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

010299

JUN 2 - 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: TELONE II (1,3-Dichloropropene) - Chronic Oral Toxicity Study in Dogs

PC Code: 029001 **Caswell No.:** 324A
MRID No.: 424410-01 **DP Barcode:** D182066
Submission No.: S424465 **Case No.:** 818694

FROM: Alan C. Levy, Ph.D., Toxicologist Alan C. Levy
Review Section IV, Toxicology Branch II 5-27-93
Health Effects Division (H7509C)

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

THRU: Jess Rowland, M.S., Acting Section Head Jess Rowland 5/27/93
Review Section IV, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D., Branch Chief mvanGemert 5/28/93
Toxicology Branch II
Health Effects Division (H7509C)

REQUEST: Review a chronic oral toxicity study in dogs with TELONE II

Registrant: DowElanco, Indianapolis, IN

CONCLUSIONS:

Telone II (1,3-Dichloropropene), administered by dietary admix to male and female dogs at doses of 0, 0.5, 2.5 and 15 mg/kg/day for one year, appeared to cause the following in the 15 mg/kg/day group only: decreased body weight gains; hypochromic, microcytic anemia (increase in erythrocytes along with decreases in hemoglobin, hematocrit, mean corpuscular volume and mean corpuscular hemoglobin) with an increase in reticulocytes and platelets as well as hematopoietic activity in bone marrow and spleen; and a possible increase in absolute liver weights in male dogs.

1 of 25

The No Observed Effect Level (NOEL) = 2.5 mg/kg/day

The Lowest Observed Effect Level (LOEL) = 15 mg/kg/day (decreased body weight gain, microcytic anemia, increase in hematopoietic activity and possible increase in absolute liver weights in males)

Classification: **Core Supplementary**

The following points arose during the review of this study and the study may be upgraded upon submission/review of the Registrant's response:

1. DOSING OF DOGS

Dogs were housed 2/pen. The Report indicated the assumption that both animals consumed exactly the same amount of food. It was stated that the dose, in mg/kg/day, was administered based on the most recent body weight and food consumption values. Food was available ad libitum. Some dogs (including control) did not gain weight during the one-year study (days -2 to 363 weights).

The Registrant is requested to comment on the accuracy of the mg/kg/day of test article in relationship to 2 dogs/pen, the dogs having different body weights as well as weight gains and the food consumption being assumed to be equal for both dogs in the same pen.

2. ALKALINE PHOSPHATASE LEVELS

There was an apparent inconsistency between the text and data regarding this parameter.

This study does not satisfy the data requirements (§83-1) for a chronic oral toxicity study in dogs and is not acceptable for regulatory purposes.

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Reviewed by: Alan C. Levy, Ph.D. Alan C. Levy
Section IV, Tox. Branch II (H7509C) 5-27-93

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Secondary Reviewer: Jess Rowland, M.S. Jess Rowland 5/27/93
Section IV, Tox. Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Chronic Oral Toxicity - Dog (§83-1)

TEST MATERIAL: TELONE II

SYNONYMS: 1,3-Dichloropropene

Chemical No.: 029001 **Caswell No.:** 324A
MRID No.: 424410-01 **DP Barcode:** D182066
Submission No.: S424465 **Case No.:** 818694

STUDY NUMBER: M-003993-024

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: One-Year Dietary Toxicity Study in Beagle Dogs

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

REPORT ISSUED: July 22, 1992

CONCLUSIONS:

Telone II (1,3-Dichloropropene), administered by dietary admix to male and female dogs at doses of 0, 0.5, 2.5 and 15 mg/kg/day for one year, appeared to cause the following in the 15 mg/kg groups only: decreased body weight gains; hypochromic, microcytic anemia (increase in erythrocytes along with decreases in hemoglobin, hematocrit, mean corpuscular volume and mean corpuscular hemoglobin) with an increase in reticulocytes and platelets as well as hematopoietic activity in bone marrow and spleen; and a possible increase in male absolute liver weights.

The No Observed Effect Level (NOEL) = 2.5 mg/kg

The Lowest Observed Effect Level (LOEL) = 15 mg/kg (decreased body weight gain, microcytic anemia, increase in hematopoietic activity and possible increase in male absolute liver weights)

Classification:

Core Supplementary - The following points arose during the review of this study and the study may be upgraded upon submission/review of Registrant's response:

1. DOSING OF DOGS

Dogs were housed 2/pen. The Report indicated the assumption that both animals consumed exactly the same amount of food. It was stated that the dose, in mg/kg/day, was administered based on the most recent body weight and food consumption values. Food was available ad libitum. Some dogs (including control) did not gain weight during the one-year study (days -2 to 363 weights).

The Registrant is requested to comment on the accuracy of the mg/kg/day of test article in relationship to 2 dogs/pen, the dogs having different body weights as well as weight gains and the food consumption being assumed to be equal for both dogs in the same pen.

