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

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MAR 30 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: TELONE II (Microencapsulated) - Subchronic Toxicity Studies in the Rat (§82-1A) and the Mouse (§82-1A)

DP Barcode: D195984 Case: 818694
Submission: S451219 PC Code: 029001
Identification No.: 029001
MRID Nos.: 429548-02 (rat); 429548-01 (mouse)
Action: 627 GENERIC DATA SUBMISSION

FROM: Alan C. Levy, Ph.D., Toxicologist Alan C. Levy 3-29-94
Review Section IV, Toxicology Branch II
Health Effects Division (7509C)

TO: Linda Propst/Judith Loranger, PM 73
Special Review and Reregistration Division (7508W)

THRU: Jess Rowland, M.S. 3/29/94
Toxicology Branch II
Health Effects Division (7509C)

and

Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (7509C) 3/29/94

REQUEST: Review subchronic toxicity studies in rats and mice with TELONE II (microencapsulated)

Registrant: DowElanco, Indianapolis, IN

EXECUTIVE SUMMARIES:

RAT (MRID No. 429548-02)

In a subchronic toxicity study, TELONE II (1,3-Dichloropropene - microencapsulated) was administered by dietary admix to Charles River Fischer 344 rats (10/sex/group) at doses of 0, 5, 15, 50 and 100 mg/kg/day for 13 weeks with an additional 10/sex in the 0 and 100 mg/kg/day groups given basal food during a 4-week recovery period. The following parameters were examined: mortality, clinical signs, body weights, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, macroscopic pathology, organ weights and microscopic pathology.

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Body weights and weight gains as well as food consumption were reduced at 50 and 100 mg/kg/day in both sexes (questionable reduction in male body weights/gains at 5 and 15 mg/kg/day). Doses of 15, 50 and 100 mg/kg/day caused hyperkeratosis and/or basal cell hyperplasia in the nonglandular portion of the stomach of both sexes. The NOEL is 5 mg/kg/day and the LOEL is 15 mg/kg/day. [MRID No. 429548-02]

Core classification is Minimum. This study satisfies the data requirement (§82-1A) for a 13-week subchronic toxicity study in rats.

MOUSE (MRID No. 429548-01)

In a subchronic toxicity study, TELONE II (1,3-Dichloropropene - microencapsulated) was administered by dietary admix to Charles River B6C3F1 mice (10/sex/group) at doses of 0, 15, 50, 100 and 175 mg/kg/day for 13 weeks. The following parameters were examined: mortality, clinical signs, body weights, food consumption, ophthalmology, hematology, clinical chemistry, macroscopic pathology, organ weights and microscopic pathology.

Body weights and weight gains were lower than the controls in males and females at 50, 100 and 175 mg/kg/day (27, 36, 39 and 58% and 7, 22, 30 and 32% at 15, 50, 100 and 175 mg/kg/day). There was a dose-response decrease in the leukocyte counts of males only. No other parameters appeared to be affected. The NOEL is 15 mg/kg/day and the LOEL is 50 mg/kg/day. [MRID No. 4295 8-01]

Core classification is Minimum. This study satisfies the data requirement (§82-1A) for a 13-week subchronic toxicity study in mice.

COMMENTS:

In rats, 15, 50 and 100 mg/kg/day caused hyperkeratosis and/or basal cell hyperplasia in the nonglandular portion of the stomach in both sexes. This observation was not made in mice at doses up to 175 mg/kg/day.

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Reviewed by: Alan C. Levy, Ph.D. Alan C. Levy 3-29-94
Section IV, Tox. Branch II (7509C)

Secondary reviewer: Jess Rowland, M.S. Jess Rowland 3-29-94
Section IV, Tox. Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Toxicity Study - Rats (§82-1A)

TEST MATERIAL: TELONE II; 1,3-Dichloropropene (cis, trans)

SYNONYMS: none

MRID No.: 429548-02 **PC Code:** 029001

STUDY NUMBER: M-003993-028
M-003993-028A (Individual Pathology Report)

SPONSOR: DowElanco, Indianapolis, IN

TESTING FACILITY: The Toxicology Research Laboratory
The Dow Chemical Company, Midland, MI

TITLE OF REPORT: Telone II Soil Fumignat: 13-Week Dietary Toxicity and 4-Week Recovery Studies in Fischer 344 Rats

AUTHORS: K.T. Haut, K.A. Johnson, S.N. Shabrang and W.T. Stott

REPORT ISSUED: January 8, 1993

EXECUTIVE SUMMARY:

In a subchronic toxicity study, TELONE II (1,3-Dichloropropene - microencapsulated) was administered by dietary admix to Charles River Fischer 344 rats (10/sex/group) at doses of 0, 5, 15, 50 and 100 mg/kg/day for 13 weeks with an additional 10/sex in the 0 and 100 mg/kg/day groups given basal food during a 4-week recovery period. The following parameters were examined: mortality, clinical signs, body weights, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, macroscopic pathology, organ weights and microscopic pathology.

Body weights and weight gains as well as food consumption were reduced at 50 and 100 mg/kg/day in both sexes (questionable reduction in male body weights/gains at 5 and 15 mg/kg/day). Doses of 15, 50 and 100 mg/kg/day caused hyperkeratosis and/or basal cell hyperplasia in the nonglandular portion of the stomach of both sexes. The NOEL is 5 mg/kg/day and the LOEL is 15 mg/kg/day. [MRID No. 429548-02]

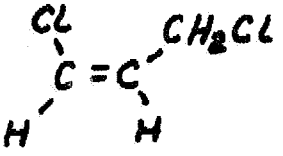
Core classification is Minimum. This study satisfies the data requirement (§82-1A) for a 13-week subchronic toxicity study in rats.

I. MATERIALS, METHODS AND RESULTS

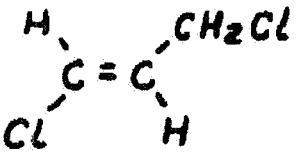
A. Test Article

Name: TELONE II; 1,3-Dichloropropene (cis, trans) [Micro-encapsulated in an 80/20 starch/sucrose matrix]

Formula:



cis



trans

Purity: TELONE II = 96.0%
Microencapsulated TELONE II = 39.1% loading by weight

Lot Numbers: TELONE II (AGR 0295646, DowElanco)
Microencapsulated TELONE II (9359-1B, Midwest Research Institute)
Placebo Microcapsules (9359-1PB, Midwest Research Institute)

B. Statistical Analysis

BARTLETT'S TEST FOR EQUALITY OF VARIANCES: body weights, body weight gains, organ weights, clinical chemistry data, appropriate hematologic data and urinary specific gravity

PARAMETRIC OR NONPARAMETRIC ANALYSIS OF VARIANCE (ANOVA): exploratory data analysis, based on outcome of Bartlett's test

DUNNETT'S TEST OR WILCOXON RANK-SUM TEST WITH A BONFERRONI CORRECTION FOR MULTIPLE COMPARISON: followed ANOVA

Alpha levels used:
Bartlett's test = 0.01
Parametric ANOVA = 0.10
Nonparametric ANOVA = 0.10
Dunnett's test = 0.05, 2-sided
Wilcoxon Rank-Sum test = 0.05 (Bonferroni correction, 2-sided)
Outlier test = 0.02, 2-sided

C. Regulatory Compliance

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

A flagging statement for potential adverse effects, 40 CFR 158.34, was included and the study neither met nor exceeded any of the applicable criteria.

