight Data (grams)

	Control		64 mg/m^3 °		145 mg/m^3 °		443 mg/m^3 °	
	M	F	M	F	M	F	M	F
Number of animals	30	24	30	24	30	24	30	24
Week 0	410	217	417	218	407	214	414	216
Week 10	514	281	514	283	510	278	484*	265*
Weight gain (weeks 0-10)	104	64	97	65	103	64	70*	49*

(°) expressed as the sum of the two isomers of 1,3-DCP and 1,2-Dichloropropane
(*) Significantly different from controls, $P < 0.05$

At study initiation (week 0), no differences in mean body weights were noted among the groups. However, after 10 weeks of exposure, significant decreases in male and female body weight gains were found in the 443 mg/m^3 group as compared to controls.

Hematology

Hematologic examinations were performed prior to study initiation and at study termination. No significant deviations from control values were noted in the treated groups with respect to hemoglobin, RBC, WBC, reticulocyte count, mean cell volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit.

Clinical Chemistry

Clinical chemistry was performed on the last three days of exposure on 10 males and 9 females per exposure group. Table 2 summarizes selected findings.

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Table 2: Clinical Chemistry Data after 10-week Exposure

	Control		64 mg/m^3		145 mg/m^3		443 mg/m^3	
	M	F	M	F	M	F	M	F
Protein (g/l)	64.3	60.9	64.2	61.2	63.4	60.8	64.1	58.0*
AST (I.U.)°	85	47	57*	45	49*	41	52*	39
ALT (I.U.)°°	73	37	48*	37	47*	36	51*	38
Ca (mm/l)	2.58	2.53	2.61	2.55	2.63	2.52	2.66*	2.51
Bilirubin (um/l)	2.5	2.7	2.8	2.8	2.8	2.9	2.9	2.8
Creatinine (um/l)	63	58	58	60	62	58	57*	60

(°) Aspartate aminotransferase
(°°) Alanine aminotransferase
(*) Significantly different from controls, $P < 0.05$

Blood protein concentration was decreased in high dose females but not in high dose males. Significant increases in calcium and decreases in creatinine were noted only in males of the highest dose group. The levels of AST and ALT were statistically decreased in males at all dosage levels tested as compared to controls. However, consistent increases in these two enzymes were not observed in females exposed to D-D. The investigators indicated that the significant differences observed were due to unexplicable high AST and ALT values found in two control animals (#68 and 71). When the values from these two animals were excluded from data analysis, recalculation by this reviewer did not reveal any statistical significance among groups. Consequently, the increases in AST and ALT are unlikely to be compound-related effects. Slight but consistent decreases in AST were noted in all treated females.

No differences relative to creatinine phosphatase, urea, uric acid, sodium, potassium, chlorine, and albumin were noted among the groups.

Urinalysis

Comparison of the urinalysis performed pre- and post-exposure to D-D did not indicate any significant differences among the control and treated groups.

Organ Weights

Organ weights were recorded from 10 males and 9 females/dosage level after 10 weeks of exposure (inhalation sub-group), from 20 males/dosage level 5 weeks after the termination of exposure (male reproductive performance sub-group), and from 15 females/dosage level 7 weeks after the termination of exposure (female reproductive performance sub-group).

Absolute weights of the brain, heart, liver, spleen, kidneys, and testes were reported. However, organ/body weight ratios were not calculated. Individual organ weight data are available but are illegible and hence could not be confirmed by this reviewer. The following table illustrates findings of interest as reported by the study authors.

Table 3: Organ Weights (grams; Adjusted for terminal body weight)

		Control	64 mg/m^3	145 mg/m^3	443 mg/m^3
ANIMALS SACRIFICED AFTER TEN-WEEK EXPOSURE (10 males and 9 females/dose level)					
Kidneys:	Male	3.00	2.94	3.12	3.44*
	Female	2.03	1.97	1.97	2.26*
Testes:	Male	3.59	3.48	3.48	3.55
Liver:	Male	16.8	16.6	16.3	18.8*
	Female	9.8	9.5	9.5	10.5*
MALES SACRIFICED 5 WEEKS AFTER EXPOSURE TERMINATION (20 males/dose level)					
Kidneys:		3.44	3.45	3.52	3.39
Testes:		3.69	3.59	3.41	3.66
Liver:		19.5	18.7	18.8	18.7
FEMALES SACRIFICED 7 WEEKS AFTER EXPOSURE TERMINATION (15 females/dose level)					
Kidneys:		2.14	2.10	2.19	2.25*
Liver:		11.7	11.6	11.8	12.0

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

In animals sacrificed right after exposure termination, statistically significant increases in kidney and liver weights were found in both males and females of the highest dose group.

Organ weight differences were not noted in males sacrificed 5 weeks post-exposure. These findings may suggest that the increased liver and kidney weights observed previously in males are reversible. However, in females sacrificed 7 weeks post-exposure, significant increases in kidney weights were still present at the highest dosage level tested (443 mg/m^3).

Necropsy Findings

Gross observations did not indicate any compound related macroscopic changes with the exception of increased renal subcapsular granularity in females of the mid and high dose groups.

Histopathologic Findings

Microscopic examinations of the animals sacrificed immediately after the termination of exposure did not reveal any changes which could account for the increased liver and kidney weights observed.

Significant changes attributable to D-D exposure could not be detected after microscopic examination of the reproductive organs of both males and females sacrificed immediately after exposure termination, as well as at 5 weeks and 7 weeks post-exposure.

2

DISCUSSION AND CONCLUSIONS

In this investigation, the authors expressed the dose levels of Technical D-D used as the sum of the two isomers of 1,3-dichloropropene plus 1,2-dichloropropane. However, it should be noted that in addition to these ingredients, Technical D-D also contains other presumably active ingredients (composition of Technical D-D is listed on page 13 of this memo). Consequently, expressing the dose levels as done in this study is misleading since all effects observed could not solely be attributed to 1,3-dichloropropene and 1,2-dichloropropane. All effects should be regarded as resulting from Technical D-D exposure. It is this reviewer's opinion that all dose levels should be rectified to correctly represent Technical D-D.

Inhalation exposure to a concentration of 443 mg/m^3 for 10 weeks significantly decreased the body weight gain of both males and females. However, the body weight reductions were not associated with other toxic manifestations or mortality. Food consumption was not measured in this study and, hence, restricts the meaning of the decrease in body weight observed in this highest dose group.

Significant differences in hematology, urinalysis, and clinical chemistry were not found among the control and treated groups. The significant decreases in AST and ALT observed in all male treated groups apparently were not compound-related due to unreasonable high values recorded in two control animals. When the AST and ALT values for these two animals (# 68 and 71) were excluded from data analysis no significant differences were detected.

