2-25-93

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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: Telone II (1,3-Dichloropropene) - Two Palatability Studies and a Range-Finding (Probe) Study in Rats

Tox. Chemical No.: 029001 **MRID No.:** 424607-01
DP Barcode: D183113 **Case:** 818694
Submission: S426736 **Identification No.:** 029001

FROM: Alan C. Levy, Ph.D., Toxicologist Alan C. Levy 2/24/93
Review Section IV, Toxicology Branch II
Health Effects Division (H7509C)

TO: Linda Propst, PM 73
Special Review and Reregistration Division (H7508W)

THRU: Elizabeth A. Doyle, Ph.D., Section Head E.A Doyle 2/25/93
Review Section IV, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D., Branch Chief Marcia van Gemert 2/25/93
Toxicology Branch II
Health Effects Division (H7509C)

REQUEST: Review two palatability studies and a probe study in rats with Telone II (1,3-Dichloropropene)

Registrant: DowElanco, Indianapolis, IN

CONCLUSIONS:

Telone II (1,3-Dichloropropene) was administered by dietary admix to rats in three studies: (1) Palatability I - 0, 3, 10, 25 or 50 mg/kg/day to males for 2 weeks; (2) Palatability II - 0, 50, 75, 100 or 125 mg/kg/day to males and females for 2 weeks; and (3) Probe - 0, 10, 25, 50 or 100 mg/kg/day to males and females for 2 weeks. The results indicated:

Palatability I: body weight gain decrease at 25 and 50 mg/kg Days 1-5; dose dependent food consumption decrease

Palatability II: dose-response decrease in body weight gains (primarily days 1-6) and food consumption

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Probe: significantly (p=0.05) lower body weights in males and females on both weighing days (8 and 15); decreased food consumption in males at 50 and 100 mg/kg during week 1 and at 100 mg/kg during week 2, with females showing a slight and inconsistent decrease; lower absolute kidney and liver weights in males only at 100 mg/kg; hyperkeratosis and thickening of the nonglandular stomach mucosa in both sexes at 50 and 100 mg/kg.

Probe Study

No Observed Effect Level (NOEL) - males: 10 mg/kg; females: 25 mg/kg

Lowest Observed Effect Level (LOEL) - males: 25 mg/kg - 1 of 5 with thickened nonglandular stomach mucosa; females: 50 mg/kg - slightly lower body weights and/or weight gains, 1 of 5 with hyperkeratosis and 3 of 5 with thickening of the nonglandular stomach mucosa

Classification: **Core Supplementary** - These three studies were not designed to fulfill a Guideline, but were intended to assist in choosing doses for longer duration rat studies.

These studies do not satisfy a Guideline requirement.

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Reviewed by: Alan C. Levy, Ph.D. Alan C. Levy 2/24/93
Section IV, Tox. Branch II (H7509C)

Secondary reviewer: Elizabeth A. Doyle, Ph.D. E.A. Doyle 2/25
Section IV, Tox. Branch II (H7509C)

DATA EVALUATION REPORT

Study Type: Two-Week Range Finding Study - Rat - ($ none)
Two Palatability Studies - Rat - ($ none)

Test Material: Telone II; 1,3-Dichloropropene

Tox. Chemical No.: 029001 **MRID No.:** 424607-01
DP Barcode: D183113 **Case:** 818694
Submission: S426736 **Identification No.:** 029001

Study Number: M-003993-026 [M-003993-026PM, -026R, -026]

Sponsor: DowElanco, Indianapolis, IN

Testing Facility: The Toxicology Research Laboratory
Health and Environmental Sciences
The Dow Chemical Company
Midland, MI 48674

Title of Report: Telone II Soil Fumigant: Palatability and Two-Week Dietary Probe Studies in Fischer 344 Rats

Authors: K.T. Haut, K.E. Stebbins, B.E. Kropscott and W.T. Stott

Report Issued: August 3, 1992

Conclusions:

Telone II (1,3-dichloropropene) was administered by dietary admix to rats in three studies: (1) Palatability I - 0, 3, 10, 25 or 50 mg/kg/day to males for 2 weeks; (2) Palatability II - 0, 50, 75, 100 or 125 mg/kg/day to males and females for 2 weeks; and (3) Probe - 0, 10, 25, 50 or 100 mg/kg/day to males and females for 2 weeks. The results indicated:

Palatability I: body weight gain decrease at 25 and 50 mg/kg Days 1-5; dose dependent food consumption decrease

Palatability II: dose-response decrease in body weight gains (primarily days 1-6) and food consumption

Probe: significantly (p=0.05) lower body weights in males and females on both weighing days (8 and 15); decreased food consumption in males at 50 and 100 mg/kg during week 1 and at 100 mg/kg during week 2 with females showing a slight and inconsistent decrease; lower absolute kidney and liver weights in males only at 100 mg/kg; hyperkeratosis and thickening of the nonglandular stomach mucosa in both

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sexes at 50 and 100 mg/kg.

