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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: TELONE II (1,3-Dichloropropene; 1,3-D; DCP) - Review of a Two-Year Chronic Toxicity/Carcinogenicity Study in Mice

FROM: Alan C. Levy, Ph.D., Toxicologist Alan C. Levy 10/21/96
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Health Effects Division (7509C)

TO: Lisa Nisenson, PM 62
Special Review and Reregistration Division (7508W)

THRU: Jess Rowland, M.S., Acting Section Head Jess Rowland 10/21/96
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

and

Yiannakis M. Ioannou, Ph.D., Acting Branch Chief Y.M. Ioannou 10/21/96
Toxicology Branch II
Health Effects Division (7509C)

EPA ID: **DP Barcode:** D229205 **MRID No.:** 43757901
PC Code: 029001 **Submission Code:** S510569
Tox. Chem. No.: [redacted]

Registrant: DowElanco, Indianapolis, IN

REQUEST: Review a two-year chronic toxicity/carcinogenicity study in mice with TELONE II.

RESPONSE: A Data Evaluation Record is attached. The Executive Summary is as follows:

In a chronic toxicity/carcinogenicity study **(MRID No. 43757901)**, TELONE II (95.8% purity, 50.7% cis and 45.1% trans) as a microencapsulated formulation (80:20 starch:sucrose matrix), was administered by dietary admix to Charles River B6C3F1 mice (50/sex/group) for 2 years at doses of 0 (placebo sucrose microcapsules), 2.5, 25 and 50 mg/kg/day.

ONE-LINER

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TELONE II - PC Code: 029001
1,3-dichloropropene

STUDY INFORMATION
Guideline §83-5)
Chronic Toxicity/Carcinogenicity
Species: Charles River B6C3F1 mice
Testing Facility: The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI
Laboratory Report No.: M-003993-032
August 9, 1995

TEST MATERIAL
TELONE II
Purity: 95.8% (50.7% cis and 45.1% trans)
Lot No.: AGR 295646; 9359-1B

MRID No.: 43757901

EXECUTIVE SUMMARY:

In a chronic toxicity/carcinogenicity study **(MRID No. 43757901)**, TELONE II (95.8% purity, 50.7% cis and 45.1% trans) as a microencapsulated formulation (80:20 starch:sucrose matrix), was administered by dietary admix to Charles River B6C3F1 mice (50/sex/group) for 2 years at doses of 0 (placebo sucrose microcapsules), 2.5, 25 and 50 mg/kg/day.

There were no test article effects on clinical signs, mortality, ophthalmology, hematology parameters, organ weights, macroscopic pathology or microscopic pathology. Lower group mean body weights and decreased weight gains occurred in both sexes at 25 and 50 mg/kg/day during the two-year study. There was an accompanying decrease in food consumption at the same doses.

Under the conditions of this study, for chronic toxicity, the NOEL was 2.5 mg/kg/day and the LOEL was 25 mg/kg/day for both sexes.

There was no evidence of carcinogenicity.

This chronic toxicity/carcinogenicity study is **Acceptable/Guideline** and satisfies the data requirement for OPPTS 870.3200 (§83-5) for a chronic toxicity/carcinogenicity study in mice.

There were no test article effects on clinical signs, mortality, ophthalmology, hematology parameters, organ weights, macroscopic pathology or microscopic pathology. Lower group mean body weights and decreased weight gains occurred in both sexes at 25 and 50 mg/kg/day during the two-year study. There was an accompanying decrease in food consumption at the same doses.

Under the conditions of this study, for chronic toxicity, the NOEL was 2.5 mg/kg/day and the LOEL was 25 mg/kg/day for both sexes based on lower body weights and a decrease in body weight gain.

There was no evidence of carcinogenicity.