Significant increases in kidney and liver weights were observed in both males and females of the 443 mg/m^3 group after ten weeks of exposure. However, histopathologic examinations did not reveal any changes which could account for these findings.

1,3-DICHLOROPROPENE

Page_____ is not included in this copy.

Pages 27 through 58 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.

STUDY REVIEW

004645

Chemical: Telone II - 1,3-Dichloropropene
Test Material: Technical 92% 1,3-dichloropropene
cis isomer 45%
trans isomer 47%
1,2-dichloropropane 2%
Epichlorohydrin 1%
Chlorinated propenes and hexenes 5%
Study/Action Type: Oncogenicity study

STUDY IDENTIFICATION

"NTP Technical Report on the Carcinogenesis Studies of Telone II®"

Testing Facility: Frederick Cancer Research Center
Frederick, Maryland
Final Report Date: 6/22/84 (Board Draft)
Report No.: NTP TR 269, NTP-83-22, NIH Publication No. 84-2525
Chemical Manager: Raymond S.H. Yang, Ph.D.
EPA Accession No.: 255013

Study Reviewed by: Quang Q. Bui, Ph.D.
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Review Approved by: Laurence D. Chitlik, D.A.B.T.
Section Head
Toxicology Branch/HED (TS-769C)

Reviewer's Note

This board draft was submitted to the Technical Reports Review Subcommittee of the National Toxicology Program Board of Scientific Counselors and as at this writing no final report has been completed by the National Toxicology Program (personal communication with Dr. J. E. Huff's office, Research Triangle Park).

Data from this board draft was submitted by the registrant as part of the data call in for Telone (EPA Accession No. 255013).

Evaluation of the data was based upon this board draft and as such will be subjected to change accordingly with the final report.

In this memo, evaluation of the oncogenic potential of Telone II is performed separately for each species tested (rats and mice) for clarity's sake using the Evaluation Procedure for Oncogenic Studies issued by the Office of Pesticide Programs/US. EPA on 12/1/84.

CONCLUSION

Under the conditions of the rat study, administration of Telone II at 25 and 50 mg/kg/day, 3 times/week, for 104 weeks was associated with sufficient evidence of oncogenicity as characterized by increased incidences of squamous cell papillomas and carcinomas of the forestomach as well as neoplastic nodules of the liver in males and increased incidence of squamous cell papillomas of the forestomach in females.

In the mouse study, the differential survival noted in the control group and the lack of animal randomization at study initiation impair the validity of this investigation. Due to the limited number of male controls at study termination (8), data evaluation had to be based upon the historical control data provided. Despite these limitations in study design and conduct, there is evidence to indicate that administration of Telone II by gavage at 50 and 100 mg/kg/day, 3 days/week for 104 weeks, resulted in sufficient evidence of oncogenicity in female mice as characterized by increased incidences of alveolar/bronchiolar adenomas of the lung, transitional cell carcinomas of the urinary bladder, and squamous cell papillomas or carcinomas of the forestomach. In male mice, there was limited evidence of oncogenicity as characterized by increased incidences of squamous cell papillomas of the forestomach, transitional cell carcinomas of the urinary bladder, and alveolar/bronchiolar adenomas and carcinomas of the lung.

Telone II, as used in this investigation, contains a known carcinogen and mutagen, epichlorohydrin (1%).

Konishi et al. (1980) reported that epichlorohydrin, in drinking water, caused forestomach papillomas in Wistar rats at 750 ppm (9/10 animals) and 1500 ppm (12/12 animals). Forestomach papilloma or carcinoma incidences of 12 and 4% were also found in male and female rats, respectively, gavaged with 2 mg/kg/day of epichlorohydrin for 104 weeks (Wester et al., 1984). Squamous cell papillomas or carcinomas of the forestomach, although occurring at a higher incidence were also found in this NTP investigation with Telone II in both rats and mice of either sex. These similar findings suggest that epichlorohydrin may have a contributive role to the positive oncogenic effect of Telone II noted in both species. However, it should be noted that neoplasms other than squamous cell papillomas of the forestomach were found in both rat and mouse studies. In the rat study, liver neoplastic nodules and thyroid follicular cell adenomas or carcinomas were found and alveolar/bronchiolar adenomas and transitional cell carcinomas of the urinary bladder were noted in the mouse. These findings collectively suggest that both 1,3-dichloropropene and epichlorohydrin are positive oncogens.

RECOMMENDATION

Rat study: 1. Oncogenicity: Core Classification: Minimum Data
(Positive oncogen at all doses tested, 25 and 50 mg/kg)

2. Chronic Toxicity: Core Classification: Supplementary Data
(only 2 dose levels used, animals gavaged only for 3 days/week lack of ophthalmology, urinalysis, and food consumption data, clinical chemistry and hematology not performed at study termination)
Chronic NOEL < 25 mg/kg (increased incidence of forestomach basal cell hyperplasia in both males and females, reduced cholinesterase levels in females, increased incidence of kidney nephropathy at lowest dose tested)

Mouse study:

1. Oncogenicity: Core Classification: Supplementary Data
(excessive mortality in control males and lack of animal randomization at study initiation - positive oncogen at all doses tested, 50 and 100 mg/kg)

2. Chronic Toxicity: Core Classification: N/A
(the study was not designed to investigate the chronic toxicity of Telone II.

Food consumption, hematology, and clinical chemistry were not measured and ophthalmologic examinations were not performed).

It should be noted that according to the Confidential Statement Formula submitted to the Agency on 2/28/85 (EPA Reg. No. 464-511), the registrant (Dow Chemical Co.) has replaced the stabilizer epichlorohydrin by [redacted] Therefore, although the rat study with Telone II (1% epichlorohydrin) is classified as Core Minimum Data, both rat and mouse carcinogenicity assays may not be used to fulfill the regulatory requirements for the new Telone formula registration. New oncogenic studies with the new Telone formula will be necessary to fully understand the oncogenic potential of Telone.

I. CARCINOGENIC STUDY IN FISCHER-344 RATS

PRODUCT IMPURITY INFORMATION IS NOT INCLUDED

PROCEDURES

Test Material: Telone II Technical (a mixture of cis-1,3-dichloropropene 45%, trans-1,3-dichloropropene 47%, 1,2-dichloropropane 2%, epichlorohydrin 1%, [redacted]

Dose Levels: 0, 25, and 50 mg/kg/day in corn oil (5 ml/kg) via gavage 3 days/weeks for 104 weeks.

