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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Interim reports for Telone II chronic inhalation study
EPA No. 464-379 Caswell No. 324 A
EPA Accession No. 260227 and 260228

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

FROM: Quang Q. Bui, PhD., DABT., Quang Q Bui 3/26/86
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Laurence D. Chitlik, DABT., 3/26/86
Section Head, Toxicology Branch
Hazard Evaluation Division (TS-769C) 3/31/86
and
Theodore M. Farber, PhD., DABT.,
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant:
The Dow Chemical Company
Midland, Michigan 48640

Action Requested:

Review of interim reports of the 2-year inhalation chronic/oncogenicity study with Telone II in mice (Accession No. 260228) and rats (Accession No. 260227) - Data submission for EPA data call-in 7/5/84.

RECOMMENDATION:

1. The mouse report only consists of data collected from ten mice per sex per dose level sacrificed at 6 or 12 months exposure and, hence, does not include all of the data which normally should be found in an interim report. It is recommended that, in its present format, this submission is considered as incomplete.

2. It is recommended that the rat interim report be classified as Core Supplementary Data. No mortalities or clinical signs were noted in any treated groups. Additionally, biologically and/or statistically significant variations in clinical chemistry, hematology, body weights, organ weights, urinalysis, and histopathology were not found in both males and females exposed to 5, 20, or 60 ppm Telone II vapor for 6 and 12 months. These findings demonstrate that, at least after 12 months of exposure, the highest dose used (60 ppm) did not elicit minimal signs of systemic toxicity. Nevertheless, determination of whether a maximum tolerated dose has been reached must await the submission of the full 2-year final report.

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MATERIALS PRODUCT IMPURITY INFORMATION IS NOT INCLUDED

Test Chemical: Telone II, lot No. T3831213-4, 92.1% :

[redacted]

Animals: Male and female B6C3F1 mice, 5-6 weeks of age, purchased from Charles River Lab. (Portage, MI)

STUDY DESIGN

Groups of 70 male and 70 female mice were exposed to Telone II vapor for 6 hours/day, 5 days/week, at 0, 5, 20, or 60 ppm. Ten mice per sex per dose group were sacrificed at 6 and 12 months after exposure. Only data collected from those animals are reported with this submission.

Exposures were conducted in 14 m^3 live-in chambers. The airflow through the chambers was maintained at approximately 2500 liters per minute. Temperature and humidity of the chambers were recorded during each exposure period. Food (Purina Certified Rodent Chow) and water (municipal water supply) were supplied ad libitum except during the inhalation exposure periods.

PROCEDURES

A copy of the study procedures is attached. When the study procedures were compared to §83-5 (chronic/oncogenic study) of the 1982 FIFRA Guidelines, the following deviations are noted:

1. Urinalysis was not conducted at 6 and 12 months.
2. Food and water consumption were not reported although they should be determined weekly during the first 13 weeks of the study and monthly thereafter.
3. Blood electrolytes were not determined.

Additionally, data generated from the main study (50 mice/sex/dose) were not included with this submission.

RESULTS

1. Analytical Determinations

The authors indicated that the analytical concentration of Telone II in each exposure chamber was measured at least once per hour using an infrared spectrometer. Nominal concentration was also calculated for each chamber on a daily basis.

The targeted concentrations of Telone II were 5, 20, and 60 ppm (corresponding to 22.7, 90.8, and 272.4 mg/m^3, respectively). The means analytical and nominal concentration of Telone II determined during the first 12 months of the study were within the acceptable ranges of the targeted concentrations. No significant

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DATA EVALUATION RECORD

Chemical: 1,3-dichloropropene
Test Material: Telone II, 92.1%
Study/Action Type: Inhalation chronic/oncogenic

STUDY IDENTIFICATION:

"Telone II soil fumigant: 2-year inhalation chronic toxicity-oncogenicity study in mice - Interim report: 6- and 12-month exposure".