A signed statement of no confidentiality claim was provided.

D. Dose Selection

1. Acute Oral Toxicity, TELONE II - LD50 (Fischer 344 rat): males = 300 mg/kg; females = 224 mg/kg

2. Two-Week Dietary Study - male and female Fischer 344 rats fed diets of approximately 0, 10, 25, 50 and 100 mg/kg/day of microencapsulated TELONE II

50 and 100 mg/kg/day: 10-20% decrease in body weight gain and decreased food consumption; histopathologically, slight thickening of nonglandular portion of the stomach in most males and females; hyperkeratosis in "a number of affected rats"

NOEL was 10 mg/kg/day in males and 25 mg/kg/day in females.

E. Study Design

The subchronic study animals (10/sex/group) were dosed (0, 5, 15, 50 and 100 mg/kg/day) for 13 weeks. The recovery animals (10/sex for groups 0 and 100 mg/kg/day) were given placebo diet for 4 weeks after the 13 weeks.

F. Test Article Stability, Concentration and Homogeneity

Tables 1, 2 and 3. Data extracted from Report Tables 1-4, pages 33-36.

Table 1

TEST ARTICLE STABILITY IN A SUBCHRONIC TOXICITY STUDY IN RATS WITH TELONE II

Day	Target conc. = 2.78×10^{-3}%			Target conc. = 1.70×10^{-1}%		
	Obs conc $\times 10^{-3}$%	Std. Dev. (% w/w)	% Day 0 conc	Obs conc $\times 10^{-1}$%	Std. Dev. (% w/w)	% Day 0 conc
0	2.90	1.82x10a	-	1.90	8.68x10a	-
3	2.59	1.80x10a	89	1.85	1.32x10b	97
7	2.49	1.30x10a	86	1.78	1.23x10b	94
10	2.89	1.10x10a	100	1.88	6.87x10a	99
14	2.65	1.20x10a	91	1.82	9.70x10a	96
21	2.58	1.54x10a	89	1.76	3.54x10b	93

a = 10^{-3}; b = 10^{-2}
No. of Samples = 6
Obs conc = Observed concentration

Table 2

TEST ARTICLE CONCENTRATION IN A SUBCHRONIC TOXICITY STUDY IN RATS WITH TELONE II

Target mg/kg/day	Males		Females	
	% Targeted dose †	Average %	% Targeted dose †	Average %
0.3 % premix	83,103,110,138	109	83,103,110,138	109
5	67,81,91,113	88	84,93,93,108	95
15	76,91,95,116	95	77,85,95,106	91
50	93,81,108,124	102	83,101,106,131	105
100	90,109,101,135	109	86,108,96,130	105

† = For % targeted dose of 83, 67, 76, 93 and 90 (males) and 83, 84, 77, 83 and 86 (females), due to initial loss of TELONE II during the premix mixing process, 15% additional micro-encapsulated TELONE II was added for the mixing of the premix to compensate for this loss via a recommendation by the study analytical chemist.

Table 3

TEST ARTICLE HOMOGENEITY IN A SUBCHRONIC TOXICITY STUDY IN RATS WITH TELONE II

Sample	Aliquots	Mean observed concentration ($\times 10^{-3}$)	Standard Deviation (% w/w)	Relative Standard Deviation
5 mg/kg/day	5	4.32	0.000544	12.59%

Analytical data for stability, concentration and homogeneity were considered to be within acceptable limits.

G. Dietary Admixes

Appropriate dietary concentrations were prepared by serial dilution of a premix with basal diet. Premixes were made every 2 weeks and diets, every week. Concentrations were adjusted each week based on the most recent body weights and food consumption. The 0 mg/kg/day (control) group received a placebo (starch/sucrose matrix only) mixed with basal diet. The amount of placebo was about the same as the microencapsulated test article at 100 mg/kg/day (Highest Dose Tested) and was prepared about every 4 weeks.

H. Animals

Male and female, 6-8 weeks old, Fischer 344 rats were received from Charles River Research Laboratories, Kingston, NY. There was an acclimation period of at least 7 days prior to study start. The animals were housed individually in stainless steel cages, "... in rooms designed to maintain adequate environmental conditions (temperature, humidity, and photocycle)." [No temperature or humidity ranges were provided. No hours for the light/dark cycle were provided.] Food and water were available ad libitum.

I. Mortality, Moribundity and Clinical Signs

Cageside observations were made A.M. and P.M. 7 days/week. The animals were handled and closely examined weekly.

There was no mortality during either the dosing period (13 weeks) or the recovery phase (4 weeks).

No clinical signs were reported which distinguished treated from control groups.

J. Body Weights

Animals were weighed prior to the start of the study and weekly during the treatment and recovery phases. Table 4.

Table 4

GROUP MEAN BODY WEIGHTS AND WEIGHT GAINS DURING A 13-WEEK DOSING AND 4-WEEK RECOVERY STUDY IN RATS WITH TELONE II

Day	0a	5	15	50	100
MALES - BODY WEIGHT					
-2	150	147	148	149	150
7	192	186	185	180*	180*
14	216	210	210	202*	200*
21	235	226	228	216*	216*
28	244	235	236	223*	222*
49	287	274*	274*	255*	250*
70	308	293*	290*	263*	261*
91	318	298*	297*	269*	267*
98R	323	-	-	-	276*
119R	339	-	-	-	300*
MALES - BODY WEIGHT GAIN					
-2-28	94	88	88	74	72
28-49	43	39	38	32	28
49-70	21	17	16	8	11
70-91	10	7	7	6	6
-2-91	160	151	149	120	117
91-119R	21	-	-	-	33
FEMALES - BODY WEIGHT					
-2	110	109	109	109	109
7	127	124	125	124	123
14	136	132	133	132	131
21	145	139	141	137*	136*
28	149	144	143	139*	137*
49	166	161	160	156*	152*
70	177	171	169	162*	158*
91	179	173	169*	163*	159*
98R	184	-	-	-	168*
119R	195	-	-	-	178*
FEMALES - BODY WEIGHT GAIN					
-2-28	39	36	34	30	28
28-49	17	17	17	17	15
49-70	11	10	9	6	6
70-91	2	2	0	1	1
-2-91	69	64	60	54	50
91-119R	16	-	-	-	19

a = mg/kg/day
R = Recovery period (10 rats/group)
No. rats/group at each weighing through day 91 (mg/kg/day): 0 = 20, 5 = 10, 15 = 10, 50 = 10 and 100 = 20
Statistical Analysis: * = $p<0.05$
Body weight gains calculated by the Reviewer.
Data extracted from Report Tables 10-17, pages 62-75.

For male body weights during dosing, there were statistically significant ($p<0.05$) lower group mean weights at all dose levels: days 49-91 for 5 mg/kg/day; days 49-91 for 15 mg/kg/day; days 7-91 for 50 mg/kg/day; and days 7-91 for 100 mg/kg/day. The percent differences at day 91 were (mg/kg/day): 5 = 6, 15 = 7, 50 = 15 and 100 = 16. Male body weight gains were reduced from the control value at all doses, but primarily at 50 and 100 mg/kg/day. During the 4 weeks of recovery, the controls gained a group mean of 21 g and the 100 mg/kg/day group gained a mean of 33 g.