This chronic toxicity/carcinogenicity study is **Acceptable/ Guideline** and satisfies the data requirement for OPPTS 870.3200 (§83-5) for a chronic toxicity/carcinogenicity study in mice.

cc: Christina Scheltema (RCAB)

TELONE II Chronic Toxicity/Carcinogenicity Study, Mice (§83-5)

EPA Reviewer: Alan C. Levy, Ph.D. Alan C. Levy, Date 10/21/96
Review Section I, Toxicology Branch II (7509C)

EPA Secondary Reviewer: Jess C. Rowland Jess Rowland, Date 10/24/96
Review Section I, Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Two-Year Chronic Toxicity/Carcinogenicity Study - OPPTS 870.4300 (§83-5)

EPA IDENTIFICATION: **PC Code:** 029001 **MRID No.:** 43757901
DP Barcode: D229205 **Submission Code:** S510569
Tox. Chem No.: 324A

TEST MATERIAL: TELONE II; 1,3-Dichloropropene

SYNONYMS: 1,3-D; DCP

TESTING FACILITY: The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI

TITLE OF REPORT: Telone® II Soil Fumigant: Two-Year Dietary Chronic Toxicity/Oncogenicity Study in B6C3F1 Mice - Final Report

AUTHORS: J.M. Redmond, K.E. Stebbins and W.T. Stott

REPORT DATE: August 9, 1995

LABORATORY REPORT NO.: M-003993-032

SPONSOR: DowElanco, Indianapolis, IN

EXECUTIVE SUMMARY:

In a chronic toxicity/carcinogenicity study (**MRID No. 43757901**), TELONE II (95.8% purity, 50.7% cis and 45.1% trans) as a microencapsulated formulation (80:20 starch:sucrose matrix), was administered by dietary admix to Charles River B6C3F1 mice (50/sex/group) for 2 years at doses of 0 (placebo sucrose microcapsules), 2.5, 25 and 50 mg/kg/day.

There were no test article effects on clinical signs, mortality, ophthalmology, hematology parameters, organ weights, macroscopic pathology or microscopic pathology. Lower group mean body weights and decreased weight gains occurred in both sexes at 25 and 50 mg/kg/day during the two-year study. There was an accompanying decrease in food consumption at the same doses.

Under the conditions of this study, for chronic toxicity, the NOEL was 2.5 mg/kg/day and the LOEL was 25 mg/kg/day for both sexes based on lower body weights and a decrease in body weight gains.

There was no evidence of carcinogenicity.

This chronic toxicity/carcinogenicity study is **Acceptable/ Guideline** and satisfies the data requirement for OPPTS 870.3200 (§83-5) for a chronic toxicity/carcinogenicity study in mice.

COMPLIANCE:

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

A signed and dated statement of no confidentiality claim was provided.

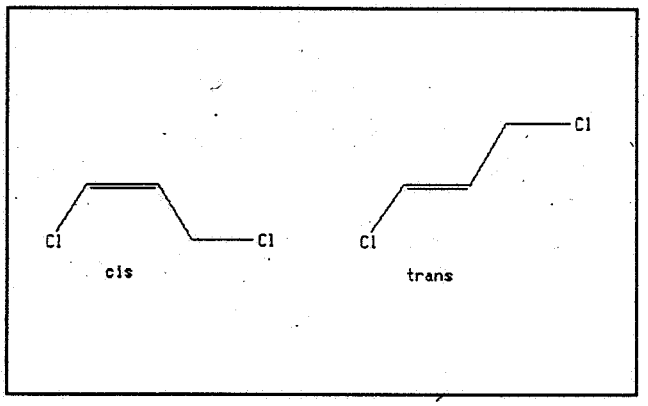
A signed and dated "Flagging statement" for potential adverse effects was included (40 CFR 158.34) and stated that the study neither meets nor exceeds any of the applicable criteria.

I. MATERIALS AND METHODS

A. Materials

1. TEST MATERIAL:

Name: TELONE II; 1,3-Dichloropropene (cis, trans)
Physical State: clear liquid
Lot No.: TELONE (AGR 295646) = 9359-1B, 80% starch/20% sucrose microcapsules
controls = 9359-1PB, placebo sucrose microcapsules
Purity: prior to initiation of the study, 95.8% (50.7% cis and 45.1% trans); loaded microcapsules were determined to contain 38.7% TELONE II Soil Fumigant by weight
CAS No.: 542-75-6
Formula:



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2. VEHICLE/CONTROL: control mice received placebo sucrose microcapsules in basal diet

