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FINAL

DATA EVALUATION REPORT

Prometryn

Study Type:
Combined Chronic Toxicity/Oncogenicity in Rats

Study Title:
104-Week Oral Toxicity/Carcinogenicity Study in Rats

Prepared for:

Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

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March 10, 1992

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41901201

Contract Number: 68D10075
Clement Number: 91-236
Work Assignment Number: 1-72
Project Officer: Mr. Jim Scott

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Guideline 83-5: Combined Chronic Toxicity/Oncogenicity

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DATA EVALUATION REPORT

STUDY TYPE: Combined chronic toxicity/oncogenicity in rats

TEST MATERIAL: Prometryn

SYNONYM: Prometryne

PC. No: 080805

MRID Number: 419012-01

Tox Chemical No: 097

STUDY NUMBER: MIN 872225

SPONSOR: CIBA-GEIGY Corporation
Agricultural Division
P.O. Box 18300
Greensboro, NC 27419

TESTING FACILITY: Division of Toxicology/Pathology
CIBA-GEIGY Corporation
556 Morris Avenue
Summit, NJ 07901

TITLE OF REPORT: 104-Week Chronic Toxicity/Carcinogenicity Study in Rats.

AUTHORS: R.Y. Chau, G.C. McCormick, and A.T. Arthur

REPORT ISSUED: March 4, 1991

CONCLUSIONS: Prometryn was fed to male and female Sprague-Dawley rats at dietary levels of 0, 10, 100, 750, or 1500 ppm (males: 0.38, 3.90, 29.45, and 60.88 mg/kg/day, respectively; females: 0.49, 4.91, 37.25, and 80.62 mg/kg/day, respectively). The following effects were noted.

LOEL = 1500 ppm based on body weight gains in males and females, and renal lesions (mineralized concretions) in the males.

NOEL = 750 ppm.

Prometryn was not oncogenic under the conditions of this study.

CORE CLASSIFICATION: Core Guideline. This study satisfies the Guideline requirements for a chronic toxicity/oncogenicity study (#83-5) in rats and is acceptable for regulatory purposes. 1, 2

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Prometryn

Composition: 2,4-Bis(isopropylamino)-6-(methylthio)-s-triazine

Batch number: FL 870991

Purity: 98.1% (reported by the sponsor)

Physical Property: White, crystalline

Stability: Stable at room temperature for duration of study (as reported by the sponsor)

2. Test Substance Analyses for Purity and Stability

Test diets were prepared at constant target concentrations of 10, 100, 750, and 1500 ppm (not adjusted for compound purity). Test diet premixes were prepared with a mortar and pestle by mixing appropriate amounts of the test article with a portion of rodent chow. Final test diets were then obtained by further mixing the premixes with basal diet in a twin-shell blender to produce a specific batch size (batch size not reported). Ground Certified Purina Rodent Chow #5002 was used as the control diet and as the basal diet in the preparation of test diets. The frequency of test diet preparation was not stated, but was reportedly based on the established stability data. Also, the study report indicated that rodent chow was used prior to its expiration date. All diets were stored at room temperature.

The homogeneity of the test substance (samples derived from the top, middle, and bottom of the batches) in the diet at concentrations of 10, 100, 750, and 1500 ppm was determined at weeks 1 and 89. In addition, homogeneity of the 1500 ppm diet was determined at week 56. The results indicated a homogeneous mix. Stability was determined for dietary mixtures (stored at room temperature) with concentrations ranging from 10 to 50,000 ppm, for up to 51 days (50,000 ppm), 63 days (50 ppm) or 62 days (10 ppm); results indicated that the test substance was stable at these time periods. The concentrations of test substance in the diet (10, 100, 750 and 1500 ppm) were determined at weeks 1, 3, 6, 7, 13, 14, 28, 29, 32, 40, 45, 47, 49, 52, 53, 54, 56, 58, 63, and 68. The concentrations of the test substance in the diets were 91 to 112% of target levels.

