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

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AUG 18 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Prometon Reviews of a Chronic Toxicity/Oncogenicity Study in Rats, an Oncogenicity Feeding Study in Mice and a 2-Generation Reproductive Toxicity Study in Rats
EPA ID No. 080804-0001000
Record No. S394514
HED Project No. 1-0908A
MRID No. 404881-01 & 02 & 403615-01
Caswell No. 096 Barcode: D181091

FROM: Vivian A. Williams, M.S.
Toxicology Section II V. Williams 7/28/92
Toxicology Branch I
Health Effects Division (H7590C)

TO: Thomas Luminello, PM Team 50
Special Review and Reregistration Division (H7508W)

THRU: Joycelyn Stewart, Ph.D. 8/1/92
Acting Section Chief
Toxicology Branch I
Health Effects Division (H7590C)
and
Karl Baetcke, Ph.D. Karl F. Baetcke 8/3/92
Chief
Toxicology Branch I
Health Effects Division (H7590C)

Registrant: Ciba-Geigy, Corp.

Action Requested:
Review the submitted rat chronic toxicity/oncogenicity study, the mouse oncogenicity study and the 2-generation reproductive toxicity study in rats for the purpose of reregistering prometon.

Conclusions:

Chronic Toxicity/ Oncogenicity Dietary Study in Rats
Oral administration of prometon technical to Sprague Dawley rats in the diet at concentrations of 0, 20, 500, or 1500 ppm (which corresponds to 0, 0.89, 23.3 or 73.3 mg/kg/d in males and 0, 1.18, 31.2 or 102.5 mg/kg/d in females) for up to 104 weeks did not result in an increase in tumor incidence and did not

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adversely affect survival. Lesions which were noted in this study at all dose levels consisted of mammary adenomas, adenomas and fibromas but they were within the range of the historical control data. As presented in the attached statistical analysis that was provided by SACB, there was a statistically significant trend for the adenocarcinoma counts and the combined (adenocarcinoma and adenoma only) tumor counts. Additionally, the pair-wise comparisons of the adenocarcinomas with the controls and the combined (adenocarcinoma and adenoma only) group with the controls were of borderline significance and the tumor incidence was within the historical control incidence. Systemic effects consisted of depressed mean body weights and body weight gains in the mid dosed females through out the study; depressed food consumption in the mid and high dosed animals; depressed urine volume in the high dosed males and increased mineralized concretions in the high dosed male kidneys. Based on the noted systemic effects, this chemical was tested at adequate dose levels.

The systemic LOEL is 500 ppm (23.3 mg/kg/d in males and 31.2 mg/kg/d in females) and the systemic NOEL is 20 ppm (0.89 in males and 1.18 mg/kg/d in females) based on the body weight depression.

This study is Core Guideline according to FIFRA guideline 83-5 for a combined chronic toxicity/oncogenicity study.

Oncogenicity Feeding Study in Mice

After oral administration of prometon at levels of 0, 10, 400, 4000, or 8000 ppm (which corresponds to 0, 1.7, 70, 737 or 1524 mg/kg/d) to CD-1 mice for 88 weeks there were decreased survival in both sexes of the two high dosed groups of animals; depressed body weights and body weight gains in both sexes of the 2 high dosed groups and statistically significantly increased mean liver weights and liver to body weight ratios in the high doses females. Non-neoplastic histologic liver changes, (such as hepatocellular disorganization, single-cell hepatocyte necrosis and centrolobular hepatocyte hypertrophy), were significantly increased in the high dosed male group and in the 2 high dosed female groups. Kidney lesions consisted of renal papillary necrosis which occurred in the high doses males at an increased incidence compared to the control male group. Based on the noted systemic effects in this study, the chemical was tested at adequate dose levels.

There was no increase in the tumor incidence in this study.

Based on decreased weight gains and histological liver changes in both sexes at the 2 highest dose levels, the LOEL for systemic toxicity is 4000 ppm (737 mg/kg/d) and the NOEL is 400 ppm (737 mg/kg/d).

This study is Core Guideline based on FIFRA Guideline 83-2 for an oncogenicity study.

2-Generation Reproductive Toxicity Study in Rats

Sprague Dawley rats were administered prometon at daily dietary levels of 0, 20, 500, or 1500 ppm (which corresponds to 0, 1.45,35.08, or 103.96 mg/kg/d for males and 0, 1.59, 39.17, 113.98 mg/kg/d for females) in a 2-generation reproductive toxicity study. At 1500 ppm parental toxicity, characterized by decreased food consumption and decreased body weight, was observed in both generations and sexes. There were additional signs of parental toxicity at 500 ppm, identified by decreased body weights in males in both generations and decreased food consumption in males in the second generation. The parental NOEL is 20 ppm; the parental LOEL is 500 ppm.

Reproductive toxicity was observed at 1500 ppm in both generations and at 500 ppm in the second generation. This was characterized by decreased pup body weight during the entire lactation period. For reproductive toxicity, the NOEL is 20 ppm and the LOEL is 500 ppm.

This study is Core Guideline based on FIFRA Guideline 83-4 for a reproductive toxicity study in rats.

Attached are the Data Evaluation Reports for the prometon combined chronic toxicity/oncogenicity feeding study in rats (including the statistical analysis), the oncogenicity study in mice and the 2-generation reproductive toxicity study in rats.

ATTACHMENTS

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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Prometon Statistical Analysis of MRID 404881-02

TO: Vivian Williams
Toxicologist
Review Section II
Toxicology Branch I

FROM: Lori L. Brunsman
Statistician
Science Support and Special Review Section
Science Analysis and Coordination Branch

THROUGH: Kerry L. Dearfield, Ph.D.
Acting Section Head
Science Support and Special Review Section
Science Analysis and Coordination Branch

The Prometon female rat study has been statistically evaluated. This study maintained 10 recovery rats from the control and the high-dose groups on an untreated basal diet for 4 weeks following 52 weeks of dosing. These animals are not included in this analysis because they cannot be compared with the non-recovery animals that were dosed during the entirety of their designated lifespans.

Mammary gland adenomas, adenocarcinomas and fibroadenomas were evaluated. The incidence of these lesions falls within the range of available historical control data. The tumor rates and Cochran-Armitage trend test and Fisher's Exact test results (p values) for the tumor counts are attached. There exists a statistically significant trend for the adenocarcinoma counts ($p < 0.01$) and the combined (adenocarcinoma and adenoma only) tumor counts ($p < 0.01$). The pair-wise comparisons of the adenocarcinomas with the controls and the combined (adenocarcinoma and adenoma only) group with the controls are of borderline significance with p values of 0.089 and 0.072, respectively.

Survival of low-, mid-, and high-dose females was increased at the termination of the study when compared to controls. Percent survival for low-, mid-, and high-dose females was 43%, 46%, and 51%, respectively, when compared to 35% survival for the control group.

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Prometon - Sprague-Dawley CD Rats Female Mammary Tumor Rates* and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors:	0	20	500	1500
Adenomas (%)	3/80 (4)	2/80 (2)	2/79 (3)	4[a]/79 (5)
p =	0.225	0.500(n)	0.506(n)	0.493
Adenocarcinomas (%)	15/80 (19)	8/80 (10)	12[b]/79 (15)	23/79 (29)
p =	0.003**	0.088(n)	0.350(n)	0.089
Combined# (%)	18/80 (22)	10/80 (12)	14/79 (18)	27/79 (34)
p =	0.002**	0.072(n)	0.290(n)	0.072
Fibroadenomas (%)	23[c]/80 (29)	17/80 (21)	21/79 (27)	25/79 (32)
p =	0.141	0.181(n)	0.449(n)	0.411

*Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor at week 36.

#Combined tumor count combines only adenomas and adenocarcinomas.

(n) Negative change from control.

[a]First adenoma observed at week 53, dose 1500 ppm.

[b]First adenocarcinoma observed at week 36, dose 500 ppm.

[c]First fibroadenoma observed at week 63, dose 0 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

DATA EVALUATION RECORD 009679

PROMETON

Dietary Chronic Toxicity Oncogenicity Study in Rats

Study Identification: O'Connor, D.J., McCormick, G.C., Green, J.D. Prometon-combined chronic toxicity/oncogenicity study in rats. (Unpublished study No. 852003 conducted by CIBA-GEIGY Corp., Summit, New Jersey, and submitted by CIBA-GEIGY Corporation Agricultural Division, Greensboro, NC, dated January 14, 1988.) MRID No. 404881-02.

REVIEWED BY:

Margaret Brower, Ph.D.
Principal Reviewer
Dynamac Corporation

Signature: Margaret Brower
Date: 3/27/92

William L. McLellan, Ph.D.
Independent Reviewer
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APPROVED BY:

Vivian A. Williams, M.S.
EPA Office of Pesticide Programs
Toxicology Branch I/HED (7509C)

Signature: Vivian A. Williams 7/2/92
Date: 7/2/92

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EPA Office of Science and Technology
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Signature: Amal Mahfouz
Date: 5/15/92

DATA EVALUATION RECORD 009679

GUIDELINE §83-5

STUDY TYPE: Chronic toxicity/oncogenicity feeding study in rats.

MRID NUMBER: 404881-02.

TEST MATERIAL: Prometon; 2,4-bis(isopropylamine)-6-methoxy-s-triazine.

SYNONYM: Methoxypropazine, Pranutol, Ontrack.

STUDY NUMBER: 852003.

SPONSOR: CIBA-GEIGY Corp., Summit, NJ.

TESTING FACILITY: CIBA-GEIGY Corp., Greensboro, NC.

TITLE OF REPORT: Combined Chronic Toxicity/Oncogenicity Study in Rats.

AUTHORS: O'Connor, D.J., McCormick, G.C., Green, J.D.

REPORT ISSUED: January 14, 1988.

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CONCLUSIONS:

Daily oral administration of prometon technical to rats in the diet at concentrations of 0, 20, 500, or 1500 ppm (corresponding to 0, 0.89, 23.3, or 73.7 mg/kg/day in males and 0, 1.18, 31.2, or 102.5 mg/kg/day in females) for up to 104 weeks produced no evidence of carcinogenicity. After 52 weeks of dosing, 10 recovery rats/sex from the control and high-dose groups were maintained on untreated basal diet for 4 weeks. Survival was higher in dosed animals when compared to concurrent controls except for the low-dose males, wherein only 21% of the animals survived to study termination. Mean body weights and body weight gains of mid- and high-dose males and high-dose females and body weight gains of mid-dose females were depressed throughout the study. Body weights of dosed males and females remained depressed following the 4-week recovery period. Food consumption of mid- and high-dose animals was concurrently depressed. Urine volume of high-dose males was depressed at study weeks 56, 78, and 103; histologically, the incidence of mineralized concretions of the kidney were found to be increased in these animals. Other histological changes in dosed animals were considered unrelated to dosing. Slight changes in organ weights were considered to be a reflection of depressed body weights in dosed males and females. The chemical was tested at adequate dosage based on significant reductions in body weight gain. The systemic LOEL is 500 ppm (23.3 mg/kg/day in males and 31.2 mg/kg/day in females), and the systemic NOEL is 20 ppm (0.89 mg/kg/day in males and 1.18 mg/kg/day in females). The incidence of mammary adenocarcinomas, adenomas, and fibroadenomas were within the range of available historical control data. However, significant trends for adenocarcinomas and combined adenocarcinomas and adenomas were calculated. Pair-wise comparison of the adenocarcinomas with the controls and the combined adenocarcinomas and adenomas with the controls were of borderline significance. Administration of prometon technical did not demonstrate any evidence of oncogenic response at the highest dose tested.

Classification: The study is Core Guideline according to FIFRA Guideline 83-5 for a combined chronic toxicity/oncogenicity study.

A. MATERIALS:

1. Test Compound: Prometon technical; description: not provided; batch No.: 841716; purity: 97-98.7%.

2. Test Animals: Species: rat; strain: Sprague-Dawley CD; age: 6 weeks at study initiation; weight: males--105.8 to 199.9 g, females--98.1 to 159.5 g; source: Charles River Laboratories, Kingston, NY.

