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

010202

APR 28 1993

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Picloram, Triisopropanolamine Salt Developmental Toxicity Study in the Rat

Tox Chem No.: ~~039~~ 663C D
Project No.: 0-1191

FROM: Brian Dementi, Ph.D., D.A.B.T. Brian Dementi 4/20/93
Review Section III
Toxicology Branch I
Health Effects Division (H7509C)

TO: Venus Eagle, PM Team #71
Reregistration Branch
Special Review and Reregistration Division (H7508W)

THRU: Karen Hamernik, Ph.D.
Acting Section Head
Review Section III
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Health Effects Division (H7509C)

K. Hamernik 4/26/93 KH 4/22/93

The Data Evaluation Review for the picloram, triisopropanolamine salt developmental toxicity study as tested via oral (gavage) administration in the rat, MRID# 413825-04, submitted by DowElanco toward satisfying reregistration §3-3 data requirements, is herewith submitted to SRRD.

In this study, the test material was evaluated at doses of 0, 100, 500 or 1000 mg/kg/day. The picloram salt did not elicit evidence of developmental toxicity at doses up to 1000 mg/kg/day (limit dose). Hence, for developmental toxicity, NOEL = 1000 mg/kg/day. Maternal toxicity was present at 1000 mg/kg/day as evidenced by increased incidence of clinical signs, decreased body weight gain and decreased food consumption. Hence, LOEL = 1000 mg/kg/day; NOEL = 500 mg/kg/day for maternal toxicity. The study is classified as Core Guideline.

The results of the dose range-finding study (Bio/Dynamics Project No. 89-3462) are presented in the review of the definitive study. (Dose Ranging Study MRID: 413825-03). 10/17

Please be advised that reviews of MRID Nos. 413825-01 and 413825-02 were previously submitted to SRRD.

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FINAL

DATA EVALUATION REPORT

PICLORAM TRIISOPROPANOLAMINE

Study Type: Developmental Toxicity

Prepared for:

Office of Pesticide Programs
Health Effects Division
Environmental Protection Agency
1921 Jefferson Davis Highway
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Prepared by:

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Principal Reviewer	Sanju Diwan, Ph.D.	Date	12/22/92
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Contract Number: 68D10075
Work Assignment Number: 1-46
Clement Number: 93-57
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Guideline Series 83-3: Developmental Toxicity

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EPA Reviewer ~~and Acting Section Head:~~ Signature Brian Dennett
~~Henry Spencer~~ Brian Dennett, Ph.D, DABT
Toxicology Branch I/HED Date 2/3/93
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Section 4, Toxicology Branch I 2/3/93

DATA EVALUATION REPORT

STUDY TYPE: Developmental toxicity - Rat

EPA IDENTIFICATION NUMBERS
P.C. Code: 005101
Tox. Chem. Number: 39

MRID Number: 413825-04

TEST MATERIAL: Picloram triisopropanolamine salt

SYNONYMS: Picloram-TIPA

SPONSOR: The Dow Chemical Company, Toxicology Research Laboratory, Midland, Michigan

STUDY NUMBER: 89-3461

TESTING FACILITY: Bio/dynamics, Inc., East Millstone, New Jersey

TITLE OF REPORT: A Teratogenicity Study in Rats with Picloram Triisopropanolamine

AUTHORS: R.E. Schroeder

REPORT ISSUED: January 19, 1990

CONCLUSIONS: A developmental toxicity study was conducted in which Sprague-Dawley rats received daily gavage doses of 0, 100, 500, or 1,000 mg/kg/day picloram triisopropanolamine (picloram-TIPA) during gestation days (GD) 6-15, inclusive. Maternal toxicity, observed at 1,000 mg/kg/day, was manifested by an increased incidence of clinical signs of toxicity and decreased body weight gain and food consumption during the dosing period. Based on these results, the maternal NOEL and LOEL were 500 and 1,000 mg/kg/day, respectively.

Developmental toxicity was not observed in this study. Consequently, the NOEL for developmental toxicity was 1,000 mg/kg/day (a limit dose) and the LOEL was >1,000 mg/kg/day.

CORE CLASSIFICATION: Core Guideline Data. This study meets the requirements set forth under Guideline Series 83-3 for a developmental toxicity study in rats.

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A. MATERIALS

Test Compound

Purity:	61.02%
Description:	Dark-brown liquid
Batch number:	AGR 276453
Sample numbers:	89-3461
Contaminants:	Not reported
Date of receipt:	June 8, 1989
Other information:	Stored at room temperature

Vehicle: Distilled, deionized water

Test Animal(s)

Species:	Rat
Strain:	CD® (Sprague-Dawley derived)
Source:	Charles River Laboratories, Inc., Portage, Michigan
Age:	72 days at start of mating
Body weight of females:	181-268 g on GD 0

B. STUDY DESIGN

This study was designed to assess the potential developmental toxicity of picloram-TIPA in rats when administered daily by gastric intubation from GD 6 through 15, inclusive.

