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FINAL

DATA EVALUATION REPORT

Prometryn Technical

Study Title:
28-Day Pilot Feeding Study in Mice

Prepared for:

Office of Pesticide Programs
U.S. Environmental Protection Agency
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Arlington, VA 22202

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DATA EVALUATION REPORT

STUDY TYPE: 28-Day range-finding study in mice

TEST MATERIAL: Prometryn technical

SYNONYM: Prometryne

MRID Number: 404575-15

PC Number: 080805

Tox Chemical Number: 097

STUDY NUMBER: 483-127

SPONSOR: Agricultural Division
Ciba-Geigy Corporation
P.O. Box 18300
Greensboro, NC 27419

TESTING FACILITY: Hazleton Laboratories America, Inc.
9200 Leesburg Turnpike
Vienna, VA 2180

TITLE OF REPORT: 28-Day Pilot feeding study in mice: Prometryn technical: Final report

AUTHORS: Vincent J. Piccirillo

STUDY COMPLETED: March 22, 1977

CONCLUSIONS: Prometryn was fed to groups of 5 male and female Charles River cesarian-derived mice at dietary levels of 0, 30, 100, 300, 600, 1000, 3000, 10,000 or 30,000 ppm for 28 days. All of the high-dose animals died by the end of week 2. Macroscopic and microscopic pathological findings in the high-dose animals were limited to the gastrointestinal tract. Clinical signs (i.e., hunched appearance, labored respiration, and thinness) and marked decreases in body weights were seen in these animals. Gross findings in the small intestine were observed in some of the mice fed 10,000 ppm; however, the gross findings were not accompanied by histological effects. Clinical signs and moderate to marked decreases in body weights were also noted in these animals. There were no effects of toxicological importance in animals receiving <10,000 ppm.

The LOEL is 10,000 ppm based on body weight decrement. The NOEL is 3000 ppm.

CORE CLASSIFICATION: Not applicable.

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Pronetryn technical

Lot number: ARS No. 10/77

Batch number: FL-761355

Purity: No reported

Physical properties: White powder containing small lumps

Stability: Not reported

Storage: Not reported

2. Test Article Analyses for Purity and Stability

Test diets were prepared weekly at target concentrations of 30, 100, 300, 600, 1,000, 3,000, 10,000, and 30,000 ppm by mixing appropriate amounts of the test material with basal diet (Purina Laboratory Chow) in a Patterson-Kelley twin-shell blender.

The test material was assumed to be 100% pure for the purposes of dosage calculations. However, the actual purity of the test material was not determined. In addition, the dietary concentration analyses, and homogeneity and stability of the test material in the diets were not determined.

3. Animals

Young albino mice (45/sex) of the Charles River cesarian-derived strain were used in this study. The address of the animal supplier was not stated. At initiation of treatment, the animals were approximately 5 weeks of age and weighed 24-29 g (males) and 21-24 g (females). They were separated by group and sex and housed 5 mice/box; there was no indication if the animals were acclimated to laboratory conditions prior to treatment. Food (Purina® Laboratory Chow) and water were available ad libitum throughout the 28-day study period. No details were provided regarding temperature and humidity conditions.

The mice were assigned to the following test and control groups based upon initial body weights to insure that there was a homogenous distribution of body weights within each sex:

Dietary Levels (ppm)	Number of Animals	
	Males	Females
0 (control)	5	5
30	5	5
100	5	5
300	5	5
600	5	5
1,000	5	5
3,000	5	5
10,000	5	5
30,000	5	5

4. Statistical Methods

Statistical analyses were not performed.

5. General Observations

(a) Mortality/moribundity/survival

Animals were observed daily for mortality.

Two high-dose males and 2 high-dose females died during week 1, as did 1 female receiving 100 ppm. The remaining 3 high-dose males and 3 high-dose females died during week 2. No deaths occurred at any dietary level during the remaining 2 weeks of treatment. The single death at 100 ppm was not considered to be treatment related. The exact time of the deaths for the individual animals affected was not tabulated in the study report.

(b) Clinical observations

Clinical observations were only recorded weekly.

Treatment-related adverse clinical signs observed in the 6 surviving high-dose animals at the end of week 1 included a hunched appearance, thinness, labored respiration, and urine stains on the fur. A hunched appearance was also observed in 4 animals receiving 10,000 ppm at the end of week 1, but was not observed during the three remaining observation periods No-

other adverse clinical signs were noted at any dietary level. Since observations were not recorded daily, it is impossible to judge the precise time of onset, duration and severity of the observed toxic signs.

(c) Body weights/ food consumption/test article intake

Body weights--Individual body weights were measured prior to the assignment of the animals to the 9 study groups (week 0) and at the end of each of the 4 weeks of treatment.