Testing Facility: Dow Chemical Co.,
Project No.: Not stated
Report Date: 9/27/85
Study Authors: Yano, BL., Calhoun, LL., Stott, WT. et al.,
EPA Accession No.: 260228

Reviewed by: Quang Q. Bui, PhD., DABT.,
Toxicologist, Section V
Toxicology Branch/HED (TS-769C)

Approved by: Laurence D. Chitlik, DABT.,
Section Head, Section V
Toxicology Branch/HED (TS-769C)

CONCLUSIONS AND RECOMMENDATION:

After 12 months of exposure to Telone II, an apparent compound-related increase in the incidences of hyperplasia and hypertrophy of the epithelial cells of the nasal turbinates was noted in male mice exposed to 20 ppm and in both males and females exposed to 60 ppm. Additionally, decreased vacuolation of the kidney and liver cells was found in the 60 ppm males. Slight to moderate hyperplasia of the urinary bladder epithelial cells was also observed in females exposed to 60 ppm after 6 and 12 months. Statistically significant decreases in body weights and body weight gains were noted in females exposed to 60 ppm Telone II for 12 months but not in males.

This report only consists of data collected from 10 mice per sex per dose level sacrificed at 6 or 12 months exposure and, hence, does not include all of the data which normally should be found in an interim report. For example, body weight and clinical observation data from mice of the main study (50 per sex per dose level) should have been incluced and reported. Therefore, in its present format, this submission is considered as incomplete.

It should also be noted that although this investigation is considered as a chronic/oncogenic study by the registrant, a number of parameters pertaining to chronic toxicity testing as listed under §83-5 of the 1982 FIFRA Guidelines were omitted from the study procedures (see "Procedures" section).

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variations in either chamber temperature or relative humidity were noted.

Table 1: Exposure Concentrations to Telone II

Target Conc.	Analytical Conc.[a]	Coefficient of variation[b]	Nominal Conc.
5 ppm	5.0 ± 0.3 (5.0 ± 0.2)[c]	6% (4%)	5.3 ± 0.5 (5.4 ± 0.5)
20 ppm	20.2 ± 0.5 (20.1 ± 0.4)	2% (2%)	19.7 ± 0.9 (19.4 ± 0.9)
60 ppm	60.2 ± 0.7 (60.1 ± 0.9)	1% (1%)	59.7 ± 1.5 (58.8 ± 1.8)

(a) values are means ± SD. Daily time weighed average (TWA) for n = 129 days (6 months) or 254 days (12 months)
(b) standard deviation of daily TWA measurements divided by the mean (x 100)
(c) values in parenthesis = 12 months data

Reviewer's note: data discussed hereafter refer to only 10 mice per sex per dose group sacrificed at 6 or 12 months.

2. Clinical Observations and Mortality

All animals were observed twice daily for overt signs of toxicity. Moribund mice were sacrificed for necropsy examination and those found dead were refrigerated and necropsied as soon as possible.

Two control males and one 20 ppm male died during the first 12 months of the study. However, it is unclear as to whether additional deaths had occurred in the groups of the main study. The authors stated that no overt signs of clinical toxicity were observed in all groups. However, no individual data are available to substantiate the reported findings.

3. Body Weights

Body weights were recorded prior to study initiation, weekly for the first 13 weeks, and monthly thereafter.

a) 6-month exposure: Significant differences in body weights and body weight gains were not found between the treated and control groups for both males and females although mice of the high dose group gained slightly less than controls (8.0 g and 7.8 g for for high dose males and females, respectively, as compared to 9.5 and 8.3 g of controls).

b) 12-month exposure: Data on body weights and body weight gains of animals sacrificed at 12 months are presented in Table 2.