Animal husbandry: Animals were acclimated to the laboratory environment for 23 days; during this time, they were examined by a veterinarian. Basal diet (Purina® Certified Rodent Chow No. 5002) and tap water were given ad libitum. Environmental parameters were as follows: light -- 12-hour light/dark cycle; temperature -- 67-73°F; and relative humidity -- 40-74%.

Mating procedure: Male and female rats were housed in stainless steel cages and mated 1:1. Females were checked daily for the presence of sperm or vaginal plugs. The day on which mating was confirmed was designated GD 0.

Group arrangement: Study groups of 30 sperm-positive females each were assigned to most nearly equalize the day 0 group mean body weights. The groups were as follows:

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Test Group	Dose Level (mg/kg/day)	Number Assigned per Group
Control	0	30
Low dose	100	30
Mid dose	500	30
High dose	1,000	30

Dosing: The selection of dose levels was based on the results of a range-finding teratology study conducted by the reporting laboratory (Bio/dynamics Project No. 89-3462) in which pregnant dams were fed picloram-TIPA in diet at 300, 600, and 1,000 mg/kg/day daily from GD 6 to 15. An increased incidence of salivation was noted in dams at all treatment levels. At 1,000 mg/kg/day, treatment-related maternal toxicity was manifested as decreased body weight gain and food consumption. However, no developmental toxicity was noted.

In the present study, rats were administered picloram-TIPA daily via gastric intubation on GD 6-15, inclusive. The test material was mixed in distilled, deionized water; adjustment was made for purity of the test material. Dose volumes were adjusted to yield a dosing volume of 5 ml/kg body weight for each dose level based on the most recent body weight of each animal. During dosing, the solutions were continuously stirred on a magnetic stir plate. The dosing solutions were prepared once prior to initiation of treatment with sufficient quantity to accommodate the entire dosing regimen and stored at room temperature. Dosing solutions were analyzed to verify the concentration of the picloram moiety prior to use. Stability and homogeneity analyses for the picloram moiety in solution were performed prior to study initiation. In a previous range-finding study, the picloram and triisopropanolamine (TIPA) moieties were analyzed. These analyses indicated that concentration, stability, and homogeneity of the TIPA moiety paralleled that of the picloram moiety. Therefore, analysis of the TIPA moiety was not considered necessary in this study.

Observations: Animals were observed twice daily for mortality, moribundity, and clinical signs of toxicity. Dead females were necropsied to determine the cause of death and pregnancy status. Body weights were recorded on GD 0, 6, 9, 12, 16, and 20. Food consumption was measured for the following intervals during gestation: GD 0-6, 6-11, 11-16, and 16-20. Surviving females were sacrificed on GD 20 by carbon dioxide asphyxiation, and fetuses were removed by cesarean section. Examination of each animal at sacrifice included the following:

- Gross postmortem evaluation
- Liver and kidney weights
- Number of corpora lutea

- Gravid uterine weight
- Number of implantation sites
- Number of live fetuses and early and late intrauterine deaths

The uteri from nongravid females were stained with 10% ammonium sulfide solution to detect early embryo loss.

Fetuses were examined in the following manner:

- Individual fetuses were weighed and sexed, and their uterine positions were recorded.
- All fetuses were examined for external anomalies, including the palate.
- Half of the fetuses were examined for internal visceral anomalies by a modification of the Staples (1974) method.
- Fetuses designated for visceral evaluation were decapitated, and the fetal heads were fixed in Bouin's solution for evaluation of malformations of the palate, eyes, and brain under a dissecting microscope.
- The remaining fetuses were examined for skeletal anomalies following evisceration, fixation for processing, and staining with alizarin Red S using a modification of the Crary method (1962).

Statistical analysis: The following methods were used.

- Maternal body weights, gravid uterine weights, food consumption, organ weights, and reproduction data were statistically evaluated by one-way analysis of variance, followed by a multiple comparison procedure if needed. Bartlett's test was performed to determine if groups had equal variance. For parametric data, the standard one-way ANOVA was performed using the frequency distribution to assess significance (if significant, Dunnett's test was performed). For nonparametric data, the Kruskal-Wallis test was used, and if differences were indicated, Dunn's summed rank test was used. A statistical trend in dose levels was also performed. In parametric cases, standard regression techniques with a test for trend and lack of fit were used. In nonparametric cases, Jonckheere's test for monotonic trend was used. All ratios were transformed via the arcsine transformation prior to analysis.
- For mortality rates, pregnancy rates, incidence of fetuses with malformations/variations, and the incidence of litters containing fetuses with malformations/variations, statistical analysis was performed using contingency tables. First, a standard chi square analysis was performed followed by Fisher's exact test and correction by the Bonferroni inequality. Armitage's test for linear trend in the dosage groups was performed as well.