3. Animals

Sprague-Dawley rats [CRL:VAF/Plus CD (SD) Br], 504 male and 487 female, were received from Charles River Laboratories, Kingston, New York, and acclimated to laboratory conditions for approximately 4 weeks prior to the initiation of dosing. Upon arrival, animals were housed by sex 2-4/cage and identified by tail markings. They were subsequently housed individually and identified by metal ear tags. Necropsies were performed on 10 randomly selected rats per sex to determine the overall suitability of the animals for the study. Of the remainder, 400/sex were selected for the study based upon the results of general observations, body weights, and physical, auditory, and ophthalmoscopic examinations. These 800 animals were then randomly assigned to the 5 treatment groups (80/sex/group). The date of group assignment is not given in the report, but was apparently at least 2 weeks prior to the initiation of dosing based upon the presentation of body weight data. The rats were approximately 7 weeks of age at the initiation of dosing, and body weights ranges were 177.3-301.1 g (males) and 135.2-226.8 g (females).

Animal room conditions included a temperature of 73±5°F, a relative humidity of 50±20%, and a 12-hour light/dark cycle. Food (Certified Purina® Rodent Chow #5002) and water (tap water) were provided ad libitum throughout the acclimation and study periods and were monitored for contaminants. Caging and sanitary conditions were reportedly maintained in accordance with the SOPs of the testing facility, but no further details were provided regarding animal housing.

The rats (80/sex/group) were randomly assigned to the following test and control groups:

Dietary Levels (ppm)	Phase	Number of Animals Males	Number of Animals Females	Number of Dose Weeks
0		80	80	
	Interim Sacrifice	10	10	52
	Chronic	20	20	104
	Carcinogenicity	50	50	104
10		80	80	
	Interim Sacrifice	10	10	52
	Chronic	20	20	104
	Carcinogenicity	50	50	104
100		80	80	
	Interim Sacrifice	10	10	52
	Chronic	20	20	104
	Carcinogenicity	50	50	104
750		80	80	
	Interim Sacrifice	10	10	52

	Chronic	20	20	104
	Carcinogenicity	50	50	104
1500		80	80	
	Interim Sacrifice	10	10	52
	Chronic	20	20	104
	Carcinogenicity	50	50	104

Dose levels were selected on the basis of a previous 90-day feeding study in rats (Chau et al., 1989. Prometryn: Pilot 13-Week Oral Feeding Study in Rats, Toxicology/Pathology report #88118); and two chronic feeding/oncogenicity studies in rats using compounds with similar chemistry (Gunderson et al., 1980. Terbutryn Technical: 2-Year Chronic Oral Toxicity Study in Rats, report number 382-008; Hazelette and Green, 1987. Ametryn: 104-Week Oral Toxicity/Oncogenicity Study in Rats, Toxicology/Pathology report number 87043). None of these studies was available for review. The primary effect noted in each of these studies was decreased body weight or body weight gain. Mean body weight gains were reduced in males (35%) and females (30%) receiving 5000 ppm prometryn for 90 days; mean body weights were also reduced in males (14%) and females (3%) at 1000 ppm. There were no treatment-related effects on clinical chemistry or gross observations. Decreases in mean body weights in males (22%) and females (30%) receiving 3000 ppm were noted in terbutryn chronic study. Mean body weights were decreased in males (18%) and females (28%) receiving 2000 ppm-ametryn. On the basis of these results, the concentration of 1500 ppm Prometryn was anticipated to produce reductions in body weights with no significant effect on survival in the 104-week study. Concentrations of 100 and 750 ppm were expected to produce minimal toxic effects. The concentration of 10 ppm was anticipated to be a no-effect level.

4. Statistical Analyses

Except for microscopic pathology data, all data were analyzed by the following methods: Bartlett's test for homogeneity of variance; analysis of variance (ANOVA) for overall equality of the predose group means; Dunnett's test for comparison of the treatment group means against the control means; and Dunnett's Multiple Comparison (T3 procedure) for unequal variances. Mortality data were analyzed by: Kaplan-Meier estimates for survival distributions for each group and sex; and the Mantel-Cox log-rank test for equality and linear trend. Microscopic pathology data were analyzed by: Peto's time-adjusted trend test; Mantel's trend test (exact or asymptomatic versions); and Fischer's exact test.

5. General Observations

(a) Mortality/moribundity/survival

Animals were observed for mortality/moribundity twice a day except on weekends and holidays when observations were made once a day.

Treatment had no effect on mortality. Percent survivals at study termination ranged from a low of 30% in the high mid-dose males to a high of 56% in the low-dose females. Survival in controls averaged 33% in males and 41% in females.