The procedures used are photocopied and attached. The following comments are noted:

1. In addition to 52 animals/sex/group for the main study, an ancillary study was conducted simultaneously under the same housing and treatment conditions with 28 animals/per sex/per group. Five animals/sex/group of the ancillary study were sacrificed at 9, 16, 21, 24, and 27 months of dosing. Gross necropsy and histopathologic examinations were conducted to evaluate the development of lesions with respect to time.
2. Animals were only treated 3 times a week (Monday, Wednesday, and Friday) by gavage.

RESULTS

1. Test Material

Analyses of the dosing preparations were performed periodically (every three months). Results of the analytical determinations indicated that all dosing solutions were within the acceptable limits of the nominal concentrations (>90%).

Re-analysis of the test material after 13 months of storage revealed no changes in the composition of the batch used (90% of 1,3 dichloropropene) which suggested that Telone II was stable under these storing conditions.

2. Body Weights

Administration of Telone for 2 years up to and including a dosage level of 50 mg/kg was not associated with body weight depression in either sex. The body weight gains in the treated groups for either sex were neither statistically nor biologically different from control values. The body weight gain data are presented in the next table.

Table 1: Body Weight Gain Data (grams)

	Control	25 mg/kg	50 mg/kg
MALES			
Weeks 1-52	319	330(103)*	292(92)
Weeks 1-100	320	325(102)	294(92)
FEMALES			
Weeks 1-52	167	169(101)	171(102)
Weeks 1-100	217	235(108)	224(103)

(*) Weight gain (% of control)

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FEMALES			
Weeks 1-52	167	169(101)	171(102)
Weeks 1-100	217	235(108)	224(103)

*, Weight gain (% of control)

3. Survivability

No significant differences in mortality rate were observed among the groups of either sex. The mortality rate for both treated and control groups was considered as reasonable for this species after 2 years as illustrated in the next table.

	Control	25 mg/kg	50 mg/kg
MALES			
# non-accidental deaths[a]	8/52	14/52	11/52
Mortality rate (%)	15.4	26.9	21.1
# accidentally killed	2/52	1/52	1/52
# sacrificed at study termination (%)	42 (81)	37 (71)	40 (77)
FEMALES			
# non-accidental deaths[a]	17/52	13/52	14/52
Mortality rate (%)	32.7	25.0	26.9
# accidentally killed	1/52	4/52	0/52
# sacrificed at study termination (%)	34 (65)	35 (67)	38 (73)

(a) including animals killed in a moribund condition

4. Clinical Chemistry and Hematology

Hematology and clinical chemistry parameters were investigated in 8 and 12 rats of each sex in each dose group, respectively. Eighteen hematologic and 25 clinical chemistry parameters were measured. The investigators stated that hematology was determined at -1, 3, 7, 11, 15, 19, 23, 27, 31, 35 and 39 weeks. The test intervals for clinical chemistry were -1, 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 39, and 69 weeks.

a. Hematology

No compound-related significant changes were observed in both sexes of all treated groups as compared to control values.

b. Clinical chemistry

Compound-related decreases in serum cholinesterase levels were observed in females of the 25 and 50 mg/kg groups at week 17 through week 69. Although the serum cholinesterase levels in males were also lower than controls beginning at week 25, statistically significant differences were not obtained.

Serum Cholinesterase Levels (MU/ML)

	MALES			FEMALES		
	0 mg/kg	25 mg/kg	50 mg/kg	0 mg/kg	25 mg/kg	50 mg/kg
Week 1	86.9	80.4	78.9	167.9	155.0	145.9*
Week 17	96.5	84.3	87.9	393.8	328.2	301.1*
Week 25	107.0	89.5*	105.2	548.3	489.5	341.8*
Week 37	126.6	108.8	122.1	507.1	449.1	298.5*
Week 69	95.2	96.2	85.3	357.5	358.7	244.5*

(*) Significantly different from controls, P <0.05

The levels of lactic acid dehydrogenase were also depressed in both treated groups. These depressions were most pronounced in rats of the 50 mg/kg dosage level.

Lactic Acid Dehydrogenase (IU/L)

	MALES			FEMALES		
	0 mg/kg	25 mg/kg	50 mg/kg	0 mg/kg	25 mg/kg	50 mg/kg
Week 1	1036	884.1	1037	849.0	810.6	781.0
Week 17	501.2	417.2	322.5*	352.3	372.8	269.2*
Week 25	558.5	447.5	363.4*	441.1	322.0	332.5*
Week 37	568.5	682.3	470.5	626.7	478.7	458.7
Week 69	835.1	408.3*	494.5*	335.0	328.1	262.0*

(*) Significantly different from controls, P < 0.05

5. Non-neoplastic findings

The incidence of non-neoplastic lesions in male and female rats dosed with Telone II for 2 years was comparable to controls except for findings in the forestomach, kidneys, and urinary bladder. Compound-related increases in forestomach basal cell hyperplasia were noted in both males and females. The percentages of males displaying this lesion were 3%, 14% and 35% for the groups receiving 0, 25, and 50 mg/kg/day, respectively. Those of females were 0%, 6%, and 40%, respectively. Increased kidney nephropathy incidences were found in females, being 15/52 (29%), 24/52 (48%), and 25/52 (48%) for the 0, 25, and 50 mg/kg groups, respectively. Edema of the urinary bladder was observed only in the 50 mg/kg group with 9/52 (17%) males and 3/52 (6%) females affected.

6. Neoplastic Findings

(Reviewer's Note: Findings from the ancillary study are also addressed in this review using 25 animals as denominator. However, it should be noted that in the ancillary study, 5 animals/sex/dose were sacrificed at 9, 16, 21, 24, and 27 months of dosing whereas all animals in the main study were terminated at month 24)

Significant and compound-related increases in the incidences of forestomach neoplasms were noted in both sexes. Positive trend increases in forestomach squamous cell papillomas were found in both sexes. An increase in the incidence of forestomach squamous cell carcinomas was also observed in males of the 50 mg/kg group (Table 3).