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B. STUDY DESIGN:

1. Animal Assignment: Animals were acclimated to laboratory conditions for 3 weeks and assigned to the following groups using a computerized randomization procedure:

Test group	Dose in diet (ppm)	Main study (104 weeks) Males	Main study (104 weeks) Females	Interim sacrifice[a] (52 weeks) Males	Interim sacrifice[a] (52 weeks) Females
1 Control	0	70	70	10	10
2 Low (LDT)	20	70	70	10	10
3 Mid (MDT)	500	70	70	10	10
4 High (HDT)	1500	70	70	10	10

[a]Ten control and high-dose animals/sex were interim sacrificed at 13 weeks. An additional 10 control and high-dose animals/sex were maintained on basal diet for a 4-week recovery period prior to sacrifice.

Doses were based on a 4-week feeding study in rats (MRID No. 231815) and a 3-month feeding study in rats (MRID Nos. 250917, 250918, and 259108). In the 4-week study, rats were fed prometon technical at levels of 0, 10, 30, 100, 300, 600, 1000, 3000, 6000, and 10,000 ppm; reduced body weight gains were observed at 1000 ppm (LEL). The NOEL was 600 ppm. In the 3-month feeding study, rats were fed prometon technical at levels of 0, 10, 50, 100 and 300 ppm. No treatment-related effects were found at levels up to 300 ppm, the highest dose tested.

Health screens and ophthalmologic examinations were performed on the animals prior to study initiation. Gross necropsy and serologic tests were performed on sentinel groups of 5 animals/sex prior to study. Clinical laboratory determinations were performed on 20 animals/sex.

Animals were housed five/cage during the acclimation period and caged individually during the study in an environmentally controlled room with a temperature of 73 ± 5°F, a relative humidity of 50 ± 20%, and a 12-hour light/dark cycle.

2. Diet Preparation: Test diets were prepared weekly from admixtures of prometon technical in powdered basal diet. Admixtures were stored at room temperature or refrigerated. Concentration analyses were performed at study initiation,

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study week 2, 4-week intervals during the first year of study, and 8-week intervals during the second year of study for a total of 21 sampling intervals. Stability analyses were conducted on low- and high-dose levels at study initiation, study day 17, and study day 45; homogeneity analyses were conducted at three sampling intervals.

Results: The test diets were found to be homogeneous; mean concentrations of the test material for three intervals of analysis were within 10% of nominal for three samples (top, middle, bottom) of the 20-, 500-, and 1500-ppm diets. The test compound was stable in the diet; after storage at room temperature for 45 days, concentrations of the 20- and 1500 ppm diets were 100 and 97% of nominal, respectively. The concentrations of the test material in the diets were within 10% of nominal concentrations for all dose levels for 21 intervals of analysis.

3. Food and Water Consumption: Animals received food (powdered certified Purina rodent chow #5002) and water ad libitum.

4. Statistics: The following procedures were utilized in analyzing the numerical data. Body weights, food consumption clinical laboratory parameters, and organ weight data were examined for homogeneity of variance using Bartlett's test. Dunnett's test was used to compare control and test groups. Data transformations and/or nonparametric tests were used if outliers or heterogeneous variances were found. Histologic incidence data were analyzed by the Fisher exact test, and tumor incidences were further analyzed by a time-adjusted analysis based on the Peto method. Survival was determined with the Kaplan-Meier life-tables, and the Mantel-Cox log rank test was performed to test for linear trend in survival.

5. Quality Assurance: A quality assurance statement was signed and dated January 14, 1988.

C. METHODS AND RESULTS:

1. Observations: The animals were observed twice daily for mortality and toxic signs, except during predose, weekends, and holidays when examinations were performed once daily. Examinations of general appearance and behavior were conducted once daily. Palpable mass examinations were conducted at 4-week intervals for the first 9 months and at 2-week intervals thereafter.

Results: Survival in mid- and high-dose males and low-, mid-, and high-dose females was increased at 104 weeks when compared to concurrent controls. Percent survival in males was 46 and 60% at the mid and high dose as compared to 34% in control males, and 43, 46, and 51% in low-, mid-, and high-dose females as compared to 36% in control females.

Clinical signs that were observed were common for rats of the age and strain used, and their incidence was generally higher in concurrent control animals. Alopecia, cachexia, red ocular discharge, inactivity, foot sores, head tilt, pallor, and labored breathing were the most frequently observed findings. Hypothermia and fur stains were slightly increased in some dosed animals as compared to controls. None of the findings were considered to be related to dosing. No significant differences were found in the incidence of palpable masses in control and dosed animals.

2. Body Weight: Animals were weighed 3 weeks and 2 weeks prior to study initiation, weekly during weeks 1 to 13, biweekly during weeks 14 to 25, and monthly thereafter. Body weight percent gain was calculated based on current weight and day 1 weight.

Results: Representative data on mean body weights and body weight gains are summarized in Tables 1, 2, and 3. Body weight percent gain data were recalculated by the reviewers; the differences in body weight gain measured in grams at selected intervals throughout the study were considered to more accurately reflect changes in mean body weight.

Mean body weights of mid- and high-dose males were significantly ($p < 0.01$) depressed throughout the study when compared to concurrent controls; significant ($p < 0.01$) reductions in body weight gain similarly occurred at the mid dose (10 to 13% depression) and at the high dose (20 to 31% depression) throughout the study. Mean body weights of high-dose females were significantly ($p < 0.01$) depressed throughout the study; mean body weights of mid-dose females were significantly ($p < 0.05$, $p < 0.01$) depressed from study weeks 5 to 84. Significant reductions in body weight gain occurred at the mid- (10 to 18% depression) and high-dose levels (19 to 37% depression) throughout the study. Following the 4-week recovery period, mean body weight gains in previously dosed males and females were 56.5 and 63.3 g, respectively, compared to gains of 12.5 (males) and 12.2 g (females) in the respective controls (Table 2). However, body weights of recovery males and females remained depressed when compared to concurrent controls; depressions in body weights were significant ($p < 0.01$) in

TABLE 1. Mean Body Weight at Selected Intervals in Rats Fed Prometon Technical for 24 Months

Dietary Level (ppm)	Mean Weight (g ± S.E.) at Week:						
	0	2	5	16	52	76	104
				Males			
0	147.9 ± 1.47	256.2 ± 1.71	388.2 ± 3.18	558.2 ± 5.93	754.3 ± 9.84	800.9 ± 17.82	783.4 ± 30.22
20	145.0 ± 1.67	250.4 ± 2.70	376.4 ± 3.68*	550.9 ± 6.42	758.3 ± 10.94	825.0 ± 15.38	745.0 ± 26.18
500	141.4 ± 1.89	245.2 ± 2.54**	366.7 ± 3.85**	502.0 ± 6.07**	664.9 ± 10.21**	730.1 ± 14.10**	711.0 ± 22.24
1500	143.8 ± 1.54	237.8 ± 2.08**	336.4 ± 2.94**	452.6 ± 5.50**	679.8 ± 7.05**	615.5 ± 9.42**	618.0 ± 13.77**
				Females			
0	123.7 ± 1.00	174.9 ± 1.43	224.8 ± 2.07	304.1 ± 3.79	425.3 ± 8.40	510.4 ± 17.36	514.4 ± 34.10
20	126.4 ± 1.17	178.7 ± 1.76	227.8 ± 2.75	309.5 ± 4.15	418.4 ± 8.03	509.9 ± 17.62	586.1 ± 32.35
500	126.7 ± 1.11	170.3 ± 1.70	216.2 ± 2.45*	280.9 ± 3.27**	371.3 ± 6.12**	445.7 ± 9.02**	466.6 ± 14.91
1500	126.7 ± 1.10	168.4 ± 1.40**	209.3 ± 1.87**	259.2 ± 2.39**	326.4 ± 4.46**	361.5 ± 7.11**	381.3 ± 12.26**

*Significantly different from control value, $p < 0.05$.

**Significantly different from control value, $p < 0.01$.

TABLE 2. Mean Body Weight at Selected Intervals in Recovery Rats Fed Prometon Technical for 52 Weeks and Basal Diet for 4 Weeks

Dietary Level (ppm)	Mean Weight (g ± S.E.) at Day[a]: Treatment Phase (Week) 1	2	52	Recovery Phase (Week) 56
		Males		
0	206.6 ± 4.29	264.2 ± 4.94	779.4 ± 27.43	791.9 ± 27.30
1500	183.5 ± 4.38**	232.9 ± 5.63**	594.4 ± 23.11**	650.9 ± 25.54**
		Females		
0	153.0 ± 2.31	174.6 ± 3.11	406.9 ± 17.31	419.1 ± 18.42
1500	144.2 ± 4.35	161.2 ± 5.09*	313.2 ± 13.25**	376.5 ± 17.30

[a]Based on 10 rats/sex/group.

*Significantly different from control value, $p < 0.05$.

**Significantly different from control value, $p < 0.01$.

TABLE 3. Mean Body Weight Gains at Selected Intervals in Rats Fed Prometon Technical for 24 Months[a]

Dietary level (ppm)	Average Weight (g) Between Weeks: 0-4	0-14	0-40	0-80	0-104
			Males		
0	207.0	391.8	564.1	669.8	635.5
20	196.2	384.0	568.7	670.9	600.0
500	185.7	343.1	489.4	579.8	569.6
1500	167.8	297.0	412.6	472.0	474.2
			Females		
0	86.1	169.7	264.3	385.3	390.7
20	89.3	172.1	261.6	408.2	459.6
500	77.6	149.9	224.2	316.1	339.9
1500	72.3	129.9	215.3	241.1	254.6

[a]Calculated by our reviewers; mean body weights at selected intervals were subtracted from body weights at study initiation for each group to obtain body weight gains at selected intervals.

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males. The significant reductions in body weight indicate that prometon was tested at adequate dosage.

3. Food Consumption and Compound Intake: Consumption was determined and mean daily diet consumption was calculated for 1 week prior to study initiation, weekly from weeks 1 to 13, biweekly from weeks 14 to 25, and monthly thereafter. Water consumption was evaluated in 10 rats/sex/group during weeks 1, 2, 52, 53, 101, and 102 to 103. Compound intake was calculated from the consumption and body weight gain data.

   Results: Representative results of mean food consumption are summarized in Table 4. The food consumption of mid-dose males was significantly ($p < 0.01$, $p < 0.05$) depressed from study initiation to study week 80; food consumption of high-dose males was significantly ($p < 0.01$) depressed to study week 88 and nonsignificantly depressed to study termination. Food consumption of high-dose females was significantly ($p < 0.05$) depressed from study weeks 1 to 18, weeks 24 to 36, and sporadically thereafter; food consumption was generally lower than concurrent controls throughout the study except at study termination; food consumption of mid-dose females was significantly ($p < 0.05$) depressed during study weeks 2, 6, and 9 to 18, and generally lower than controls except at study termination. Food consumption increased in recovery animals at week 56 when compared to concurrent controls. Food efficiency data were not provided. The calculated compound consumption over the 104 weeks of the study was 0.89, 23.3, and 73.68 mg/kg/day in males and 1.18, 31.23, and 102.52 mg/kg/day in females. The water consumption of mid- and/or high-dose males was slightly (13 to 19%) lower than concurrent controls at sporadic intervals (2 to 4 intervals); these changes are not considered to be toxicologically significant.

4. Ophthalmological Examinations: Ophthalmological examinations were performed prior to dosing and during study weeks 26, 52, 78, and 103.

   Results: There were no compound-related ophthalmological findings.

