8-16-93

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FINAL

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DATA EVALUATION REPORT

PICLORAM

Study Type: Reproductive Toxicity

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
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Guideline Series 83-4: Reproductive Toxicity

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DATA EVALUATION REPORT

STUDY TYPE: Reproductive toxicity

EPA IDENTIFICATION NUMBERS

PC Code: 005101

Tox Chem. Number: 039

MRID Number: 420787-01

TEST MATERIAL: 4-amino-3,5,6-trichloropicolinic acid

SYNONYM: Picloram

SPONSOR: DowElanco, The Dow Chemical Company, Midland, MI

STUDY NUMBER: K-038323-057

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

TITLE OF REPORT: Picloram: Two-Generation Dietary Reproduction Study in Sprague-Dawley Rats

AUTHORS: W.J. Breslin, G.J. Zielke, and R.J. Kociba

REPORT ISSUED: October 2, 1991

CONCLUSIONS: In a two-generation reproduction study, male and female Sprague-Dawley rats were fed diets containing picloram at 0, 20, 200, or 1,000 mg/kg/day.

Parental NOEL = 200 mg/kg/day
Parental LOEL = 1000 mg/kg/day based on histopathological lesions in the kidney, primarily of the tubules and papilla(e) of males of both generations and some females. In addition, in high dose adult males of one or both generations, blood in the urine, decreased urine specific gravity, increased absolute and relative kidney weight, and decreased body weight gain was noted.

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Reproductive NOEL = 1000 mg/kg/day
Reproductive LOEL = not determined

CORE CLASSIFICATION: Core Minimum Data. This study meets the minimum requirements set forth under Guideline Series 83-4 for a two-generation reproductive toxicity study in the rat.

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A. MATERIALS

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Test Compound

Purity:	80.3%
Description:	Solid, white with chlorine-like odor
Lot number:	AGR 274601
Batch number:	Not reported
Receipt date:	Received on March 13, 1989, from the Agricultural Products Department, The Dow Chemical Company, Midland, MI

Vehicle(s): None specified; test material was administered in the diet.

Test Animal

Species:	Rat
Strain:	Sprague-Dawley
Source:	Charles River Breeding Laboratory, Kingston, NY
Age:	Approximately 6 weeks of age at study initiation
Body weight:	Females--174.9 g, males--223.7 g, 2 days before study initiation

B. STUDY DESIGN

This study was designed to assess the potential of picloram to cause reproductive toxicity when administered continuously in the diet for two successive generations. Rats were acclimated to laboratory conditions for 14 days. Each animal was uniquely identified by a coded alphanumeric metal ear tag.

Animal Husbandry: Prior to mating, animals were housed individually in stainless steel wire mesh cages. Basal diet (Purina® Certified Rodent Chow #5002) and tap water were provided ad libitum. Environmental parameters such as temperature, relative humidity, airflow, and lighting, were maintained adequately for the species on test. However, specific conditions were not reported by the study authors.

Mating Procedure: The F_0 and F_1 parental animals were mated after 10 and 12 weeks, respectively, of dietary treatment. Each breeding regimen was comprised of three 7-day cohabitation periods with one female and one male from the same dose group. Vaginal lavage samples were examined daily for the presence of sperm. The day the sperm was detected was designated day 0 of gestation. Sibling matings were avoided. Females that failed to mate during the first 7-day mating period were placed with an alternate male from the same dose group for the second 7-day period; the same procedure was followed for the third 7-day mating period.

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Group Arrangement: F_0 and F_1 animals were randomly assigned by body weight to groups as follows:

Test Group	Dose Level (mg/kg/day)	Number Assigned per Group			
		F_0		F_1	
		Males	Females	Males	Females
Control	0	30	30	30	30
Low dose	20	30	30	30	30
Mid dose	200	30	30	30	30
High dose	1,000	30	30	30	30

Dose Administration: The test material was administered continuously in the diet for two consecutive generations. Test diets were prepared in advance (frequency of preparation not reported) by serially diluting a test material/feed concentrate (premix) and then were adjusted weekly for body weight. Efforts were made to maintain targeted dose levels on a mg/kg body weight/day basis. Concentrations were also adjusted for percentage of active ingredient. Reference samples (one/sex/dose for the final mix and the premix) were retained and stored at ambient temperature. Analyses of the test diets were performed at least three times per generation to determine test material concentration. Homogeneity and stability of the test diets at 20 and 200 mg/kg/day were assessed prior to initiation of the study.

Dose levels were selected based on the results of previously reported dietary studies in rats in which changes in liver weight and histopathology were observed at 60 mg/kg/day after 6 months of exposure. The NOEL in this previously reported study was 20 mg/kg/day after 12 months of exposure.