Table 3: Fore-Stomach Neoplastic Findings
(Extracted from Table 5 of the NTP report, page 50)

	Control	25 mg/kg	50 mg/kg
MALES			
Squamous Cell Papilloma			
Main Study Total	1/52 (2%)	1/52 (2%)	9/52 (17%)*
Terminal Rates °	1/43 (2%)	0/38 (0%)	7/40 (18%)*
Ancillary Study	0/25 (0%)	0/25 (0%)	4/25 (16%)[a] *
Overall Rates †	1/77 (1%)	1/77 (1%)	13/77 (17%) *
Squamous Cell Carcinoma			
Main Study Total	0/52 (0%)	0/52 (0%)	4/52 (8%)
Terminal Rates °	0/43 (0%)	0/38 (0%)	4/40 (10%)
Ancillary Study	0/25 (0%)	0/25 (0%)	0/25 (0%)
Overall Rates †	0/77 (1%)	0/77 (1%)	4/77 (5%)
Squamous Cell Papilloma and Carcinoma - Combined			
Main Study Total	1/52 (2%)	1/52 (2%)	13/52 (25%)*
Terminal Rates °	1/43 (2%)	0/38 (0%)	11/40 (28%)*
Ancillary Study	0/25 (0%)	0/25 (0%)	4/25 (16%)[a] *
Overall Rates †	1/77 (1%)	1/77 (1%)	17/77 (22%)*
FEMALES			
Squamous Cell Papilloma			
Main Study Total	0/52 (0%)	2/52 (4%)	3/52 (6%)
Terminal Rates °	0/34 (0%)	1/36 (3%)	2/38 (5%)
Ancillary Study	0/25 (0%)	0/25 (0%)	5/25 (20%)[b]*
Overall Rates †	0/77 (0%)	2/77 (3%)	8/77 (10%)*

(°) Combined findings in animals killed at termination and died during period of final sacrifice
(†) Pooled results from the 2-year and the ancillary studies
(a) Neoplasms found in 2 and 2 animals sacrificed at the 24- and 27-month periods, respectively
(b) Neoplasms found in 5 animals sacrificed at the 27-month period
(*) $P < 0.05$, Fischer's Exact Test

The incidences of liver tumors in the treated females were not significantly higher than those of the controls. However, in the males, positive trend increases in neoplastic findings in the liver were noted with statistically significantly higher incidences attained at both dosage levels as compared to controls (Table 4).

Table 4: Liver Neoplastic Findings

MALES	Control	25 mg/kg	50 mg/kg
Neoplastic Nodules			
Main Study Total	1/52 (2%)	6/52 (12%)	7/52 (13%)*
Terminal Rates°	1/43 (2%)	6/38 (16%)	7/40 (18%)*
Ancillary Study	0/25 (0%)	0/24 (0%)	1/25 (4%) [a]
Overall Rates †	1/77 (1%)	6/76 (8%)	8/77 (10%)*
Hepatocellular Carcinoma			
Main Study Total	0/52 (0%)	0/52 (0%)	1/52 (2%)
Terminal Rates°	0/43 (0%)	0/38 (0%)	1/40 (2%)
Ancillary Study	0/25 (0%)	0/24 (0%)	0/25 (0%)
Overall Rates †	0/77 (0%)	0/76 (0%)	1/77 (1%)
Neoplastic Nodules and Carcinoma - Combined			
Main Study Total	1/52 (2%)	6/52 (12%)	8/52 (15%)*
Terminal Rates°	1/43 (2%)	6/38 (16%)*	8/40 (20%)*
Ancillary Study	0/25 (0%)	0/24 (0%)	1/25 (4%) [a]
Overall Rates †	1/77 (1%)	6/76 (8%)	9/77 (12%)*
FEMALES: Neoplastic Nodules			
Main Study Total	6/52 (12%)	6/52 (12%)	10/52 (19%)
Terminal Rates°	5/34 (15%)	4/36 (11%)	10/38 (26%)
Ancillary Study	0/25 (0%)	2/25 (8%)	2/25 (8%) [b]
Overall Rates †	6/75 (8%)	8/77 (10%)	12/77 (16%)

In females, the frequency of mammary gland adenoma or fibroadenoma in the treated groups was not significantly (P = 0.052) higher than that of the controls. A positive trend increase in neoplasms of the thyroid was observed in the treated females but statistical significance was not attained.

Table 5: Mammary Gland and Thyroid Neoplasms - Females

Mammary Gland Adenoma or Fibroadenoma			
Main Study Total	15/52 (29%)	20/52 (38%)	24/52 (46%)
Terminal Rates°	11/34 (32%)	17/36 (47%)	20/38 (53%)
Ancillary Study	2/12 (17%)	3/11 (27%)	4/12 (33%) [c]
Overall Rates †	17/64 (27%)	23/63 (37%)	28/64 (44%)
Thyroid Follicular Cell Adenoma or Carcinoma			
Main Study Total	0/52 (0%)	2/52 (4%)	4/52 (8%)
Terminal Rates°	0/34 (0%)	2/36 (6%)	3/38 (8%)
Ancillary Study	0/23 (0%)	0/25 (0%)	1/25 (4%) [a]
Overall Rates †	0/75 (0%)	2/77 (3%)	5/77 (6%)

(°) Findings in animals at terminal sacrifice
(†) Pooled results from the 2-year and the ancillary studies
(a) Finding at 24-month period
(b) Findings at 27-month period
(c) Found in 1, 1, and 2 animals sacrificed at 21, 24, and 27 months, respectively

In male rats, the frequency of pheochromocytoma in the treated groups was higher than controls but statistical differences were found only at the low dose group (25 mg/kg). This neoplasm may be compound-related but a dose-response relationship was not evident from the submitted data.

Table 6: Pheochromocytoma - Males

	Control	25 mg/kg	50 mg/kg
Main Study Total	2/52 (4%)	8/52 (15%)*	6/52 (12%)
Terminal Rates°	2/43 (5%)	8/38 (21%)*	3/40 (7%)
Ancillary Study	2/25 (8%)	6/25 (24%)	4/24 (17%)[a]
Overall Rates †	4/77 (5%)	14/77 (18%)*	10/76 (13%)

(°) Findings in animals at terminal sacrifice
(†) Pooled results from the 2-year and the ancillary studies
(a) 1 finding at each of the 16, 21, 24, and 27 month intervals
(*) $P < 0.05$, Fischer's Exact Test

Other incidences of neoplastic findings were neither statistically nor biologically different from controls.

DISCUSSION

1. Chronic Toxicity

Administration of Technical Telone II up to and including a dosage level of 50 mg/kg for 104 weeks did not affect survivability, weight gain, and hematology in the treated animals of either sex. However, compound-related decreases in serum cholinesterase levels were observed in females of the 25 and 50 mg/kg groups at week 17 through week 69. Significant decreases in lactic acid dehydrogenase were also noted in both sexes of the 50 mg/kg dosage level. Compound-related increases in forestomach basal cell hyperplasia were noted in both males and females. This pathological finding was noted in 3%, 14%, and 35% males and 0%, 6%, and 40% females of the 0, 25, and 50 mg/kg groups, respectively. Increased kidney nephropathy findings were also found in treated females, being 29%, 48%, and 48% for the 0, 25, and 50 mg/kg groups, respectively.