5. Hematology and Clinical Chemistry: Blood was collected by orbital sinus puncture from 20 rats/sex at study initiation, 10 control and high-dose rats at study weeks 13 and 56, and 10 rats/sex/group at 104 weeks for hematology and clinical analysis. The CHECKED (X) parameters were examined:

TABLE 4. Food Consumption at Selected Intervals in Rats Fed Prometon Technical for 24 Months

Dietary Level (ppm)	Mean Food Consumption (g/week ± S.E.) at Week: 1	14	28	52	72	104	Mean Compound Consumption (mg/kg/day ± S.E.)
				Males			
0	166.8 ± 1.03	207.4 ± 2.39	196.1 ± 1.67	204.1 ± 2.33	190.3 ± 3.36	161.1 ± 8.63	0
20	166.1 ± 1.96	208.0 ± 2.69	193.7 ± 2.91	202.7 ± 2.80	194.6 ± 3.87	152.5 ± 11.85	0.89 ± 0.368
500	159.6 ± 1.41**	190.6 ± 2.58**	187.1 ± 2.24**	195.0 ± 2.36*	189.0 ± 2.93	161.5 ± 5.97	23.30 ± 8.565
1500	158.7 ± 1.27**	176.1 ± 3.08**	179.2 ± 1.99**	183.9 ± 2.43**	169.4 ± 3.14**	155.9 ± 4.29	73.68 ± 23.880
				Females			
0	136.1 ± 1.23	157.2 ± 2.67	157.7 ± 2.51	165.1 ± 5.56	152.4 ± 3.81	127.8 ± 6.36	0
20	139.6 ± 1.17	153.6 ± 2.41	159.5 ± 2.69	155.7 ± 2.83	149.2 ± 4.43	137.0 ± 7.17	1.18 ± 0.39
500	136.6 ± 1.42	146.5 ± 2.45*	152.5 ± 2.21	155.0 ± 2.16	147.8 ± 2.47	138.9 ± 1.14	31.23 ± 8.78
1500	131.8 ± 1.07*	143.3 ± 2.21	148.8 ± 1.94*	157.0 ± 2.66	137.9 ± 2.65*	139.3 ± 5.01	102.52 ± 22.71

*Significantly different from control, $p < 0.05$.

**Significantly different from control, $p < 0.01$.

a. Hematology:

X	Hematocrit (HCT)†	X	Leukocyte differential count
X	Hemoglobin (HGB)†		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)†		Mean corpuscular HGB concentration (MCHC)
X	Erythrocyte count (RBC)†		Mean corpuscular volume (MCV)
X	Platelet count†	X	Coagulation: thromboplastin time (PT)
X	Reticulocyte count (RETIC)*		
X	Red cell morphology		

Results: No toxicologically important effects on hematology parameters were observed. Slight changes occurred in RBC and WBC parameters; however, these changes were within the range of those of historical controls[1] and were isolated or sporadic, without a dose-response pattern; these changes were not considered to be a result of dosing.

b. Clinical chemistry:

	Electrolytes		Other
X	Calcium†	X	Albumin†
X	Chloride†	X	Albumin/globulin ratio
	Magnesium†		Blood creatinine†
X	Phosphorus†	X	Blood urea nitrogen†
X	Potassium†	X	Cholesterol†
X	Sodium†	X	Globulins
		X	Glucose†
	Enzymes	X	Total bilirubin†
X	Alkaline phosphatase (ALP)		Direct bilirubin
	Cholinesterase	X	Total protein†
X	Creatine phosphokinase†		Triglycerides
X	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (SGPT)†		
X	Serum aspartate aminotransferase (SGOT)†		
X	Gamma glutamyltransferase (GGT)		

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†Recommended by Subdivision F (November 1984) Guidelines.

*Reticulocytes were evaluated in control and high-dose animals only.

[1]Hazleton Laboratories. 1984. Sprague-Dawley Rat Reference Ranges - Hematology. In: Representative Historical Control Data for Rats and Mice.

Results: Table 5 summarizes mean blood-urea-nitrogen changes in male and female rats fed prometon for 24 months. BUN levels of high-dose females were sporadically increased throughout the study when compared to concurrent controls; increases ranged from 2 to 19%. However, all BUN levels were within the range of historical controls,[2] the largest increase in BUN in females was in the high-dose group at the 56-week recovery interval, changes were not consistent, and similar changes did not occur in high-dose males. The study authors considered these changes to be unrelated to dosing. Other slight changes (glucose, bilirubin, cholesterol, total protein, albumin, SGOT, SGPT, sodium, and calcium) occurred sporadically; however, all levels were within the range of historical controls, and changes were marginal and inconsistent and without a dose-response effect. These changes were considered to be incidental.

6. Urinalysis: Urine was collected from animals prior to study initiation, and at weeks 13, 56, and 104. The CHECKED (X) parameters were examined:

X	Appearance[†]	X	Glucose[†]
X	Volume[†]	X	Ketones
X	Specific gravity[†]	X	Bilirubin[†]
X	pH	X	Blood[†]
X	Sediment (microscopic)[†]		Nitrate
X	Protein[†]	X	Urobilinogen

Results: Urine volume of high-dose males was depressed during weeks 56 (8% depression), 78 (18% depression), and 103 (46% depression) when compared to concurrent controls; urine volume of high-dose females was depressed only at study week 103 (18.5% depression). Specific gravity was slightly increased in high-dose females at week 103. No comparable effect was seen in males. The study authors did not consider these changes to be of any toxicological significance.

[†]Recommended by Subdivision F (November 1984) Guidelines.

[2]Hazleton Laboratories. 1984. Sprague-Dawley Rat Reference Ranges - Clinical Chemistry. In: Representative Historical Control Data for Rats and Mice.

TABLE 5. Mean Blood Urea Nitrogen Levels (BUN) in Rats Fed Prometon Technical for 24 Months

Dietary level (ppm)	Mean BUN (mg/dL) ± SE) During Study Week: 13	26	52	56	78	103
			Males			
0	13.9 ± 0.67	12.5 ± 0.34	14.0 ± 0.43	17.9 ± 0.57	25.4 ± 9.83/15.6[c]	34.0 ± 14.15/20.0[c]
20	--[b]	12.4 ± 0.50	19.2 ± 2.81 (37%)	--	41.2 ± 17.41/13.5[c]	15.0 ± 0.98
500	--	14.3 ± 0.62[a] (14%)[d]	16.6 ± 0.78 (19%)	--	14.4 ± 0.73	16.4 ± 1.00
1500	14.0 ± 0.58 (<1%)	12.1 ± 0.55	15.1 ± 0.53 (8%)	18.8 ± 0.36 (5%)	14.7 ± 0.58	17.5 ± 0.58
			Females			
0	16.0 ± 0.56	12.6 ± 0.60	14.5 ± 0.54	17.2 ± 1.06	14.7 ± 0.87	15.4 ± 0.85
20	--	13.4 ± 0.65 (6%)	14.5 ± 0.50	--	15.5 ± 1.09 (5%)	15.9 ± 1.30 (3%)
500	--	14.5 ± 0.82 (15%)	14.1 ± 0.59	--	14.2 ± 1.25	14.8 ± 0.86
1500	16.8 ± 1.43 (5%)	15.3 ± 0.86[a] (21%)	15.1 ± 0.68 (4%)	21.1 ± 1.01 (23%)	15.0 ± 0.45 (2%)	18.1 ± 1.18 (18%)

[c]High mean value resulted from one control male with BUN = 104 during week 78 and one control male with BUN = 132 during week 103; excluding these animals yielded the average values calculated by our reviewers.

[b]BUN not determined in low- and mid-dose animals at weeks 13 and 56.

[c]High mean values resulted from two low-dose males with BUN values of 180 and 97 during week 78; excluding these animals yielded the average values calculated by our reviewers.

[d]Value in ( ) = percent increase over control.

[a]Significantly different from control, $p < 0.05$.

7. Sacrifice and Pathology: All animals that died and that were sacrificed on schedule were subject to gross pathological examination, and the CHECKED (X) tissues were collected for histological examination. In addition, the (XX) organs were weighed:

Digestive System	Cardiovasc./Hemat.	Neurologic
X Tongue	X Aorta†	XX Brain
X Salivary glands†	XX Heart†	X Peripheral nerve (sciatic nerve)†
X Esophagus†	X Bone marrow†	X Spinal cord (3 levels)
X Stomach†	X Lymph nodes†	X Pituitary†
X Duodenum†	XX Spleen†	X Eyes (optic nerve)†
X Jejunum†	X Thymus†	
X Ileum†		
X Cecum†		
X Colon†		
X Rectum†	**Urogenital**	**Glandular**
XX Liver†	XX Kidneys†	XX Adrenals†
Gallbladder†	X Urinary bladder†	Lacrimal gland
X Pancreas†	XX Testes†	X Mammary gland†
	XX Epididymides	XX Thyroids†
	X Prostate	XX Parathyroids†
	X Seminal vesicle	Harderian glands
Respiratory	XX Ovaries	
X Trachea†	X Uterus	
XX Lung†	X Vagina	

Other
X Bone (sternum)†
X Skeletal muscle†
X Skin
X All gross lesions and masses
X Larynx/pharynx

Results:

a. Organ weights: Slight changes in organ weights (brain, heart, adrenals, kidney, liver, lung, spleen, testes, thyroid, and ovaries) of high-dose males and females were considered to be a reflection of depressed body weights in these animals.

b. Gross pathology: All of the gross findings were those commonly found in rats of the same age and strain. In addition, incidences were similar in dosed and control animals.

†Recommended by Subdivision F (November 1984) Guidelines.

c. Microscopic pathology:

1) Nonneoplastic: Table 6 summarizes incidence data for nonneoplastic findings of rats fed prometon at the 12-month phase of the study, and Table 7 summarizes similar data for selected organs/tissues in the 24-month phase of the study.

The incidence of hyperplasia of the pituitary was increased in low-dose males and all dosed females relative to the concurrent controls at 12 months and all dosed males and high-dose females at 24 months; the increased incidence was significant ($p < 0.05$) only at 12 months in low-dose females (7/10, as compared to 2/11 concurrent controls).

The incidence of atrophy of seminiferous tubules was significantly ($p < 0.05$) increased in low-dose males (31/70) as compared to concurrent controls (19/70). These lesions were not considered to be related to dosing, since the incidence was highest at the lowest dose levels, the increase was not dose related, and the increase was not consistent at 12 and 24 months.

The incidence of mineralized concretions of the kidney were increased in high-dose males (15/70) at 24 months when compared to concurrent controls (8/70).

Other frequent nonneoplastic findings were chronic myocarditis, galactocele and lactation of the mammary gland, and focal C-cell hyperplasia of the thyroid. These findings were more severe at 24 months than at the 12-month sacrifice. However, the incidence in control and dosed animals was similar.

2) Neoplastic: Table 8 summarizes neoplastic findings of animals fed prometon for 24 months. Daily oral administration of prometon produced no evidence of carcinogenicity. Even though the incidence of mammary lesions consisting of adenocarcinomas, adenomas, and fibroadenomas was nonsignificantly increased in high-dose females when compared to concurrent controls,

TABLE 6. Nonneoplastic Histologic Findings in Rats Fed Prometon--12-Month Phase of Study

Tissue/Organ	Dietary Level (ppm)							
	Males				Females			
	0	20	500	1500	0	20	500	1500
Adrenal	(9)*	(9)	(10)	(9)	(11)	(10)	(10)	(10)
Cortical hypertrophy/ cystic degeneration	0	1	0	1	6	9	5	6
Heart	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Chronic myocarditis	5	7	4	5	2	1	2	0
Kidney	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Mineralized concretions	0	1	0	2	4	2	1	4
Pituitary	(10)	(9)	(10)	(10)	(11)	(10)	(10)	(10)
Hyperplasia	1	3	1	1	2	7*	4	6
Mammary	(8)	(8)	(10)	(9)	(11)	(10)	(10)	(10)
Galactocele	0	1	0	0	2	4	4	6
Hyperplasia	0	0	0	0	0	0	0	1
Lactation	0	0	0	0	3	7	4	6
	Recovery (56 weeks)							
Adrenals	(10)			(9)	(9)			(10)
Cortical hypertrophy/ cystic degeneration	0			0	5			6
Heart	(10)			(10)	(9)			(10)
Chronic myocarditis	7			9	0			2
Kidney	(10)			(10)	(9)			(10)
Mineralized concretion	9			7	2			2
Pituitary	(10)			(10)	(9)			(10)
Hyperplasia	1			0	0			3
Mammary	(8)			(10)	(9)			(10)
Galactocele	0			0	3			3
Lactation	0			0	4			5

*Numbers in parentheses equal the number of tissues examined.