Observations: Animals were observed at least once daily for overt signs of toxicity. Body weights and food consumption for all animals were determined weekly prior to breeding. Thereafter, male body weights were recorded weekly throughout the duration of the study. Mated females were weighed on days 0, 7, 14, and 21 of gestation, and females that delivered litters were weighed on days 1, 4, 7, 14, and 21 of lactation. Food consumption was not measured during mating. Following completion of the mating periods, food consumption was recorded weekly in males; weekly during gestation in mated females; and twice a week through the first 2 weeks of lactation and at 2-3-day intervals during the last week of lactation in females with live litters. A comparable protocol was utilized for the F_1 generation.

The following data were recorded for each litter:

- Litter size on day 0 postpartum;
- Total number of live and dead pups, sex, and individual pup weight on days 1, 4, 7, 14, and 21 postpartum; and
- Daily clinical observations.

On day 4 postpartum, litters were culled to a maximum of eight pups, four males and four females, when possible. Thirty male and female F_1 pups were selected at random to serve as F_1 parental animals.

Urinalysis (color and appearance, microsediment, pH, specific gravity, bilirubin, glucose, protein, ketones, blood, and urobilinogen) was performed on 10 randomly selected F_1 male rats per dose group prior to mating.

All F_0 and F_1 adults, including those found dead, were necropsied. Pups found dead during the lactation phase were examined grossly and discarded. Adults were fasted overnight, weighed, anesthetized with methoxyflurane, and euthanized. Pups were also anesthetized with methoxyflurane and euthanized. All animals were subjected to gross macroscopic examination. The following tissues and organs were collected from all parental animals and preserved in a 10% neutral buffered formalin solution:

- Adrenals
- Aorta
- Auditory sebaceous glands
- Bone
- Bone marrow
- Brain
- Cecum
- Cervix*
- Coagulating glands*
- Colon
- Duodenum
- Epididymides
- Esophagus
- Eyes
- Gross lesions*
- Heart
- Ileum
- Jejunum
- Kidneys*
- Lacrimal/harderian glands
- Larynx
- Liver*
- Lungs
- Mammary glands
- Mediastinal lymph nodes
- Urinary bladder
- Vagina*
- Mediastinal Tissues
- Mesenteric Lymph Nodes
- Mesenteric Tissues
- Nasal Tissues
- Oral Tissues
- Ovaries*
- Oviducts*
- Pancreas
- Parathyroid glands
- Peripheral nerves
- Pituitary*
- Prostate*
- Rectum
- Salivary glands
- Seminal vesicles*
- Skeletal muscles
- Skin
- Spinal cord
- Spleen
- Stomach
- Testes*
- Thymus
- Thyroid glands
- Tongue
- Trachea
- Uterus*

Tissues with an asterisk (*) from the control and high-dose groups were examined histologically. Kidneys and all gross lesions from all parental dose groups and livers from all F_0 females were also examined histologically. Kidney, testis, and epididymal weights were recorded for all parental animals.

At weaning, 10 pups/sex/dose from the F_1 and F_2 litters were randomly selected for a complete necropsy. Tissues routinely collected (as listed above) were preserved in a formalin solution. Histologic examination was not performed.

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Statistical Analysis: The following analyses were conducted.

- Body weights, urinary specific gravity, and absolute and relative organ weights--Bartlett's test for equality of variances; parametric or nonparametric analysis of variance (ANOVA); and Dunnett's test or the Wilcoxon Rank-Sum test with Bonferroni's correction
- Food consumption--Descriptive statistics (statistical outliers were identified)
- Gestation length and average time to mating--nonparametric ANOVA and Wilcoxon Rank-Sum test with Bonferroni's correction
- Fertility indices--Fisher's exact test with Bonferroni's correction
- Sex ratio--binomial distribution test
- Survival indices--Wilcoxon test as modified by Haseman and Hoel (1974).

Compliance

- A signed Statement of Compliance with FDA, EPA, MAFF, and OECD Good Laboratory Practice Standards, dated October 2, 1991, was provided.
- A signed Quality Assurance Statement, dated September 26 and October 1, 1991, was provided.
- A signed Statement of No Data Confidentiality Claim, dated September 26, 1991. was provided.

C. RESULTS

1. Test Material Analysis

Purity of the test material ranged from 80.3% to 82.8% as determined on four occasions prior to study initiation. Mean concentrations of the test material in the diets ranged from 90% to 100% of nominal values. Homogeneity analyses of the 20- and 200-mg/kg/day test diets (based on several determinations for the top, middle, and bottom portions of separate core samples) revealed mean concentrations from 95% to 103% of nominal values. Analyses for stability of the test material in the test diets after 92 days of storage revealed a mean concentration of 96% of day 0 concentration.

2. Parental Toxicity

Mortality: No treatment-related mortality was observed.