2. ALKALINE PHOSPHATASE LEVELS

There was an apparent inconsistency between the text and data regarding this parameter.

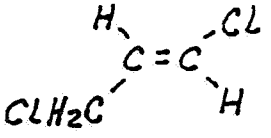
This study does not satisfy the data requirements (§83-1) for a chronic oral toxicity study in dogs and is not acceptable for regulatory purposes.

I. MATERIALS, METHODS AND RESULTS

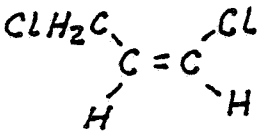
A. Test Article Description

Name: TELONE II, 1,3-Dichloropropene

Formula:



Trans Isomer



Cis Isomer

Purity: 95.8% (before and after microencapsulation) - approximately equal mixture of cis and trans isomers

Lot No.: MM880202 INERT INGREDIENT INFORMATION IS NOT INCLUDED

Test Material: microencapsulated [redacted] matrix (Lot # 9359-1A)

B. Dose Selection

The doses used in this one-year dietary admix dog study were 0 (control), 0.5, 2.5 and 15 mg/kg body weight per day. The control received feed with the microencapsulation matrix (approximately the amount received by the high-dose [15 mg/kg] dogs).

In a 13-week subchronic dietary admix study in beagle dogs the following were reported:

35-40 mg/kg - body weights and food consumption decreased compared to controls; erythrocytes, hemoglobin and hematocrit decreased; no decrease in blood forming cells on microscopic bone marrow examination; hematological recovery was noted when dogs were placed on control feed plus iron supplements

12-15 mg/kg - slight depression of hemoglobin and hematocrit

4-5 mg/kg - No-Observed-Effect Level (NOEL)

INERT INGREDIENT INFORMATION IS NOT INCLUDED

C. Test Article Analyses for Purity, Stability and Homogeneity

PURITY - No analytical data were included in the Report. Materials and Methods, Test Material which appeared on Report page 13(11), stated the following, "The purity of the test compound before and after microencapsulation was reported to be 95.8% by gas chromatography and the identity of the sample was confirmed by capillary gas chromatography/mass spectroscopy (Chritz et al., 1989; Ghaoui, 1989)." [The references are listed as Dow Analytical reports.]

STABILITY - In the Results and Discussion section of the Report, Delivery of Test Material (page 22(20)), "Repeated analysis of microencapsulated TELONE II confirmed the stability of 1,3-dichloropropene within the [redacted] of the microcapsules under study conditions for over 12 months, a period exceeding the length of the study (data not shown)."

Representative data for stability and homogeneity are presented in Table 1.

Table 1

A SUMMARY OF ANALYTICAL DATA FOR STABILITY AND HOMOGENEITY OF TELONE II IN A ONE-YEAR DIETARY ADMIX DOG STUDY

STABILITY

(Target concentration = 1.0 x 10^{-1}%)

Day	N	Observed conc. (x10^{-2}%)	% Target conc.	% Day 0 conc.
0	18	8.56±0.69	86	-
5	18	8.35±0.40	84	98
20	18	8.35±0.29	84	98
35	18	7.82±0.25	78	91

HOMOGENEITY

(Target concentrations of 1.0 x 10^{-1} and 1.3 x 10^{-2}%)

Location	Side 1	Center	Side 2
Top	9.422/1.17†	9.035/1.16	8.653/1.18
Middle	8.735/1.09	6.901/1.17	8.697/1.23
Bottom	8.685/1.20	8.513/1.13	8.429/1.29

NOTE: Observed concentrations expressed in x 10^{-2}%

Overall Mean ± S.D. was 8.56 ± 0.69 x 10^{-2}% and 1.18 ± 0.06 x 10^{-2}%

Overall percent of respective target concentrations was 89% and 91%

† = Two target concentrations

Table 1 (continued)

DIETARY SAMPLES (Percent of Targeted Dose Level)

Month	M & F Premix mg/kg =	Males 0.5	Males 2.5	Males 15	Females 0.5	Females 2.5	Females 15
1	102	97	109	95	93	107	102
6	89	109	75	91	109	86	90
12	124	87	103	109	98	109	101
Avg.†	100	94	95	99	100	94	95

† = Averages of samples at months 1, 3, 6, 9 and 12.

Data extracted from Report Tables 1, 2 and 3, pages 34(32) - 36(34).

Based upon the statements in the Report plus the analytical data presented, the purity, stability and homogeneity of the TELONE II dietary admixes appear to be within acceptable limits.