In females, body weights during dosing were less than controls ($p<0.05$) at 50 and 100 mg/kg/day from days 21-91. The percent differences at day 91 were (mg/kg/day): 5 = 3, 15 = 6, 50 = 9 and 100 = 11. Body weight gains during the 13 week period were 69, 66, 60, 54 and 50 g for the 0, 5, 15, 50 and 100 mg/kg/day groups, respectively. During the 4 weeks of recovery, the controls gained a group mean of 16 g and the 100 mg/kg/day group gained a mean of 19 g.

K. Food Consumption

Measurements were made for the week prior to test article administration and weekly throughout the dosing as well as recovery periods. See Table 5.

Table 5

SELECTED GROUP MEAN FOOD CONSUMPTION (g/rat/day) DURING A 13-WEEK DOSING AND 4-WEEK RECOVERY STUDY IN RATS WITH TELONE II

Days	0a	5	15	50	100
MALES					
-8-2	16.2	15.8	16.1	16.0	16.4
1-9	19.0	18.3	17.8	17.3	16.7
16-23	19.4	19.1	18.6	18.0	18.0
30-37	18.1	17.5	17.0	16.9	17.0
44-51	18.4	17.5	17.4	17.9	17.7
59-66	18.0	17.4	17.3	15.9	16.4
72-79	17.9	17.1	16.6	15.6	16.1
86-93	18.3	17.3	16.9	17.4	17.2
93-119R	17.8	-	-	-	16.5
FEMALES					
-8-2	12.6	12.6	12.3	12.5	12.8
1-9	13.5	13.4	13.3	12.7	12.5
16-23	14.0	13.9	13.6	12.5	12.6
30-37	13.2	13.5	12.6	11.7	11.4
44-51	13.6	13.6	12.6	11.7	12.0
59-66	13.5	13.9	13.3	11.9	12.4
72-79	13.4	13.9	13.3	12.2	11.8
86-93	13.6	13.7	12.7	11.6	11.2
93-119R	13.2	-	-	-	12.8

a = mg/kg/day; R = Recovery period (10 rats/group)
No. rats/group at each weighing during days -8 through 93 (mg/kg/day): 0=20, 5=10, 15=10, 50=10 and 100=20
Data extracted from Report Tables 15-21, pages 76-81.

Food consumption (g/rat/day) was generally below control values for males and females in the 50 and 100 mg/kg/day groups. The Report Authors indicated that this decrease in addition to decreases in body weights and weight gains, "suggest a palatability problem with the higher dosage diets." During the 4-week recovery period, the 100 mg/kg/day males ate an average of 16.5 g/rat/day compared with 17.8 g for controls; whereas, for females, the food consumption was about equal (13.2 and 12.8 group mean g/rat/day at 0 and 100 mg/kg/day, respectively).

L. Ophthalmology

All animals were examined prior to the start of the study and at the time of necropsy.

There were no findings which were considered to be related to test article administration.

M. Clinical Pathology

After an overnight fast, the animals were anesthetized with methoxyflurane and blood was removed at the time of necropsy from the orbital sinus. Urine samples were obtained from nonfasted rats (manual compression of the abdomen) during the week before the scheduled sacrifice. For recovery groups, only parameters statistically different from controls during the 13-week dosing period were examined.

1. HEMATOLOGY

The following parameters were examined:

Hematocrit*	Leukocyte Differential*
Hemoglobin*	Platelet morphology
Leukocyte count*	Platelet count*
Erythrocyte count*	

* = EPA Guideline Requirement

The only statistically significant ($p<0.05$) difference between treated and control groups at 13 weeks was an increase in the group mean platelet counts (10^3/cu mm) in males at 50 and 100 mg/kg/day (control = 460 ± S.D. of 29, 50 = 500 ± 28 and 100 = 503 ± 33) and females at 50 mg/kg/day (control = 465 ± 36, 50 = 506 ± 28 and 100 = 499 ± 42). Recovery males (females not examined) had group values of 451 ± 43 for controls and 458 ± 36 for 100 mg/kg/day rats.

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2. CLINICAL CHEMISTRY

The following parameters were examined:

Calcium*	Albumin*	Alkaline phosphatase
Chloride*	Creatinine*	Creatinine phosphokinase
Phosphorus*	Urea nitrogen*	Serum alanine aminotransferase*
Potassium*	Cholesterol	Serum aspartate aminotransferase*
Sodium*	Globulins	
	Glucose*	
	Total bilirubin*	
	Total protein*	
	Triglycerides	

* = EPA Guideline requirements

The following parameters showed statistical significance:

Table 6

CLINICAL CHEMISTRY PARAMETERS WHICH SHOWED STATISTICAL SIGNIFICANCE IN A 13-WEEK DOSING AND 4-WEEK RECOVERY STUDY IN RATS WITH TELONE II

	0a	5	15	50	100
MALES (13 weeks)					
Alkaline Phos	142±11	136±10	133±11	120±8*	119±8*
Cholesterol	65±7	63±6	65±4	71±7	78±5*
Triglycerides	92±21	87±22	72±8*	58±11*	59±14*
Creatinine	0.7±0.1	0.6±0.1*	0.6±0.1	0.6±0.0*	0.7±0.1
MALES (recovery)					
Alkaline Phos	147±10	-	-	-	156±5*
Cholesterol	52±4	-	-	-	49±2*
Triglycerides	91±20	-	-	-	77±14
Creatinine	-	-	-	-	-
FEMALES (13 weeks)					
Total Protein	6.8±0.3	6.7±0.3	6.5±0.2	6.5±0.2*	6.3±0.3*
Albumin	3.4±0.1	3.3±0.1	3.3±0.1	3.3±0.1	3.2±0.1*
Globulin	3.4±0.2	3.4±0.3	3.3±0.1	3.2±0.2*	3.1±0.2*
FEMALES (recovery)					
Total Protein	7.1±0.3	-	-	-	6.7±0.3*
Albumin	3.5±0.1	-	-	-	3.4±0.1
Globulin	3.5±0.2	-	-	-	3.3±0.2*

a = mg/kg/day
± = mean ± Standard Deviation
- = parameter not examined
Statistical Significance: * = $p<0.05$
Alkaline Phos - MU/IL
Cholesterol - MG/DL
Triglycerides - MG/IL
Creatinine - MG/DL
Total Protein - G/DL
Albumin - G/DL
Globulin - G/DL
Data extracted from Report Tables 31-36, pages 97-102.

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None of the statistically significant differences in the clinical chemistry parameters appeared to be of toxicological significance.

3. URINALYSIS (not required by EPA Guidelines)

The following parameters were examined:

Color	Appearance	Specific gravity
pH	Sediment	Protein
Glucose	Ketones	Bilirubin
Blood	Urobilinogen	

There were no apparent differences between treated and control groups regarding any urinalysis parameters.

M. Sacrifice and Pathology

At the time of scheduled necropsy, animals were anesthetized with methoxyflurane and, after the trachea was exposed and clamped, they were decapitated. A complete gross examination was conducted. The following organs were weighed and organ-to-body weight ratios were calculated: brain, liver, kidneys, heart, adrenals and testes/ovaries. All tissues from the 0 and 100 mg/kg/day rats were processed and examined by light microscopy. The following tissues from the 5, 15 and 50 mg/kg/day animals were processed and examined: lungs, liver, kidneys, stomach, mesenteric tissues (females only), tissues with gross lesions and target tissues identified in the 100 mg/kg/day rats.