Probe Study

No Observed Effect Level (NOEL) - males: 10 mg/kg; females: 25 mg/kg

Lowest Observed Effect Level (LOEL) - males: 25 mg/kg - 1 of 5 with thickened nonglandular stomach mucosa; females: 50 mg/kg - slightly lower body weights and/or weight gains, 1 of 5 with hyperkeratosis and 3 of 5 with thickening of the nonglandular stomach mucosa

Classification: **Core Supplementary** - These three studies were not designed to fulfill a Guideline, but were intended to assist in choosing doses for longer duration rat studies.

These studies do not satisfy a Guideline requirement.

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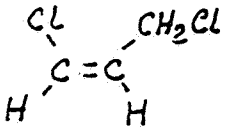
NOTE: There were 3 "studies" included in this Report (MRID No. 424607-01; Registrant Study No.: M-003993-026):

1. Palatability I: 0, 3, 10, 25 or 50 mg/kg/day - males
2. Palatability II: 0, 50, 75, 100 or 125 mg/kg/day - males and females
3. Probe: 0, 10, 25, 50 or 100 mg/kg/day - males and females

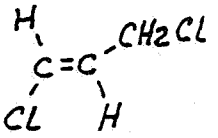
I. MATERIALS, METHODS AND RESULTS

A. Test Article Description

Name: Telone II; 1,3-Dichloropropene; 1,3-D; DCP
Formula:



cis



trans

Lot Number: MM880202, Microencapsulated

Formulation: Telone II microencapsulated [redacted]

Purity: 95.8% (50.6% cis/45.2% trans) Microencapsulated - 42.7% Telone II

Analysis Conducted: Prior to study start.

B. Concentration, Homogeneity and Stability

Table 1 presents a summary of analytical data for concentration, homogeneity and stability of Telone II (microencapsulated) for the palatability and probe studies in rats.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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Table 1

SUMMARY OF THE CONCENTRATION, HOMOGENEITY AND STABILITY ANALYTICAL DATA IN PALATABILITY AND PROBE STUDIES WITH TELONE II

CONCENTRATION

Dose (mg/kg)	Sex	Percent Targeted Dose
0.5% premix	M/F	94†
100	M/F	90/88
50	M/F	84/89
25	M/F	90/92
10	M/F	84/89

HOMOGENEITY

Dose (mg/kg)	Sex	No. of Aliquots	% of Target Concentration Mean	Range
50	M	9	103a	87-121
5	M	6	95b	80-108

STABILITY

Dose (mg/kg)	No. of Aliquots	Day	Sex	% Targeted Dose	% Day 0 Concentration
5	6	0	M	95	-
5	4	8	M	81	86
5	4	15	M	97	102
5	8	20	M	82	86
5	20	35	M	86	91

M = Male F = Female
† = Single sample
a = Individual values = 121, 118, 105, 104, 102, 99, 98, 90 and 87
b = Individual values = 108, 100, 98, 93, 92 and 80
Data extracted from Report Tables 1-4, pages 30-33.

Concentration, homogeneity and stability data indicated that these were within acceptable limits.

C. Dose Preparation and Dosing

Telone II (1,3-dichloropropene) was administered by dietary admix as a microencapsulated formula in [redacted]

[redacted] INERT INGREDIENT INFORMATION IS NOT INCLUDED

Palatability I Study: 0, 3, 10, 25 or 50 mg/kg/day; 3 males/group for 2 weeks

Palatability II Study: 0, 50, 75, 100 or 125 mg/kg/day; 3 males and 3 females/group for 2 weeks

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INERT INGREDIENT INFORMATION IS NOT INCLUDED

Probe Study: 0, 10, 25, 50 or 100 mg/kg/day; 5 males and 5 females/group for 2 weeks

Desired concentrations of dietary admix were obtained by combining a premix with ground feed. Both premix and diets were made at the start of each of the 2-week studies. For the palatability studies, historical control data were used to calculate the mg/kg body weight/day of the test article dietary admixes. Body weights and food intake data prior to test article addition were used to calculate mg/kg body weight/day in the probe study. Report page 17 stated, "The premix was adjusted for percent loading (42.7% TELONE II) in the microencapsulated material and the diet concentrations were mg TELONE II/kg body weight/day." The control group received the [redacted] in ground feed (the amount equivalent to the vehicle in the high-dose concentrations).