D. Animals

Beagle dogs, apparoximately 4 months old, were received from Marshall Research Laboratory, North Rose, NY. The animals were subjected to complete physical examinations by a veterinarian and were acclimated for at least 30 days. The dogs were housed 5/pen for about 3 weeks after arrival and 2/pen during the prestudy as well as the study phases. The pens were, "... in rooms designed to maintain adequate environmental conditions (temperature, humidity and photocycle) for the species being housed." Food and water were available ad libitum. The dogs were assigned to test groups by computer-generated randomization based on body weights.

Dogs were placed 4/sex/group and given diets so that they would receive 0, 0.5, 2.5 or 15 mg/kg body weight/day for one year. Based upon the 13-week study, it was expected that 15 mg/kg would cause some hematocrit and hemoglobin depression.

Concentrations of TELONE II in the diets were adjusted weekly for the first 13 weeks and monthly thereafter. Dietary concentrations were based on the most recent body weight and food consumption information.

E. General Observations

1. MORTALITY AND CLINICAL SIGNS

The dogs were observed at least once/day during the workweek for treatment-related effects. They were also observed a 2nd time daily (AM) in addition to twice/day on weekends and holidays for morbidity/mortality/feed/water. A detailed examination was performed prior to the start of the study and weekly thereafter.

All dogs survived the 12-month study.

The only clinical sign that was considered to be related to test article administration, was paleness of the mucous membranes of 2/4 males and 1/4 females in the 15 mg/kg group. Report page 22(20) states, "This change was consistent with the lower erythroid parameters observed in these animals (see Hematology)." In addition, 15 mg/kg male (No. 90A1491), "... was noted to be underweight and displayed bilateral alopecia, roughened skin, and, occasionally, generalized redness of the skin."

2. BODY WEIGHTS

These were recorded for individual dogs weekly for the first 13 weeks and at every 4 weeks thereafter. See Table 2.

Table 2

GROUP MEAN BODY WEIGHTS AND WEIGHT GAINS OF DOGS ADMINISTERED TELONE II AS A DIETARY ADMIX FOR ONE YEAR

	Males				Females			
Test Day mg/kg =	0	0.5	2.5	15	0	0.5	2.5	15
BODY WEIGHTS (kg)								
-2	9.4	9.2	9.1	9.2	7.5	7.7	7.9	7.6
6	9.5	9.6	9.2	9.0	7.6	7.7	7.8	7.6
13	9.7	9.8	9.4	9.2	7.6	7.8	7.9	7.7
20	9.9	10.0	9.6	9.1	7.8	8.1	8.1	7.8
27	9.7	10.1	9.6	9.1	7.9	8.2	8.4	7.8
55	10.1	10.1	9.9	9.1	8.1	8.4	8.5	7.7
90	10.6	10.6	10.2	9.3	8.4	8.8	9.0	7.9
174	11.1	10.9	10.2	9.4	8.9	9.3	9.2	8.0
258	11.8	11.1	10.4	9.6	8.8	9.7	9.4	8.3
363	11.5	11.0	10.7	10.0*	9.2	10.2	9.6	8.2

NOTE: Report Table 23, pages 159(157) and 160(158), Summary of Statistically Identified Differences (p value table; alpha <0.05) - * Time = 0.003.

Table 2 (Continued)

GROUP MEAN BODY WEIGHTS AND WEIGHT GAINS OF DOGS ADMINISTERED TELONE II AS A DIETARY ADMIX FOR ONE YEAR

	Males				Females			
Test Day mg/kg =	0	0.5	2.5	15	0	0.5	2.5	15
BODY WEIGHT GAINS (kg)								
-2 to 27	0.3	0.9	0.5	-0.1	0.4	0.5	0.5	0.2
-2 to 90	1.2	1.4	1.1	0.1	0.9	1.1	1.1	0.3
-2 to 174	1.7	1.7	1.1	0.2	1.4	1.6	1.3	0.4
-2 to 258	2.4	1.9	1.3	0.4	1.3	2.0	1.5	0.7
-2 to 363	2.1	1.8	1.6	0.8	1.7	2.5	1.7	0.6

Data extracted (or calculated by the Reviewer) from Report Tables 7 and 8, pages 86(84)-89(87).

Male No. 90A1491, 15 mg/kg, had an initial (day -2) weight of 8.7 kg and on day 41 weighed 7.7 kg. Throughout the 52 weeks, this dog had weights which fluctuated from this low of 7.7 kg to a high of 9.2 kg with a day-363 weight of 8.3 kg.

There were individual males and females at various dose levels (including controls) which essentially weighed the same at study termination as they did at study initiation (Report Tables A-5 and A-6, pages 184(182)-187(185), individual body weights).

The 15 mg/kg males gained a group mean of 0.8 kg during the 52 weeks campared with a control value of 2.1 kg. The 0.5 and 2.5 mg/kg groups gained 1.8 and 1.6 kg, respectively. For females, the 15 mg/kg dogs gained a group mean of 0.6 kg (day -2 to day 363) compared with 1.7, 2.5 and 1.7 kg for the 0, 0.5 and 2.5 mg/kg groups, respectively.