For recovery animals, all organs weighed at the 13-week necropsy were weighed. Macroscopic pathology observations were made. Tissues examined microscopically were only those identified as target tissues at the 13-week sacrifice.

The following tissues were preserved and examined; those with an "x" were weighed:

DIGESTIVE
- Tongue
- Salivary glands*
- Esophagus*
- Stomach*
- Duodenum*
- Jejunum*
- Ileum*
- Cecum*
- Colon*
- Rectum*
- xLiver*
- Pancreas*

RESPIRATORY
- Trachea*
- Lung*

CARDIOVASCULAR
- Aorta*
- xHeart*
- Bone marrow*
- Lymph nodes*
- Spleen*
- Thymus*

UROGENITAL
- xKidneys*
- Urinary bladder*
- xTestes*
- Epididymides
- Prostate
- Seminal vesicles
- xOvaries
- Uterus*
- Cervix
- Oviducts
- Vagina

NEUROLOGIC	GLANDULAR	OTHER
xBrain*	xAdrenals*	Bone*
Peripheral nerve*	Lacrimal gland*	Skeletal muscle*
Spinal cord (3 levels)*	Harderian gland	Skin
Pituitary*	Mammary gland*	All gross lesions and masses*
Eyes*	Parathyroid*	Sebaceous gland
	Thyroid*	Coagulating gland
		Larynx
		Nasal tissues
		Oral tissues

* = EPA Guideline Requirements

1. MACROSCOPIC

The only reported gross necropsy findings were decreased body fat of most 50 and 100 mg/kg/day females. This observation was noted to be most apparent in mesometrial adipose tissue. The Report Authors pointed out that this decrease in adipose tissue was not observed in males even though they had greater body weight decreases than did females. There were no 4-week recovery findings which were considered to be related to TELONE II administration.

2. ORGAN WEIGHTS (See Table 7)

Table 7

GROUP MEAN ABSOLUTE AND RELATIVE ORGAN WEIGHTS IN A 13-WEEK DOSING AND 4-WEEK RECOVERY STUDY IN RATS WITH TELONE II

Dose a	Body Wt	Adrenals	Brain	Heart	Kidneys	Liver	Gonads
MALES 13WK							
0	291	.05/.01b	1.9/.66	.87/.30	1.9/.56	8.3/2.7	3.0/1.0
5	276	.05/.02	1.9/.69	.84/.31	1.9/.67	7.7/2.8	3.0/1.1*
15	273*	.05/.02	1.9/.69	.87/.32	1.8/.68	7.6/2.8	3.1/1.1*
50	246*	.04/.02	1.8/.750	.77*/.32	1.7*/.70	7.6/2.89	2.8/1.1
100	245*	.04/.02	1.8/.760	.76*/.31	1.7*/.70	7.1/2.95	3.1/1.3*
MALES RECOV							
0	318	.05/.02	1.9/.61	.93/.29	2.0/.64	8.6/2.7	3.1/.97
100	280*	.05/.02	1.9/.69*	.87/.31	1.9/.69*	8.2/2.9*	3.0/1.1*

Table 7 (CONTINUED)

Dose a	Body Wt	Adrenals	Brain	Heart	Kidneys	Liver	Gonads
FEMALES 13 WK							
0	159	.05/.03	1.7/1.1	.62/.39	1.2/.75	4.5/2.8	.07/.04
5	159	.05/.03	1.7/1.1	.61/.38	1.2/.73	4.4/2.8	.07/.05
15	155	.05/.03	1.7/1.1	.60/.39	1.2/.76	4.4/2.8	.07/.04
50	149*	.05/.03	1.7/1.2*	.58/.39	1.2/.78	4.3/2.9	.07/.05
100	143*	.05*/.03	1.7/1.2*	.55*/.38	1.1/.79	4.1*/2.9	.07/.05
FEMALES RECOV							
0	179	.06/.03	1.8/1.0	.65/.36	1.3/.70	5.0/2.8	-
100	163*	.06/.04*	1.8/1.1*	.65/.38	1.2/.70*	4.7*/2.9	-

a = mg/kg/day
b = absolute weight (g)/relative weight (g per 100 g body weight)
Body Wt = fasted final body weight (g)
- = not examined
Statistical Significance (Dunnett's or Wilcoxon's Tests):
* = p<0.05; $ = p<0.05 for both absolute and relative
Number of rats: 10/sex/group
Data extracted from Report Tables 39-42, pages 105-108.

All statistically significant (p<0.05) differences in absolute or relative organ weights appear to be a reflection of lower fasted final body weights in treated animals.

3. MICROSCOPIC PATHOLOGY

The only apparent test article related findings involved the stomach. Table 8.

The nonglandular portion of the stomach showed hyperkeratosis in both males and females primarily at 50 and 100 mg/kg/day and basal cell hyperplasia in both males and females at 15, 50 and 100 mg/kg/day at the end of the 13-week dosing period. After 4 weeks of recovery, 8/10 males and 6/10 females showed very slight basal cell hyperplasia.

Table f

MICROSCOPIC STOMACH FINDINGS IN A 13-WEEK DOSING AND A 4-WEEK RECOVERY STUDY IN RATS WITH TELONE II

mg/kg/day =	Males					Females				
	0	5	15	50	100	0	5	15	50	100
13-WEEK DOSING										
Number of tissues examined ..	10	10	10	10	10	10	10	10	10	10
Within normal limits	7	8	3	0	0	9	10	5	0	0
Cystic dilitation,glandular mucosa, focal-very slight .	0	0	0	0	0	0	0	2	1	0
Hyperkeratosis,nonglandular mucosa-slight	0	0	1	3	3	0	0	0	3	5
Mineralisation,glandular mucosa,multifocal-very slight	3	2	4	2	5	0	0	0	0	0
Hyperplasia,Basal cell, nonglandular mucosa-very slight	0	0	4	9	6	1	0	3	10	6
Hyperplasia,Basal cell, nonglandular mucosa-slight	0	0	0	1	4	0	0	0	0	4
4-WEEK RECOVERY										
Number of tissues examined ..	10	0	0	0	10	10	0	0	0	10
Within normal limits	3	-	-	-	2	7	-	-	-	3
Cystic dilitation,glandular mucosa, focal-very slight .	0	-	-	-	0	2	-	-	-	1
Mineralisation,glandular mucosa,multifocal-very slight	7	-	-	-	5	1	-	-	-	1
Hyperplasia,Basal cell, nonglandular mucosa-very slight	0	-	-	-	8	0	-	-	-	6

- = not examined
Data extracted from Report Tables 45 and 46, pages 120 and 124.

II. DISCUSSION

Analytical data for test article stability, concentration and homogeneity were considered to be within acceptable limits.

There was no mortality during either the dosing or recovery phases of the study. No clinical signs attributed to TELONE II administration were reported during the treatment or recovery portions of the study.