Table 1 summarizes data on mean body weights in male and female mice. Mean body weights in the 3 surviving high-dose males and 3 surviving high-dose females were markedly lower (42% in males; 37% in females) than those of controls at the end of week 1; mean body weight in the 2 high-dose females which died during week 1 were also markedly lower (37% in males; 62% in females). The decrease in body weight was especially severe in the one high-dose female (50% lower body weight than the other 5 females) that died during week 1. Mean body weights in the high-dose males and females remained lower than controls during week 2. Loss of mean body weight gain in the high-dose males and females was 9.73 g and 8.33 g, respectively, at week 2. Mean body weights in mice receiving 10,000 ppm were also markedly lower (33% in males; 24% in females) than those of controls during week 1. Mean body weights in the males and females receiving 10,000 ppm remained lower (0.3-28% in males; 7.3-24% in females) than those of controls at weeks 2, 3, and 4. Overall mean body weight gain at (week 4) in males receiving 0 or 10,000 ppm were 7.8 g and 0.22 g, respectively. Overall mean body weight gain in females receiving 0 or 10,000 ppm were 1.9 g and 0.36 g, respectively. Individual body weights were decreased in all males receiving 100 ppm dietary level during the first week, but increased drastically during the following week and were nearly equal to control values by the end of the study. A similar decrease in body weight during the first week was noted by the authors in females; however, this decrease is eliminated if the postmortem weight of the 1 female which died during week 1 is excluded from the calculation of mean body weights. The decrease in mean body weight of males receiving 100 ppm dietary level is not considered by the reviewers to be treatment related since similar decreases were not observed at the intermediate dietary levels (300-3000 ppm).

Food consumption--Mean food consumption (g/animal/week) was estimated weekly on the basis of total food consumption divided by the number of animals present in the cage.

Mean food consumption in males receiving 100-ppm, and in males and females receiving 10,000-ppm were slightly lower (23% in 100 ppm males; 12% in 10,000-ppm males; 19% in 10,000-ppm females) than those of controls during week 1, but were approximately equivalent to those of controls for the remainder of the treatment period. Mean food consumptions in the high-dose males

TABLE 1. Mean Body Weights (g ± SD) at Weekly Intervals for Mice Given Diets Containing Prometryn Technical for 4 Weeks[a]

Dose Level (ppm)	Week 0	1	2	3	4
			Males		
0	25.60±1.67	29.48±1.59	32.36±1.50	31.12±1.57	32.78±1.63
30	25.60±1.82	30.76±3.58	32.96±1.95	29.38±1.66	33.00±2.50
100	25.60±1.82	21.32±2.27	29.22±1.81	31.10±2.00	30.50±2.66
300	25.60±2.07	30.04±4.96	30.96±4.92	31.28±4.34	32.16±4.45
600	25.60±1.52	25.24±3.33	29.10±2.12	31.48±1.92	32.64±1.98
1000	25.60±1.52	29.26±3.96	31.50±1.05	31.36±1.11	33.16±1.28
3000	25.60±1.52	25.04±1.33	29.00±1.88	30.92±3.11	32.68±2.41
10000	25.60±1.52	19.82±2.23	23.16±1.52	23.76±1.66	25.82±2.72
30000	25.60±1.52	17.06±2.49 [b]	15.87±1.86 [c]	-----	-----
			Females		
0	22.00±1.22	23.98±2.42	25.32±1.16	23.34±1.85	23.90±1.60
30	22.00±1.22	22.56±2.76	23.02±1.78	23.62±1.02	23.70±1.79
100	22.00±1.22	20.84±5.73 [d]	24.35±2.22 [e]	26.23±2.26 [e]	25.15±1.93 [e]
300	22.00±1.22	23.98±1.82	24.50±1.20	25.40±1.95	25.34±1.33
600	22.00±0.71	24.18±2.19	25.26±0.80	25.40±0.71	26.92±2.08
1000	22.00±0.71	21.98±1.32	24.44±1.80	25.82±1.69	26.32±2.04
3000	21.80±0.45	21.78±1.34	24.80±1.34	26.06±1.23	27.28±1.09
10000	21.80±0.45	18.22±1.47	19.28±2.01	20.74±1.96	22.16±1.
30000	21.80±0.45	12.68±4.17 [b]	13.47±0.81 [c]	-----	-----

[a]Data extracted from Study no. 483-127, Table 1 and Appendix 1.
[b]Includes postmortem weights for 2 animals.
[c]Calculated from postmortem weights.
[d]Includes postmortem weight for 1 animal.
[e]Based upon four surviving animals.