3. TEST ANIMALS

Species: mouse
Strain: B6C3F1
Age/Weight at Study Initiation: about 7 weeks old; body weights of group means on study day -3: males = 22.7-22.9 g and females = 19.3-19.5 g
Source: Charles River Laboratories, Portage, MI
Housing: 1/cage
Diet: basal Purina Certified Chow #5002 ad libitum
Water: tap water ad libitum
Environmental Conditions: temperature = 22.3°C (average); humidity = 51% (average); 12 hour light/dark cycle; airflow = 10-12 changes/hour
Acclimation Period: 15 days

B. Study Design

1. IN-LIFE DATES:

Start of dosing: August 6, 1992
12-month sacrifice: August 17, 1993
Terminal sacrifice: August 8-11, 1994

2. ANIMAL ASSIGNMENT: computer generation randomization

Table 1

STUDY DESIGN FOR A 2-YEAR DIETARY ADMIX STUDY IN MICE WITH TELONE II

Dose (mg/kg/day)	Number of Mice/Group			
	12-Month Sacrifice		Terminal Sacrifice	
	males	females	males	females
0	10	10	50	50
2.5	10	10	50	50
25	10	10	50	50
50	10	10	50	50

Data extracted from Report page 17.

3. DOSE SELECTION (Report pages 13 and 14)

Oral LD50: in male and female Fischer 344 rats was 300 and 224 mg/kg, respectively

2-Week Dietary Probe Study: This was conducted in male and female B6C3F1 mice fed micro-encapsulated TELONE II in the diet at targeted dose levels of 0, 25, 50, 100 and 175 mg/kg/day. Statistically significant decreases in body weight were observed in males at 100 and 175 mg/kg/day and in females at 175 mg/kg/day. There was lower feed consumption in both sexes at 175 mg/kg/day (may not have been palatable). The absolute and relative 175 mg/kg/day male liver weights were lower than controls. The only histopathology was a decreased hepatocellular size in most males at 175 mg/kg/day. This was consistent with decreased hepatocellular cytoplasmic glycogen. Based on body weight changes, the NOEL was 50 mg/kg/day for males and 100 mg/kg/day for females.

13-Week Dietary Study: This was conducted in male and female B6C3F1 mice (10/sex/dose) at targeted dietary dose levels of 0, 15, 50, 100 and 175 mg/kg/day. Body weights and gains were below controls in males and females at ≥50 mg/kg/day (occasionally in 15 mg/kg/day males). Histopathologically, only males appeared to be effected: slightly decreased size of hepatocytes with decreases in cytoplasmic glycogen in most males at all doses; decreased vacuolation of tubular epithelial cells (kidney) with decreased cytoplasmic fat in several males at 175 mg/kg/day. The NOEL was stated to be 15 mg/kg/day for both sexes based on body weight changes.

Chronic Oral Study: This refers to the NTP study (1985). Female B6C3F1 mice were administered a previous epoxide-stabilized formulation of TELONE at 50 or 100 mg/kg (not microencapsulated) in corn oil vehicle via gavage 3 times/week for up to 2 years. Results included hyperplasia and tumors of the nonglandular portion of the stomach and urinary bladder mucosa; and benign liver and lung tumors. A NOEL was not established.

4. DIET PREPARATION AND ANALYSIS

Diet concentrations were prepared by serially diluting a premix. Premixes were made at least every 2 weeks based on stability of the test material in the feed. The premixes were adjusted for 38.7% micro-encapsulation loading of the test article and the concentrations were then calculated on a mg/kg/day basis. Test diets were prepared weekly based on the most recent body weights and feed consumption for the first 13 weeks and then adjusted every 4 weeks thereafter. The control (starch/sucrose encapsulation matrix) was mixed with ground feed every 4 weeks during the entire study.

a. Test Article Purity (Report page 25; Table 3, page 45)

Purity was 95.8 ± 0.8%. The material consisted of 50.7 ± 0.6 weight percent of cis-1,3-D and 45.1 ± 0.5 weight percent trans-1,3-D. The test material was stable during the entire dosing period.

b. Homogeneity (Report Table 4, pages 46-48)