3. FOOD CONSUMPTION

This was calculated at weekly intervals for the first 13 weeks and every 4 weeks thereafter (full and empty feeders from each pen were weighed). **NOTE:** There were 2 dogs/pen throughout the study. Food consumption was expressed as g/dog/day.

Males dosed with 15 mg/kg appeared to eat more food than did dogs from the other 3 groups. Presented as g/dog/day, food consumption for the 0, 0.5 and 2.5 mg/kg groups, ranged from 313-415; whereas, in the 15 mg/kg group, it ranged from 352-505 with 20/24 intervals indicating >400. [Report Tables 9 and 10, pages 90(88)-93(91).]

There were little or no differences between groups regarding the amount of food consumed by females.

4. OPHTHALMOLOGY EXAMINATIONS

These were performed, using an indirect ophthalmoscope, on all dogs prior to the start of the study and at about one week before study termination.

There were no apparent treatment related effects.

F. Clinical Pathology

Blood samples for hematology and clinical chemistry were taken from the jugular vein of fasted dogs (overnight) at least twice prior to study initiation as well as at 3, 6, and 9 months plus during the week prior to study termination.

Urine specimens were obtained from the urinary bladder at necropsy.

1. HEMATOLOGY - The (x) parameters were examined.

x Hematocrit (HCT)*	x Leukocyte differential count*
x Hemoglobin (HGB)*	x Mean Corpuscular HGB (MCH)
x Leukocyte count (WBC)*	x Mean Corpusc. HGB conc. (MCHC)
x Erythrocyte count (RBC)*	x Mean Corpusc. volume (MCV)
x Platelet count*	x Reticulocyte count

* = EPA Guideline Requirement

The Report indicated statistically significant differences in erythrocyte, hemoglobin and hematocrit values in both sexes at most intervals for the 15 mg/kg group only. There were increases in erythrocytes and decreases in both hemoglobin concentration as well as hematocrits. In addition, the mean corpuscular volume and mean corpuscular hemoglobin values in this group were lower than the control and other dose-group values. An increase in the number of platelets in the 15 mg/kg dogs was also reported.

At the 9 and 12 month bleedings, male No. 90A1491, 15 mg/kg, had erythrocyte, hemoglobin and hematocrit values lower than any of the other 3 dogs in this group (RBC: 5.9, 6.5 versus 8.3-9.9; HGB: 7.8, 8.6 versus 10.7-14.5; and HCT: 26, 28 versus 33-50). Values for this one dog therefore decreased the group means.

Table 3 presents selected hematology parameters.

Table 3

SELECTED GROUP MEAN HEMATOLOGY PARAMETERS FOR DOGS ADMINISTERED TELONE II FOR ONE YEAR

MALES

Interval	mg/kg	RBC	HGB	HCT	MCV	MCH	Plat.
pre: 1	0	6.1	13.8	46	-	-	372
	0.5	6.1	13.6	46	-	-	338
	2.5	6.2	13.8	47	-	-	334
	15	5.8	12.8	44	-	-	392
pre: 2	0	6.3	13.8	47	-	-	359
	0.5	5.8	12.6	42	-	-	294
	2.5	6.4	13.7	46	-	-	320
	15	6.1	12.9	44	-	-	372
3 month	0	7.2	15.7	54	75	22	355
	0.5	7.2	15.6	54	75	22	299
	2.5	8.0	16.2	56	71	20	340
	15	7.5	11.2	39	52	15	554
6 month	0	7.3	16.7	54	74	23	323
	0.5	7.6	17.1	56	73	23	304
	2.5	8.1	16.9	56	69	21	314
	15	8.3	11.3	37	44	14	636
9 month	0	7.4	16.4	53	72	22	324
	0.5	7.5	16.7	54	72	22	299
	2.5	7.9	16.2	53	68	21	314
	15	8.2	11.2	35	43	14	611
12 month	0	7.8	17.4	57	73	22	365
	0.5	7.8	17.5	57	72	22	313
	2.5	8.1	17.0	56	69	21	316
	15	8.8	12.3	41	46	14	554

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Table 3 (Continued)