At 1,000 mg/kg/day, two F_0 females were found dead; one on test day 103 and another on day 117. The cause of death could not be determined for either female. One F_0 male from the same dose group was sacrificed moribund on day 105 because of loss of its upper incisors. One male rat from the 200-mg/kg/day group was euthanized on day 83; this rat exhibited malocclusion of incisors, excessive chromodacryorrhea, and swelling of the right paw.

One F_1 female from the 20-mg/kg/day group was sacrificed at parturition because of dystocia. However, the cause of dystocia could not be determined. 010535

Clinical Observations: Treatment-related renal toxicity was observed at 1,000 mg/kg/day in 19 of 30 (63%) F_0 males and 13 of 30 (43%) F_1 males as indicated by the presence of blood in the urine and as indicated by reddish urine in 6 of 30 (20%) F_0 males. Incidental clinical signs were noted in all dose groups for both sexes and generations and included excessive alopecia, chromodacryorrhea, chromorhinorrhea, malocclusion, and perineal soiling.

Body Weight: Summaries of body weight gain from selected time intervals are presented in Tables 1 and 2. Compound-related transient effects were observed at 1,000 mg/kg/day in F_1 males during the postmating period and at 200 (possibly) and 1,000 mg/kg/day in F_1 males during the premating period. Detailed results are discussed below.

In the F_0 generation, no treatment-related effects on body weight (see Appendix, Table 12 for F_0 male body weight data) or body weight gain (Table 1) were observed at any dose level in males or in females during the premating (Table 1), gestation (Table 2), or lactation (Table 3) periods. The following incidental variations in body weight gain were observed in females: 61% increase ($p<0.01$) at 200 mg/kg/day on premating days 27-34; 46% increase ($p<0.05$) at 1,000 mg/kg/day on premating days 27-34; and 40% decrease ($p<0.05$) at 200 mg/kg/day on lactation days 7-14.

In the F_1 generation, body weights (see Appendix, Table 34 for F_1 male body weight data) were consistently decreased (≤5%) for males at 1,000 mg/kg/day. However, the decrease (≥17%) in body weight was significant ($p<0.05$) only from day 111 through 154 of the postmating period. The body weight gain (Table 1) was significantly ($p\leq0.05$) reduced (≥5%) for males at 200 and 1,000 mg/kg/day during the first week of the premating period and on days 104-111 of the postmating period. Significant ($p\leq0.05$) decreases (≥27%) in body weight gain were also noted at 1,000 mg/kg/day on days 146-154 of the postmating period and for the entire postmating period. For females, body weight (data not shown) was significantly ($p<0.05$) decreased (≥5%) at 200 mg/kg/day on days 13-34 and at 1,000 mg/kg/day on days 20-41 of the premating period. Body weight gain (Table 1) for these females was not affected at any dose level. No adverse effects on body weight (data not shown) and body weight gain were noted in treated females during the gestation (Table 2) and lactation (Table 3) periods.

Food Consumption: No apparent treatment-related effects on food consumption were observed for either sex or generation (data not shown). However, food consumption data were not statistically analyzed; the report included mean values (±S.D.) only.

Table 1. Summary of Mean Body Weight Change During the Premating and Postmating Periods for Rats Fed Picloram for Two Successive Generations[a]