D. Dose Selection

Palatability Study I doses were based upon a 1985 National Toxicology Program (NTP) study (Toxicology and Carcinogenesis Studies of Telone II in F344/N Rats and B6C3F1 Mice, Gavage Studies, NTP Tech. Report No. 269, Gov. Print. Office, Wash., D.C.) where the gavage doses of 25 or 50 mg/kg/day of a prior formulation were administered to males and females, 3 days/week, for up to 2 years.

Results from Palatability Study I were used to choose doses for Palatability Study II.

Doses for the Probe Study were selected from the palatability studies' data.

E. Animals

Fischer 344 rats, 6-8 weeks old at study start, were obtained from Charles River Laboratories, Kingston, NY. Upon arrival, the animals were examined by a veterinarian. Rats were individually housed in stainless steel cages in rooms, "... designed to maintain adequate environmental conditions (temperature, humidity and photocycle) ..." The acclimation period was at least 7 days. Dietary admixes and water were available ad libitum.

Randomization for the Palatability I and II Studies was by a random numbers table. In the Probe Study, randomization was based on body weights.

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F. General Observations

1. MORTALITY AND MORIBUNDITY

Observations were made A.M. and P.M. daily, including weekends.

There were no deaths in any of the 3 studies.

2. CLINICAL OBSERVATIONS

These were made in the P.M. only, Mondays-Fridays only (not weekends).

There were no clinical signs reported for any animal in the 3 studies.

3. BODY WEIGHTS

Weights were recorded prestudy and 3 times/week for the Palatability studies, and prestudy and weekly for the Probe study.

Palatability Study I (males only) - weights recorded on days: -6, 1, 3, 5, 8, 10, 12 and 15

Palatability Study II (males and females) - weights recorded on days: -8, -2, 1, 3, 6, 8, 10, 13 and 15

Probe Study (males and females) - weights recorded on days: -8, -2, 1, 8 and 15

Table 2 presents a summary of group mean body weights and weight gains for Palatability Study I, Palatability Study II and a Probe Study.

Table 2

A SUMMARY OF GROUP MEAN BODY WEIGHTS AND WEIGHT GAINS IN PALATABILITY STUDY I, PALATABILITY STUDY II AND A PROBE STUDY WITH TELONE II IN RATS

Day	Males					Females				
PALATABILITY I (a)					BODY WEIGHTS (g)					
mg/kg =	0	3	10	25	50	-	-	-	-	-
1	95	94	95	95	97	-	-	-	-	-
5	111	109	109	106	107	-	-	-	-	-
10	128	128	124	122	123	-	-	-	-	-
15	150	150	144	144	144	-	-	-	-	-
					BODY WEIGHT GAINS (g)					
1-5	16	15	14	11	10	-	-	-	-	-
1-10	33	34	29	27	26	-	-	-	-	-
1-15	55	56	49	49	47	-	-	-	-	-
PALATABILITY II (b)					BODY WEIGHTS (g)					
mg/kg =	0	50	75	100	125	0	50	75	100	125
1	171	165	165	162	166	116	113	114	113	113
6	192	180	175	168	171	131	125	122	119	118
10	199	183	179	172	176	134	127	125	120	120
15	216	195	188	177	180	145	136	134	129	126
					BODY WEIGHT GAINS (g)					
1-6	21	15	10	6	5	15	12	8	6	5
1-10	28	18	14	10	10	18	14	11	7	7
1-15	45	30	23	15	14	29	23	20	16	13
PROBE (c)					BODY WEIGHTS (g)					
mg/kg =	0	10	25	50	100	0	10	25	50	100
1	165	164	170	163	161	114	115	115	116	116
8	201	202	204	192*	180*	130	131	132	129	127
15	224	223	228	213*	197*	140	140	140	136	134
					BODY WEIGHT GAINS (g)					
1-8	36	38	34	29	19	16	16	17	13	11
1-15	59	59	58	50	36	26	25	25	20	18

a = 3 rats/group (males only)
b = 3 rats/sex/group
c = 5 rats/sex/group
Statistical Significance: * = Alpha of 0.05 (Dunnett's Test)
Data extracted from Report Tables 5, 6, 7, 12 and 13, pages 34, 35, 36, 41 and 42.

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In Palatability I and II, no statistical analyses were performed on body weights.

There was a decrease in body weight gains from days 1-5 in Palatability I at 25 and 50 mg/kg. From days 5-10 or 10-15, the gains were similar for all groups.