Interval	mg/kg	RBC	HGB	HCT	MCV	MCH	Plat.
FEMALES							
pre: 1	0	6.4	14.5	49	-	-	338
	0.5	6.5	14.1	48	-	-	403
	2.5	6.5	14.4	49	-	-	394
	15	6.2	13.5	46	-	-	246
pre: 2	0	6.5	14.4	48	-	-	319
	0.5	6.6	13.9	47	-	-	385
	2.5	6.6	14.6	49	-	-	387
	15	6.4	13.7	47	-	-	257
3 month	0	6.8	15.2	52	77	22	296
	0.5	7.3	15.6	54	74	21	416
	2.5	7.8	16.3	56	73	21	343
	15	7.7	11.5	40	52	15	469
6 month	0	7.3	17.2	54	75	24	297
	0.5	7.7	17.0	56	73	22	412
	2.5	7.8	16.3	56	71	21	407
	15	8.5	11.3	37	43	13	559
9 month	0	7.1	15.9	52	74	22	306
	0.5	7.6	16.3	54	71	22	394
	2.5	8.1	16.2	55	68	20	377
	15	8.9	11.6	37	42	13	708
12 month	0	7.7	17.3	57	75	23	320
	0.5	7.8	17.1	57	73	22	429
	2.5	8.4	18.0	60	72	21	373
	15	9.6	12.6	41	43	13	665

- = Not examined
RBC = Red Blood Cells - 10^6/cu mm
HGB = Hemoglobin - g/dl
HCT = Hematocrit - %
MCV = Mean Corpuscular Volume - cubic microns
MCH = Mean Corpuscular Hemoglobin -micro micrograms
Plat. = Platelets - 10^3/cu mm

Data extracted from Report Tables 11 and 12, pages 94(92)-117(115).

2. BLOOD CHEMISTRY - The (x) parameters were examined.

Other	Electrolytes
x Albumin*	x Calcium*
x Blood creatinine*	x Chloride*
x Blood urea nitrogen*	x Phosphorous*
x Cholesterol*	x Potassium*
x Globulin	x Sodium*
x Glucose*	
x Total bilirubin*	
x Total protein*	
x Triglycerides	

Enzymes
x Alkaline phosphatase
x Creatine phosphokinase*
x Serum alanine aminotransferase (SGPT)*
x Serum aspartate aminotransferase (SGOT)*

* = EPA Guideline Requirement

Reviewer's Comment: Report page 25(23), "Clinical Chemistry Parameters" includes the following statement (second sentence), "A statistically-identified **Decrease** [bold by Reviewer] in serum AP activity and increase in serum CK activity was observed in high-dose group males and females, respectively, relative to controls following 3, 6, 9 and 12 month dosing."

The following table (No. 4) presents the group mean interval values (extracted from Report Tables 15 and 17, pages 120(118)-125(123) and 132(130)-137(135).

Table 4

GROUP MEAN ALKALINE PHOSPHATASE VALUES (MU/ML) FOR DOGS ADMINISTERED TELONE II FOR ONE YEAR

Sex	mg/kg	pre: 1	pre: 2	3	6	9	12
Male	0	342	339	170	123	90	80
	0.5	203	177	127	107	91	74
	2.5	216	198	121	90	75	66
	15	193	189	112	101	**103**	69
Female	0	218	215	108	89	68	61
	0.5	193	196	111	94	91	77
	2.5	205	209	111	75	82	61
	15	261	299	**160**	**127**	**123**	**115**

The Registrant's attention is directed to the **BOLD** values where the numbers are **larger** than the control. The Registrant is therefore requested to review the text on Report page 25(23) based upon the above **BOLD** values and comment accordingly.

Other clinical chemistry parameters appeared to be within normal/historical limits.

3. URINALYSIS - The (x) parameters were examined.

x Appearance*	x Glucose*
- Volume*	x Ketones*
x Specific gravity*	x Bilirubin*
x pH	x Blood*
x Sediment (microscopic)*	x Urobilinogen
x Protein*	

* = EPA Guideline Requirements "-" = Not examined

G. Sacrifice and Pathology

After one year, fasted terminal body weights were taken and the dogs were sacrificed by sodium pentobarbital and exsanguination. Necropsies were performed by a veterinary pathologist. The (x) tissues were collected for histological examination. The (xx) organs were weighed.

Digestive	Respiratory	Urogenital
x Tongue	x Trachea*	xx Kidneys*
x Salivary glands*	x Lung*	x Urinary bladder*
x Esophagus*		xx Testes*
x Stomach*	Cardio./Hemat.	x Epididymides*
x Duodenum*	x Aorta*	x Prostate*
x Jejunum*	xx Heart*	- Seminal vesicle*
x Ileum*	x Bone marrow*	xx Ovaries*
x Cecum*	x Lymph nodes*	x Uterus*
x Colon*	x Spleen*	x Cervix
x Rectum*	x Thymus*	x Oviducts
xx Liver*		x Vagina
x Gallbladder*		
x Pancreas*		

Neurologic	Glandular	Other
xx Brain*	xx Adrenals*	x Bone*
x Peripheral nerve*	x Mammary gland*	x Skeletal muscle*
x Spinal cord (x3)*	x Parathyroids*	x Skin*
xx Pituitary*	xx Thyroids*	x All gross lesions/masses*
x Eyes*		x Larynx, nasal tissue, oral tissue, tonsils

* = EPA Guideline Requirement "-" = Not examined

1. MACROSCOPIC

Dog 90A1491, a 15 mg/kg male, was considered by the Report authors to have gross necropsy findings, "suggestive of a treatment-related effect." There was a generalized decrease in body size along with a decrease in body fat. Alopecia was also observed.