8/23/[illegible] KLH

Study Day	0 mg/kg/day Group	20 mg/kg/day Group	300 mg/kg/day Group	1000 mg/kg/day Group
	Mean Body Weight Change (g ± S.D.)			
F_0 Males – Premating				
-2 - 6	52.3 ± 14.9	51.1 ± 5.2	53.8 ± 6.4	54.7 ± 13.3
13 - 20	39.3 ± 20.0	35.2 ± 7.8	38.7 ± 7.7	37.7 ± 8.0
27 - 34	26.4 ± 5.0	27.4 ± 4.8	28.7 ± 6.2	26.5 ± 6.6
41 - 48	20.3 ± 24.6	16.7 ± 5.6	19.3 ± 17.3	11.7 ± 13.3
55 - 69	28.5 ± 8.2	30.0 ± 9.1	28.6 ± 11.1	24.9 ± 15.8
-2 - 69	302.0 ± 36.4	308.4 ± 33.4	317.3 ± 36.1	292.9 ± 52.4
F_0 Males – Mating/Postmating				
76 - 83	19.3 ± 4.9	18.8 ± 5.8	17.5 ± 7.9	21.5 ± 12.2
90 - 97	12.0 ± 5.4	9.0 ± 7.2	10.5 ± 9.5	8.5 ± 14.8
104 - 111	7.2 ± 7.4	5.7 ± 7.0	4.7 ± 7.2	5.7 ± 10.8
118 - 125	11.7 ± 5.2	17.0 ± 9.3	13.1 ± 7.9	14.3 ± 8.5
132 - 139	6.6 ± 5.5	6.9 ± 5.0	6.6 ± 9.9	2.1 ± 17.3
76 - 139	100.7 ± 21.7	94.1 ± 19.8	92.8 ± 39.1	97.4 ± 89.4
F_0 Females – Premating				
-2 - 6	18.1 ± 8.8	20.8 ± 9.4	21.3 ± 7.8	19.9 ± 7.9
13 - 20	16.7 ± 4.8	15.7 ± 9.7	18.4 ± 7.3	19.4 ± 6.0
27 - 34	9.2 ± 5.7	11.5 ± 5.3	14.8 ± 6.9**	13.4 ± 7.2*
41 - 48	4.8 ± 4.9	5.0 ± 6.0	4.9 ± 4.6	6.4 ± 7.4
55 - 69	13.1 ± 6.2	13.8 ± 6.5	13.9 ± 10.6	15.7 ± 7.4
-2 - 69	131.1 ± 28.5	143.2 ± 25.9	147.1 ± 32.3	140.6 ± 18.3
F_1 Males – Premating				
-2 - 6	68.4 ± 7.1	65.7 ± 7.1	64.1 ± 6.6*	61.1 ± 7.1**
13 - 20	59.5 ± 8.2	56.7 ± 9.2	58.3 ± 8.7	56.4 ± 6.7
27 - 34	33.1 ± 9.7	33.3 ± 9.0	34.8 ± 8.9	32.5 ± 9.1
41 - 48	25.8 ± 6.2	24.9 ± 7.6	26.2 ± 6.2	24.3 ± 7.1
55 - 62	25.9 ± 5.0	26.7 ± 7.3	26.3 ± 6.5	25.2 ± 6.4
69 - 83	31.6 ± 9.5	28 ± 10.3	28.3 ± 8.0	29.0 ± 12.7
-2 - 83	427.3 ± 52.6	416.8 ± 71.7	419.9 ± 54.1	397.9 ± 44.3
F_1 Males – Mating/Postmating				
90 - 97	19.5 ± 7.7	15.9 ± 13.4	18.3 ± 10.4	20.8 ± 7.0
104 - 111	10.6 ± 7.0	7.7 ± 8.3	6.4 ± 6.2*	0.7 ± 9.8**
118 - 125	7.5 ± 7.2	7.6 ± 8.2	5.8 ± 8.9	3.3 ± 10.7
132 - 139	6.4 ± 6.9	6.5 ± 6.2	3.5 ± 23.7	5.6 ± 6.4
146 - 154	4.7 ± 5.9	6.0 ± 6.7	7.4 ± 6.2	0.1 ± 10.6*
90 - 154	106.7 ± 27.2	102.0 ± 26.5	101.1 ± 15.7	77.5 ± 23.7**
F_1 Females – Premating				
-2 - 6	37.0 ± 5.5	37.7 ± 6.4	34.8 ± 6.0	38.6 ± 14.4
13 - 20	25.7 ± 5.8	24.1 ± 5.1	24.1 ± 6.1	23.0 ± 8.1
27 - 34	13.4 ± 5.8	13.5 ± 7.2	12.8 ± 4.8	13.5 ± 8.6
41 - 48	12.9 ± 5.7	12.4 ± 5.6	13.9 ± 5.5	16.3 ± 15.8
55 - 62	7.0 ± 7.0	7.1 ± 9.6	7.6 ± 5.8	6.4 ± 5.3
69 - 83	13.7 ± 7.5	11.5 ± 9.9	12.7 ± 7.0	12.5 ± 8.6
-2 - 83	189.8 ± 25.6	184.5 ± 22.6	188.7 ± 30.3	188.8 ± 42.2

[a]Data were extracted from study no. K-038323-057, Tables A-3, A-4, A-21, and A-22 and analyzed by the reviewers using ANOVA.

*Significantly different from controls ($p<0.05$)
**Significantly different from controls ($p<0.01$)

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Table 2. Summary of Mean Body Weight Change During Gestation in Rats Fed Picloram for Two Successive Generations[a]

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Dietary Concentrations (mg/kg/day)	Mean Body Weight Change (g ± SD)			
	Study Weeks 0-7	Study Weeks 7-14	Study Weeks 14-21	Study Weeks 0-21
F_0 Females				
0	34.0 ± 9.8	34.4 ± 6.6	100.1 ± 12.9	168.5 ± 21.2
20	35.3 ± 7.3	33.8 ± 6.6	101.8 ± 14.0	168.9 ± 16.8
200	33.1 ± 10.1	25.4 ± 8.3	92.5 ± 23.0	155.1 ± 33.8
1,000	30.7 ± 9.2	34.7 ± 9.7	92.9 ± 18.8	159.2 ± 25.1
F_1 Females				
0	28.5 ± 9.9	25.9 ± 12.6	97.5 ± 15.0	151.9 ± 16.7
20	30.2 ± 10.3	26.9 ± 7.1	97.5 ± 23.2	154.5 ± 26.7
200	30.4 ± 6.5	23.9 ± 9.4	83.7 ± 24.6	135.9 ± 29.9
1,000	33.4 ± 9.4	26.2 ± 7.4	93.2 ± 19.3	153.1 ± 25.4

[a]Data were extracted from study no. K-038323-057, Tables 16 and 38.