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Table 2: Body Weights (in grams) - 12-month Exposure

	Day -2		Day 174		Day 342	
	M	F	M	F	M	F
0 ppm	21.2	18.7	32.2	27.1	32.7	28.5
5 ppm	21.7	19.0	31.8	27.5	32.2	28.1
20 ppm	22.5	19.0	31.4	27.2	32.0	28.7
60 ppm	22.0	18.8	30.8	26.1	30.7	26.3*
BW Gain (in grams)						
0 ppm			11.0	8.4	11.5	9.8
5 ppm			10.1	8.5	10.5	9.1
20 ppm			8.9	8.2	9.5	9.7
60 ppm			8.8	7.3	8.7	7.5*

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

During the first 6 months of the study (from day -2 to 174), a slight decrease in weight gain was observed in both males and females of the 20 and 60 ppm groups. By day 342, a treatment- and dose-related decrease in weight gain was apparent in males and a statistically significant difference in weight gain was also noted in high dose females as compared to the controls. Since food consumption was not measured in this study, it is unclear as to whether the decrease in weight gain was related to food consumption.

3. Hematology

a) 6-month exposure: No treatment-related toxicologic effects were found in mice sacrificed after 6 months of exposure. A significant decrease in hemoglobin was found in high dose males but a similar finding was not detected in high-dose females.

b) 12-month exposure: In the groups exposed to Telone II vapor for 12 months, no biological or statistical significances in hematology were noted among the treated and control groups for both males and females.

4. Clinical Chemistry

a) 6-month exposure: A statistically significant increase in albumin from 2.5 $\pm$ 0.1 g/dl (control) to 2.6 $\pm$ 0.1 g/dl was noted in high dose males. However, consistent effects were not found in high dose females. A statistically significant decrease in globulin was also determined in high dose males (2.2 $\pm$ 0.1 of control vs 2.0 $\pm$ 0.2 g/dl of high dose males) but not in females. Other clinical chemistry parameters were neither statistically nor biologically different from controls.

b) 12-month exposure:

A statistically significant increase in albumin from 2.4 $\pm$ 0.1 (control) to 2.5 $\pm$ 0.1 g/dl was noted in high dose males but not in high dose females.

Other clinical chemistry parameters were similar between control and treated groups for both males and females.

5. Organ Weights

a) 6-month exposure: Decreases in absolute and relative heart, kidney, and liver weights were noted in both high dose males and females with statistically significant differences found only in males.

b) 12-month exposure: The significant differences in relative and absolute kidney and liver weights observed in high dose males sacrificed at 6 months were still evident in high dose males sacrificed after 12 months of exposure. Additionally, a significant decrease in absolute liver weight was found in 20 ppm males and a statistically significant increase in absolute testes weight was noted in high dose males. No alterations in absolute and relative organ weights were noted in the treated females.

6. Histopathology

a) 6-month exposure:

Hyperplasia and hypertrophy of the respiratory epithelium was noted in 1, 0, 3, and 10 males and 0, 0, 0, and 7 females of the 0, 5, 20, and 60 ppm, respectively. Moderate hyperplasia of the epithelial cells of the urinary bladder was noted only in the 60 ppm group affecting 1 male and 4 females. Seven out of 10 high dose males had decreased vacuolation of liver cells as compared to 0/10 controls while decreased vacuolation of kidney cells was noted in 9/10 high dose males as compared to 4/10 controls. Similar histopathologic changes in the kdineys and liver were not found in the treated females.

b) 12-month exposure:

Hyperplasia and hypertrophy of the respiratory epithelium found in animals sacrificed at 6 months was also present in 1, 0, 7, and 10 males and 0, 0, 0, and 8 females of the 0, 5, 20, and 60 ppm groups, respectively. Slight to moderate hyperplasia of the urinary bladder epithelial cells was found in 0, 0, 1, and 9 females in the groups exposed to, respectively, 0, 5, 20, and 60 ppm. Decreased vacuolation of kidney cells was noted in 9/10 high dose males as compared to 1/10 controls. Decreased vacuolation of liver cells was also found in 1/10 mid dose and 5/10 high dose males as compared to 1/10 controls. Similar histopathologic changes in the liver and kidneys were not observed in the treated females.