*Significantly different from control incidence, $p < 0.05$.

TABLE 7. Representative Nonneoplastic Histologic Lesions in Rats Fed Prometon for 24 Months

Organ/Finding	Dietary Level (ppm)							
	Males				Females			
	0	20	500	1500	0	20	500	1500
Heart	(70)[a]	(70)	(70)	(70)	(70)	(70)	(70)	(70)
Chronic myocarditis	43	45	39	33	21	19	27	12
Kidney	(70)	(70)	(70)	(70)	(70)	(70)	(70)	(70)
Mineralized concretions	8	8	7	15	39	27	28	31
Pituitary	(70)	(69)	(70)	(70)	(70)	(70)	(70)	(70)
Hyperplasia	3	5	5	6	2	2	3	4
Prostate	(70)	(70)	(69)	(70)				
Subacute purulent inflammation	37	36	36	43				
Mammary	(56)	(48)	(49)	(52)	(70)	(70)	(70)	(70)
Galactocele	4	3	2	1	12	11	15	10
Lactation	14	11	7	5	24	28	32	30
Testis	(70)	(70)	(70)	(70)				
Atrophy	19	31*	20	12				
Thyroid	(69)	(69)	(70)	(70)	(69)	(70)	(70)	(70)
Focal C-cell hyperplasia	4	2	2	7	6	4	6	5

[a]Numbers in parentheses equal the number of tissues examined.

*Significantly different from control incidence. $p < 0.05$.

TABLE 8. Representative Neoplastic Lesions in Rats Fed Prometon for 24 Months[a]

Organ/Neoplasm	Dietary Level (ppm)							
	Males				Females			
	0	20	500	1500	0	20	500	1500
Brain	(80)[b]	(79)	(80)	(80)	(81)	(80)	(80)	(80)
Astrocytoma, malignant	0	1	1	0	0	2	2	0
Oligodendroglioma, malignant	0	0	0	1	0	1	0	0
Liver	(80)	(80)	(80)	(80)	(81)	(80)	(80)	(80)
Hepatocarcinomas	1	2	1	3	1	0	0	0
Ovary					(81)	(80)	(80)	(80)
Granulosa cell tumor, malignant					0	1	0	1
Granulosa theca cell tumor					0	0	1	0
Parathyroid	(77)	(76)	(75)	(76)	(75)	(78)	(79)	(77)
Adenoma	5	5	4	8	0	1	1	0
Pituitary	(80)	(78)	(80)	(80)	(81)	(80)	(80)	(80)
Adenoma	57	60	51	44	66	67	61	65
Mammary	(64)	(56)	(59)	(61)	(81)	(80)	(80)	(80)
Adenocarcinoma	0	0	1	0	15	8	12	23
Adenoma	0	1	0	0	3	3	2	6
Fibroadenoma	2	3	1	0	23	17	21	25
Thyroid	(79)	(80)	(80)	(80)	(80)	(80)	(80)	(80)
C-cell adenoma	6	6	6	9	5	5	6	5
C-cell carcinoma	1	0	3	4	3	1	1	0
Follicular adenoma	2	1	1	3	0	1	1	1
Follicular adenocarcinoma	1	0	1	2	1	0	2	1

[a]Includes animals sacrificed at 12 and 24 months as well as those that died or were sacrificed moribund. Recovery animals were not included.

[b]The numbers in parentheses are the numbers of tissues examined histologically.

the incidence is within the range of historical controls. The historical range[3] for adenocarcinomas in female Sprague-Dawley rats was 10-30% (mean of eight studies was 17.1%, 49/286) as compared to 29% in high-dose females. The historical range for adenomas in this same strain and sex was 3-9% (mean of four studies was 2.4%, 7/286) as compared to 7.5% in high-dose females. The historical range for fibroadenomas was 22-55% (mean of 8 studies was 38.5%, 110/286) as compared to 31% in high-dose females. In addition, the analysis of mammary lesions in females was nonsignificant for tumor trend as evaluated by Peto analysis. However, there is a significant trend for adenocarcinoma counts ($p < 0.01$) and combined adenocarcinoma and adenoma tumor counts ($p < 0.01$) as calculated by the Cochran-Armitage test for trend analysis. The pair-wise comparisons of the adenocarcinomas with the controls and the combined adenocarcinomas and adenomas with the controls are of borderline significance with p values of 0.089 and 0.072, respectively, as calculated by Fisher's Exact test. (Statistical analyses of MRID 404881-02 from L. Brunsman, Science Analysis and Coordination Branch).

The incidence of adenomas of the pituitary of control and low-dose males was slightly increased when compared to historical controls.[3] The historical range for pituitary adenomas in male Sprague-Dawley rats was 17 to 63% as compared to 71% in control males and 77% in low-dose males. This finding was not increased at the mid and high dose and is not considered to be a result of dosing.

The incidence of C-cell adenomas of the thyroid of control and dosed males were slightly increased when compared to historical controls.[3] The historical range for C-cell adenomas of the thyroid of male Sprague-Dawley rats was 2 to 7% as compared to 7.6% in control, low-, and mid-dose males, and 11.3% in high-dose males. The incidence of C-cell adenomas in dosed females was

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[3]Hazleton Laboratories. 1984. Summary of Neoplasia in Sprague-Dawley Rats--Untreated Controls. In: Representative Historical Control Data for Rats and Mice.

within the range of historical controls. Since the increase in males was found in the control and dosed groups and increases were slight and not found in females, the reviewers do not consider this finding to be of toxicological significance.

D. STUDY AUTHORS' CONCLUSIONS:

Prometon was administered for 2 years to Sprague-Dawley rats at dietary levels of 0, 20, 500, or 1500 ppm. After 52 weeks of dosing, 10 recovery rats/sex from the control and high-dose groups were maintained on untreated basal diet. Survival was increased in dosed animals when compared to concurrent controls. Statistically significant depressions of mean body weights and weight gains were observed in mid- and high-dose groups; these changes were considered related to dosing. Food intake was lower in males and females of the mid- and high-dose groups throughout the study. Alterations in organ weights were attributable to body weight depressions. Most parameters showed evidence of reversibility during the 4-week recovery period. The LOAEL is 500 ppm, and the NOEL is 20 ppm, the lowest dose tested.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS:

The conduct and reporting of the study were acceptable. The reviewers agree with the study authors' assessment that prometon produced no evidence of carcinogenicity.

The chemical was tested at adequate dosage based on significant reductions in body weight gain. Based on depressed body weights and body weight gains in males and depressed body weight gains in females, the systemic LOEL is 500 ppm (23.3 mg/kg/day in males and 31.2 mg/kg/day in females). The systemic NOEL is 20 ppm (0.89 mg/kg/day in males and 1.18 mg/kg/day in females), the lowest dose tested. Administration of prometon technical at the doses tested was not accompanied by an increased tumor incidence when compared to the controls.

DATA EVALUATION RECORD

PROMETON

Oncogenicity Feeding Study in Mice

Study Identification: Osheroff, M.R. Lifetime oncogenicity study in mice with prometon. (Unpublished study No. 483-234 conducted by Hazleton Laboratories, Vienna, VA, and submitted by CIBA-GEIGY Corporation, Agricultural Division, Greensboro, NC; dated January 19, 1988.) MRID No. 404881-01.

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DATA EVALUATION RECORD

GUIDELINE §83-2

STUDY TYPE: Oncogenicity feeding study in mice.

MRID NUMBER: 404881-01.

TEST MATERIAL: Prometon; 2,4-bis(isopropylamine)-6-methoxy-s-triazine.

SYNONYMS: Methoxypropazine, Pranutol, Ontrack.

STUDY NUMBERS: 483-234.

SPONSOR: Ciba-Geigy Corp., Agricultural Division, Greensboro, NC.

TESTING FACILITY: Hazleton Laboratories, Vienna, VA.

TITLE OF REPORT: Lifetime Oncogenicity Study in Mice with Prometon Technical.

AUTHOR: M.R. Osheroff.

REPORT ISSUED: January 19, 1988.

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CONCLUSIONS: Groups of 50 CD-1 mice/sex were fed levels of 0, 10, 400, 4,000 or 8,000 ppm (0, 1.7, 70, 737, or 1,524 mg/kg/day) prometon for 88 weeks. The high-dose group received 12,000 ppm for the first 9 weeks, after which the dose was reduced because of excessive toxicity. Survival was decreased in the 4,000- and 8,000-ppm male groups and in high-dose females. Body weights and weight gains were significantly depressed in both sexes at the two highest doses throughout the study ($p < 0.05$). Overall weight gains were 14 and 13% lower than controls in males and females receiving 4,000 ppm and 28 and 13% in males and females at the highest dose. Mean liver weights and liver to body weight ratios were significantly ($p < 0.05$) increased in high-dose females (17 and 31% compared to controls). Kidney weights (but not kidney to body weight ratios) were decreased in males at 4,000 and 8,000 ppm and in females at 4,000 ppm; the changes in kidney weight are of equivocal importance since no clear dose trend was observed. Nonneoplastic histologic liver changes were significantly increased in males receiving 8,000 ppm and in females receiving 4,000 or 8,000 ppm. Hepatocellular disorganization was present in 10/50 males at 8,000 ppm (0.05) and 16/50 and 18/50 females at 4,000 or 8,000 ppm ($p < 0.01$) but absent in controls. Single-cell hepatocyte necrosis was increased in mid- and high-dose females ($p < 0.01$) and centrolobular hepatocyte hypertrophy was present in 35, 50, or 66% of females and 74, 89, or 95% of males for controls, mid- and high-dose mice that died or were sacrificed after 53 weeks. Renal papillary necrosis was present in 12/50 high-dose males ($p < 0.05$) compared to 3/50 controls. Other lesions that were increased in dosed mice (e.g., spleen) were considered to be agonal rather than compound-related changes. Other lesions were incidental and had similar frequencies between groups. There was no oncogenic response to dosing. Based on decreased weight gains and histological liver changes in both sexes at 4,000 and 8,000 ppm, the LOEL for systemic toxicity is 4,000 ppm (737 mg/kg/day) and the NOEL is 400 ppm (70 mg/kg/day).

Core Classification: The study is considered Core Guideline according to FIFRA guideline 83-2 for an oncogenicity study.

A. MATERIALS:

1. Test Compound: Prometon technical; description: white powder; batch No.: FL 841716; purity: 97-98.7%.

2. Test Animals: Species: mouse; strain: Crl:CD(ICR)BR; age: approximately 6 weeks at initiation; weight: males--22.8 to 30.1 g, females--17.6 to 24.4 g; source: Charles River Laboratories, N. Kingston, NY.

B. STUDY DESIGN:

1. Animal Assignment: The mice were acclimatized to laboratory conditions for approximately 2 weeks. Following examination for general physical condition and ophthalmologic abnormalities, healthy mice were randomized according to weight and assigned to the following groups:

Test group	Dose in diet (ppm)	Main study (22 months) Males	Females
1 Control	0	50	50
2 Low (LDT)	10	50	50
3 Mid 1 (MDT)	400	50	50
4 Mid 2 (MDT)	4000	50	50
5 High (HDT)	12000/8000[a]	50	50

[a]The level was lowered from 12,000 to 8,000 ppm at 10 weeks because of toxicity and deaths.

The mice were caged individually and housed in a temperature (69 to 75°F) and humidity (33 to 75%) controlled room with a 12-hour light/dark cycle.

2. Diet Preparation: A premix was prepared by weighing an appropriate amount of Prometon technical (adjusted for 100% purity) with 200 g of feed and mixing for 2 minutes in a Waring blender. Premix was added to the required amount of feed and mixed in a Patterson-Kelly twin-shell mixer with an intensifier bar for 1 minute/kg. Fresh diets were prepared weekly. Homogeneity was tested prior to initiation at all dose levels; samples were collected at three levels of the mixer. Stability analyses were determined for 0, 7, 4, and 35 days storage at room temperature. Concentration analyses were conducted for weeks 1 to 4 and monthly, thereafter.