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

2. ORGAN WEIGHTS

The following organs were weighed and the weights expressed as absolute (g) and relative (organ weight to final body weight ratio - g/100 g): brain, liver, kidneys, thyroids (with parathyroids), pituitary, adrenals, heart, ovaries and testes.

Statistical analysis was made on a male/female combined population. Changes were: "increased relative heart, absolute and relative liver, absolute and relative pituitary gland weights in high dose group animals [15 mg/kg]. In addition, the absolute kidney weights of dogs ingesting 0.5 or 2.5 mg/kg/day TELONE II were statistically identified as increased relative to controls."

Table 5 presents liver and kidney weights.

Control male absolute liver weight had a group mean of 261 g with a range of 255-268 g. The 0.5 mg/kg group had a mean of 303 g with a range of 272-333 g. There was a mean and range in the 2.5 mg/kg group of 267 and 251-278, respectively. At 15 mg/kg, the mean was 318 g with a range of 291-334.

Historical Control data supplied by the Registrant (Report Table 24, pages 161(159)-164(162) were as follows:

Table 6

SELECTED REGISTRANT'S HISTORICAL CONTROL DATA FOR DOG LIVER AND KIDNEY WEIGHTS

	Liver				Kidney			
	absolute		relative		absolute		relative	
Sex	mean	range	mean	range	mean	range	mean	range
Male	307	291-334	2.5	2.4-2.7	64	61-68	None given	
Female	264	239-306	2.5	2.1-2.8	44	41-46	in report	

Total number of dogs: 22 males and 22 females
Total number of studies: 5; 4 studies with 4/sex, 1 study with 6/sex.

Table 5

GROUP MEAN AND INDIVIDUAL LIVER AND KIDNEY ABSOLUTE AND RELATIVE (TO BODY WEIGHT) ORGAN WEIGHTS OF DOGS ADMINISTERED TELONE II BY DIETARY ADMIX FOR ONE YEAR

Dose	Male						Female					
	Dog	Final	Liver		Kidney		Dog	Final	Liver		Kidney	
mg/kg	No.	B.W.	Abs	Rel	Abs	Rel	No.	B.W.	Abs	Rel	Abs	Rel
0	477	9.0	268	3.0	55	.62	493	7.6	260	3.4	33	.43
	478	13.7	255	1.9	55	.41	494	8.9	238	2.7	43	.49
	479	11.1	260	2.3	37	.33	495	10.1	192	1.9	35	.35
	480	10.4	261	2.5	43	.41	496	8.8	271	3.1	40	.45
	MEAN	11.1	261	2.4	48	.44	MEAN	8.8	240	2.8	38	.43
0.5	481	9.9	333	3.4	a	b	497	8.6	272	3.2	43	.51
	482	10.6	286	2.7	57	.54	498	10.1	290	2.9	42	.42
	483	10.1	272	2.7	65	.64	499	10.4	227	2.2	44	.42
	484	11.7	322	2.8	66	.56	500	9.8	267	2.7	35	.36
	MEAN	10.6	303	2.9	63	.58	MEAN	9.7	264	2.7	41	.43
2.5	485	10.3	276	2.7	68	.66	501	9.8	232	2.4	39	.40
	486	10.6	251	2.4	68	.63	502	9.2	298	3.2	45	.49
	487	10.4	278	2.7	58	.56	503	10.0	250	2.5	42	.42
	488	10.4	262	2.5	64	.61	504	7.6	226	3.0	38	.50
	MEAN	10.4	267	2.6	64	.62	MEAN	9.1	252	2.8	41	.45
15	489	10.5	291	2.8	52	.49	505	7.4	273	3.7	43	.58
	490	9.6	334	3.5	61	.64	506	8.4	234	2.8	39	.46
	491	8.0	332	4.1	56	.69	507	7.3	228	3.1	34	.46
	492	9.3	315	3.4	53	.57	508	8.2	270	3.3	43	.52
	MEAN	9.4	318	3.4	56	.60	MEAN	7.8	251	3.2	39	.51

B.W. = dog body weights in kg
Values excluded from analysis: a = 1.664; b = 0.017
Absolute Weight = g; Relative Weight = g/100 g body weight
Data extracted from Report Tables A-19 and A-20, pages 259(257)-261(259).

Isolated increases or decreases in absolute or relative organ weights were reported, but none was considered to be probably related to Telone II administration.

3. MICROSCOPIC

Group histopathological data were presented in Report Table 22, pages 150(148)-158(156).