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Table 3. Summary of Mean Body Weight Change During Lactation in Rats Fed Picloram for Two Successive Generations[a]

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Dietary Concentrations (mg/kg/day)	Mean Body Weight Change (g ± SD)			
	Study Weeks 1-4	Study Weeks 4-7	Study Weeks 7-14	Study Weeks 0-21
F_0 Females				
0	10.6 ± 11.2	5.2 ± 11.2	23.2 ± 11.5	21.7 ± 24.2
20	4.2 ± 13.3	5.4 ± 12.4	17.8 ± 22.6	13.2 ± 17.2
200	8.8 ± 11.1	7.0 ± 10.4	13.7 ± 12.4*	11.8 ± 16.0
1,000	6.6 ± 11.3	6.5 ± 16.4	25.4 ± 14.5	17.9 ± 16.9
F_1 Females				
0	5.1 ± 10.5	8.3 ± 10.5	15.3 ± 17.6	26.4 ± 19.4
20	4.3 ± 16.7	4.4 ± 9.7	14.7 ± 14.8	21.5 ± 25.5
200	7.6 ± 9.1	2.6 ± 11.1	15.5 ± 10.5	14.1 ± 15.9
1,000	9.1 ± 11.4	7.6 ± 11.4	20.3 ± 18.1	23.9 ± 21.4

[a]Data were extracted from study no. K-038023-057, Tables 17 and 39.

*Significantly different from control by Wilcoxon's test, alpha=0.05

Gross and Microscopic Pathology: Treatment-related gross and microscopic changes in the kidney were observed in F_0 or F_1 males at 1,000 mg/kg/day. Selected organ weights and associated histopathological findings are presented in Tables 4 and 5, respectively. Detailed results are discussed below. 10535

In the F_0 generation, statistically significant increases in absolute and relative kidney weights (Table 4) accompanied by corresponding histopathological changes were observed in males at 1,000 mg/kg/day. The significant increase in epididymal weights at 20 mg/kg/day was considered to be an isolated finding (data not shown).

In the F_1 generation, slight increases in absolute kidney weights and statistically significant increases in relative kidney weights were observed in males at 1,000 mg/kg/day (Table 4). These increases were accompanied by histologic lesions in the kidneys and, therefore, were considered to be treatment related. The significant increase in mean relative testis weight was possibly the result of lower body weight in these animals (data not shown). The decrease in mean absolute kidney weight of females at 200 mg/kg/day was not considered treatment related because of the absence of this finding at 1,000 mg/kg/day. No statistically significant increases in absolute and relative kidney weights were noted in females of either the F_0 or F_1 generation.

Gross lesions in the kidney in 18 of 29 (62%) F_0 male rats at 1,000 mg/kg/day (Table 5) were described as roughened surface and/or pale or depressed areas of the kidney cortex. In 6 six of these rats, the kidney effects were accompanied by the presence of darkened urine in the urinary bladder. Histopathological changes consisting of renal tubular degeneration/regeneration and inflammation were seen in 20 of the 29 males (=69%) and 5 of 28 (=18%) females at 1,000 mg/kg/day. These changes ranged from focal to multifocal and were either unilateral or bilateral. [redacted] KLH 8/25/95 Lesions of the papillae were characterized by changes similar to those seen in the tubules. Affected papillae were found in 18 of 29 (62%) males and 2 of 30 (7%) females at 1,000 mg/kg/day. (One high dose F_0 unscheduled death female (day 10) also had slight, bilateral multifocal papillar lesions). In the F_1 generation at 1,000 mg/kg/day, gross lesions of the kidney (Table 5) described as roughened surface of the kidney cortex, found in 19 of 30 (63%) males, were accompanied by the presence of darkened urine in the urinary bladder in 4 of the 30 (13%) males. Histopathological changes were consistent with renal toxicity. The tubular lesions were seen in 16 of 30 (53%) males fed 1,000 mg/kg/day. Lesions of the renal papillae were found in 21 of 30 (70%) males and 4 of 30 (13%) females fed 1.000 mg/kg/day. The histological changes in the renal tubules and papillae were similar to those seen in F_0 animals. Occurrence of red blood cells in the urine present in the urinary bladder of males at 1,000 mg/kg/day is considered to result from the kidney lesions.