Results: Prometon was stable in the diets for at least [illegible] days when stored at room temperature, and diets were homogeneous in respect to prometon concentrations. The overall mean percent of target (±S.D.) for the 25 intervals of analyses was 103 ± 11.7, 97 ± 4.0, 97 ± 4.4, and [illegible] 3.9 at nominal levels of 10, 400, 4,000, and 12,000 ppm prometon; the percent of nominal in the high-dose group while receiving 8,000 ppm was 99 ± 4.5.

3. Food and Water Consumption: Purina Certified Rodent Chow #5002 and tapwater were available ad libitum.

4. Statistics: Levene's test for homogeneous variance was performed, and heterogeneous data were transformed in the order of log, square, square root, reciprocal, arcsine, or rank until homogeneous. ANOVA for homogeneous or heterogeneous data were performed and Dunnett's test was used for pairwise group comparison with controls. Trend was analyzed by the Terpstra-Jonckheere test and by simple linear regression. Survival data were analyzed with the NCI package using life-table techniques and the Kaplan-Meier limit test. Neoplastic and nonneoplastic incidence data were analyzed with the Fisher-Irwin exact test for pairwise comparisons, and the trend test was performed if the incidences in the mid and high doses were increased.

5. Quality Assurance: A quality assurance statement signed and dated 1/14/88 was present. A GLP compliance statement was also present and similarly dated.

C. METHODS AND RESULTS:

1. Observations: Animals were observed twice daily for mortality and moribundity. Clinical observations for signs of toxicity were performed daily, and animals received a detailed physical examination weekly.

Results: Table 1 summarizes survival data at representative study intervals. Survival in males was significantly decreased at 4,000 ppm ($p < 0.05$) and 8,000 ppm ($p < 0.01$) by pairwise comparison with control survival, and there was a significant positive trend ($p < 0.01$) for mortality. In females, mortality was significantly increased at 8,000 ppm ($p < 0.01$) and there was a positive trend ($p < 0.01$). The study was terminated when survival at the highest dose approached 25% (88 weeks). Increased incidences of thinness and hunched appearance were noted in mice of both sexes receiving 4,000 ppm or the highest dose when compared to controls. Other findings seen were considered common to mice of the age and strain and had similar incidences in all groups. These findings included hair loss, rough coat, urine stains, swollen areas, or body sores.

2. Body Weight: Body weights were recorded weekly for the first 13 weeks and every 2 weeks thereafter. Mean weights and weight gains were statistically analyzed at 13, 26, 52, 78 and 88 weeks.

Results: Table 2 summarizes body weight data at representative study intervals. Mean body weights were

TABLE 1. Percent Survival in Mice Fed Prometon for 88 Weeks

Dietary level (ppm)	Percent survival at week: 13	52	64	78	88
			Males		
0	100	100	94	72	54
10	100	96	88	60	42
400	94	88	82	62	32
4,000	100	94	86	60	28
8,000	98	78	70	44	26
			Females		
0	100	96	86	56	46
10	94	88	82	56	30
400	100	100	94	74	48
4,000	100	90	84	68	52
8,000	90	72	56	36	24

TABLE 2. Mean Body Weights and Gains at Selected Intervals in Mice Fed Prometon for 88 Weeks

Dietary level (ppm)	Mean weight (g) and (weight gain) between initiation and week:									
	13		26		52		78		88	
Males										
0	36.7	(9.6)	38.3	(11.2)	39.8	(12.7)	39.2	(12.2)	38.8	(11.8)
10	36.6	(10.0)	38.2	(11.6)	39.1	(12.6)	38.7	(12.2)	38.4	(12.1)
400	36.2	(9.2)	37.8	(10.9)	38.8	(12.0)	37.9	(11.2)	37.4	(10.5)
4,000	34.5*	(7.7*)	35.8*	(9.0*)	37.1*	(10.3*)	36.9*	(9.9*)	36.6	(9.3*)
8,000	32.8*	(6.2*)	34.1*	(7.5*)	36.2*	(9.6*)	35.4*	(9.1*)	35.0*	(8.8*)
Females										
0	29.5	(8.5)	31.3	(10.3)	33.9	(12.9)	35.4	(14.4)	35.3	(14.3)
10	30.0	(9.2)	32.1	(11.3)	34.4	(13.5)	35.2	(14.5)	34.9	(14.2)
400	29.6	(8.7)	31.2	(10.1)	33.1	(12.0)	34.6	(13.5)	34.7	(13.6)
4,000	29.1	(8.5)	30.6	(10.0)	32.3*	(11.7*)	32.3*	(11.7*)	32.8*	(12.4)
8,000	27.3*	(6.5*)	29.6*	(7.8*)	31.4	(10.7*)	31.4*	(10.8*)	33.2	(12.6)

*Significantly different from control value, $p < 0.05$

significantly ($p < 0.05$) lower than control weights at all intervals of analysis for males receiving 4,000 ppm and for both sexes at the highest dose. A significant negative trend ($p < 0.05$) was observed for dosed females at 52 and 88 weeks and for males at all intervals. Mean weight gains were significantly ($p < 0.05$) decreased in males receiving 4,000 and 8,000 ppm at all intervals of analysis, and in females at 8,000 ppm at all intervals and females at 4,000 ppm at 52, 78, and 88 weeks. Trends were significant ($p < 0.05$) in both sexes at 52, 78, and 88 weeks. Overall mean weight gains were 14 and 28% lower than control gains in males at 4,000 and 8,000 ppm and 13% lower than controls in the same groups of females.

3. Food Consumption and Compound Intake: Food consumption was recorded weekly for 14 weeks and every 2 weeks thereafter. Food efficiency was calculated from consumption and weight gain, and mean compound consumption was calculated from food consumption and body weight data.

   Results: Mean food consumption values in all groups fluctuated considerably from week to week. Positive and negative dose trends occurred at various weeks of analysis. Overall food consumption tended to be higher in the groups of both sexes receiving 8,000 ppm when compared to controls. From week 9 to study termination, mean food efficiency data were similar in all groups. Mean compound consumption (excluding the values at the 12,000-ppm dose between weeks 1 and 9) was 1.5, 61.5, 641.5, and 1384.9 mg/kg/day in males in groups 2, 3, 4, and 5, respectively, and 1.9, 77.7, 832.9, and 1664.3 mg/kg/day in females in the same groups.

4. Ophthalmological Examinations: Ophthalmoscopic examinations were performed on all animals prior to initiation and on control and high-dose animals at 26, 72, and 88 weeks (termination).

   Results: No ocular lesions were seen prior to initiation, and there was no indication of dose- or compound-related effects at 78 or 88 weeks. High-dose males had an increased incidence of corneal abrasion at 26 weeks (14/47 compared to 7/50 for controls); this was not considered related to dosing.

5. Hematology and Clinical Chemistry:

   a. Hematology: Blood was collected from the tail during weeks 26, 52, 78, and 88. A differential blood count was performed on smears from control and high-dose groups. If major discrepancies were observed at the high-dose level, smears were evaluated from the low-

and mid-dose groups. Beginning at week 64, blood smears were prepared for animals sacrificed in extremis.

Results: No findings of toxicological importance were observed. Some statistically significant changes in differential white cell percentages were reported at 26 and 52 weeks, but there were no consistent patterns between sexes, between the two intervals, or any dose-related pattern when differential counts were performed on the low- and mid-dose groups. At 78 and 88 weeks, control and 8,000-ppm groups had similar values.

b. Clinical Chemistry and Urinalysis: These parameters were not evaluated in accord with acceptable protocols.

6. Sacrifice and Pathology: All animals that died or were sacrificed in extremis during the study and all those sacrificed at termination were necropsied and findings were recorded. The CHECKED (X) tissues were collected for histological examination. In addition, the (XX) organs were weighed:

Digestive System	Cardiovasc./Hemat.	Neurologic
X Tongue	X Aorta†	XX Brain
X Salivary glands (mandibular)†	X Heart†	X Peripheral nerve (sciatic nerve)
X Esophagus†	X Bone marrow†	X Spinal cord (3 levels)
X Stomach†	X Lymph nodes†	X Pituitary†
X Duodenum†	X Spleen	Eyes (optic nerve)
X Jejunum†	X Thymus	
X Ileum†		
X Cecum†		
X Colon†	Urogenital	Glandular
X Rectum	XX Kidneys†	XX Adrenals†
XX Liver† and gallbladder	X Urinary bladder†	Lacrimal gland
X Pancreas†	XX Testes†	X Mammary gland†
	X Epididymides	X Thyroids†
	X Prostate	X Parathyroids†
Respiratory	X Seminal vesicle	X Harderian glands
X Trachea†	XX Ovaries	
X Lung†	X Uterus	Other
		X Bone (femur)†
		X Skeletal muscle
		X Skin
		X All gross lesions and masses

A complete complement of tissues was examined for all dosed groups.

Results:

a. Organ Weights: Table 3 summarizes mean organ weight and organ-to-body weight data for liver and kidneys. The absolute and relative liver weights of females receiving 8,000 ppm were significantly increased compared to controls; the percent increases over controls were 17 and 34% for absolute and relative weights. No similar effect was seen in males; the trend for increased liver-to-body weight ratios in dosed males was related to decreased body weights. Absolute kidney weights were slightly but significantly ($p < 0.05$) decreased in males receiving 4,000 or 8,000 ppm and in females receiving 4,000 ppm. This was considered probably unrelated to dosing since the changes were slight and no correlating gross or histologic kidney lesions were found. Slight changes in absolute and relative adrenal weights were found, but these were considered incidental since there was a lack of dose-response and no associated histologic lesions.

b. Gross Pathology: The incidence of gross pathology findings were comparable between control and dosed groups and were common for the strain and age of mice and not considered to be compound-related.

c. Microscopic Pathology:

1) Nonneoplastic: Table 4 summarizes data from nonneoplastic lesions that were increased in dosed groups. The incidence of hepatocellular hypertrophy was increased in males receiving 8,000 ppm and in females receiving 4,000 or 8,000 ppm. For mice that died or were sacrificed after 53 weeks, the percent incidence was 95% (38/40) in high-dose males compared to 74% (37/50) in controls; incidence in females receiving 4,000 and 8,000 ppm was 50 or 66% (23/46 or 23/35) compared to 35% (17/48) in controls. It was reported that the average group severity of hepatocellular centrolobular hypertrophy was also increased in 8,000-ppm males; a check of the individual animal pathology sheets indicated only a slight increase in severity. Incidence of single-cell hepatocyte necrosis was also increased in the second year of the study for males at 8,000 ppm (35% vs. 22% for controls) and females receiving 4,000 or 8,000 ppm (35 or 43% compared to 2% for controls).

TABLE 3. Organ Weight (g) and Organ-to-Body Weight Ratios for Liver and Kidney of Mice Fed Prometon for 88 Weeks

Dietary level (ppm)	Liver		Kidneys	
	(g)	(% of bw)	(g)	(% of bw)
		Males		
0	1.63 ± 0.49	4.94 ± 1.71	0.69 ± 0.10	2.07 ± 0.25
10	1.60 ± 0.25	4.87 ± 0.76	0.74 ± 0.12	2.25 ± 0.32
400	1.75 ± 0.36	5.37 ± 1.28	0.69 ± 0.08	2.09 ± 0.21
4,000	1.82 ± 0.63	5.83 ± 2.12	0.61 ± 0.07*	1.94 ± 0.22
8,000	1.63 ± 0.29	5.40 ± 0.84T	0.57 ± 0.08*	1.88 ± 1.76
		Females		
0	1.60 ± 0.26	5.28 ± 0.56	0.53 ± 0.09	1.76 ± 0.34
10	1.63 ± 0.28	5.43 ± 0.77	0.54 ± 0.08	1.79 ± 0.19
400	1.44 ± 0.22	4.92 ± 0.58	0.53 ± 0.10	1.84 ± 0.39
4,000	1.58 ± 0.30	5.73 ± 0.87	0.47 ± 0.05*	1.71 ± 0.20
8,000	1.87 ± 0.46*T	6.90 ± 1.64*	0.49 ± 0.08T	1.80 ± 0.18

*Significantly different from control value, $p < 0.05$.