The only findings considered to be likely related to test article administration were in the 15 mg/kg/day group:

a. Bone Marrow - 4/4 males and 4/4 females had increased hematopoiesis

b. Spleen - 2/4 males and 2/4 females had increased extramedullary hematopoiesis

c. Tongue - 2/4 males had very slight, multifocal chronic active inflammation of the mucosa. The Report authors stated:

> "This alteration was interpreted to be suggestive of direct irritation of TELONE II to the lingual mucosa. It is speculated that the encapsulated material may have been dissolved by the saliva, with the release of the TELONE II causing the irritation. There were no histopathologically recognized treatment-related alterations in the sections examined from the esophagus, stomach, or intestinal tract of any dog ingesting TELONE II."

High-dose (15 mg/kg) male No. 90A1491, in addition to anemia, was reported to have, "... a diffuse epidermal hyperplasia, parakeratosis, and sebaceous gland hyperplasia of the skin; and very slight, multifocal hypoplasia of testicular seminiferous tubules; all of which were interpreted to be manifestations of its compromised physical condition."

The Reviewer has no comments to make regarding Materials and Methods.

A copy of the statistical analyses used in this study is attached to this Data Evaluation Report.

H. Regulatory Compliance

The criteria of 40 CFR 158.34 for flagging studies for potential adverse effects have been applied to the results of the attached study. This study neither meets nor exceeds any of the applicable criteria.

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

II. DISCUSSION

REVIEWER'S COMMENTS

The Registrant is requested to respond to the following comments:

1. DOSING OF DOGS

Dogs were housed 2/pen. The Report indicated the assumption that both animals consumed exactly the same amount of food. It was stated that the dose, in mg/kg/day, was administered based on the most recent body weight and food consumption values. Food was available ad libitum. Some dogs (including control) did not gain weight during the one-year study (days -2 to 363 weights).

The Registrant is requested to comment on the accuracy of the mg/kg/day of test article in relationship to 2 dogs/pen, the dogs having different body weights as well as weight gains and the food consumption being assumed to be equal for both dogs in the same pen.

2. ALKALINE PHOSPHATASE LEVELS

Table 4 (page 11) of this Data Evaluation Report pertains to alkaline phosphatase values and statements in the Report text which appear to be inconsistent.

Based upon the statements in the Report plus the analytical data presented, the purity, stability and homogeneity of the TELONE II dietary admixes appear to be within acceptable limits.

All dogs survived this one-year study. Paleness of the mucous membranes of 2 males and 1 female in the 15 mg/kg group was the only clinical sign considered to be related to test article administration. The Report authors attributed this to the, "... lower erythroid parameters observed ..." A 15 mg/kg male (No. 90A1491) lost about 0.4 kg body weight (initial to one-year weight), had alopecia, roughened skin and, at times, redness of the skin.

There appeared to be a decrease in body weight gain in 15 mg/kg males (initial versus final weights). The group means (kg) for weight gains were (mg/kg): 0 = 2.1, 0.5 = 1.8, 2.5 = 1.6 and 15 = 0.8. If the body weight data for No. 90A1491 are excluded from the calculations of the mean, the body weight gain for the 15 mg/kg males would have been 1.2 kg. The Report indicated that the lower body weights for the 15 mg/kg group were statistically significant.

Body weight gains for females showed a decrease in gain in the 15 mg/kg group compared with the control and other dosed groups. The values for the 4 groups (kg) were (mg/kg): 0 = 1.7, 0.5 = 2.5, 2.5 = 1.7 and 15 = 0.6.

Food consumption for the 15 mg/kg males appeared to be greater than for the control and other dose groups throughout the study. This was also noted for the prestudy period of days -6 to -1 where the group mean consumptions in g/dog/day were (mg/kg): 0 = 325, 0.5 = 322, 2.5 = 364 and 15 = 551. The day -2 group mean body weights were (kg) 9.4, 9.2, 9.1 and 9.2 for the 0, 0.5, 2.5 and 15 mg/kg groups, respectively. No explanation for the difference in food consumption between the 15 mg/kg males and the other 3 groups was given.

For females, food consumption was relatively the same for all 4 groups throughout the study.

There were no apparent treatment related effects regarding ophthalmic examinations.

The primary response of the animals to TELONE II administration was an effect on "erythroid indices" in 15 mg/kg males and females. This was noted at the 3, 6, 9 and 12 month sampling intervals. There was an increase (statistically significant) in the group mean number of erythrocytes (11-14% in males and 13-25%[Report said 26] in females with the exception of 3-month males (4% increase). Hemoglogin and hematocrit group mean values were 23-34% [Report states 23-39%] below respective control values.

Mean Corpuscular Volume (MCV) and Mean Corpuscular Hemoglobin (MCH) calculated values were lower in the 15 mg/kg males and females compared with respective controls. The MCV control as well as 0.5 and 2.5 mg/kg values had a range (throughout the study, males and females) of 68-77 cubic microns; whereas, the 15 mg/kg values were 42-52 cubic microns. For MCH, the number of micro micrograms for the 0, 0.5 and 2.5 mg/kg groups (both sexes) was 20-24, with the 15 mg/kg range being 13-15.