Table 2

TEST ARTICLE HOMOGENEITY IN A TWO-YEAR DIETARY ADMIX TOXICITY STUDY IN MICE WITH TELONE II

Location	2.5 mg/kg female 8/4/92			2.5 mg/kg female 11//9/92			25 mg/kg female 11/9/92		
	Side 1	Center	Side 2	Side 1	Center	Side 2	Side 1	Center	Side 2
Top	1.238	0.780	0.965	1.464	1.870	2.064	1.730	1.576	1.581
Middle	1.154	0.994	1.713	1.717	1.222	2.105	1.769	1.607	2.039
Bottom	1.449	1.092	1.651	1.517	1.607	1.736	1.800	1.921	1.682

2.5 mg/kg 8/4/92 = target concentration of 1.2×10^{-3}%
2.5 mg/kg 11/9/92 = target concentration of 1.46×10^{-3}%
25 mg/kg 11/9/92 = target concentration of 1.45×10^{-2}%
NOTE: one aliquot was analyzed from each location

c. Concentration (Report Table 5, page 49)

The concentration of TELONE II in the diet for each dose/sex was measured 10 times during the study. The mean values ± standard deviation (for percent of target concentration) were as follows: (mg/kg/day): males: 2.5 = 100 ± 9, 25 = 104 ± 10 and 50 = 108 ± 7; females: 2.5 = 92 ± 13, 25 = 103 ± 9 and 50 = 112 ± 11. For the premix, the value was 115 ± 9.

Analytical data for purity, homogeneity and concentration were considered to have been within acceptable limits.

5. ANIMALS RECEIVED FRESH DIET: weekly

6. STATISTICS (Report pages 23-25)

Means and standard deviations were reported for feed consumption, feed efficiency and leukocyte differential counts. Body weights, organ weights and appropriate hematology values were evaluated by Bartlett's test for equality of variances. Based on Bartlett's test results, exploratory data analysis was performed by a parametric or nonparametric ANOVA, followed by Dunnett's test or the Wilcoxon Rank-Sum test with a Bonferroni correction for multiple group comparisons. Statistical outliers were identified by a sequential test (Grubbs, 1969), but routinely excluded only from feed consumption statistics.

The incidence of specific observations, for tissues where all animals were scheduled to be examined, were first tested for deviation from linearity using ordinal spacing of the doses. If linearity was not rejected, the data were then tested for linear trend using Cochran-Armitage Trend test. If the trend was statistically significant, or if significant deviation from linearity was found, the incidences for each dose group were compared to those of the control group using a pairwise Chi-square test with Yates' continuity correction.

Differences in mortality patters were tested by the Gehan-Wilcoxon procedure on data from all animals scheduled for the 24-month sacrifice.

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C. Methods

1. OBSERVATIONS

All mice were observed cageside at least twice daily. Clinical examinations were performed on all mice before the start of the study and weekly thereafter.

2. BODY WEIGHTS

Each mouse was weighed prior to the start of the study, weekly during the first 13 weeks and at about monthly intervals thereafter.

3. FOOD CONSUMPTION

This was measured prior to the start of the study, weekly for the first 13 weeks and for a one-week period each month thereafter. Food efficiency was calculated using mean body weight gain and mean food consumption data. Feed Efficiency (g of feed consumed/kg bw gain/day) = g feed consumed/day ÷ kg bw gain/day.

4. OPHTHALMOSCOPIC EXAMINATION

These were performed on all mice before the start of the study (pen light illumination) and at the scheduled 12- and 24-month necropsies (moistened slide/fluorescent light technique).

5. CLINICAL PATHOLOGY (only hematology)

Blood was obtained from the 10/sex/dose from the satellite group after about 12 months of dosing and at about 18 as well as 24 months on the first 10 and 20 survivors/sex/dose from the terminal sacrifice group, respectively. Samples were taken from the orbital sinus (methoxyflurane anesthesia). At the 12-month interim sacrifice, as well as at the 18- and 24- month intervals, the following parameters were examined: hematocrit, hemoglobin, erythrocyte count, total leukocyte count, platelet count and differential leukocyte counts.

6. SACRIFICE AND PATHOLOGY

Terminal body weights were taken and the mice were anesthetized with methoxyflurane prior to decapitation. A complete necropsy was performed. The following organs were weighed and their weights presented as absolute and relative to body weight: brain, heart, liver, kidneys and testes. Mice which died or were sacrificed moribund were subjected to a complete necropsy, but no blood samples, terminal body weights or organ weights were taken.