Based upon the above findings, the systemic NOEL is determined to be < 25 mg/kg (lowest dose tested). The chronic section of this study is classified as Core Supplementary Data (only two dose levels tested; animals gavaged for only 3 days/week; lack of ophthalmology, urinalysis, and food consumption data; clinical chemistry and hematology not performed at study termination).

2. Oncogenicity

Statistically significant and dose-related increases in the frequency of several neoplasms were observed in this study.

Forestomach:

Statistically significant and compound-related increases in the incidences of squamous cell papillomas were noted in both males and females and squamous cell carcinomas noted in males. Squamous cell papilloma is uncommon in female rats (historical data = 0.4%), hence, findings of this neoplasm in the treated females (Table 3) must be regarded as compound-related.

Liver

A positive trend increase in neoplastic nodules was found in the treated males (Table 4). Incidences of neoplastic nodules in treated females were not significantly different from vehicle control females when data from the two-year study were either evaluated separately or combined with those of the ancillary study.

Mammary Gland

The incidence of mammary gland adenoma or fibroadenoma was not significantly different from control (Table 5) when data from the 2-year study were either evaluated separately or combined with those of the ancillary study (Table 5).

Thyroid

Positive trend increase in thyroid follicular cell adenomas or carcinomas was noted in the treated females. However, statistically significant differences were not attained for both dosage levels. No difference in thyroid neoplasm incidence was found in treated males.

One important factor that has to be taken into consideration is the presence of the stabilizer epichlorohydrin (1%) used in Telone II. Epichlorohydrin is a known mutagen and carcinogen. Forestomach squamous cell papillomas were found in Wistar rats fed with 750 or 1500 ppm epichlorohydrin in drinking water (Konishi et al., 1980). Wester et al. (1984) also reported that squamous cell carcinomas or papillomas of the forestomach were found in both male and female rats gavaged with epichlorohydrin at 2 mg/kg/day for 104 weeks. In this NTP investigation with Telone II, squamous cell papillomas and carcinomas of the forestomach were also observed in both male and female rats. However, neoplasms other than forestomach squamous cell papillomas and carcinomas were also found: increased liver neoplastic nodules in males and increased thyroid follicular cell adenomas or carcinomas in females. The presence of these neoplasms suggest that both 1,3-dichloropropene and epichlorohydrin are positive oncogens. Since squamous cell papillomas and carcinomas of the forestomach were found in all three studies involving epichlorohydrin, it can be concluded that epichlorohydrin used as a stabilizer in Telone II (1%) may have a contributive role to the positive oncogenic effect of Telone II.

It is recommended that the oncogenic section of this study be classified as Core Minimum Data and there is sufficient evidence to indicate that Telone II (1% epichlorohydrin) is a positive oncogen in the rat at 25 and 50 mg/kg/day.

It should be noted that according to the Confidential Statement of Formula submitted to the Agency on 2/28/85 (EPA Reg. No. 464-511), the registrant (Dow Chemical) has proposed to substitute epichlorohydrin with [redacted] Therefore, it is suggested that chronic/oncogenic studies should be conducted with the new Telone formulation to fully understand the oncogenic potential of this chemical.

II. CARCINOGENICITY - B6C3F$_1$ MICE

PROCEDURES

Test Material: Telone II Technical 92% (a mixture of cis-1,3-dichloropropene 45%, trans-1,3-dichloropropene 47%, epichlorohydrin 1%, 1,2-dichloropropane 2%, [redacted]

Dose levels: 0, 50, or 100 mg/kg in corn oil via gavage (5 ml/kg) 3 times/week (Monday, Wednesday, Friday) for 104 weeks

A copy of the procedures used is appended. The following comments are noted:

1. Three shipments of mice were received at Frederick Cancer Research Center at 2-week intervals. Randomized distribution of the animals was not performed: animals of the vehicle control group were from the first shipment whereas those of the 50 mg/kg were from the first and second shipments and those of the 100 mg/kg group were from the second and third group of animals. Consequently, disparity relative to the initial weight and age of the animals among all groups was evident in this study and restricted its usefulness.

2. Clinical chemistry and hematology determinations were not conducted in the mouse study.

RESULTS

1. Mortality

The survival data are presented in Table 6.

Table 6: Mice Survivability Data

	Control	50 mg/kg	100 mg/kg
# animals initially on test per sex	50	50	50
# non-accidental deaths[a] after one year			
Male	27	3	3
Female	0	0	3
Mortality Rate (%) for the first year			
Male	54	6	6
Female	0	0	6
# non-accidental deaths[a] before study termination			
Male	42	22	19
Female	4	5	14
Mortality Rate (%) over 2 years			
Male	84	44	38
Female	8	10	28

(a) including animals killed in a moribund condition

PRODUCT IMPURITY INFORMATION NOT INCLUDED

Twenty five (50%) of control male mice died during the period weeks 48-51. The investigators stated that suppurative inflammation of the heart (myocarditis) was the causative factor. During the entire investigation, myocarditis was diagnosed as the cause of death for 39, 13, and 5 animals of the control, low, and high dose groups, respectively. It is unclear as to why the outbreak of myocarditis apparently was mostly confined to control males. Nevertheless, due to excessive mortality encountered in the control males, only 8 were remained to be sacrificed at study termination. The limited number of control males at study termination would therefore restrict the statistical reliability as well as the biological significance of all findings in this investigation.

2. Body weights

Differences in initial body weights were noted between the control and 100 mg/kg group (13% and 22% less than control weight for males and females, respectively) and apparently were the results of the non-randomization process. The body weight gain data is presented in the following table.

Table 7: Body Weight Gain Data - Mice (grams)

	Control	50 mg/kg	100 mg/kg
MALES			
Weeks 0-52	17	18	17
Weeks 0-100	17	18	18
FEMALES			
Weeks 0-52	14	13	16
Weeks 0-100	17	15	19

Significant differences relative to body weight gains were not observed in any of the treated groups for either sex.

3. Neoplastic Findings

(Reviewer's note: In this report, tumor incidences were analyzed and statistically compared among all groups using N as the total number of animals initially placed on study (50 animals/sex/group). However, the reader is reminded that over 50% of control males died during the first year, a time when neoplastic lesions are not expected to occur. Hence, in this memo, the neoplastic findings in the treated groups must be compared with the historical control male incidences.

Table 8: Urinary Bladder Transitional Cell Carcinomas

FEMALES	Control	50 mg/kg	100 mg/kg
Terminal Rates°	0/46 (0%)	7/45 (16%)*	19/35 (54%)*
Overall Rates	0/50 (0%)	8/50 (16%)*	21/48 (44%)*

(°) Findings in animals at terminal sacrifice
(*) $P < 0.05$; Fischer's Exact Test

A positive trend increase in urinary bladder transitional cell carcinomas was noted in females as shown in table 8 above. The incidences in the treated groups.

were significantly different from the vehicle control group.
In males, this urinary bladder neoplasm was noted in two animals of the highest dose group (100 mg/kg) and none in the control and 50 mg/kg groups.