TABLE 2. Mean Food Consumption (g/wk) at Weekly Intervals for Mice Given Diets Containing Prometryn Technical for 4 Weeks[a]

Dose Level (ppm)	Week							
	Males				Females			
	1	2	3	4	1	2	3	4
0	31.4	33.0	36.8	41.7	31.9	31.9	34.6	36.9
30	37.2	33.5	34.7	37.4	26.7	29.4	28.6	29.7
100	24.1	42.8	42.3	38.8	29.	30.0[b]	41.2[b]	41.6[b]
300	34.7	41.5	35.0	34.9	32.0	32.3	29.1	35.8
600	32.5	38.1	36.9	37.3	30.3	32.8	30.3	36.3
1000	33.2	35.7	34.2	36.3	30.1	35.9	33.6	35.4
3000	32.4	38.3	34.5	35.2	29.7	33.8	37.0	41.4
10000	27.7	42.2	33.3	42.2	25.8	42.0	38.7	36.1
30000	26.3[c]	----	----	----	26.3[c]	----	----	----

[a]Data extracted from Study no. 483-127, Table 1.
[b]Based on four surviving animals.
[c]Based on three surviving animals.

and females were slightly lower (16% in males; 18% in females) during week 1.

Compound consumption--Compound intakes (mg/kg/day) were not calculated.

(d) Ophthalmoscopic examination

Ophthalmoscopic examinations were not performed..

6. Clinical Pathology

Hematology, clinical chemistry, and urinalysis parameters were not measured.

7. Sacrifice and Pathology

Gross necropsies were performed on those animals which died during the study, as well as on all animals which survived to termination. Surviving animals were sacrificed on day 28 by exsanguination following sodium pentobarbitol anesthesia. For the animals that died during the study, histologic examinations were performed on those tissues in which gross findings were present. The tissues marked with an "X" were examined histologically following hematoxylin and eosin staining. No organs were weighed.

Digestive System	Cardiovascular/Hematologic	Neurologic
Salivary glands	Aorta	Brain
Esophagus	Heart	Sciatic nerve
X Stomach	Bone marrow	Pituitary
X Duodenum	Lymph nodes	
X Jejunum	Spleen	
X Ileum		
X Cecum		
X Colon	Urogenital	Glandular
Rectum	X Kidneys	Adrenals
X Liver	X Urinary bladder	Thyroids
Gallbladder	Testes	
Pancreas	Epididymides	
	Ovaries	
	Uterus	

Respiratory
Trachea
X Lung

Other
Bone (sternum and femur)
X All gross lesions and masses

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(a) Macroscopic

The only treatment-related gross pathological findings which were noted in animals surviving to termination were dark-pink colored small intestines in 2 males and 1 female at the 10,000 ppm dose level. Treatment-related necropsy findings in the 30,000 ppm animals which died during the study included reddening of the gastrointestinal tract mucosa in 4 males and 2 females, and dark-colored contents of the gastrointestinal tract in 4 males and 2 females. Incidental findings included dark red areas on the lungs of 1 male and 2 females, a dark red area on the liver of one female, dark red fluid in the urinary bladder of 1 female, and autolysis in 3 males and 4 females. Necropsy findings in the 1 female receiving 100 ppm and that died during the study included an atrophied right kidney and thickened urinary bladder walls.

(b) Microscopic

Histopathological findings in the high-dose animals included focal erosion and hemorrhaging of the stomach in 1 female, focal erosion of the stomach in 1 male, brown granular material in the small intestines in 1 male and 1 female and in the large intestine in 1 male. Incidental findings included lung congestion in 1 male and 2 females, and liver congestion in 1 female. Findings in the 100 ppm female that died during the study included hydronephrosis, pyelonephritis, and papillitis in the kidney, and chronic proliferative cystitis in the urinary bladder; these findings were considered by the study author to be incidental.

B. REVIEWER'S DISCUSSION

Although the overall design of this study was reasonable for a 4-week repeated oral dosing range-finding study in mice, several study deficiencies were noted. These include the following:

1. Purity, stability, homogeneity, and concentration analyses of the test material in the diets were not performed.

2. Individual data on mortality and clinical signs were not provided.

3. Hematology and clinical chemistry evaluations were not performed.

4. Weights of major organs were not determined.

5. Histological findings in 1 high-dose female (No. 30876) were not tabulated in the individual histopathology table presented in the addendum to the study report.

6. Individual food consumption was not determined.

No major target organs were affected following oral administration of the test material. Treatment-related gross findings in the high-dose animals that died

during the first 2 weeks of the study were limited to the gastrointestinal tract. Histological effects in the gastrointestinal tract were also noted in some of these high-dose animals. Clinical signs (i.e., hunched appearance, thinness, and labored breathing) and marked decreases in body weights were seen in these animals.

Although possible treatment-related gross findings in the small intestines of several mice (2 male and 1 female) receiving 10,000 ppm were observed, no corresponding histological effects were noted. Clinical signs and decreases in body weights were also observed in these animals.

There were no effects of toxicological importance reported in mice receiving dose levels <10,000 ppm.

Based on body weight decrement, the LOEL is 10,000 ppm. The NOEL is 3000 ppm. This study provides information for setting dietary levels to be used in a subchronic mouse study.