DIGESTIVE	RESPIRATORY	UROGENITAL
xTongue	xTrachea*	xxKidneys*
xSalivary glands*	xLungs*	xUrinary bladder*
xEsophagus*	xNasal tissues	xxTestes*
xStomach*		xEpididymides*
xDuodenum*	CARDIOV/HEMAT	xProstate*
xJejunum*	xAorta*	xSeminal vesicles*
xIleum*	xxHeart*	xOvaries*
xCecum*	xBone marrow*	xUterus*
xColon*	xLymph nodes*	xCervix
xRectum*	xSpleen*	-Oviducts
xxLiver*	xThymus	xVagina
xPancreas*		
xGallbladder*		

NEUROLOGIC	GLANDULAR	OTHER
xxBrain*	xAdrenals*	xBone*
xPeripheral n.*	xLacrimal gland	xSkeletal muscle*
xSpinal cord (3 levels)*	xMammary gland*	xSkin*
xPituitary*	xParathyroids*	xAll gross lesions and masses*
xEyes*	xThyroids*	xCoagulating glands
		xHarderian gland
		xLarynx
		xOral tissues

* = EPA Guideline requirement x = examined - = not examined
xx = organ weighed

Tissues from the above list were examined microscopically from the control and 50 mg/kg/day (HDT) dose group. For bone and bone marrow evaluation, the sternum, 3 sections of vertebrae and 2 sections of skull and nasal tissue were decalcified and evaluated. When possible, all tissues were also examined from all mice which died or were sacrificed moribund. The following tissues from the 2.5 and 25 mg/kg/day groups of both sexes were also processed for histologic examination: liver, kidneys, lungs, stomach and gross lesions.

II. RESULTS

A. Observations

1. CLINICAL SIGNS (Report Tables 9 and 10, pages 53-56)

There were no clinical signs which appeared to be related to test article administration.

2. MORTALITY (Report Tables 6 and 7, pages 50 and 51)

There were no adverse effects on mortality in in either males or females. Cumulative mortality for the 50/sex/group mice which were scheduled for terminal sacrifice (2 years) was as follows (percent; 0, 2.5, 25 and 50 mg/kg/day): males = 20, 22, 20 and 22; females = 26, 22, 20 and 28.

B. Body Weight

Table 3

GROUP MEAN BODY WEIGHTS AND WEIGHT GAINS IN A TWO-YEAR DIETARY ADMIX STUDY IN MICE WITH TELONE II

Week	Males (mg/kg/day)				Females (mg/kg/day)			
	0	2.5	25	50	0	2.5	25	50
BODY WT-g								
0	22.8	22.7	22.7	22.9	19.4	19.4	19.5	19.3
25	32.8	32.1	29.2*	28.1*	28.9	28.3	26.6*	25.8*
53	38.8	38.0	32.6*	30.8*	32.1	33.0	28.9*	27.3*
78	41.0	39.3	33.1*	31.6*	33.0	35.3*	29.2*	28.9*
104	36.9	35.9	31.3*	30.6*	31.3	32.5	29.6*	28.7*
B.W. GAIN								
0-53 g	+16.0	+15.3	+9.9	+7.9	+12.7	+13.6	+9.4	+8.0
%	-	96	62	49	-	107	74	63
53-104 g	-1.9	-2.1	-1.3	-0.2	-0.2	-0.5	+0.7	+1.4
%	-	---	---	---	-	---	---	---
0-104 g	+14.1	+13.2	+8.6	+7.7	+11.9	+13.1	+10.1	+9.4
%	-	94	61	55	-	110	85	79

No. of mice: weeks 0-53=58-60; weeks 54-104=39-49 for males and 36-50 for females
--- = percent not calculated % = percent of control
NOTE: interim sacrifice of 10/sex/group after week 53 weighing
Body weight gains calculated by Reviewer
Week "0" = day -3
Statistical Significance(Dunnett's or Wilcoxon's tests): * = $p<0.05$
Data extracted from Report Tables 11-14, pages 57-78.