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Compliance

- A signed Statement of No Data Confidentiality Claim, dated January 31, 1990, was provided.
- A signed Quality Assurance Statement, dated January 4, 1990, was provided.
- A signed Statement of Compliance with EPA, OECD, and MAFF GLPs, dated January 17 and 18, 1990, was provided.

C. RESULTS

Test Material Analysis

The purity of the test compound, as determined by high-performance liquid chromatography, was 61.02%. Analyses conducted prior to dosing revealed concentrations of the picloram moiety ranging from 94.0% to 96.4% of nominal values. Chemical stability of all three test solutions was ≥99% over a 40-day period. Results of homogeneity analysis revealed that for each dosing solution, the concentration was within ±6% of the targets (94.01-96.4%).

Maternal Toxicity

Mortality: No mortality was observed.

Clinical observations: A compound-related clinical observation was reported at 1,000 mg/kg/day consisting of an increase in the incidence of animals with excessive salivation (0, 1, 2, and 8 dams in the control, low-, mid and high-dose groups, respectively).

Body weight: Compound-related body weight change was observed at 1,000 mg/kg/day. A summary of maternal body weight gain and corrected body weight gain data is presented in Table 1. Mean body weights during gestation (data not shown) were comparable in the control and treated groups. In the high-dose group, mean body weight gain during GD 6-9 was significantly ($p \leq 0.05$) lower (=44%) compared to controls (data not shown). Although mean body weight gain for these dams was slightly lower (=8%) than controls for the entire dosing period (GD 6-16), the difference was not statistically significant. The corrected mean body weight gain for the entire gestation period for high-dose females was significantly ($p \leq 0.05$) lower (11%) than controls (calculated by the reviewers).

Food consumption: A compound-related effect in food consumption was observed at 1,000 mg/kg/day. A summary of food consumption data (g/kg/day) is presented in Table 2. Significantly decreased food consumption was noted in dams at the high-dose level during GD 6-11 (=11%) and 11-16 (=5%).

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Table 1. Mean Body Weight Gain (g ± S.D.)[a]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-6)	Dosing Period (GD 6-16)	Post-Dosing Period (GD 16-20)	Entire Gestation Period (GD 0-20)[b]	Corrected Body Weight Gain (GD 0-20)[b,c]
0	34 ± 6	51 ± 8	58 ± 9	142 ± 17	72 ± 12
100	34 ± 8	53 ± 8	60 ± 7	148 ± 13	73 ± 12
500	35 ± 6	51 ± 7	59 ± 10	145 ± 16	73 ± 12
1,000	33 ± 7	47 ± 10	60 ± 10	140 ± 14	64 ± 11*

[a]Data extracted from study no. 89-3461, Appendices D and E

[b]Calculated by the reviewers using ANOVA

[c](GD 20 body weight - GD 0 body weight) - gravid uterine weight

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

Table 2. Mean Food Consumption (g/kg/day ± S.D.)[a]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-6)	Dosing Period (GD 6-11)	Dosing Period (GD 11-16)	Post-Dosing Period (GD 16-20)
0	107 ± 8	97 ± 7	99 ± 7	95 ± 6
100	104 ± 8	93 ± 7	95 ± 6	94 ± 6
500	108 ± 8	92 ± 8	94 ± 8	94 ± 6
1,000	104 ± 9	86 ± 7**	94 ± 8*	94 ± 7

[a]Data extracted from study no. 89-3461, Appendix F

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

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

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Gross pathological observations: No compound-related effects were noted in maternal liver and kidney weights and in gross and histopathological examinations of selected organs and tissues.

Cesarean section observations: No significant compound-related effects were observed for any parameter. A summary of cesarean section data is presented in Table 3. In the low-dose group, the mean number of male fetuses was slightly lower than controls (data not shown), and there was a corresponding increase in the mean number of female fetuses. Since no dose response was evident, this was considered to be normal variation.

Developmental Toxicity

No treatment-related increases in external, visceral, or skeletal anomalies were observed in this study. Incidences of external and visceral anomalies are presented in Table 4. Incidences of selected skeletal anomalies are presented in Tables 5 and 6.