Table 9: Hepatocellular Adenomas or Carcinomas

	Control	50 mg/kg	100 mg/kg	Histo. Data[a]
Hepatocellular Adenomas				
Male, Terminal Rate°	0/8 (0%)	1/28 (4%)	2/31 (6%)	
Overall Rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	12.3%
Female, Terminal Rate°	0/46 (0%)	4/45 (9%)	2/36 (6%)	
Overall Rate	0/50 (0%)	5/50 (10%)	3/50 (6%)	4.0%
Hepatocellular Carcinomas				
Male, Terminal Rate°	1/8 (13%)	5/28 (18%)	7/31 (23%)	
Overall Rate	4/50 (8%)	6/50 (12%)	10/50 (20%)	20.5%
Female, Terminal Rate°	1/46 (2%)	3/45 (7%)	0/36 (0%)	
Overall Rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	2.9%
Hepatocellular Carcinomas and Adenomas				
Male, Terminal Rate°	1/8 (13%)	6/28 (21%)	9/31 (29%)	
Overall Rate	5/50 (10%)	7/50 (14%)	13/50 (26%)	31.4%
Female, Terminal Rate°	1/46 (2%)	7/45 (16%)	2/36 (6%)	
Overall Rate	1/50 (2%)	8/50 (16%)	3/50 (6%)	6.8%

(°) Findings in animals at terminal sacrifice
(a) provided by NTP; data as of 3/16/83 and comprised of data from over 1000 male and female mice gavaged with corn oil in studies of at least 104 weeks.

The incidences of hepatocellular adenomas, carcinomas, and adenomas and carcinomas combined, of the treated males were within the historical range provided. However, primary comparison is to concurrent controls and a dose-response increase in this neoplasm in males at terminal sacrifice (13%, 21%, and 29%) as well as in overall rate (10%, 14%, and 26%) was noted. Findings of hepatocellular adenomas and carcinomas were significantly increased in females in the 50 mg/kg group but not in those at the 100 mg/kg dosage level.

Table 10: Forestomach, Squamous Cell Papillomas or Carcinomas

Stomach, Squamous Cell Papilloma				
Male, Terminal Rate°	0/8 (0%)	1/28 (4%)	1/31 (3%)	
Overall Rate	0/50 (0%)	2/50 (4%)	3/50 (6%)	0.6%
Female, Terminal Rate°	0/46 (0%)	1/45 (2%)	2/36 (6%)	
Overall Rate	0/50 (0%)	1/50 (2%)	2/50 (4%)	0.3%
Stomach, Squamous Cell Carcinomas				
Male, Terminal Rate°	0/8 (0%)	0/28 (0%)	0/31 (0%)	
Overall Rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	0.1%
Female, Terminal Rate°	0/46 (0%)	0/45 (0%)	2/36 (6%)	
Overall Rate	0/50 (0%)	0/50 (0%)	2/50 (4%)	0.1%

Table 10: Forestomach Squamous Cell Papillomas or Carcinomas (con't)

	0 mg/kg	50 mg/kg	100 mg/kg	Hist.Cont
Squamous Cell Papillomas and Carcinomas				
Male, Terminal Rate°	0/8 (0%)	1/28 (4%)	1/31 (3%)	
Overall Rate	0/50 (0%)	2/50 (4%)	3/50 (6%)	0.6 %
Female, Terminal Rate°	0/46 (0%)	1/45 (2%)	3/36 (8%)	
Overall Rate	0/50 (0%)	1/50 (2%)	4/50 (8%)	0.6%

(°) Findings in animals at terminal sacrifice

Squamous cell carcinomas or papillomas of the forestomach were not found in the control group of either sex and occurred at a very low incidence (0.6%) in the historical control data provided. Increases in this neoplasm were noted in both sexes of treated groups. Findings of these neoplasms apparently were compound-related.

Table 11: Lung Alveolar/Bronchiolar Adenoma or Carcinoma

Lung Adenomas				
Male, Terminal Rate°	0/8 (0%)	7/28 (25%)	7/31 (23%)†	
Overall Rate	1/50 (2%)	11/50 (22%)	9/50 (18%)†	9.1%
Female, Terminal Rate°	0/46 (0%)	3/45 (7%)	7/36 (19%)*	
Overall Rate	0.50 (0%)	3/50 (6%)	8/50 (16%)*	3.3%
Lung Carcinomas				
Male, Terminal Rate°	0/8 (0%)	2/28 (7%)	1/31 (3%)	
Overall Rate	0/50 (0%)	2/50 (4%)	3/50 (6%)	5.4%
Female, Terminal Rate°	2/46 (4%)	1/45 (2%)	0/36 (0%)	
Overall Rate	2/50 (4%)	1/50 (2%)	0/50 (0%)	1.5%
Lung Carcinomas and Adenomas				
Male, Terminal Rate°	0/8 (0%)	9/28 (32%)	8/31 (26%) †	
Overall Rate	1/50 (2%)	13/50 (26%)	12/50 (24%)†	14.3%
Female, Terminal Rate°	2/46 (4%)	4/45 (9%)	7/36 (19%)*	
Overall Rate	2/50 (4%)	4/50 (8%)	8/50 (16%)*	4.7%

(°) Findings in animals at terminal sacrifice
(*) $P < 0.05$; Fischer's Exact Test
(†) Fischer's Exact Test not performed for males.

In the male, compound-related and significant increases in the incidences of lung adenomas and combined lung adenomas and carcinomas were found as compared to the concurrent control terminal rate as well as to the historical control range provided. Statistically significant increases in the incidences of lung adenomas and lung adenomas/carcinomas were also noted in females of the 100 mg/kg group.

5. Non-Neoplastic Findings

Compound-related increases in the incidences of hyperplasia of the urinary bladder, hyperplasia of the stomach, hydronephrosis, and hyperplasia of the uterus were found in treated animals as summarized in the next table:

Table 12: Non-Neoplastic Findings

	Control	50 mg/kg	100 mg/kg
Urinary Bladder, hyperplasia			
Males	0/50	9/50 (18%)	18/50 (36%)
Females	2/50 (4%)	15/50 (30%)	19/50 (40%)
Stomach, Hyperplasia Epithelial			
Males	0/50	0/50	4/50 (8%)
Females	1/50 (2%)	1/50 (2%)	21/50 (42%)
Uterus, Hyperplasia			
Females	4/50 (8%)	3/50 (6%)	9/50 (18%)
Hydronephrosis			
Males	1/50 (2%)	0/50	0/50
Females	0/50	2/50 (4%)	14/50 (28%)

DISCUSSION

MOUSE STUDY

The differential survival noted in this study, especially for control males, complicates and may lead to serious misinterpretation of data from this investigation. Due to the limited number of control males at final sacrifice (8), determination of the oncogenic potential of Telone in mice has to be based on both the concurrent as well as the historical control data provided. The deficiency in animal randomization at study initiation further complicates the evaluation process and impairs the utility of this study.