Urinalysis: Urinalysis was conducted only for the F_1 generation rats. At 1,000 mg/kg/day, F_1 male rats showed a statistically significant decrease in specific gravity (1.047, 1.046, 1.044 and 1.035 at 0, 20, 200, and 1,000 mg/kg/day, respectively) and an increase in the number

Table 4. Mean Absolute and Relative Kidney Weights in Rats Fed Picloram for Two Successive Generations[a]

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Parameters	Kidney Weights (± S.D.) 0-mg/kg/day Group	20-mg/kg/day Group	200-mg/kg/day Group	1,000-mg/kg/day Group
F_0 Generation - Males				
Absolute (g)	3.807 ± 0.482	3.805 ± 0.282	3.910 ± 0.490	4.401 ± 0.644*
Relative (g/100g bw)	0.650 ± 0.070	0.646 ± 0.038	0.657 ± 0.062	0.773 ± 0.132*
F_0 Generation - Females				
Absolute (g)	2.407 ± 0.228	2.402 ± 0.239	2.441 ± 0.219	2.561 ± 0.290
Relative (g/100g bw)	0.758 ± 0.072	0.728 ± 0.044	0.732 ± 0.065	0.789 ± 0.080
F_1 Generation - Males				
Absolute (g)	4.293 ± 0.593	4.166 ± 0.500	4.257 ± 0.436	4.493 ± 0.550
Relative (g/100g bw)	0.650 ± 0.059	0.643 ± 0.064	0.664 ± 0.045	0.760 ± 0.096*
F_1 Generation - Females				
Absolute (g)	2.540 ± 0.285	2.392 ± 0.234	2.389 ± 0.189**	2.496 ± 0.230
Relative (g/100g bw)	0.728 ± 0.088	0.694 ± 0.076	0.712 ± 0.074	0.738 ± 0.062

[a]Data were extracted from study no. K-038023-057, Tables 18, 19, 46, and 47.

*Statistically different from control by Wilcoxon's test, alpha=0.05
**Statistically different from control by Dunnett's test, alpha=0.05

Table 5. Incidences[b] of Selected Gross and Histopathological Findings in F_0 and F_1 Generation Rats Fed Picloram for Two Successive Generations[a]

	Incidences							
	Dose Group (Males)				Dose Group (Females)			
Organs/Findings	0	20	200	1000	0	20	200	1000
GROSS OBSERVATIONS								
F_0 Generation								
Kidneys								
No. examined	30	30	29	29	30	30	30	28
-Area pale, cortex, unilateral, focal (slight)	1	0	0	3	0	0	0	0
-Area pale, cortex, bilateral, focal (slight)	0	0	0	12	0	0	0	1
-Roughened surface, cortical surface, unilateral	1	0	0	2	0	0	0	0
-Roughened surface, cortical surface, bilateral	0	0	0	14	0	0	0	1
Urinary Bladder								
No. examined	30	30	29	29	30	30	30	28
-Blood in urine	0	0	0	6	0	0	0	0
F_1 Generation								
Kidneys								
No. examined	30	30	30	30	30	29	30	30
-Roughened surface, cortical surface, bilateral	0	0	0	19	0	0	0	0
Urinary Bladder								
No. examined	30	30	30	30	30	29	30	30
-Urine - dark, lumen	0	3	0	4	0	0	0	0
HISTOPATHOLOGICAL OBSERVATIONS								
F_0 Generation								
Kidney								
No. examined	30	30	29	29	30	30	30	28
Degeneration/regeneration and inflammation, tubule(s),								
-unilateral, focal (slight)	0	0	0	1	0	0	0	0
-bilateral, focal (slight)	3	0	0	3	0	0	0	0
-unilateral, multifocal (slight)	0	0	0	0	0	0	0	1
-bilateral, multifocal (slight)	0	0	0	8	0	0	0	3
(moderate)	0	0	0	8	0	0	0	1
Degeneration/regeneration and inflammation with or without necrosis, papilla(e)								
-unilateral, focal (slight)	0	0	0	1	0	0	0	0
-bilateral, focal (slight)	0	0	0	2	0	0	0	1
-bilateral, multifocal (slight)	0	0	0	4	0	0	0	1
(moderate)	0	0	0	11	0	0	0	0

Table 5 (continued)

Organs/Findings	Incidences							
	Dose Group (Males)				Dose Group (Females)			
	0	20	200	1000	0	20	200	1000
F_1 Generation								
Kidney								
No. examined	30	30	30	30	30	29	30	30
Degeneration/regeneration and inflammation, tubule(s),								
-unilateral, focal (slight)	0	0	0	4	0	0	0	0
-bilateral, focal (slight)	0	0	0	6	0	0	0	0
-bilateral, multifocal								
(slight)	0	0	0	1	0	0	0	0
(moderate)	0	0	0	5	0	0	0	0
Degeneration/regeneration and inflammation with / without necrosis, papilla(e)								
-unilateral, focal (slight)	0	0	0	3	0	0	0	3
-bilateral, focal (slight)	0	0	0	2	0	0	0	1
-bilateral, multifocal								
(slight)	0	0	0	2	0	0	0	0
(moderate)	0	0	0	14	0	0	0	0

[a]Data were extracted from study no. K-038323-057, Tables 21, 23, 49, and 51.