Statistically ($p<0.05$) lower male body weights were observed at 50 and 100 mg/kg/day throughout the 13-week treatment period; and at 5 and 15 mg/kg/day, this significant ($p<0.05$) observation was made from day 49 until sacrifice. Body weight gains were reduced by 10, 11, 29 and 30% for males at 5, 15, 50 and 100 mg/kg/day for the 13-week period. During the 4-week recovery period, the 100 mg/kg/day male weights remained less ($p<0.05$) than controls, although there was a group mean gain of 33 g compared with a control group mean gain of 21 g. An effect on day 91 group mean body weights in the 5 and 15 mg/kg/day groups is questionable as the standard deviations were 13.1-16.5 with mean differences of 17-21 g.

For females, group mean body weights were less than controls ($p<0.05$) from day 21 until day 91 at 50 and 100 mg/kg/day. Although the day 91 group mean weight of the 15 mg/kg/day rats was significantly ($p<0.05$) less than controls, the values were 169 g versus 179 g. Body weight gains were 4, 13, 22 and 26% less than the control at 5, 15, 50 and 100 mg/kg/day doses. During the 4-week recovery period, the controls gained a group mean of 16 g and the 100 mg/kg/day rats gained a group mean of 19 g. Therefore, in females, there is a test article effect on body weight at 50 and 100 mg/kg/day.

Food consumption was generally less than in the respective control group for males and females at 50 and 100 mg/kg/day. This coincides with the body weight observations.

There were no ophthalmic findings associated with test article administration.

The only hematological parameter which had a difference between treated and control groups was an increase ($p<0.05$) in group mean platelet counts at week 13 in the 50 and 100 mg/kg/day males, and in females, only at 50 mg/kg/day. Even though there were statistically significant differences, it is not considered that these observations are of toxicological significance. Recovery males (females not examined) had similar group means (451 and 458 10^3/cu mm).

The statistically significant ($p<0.05$) differences reported for clinical chemistry parameters did not appear to be of toxicological significance as, not only were the group mean differences relatively small, but the parameters effected were noted in only one sex and the values were within expected limits.

There were no apparent test article effects on any urinalysis parameters.

Gross necropsy findings revealed an apparent decrease primarily in the amount of mesenteric adipose tissue in 50 and 100 mg/kg/day females only.

Although there were statistically significant ($p<0.05$) differences in absolute and/or relative (to body weight) organ weights in males and females at 50 and/or 100 mg/kg/day, these differences appeared to be a reflection of the fasted final body weights. The same was evident for the recovery animals.

TELONE II appeared to cause microscopic changes in the nonglandular portion of the stomach. Hyperkeratosis was noted primarily at 50 and 100 mg/kg/day in males and females. Basal cell hyperplasia was reported for both sexes at 15, 50 and 100 mg/kg/day. Basal cell hyperplasia was reported in 8/10 males and 6/10 females after the recovery period (none in controls). The severity of these changes were considered by the pathologist to be "very slight" or "slight."

TELONE II did not induce any histopathological changes in the nonglandular or glandular portions of the stomach of mice fed diets containing TELONE II at 0, 15, 50, 150 or 175 mg/kg/day (MRID No. 429548-01).

III. CONCLUSIONS:

In a subchronic toxicity study, TELONE II (1,3-Dichloropropene - microencapsulated) was administered by dietary admix to Charles River Fischer 344 rats (10/sex/group) at doses of 0, 5, 15, 50 and 100 mg/kg/day for 13 weeks with an additional 10/sex in the 0 and 100 mg/kg/day groups given basal food during a 4-week recovery period. The following parameters were examined: mortality, clinical signs, body weights, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, macroscopic pathology, organ weights and microscopic pathology.

Body weights and weight gains as well as food consumption were reduced at 50 and 100 mg/kg/day in both sexes (questionable reduction in male body weights/gains at 5 and 15 mg/kg/day). Doses of 15, 50 and 100 mg/kg/day caused hyperkeratosis and/or basal cell hyperplasia in the nonglandular portion of the stomach of both sexes. The NOEL is 5 mg/kg/day and the LOEL is 15 mg/kg/day. [MRID No. 429548-02]

Core classification is Minimum. This study partially fulfills the data requirement (§82-1A) for a 13-week subchronic toxicity study in rats.

Reviewed by: Alan C. Levy, Ph.D. Alan C. Levy 3-29-94
Section IV, Tox. Branch II (7509C)

Secondary reviewer: Jess Rowland, M.S. Jess Rowland 3-29-94.
Section IV, Tox. Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Toxicity Study - Mice (§82-1A)

TEST MATERIAL: TELONE II; 1,3-Dichloropropene (cis, trans)

SYNONYMS: none

MRID Number: 429548-01 **PC Code:** 029001

STUDY NUMBER: M-003993-029

SPONSOR: DowElanco, Indianapolis, IN

TESTING FACILITY: The Toxicology Research Laboratory
The Dow Chemical Company, Midland, MI

TITLE OF REPORT: Telone II Soil Fumignat: 13-Week Dietary Toxicity Study in B6C3F1 Mice

AUTHORS: K.T. Haut, K.E. Stebbins, S.N. Shabrang and W.T. Stott

REPORT ISSUED: January 8, 1993

EXECUTIVE SUMMARY:

TELONE II (1,3-Dichloropropene - microencapsulated) was administered by dietary admix to Charles River B6C3F1 mice (10/sex/group) at doses of 0, 15, 50, 100 and 175 mg/kg/day for 13 weeks. The following parameters were examined: mortality, clinical signs, body weights, food consumption, opthalmology, hematology, clinical chemistry, macroscopic pathology, organ weights and microscopic pathology.

Body weights and weight gains were lower than the controls in males and females at 50, 100 and 175 mg/kg/day (27, 36, 39 and 58% and 7, 22, 30 and 32% at 15, 50, 100 and 175 mg/kg/day). There was a dose-response decrease in the leukocyte counts of males only. No other parameters appeared to be affected. The LOEL is 15 mg/kg/day and the LOEL is 50 mg/kg/day. (MRID No. 429548-01)

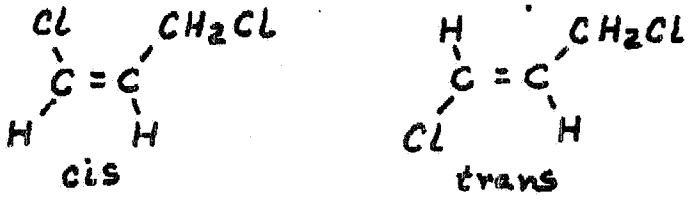
Core classification is Minimum. This study satisfies the data requirement (§82-1A) for a 13-week subchronic toxicity study in mice.

I. MATERIALS, METHODS AND RESULTS

A. Test Article

Name: TELONE II; 1,3-Dichloropropene (cis, trans) [Micro-encapsulated in an 80/20 starch/sucrose matrix]

Formula:



Purity: TELONE II = 96.0%
Microencapsulated TELONE II = 39.1% loading by weight

Lot Numbers: TELONE II (AGR 0295646, DowElanco)
Microencapsulated TELONE II (9359-1B, Midwest Research Institute)
Placebo Microcapsules (9359-1PB, Midwest Research Institute)

B. Statistical Analysis

BARTLETT'S TEST FOR EQUALITY OF VARIANCES: body weights, body weight gains, organ weights, clinical chemistry data and appropriate hematologic data

PARAMETRIC OR NONPARAMETRIC ANALYSIS OF VARIANCE (ANOVA): exploratory data analysis, based on outcome of Bartlett's test

DUNNETT'S TEST OR WILCOXON RANK-SUM TEST WITH A BONFERRONI CORRECTION FOR MULTIPLE COMPARISON

ALPHA LEVELS USED:
Bartlett's test = 0.01
Parametric ANOVA = 0.10
Nonparametric ANOVA = 0.10
Dunnett's test = 0.05, 2-sided
Wilcoxon Rank-Sum test = 0.05 (Bonferroni correction, 2-sided)
Outlier test = 0.02, 2-sided

C. Regulatory Compliance

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

A flagging statement for potential adverse effects, 40 CFR 158.34, was included and the study neither met nor exceeded any of the applicable criteria.