A relative dose-dependent decrease in body weight gains was observed for males and females in Palatability II. This occurred primarily during the period of days 1-6.

For the Probe study, statistically significant ($p=0.05$) lower weights were in the 50 and 100 mg/kg males at the day 8 and 15 weighings. A slight decrease in weight gains was observed in these same dose groups for females (not significant).

4. FOOD CONSUMPTION

This parameter was measured 3 times/week for Palatability I and II and weekly during the Probe study.

No statistical analyses were made for any of the three studies.

There was a slight, dose-dependent decrease in food consumption in Palatability I with the exception of the days 8-10 interval.

In Palatability II, a slightly more severe dose-related decrease was reported for most intervals in males and females.

For the Probe study, during the first week, males at 50 and 100 mg/kg had lower food consumption; whereas, during the 2nd week, only the 100 mg/kg group showed this effect. A slight and inconsistent decrease was observed for females.

5. OPHTHALMOSCOPIC EXAMINATIONS

These were conducted only on Probe animals at necropsy (test day 16).

There were "no remarkable observations" reported.

G. Clinical Pathology

Hematology (not blood chemistry or urinalysis) parameters were examined only on Probe rats. Blood samples were obtained at the time of necropsy from the orbital sinus under light methoxyflurane anesthesia following an overnight fast. The following parameters were examined: hematocrit, hemoglobin, erythrocyte count, total leukocyte count, platelet count and a blood smear (erythrocyte, leukocyte and platelet morphology).

There were no apparent test article related differences between the treated and control groups.

H. Sacrifice and Pathology

Palatability I and II animals were sacrificed at the end of each study by CO_2 asphyxiation. For the Probe study, at termination, fasted rats were amesthetized with methoxyflurane and decapitated (trachea clamped).

From the Probe study only, the following organs were weighed with weights presented as absolute and organ-to-body weight ratios: brain, heart, liver, kidneys and testes. About 53 tissues were collected and preserved. The following were examined microscopically from the control and high-dose group (100 mg/kg) of the Probe study: liver, kidneys, esophagus, stomach, urinary bladder and gross lesions. In addition, liver, kidneys, stomach and gross lesions were examined from the other dose groups (10, 25 and 50 mg/kg).

1. MACROSCOPIC

None were considered related to test article administration.

2. ORGAN WEIGHTS

Table 3 presents absolute and relative kidney and liver weights. [Report page 24, Anatomic Pathology, Organ and Organ/Body Weight concerning males states, "The absolute liver and kidney weight decreases at the 100 mg/kg/day dose level were considered treatment-related changes, however, there were no associated histopathologic changes observed."]

Table 3

GROUP MEAN ABSOLUTE AND RELATIVE KIDNEY AND LIVER WEIGHTS FOR RATS IN A TWO-WEEK PROBE STUDY WITH TELONE II

	Males					Females				
mg/kg =	0	10	25	50	100	0	10	25	50	100
Final Body Wt.	198	196	201	189*	174*	124	124	123	120	119
Kidneys absol.	1.62	1.58	1.63	1.56	1.46*	1.02	1.03	1.02	1.01	0.98
rel. to B.W.	0.82	0.81	0.81	0.83	0.84	0.82	0.83	0.83	0.84	0.83
Liver absol.	6.73	7.03	7.07	6.55	6.03*	3.92	3.92	4.05	3.86	3.83
rel. to B.W.	3.41	3.59	3.52	3.48	3.46	3.17	3.17	3.28	3.22	3.23

absol. = absolute weight (g)
rel. to B.W. = relative to Body Weight (g/100 g body weight)
Statistical Significance: * = Alpha of 0.05 (Dunnett's Test)
Data extracted from Report Tables 18 and 19, pages 47 and 48.

For males, final body weights were lower than the control (p=0.05) at 50 and 100 mg/kg. Absolute (not relative) kidney and liver weights in the 100 mg/kg group were below respective controls (p=0.05). In addition, relative brain and testes weights at 50 and 100 mg/kg were greater (p=0.05) than controls, but this was considered to be a reflection of the lower final body weights.

There were no final body weights or absolute relative organ weights in females which were statistically different from the control.

3. MICROSCOPIC

The only treatment related histopathological changes concerned the stomach. These findings are presented in Table 4.