TSignificant trend, $p < 0.05$.

TABLE 4. Representative Nonneoplastic Histologic Lesions in Mice Fed Prometon for 88 Weeks

	Dietary Level (ppm)									
	Males					Females				
Organ/Finding	0	10	400	4,000	8,000	0	10	400	4,000	8,000
Liver	(50)	(49)	(50)	(49)	(50)	(50)	(50)	(50)	(50)	(48)
Hepatocellular disorganization	0	0	0	0	5*	0	0	0	8*	9*
Hypertrophy, centrolobular	36	32	36	41	44*	17	9	17	22	18
Hypertrophy, random	1	0	2	3	1	1	0	1	4	**
Necrosis, single cell	11	6	10	12	14	1	2	4	16*	15*
Necrosis, centrolobular	0	0	0	0	3	0	1	0	0	2
Necrosis, n.o.s.	6	10	12	2	4	15	8	13	8	3
Hepatocyte hyperplasia	0	0	2	0	2	0	1	0	1	1
Spleen	(50)	(49)	(49)	(49)	(48)	(50)	(50)	(50)	(50)	(50)
Lymphoid depletion	2	4	8*	15**	18**	2	7	7	14**	17**
Atrophy generalized	1	3	2	9**	9**	3	6	4	9	10*
Pigment	36	48	44	46	43	46	48	50	47	45
Increased extramedullary hematopoiesis	5	7	10	17**	8	10	10	11	9	16
Kidney	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(50)	(50)
Renal papillary necrosis	3	3	2	3	12*	2	0	1	2	4
Amyloidosis	42	38	37	43	37	39	42	47	46	39
Harderian gland	(43)	(40)	(47)	(46)	(47)	(48)	(41)	(49)	(34)	(43)
Chronic inflammation	8	13	18*	19*	13	24	14	24	10	19
Ovary						(50)	(50)	(49)	(49)	(48)
Dist. bursa						5	7	12	9	1

*Significantly different from control incidence, $p < 0.05$.

**Significantly different from control incidence, $p < 0.01$.

Disorganization of hepatocytes was seen only in the second year and was increased in the same groups as above. The disorganization was accompanied by inflammation, hypertrophy, and single-cell necrosis.

Histologic changes observed in the spleen were considered by the study author to be agonal changes and not compound-related. In males and females at terminal sacrifice, there was not a dose-related trend for splenic lymphoid depletion; the incidence was 0, 5, 7, 28, and 8% in males receiving 0, 10, 400. 4,000 or 8,000 ppm and 0, 0, 8, 36 and 18% in females at the same doses. However, there was a dose-related trend for mice with unscheduled deaths from weeks 53 to termination and a statistically significant increase in total incidence for males at the three highest doses and for females at the two highest doses (Table 4).

Males receiving 8,000 ppm had an increased incidence of renal papillary necrosis; the implication of this finding is not clear since it occurred in 11/37 high-dose males that died and only 1/13 at terminal sacrifice. Amyloidosis in multiple organs was frequent in all groups; the author stated it was not considered to affect the evaluation of oncogenicity. Incidence of amyloidosis in controls was about 82% for kidneys, 54% for ileum, and 25% for liver. Other nonneoplastic lesions were comparable in all groups and considered to be normal spontaneous or agonal changes.

2) Neoplastic: No increases in neoplastic incidence were observed; Table 5 shows the incidence of liver tumors, lung tumors, and hematopoietic tumors. At all other sites, neoplastic incidence generally was 4% or less in any group, which is consistent with normal background for the mice of this age and strain. The incidence of liver, lung, and hemolymphoreticular neoplasms was also within the normal range.

TABLE 5. Incidence of Selected Neoplastic Findings in Mice Fed Prometon for 88 Weeks[a]

Site/Neoplasm	Dietary level (ppm)									
	Males					Females				
	0	10	400	4,000	8,000	0	10	400	4,000	8,000
Liver	(50)[b]	(49)	(50)	(49)	50)	(50)	(50)	(50)	(50)	(49)
Hepatocellular adenoma	4	4	6	8	4	1	3	0	3	4
Hepatocellular carcinoma	2	1	3	2	3	0	3	0	3	1
Adenoma, carcinoma	6	5	8	10	6	1	3	0	3	4
Hemangiosarcoma	1	1	5	3	1	1	2	0	3	1
Lung	(50)	(49)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Alveolar bronchiolar adenoma	8	4	3	6	6	5	7	3	3	4
Alveolar bronchiolar carcinoma	2	2	4	2	4	1	1	1	1	2
Reticulcendothelial system										
Malignant lymphoma	4	3	1	3	1	14	9	3	6	4
Lymphocytic	3	3	1	3	1	9	7	2	5	4
Mixed	1	3	3	3	3	2	1	1	2	0
Histiocytic	3	3	3	3	3	3	2	3	3	0

[a]Neoplasms are not tabulated if their incidence in all groups was 5% or less. No significant increases were found by pairwise comparison.

[b]The numbers in parentheses are the number of animals with tissue examined.

D. STUDY AUTHOR'S CONCLUSIONS:

Administration of prometon in the diet to CD-1 mice for 88 weeks failed to demonstrate oncogenic potential. A significant compound-related increase in mortality was seen in males and females at 4,000 or 8,000 ppm (groups 4 and 5). At the same doses, decreases in mean body weights and weight gains were decreased. Absolute kidney weights were decreased in group 4 males and females and in group 5 males, and absolute and relative (to body weight) liver weights were significantly increased in high-dose females. Hepatocellular hypertrophy, single-cell hepatic necrosis, or hepatocellular disorganization were increased in group 5 males and in groups 5 and 6 females; an increased incidence of papillary necrosis was seen in high-dose males. Histologic changes in the spleen were probably not related to dosing. The no-observable effect level in both sexes is 400 ppm.

E. REVIEWER'S DISCUSSION AND INTERPRETATION OF RESULTS:

The study was adequately conducted and reported. The reviewer agrees with the study author's interpretation of results. A maximum tolerated dose was achieved, and survival at termination was sufficient (24 to 26%) to assess oncogenic potential. A complete histopathologic examination was performed, including low- and mid-dose groups, and the tissue accountability was acceptable.

009679

DATA EVALUATION RECORD

PROMETON TECHNICAL

Two-Generation Reproductive Toxicology Study in Rats

STUDY IDENTIFICATION: Salamon, C.M. Two-generation reproduction study in rats. (Unpublished study No. 450-2208 conducted by American Biogenics Corporation, Decatur, IL, and submitted by Ciba-Geigy Corporation, Agricultural Division, Greensboro, NC; dated June 18, 1987.) MRID No. 403615-01.

009679

1. CHEMICAL: 2,4-Bis(isopropylamino)-6-methoxy-s-triazine.

2. TEST MATERIAL: Prometon technical, purity 97-98.7%; white powder; lot No. FL 841716.

3. STUDY/ACTION TYPE: Two-generation reproduction study in rats.

4. STUDY IDENTIFICATION: Salamon, C.M. Two-generation reproduction study in rats. (Unpublished study No. 450-2208 conducted by American Biogenics Corporation, Decatur, IL, and submitted by Ciba-Geigy Corporation, Agricultural Division, Greensboro, NC; dated June 18, 1987.) MRID No. 403615-01.

5. REVIEWED BY:

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009675

DATA EVALUATION RECORD

STUDY TYPE: Reproductive toxicity. Guideline § 83-4.

MRID NUMBER: 403615-01.

TEST MATERIAL: Prometon technical, purity 97-98% : white powder; lot No. FL 341716.

SYNONYMS: Pramitol, Gesafram 50, Ontracic 800, Primatol 25E.

STUDY NUMBER: 450-2208.

SPONSOR: Ciba-Geigy Corporation, Agricultural Division, Greensboro, NC.

TESTING FACILITY: American Biogenics Corporation, Decatur, IL.

TITLE OF REPORT: Two-Generation Reproduction Study in Rats.

AUTHOR: Salaman, C.M.

REPORT ISSUED: June 18, 1987.

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CONCLUSIONS:

In a two-generation reproductive toxicity study, Sprague-Dawley rats were fed diets containing prometon technical at 0, 20, 500, or 1500 ppm during the premating period, for males 0, 1.45, 35.08, or 103.98 mg/kg/day; for females 0, 1.59, 39.17, or 113.98 mg/kg/day). Parental toxicity was observed at 1500 ppm as decreased food consumption and body weight in both generations and sexes, and at 500 ppm as decreased body weight in males in both generations and decreased food consumption in males in the second generation. Based on these results, the NOEL and LOEL for parental toxicity were 20 and 500 ppm, respectively.

Reproductive toxicity, observed at 1500 ppm in both generations and at 500 ppm in the second generation, was evident as decreased pup body weight during the entire lactation period. Therefore, the NOEL and LOEL for reproductive toxicity were 20 and 500 ppm, respectively.

Classification: CORE Guideline Data. This study meets the requirements set forth under Guideline § 83-4 for a two-generation reproductive toxicity study in rats.

A. MATERIALS:

Test Compound: Purity: 97-98.7%.
Description: White powder.
Lot No.: FL 841716.

Vehicle: None used; the test material was administered in the diet.

Test Animals: Species: Rat.
Strain: Sprague-Dawley, Crl:CD (SD)BR.
Source: Charles River Breeding Laboratories, Portage, MI.
Age: 49 days at start of study.
Weight: F_0 males--157-266 g, F_0 females--145-211 g at start of study.

B. STUDY DESIGN:

This study was designed to assess the potential of prometon technical to cause reproductive toxicity when administered continuously in the diet for two successive generations.

Mating: After approximately 14 days of acclimatization and 12 weeks of dietary treatment, the F_0 parental animals were mated (one male:one female) for a maximum of 21 days. Daily examinations were made for a copulatory plug or a sperm-positive smear. The day on which evidence of breeding was observed was designated as gestation day 0 and the female was then housed individually. F_1 parental animals were mated in a similar way following 14 weeks of dietary treatment. Sibling matings were avoided.

Group Arrangement: F_0 and F_1 parental animals were randomly allocated to groups via a computer program (Applied Numerical Methods, Wiley, 1969) as follows:

Test Group	Dietary Concentration (ppm)	Number Assigned per Group F_0 Males	F_0 Females	F_1 Males	F_1 Females
Control	0	30	30	30	30
Low dosage	20	30	30	30	30
Mid dosage	500	30	30	30	30
High dosage	1500	30	30	30	30

Dosing: The test material was administered continuously in the diet for two consecutive generations. The test diets (mixtures of test material and Purina Certified Rodent Chow #5002, offered fresh every week) were stored at room temperature. Homogeneity of the test material in the diet was determined on 20-, 40-, and 80-kg batches of diets mixed at three different times during the study. Stability of the test material in the diet for 22 days was assessed prior to or concurrent with the start of the study. Concentration analyses of the test material in the diet were conducted for every other mix on samples from each dosage level. No rationale was reported for the selection of dosages.

Observations: Animals were observed twice a day for mortality, moribundity, and overt signs of toxicity. A more detailed clinical examination was performed weekly. Body weights of males and nonpregnant females were recorded weekly throughout the study; body weights of pregnant females were recorded weekly during the premating period, on gestational days (GD) 0, 7, 14, and 20, and on lactational days 0, 4, 7, 14, and 21. Food consumption for males and nonpregnant females was recorded weekly during the premating period; for pregnant females it was recorded weekly during the premating period, on GD 0, 7, 14, and 20, and on lactational days 7 and 14.

The following data were recorded for each litter:

- Number of stillborn and live pups on lactational day 0;
- Number of live pups, individual body weight, sex, and external anomalies on lactational days 0, 4, 7, 14, and 21; and
- Daily observations for mortality and changes in behavior.

Pups found dead and pups culled on day 4 were given a gross examination, including the external body surface, the thoracic abdominal and pelvic cavities, and the brain and palate. Following weaning on day 21, 30 male and 30 female F_{1A} pups per litter were randomly (Applied Numerical Methods, Wiley, 1969) selected as F_1 parental animals. Ten F_{1A} and F_{2A} pups/sex/dosage group were selected for a complete necropsy and histopathological examination. The remaining F_{1A} and F_{2A} pups were subjected to complete gross necropsy procedures.