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. ISCUSSION

In this report, the registrant had submitted data pertaining only to groups of 10 mice per sex each exposed to 0, 5, 20, or 60 ppm and sacrificed after 6 and 12 months exposure. Theretore, in its present submission this report does not adequately represent data normally found in an interim report which should include data from all animals (70 animals/sex/group) studied.

Three animals of the pre-designated 12-month sacritice groups died, 2 control males and 1 male of the 20 ppm dosage level. However, it is unclear as to whether additional deaths had occurred in the main groups (50 animals/sex/dose level) of this study. No overt signs of toxicity were reported by the investigators but individual animal data are not available to substantiate the reported findings.

After 12 months of exposure, mice exposed to 60 ppm of Telone II exhibited treatment-related decreases in body weights and body weight gains. Compound-related histopathologic changes were noted in the kidney, liver, urinary bladder, and nasal turbinates of the treated animals. Hyperplasia and hypertrophy of the respiratory epithelium cells were present in males exposed to 20 ppm and in males and females exposed to 60 ppm sacrificed at 6 and 12 months. Slight to moderate hyperplasia of the urinary bladder epithelial cells was found in high dose females sacrificed at 6 and 12 months. Decreased vacuolation of the kidney and liver cells were observed in males exposed to 60 ppm but not in females. These histopathologic changes may correspond to the significant decreases in both absolute and relative weights of the kidneys and liver observed in the high dose males.

Variations in clinical chemistry were also noted in the high dose males as characterized by significant increases in albumin levels found in mice sacrificed at both 6 and 12 months exposure. The biological significance of these findings remains unclear pending the submission of the full 2-year report.

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____ 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.

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DATA EVALUATION RECORD

Chemical: 1,3-dichloropropene
Test Material: Telone II, 92.1%
Study/Action Type: Chronic/oncogenic

STUDY IDENTIFICATION:

"Telone II soil fumigant: 2-year inhalation chronic toxicity-oncogenicity study in rats - Interim report: 6-and 12- month interim sacritice of rats:.

Testing Facility: Dow Chemical Co.,
Project No.: Not stated
Report Date: 9/27/85
Study Authors: Sttot, WT., Lomax, LG., Calhoun, LL., et al.
EPA Accession No. 260227

Reviewed by: Quang Q. Bui, PhD., DABT.,
Toxicologist, Section V
Toxicology Branch/HED (TS-769C)

Approved by: Laurence D. Chitlik, DABT.,
Section Head, Section V
Toxicology Branch/HED (TS-769C)

CORE CLASSIFICATION: Supplementary Data (Interim Report)

CONCLUSIONS:

Statistically significant variations in clinical chemistry, hematology, body weights, organ weights, urinalysis, and histopathology were not found in both male and female rats exposed to 5, 20, or 60 ppm Telone II vapor for 6 and 12 months. Additionally, no mortalities and clinical signs were noted in any treated groups. These findings demonstrate that, at least after 12 months of exposure, the highest dose used (60 ppm) did not elicit minimal signs ot systemic toxicity. It should be noted, however, that for risk assessment and regulation purposes, the highest dose tested in a chronic/oncogenic investigation "should be sufficiently high to elicit signs of minimal toxicity without altering the normal life span" (1982 FIFRA Guidelines, §83-2) and "should elicit signs of toxicity without substantially altering the normal life span due to effects other than tumors" (1982 FIFRA Guidelines, §83-5).

Although this study was designed as a combined chronic/oncogenic investigation, a number of parameters as required by §83-5 ot the 1982 FIFRA Guidelines were not performed (see "Procedures" section). These deficiencies in conjunction with the absence ot a maximum tolerated dose may preclude the use ot this study in fulfilling regulatory requirements for chronic/oncogenic testing. Nevertheless, determination ot whether a maximum tolerated dose has been reached must await the submission of the full 2-year final report.