Report pages 24 and 25 stated, "The stomach alteration was characterized as slight thickening of the nonglandular mucosa. Microscopically the affected mucosa was up to twice as thick as the mucosa in control group rats. This alteration was accompanied by hyperkeratosis of the nonglandular mucosa in 2 males and 1 female given 50 mg/kg/day and 4 males and 4 females given 100 mg/kg/day. These changes are consistent with a response to localized irritation of the gastric mucosa. A possible factor contributing to this change is increased stress caused by decreased body weight and feed consumption "

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Table 4

HISTOPATHOLOGICAL STOMACH CHANGES REPORTED IN A TWO-WEEK PROBE RAT STUDY WITH TELONE II

	Males					Females				
mg/kg =	0	10	25	50	100	0	10	25	50	100
No. Tissues Examined	5	5	5	5	5	5	5	5	5	5
Within normal limits	5	5	4	0	0	5	5	5	2	1
Hyperkeratosis, nonglandular mucosa	0	0	0	2	4	0	0	0	1	4
Thickened, nonglandular mucosa	0	0	1	5	5	0	0	0	3	4

Data extracted from Report Table 21, page 50.

The Reviewer has no comments regarding the Methods and Materials section of this Report.

Statistical analysis procedures were described in the Report.

A Good Laboratory Practice Compliance statement, A Quality Assurance statement and list of Quality Assurance inspections were included.

II. DISCUSSION

Concentration, homogeneity and stability data were considered to be within acceptable limits.

There was no mortality nor treatment related clinical signs in either of the palatability studies or the probe study.

A decrease in body weight gain was noted for days 1-5 only in Palatability I at 25 and 50 mg/kg (only males in this study). In Palatability II, a dose-response decrease in weight gains in both sexes was noted primarily during days 1-6. There were significantly ($p=0.05$) lower body weights at 50 and 100 mg/kg in males only in the weighings on days 8 and 15 of the Probe study; a slight decrease in female weight gains was noted at 50 and 100 mg/kg.

Food consumption in both Palatability studies was decreased dose-dependently at most intervals. Males in the Probe study at 50 and 100 mg/kg consumed less food during week one; only the 100 mg/kg group ate less during the 2nd week. Females in the Probe study showed a slight and inconsistent decrease.

Opnthalmologic findings were reported as, "no remarkable observations."

There were no hematological findings that were considered to be TELONE II related.

No macroscopic necropsy findings were reported.

Absolute kidney and liver weights in males only were significantly (p=0.05) lower than controls at 100 mg/kg (Probe study - no organ weights measured in the Palatability studies). The relative weights of these two organs were similar in all groups. The Report authors considered (page 9 of this Data Evaluation Report) that these lower absolute kidney and liver weights were treatment related. This Reviewer points out that these lower absolute values could be the result of lower body weights.

Microscopically, Telone II appeared to cause hyperkeratosis and thickening of the nonglandular stomach mucosa in males and females at 50 and 100 mg/kg. [Histopathology only in the Probe study.] One of 5 males (0/5 females) showed thickening only at 25 mg/kg (the Study Authors stated that this was treatment related). The Report indicated that the Authors considered these effects on the nonglandular mucosa to be, "... consistent with an irritative effect by the test material and/or stress due to depressed feed consumption and body weight..."

III. CONCLUSIONS

Telone II (1,3-dichloropropene) was administered by dietary admix to rats in three studies: (1) Palatability I - 0, 3, 10, 25 or 50 mg/kg/day to males for 2 weeks; (2) Palatability II - 0, 50, 75, 100 or 125 mg/kg/day to males and females for 2 weeks; and (3) Probe - 0, 10, 25, 50 or 100 mg/kg/day to males and females for 2 weeks. The results indicated:

Palatability I: body weight gain decrease at 25 and 50 mg/kg days 1-5; dose dependent food consumption decrease

Palatability II: dose-response decrease in body weight gains (primarily days 1-6) and food consumption

Probe: significantly (p=0.05) lower body weights in males and females on both weighing days (8 and 15); decreased food consumption in males at 50 and 100 mg/kg during week 1 and at 100 mg/kg during week 2 with females showing a slight and inconsistent decrease; lower absolute kidney and liver weights in males only at 100 mg/kg; hyperkeratosis and thickening of the nonglandular stomach mucosa in both sexes at 50 and 100 mg/kg.

Probe Study

No Observed Effect Level (NOEL) = males: 10 mg/kg
females: 25 mg/kg

Lowest Observed Effect Level (LOEL) = males: 25 mg/kg - 1 of 5 with thickened nonglandular stomach mucosa; females: 50 mg/kg - slightly lower body weights and/or weight gains, 1 of 5 with hyperkeratosis and 3 of 5 with thickening of the nonglandular stomach mucosa

Classification: **Core Supplementary** - These three studies were not designed to fulfill a Guideline, but were intended to assist in choosing doses for longer duration rat studies.

These studies do not satisfy a Guideline requirement.