(b) Clinical signs

Observations were made for adverse clinical effects once daily prior to the initiation of dosing and throughout the study.

No treatment-related clinical effects were observed.

(c) Body weights/food and water consumption/test material intake

Body weights--Body weights were recorded on days -15 and -8, prior to dosing on day 1 of the study, weekly during weeks 1 to 12, biweekly (every 2 weeks) during weeks 14 to 25, and monthly (every 4 weeks) thereafter.

Summary body weight and body weight gain data are presented in Tables 1 and 2. Although mean absolute body weight of all dose groups was approximately equal at week -2 (the probable date of group assignment), a decrease was apparent in the high-dose males at the initiation of dosing (week 0). Significant ($p \leq 0.05$) decreases were noted in both males and females by the end of week 1. Despite the use of analysis of covariance using the initial body weights as the covariant, mean absolute body weight of the high-dose males and females remained significantly lower ($p \leq 0.05$) than control values through week 84 (16 months) and the end of the study, respectively. Mean cumulative body weight gain in the high-dose males and females was about 9% and 18% lower than that of control animals at approximately week 12. The decrease in cumulative body weight gains in the high-dose male and females were considered treatment related by the study authors. Mean cumulative body weight gain the in the high-dose males and females were approximately 11% and 19% lower than those of controls at week 52.

Food consumption--Food consumption was measured weekly from week -1 to week 13, biweekly (every 2 weeks) during weeks 14 to 25, and monthly (every 4 weeks) thereafter.

Table 3 summarizes selected data on food consumption. Significant ($p \leq 0.05$) decreases in food consumption were noted in the high-dose males (weeks 1 and 2) and in the high-dose females (weeks 1-9), and in the high mid-dose males (week 1) and in the high mid-dose females (weeks 1, and 3-4). The study authors attributed the decreases in food consumption to the decreased palatability of the diet at these concentration levels. The

TABLE 1. Mean Body Weights (g ± SD) at Selected Intervals for Rats Fed Prometryn for Two Years[a,b] *

Dietary Level (ppm)	Weeks						
	-2	0	6	12	28	56	104
				Males			
0	145.9±1.2	261.8±2.1	464.8±4.2	560.8±5.3	695.4±9.0	826.3±14.8	745.7±31.4
10	144.2±1.3	257.5±2.2	467.6±4.6	559.9±6.3	708.1±9.8	833.1±14.2	839.4±26.8
100	146.3±1.4	258.8±2.0	464.1±3.7	557.8±5.1	702.9±8.5	838.2±13.7	781.0±30.8
750	148.1±1.3	250.3±2.5	459.9±3.7	551.2±4.8	693.0±7.8	819.9±12.3	747.7±32.4
1500	145.4±1.4	244.5±3.0	433.0±3.4**	517.8±4.4**	636.8±7.3*	751.6±10.7*	762.9±25.3
				Females			
0	126.7±1.2	185.2±1.7	277.7±3.1	315.8±3.8	382.6±6.3	475.4±9.4	530.7±24.6
10	126.1±1.1	181.1±1.7	274.5±2.9	311.5±3.5	375.3±5.7	475.4±8.5	541.4±22.9
100	128.4±1.1	183.3±1.4	274.2±2.2	310.5±2.9	378.2±5.1	474.4±9.6	519.9±26.6
750	126.6±1.1	173.8±2.0	271.3±2.6*	307.7±3.3	372.9±5.7	458.5±7.5	527.0±19.6
1500	128.3±1.2	179.3±1.7	254.0±2.5**	286.8±3.0**	345.6±5.7**	412.9±8.1**	444.7±23.2*

[a]Data extracted from Study Report, Table 8.6.
[b]Data exclude those animals which died during the study, those sacrificed moribund, and those sacrificed at interim.

* Significantly different from control values, $p \leq 0.05$.
** Significantly different from control values, $p \leq 0.01$.