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MATERIALS PRODUCT IMPURITY INFORMATION NOT INCLUDED

Test Chemical: Telone II, Lot No. TB831213-4, 92.1%; [redacted]

Animals: Male and female Fischer 344 albino rats (6-8 weeks of age) purchased from Charles River (Kingston, NY.)

STUDY DESIGN

Groups of 70 animals per sex were exposed to Telone II vapor for 6 hours/day, 5 days/week, at 0, 5, 20, and 60 ppm. Ten animals per sex per dose level were sacrificed at 6 and 12 months after study initiation. Data collected from these pre-designated sacrifice groups are reported with this submission.

Inhalation exposures were conducted in live-in 14 m^3 epoxy-resin coated chambers having 15 air changes/hr (2500 L/min). Temperature and humidity of the chambers were monitored throughout the entire study. All animals had access to water and food (Purina certified rat chow #5002) ad libitum.

PROCEDURES

A copy of the study procedures is appended. When the study procedures were compared to §83-5 (chronic/oncogenic study) of the 1982 FIFRA Guidelines, the following deviations are noted:

1. Clinical observations for all animals were not submitted.
2. Blood total cholesterol and bilirubin levels were not performed.
3. Blood electrolytes were not measured.
4. Food and water consumption were not reported although they should be determined weekly during the first 13-weeks of the study and monthly thereafter.

RESULTS

1. Analytical Determinations

The targeted concentrations of Telone II were 5, 20, and 60 ppm (22.7, 90.8, and 272 mg/m^3, respectively). The nominal and analytical concentrations of Telone II in the chamber determined during the first 12 months of the study are tabulated on the next page. Significant deviations from the targeted concentrations were not observed. Furthermore, no significant variations in either chamber temperature or relative humidity were noted.

Telone II: Exposure Concentrations

Target Conc.	Analytical Conc.[a]	Coefficient of variation[b]	Nominal Conc.
5 ppm	5.0 ± 0.3 (5.0 ± 0.2)[c]	6% (4%)	5.3 ± 0.5 (5.4 ± 0.5)
20 ppm	20.2 ± 0.5 (20.2 ± 0.4)	2.5% (2%)	19.6 ± 0.9 (19.4 ± 0.9)
60 ppm	60.1 ± 1.0 (60.1 ± 0.9)	1.7% (1.5%)	59.7 ± 1.5 (58.8 ± 1.8)

(a) Values are means ± SD daily time-weighed average (TWA) for n = 128 days (6 month) and n = 254 days (12 months).
(b) Standard deviation of daily TWA measurements divided by the mean x 100
(c) Values in parenthesis = 12-month data

2. Clinical Observations and Mortality

The authors stated that all animals were observed twice daily for overt signs of toxicity and mortality. No mortalities and treatment-related toxic signs were reported. However, no individual animal data were submitted to substantiate the reported findings.

3. Body Weights

a) 6-month exposure (10 animals/sex/group)

Treatment-related effects were not evident from the data submitted for any dose groups. The body weight gains of the 0, 5, 20, and 60 ppm groups sacrificed after 6 months were, respectively, 215.5, 217.0, 216.1, and 203.5 g for males, and 98.8, 106.3, 99.9, and 94.8 g for females. The differences in weight gains observed in both high dose males and females were not significantly different from those of the respective controls.

b) 12-month exposure (10 animals/sex/group)

Males sacrificed after 12 months gained 255.6, 285.3, 267.4, and 262.3 g for the 0, 5, 20, and 60 ppm, respectively. Respective weight gains of 129.1, 124.8, 121.5, and 124.7 g were found for female rats. No significant differences were noted between the treated and control groups.

c) 12-month exposure (70 animals/sex/group)

Data generated from all animals (interim sacrifice and terminal sacrifice groups) were also submitted by the investigators to demonstrate that the lack of a statistically significant difference in body weight observed above was related to the small number of animals (10 per sex per dose) studied.