A signed statement of no confidentiality claim was provided.

D. Dose Selection

1. ACUTE ORAL TOXICITY, TELONE II - LD50 (Fischer 344 rat): males = 300 mg/kg; females = 224 mg/kg

2. TWO-WEEK DIETARY PROBE STUDY - male and female B6C3F1 mice fed diets of approximately 0, 25, 50, 100 and 175 mg/kg/day TELONE II [Report, page 13, did not say MICROENCAPSULATED]

100 and 175 mg/kg/day - depression of body weights in males at 100 and 175 mg/kg/day; depression of body weights in females at 175 mg/kg/day; decreased food consumption at 175 mg/kg/day; decrease in size of hepatocytes in most males at 175 mg/kg/day

NOEL: males = 50 mg/kg/day; females = 100 mg/kg/day

E. Study Design

Ten mice/sex/dose level: 0 (placebo), 15, 50, 100 and 175 mg/kg/day.

F. Test Article Homogeneity, Stability and Concentration

Tables 1, 2 and 3. Data extracted from Report Tables 1-4, pages 29-32.

Table 1

TEST ARTICLE HOMOGENEITY IN A SUBCHRONIC TOXICITY STUDY IN MICE WITH TELONE II

Sample	No. Aliquots	Target concentration	Mean observed concentration ($\times 10^{-3}$%)	Standard deviation (% w/w)	Relative standard deviation
15 mg/kg/day	5	5.62×10^{-3}%	4.32	0.000544	12.59%

Table 2

TEST ARTICLE STABILITY IN A SUBCHRONIC TOXICITY STUDY IN MICE WITH TELONE II

Day	Target conc. = 2.78×10^{-2}%			Target conc. = 1.70×10^{-1}%		
	Obser. conc ($\times 10^{-2}$%)	S.D. (% w/w)	% Day 0 Conc	Obser. conc ($\times 10^{-1}$%)	S.D. (% w/w)	% Day 0 Conc
0	2.90	1.82x10a	-	1.90	8.65x10a	-
3	2.59	1.80x10a	89	1.85	1.32x10b	97
7	2.49	1.30x10a	86	1.78	1.23x10b	94
10	2.89	1.10x10a	100	1.88	6.87x10a	99
14	2.65	1.20x10a	91	1.82	9.70x10a	96
21	2.58	1.54x10a	89	1.76	3.54x10b	93

a = 10^{-3}; b = 10^{-2}
Number of Samples = 6
Data extracted from Report Tables 1-4, pages 29-32.

Table 3

TEST ARTICLE CONCENTRATION IN A SUBCHRONIC TOXICITY STUDY IN MICE WITH TELONE II

Target mg/kg/day	Males		Females	
	% Target dose	Average %	% Target dose	Average %
0.3% Premix	107,109,104	107	107,109,104	107
15	104,85,99	96	101,84,103	96
50	130,103,105	113	133,100,103	112
100	98,89,117	101	129,100,114	114
175	91,103,122	106	101,94,121	105

Data extracted from Report Tables 1-4, pages 29-32.

Analytical data for test [illegible] and concentration were considered to be within acceptable limits.

e. Dietary Admixes

Appropriate dietary concentrations were prepared by serial dilution of a premix with basal diet. Premixes were made every 2 weeks and diets, every week. Concentrations were adjusted each week based on the most recent body weights and food consumption. The 0 mg/kg/day (control) group received

a placebo (starch/sucrose matrix only) mixed with basal diet. The amount of placebo was about the same as the microencapsulated test article at 175 mg/kg/day (Highest Dose Tested) and was prepared about every 4 weeks.

H. Animals

Male and female, 6-8 weeks old, B6C3F1 mice were received from Charles River Research Laboratories, Portage, MI. There was an acclimation period of at least 7 days prior to study start. The animals were housed individually in stainless steel cages, " ... in rooms designed to maintain adequate environmental conditions (temperature, humidity, photocycle)." [No temperature or humidity ranges were provided. No hours for the light/dark cycle were provided.] Food and water were available ad libitum.

I. Mortality, Moribundity and Clinical Signs

Cageside observations were made A.M. and P.M. 7 days/week. The animals were handled and closely examined weekly.

There was no mortality during the study.

No clinical signs were reported which distinguished treated from control groups.

J. Body Weights

Animals were weighed prior to the start of the study and weekly thereafter. Table 4.

In males and females, there were dose-dependent lower group mean body weights primarily in the 50, 100 and 175 mg/kg/day groups throughout the study with statistical significance ($p \leq 0.05$) at almost every weighing interval with the major decrease being during the first 4 weeks. Group mean body weight gains for males were 6.6, 4.8, 4.2, 4.0 and 2.8 g during the 13 weeks for the 0, 15, 50, 100 and 175 mg/kg/day groups, respectively. In females, the group mean body weight gains were 7.6, 7.1, 5.9, 5.3 and 3.2 g for the respective dose groups. The lower weight gains were primarily during the first 4 weeks of the study.

Table 4

GROUP MEAN BODY WEIGHTS AND WEIGHT GAINS IN A 13-WEEK DIETARY ADMIX MOUSE STUDY WITH TELONE II

Day	Males (mg/kg/day)					Females (mg/kg/day)				
	0	15	50	100	175	0	15	50	100	175
B.W.										
-8	20.3	20.2	20.2	20.1	20.2	17.3	17.2	17.3	17.3	17.2
-2	21.9	22.3	22.7	21.9	22.1	18.7	18.3	18.5	18.4	18.2
6	23.4	23.3	22.7	22.2	22.1	20.1	19.6	19.4	18.9	18.9
13	24.1	23.4	22.6	22.5	21.9	20.6	20.2	19.3	18.7	18.7
20	24.7	24.1	23.4	23.0	22.6	21.7	20.9	20.1	19.5	19.4
27	25.4	24.4	23.9	23.2	22.6	22.7	21.9	21.0	20.1	20.1
48	26.1	25.3	24.8	23.6	23.3	23.9	22.7	22.6	21.7	21.4
69	27.5	26.8	26.4	25.5	24.1	25.7	24.9	24.2	23.3	23.3
90	28.5	27.1	26.9	25.9	24.9	26.3	25.4	24.9	23.7	23.4
GAIN										
-2-27	3.5	2.1	1.7	1.3	0.5	4.0	3.6	2.5	1.7	1.9
27-48	0.7	0.9	0.9	0.4	0.7	1.2	0.8	1.6	1.6	1.3
48-69	1.4	1.5	1.6	1.9	1.6	1.8	2.2	1.6	1.6	1.9
69-90	1.0	0.3	0.0	0.4	0.0	0.6	0.5	0.2	0.4	0.1
-2-90	6.6	4.8	4.2	4.0	2.8	7.6	7.1	5.9	5.3	5.2

Number of mice = 10/sex/group at each interval
NOTE: Body weight gains calculated by the Reviewer.
Statistical Significance: unmarked = $p<0.05$
B.W. = Body Weight (g)
GAIN = Body Weight Gain (g)
Data extracted from Report Tables 8-10, pages 54-63.