Following selection of the F_1 parental animals, the F_0 males and females were sacrificed at 190-194 days (by CO_2 inhalation and then exsanguination) and subjected to a detailed gross examination (including the number of implantation sites for females). Evaluation of F_1 parental animals (sacrificed at 173-193 days) was similar to that of F_0 parental animals. Parental animals sacrificed prior to schedule or found dead were given a detailed gross examination. The following tissues from parental animals were preserved in 10% neutral buffered formalin for processing and histopathological examination:

- Seminal vesicles
- Prostate
- Coagulating gland
- Uterus
- Ovaries*
- Gross lesions
- Testes*
- Epididymides
- Cervix
- Vagina
- Pituitary

For tissues with an asterisk (*), organ weight was recorded. Histopathological evaluations were carried out on tissues from the control and high-dose groups only.

Statistical Analysis: The following analyses were conducted:

- Parental body weight, food consumption, and progeny population and survival data--ANOVA and Tukey's or Scheffe's multiple comparison test;
- Progeny body weight--ANCOVA and Dunnett's t-test; and
- Organ weight ratios--Kruskal-Wallis and Chi-square analysis or Fisher's Exact test.

The levels of significance were p <0.05 and p <0.01.

Compliance:

- A signed Statement of No Data Confidentiality Claim, dated August 27, 1987, was provided;
- A signed Statement of Compliance with EPA and OECD GLPs, dated August 27, 1987, was provided; and
- A signed Quality Assurance Statement, dated June 19, 1987, was provided.

C. RESULTS:

The following results were reported by the study author:

1. Test Material Analysis: Concentrations of the test material in the diets ranged from 81 to 104% of the nominal values. Homogeneity analyses revealed concentrations of 93-110% of nominal values. Analyses for stability of the test material in the diet up to 22 days varied <5%.

2. Parental Toxicity:

   Mortality: No compound-related mortality was observed. One F_1 female at 500 ppm was found dead on day 162 with her teeth caught in the wire mesh.

   Clinical Observations: No compound-related clinical signs were observed. Frequent observations occurring in all dosage groups, including the control group, were alopecia, misaligned and/or broken incisors, crusty eyes and nose, trimmed lower incisors, and enlarged mammary glands (females only, postweaning).

   Body Weight: Summaries of body weights from selected time intervals are presented in Tables 1, 2, and 3. Detailed results are presented in the text.

   In the F_0 generation, male body weight was significantly decreased during the premating phase (Table 1) at 1500 ppm from week 1, and at 500 ppm from week 6, and remained significantly decreased through the postmating phase (data not shown). Total weight change was significantly decreased to 86 and 72% of controls at 1500 and 500 ppm, respectively. Female body weight was significantly decreased at 1500 ppm on weeks 3-12 during the premating phase (Table 1), on GD 0-14 (Table 2), and on lactational days 0, 4, and 14 (Table 3). Total weight change was significantly decreased to 81% of controls at 1500 ppm.

TABLE 1. Summary of Body Weights During the Premating Period for Rats Fed Prometon Technical for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Body Weight (g ± SD) on Study Week: 0	3	6/7[b]	9/10[b]	12/14[b]
F_0 Males					
0	226.8 ± 23.5	349.3 ± 27.7	425.2 ± 34.9	476.3 ± 39.6	507.7 ± 40.9
20	225.6 ± 21.7	345.9 ± 25.6	421.9 ± 33.3	473.3 ± 41.6	505.4 ± 48.1
500	226.1 ± 21.3	332.7 ± 24.4	402.0 ± 26.7*	443.1 ± 29.3**	471.2 ± 32.2**
1500	225.0 ± 23.3	317.4 ± 29.4**	374.2 ± 33.6**	409.8 ± 36.5**	428.7 ± 44.8**
F_0 Females					
0	179.5 ± 13.5	234.8 ± 21.3	266.2 ± 27.5	286.1 ± 29.1	301.3 ± 29.5
20	179.9 ± 12.7	237.8 ± 18.6	270.5 ± 22.6	29[illegible] ± 26.0	307.5 ± 27.1
500	180.0 ± 12.5	234.0 ± 17.3	263.2 ± 20.9	282.6 ± 24.6	295.4 ± 26.7
1500	179.8 ± 12.7	221.7 ± 17.0*	247.6 ± 20.3*	263.4 ± 20.7**	273.7 ± 22.4**
F_1 Males					
0	46.9 ± 8.9	261.6 ± 27.9	410.7 ± 47.1	496.3 ± 60.3	531.1 ± 58.2
20	47.8 ± 6.3	256.5 ± 28.1	414.9 ± 32.8	507.6 ± 43.7	547.9 ± 49.9
500	47.1 ± 4.6	260.9 ± 19.4	397.7 ± 29.4	470.4 ± 38.7	504.0 ± 44.0
1500	44.1 ± 6.5	228.1 ± 25.4**	351.9 ± 37.2**	410.8 ± 43.9**	436.6 ± 49.0**
F_1 Females					
0	45.5 ± 8.3	182.0 ± 18.8	242.4 ± 26.5	274.6 ± 29.6	288.0 ± 30.7
20	45.5 ± 6.6	179.3 ± 18.1	247.3 ± 25.2	281.5 ± 32.0	295.7 ± 33.0
500	44.6 ± 5.2	178.3 ± 15.0	237.7 ± 20.0	268.1 ± 24.9	277.6 ± 26.1
1500	41.2 ± 7.9	160.6 ± 19.4**	213.7 ± 24.5*	239.6 ± 26.5**	249.2 ± 25.1**

[a]Data were extracted from study No. 450-2208, Table 4.

[b]F_0 generation/F_1 generation.

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

**Significantly different from controls ($p < 0.01$).

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TABLE 2. Summary of Maternal Body Weights During Gestation in Rats Fed Prometon Technical for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Body Weight (g ± S.D.) on Gestational Day: 0	7	14	20
F0 generation				
0	304 ± 33.5	332 ± 38.5	358 ± 39.8	424 ± 48.2
20	311 ± 26.8	338 ± 28.8	365 ± 29.1	430 ± 35.1
500	293 ± 28.4	323 ± 33.2	350 ± 32.8	416 ± 43.6
1500	270 ± 19.6**	297 ± 22.4**	325 ± 26.5**	393 ± 33.3
F1 generation				
0	286 ± 31.5	313 ± 34.3	339 ± 37.3	394 ± 39.5
20	294 ± 35.1	320 ± 35.5	344 ± 36.7	405 ± 37.9
500	279 ± 27.1	305 ± 30.0	329 ± 33.5	394 ± 41.0
1500	248 ± 24.0**	274 ± 27.4**	300 ± 29.3**	357 ± 38.3*

[a]Data were extracted from study No. 450-2208, Table 5.

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

**Significantly different from controls ($p < 0.01$).

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TABLE 3. Summary of Maternal Body Weights During Lactation in Rats Fed Prometon Technical for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Body Weight (g ± S.D.) on Lactational Day: 0	7	14	21
F_0 generation				
0	335 ± 45.3	336 ± 34.7	357 ± 33.3	349 ± 32.2
20	343 ± 30.1	344 ± 25.2	358 ± 22.2	349 ± 30.1
500	327 ± 35.3	333 ± 30.0	354 ± 30.4	352 ± 27.4
1500	301 ± 27.3**	314 ± 29.0	332 ± 27.5*	330 ± 24.9
F_1 generation				
0	315 ± 37.7	322 ± 31.2	341 ± 35.2	328 ± 31.6
20	324 ± 37.7	325 ± 26.5	340 ± 26.7	327 ± 26.7
500	307 ± 28.4	313 ± 27.2	331 ± 27.3	324 ± 26.9
1500	273 ± 29.4**	288 ± 27.5**	307 ± 27.6**	309 ± 29.6

[a]Data were extracted from study No. 450-2208, Table 5.

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

**Significantly different from controls ($p < 0.01$).

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In the F_1 generation, male body weight was significantly decreased during the premating phase (Table 1) at 1500 ppm from week one, and remained significantly decreased through the postmating phase (data not shown). In addition, at 500 ppm, it was significantly decreased from week 20 during the postmating phase to termination. Total weight change among males was significantly decreased to 92 and 78% of controls at 1500 and 500 ppm, respectively. Female body weight was significantly decreased at 1500 ppm, on weeks 1-14 during the premating phase (Table 1), on GD 0-20 (Table 2), and on lactational days 0-14 (Table 3). Total weight change was significantly decreased to 88% of controls at 1500 ppm.

Food Consumption: Summaries of food consumption from selected time intervals are presented in Tables 4, 5, and 6. Detailed results are presented in the text.

In the F_0 generation, daily food consumption among males (reported only for the premating period) was significantly decreased at 1500 ppm during the entire premating phase (Table 4), at 500 ppm during premating weeks 2 and 4, and at 20 ppm during premating week 2. Daily food consumption among females was significantly decreased at 1500 ppm during premating weeks 1, 6, and 9, and at 1500 and 500 ppm on GD 0 (Table 5). The daily mean test material intake (data not shown) for the premating phase was 1.39, 34.50, and 97.90 mg/kg for males and 1.53, 37.88, and 107.06 mg/kg for females in the low-, mid-, and high-dosage groups, respectively.

In the F_1 generation, daily food consumption among males (reported only for the premating period) was significantly decreased at 1500 ppm during the entire premating phase (Table 4), at 500 ppm during premating weeks 2 and 4-14, and at 20 ppm during premating week 8. Daily food consumption among females was significantly decreased at 1500 ppm during the entire premating phase; at 500 ppm, during premating weeks 6, 8, and 11; at 20 ppm during premating weeks 8, 10, and 11; at 1500 ppm on GD 0 (Table 5); and at 20 ppm on GD 14. The daily mean test material intake (data not shown) for the premating phase was 1.51, 35.65, and 110.01 mg/kg for males and 1.64, 40.46, and 120.90 mg/kg for females in the low-, mid-, and high-dosage groups, respectively.

TABLE 4. Food Consumption for Selected Weeks During the Premating Period for Rats Fed Prometon Technical for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Food Consumption (g/animal/day ± SD) for Study Week: 1	3	6/7[b]	9/10[b]	12/14[b]
F_0 Males					
0	22.3 ± 4.2	25.2 ± 2.1	26.1 ± 3.1	27.6 ± 3.4	25.1 ± 3.0
20	22.9 ± 1.7	24.5 ± 2.5	26.3 ± 3.2	28.6 ± 4.2	25.8 ± 3.1
500	21.1 ± 1.9	23.3 ± 2.2	24.7 ± 2.1	26.5 ± 2.5	25.2 ± 2.5
1500	15.2 ± 2.4**	21.6 ± 3.6**	22.6 ± 2.8**	23.0 ± 3.2**	22.8 ± 4.3
F_0 Females					
0	15.4 ± 1.8	17.6 ± 2.2	18.8 ± 3.2	21.1 ± 2.7	18.8 ± 2.9
20	16.5 ± 2.4	18.0 ± 3.1	19.3 ± 2.9	22.0 ± 3.1	18.3 ± 3.3
500	14.4 ± 2.0	17.6 ± 2.0	18.7 ± 2.5	20.5 ± 3.7	18.2 ± 2.8
1500	9.4 ± 2.7**	15.9 ± 2.6	16.9 ± 2.4*	17.5 ± 2.8**	18.0 ± 2.8
F_1 Males					
0	20.0 ± 2.0	26.4 ± 2.9	27.9 ± 3.5	28.8 ± 3.9	28.3 ± 5.4
20	19.2 ± 2.2	25.5 ± 2.6	27.0 ± 3.2	30.4 ± 3.3	28.5 ± 3.3
500	19.4 ± 1.7	25.8 ± 2.2	24.2 ± 2.3**	25.5 ± 2.8**	25.3 ± 3.4*
1500	17.2 ± 2.6**	23.0 ± 1.9**	21.7 ± 2.2**	21.7 ± 2.4**	23.8 ± 3.1**
F_1 Females					
0	16.0 ± 1.8	18.9 ± 2.2	18.7 ± 2.7	19.5 ± 2.7	19.0 ± 3.5
20	15.8 ± 1.4	18.8 ± 3.3	18.7 ± 2.4	21.4 ± 2.7*	18.7 ± 2.6
500	17.7 ± 1.3	18.7 ± 2.0	17.4 ± 1.9	19.5 ± 2.8	18.0 ± 3.5
1500	14.5 ± 1.8**	16.1 ± 1.7**	14.2 ± 2.4**	16.0 ± 1.8**	16.4 ± 2.3**

[a]Data were extracted from study No. 450-2208, Table 6.