Comparable body weight gains were noted in the treated groups up to and including a dosage level of 100 mg/kg. No clinical or hematologic investigations were conducted in this study.

Target organ toxicity and oncogenesis were found in both the 50 and 100 mg/kg groups.

a) Forestomach

Squamous cell papilloma or carcinoma was not found in the concurrent control of either sex and occurred at a very low frequency in the historical control data (0.6%). Squamous cell carcinoma was not found in any male, control female, and low dose female groups. However, 2 females of the 100 mg/kg group were

associated with this neoplasm. Squamous cell papilloma was noted in 2 and 3 males, and in 1 and 2 females in the 50 and 100 mg/kg groups, respectively. In the absence of similar findings in the concurrent control, forestomach squamous cell papillomas and carcinomas observed in the treated male and female mice apparently were compound-related.

b) Liver

Positive trend increases in hepatocellular adenomas or carcinomas were found in the treated groups. At terminal sacrifice, hepatocellular adenoma was noted in males at 0%, 4%, and 6%, and in females at 0%, 9%, and 6% in the groups receiving 0, 50, and 100 mg/kg, respectively. Respectively, hepatocellular carcinoma was noted at 13%, 18%, and 23% in males and at 2%, 7%, and 0% in females terminally sacrificed. Since over 50% of control males died during the first year, a time when neoplastic lesions are not expected to occur, all findings must also be compared with the historical control data. The historical control listed incidences of 12.3% and 20% for male adenoma and carcinoma, respectively, and 4% and 2.9% for female adenoma and carcinoma, respectively. Therefore, although the incidence of male carcinoma was statistically increased at the 100 mg/kg dosage level as compared to concurrent control values, it was statistically comparable to the historical control data. In females, the incidences of hepatocellular adenomas or carcinomas when evaluated separately or combined did not follow a dose response relationship. Thus, these findings in female mice were of questionable toxicologic importance.

c) Urinary Bladder

Transitional cell carcinomas were detected in 4% of high dose males and 16% and 44% in females of the low and high dose groups, respectively. This neoplasm is considered as rare in this species as illustrated by a zero incidence in both the concurrent and historical control data (over 1000 animals/sex). The findings of transitional cell carcinomas were thus associated with the administration of Teione. In conjuction with this finding, hyperplasia of the urinary bladder was increased in both males and females of the treated groups.

d) Lung

Significant increases in alveolar/bronchiolar adenomas or carcinomas were found in the treated groups. Compound-related increases in alveolar/bronchiolar adenomas were found in both treated males and females. No evidence of increased incidences of alveolar/bronchiolar carcinoma was noted in treated males and females. When the neoplasms of the lung were evaluated together, positive trend increases were noted for both males and females. The combined incidences of lung adenoma and carcinoma were 2%, 26%, and 24% for males, and 4%, 8%, and 16% for females of the 0, 50, and 100 mg/kg dosage levels, respectively.

e) Non-neoplastic findings

Compound-related increases in urinary bladder hyperplasia were found in both males and females and in stomach hyperplasia and kidney hydronephrosis in females.

Although several deficiencies in the mouse study design and conduct were noted, there is some evidence to suggest that Telone II is an oncogen when compared with data from both concurrent control and historical control data provided. There is sufficient evidence of oncogenicity in female mice as characterized by increased incidences of alveolar/bronchiolar adenomas, forestomach squamous cell papillomas or carcinomas, and transitional cell carcinomas of the urinary bladder. In the male, there is limited evidence of oncogenicity (due to excessive mortality in control animals) as characterized by increased incidences of forestomach squamous cell papillomas, transitional cell carcinomas of the urinary bladder, and alveolar/bronchiolar adenomas and carcinomas. However, the differential survival noted in the control males and the lack of randomization at study initiation impair the validity of this mouse investigation. It is recommended that this mouse oncogenic study be classified as Core Supplementary Data.

It should be noted that forestomach squamous cell papilloma/carcinoma was also observed in this mouse study. As indicated previously in the rat study, these types of neoplasm were also observed in rats treated with epichlorohydrin (Konishi et al., 1980, Wester et al., 1984). Therefore, the possibility that the stabilizer epichlorohydrin used in Telone II may have a contributive role to the positive oncogenic effect of Telone II could not be neglected.

All neoplastic findings in the rat and mouse reported in this memo are in consent with Louis Kasza, DVM, Ph.D., Toxicology Branch Pathologist.

REFERENCES

Konishi, Y., Kawabata, A., Denda. A. et al., 1980. Forestomach tumors induced by orally administered epichlorohydrin in male Wistar rats. Gann 71: 922-923.

Wester p.W., Van der Heijen, C.A., Bisschop A., and Van Esch, G.J.,: Carcinogenicity study with Epichlorohydrin. Final report No. 627805 005, Rijksinstituut voor volksgezondheid en millieuhygiene, September 24, 1984.

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II® (a)