K. Food Consumption

Measurements were made for the week prior to test article administration and weekly throughout the study. Table 5.

There was a decrease in food consumption (g/animal/day) in males only (all doses) during the first 2 weeks of the study. Females dosed with 100 and 175 mg/kg/day had decreased consumption during the 1st week. The Report Authors suggested that this observation, plus decreases in body weight gain, indicated a palatability problem with, at least, the 2 higher doses. Animals at the higher dose levels animals were reported to, "scratch their feed more than the animals fed the control and lower dose levels." [The Report stated that, "A subsequent TELONE II dietary study using additional scratch resistant mechanisms showed reduced food consumption at the higher dose levels relative to controls which is corroborating evidence that a palatability problem exists at the higher dose levels (Preliminary Data)."]

Table 5

SELECTED GROUP MEAN FOOD CONSUMPTION VALUES (g/mouse/day) IN A 13-WEEK DIETARY ADMIX MOUSE STUDY WITH TILONE II

Days	Males (mg/kg/day)					Females (mg/kg/day)				
	0	15	50	100	175	0	15	50	100	175
-8-2	4.6	4.6	4.5	4.6	4.8	4.4	4.3	4.3	4.4	4.3
1-8	5.0	4.6	4.3	4.2	4.2	4.6	4.9	4.7	4.2	4.3
8-15	5.3	4.7	4.5	4.9	4.8	4.6	5.2	5.1	4.9	5.0
15-22	5.1	5.5	5.1	5.2	5.2	5.2	5.6	6.2	5.7	6.0
22-29	5.6	5.9	5.4	6.0	5.9	5.5	6.2	6.4	6.3	6.7
42-50	6.0	5.8	5.7	6.0	6.5	6.6	7.1	6.5	6.8	7.1
64-71	5.6	5.4	5.4	5.3	5.6	6.6	5.8	6.1	5.9	5.9
85-92	5.3	5.5	5.7	5.8	5.5	6.2	6.0	6.1	5.9	6.5

NOTE: values are means from 8-10 mice.
Data extracted from Report Tables 12 and 13, pages 64-67.

L. Ophthalmology

All animals were examined prior to the start of the study and at the time of necropsy.

There were no findings which were considered to be related to test article administration.

M. Clinical Pathology

Animals were anesthetized with methoxyflurane and blood was removed at the time of necropsy from the orbital sinus. [The Report did not say whether or not the mice were fasted.]

HEMATOLOGY

The following parameters were examined:

Hematocrit*	Leukocyte count*
Hemoglobin*	Leukocyte differential*
Erythrocyte count*	Erythrocyte, leukocyte and platelet morphology
Platelet count*	

* = EPA Guideline requirement

The only statistically significant (p<0.05) difference reported was a decrease in the group mean leukocyte counts of males only at the 175 mg/kg/day dose. Group mean ± S.D. values for the male 0, 15, 50, 100 and 175 mg/kg/day groups were

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2.0±0.5, 2.0±0.6, 1.7±0.6, 1.5±0.6 and 1.1*±0.5 x 10^3/CU MM. The individual mouse counts were: control = 3.0, 2.6, 2.4, 2.2, 2.2, 1.8, 1.6, 1.6, 1.6 and 1.4; 175 mg/kg/day = 2.0, 1.6, 1.4, 1.2, 1.2, 1.2, 0.8, 0.8, 0.6 and 0.6. As there was a dose-response decrease in the group mean values, it appears that this observation may be related to test article administration.

CLINICAL CHEMISTRY

The following parameters were examined:

Sodium*	Urea nitrogen*	Alkaline phosphatase
Potassium*	Creatinine*	Alanine aminotransferase*
Phosphorus*	Total protein*	Aspartate aminotransferase*
Chlorine*	Albumin*	
Calcium*	Globulin	
	Glucose*	
	Total bilirubin*	
	Cholesterol	
	Triglycerides	

* = EPA Guideline Requirement

The following parameters showed statistical significance:

Table 6

STATISTICALLY SIGNIFICANT CLINICAL CHEMISTRY PARAMETERS IN A 13-WEEK DIETARY ADMIX STUDY IN MICE WITH TELONE II

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	15	50	100	175	0	15	50	100	175
Urea nitrogen	32	28	36*	24*	27	21	19	20	21	20
Glucose.....	190	186	184	173	162*	192	191	187	181	165
Triglycerides	94	84	79	75	81	75	63	61	56*	52*
Chlorine	129	128	131	131	131	128	129	130	133*	130

Urea nitrogen = MG/DL
Glucose = MG/DL
Triglycerides = MG/DL
Chlorine = MMOL/L
Statistical Significance: * = $p \leq 0.05$
Data extracted from Report Tables 18 and 19, pages 80-83.

These differences were not considered to be of toxicological significance as they were not dose dependent and/or were observed only in one sex and/or were within expected ranges and/or lacked histopathological corroboration.

N. Sacrifice and Pathology

At the time of scheduled necropsy, nonfasted animals were anesthetized with methoxyflurane, and after the trachea was clamped, they were decapitated. A complete gross examination was conducted. The following organs were weighed and organ-to-body weight ratios were calculated: brain, liver, kidneys, heart and testes. All tissues from the 0 and 175 mg/kg/day mice were processed and examined by light microscopy. The following tissues from the 15, 50 and 100 mg/kg/day animals were processed and examined: lung, liver, kidney, stomach, gross lesions and target tissues identified in the 175 mg/kg/day mice.

The following tissues were preserved and examined; those organs with an "x" were weighed:

DIGESTIVE	RESPIRATORY	UROGENITAL
Tongue	Trachea*	xKidneys*
Salivary glands*	Lung*	Urinary bladder*
Esophagus*		xTestes*
Stomach*	CARDIOV/HEMAT	Epididymides
Duodnum*	Aorta*	Prostate
Jejunum*	xHeart*	Seminal vesicles
Ileum*	Bone marrow*	Ovaries
Cecum*	Lymph nodes*	Uterus*
Colon*	Spleen*	Cervix
Rectum*	Thymus*	Oviducts
xLiver*		Vagina
Pancreas*		
Gallbladder		

NEUROLOGIC	GLANDULAR	OTHER
xBrain*	Adrenals*	Bone*
Peripheral nerve*	Lacrimal gland*	Skeletal muscle*
Spinal cord (3 levels)*	Mammary gland*	Skin
Pituitary*	Parathyroid*	All gross lesions and masses*
Eyes*	Thyroid*	

Coagulating gland, Larynx, Nasal tissues, Sebaceous gland, Harderian gland, Oral tissues

* = EPA Guideline Requirements

MACROSCOPIC

There were no gross necropsy findings which were considered to be test article related.

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ORGAN WEIGHTS

NOTE: FINAL BODY WEIGHTS - Report page 17 stated that "Terminal, nonfasted [bold by Reviewer] body weights were recorded for all mice."