[b]F_0 generation/F_1 generation.

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

**Significantly different from controls ($p < 0.01$).

TABLE 5. Summary of Maternal Food Consumption During Gestation in Rats Fed Prometon Technical for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Food Consumption (g/animal/day ± S.D.) on Gestational Day: 0	7	14	20
F_0 generation				
0	19.3 ± 3.3	23.7 ± 4.5	24.8 ± 4.0	20.8 ± 4.6
20	17.4 ± 2.8	24.7 ± 4.3	24.6 ± 3.6	21.1 ± 3.5
500	16.2 ± 4.1*	22.8 ± 3.0	24.3 ± 3.2	24.1 ± 5.9
1500	14.8 ± 3.8**	22.3 ± 2.4	23.2 ± 3.8	20.4 ± 5.2
F_1 generation				
0	18.8 ± 3.3	22.6 ± 3.3	24.2 ± 2.8	21.1 ± 4.8
20	16.8 ± 2.7	21.7 ± 3.1	27.0 ± 2.7**	20.6 ± 5.7
500	18.0 ± 3.6	21.2 ± 3.1	23.2 ± 3.3	22.5 ± 4.2
1500	15.6 ± 3.8*	19.6 ± 3.0	21.6 ± 3.5*	20.1 ± 5.3

[a]Data were extracted from study No. 450-2208, Table 7.

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

**Significantly different from controls ($p < 0.01$).

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TABLE 6. Summary of Maternal Food Consumption During Lactation in Rats Fed Prometon Technical for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Food Consumption (g/animal/day ± S.D.) on Lactational Day: 7	14
F1 generation		
0	45.2 ± 10.2	62.1 ± 7.7
20	40.7 ± 7.5	58.7 ± 11.1
500	45.8 ± 7.5	62.3 ± 11.7
*500	43.7 ± 9.3	58.6 ± 8.5
F2 generation		
0	45.8 ± 8.7	58.1 ± 10.2
20	45.8 ± 7.9	59.4 ± 4.6
500	42.3 ± 7.5	57.3 ± 7.7
*500	44.2 ± 6.9	57.8 ± 6.7

[a]Data were extracted from study No. 450-2208, Table 7.

Gross and Microscopic Pathology: Summaries of parental reproductive organ weights are presented in Table 7. In the F_0 generation, the testes to body weight ratio was significantly increased at 1500 ppm; in the F_1 generation, the testes and ovaries to body weight ratios were significantly increased at 1500 ppm. Microscopic examination of tissues from animals in both generations revealed no compound-related differences between the control and treated groups.

3. Reproductive Toxicity: The effects of dietary administration of the test material on reproductive parameters are summarized in Tables 8 and 9. Pup body weights were significantly decreased during the entire lactation period at 1500 ppm in the F_{1A} offspring and at 1500 and 500 ppm in the F_{2A} offspring. Incidental clinical observations and external anomalies in pups were observed in both generations and all dosage groups, including the control groups.

D. REVIEWERS' DISCUSSION/CONCLUSIONS:

1. Test Material Analyses: Homogeneity and stability (for 22 days at room temperature) of the test compound in the diet were confirmed. Throughout the study, concentrations of the test compound in the diet were within ±20% of nominal concentrations.

2. Parental Toxicity: Compound-related parental toxicity was observed at 1500 and 500 ppm. At 1500 ppm, significant decreases were consistently present in body weight and in total body weight change at termination for both sexes and generations. In the F_0 generation, significant decreases in body weight mostly occurred without accompanying decreases in food consumption. In the F_1 generation, on the other hand, body weight changes frequently accompanied significant decreases in food consumption. At 500 ppm, significant decreases were observed in F_0 male body weight without accompanying decreases in food consumption. Decreased body weight that occurred without decreased food consumption (F_0 females at 1500 ppm during premating and gestation; F_0 males at 500 ppm during pre- and postmating) was considered to be a compound-related toxic effect. The sporadic changes in body weight noted at 20 ppm were not considered to be biologically important.

The increases in relative testicular and ovarian weights were secondary effects due to the weight loss that the animals experienced at this dosage level and were therefore considered to be unrelated to the test material.

TABLE 7. Ovary and Testes Weights for Rats Fed Prometon Technical for Two Successive Generations[a]

Organ	Dietary Concentration (ppm) 0	20	500	1500
TESTES				
F_0 generation:				
Absolute (g)	5.22 ± 0.77	5.21 ± 0.37	5.30 ± 0.42	5.12 ± 0.53
Organ/Body weight (g/100 g)	0.90 ± 0.16	0.90 ± 0.11	0.99 ± 0.10	1.06 ± 0.11**
F_1 generation:				
Absolute (g)	5.52 ± 0.61	5.66 ± 0.45	5.69 ± 0.49	5.51 ± 0.59
Organ/Body weight (g/100 g)	0.99 ± 0.11	0.89 ± 0.10	1.00 ± 0.13*	1.13 ± 0.12*
OVARIES				
F_0 generation:				
Absolute (g)	0.16 ± 0.06	0.14 ± 0.03	0.16 ± 0.04	0.13 ± 0.03
Organ/Body weight (g/100 g)	0.05 ± 0.02	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.01
F_1 generation:				
Absolute (g)	0.11 ± 0.02	0.11 ± 0.02	0.12 ± 0.02	0.12 ± 0.03
Organ/Body weight (g/100 g)	0.03 ± 0.01	0.03 ± 0.01	0.04 ± 0.01	0.04 ± 0.01**

[a]Data were extracted from Study No. 45-2208, Table 17.

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

**Significantly different from controls ($p < 0.01$).

TABLE 8. Summary of Effects of Dietary Administration of Prometon Technical on F_1 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Concentration (ppm)			
	0	20	500	1500
No. matings	30	30	30	30
No. pregnancies	26	23	27	26
Fertility index-female (%)[b]	86.7	76.7	90.0	86.7
Gestation index (%)[c]	100.0	100.0	92.6	100.0
Gestation length (days)	22	22	22	22
Total No. live pups				
Day 0	346	287	357	362
Day 4 (precull)	340	279	350	349
Day 21	206	177	200	199
Mean No. live pups/litter				
Day 0	13.3	12.5	14.3	13.9
Day 4 (precull)	13.1	12.1	14.3	13.4
Day 21	7.9	7.7	8.3	7.7
Live birth index (%)[d,e]	97.9	95.4	96.9	98.4
Viability index (%)[e,e]	98.0	97.0	98.1	97.1
Lactation index (%)[f,e]	99.0	100.0	100.0	99.0
Mean pup body weight/litter (g)				
Day 0	6.2	6.4	6.2	5.9**
Day 4 (precull)	9.2	9.5	8.9	8.5**
Day 14	28.8	28.3	28.6	27.4*
Day 21 male	47.8	47.3	46.4	42.8**
female	46.1	45.1	44.8	42.3**
Sex ratio (% male, day 0)[e]	50.6	56.3	51.3	44.7

[a]Data were extracted from study No. 450-2208, Tables 11-14 and Appendix C.

[b]Female fertility index was calculated as: $\frac{\text{No. of pregnancies}}{\text{No. of females mated}} \times 100.$

[c]Gestation index was calculated as: $\frac{\text{No. of parturitions}}{\text{No. of pregnancies}} \times 100.$

[d]Live birth index was calculated as: $\frac{\text{No. of live pups born}}{\text{No. of live and dead pups born}} \times 100.$

[e]Viability index was calculated as: $\frac{\text{No. of pups alive on Day 4 precull}}{\text{No. of pups alive on day 0}} \times 100.$

[f]Lactation index was calculated as: $\frac{\text{No. of pups alive on Day 21}}{\text{No. of pups alive on Day 4 postcull}} \times 100.$

[e]Calculated by the reviewers.

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

**Significantly different from controls ($p < 0.01$).

TABLE 9. Summary of Effects of Dietary Administration of Prometon Technical on F_2 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Concentration (ppm) 0	20	500	1500
No. matings	30	30	30	30
No. pregnancies	23	26	25	26
Fertility index-female (%)[b]	76.7	86.7	83.3	86.7
Gestation index (%)[c]	100.0	100.0	100.0	100.0
Gestation length (days)	22	22	22	22
Total No. live pups				
Day 0	280	342	343	339
Day 4 (precull)	274	332	335	316
Day 21	177	196	187	200
Mean No. live pups/litter				
Day 0	12.2	13.2	13.7	13.0
Day 4 (precull)	11.9	12.8	13.4	12.2
Day 21	7.7	7.5	7.5	7.7
Live birth index (%)[d,§]	93.6	96.3	93.2	97.4
Viability index (%)[e,§]	98.0	94.2	93.8	92.7
Lactation index (%)[f,§]	100.0	98.0	100.0	99.0
Mean pup body weight/litter (g)				
Day 0	6.0	6.0	5.8**	5.6**
Day 4 (precull)	9.1	8.9	8.4**	8.1**
Day 14	28.2	28.8	27.1*	26.3**
Day 21, male	47.8	48.4	44.5**	41.7**
female	45.7	46.7	42.3**	39.4**
Sex ratio (% male, day 0)[§]	52.7	49.6	41.5	47.3

[a]Data were extracted from study No. 450-2208, Tables 11-14 and Appendix F.

[b]Female fertility index was calculated as: $\frac{\text{No. of pregnancies}}{\text{No. of females mated}} \times 100.$

[c]Gestation index was calculated as: $\frac{\text{No. of parturitions}}{\text{No. of pregnancies}} \times 100.$

[d]Live birth index was calculated as: $\frac{\text{No. of live pups born}}{\text{No. of live and dead pups born}} \times 100.$

[e]Viability index was calculated as: $\frac{\text{No. of pups alive on Day 4 precull}}{\text{No. of pups alive on Day 0}} \times 100.$

[f]Lactation index was calculated as: $\frac{\text{No. of pups alive on Day 21}}{\text{No. of pups alive on Day 4 postcull}} \times 100.$

[§]Calculated by the reviewers.

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

**Significantly different from controls ($p < 0.01$).

Based on decreased body weight in F_0 males, the parental toxicity NOEL and LOEL were 20 and 500 ppm, respectively.

3. Reproductive Toxicity: Reproductive toxicity was observed at 1500 and 500 ppm. During the entire lactation period, pup body weight was significantly decreased at 1500 ppm in the F_{1A} pups and at 1500 and 500 ppm in the F_{2A} pups.

The fertility indices for F_0 females at 20 ppm and F_1 females at 0 ppm were slightly lower than those observed in other dosage groups. Since they were not significantly different from other groups, did not occur in a dosage-related manner, and were not reproducible across generations, the reduced indices were considered to be normal biological variations.

The slight variations in sex ratio (% male on day 0; 41.5 to 56.3) were not considered to be compound-related effects because they were not dosage-dependent and they were not reproducible across generations.

Based on decreased body weight in F_{2A} offspring, the NOEL and LOEL for reproductive toxicity were 20 and 500 ppm, respectively.

4. Reporting Deficiencies:

Although a protocol was not submitted, the procedures, as reported, were adequate.

E. CLASSIFICATION: CORE Guideline Data.

Parental Toxicity NOEL = 20 ppm (1.5 mg/kg/day).

Parental Toxicity LOEL = 500 ppm (37 mg/kg/day).

Reproductive Toxicity NOEL = 20 ppm (1.5 mg/kg/day).

Reproductive Toxicity LOEL = 500 ppm (37 mg/kg/day).

F. RISK ASSESSMENT: Not Applicable.

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