Treatment had no adverse effect on mean body weights or body weight gains of male or female mice at 2.5 mg/kg/day. Body weights of 25 and 50 mg/kg/day males were about 11-14% below controls during most of the study. These body weights were below the control value about 11-23% during the last 18 months of the study. Body weight gains during the entire 104 weeks for 25 and 50 mg/kg/day males were 49-62% of the control value.

For females, the 25 and 50 mg/kg/day mice had group mean body weights about 7-9% below the control during most of the study. Body weight gains during the entire 104 weeks for the 25 and 50 mg/kg/day females were 63-85% of the control.

C. Food Consumption and Compound Intake

1. FOOD CONSUMPTION (Report Tables 15 and 16, pages 79-86)

Food consumption was slightly lower for males and females administered 25 and 50 mg/kg/day during most of the study.

2. FOOD EFFICIENCY (Report Table 19 and 20, pages 93-100)

Food efficiency values for 25 and 50 mg/kg/day males were greater than for the controls for most of the 2 years. For females at these doses, the values were greater than the controls only during the last 12 months. For males and females, this was concomitant with lower body weights in these groups.

3. COMPOUND INTAKE (Report Tables 17 and 18, pages 87-92)

Report page 28 stated, " Based upon analytically determined concentrations of test material in the diets, body weight data, and feed consumption data, the calculated dosage of Telone II received by animals was within 10% of targeted values."

D. Ophthalmoscopic Examination (Report Table 8, page 52)

There were no ophthalmoscopic findings which were considered to have been related to test article administration.

E. Hematology (Report Tables 21-38, pages 101-128)

There were no parameters which appeared to be consistently effected by the administration of the test article in either males or females.

F. Sacrifice and Pathology

1. ORGAN WEIGHTS (Report Tables 39-42, pages 129-132)

Report page 30 stated [12-month sacrifice], "The liver weight change in the high-dose male mice was the only weight change that correlated with microscopic changes described in the histopathology section." The organ weights (absolute or relative) for females at 12 months, or males and females at the 24-month terminal sacrifice, did not appear to have been effected by the administration of TELONE II.

Table 4

GROUP MEAN ± STANDARD DEVIATION LIVER WEIGHTS AT THE 12-MONTH AND 24-MONTH SACRIFICES IN A TWO-YEAR DIETARY ADMIX STUDY IN MICE WITH TELONE II

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	2.5	25	50	0	2.5	25	50
12 MONTH								
Body Wt.	39.0	36.2	33.2*	28.9*	32.2	31.3	29.4	28.6
Absolute	1.88	1.73	1.67*	1.51*	1.69	1.68	1.59	1.45*
S.D.	0.15	0.40	0.09	0.11	0.13	0.08	0.12	0.13
Relative	4.85	4.75	5.05	5.25*	5.28	5.39	5.43	5.12
S.D.	0.34	0.34	0.22	0.35	0.32	0.38	0.25	0.37
24 MONTH								
Body Wt.	37.2	36.4	31.7*	30.6*	31.2	32.1	29.8*	28.4*
Absolute	2.21	2.27	2.13*	1.82*	1.85	1.75	1.68*	1.66*
S.D.	0.66	0.55	0.78	0.39	0.54	0.31	0.59	0.79
Relative	5.98	6.27	6.68*	5.96	5.90	5.44	5.60	5.80
S.D.	1.75	1.56	2.28	1.16	1.42	0.78	1.51	2.43

Absolute = g
Relative = g/100 g body weight
Body Wt. = final body weight (g)
Statistical Significance: * = $p<0.05$

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2. MACROSCOPIC PATHOLOGY (Report Tables 43-44, pages 133-148)

There were no macroscopic findings at either the 12-month or 24-month sacrifices which appeared to have been related to test article administration.

3. MICROSCOPIC PATHOLOGY (Report Tables 45-48, pages 149-198)

a. Non-Neoplastic Lesions

The only effect reported concerned the liver of 12-month sacrifice 50 mg/kg/day males only. Report page 32 stated, "The liver effect consisted of diffuse, slight decreased size of hepatocytes, which was attributed to a decrease in hepatocellular cytoplasmic area as compared to hepatocytes from control group mice. This change was consistent with a decrease in hepatocellular cytoplasmic glycogen, and corresponded to a statistically identified decrease in absolute liver weights at this dose level. Decreased size of hepatocytes was only noted in rats from the 12-month sacrifice, affecting 6/10 males administered 50 mg/kg/day TELONE II. The decreased size of hepatocytes was not considered to be a primary effect of treatment but, rather, reflected the lower body weights of these rats." [Report page 153]

b. Neoplastic Lesions (Report Tables 46 and 48, pages 160 and 191-198)

There was no apparent effect of test article administration on the incidences of microscopic tumors in males or females at either the 12-month or 24-month sacrifices (includes found dead and sacrificed moribund mice).