TABLE 2. Mean Body Weight Gain (g) at Selected Intervals for Rats Fed Diets Containing Prometryn for Two Years[a]

Dietary Level (ppm)	Weeks						
	1	6	12	28	56	84	104
				Males			
0	52.2	203.0	298.9	433.5	564.5	600.2	484.0
10	52.3	210.1	302.4	450.6	575.7	643.5	581.9
100	52.0	205.3	299.0	444.1	579.4	608.2	522.2
750	50.3	209.6	300.9	442.7	569.6	580.5	497.4
1500	42.7	188.5	273.3	392.3	507.1	534.4	518.4
				Females			
0	24.9	92.5	130.7	197.5	290.3	359.6	345.5
10	23.6	93.4	130.4	194.1	294.2	377.5	360.3
100	23.6	90.9	127.2	194.9	291.0	337.5	336.5
750	27.1	97.5	133.9	199.2	284.8	363.7	353.3
1500	16.5	74.7	107.5	166.3	233.7	267.7	265.4

[a]Body weight gains calculated by the reviewers.

TABLE 3. Mean Food Consumption (g) at Selected Intervals for Rats Fed Diets Containing Prometryn for Two Years[a]

Dietary Level (ppm)	Weeks						
	0	1	6	12	28	56	104
				Males			
0	184.6	188.1	194.5	183.1	178	198.0	168.9
10	185.1	181.1**	195.3	187.2	185.0	188.7*	178.0
100	186.8	186.4	203.8**	188.5	183.1	196.5	179.6
750	178.7	175.5**	199.5**	189.9**	181.7	188.2	162.3
1500	179.3	161.1**	189.0	178.5	177.6	178.2**	171.0
				Females			
0	143.4	136.2	150.2	139.0	129.5	141.2	128.2
10	142.7	135.4	154.4	139.5	129.2	136.7	136.7
100	144.0	137.8	150.0	137.9	131.1	138.5	129.2
750	140.2	125.9*	147.6	140.3	130.4	137.2	139.9
1500	140.0	115.7*	137.7**	134.2	129.2	135.4	134.8

[a]Data extracted from Table 8.6 of the Study Report.
[b]Data exclude those animals which died during the study, those sacrificed moribund, and those sacrificed at interim.

*Significantly different from control values, $p \leq 0.05$.
**Significantly different from control values, $p \leq 0.01$.

decreases in food consumption in these animals were considered to be treatment related by the study authors. Significant decreases were also noted at the high-dose level during weeks 11, 14-16, 36-40, and 56 (males) and week 40 (females). However, these latter decreases were considered to be incidental by the study authors due to a lack of a dose-response relationship and the large number of similar sporadic significant changes in food consumption which were observed in males at all dose levels and in females at doses ≥ 750 ppm.

Water consumption--Water consumption measurements were made during the same intervals that urine volume was measured, including weeks 11, 24, 50-51, 76, and 101.

Statistically significant decreases in water consumption were observed in the high-dose males at week 101 and in low mid-dose females at week 52; the decreases were considered to be incidental by the study authors.

Test article intake--Actual achieved dosages (mg/kg/day) were calculated for the same periods as food consumption measurements using the following equation: Dose = Feed Consumption (g/day) x Target Compound Concentration (mg/kg of feed)/Average Group Mid-Period Body Weight (g). In calculating the group means for the duration of the study from the weekly mean daily doses, the authors used the mean daily doses from 2- and 4-week periods 2 and 4 times, respectively.

Mean daily doses for the duration of the study for the low-, low mid-, high mid-, and high-dose males were 0.38, 3.90, 29.45, and 60.88 mg/kg/day, respectively; and mean daily doses for the duration of the study for females receiving the same doses were 0.49, 4.91, 37.25, and 80.62 mg/kg/day, respectively.

(d) Ophthalmoscopic examination

Ophthalmoscopic examinations were conducted on all animals during weeks -2 to -1, and during weeks 26, 52, and 103.

No treatment-related ocular changes were observed.

6. Clinical Pathology

Blood smears were prepared from samples taken from all animals during weeks 52-55, 79-81, and at terminal necropsy, as well as from any animals which were sacrificed moribund. Differential counts and red blood cell morphology were evaluated for control, high-dose, and moribund animals. In addition, during the baseline period prior to initiation of dosing (week -1), complete hematology and biochemistry evaluations were conducted on 10 animals/sex/chronic subgroup, with the exception of reticulocyte counts and Heinz Body determinations which were performed on only 5 of these 10 animals in the control and high-dose groups. Analyses were made using the same 10

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animals/sex/chronic sub-group during the dosing period (weeks 13, 27, 52, 79, and 104). During the study all blood samples were drawn from the right orbital sinus of ether-anesthetized animals. Samples were drawn from the abdominal aorta of animals sacrificed moribund and at terminal necropsy. Those hematology and clinical chemistry parameters indicated by an "X" were examined:

(a) Hematology

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

* = Recommended by Subdivision F (November 1984) Guidelines

Statistically significant decreases in hemoglobin and hematocrit levels in the high-dose females at weeks 52 and 79, and a non-significant decreasing trend in these parameters was noted at week 104 in this same group. The study authors attributed these decreases to the treatment-related decreases in the mean body weights. Significant but incidental changes observed in males included decreases in percent monocytes at week 27 (10 and 750 ppm), and increased prothrombin time at week 13 (10 ppm). Significant but incidental changes observed in females included decreases in reticulocytes at week 13 (high-dose), increased percent eosinophils at week 13 (high mid-dose), decreased percent lymphocytes at week 79 (low mid-dose), decreased prothrombin time at week 52 (low mid-dose), increased platelet count at week 79 (low mid-dose), and increased RBC and hemoglobin at week 27 (low-dose). Red blood cell morphological changes characteristic of older animals were observed in animals from all groups.

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(b) Blood (clinical) chemistry

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

* = Recommended by Subdivision F (November 1984) Guidelines

No treatment-related changes in clinical chemistry parameters were observed. Significant but incidental changes in males included decreased sodium at week 27 (all doses), decreased creatinine at week 27 and calcium at week 52 (high-dose), increased GGT at week 104 and decreased sodium at week 13 (high mid-dose), increased lactic acid dehydrogenase at week 104 (low-dose),and decreased calcium at week 104 (low-dose), and decreased phosphorus at week 13 (low-dose). Significant but incidental changes in females included decreased triglycerides and total bilirubin at week 13 and decreased potassium at weeks 13 and 27 (high-dose).

(c) Urinalysis

Urine volume and water consumption were determined over a 24-hour period for 10 animals/sex/chronic subgroup during weeks 11, 24, 50-51, 76, and 101. Animals were housed in metabolism cages during these periods, and consumption was determined using water bottles to which these animals were acclimated for at least 5 days prior to collection. Other urinalysis parameters were measured from samples collected from the same 10 animals/sex/chronic subgroup during weeks -1, 12-13, 27-28, 52, 78, and 104. Those parameters indicated by an "X" were examined:

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

* = Recommended by Subdivision F (November 1984) Guidelines

There were no treatment-related changes observed in any urinalysis parameters. Significant, but incidental, changes included increased specific gravity in the high mid-dose males at week 12 and females at week 27, and in the low mid-dose females at week 52; and decreased urine volume in the low mid-dose and high mid-dose females at during week 12. Although the study report indicated that predose urinalyses were performed during week -1, data for this predose period were not presented.

7. Sacrifice and Pathology

All animals that died during the study or were sacrificed moribund after 52 weeks, or at study termination (104 weeks), were exsanguinated and necropsied. All scheduled sacrifices were preceded by a 12-hour fast. Gross examination included verification of any palpable masses which were detected during the dosing period. Samples of those tissues and organs which are indicated by an "X" in the following list were taken from all animals, preserved in 10% neutral buffered formalin, and examined microscopically. In addition, those organs indicated by "XX" were weighed prior to fixation.

Digestive System	Cardiovascular/Hematologic	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 (three levels)
X Stomach*	X Lymph nodes*	X Pituitary*
X Duodenum*	XX Spleen	X Eyes (Optic nerve)*
X Jejunum*	X Thymus	
X Ileum*		Glandular
X Cecum*	Urogenital	
X Colon*		X Adrenals*
X Rectum	XX Kidneys*	X Lacrimal gland
XX Liver*	X Urinary bladder*	X Mammary gland
Gallbladder*	XX Testes*	X Thyroids*
X Pancreas*	XX Epididymides	X Parathyroids*
	XX Prostate	X Harderian glands
Respiratory	X Seminal vesicle	
	XX Ovaries	
X Trachea*	XX Uterus	
XX Lung*		

Other

X Bone (sternum and femur)*
X Skeletal muscle*
X Skin
X All gross lesions and masses

* = Recommended by Subdivision F (November 1984) Guidelines

(a) Macroscopic

No treatment-related gross pathological changes were observed.