The mean body weights and body weight gains of all animals are presented in the next table.

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Body Weight Data (in grams) - 12 months exposure (all animals)

	Day -1			Day 341	
	M	F		M	F
Body Weights	N		N		
Control	70	150.8	60	418.1	236.7
5 ppm	70	151.7	60	422.3	237.6
20 ppm	70	152.1	60	413.8	232.4
60 ppm	70	148.4	60	405.9	232.0
Body Weight Gains					
Control				267.3	127.9
5 ppm				270.6	129.6
20 ppm				261.7	124.0
60 ppm				257.5	124.9

Significant differences in either body weights or body weight gains were not found between the control and treated groups when data from all animals were considered.

4. Urinalysis

No compound-related effects were noted in both males and females sacrificed at either 6 or 12 months.

5. Hematology

a) 6-month exposure:

All hematologic parameters investigated were comparable between the control and treated groups.

b) 12-month exposure:

A significant increase in white blood cells was noted in the 60 ppm females but not in males. Consequently, the biological significance of this finding is unclear. Other hematologic parameters were comparable between the treated and control groups.

6. Clinical Chemistry

a) 6-month exposure:

In the males, no alterations in clinical chemistry parameters were found. However, significant decreases in BUN, total protein, and albumin were observed in high dose females.

b) 12-month exposure

The significant decreases in BUN, total protein, and albumin observed in high dose females sacrificed at 6 months were not present in high dose females

sacrificed at 12 months. In the absence of persistency, these findings in the 6-month animals should be considered as normal experimental variations. No biologically or statistically significant differences were noted in the treated males. A significant decrease of the enzyme GPT was found in 60 ppm females. In the absence of a dose response relationship, the significance of this finding is unclear.

7. Organ Weights

No alterations in absolute and relative organ weights were noted in both Telone II exposed males and females exposed for either 6 or 12 months.

8. Histopathology

Histopathologic examinations of all tissues required by the 1982 FIFRA Guidelines as well as those of the respiratory system were conducted by the study investigators. Examination of the data of animals sacrificed at either 6 or 12 months did not reveal any evidence of a compound-related effect. All findings reported in the individual animal data sheets were accurately accounted for in the submitted report. The only incidence of interest that was found in treated animals but not in controls was atrophy of the testes noted in 1 male each in the 20 and 60 ppm groups. Due to the small number of animals examined at interim sacrifice (10 per group), the biological significance of this finding remains uncertain pending the submission of the full 2-year final report.

DISCUSSION

A compound-related effect was not evident in any of the parameters investigated (clinical chemistry, hematology, body weights, urinalysis, organ weights, and histopathology). Scattered incidences of significant differences in clinical chemistry and hematology were noted in the 60 ppm group. However, in the absence of a dose-response relationship and consistency of effects, the relevance of those findings is unclear.

The investigators mentioned that the lack of a statistical difference in body weights between the interim sacrifice high dose group and the control was due to the small number of animals in each group (n = 10). They indicated that this finding may become biologically or statistically significant when data from all animals in this study (n = 70) will be taken into consideration in the final 2-year report. However, evaluation of individual animal data indicated that significant differences were still not evident when body weight data of all animals (70 animals/sex/dose) were compiled and presented on page 11 of this memo. Therefore, at least after 12 months of exposure, the highest dose used (60 ppm) did not elicit minimal signs of systemic toxicity.

It should be noted, however, that several parameters pertaining to chronic toxicity testing were not performed in this study (see "Procedures" section). These deficiencies in conjunction with the absence of a maximum toterated dose may preclude the use of this study in fulfilling regulatory requirements for chronic/oncogenic testing. Nevertheless, assessment of whether a maximum tolerated dose has been reached in this study should await the submission of the full 2-year final report.

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