[b] For animals terminated at the end of the study. KAH 8/23/93

Table 6. Summary of Effects of Dietary Administration of Picloram on F_0 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

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Parameter		Dietary Concentration (mg/kg/day) 0	20	200	1,000
No. matings (F_0 parents)		30	30	30	30
No. mated		30	29	30	30
No. pregnancies		26	28	25	27
Fertility index--female (%)[b]		86.7	93.3	83.3	90.0
Gestation index[c]		100	100	100	100
Mean gestation length (days)		21.6	21.8	21.9*	21.8
Total no. live pups					
Day 0		405	444	358	395
Day 4		396	429	351	382
Day 21		204	218	187	196
Mean no. live pups/litter					
Day 0		15.6	15.9	14.3	14.6
Day 4 precull		15.2	15.3	14.0	14.1
Day 21		7.8	7.8	7.5	7.8[d]
Live birth index (%)[e]		98.1	98.0	98.6	98.0
Viability index (%)[f]		97.8	96.6	98.0	96.7
Lactation index (%)[g]		98.1	99.1	98.9	99.5
Mean pup body weight (g)					
Day 1	male	6.9	6.8	7.0	7.1
	female	6.5	6.5	6.7	6.7
Day 4 precull	male	9.8	9.5	10.0	10.1
	female	9.2	9.1	9.6	9.5
Day 14	male	31.7	31.3	32.1	32.2
	female	30.4	30.5	30.7	30.9
Day 21	male	52.1	51.5	52.3	53.7
	female	49.8	49.9	50.3	51.3
Sex ratio (% males)		51.5	52.5	53.5	52.5

[a]Data were extracted from study no. K-038323-057, Tables 24, 25, 26, A-13, A-14, and A-15.

[b]$\frac{\text{No. of females bearing litters}}{\text{No. of females copulating}} \times 100$

[c]$\frac{\text{No. of litters with at least one live pup}}{\text{No. of litters}} \times 100$

[d]Death of all pups within two litters

[e]$\frac{\text{No. of pups born alive}}{\text{No. of pups born}} \times 100$

[f]$\frac{\text{No. of pups alive on day 4}}{\text{No. of pups born alive}} \times 100$

[g]$\frac{\text{No. of pups alive on day 21}}{\text{No. of pups alive on day 4 postcull}} \times 100$

*Significantly different from control by Dunnett's test, alpha=0.05

Table 7. Summary of Effects of Dietary Administration of Picloram on F_1 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter		Dietary Concentration (mg/kg/day) 0	20	200	1,000
No. matings (F_1 parents)		30	30	30	30
No. mated		28	29	28	29
No. pregnancies		22	22	24	25
Fertility index--female (%)[b]		73.3	73.3	80.0	83.3
Gestation index[c]		100	100	100	100
Mean gestation length (days)		21.5	21.8	21.7	21.8
Total no. of live pups					
Day 0		319	298	301	362
Day 4		292	270	284	351
Day 21		145	145	160	186
Mean no. live pups/litter					
Day 0		14.5	13.5	12.5	14.5
Day 4 precull		13.3	12.3	11.8	14.0
Day 21		6.9	6.6	6.6	7.4
Live birth index (%)[d]		99.1	98.3	96.5	97.3
Viability index (%)[e]		94.7	90.6	94.4	97.0
Lactation index (%)[f]		87.3	92.4	97.0	94.4
Mean pup body weight (g)					
Day 1	male	6.7	6.7	7.0	6.8
	female	6.4	6.3	6.5	6.5
Day 4 precull	male	8.2	8.4	9.2	8.7
	female	7.7	8.0	8.6	8.2
Day 14	male	27.9	28.1	30.7	29.6
	female	25.3	28.2	29.0	28.2
Day 21	male	45.7	47.0	49.0	47.4
	female	43.4	45.5	46.0	44.8
Sex ratio (% males)		48.5	50.5	44.6	49.5

[a]Data were extracted from study no. K-038323-057, Tables 52, 53, 54, A-31, A-32, and A-33.