Report pages 55 and 57 (Tables 8 and 9) present the group mean day 90 body weights. Report pages 84 and 85 (Tables 20 and 21) present the group mean "Final Body Weight". The following are the values (0, 15, 50, 100 and 175 mg/kg/day):

Page 55, males = 28.5, 27.1, 26.4, 25.9, 24.9
Page 84, males = 26.8, 25.4, 24.6, 23.9, 22.8

Page 57, females = 26.2, 25.4, 24.4, 23.7, 23.4
Page 85, females = 25.2, 23.9, 23.1, 22.3, 21.9

The differences between the day 90 and final body weights (nonfasted) are not considered by the Reviewer to have a negative impact on this study.

Table 7

GROUP MEAN ABSOLUTE AND RELATIVE ORGAN WEIGHTS IN A 13-WEEK DIETARY ADMIX STUDY IN MICE WITH TELONE II

Dose	Body Wt.	Brain	Heart	Kidneys	Liver	Testes
MALE						
0a	26.8	.51/1.9b	.15/.54	.50/1.9	1.4/5.1	.23/.86
15	25.4*	.50/2.0	.15/.58	.50/1.9	1.3/5.1	.24/.93
50	24.6*	.49/2.0	.14/.56	.48/1.9	1.2*/5.0	.23/.94*
100	23.9*	.49/2.1*	.14/.58	.45*/1.9	1.1*/4.8	.23/.98*
175	22.8*	.49/2.1*	.13*/.56	.41*/1.8	1.1*/4.7	.22/.96*
FEM						
0	25.2	.50/2.0	.14/.55	.37/1.4	1.4/5.4	
15	23.9*	.50/2.1	.13*/.53	.35/1.5	1.2*/5.1	
50	23.1*	.49/2.1*	.13*/.56	.34*/1.5	1.2*/5.2	
100	22.3*	.50/2.2*	.12*/.55	.34*/1.5	1.2*/5.2	
175	21.5*	.50/2.3*	.11*/.54	.31*/1.4	1.1/5.10	

FEM = FEMALES
a = mg/kg/day
b = absolute weight in g/relative weight in g per 100 g body weight
Body Wt. = nonfasted final body weight
Statistical Significance (Dunnett's or Wilcoxon's Tests): * = p<0.05
@ = p<0.05 for absolute and relative weights
Number of mice/sex/group = 10
Data extracted from Report Tables 20 and 21, pages 84 and 85.

All statistically significant ($p<0.05$) differences in absolute or relative organ weights appear to be a reflection of lower nonfasted final body weights in treated animals.

MICROSCOPIC PATHOLOGY

Kidney and liver changes may have been due to test article administration. Table 8

Table 8

MICROSCOPIC KIDNEY AND LIVER FINDINGS IN A 13-WEEK DIETARY ADMIX STUDY IN MICE WITH TELONE IX

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	15	50	100	175	0	15	50	100	175
KIDNEY										
Number tissues examined	10	10	10	10	10	10	10	10	10	10
Within normal limits ...	7	9	6	8	3	9	10	9	9	10
Aggregate(s) of mononuclear (predominately lymphoid) cells, interstitium, unilateral, focal-very slight	2	0	1	0	3	0	0	0	0	0
Aggregate(s) of mononuclear (predominately lymphoid) cells, interstitium, bilateral, multifocal-very slight	0	0	0	1	0	0	0	0	0	0
Degeneration, tubule(s), unilateral, focal-very slight	0	1	1	1	2	1	0	1	1	0
Degeneration, tubule(s), bilateral, multifocal-very slight	1	0	0	0	1	0	0	0	0	0
Vacuolation-decreased tubule(s)	0	0	0	0	3	0	0	0	0	0
LIVER										
Number tissues examined	10	10	10	10	10	10	10	10	10	10
Within normal limits	3	2	4	2	1	0	2	3	2	0
Decreased size, hepatocellular, diffuse-very slight	1	5	6	6	8	0	0	0	0	0
Aggregates of RE cells frequently adjacent to degenerative or necrotic hepatocytes-very slight	6	5	0	2	1	10	8	7	8	10

Data extracted from Report Table 23, pages 98 and 99.

The Report Authors indicated that these observations " ... were considered secondary to the lowered body weight of animals at these dose levels and their reduced nutritional status." In the kidney, very slight unilateral focal tubular degeneration and decreased tubular vacuolation were reported in 2/10 and 3/10 mice, respectively, in 175 mg/kg/day males compared with 0/10 in controls. Regarding the liver, there was an increase in the number of only male mice (versus control) with very slight, diffuse, decreased hepatocellular size."

II. DISCUSSION

Analytical data for test article stability, concentration and homogeneity were considered to be within acceptable limits.

There was no mortality. No clinical signs were attributed to TELONE II administration.

In both males and females there were lower group mean body weights and weight gains primarily at the 50, 100 and 175 mg/kg/day doses. Day 90 body weights of the 15, 50, 100 and 175 mg/kg/day groups were the following percent less than the respective control: males = 5, 7, 9 and 13; females = 3, 7, 10 and 11. The major treatment related effect occurred during the first 4 weeks of dosing.

There was a slight reduction in food consumed for all dosed males during the first 2 weeks of the study and in the 100 and 175 mg/kg/day females during the 1st week. This coincides with a decrease in body weight gain and is probably related to palatability.

There were no ophthalmic findings associated with test article administration.

The only hematology parameter effected appeared to be a dose-response decrease in group mean leukocyte counts in males only. Statistical significance ($p<0.05$) occurred only in the 175 mg/kg/day mice. This decrease may be attributed to lower body weights and/or to a reduced nutritional status (secondary effects) rather than to treatment, as there were no corroborative histopathological changes in the bone marrow but was a similar decrease noted in females.

No clinical chemistry parameter differences were considered to be of toxicological significance.

There were no macroscopic test article related findings. Absolute and/or relative (to body weight) organ weight differences appeared to be a reflection of lower nonfasted final body weights in treated mice.

Kidney and liver microscopic findings were not only very slight, but were in small odds, and were considered by the Study Authors to have been related to a decrease in body weight gain. The observa-

tions do not appear to be of severe toxicological significance. [NOTE: There were no reported changes in the histopathology of the nonglandular portion of the stomach as was the observation in the 13-week rat study. (MRID No. 429548-02)]

III. CONCLUSIONS

In a subchronic toxicity study, TELONE II (1,3-dichloropropene - microencapsulated) was administered by dietary admix to Charles River B6C3F1 mice (10/sex/group) at doses of 0, 15, 50, 100 and 175 mg/kg/day for 13 weeks. The following parameters were examined: mortality, clinical signs, body weights, food consumption, ophthalmology, hematology, clinical chemistry, macroscopic pathology, organ weights and microscopic pathology.

Body weights and weight gains were lower than the controls in males and females at 50, 100 and 175 mg/kg/day (27, 36, 39 and 58% and 7, 22, 30 and 32% at 15, 50, 100 and 175 mg/kg/day). There was a dose-response decrease in the leukocyte counts of males only. No other parameters appeared to be affected. The NOEL is 15 mg/kg/day and the LOEL is 50 mg/kg/day. [MRID No. 429548-01]

Core classification is Minimum. This study satisfies the data requirement (§82-1A) for a 13-week subchronic toxicity study in mice.