An increase in the number of erythrocytes along with a decrease in hemoglobin, hematocrit, MCV and MCH, indicated that the 15 mg/kg dogs had microcytic anemia. Microscopic examination of the erythrocytes (stained peripheral blood) also showed these cells to be hypochromic. In addition, these animals had increases in reticulocytes which was considered to be evidence of a "regenerative nature" of the hematologic effect.

Microscopic pathology corroborated these peripheral blood observations.

"These animals had increased hematopoiesis in the bone marrow which was characterized by increased numbers of erythrocytic, myelocytic and megakaryocytic cells, and a concomitant decrease in the amount of fat in the marrow. The maturation of erythroid and myeloid cell lines appeared normal. Two high dose group males and 2 high dose group females also had increased extramedullary hematopoiesis of the spleen, consisting of increased numbers of erythroid and myeloid precursors, and megakaryocytes. These changes were consistent with a regenerative response to the hypochromic, microcytic anemia that was present in all high dose group animals. There was no evidence of hemolysis or increased sequestration of blood cells in the tissues examined from any dog."

There were no urinalysis findings which were considered to be treatment related. Statistically significant changes in alkaline phosphatase, creatine phosphokinase and aspartate aminotransferase are not considered to have been of great toxicological significance. See the **Reviewer's Comment** at the beginning of this **DISCUSSION** section regarding alkaline phosphatase.

Group mean and individual male absolute liver weights at 15 mg/kg strongly suggested a test article caused increase when compared to control values (Table 5). Relative liver weights were also higher, but this appeared to be a reflection of decreased body weight gains/ lower terminal body weights. The liver weight differences were not noted for females. Historical liver weights as included in the Report (DER Table 6) indicate that the individual and group mean absolute values for male livers at 15 mg/kg in the present study did not fall outside the historical range. There was no microscopic finding which indicated an effect of TELONE II on the liver. The increased male liver absolute weights over controls in this study are considered to be suggestive of a possible test article effect.

Absolute group mean and individual male kidney weights in the 0.5 and 2.5 mg/kg dogs appeared to be greater than the control values. The 15 mg/kg group mean was 56 g compared with a control mean of 48. However, there were some individual values for controls (37, 43, 55, 55) that were similar to the treated dogs (52, 53, 56, 61)) so that, considering the relatively small number of animals/sex/group (4), it does not appear that the kidney weight differences are conclusively the result of TELONE II administration.

Other than the hematopoietic histopathological findings, the only additional observation considered to be test article related, was a, "very slight, multifocal, chronic-active mucosal inflammation of the tongue of two high dose [15 mg/kg] males. The Report authors attributed this to direct irritation of TELONE II to the lingual mucosa, and indicated that it may have been due to the dissolving of the encapsulated material by saliva.

III. CONCLUSIONS

Telone II (1,3-Dichloropropene), administered by dietary admix to male and female dogs at doses of 0, 0.5, 2.5 and 15 mg/kg/day for one year, appeared to cause the following in the 15 mg/kg groups only: decreased body weight gains; hypochromic, microcytic anemia (increase in erythrocytes along with decreases in hemoglobin, hematocrit, mean corpuscular volume and mean corpuscular hemoglobin) with an increase in reticulocytes and platelets as well as hematopoietic activity in bone marrow and spleen; and a possible increase in male absolute liver weights.

The No Observed Effect Level (NOEL) = 2.5 mg/kg

The Lowest Observed Effect Level (LOEL) = 15 mg/kg (decreased body weight gain, microcytic anemia, increase in hematopoietic activity, and possible increase in male absolute liver weights)

Classification:

Core Supplementary - The following points arose during the review of this study and the study may be upgraded upon submission/review of the Registrant's response:

1. DOSING OF DOGS

Dogs were housed 2/pen. The Report indicated the assumption that both animals consumed exactly the same amount of food. It was stated that the dose, in mg/kg/day, was administered based on the most recent body weight and food consumption values. Food was available ad libitum. Some dogs (including control) did not gain weight during the one-year study (days -2 to 363 weights).

The Registrant is requested to comment on the accuracy of the mg/kg/day of test article in relationship to 2 dogs/pen, the dogs having different body weights as well as weight gains and the food consumption being assumed to be equal for both dogs in the same pen.

2. ALKALINE PHOSPHATASE LEVELS

There was an apparent inconsistency between the text and data regarding this parameter.

This study does not satisfy the data requirements (§83-1) for a chronic oral toxicity study in dogs and is not acceptable for regulatory purposes.

Telone

Page_____ is not included in this copy.

Pages 23 through 25 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

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