(b) Organ weights and body weight ratios

Significant increases in absolute and relative (to body and brain weight) kidney weights were observed in the high-dose females at both the interim and terminal sacrifices. The study authors considered this increase to be treatment related but noted that the increase was minimal and not accompanied by any significant histopathological changes.

Other significant changes were observed in all treatment groups except for the low-dose females, however, these were considered to be incidental due to the lack of a dose- or time-response relationship, isolated occurrence, absence of change in absolute weights (given the decreased body weights at the high-dose), or lack of histopathological correlates. At the high-dose these changes included: increased relative (to body weight) brain, testes, and epididymides weights in males at interim sacrifice, and increased absolute and relative (to body and brain weight) testes and epididymides weights at terminal sacrifice; decreased absolute and relative (to brain weight) spleen weights in males at 12 months; decreases in relative (to brain weight) heart weight in males at 24 months; increased relative (to body weight) heart weight in females at 24 months; and increased relative (to body weight) liver weight in females at 12 and 24 months.

(c) Microscopic

There was no increase in the incidence of benign or malignant neoplasms in treated groups verses controls.

The only non-neoplastic microscopic finding observed which was considered by the study authors to be treatment related was a moderate increase in the incidence of mineralized concretions in the renal pelvis of high-dose males treated with Prometryn for 104 weeks. The incidence of this renal lesion was increased in the early-death (males that died during the study and males sacrificed moribund) high-dose males [(4/48, 0/49, 9/48, 8/50, and 10/41 in control, low-, low mid-, high-mid, or high-dose males, respectively, (p=0.002)], and in the terminal and sacrifice high-dose males [(3/22, 1/21, 2/22, 2/20, and 10/29 in control, low-, low mid-, high mid-, or high-dose males, respectively, (p=0.015)]. The increase in the combined incidence (7/70, 1/70, 11/70, 10/70, and 20/70 in control, low-, low mid-, high mid-, or high-dose males, respectively) of this renal lesion in the high-dose males treated for 104 weeks (early deaths and terminal sacrifice) was also statistically significant and treatment related. Although the incidence of mineralized concretions in the kidneys was increased in the high-dose males sacrificed at the 52 week interim period, the test for trend

indicated that the increase was not statistically significant. Although the renal finding was also observed in terminal sacrifice high-dose females (18 of 22 high-dose females vs. 14 of 28 control females); the study authors considered the finding to be incidental due to the lack of a dose-response relationship and comparable overall occurrences in treated and concurrent control animals.

B. DISCUSSION

The design and conduct of this study are acceptable for a combined chronic toxicity and oncogenicity study in rats. A rationale for dose selection was provided. Historical control data were included in the study report. The reviewers noted the presence of moderate to severe autolysis of the digestive tract in many of the control and treated males and females that died during the study.

Based on decreased body weights and body weight gains in the high-dose males and females, the doses selected were considered adequate for testing carcinogenic potential. The reductions in body weights and body weight gains in the high-dose males and females were seen during the first and second year of the study. Significant ($p \leq 0.05$) decreases in food consumption were noted in the high-dose males (weeks 1 and 2) and in the high-dose females (weeks 1-9); and in the high mid-dose males (week 1) and females (weeks 1, and 3-4). The decreases in food consumption in these animals noted during the early weeks of the study may have been due to unpalatability of the test material in the mid- and high-dose diets.

The results of histologic examinations indicated that the kidney in male rats as a possible target organ. In the high-dose males, renal findings included an increase in the incidence of mineralized concretions in the kidney. This renal finding was observed in males found dead or sacrificed in a moribund conditions during the 104 week treatment period and in males sacrificed at termination (week-104). Although the incidence of mineralized concretions in the kidneys was increased in the high-dose males sacrificed at interim, the test for trend indicated that the increase was not statistically significant. Examination of individual animal data indicated that the severity of the renal lesion was minimal in all animals with the exception of one male that exhibited a moderate severity of this lesion. This male died after approximately 90 weeks of treatment. Chemical composition of the mineralized concretions in the kidney was not reported. The renal lesions did not correlate with changes in absolute or relative kidney weights.

The reviewers agree with the study authors' conclusions that the no-observed-effect-level for chronic effects (decreased body weight gains in males and females, and renal histologic findings in males) was 750 ppm, and that there was no oncogenic effect under the conditions of this study.

RIN # 0615-00

MRID # 41901201 (DERs)

Page_____ is not included in this copy.

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