[b]$\frac{\text{No. of females bearing litters}}{\text{No. of females copulating}} \times 100$

[c]$\frac{\text{No. of litters with at least one live pup}}{\text{No. of litters}} \times 100$

[d]$\frac{\text{No. of pups born alive}}{\text{No. of pups born}} \times 100$

[e]$\frac{\text{No. of pups alive on day 4}}{\text{No. of pups born alive}} \times 100$

[f]$\frac{\text{No. of pups alive on day 21}}{\text{No. of pups alive on day 4 postcull}} \times 100$

of red blood cells in the urine. The effects on urinary parameters were consistent with the clinical observation of bloody urine and the histological lesions in the kidneys of F_0 and F_1 high-dose males (see Appendix for Table 7 and 29 from [redacted] report). HEA 8/23/93

3. Reproductive Toxicity

The effects of dietary administration of the test material on reproductive parameters are summarized in Table 6 and 7. No treatment-related effects were observed on the male or female fertility indices, length of gestation, precoital interval, pup sex ratio, litter size, pup viability, or body weights during lactation for any generation or dose group.

In the F_0 generation (Table 6), mean gestation length was significantly prolonged in females at 200 mg/kg/day. Since this effect was not observed in a dose-related fashion and was not observed in the F_1 generation, it was considered to be a normal variation and unrelated to treatment. The pup body weights in the high-dose group were slightly higher than controls. All other reproductive parameters were comparable in all dose groups.

In the F_1 generation (Table 7), mean gestation length was slightly prolonged in treated females for all three dose groups compared to the controls. Pup body weights were slightly higher in all treated groups. These findings were not considered to be treatment related. All other parameters were comparable to controls.

No compound-related clinical observations or gross findings (data not shown) were noted in F_1 or F_2 pups.

D. REVIEWERS' DISCUSSION/CONCLUSIONS

1. Test Material Analyses

Purity of the test compound as well as homogeneity and stability of the test compound in the diet were confirmed. The concentrations of the test compound in the diet were within ±10% of nominal values.

2. Parental Toxicity

Treatment-related renal toxicity was observed at 1,000 mg/kg/day in F_0 and F_1 males and females.

In the F_0 parental generation at 1,000 mg/kg/day, absolute and relative kidney weights increased in males. Increased incidences of gross pathological findings including pale and depressed areas of the kidney cortex, roughened surface of the kidney cortex, and histopathological changes in renal tubules and papillae consisting of focal or multifocal degeneration/regeneration with or without necrosis or inflammation were also reported. No adverse effects on body weight, weight gain, or food consumption were noted at any dose level for either sex.

In the F_1 parental generation, body weights and weight gains remained consistently lower at 1,000 mg/kg/day in males during the premating

and post-mating periods. The statistically significant decreases in body weight gain noted in F1 males at 200 mg/kg/day were transient. Only the decrease in body weight gain noted in high dose group males were considered to be toxicologically significant. There were no adverse effects on body weight or body weight gain for females during the gestation period. Both body weight and weight gain were slightly lower at all dose levels during lactation. Increases in relative and/or absolute kidney weights in males at 1,000 mg/kg/day were accompanied by histopathological changes similar to those observed in the F_0 generation rats. These changes were not seen at 200 mg/kg/day. Since the statistically significant decreases in body weight gain in F1 males occurred at the same dose as did microscopic changes in the kidney (at 1,000 mg/kg/day), they were considered to be treatment related.

Based on decreased kidney weights in males accompanied by gross and histopathological changes and urological findings, the LOEL for parental toxicity was 1,000 mg/kg/day; the NOEL was 200 mg/kg/day.

3. Reproductive Toxicity

No compound-related reproductive toxicity was observed in either generation at any dose level. Fertility indices, length of gestation, and pup viability, body weight, and sex ratio were unaffected by the treatment. Although the length of gestation was slightly prolonged at 1,000 mg/kg/day in both F_0 and F_1 females compared to controls, this effect did not occur at significant levels. No adverse gross or histopathological changes were noted upon necropsy of pups.

Based on these results, the NOEL for reproductive toxicity was 1,000 mg/kg/day; the LOEL was not established.

4. Reporting Deficiencies

No protocol was submitted. Statistical analysis was not performed on food consumption data; only descriptive statistics were provided. These deficiencies, however, did not alter the outcome of the study.

E. CORE CLASSIFICATION: Core Minimum Data

Parental Toxicity NOEL = 200 mg/kg/day

Parental Toxicity LOEL = 1,000 mg/kg/day based on renal toxicity observed predominantly in males as indicated by clinical findings, decreased body weight gain, increased kidney weight (absolute and relative in F_0 and F_1 males), and gross and histopathological changes in kidney (lesions of the tubules and papillae); kidney histopathology was also noted in some females.

Reproductive Toxicity NOEL = 1,000 mg/kg/day

Reproductive Toxicity LOEL = Not determined

F. RISK ASSESSMENT: Not applicable

APPENDIX*

Tables were extracted from the study report.

Page _____ is not included in this copy.

Pages 20 through 25 are not included in this copy.

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