EXPERIMENTAL DESIGN	
Size of Test Groups	52 male and 52 female rats; 50 male and 50 female mice
Doses	Rats--0, 25, or 50 mg/kg Telone II® in corn oil via gavage 3 x wk; mice--0, 50, or 100 mg/kg; dose vol: 5.0 ml/kg for both species
Date of First Dose	Rats--2/25/77; mice--7/7/78
Date of Last Dose	Rats--2/21/79; mice--7/2/80
Duration of Dosing	104 wk; 3 × wk (Mon., Wed., Fri.)
Type and Frequency of Observation	Observed 2 × d for moribundity and mortality; clinical exam and palpation for masses--1 × wk; weighed 1 × wk
Necropsy and Histologic Examination	Necropsies, consisting of gross examination of major tissues, major organs and all gross lesions, performed on all animals. Tissues/organs examined histopathologically: gross lesions and tissue masses, blood smears, submandibular and mesenteric lymph nodes, salivary glands, femur (including marrow), thyroid, parathyroids, small intestine (one section), colon, liver, prostate/testes or ovaries/uterus, lungs and bronchi, mammary gland, skin, esophagus, stomach, brain (cerebellum and cerebrum), heart, thymus, trachea, pancreas, spleen, kidneys, adrenals, urinary bladder, pituitary, gallbladder (mice only)
ANIMALS AND ANIMAL MAINTENANCE	
Species	F344/N rats and B6C3F$_1$ mice
Animal Source	Frederick Cancer Research Center (Frederick, MD)
Testing Laboratory	Frederick Cancer Research Center (Frederick, MD)
Time Held Before Start of Test	Rats--3 wk; mice--2-5 wk
Age When Placed on Study	Rats--6 wk; mice--6-10 wk
Age When Killed	Rats--112-113 wk; mice--111-117 wk
Necropsy Dates	Rats--3/6/79-3/20/79; mice--7/10/80-7/25/80
Method of Distribution	Rats--assigned to cages so that average cage weights were approximately equal; mice--assigned to control (first shipment), low dose (first and second shipments), and high dose (second and third shipment) groups as animals arrived
Feed	Wayne Sterilizable Lab meal (Allied Mills, Chicago, IL) ad libitum in suspended stainless steel hoppers
Bedding	None; stainless steel wire grids (Lab Products, Rochelle Park, NJ) were placed in the bottom of the cages
Water	Acidified to pH 2.5 with HCl; available ad libitum from glass bottles; changed 2 × wk

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II[a] (CONTINUED)

ANIMALS AND ANIMAL MAINTENANCE (Continued)	
Cages	Polycarbonate (Lab Products, Inc., Garfield, NJ)
Cage Filters	Nonwoven polyester fiber (Hoeltge, Inc., Cincinnati, OH)
Animals per Cage	Rats—4; mice—5
Animal Room Environment	Rats—temp 22°-24°C; rel humidity about 45%-55%; 15 changes room air/h; 12 h fluorescent light/d; mice—same as rats but 12-15 room air changes/h and 10 h light and 14 h dark cycles
Other Chemicals on Test in Same Room	None
CHEMISTRY	
Lot Numbers Used	EXP-N-3993
Supplier	Dow Chemical USA (Freeport, TX)
CHEMICAL/VEHICLE	
Preparation	Appropriate amounts of Telone II® and corn oil were mixed to give the desired concentrations. The solutions were homogenized for 1-2 minutes in a Lourdes® blender
Maximum Storage Time	Freshly prepared each day of dosing
Storage Conditions	Not stored

(a) Documentation not available for short-term studies; see text for the experimental design of the ancillary studies.

STUDY REVIEW

004645

Chemical: Telone II ; 1,3-Dichloropropene
Test Material: cis 1,3-Dichloropropene
Study/Action Type: Chronic/Oncogenic

STUDY IDENTIFICATION:

"Carcinogenicity of Halogenated Olefinic and Aliphatic Hydrocarbons in Mice"

Testing Facility: New York University Medical Center
New York, New York 10016
Study Authors: Van Duuren et al.,
Final Report No.: Dow Chemical Co. Reference No. 54
Final Report Date: Article published in JNCI, Vol. 63, No. 6, pp. 1433-1439
December 1979
EPA Accession No.: 255013

Study Reviewed by: Quang Q. Bui, Ph.D.
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Review Approved by: Laurence D. Chitlik, D.A.B.T.
Section Head
Toxicology Branch/HED (TS-769C)

CORE CLASSIFICATION

It is recommended that this study be classified as Core Supplementary Data. The experiment was only designed to investigate the carcinogenic potential of one dosage level of cis 1,3-Dichloropene after dermal or subcutaneous injection in female Swiss mice. The results were summarized and tabulated for journal publication and, hence, did not contain necessary data as would be expected from a study submitted for registration purposes (i.e., body weight data, food consumption, clinical chemistry, histopathology, necropsy data, hematology,...).

PROCEDURES

Test Material: Cis 1,3-Dichloropropene, purified (percentage a.i., unknown)
Species: Female Ha:ICR Swiss Mice

a) Skin Initiation Promotion Experiments:

Cis 1,3-Dichloropropene was applied to the shaved dorsal skin of female mice (30 animals) at 122 mg/mouse/application in 0.2 ml acetone followed 14 days later by 5 ug of phorbol myristate acetate (PMA) in 0.2 ml acetone three times weekly for 428 to 576 days. Days to first tumor appearance was recorded.

b) Repeated Application

122 mg/mouse of cis 1,3-Dichloropropene was applied to the shaved dorsal skin of female mice (30 per group) three times weekly in 0.2 ml acetone. All animals were sacrificed at study termination (from 440 - 594 days) and a complete necropsy was performed.

c) Subcutaneous Injection

Thirty female mice received weekly injection of cis 1,3-Dichloropropene (3 mg/mouse) in 0.05 ml trioctanoin in the left flank. The duration of the test was 538 days.

RESULTS

The carcinogenic potential of cis 1,3-Dichloropropene after repeated dermal exposure apparently was negative in female Swiss mice. Concurrent administration of the promoting agent PMA with cis 1,3-Dichloropropene was also inactive.

	Control	Cis 1,3-DCP
Initiation Promotion Experiment		
Skin papillomas	9/120	4/30
Repeated Dermal Application		
Lung tumors (benign)	30/100	17/30
Forestomach, papillomas	5/100	0/30
Skin papillomas and carcinomas	0/100	1/30
Subcutanous Injection		
Fibrosarcomas	0/100	6/30

The investigators stated that the number of animals with skin papillomas after cis-1,3-DCP treatment in the initiation promotion experiment was not significantly different from controls. In the repeated dermal application

study, 1/30 treated female mice had skin papillomas or carcinomas. Statistical significance was not attained at the 0.05 level.

Positive findings in fibrosarcomas at the site of injection were noted in the subcutaneous injection experiment. Six out of 30 mice treated with cis-1,3-DCP were described with this neoplasm as compared to 0/100 control animals.

DISCUSSION AND CONCLUSIONS

Weekly injections of 3 mg/mouse of cis 1,3-Dichloropropene in 0.05 ml of trioctanoin for 538 days produced fibrosarcomas at the site of injection (left flank) in 6/30 female Swiss mice. Under the conditions of this experiment, it may be concluded that cis 1,3-Dichloropropene increased the incidence of this neoplasm (fibrosarcomas) at the site of subcutanous injection.

Since all reported findings were summarized and tabulated for journal publication, the authors' conclusion as well as the statistical tests used could not be confirmed or verified.

It is recommended that this study be classified as Core Supplementary Data. This study cannot be upgraded in light of numerous deficiencies (lack of body weight data, food consumption, hematology, clinical chemistry, necropsy, histopathology, etc.,...).