III. DISCUSSION

Analytical data for purity, homogeneity and concentration were within acceptable limits.

The following parameters were not effected by test article administration: clinical signs, mortality, ophthalmology, hematology parameters, organ weights, macroscopic pathology or microscopic pathology.

In both males and females at 25 and 50 mg/kg/day, there were statistically significant lower body weights throughout the study. Body weight gains were also lower than controls at these doses for both sexes. Accompanying the lower body weights was a decrease in food consumption.

Absolute and relative organ weights in the 25 and 50 mg/kg/ mg/kg/day males and females, in most part, reflected the lower body weights.

The one correlation between an effect on organ weights and other findings concerned a decrease in absolute liver weights of 50 mg/kg/day group males (only at 12 months; not for females at either interval) accompanied by the observation that hepatocytes were slightly decreased in size with smaller cytoplasmic volume than in the controls. This change was consistent with decreased cellular glycogen content.

There was no evidence of carcinogenicity at the dose levels tested. For chronic toxicity, the NOEL was 2.5 mg/kg/day and the LOEL was 25 mg/kg/day based on lower body weights and a decrease in body weight gain.

Summaries of other chronic toxicity/carcinogenicity studies are provided below:

In a chronic/carcinogenicity study in Charles River Fischer 344 rats (MRID No. 43763501; HED Doc. No. 011743), TELONE II (96.0% purity, cis/trans isomers), as microcapsules, was administered by dietary admix at doses of 0, 2.5, 12.5 and 25 mg/kg/day body weight/day for 2 years. There was an increase in liver masses/ nodules in males only at 12.5 and 25 mg/kg/day. An increased incidence was reported for basal cell hyperplasia of nonglandular mucosa of the stomach of both sexes at the 12- and 24-month sacrifices at 12.5 and 25 mg/kg/day. The number of males with primary hepatocellular adenomas was increased over controls at 12.5 and 25 mg/kg/day (2/50, 1/50, 6/50 and 9/50 for the control, low, mid and high-dose groups, respectively) with the number of females being increased only at 25 mg/kg/day (0/50, 0/50, 0/50 and 4/50 for the control, low, mid and high-dose groups, respectively).

An NTP study (1985, MRID Nos. 00141492 and 00144714) was conducted in male and female Fischer 344 rats with TELONE II (25 or 50 mg/kg/day, epoxide stabilized formulation) administered by gavage 3 days/week for up to two years. Hyperplasia and tumors of of the nonglandular portion of the stomach were reported for males and females in addition to benign tumors of the liver in males.

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In another NTP study (1985, MRID Nos. 00141492 and 00144714), TELONE II was administered to female B6C3F1 mice (50 or 100 mg/kg/day, epoxide stabilized formulation) 3 times/week for up to two years. There were hyperplasia and tumors of the nonglandular portion of the stomach and urinary bladder mucosa as well as benign liver and lung tumors.

Taking into consideration the two rat studies (NTP, gavage, epoxide stabilized formulation, dosed 3 times/week at 25 or 50 mg/kg/day and the dietary admix study with micronized formulation, at 2.5, 12.5 and 25 mg/kg/day) as well as the two mouse studies (NTP, gavage, epoxide stabilized formulation, dosed 3 times/week at 50 or 100 mg/kg/day and the current dietary admix study with micronized formulation, at 2.5, 25 and 50 mg/kg/day), there appears to be evidence that 25 mg/kg/day causes hepatocellular adenomas in male and possibly in female Fischer 344 rats. These liver tumors were noted in the NTP (not microencapsulated) B6C3F1 female mice (50 or 100 mg/kg/day), but not in the same strain of mouse administered micronized material at up to 50 mg/kg/day by diet.