External examination: Malformations were observed in two fetuses (two litters) from the control group and one fetus from the high-dose group (Table 4). In the control group, one fetus had severe multiple cranial defects; the other fetus had a filamentous tail. In the high-dose group, one fetus had severe cranial malformations. Variations were noted in the control and high-dose groups and consisted of shiny appearance and/or subcutaneous hemorrhage.

Visceral examination: Malformations were observed in two control fetuses and two high-dose fetuses (separate litters) and consisted of distention of one or more ventricles of the brain and distended renal pelvis (Table 4). Variations were noted in all dose groups and included variations of the ureter, renal pelvis, and urinary tract.

Skeletal examination: Malformations were observed in five control fetuses (four litters) and three high-dose fetuses (three litters) (Table 5). In fetuses from the control group, malformations included cranial defects, absent vertebrae, and/or wavy ribs. In fetuses from the high-dose group, multiple skeletal malformations were noted in the head and neck region. Additional malformations involved bones of the fore- and hindlegs. A variety of skeletal variations were seen in fetuses from all groups (Table 6) and included variations of thoracic centra; thoracic cervical, lumbar, and caudal transverse processes; sternebrae; and ribs. The incidence of fetuses and litters with unossified 6th vertebrae was higher in all dose groups compared to controls, but no dose response was evident. Since no other effects were noted in the fetuses, this was considered a normal variation.

Table 3. Cesarean Section Observations[a,b]

Parameter	Dose Group (mg/kg/day)			
	0	100	500	1,000
No. of females assigned	30	30	30	30
No. of females pregnant	30	28	27	27
No. of females with viable offspring	30	28	27	27
Pregnancy rate (%)	100	93.3	90.0	90.0
Maternal wastage				
No. died/pregnant	0	0	0	0
No. nonpregnant	0	2	3	3
No. aborted	0	0	0	0
No. with resorptions	13	10	17	14
Mean gravid uterine weight (g)[c]	69.8 ± 14.4	74.5 ± 7.8	71.9 ± 15.6	76.1 ± 11.0
Total no. of corpora lutea	464 (30)	432 (28)	415 (27)	432 (27)
Corpora lutea/dam[c]	15.5 ± 2.4	15.4 ± 2.2	15.4 ± 1.8	16.0 ± 1.9
Total no. of implantations	423 (30)	403 (28)	396 (27)	406 (27)
Implantations/dam[c]	14.1 ± 2.5	14.4 ± 1.5	14.7 ± 3.1	15.0 ± 2.2
Total no. of live fetuses	398 (30)	387 (28)	369 (27)	391 (27)
No. of live fetuses/litter[c]	13.3 ± 2.9	13.8 ± 1.5	13.7 ± 3.1	14.1 ± 2.2
Total no. of resorptions	25	16	27	25
Early resorptions	25	15	26	24
Late resorptions	0	1	1	1
No. of resorptions/litter[c]	0.8 ± 1.6	0.6 ± 0.9	1.0 ± 1.0	0.9 ± 1.1
Total no. of dead fetuses	0	0	0	0
Preimplantation loss (%)	8.7	5.8	6.2	6.1
Postimplantation loss (%)	6.1	3.8	6.7	6.0
Mean fetal body weight/litter (g)[c]	3.3 ± 0.3	3.4 ± 0.2	3.3 ± 0.2	3.4 ± 0.2
Sex ratio (% male)	52.8	42.6	49.3	49.3

[a]Data extracted from study no. 89-3461, Appendices G and E

[b]Litter incidence within parentheses

[c]Mean ± S.D.

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Table 4. Summary of External and Visceral Fetal Anomalies[a,b,c]

Findings	Dose Group (mg/kg/day) 0	100	500	1,000
External Malformations				
No. of fetuses examined	398 (30)	387 (28)	369 (27)	381 (27)
Filamentous tail	1	0	0	0
Elongated snout	1	0	0	0
Absence of mouth opening	1	0	0	1
Absence of eye bulge	1	0	0	0
Agnathia	1	0	0	1
Exencephaly	0	0	0	1
Open eye, absence of eyelid(s)	0	0	0	1
Ectopic eye	1	0	0	0
Total no. of fetuses with external malformations	2 (2)	0	0	1
External Variations				
Shiny appearance	1	0	0	1
Subcutaneous hemorrhage(s)	0	0	0	3 (1)
Total no. of fetuses with external variations	1	0	0	4 (2)
Visceral Malformations				
No. of fetuses examined	210 (30)	201 (28)	191 (27)	197 (27)
Distended lateral ventricles	0	0	0	2 (2)
Distended third ventricle	1	0	0	1
Distended renal pelvis, papilla absent	1	0	0	0
Total no. of fetuses with visceral malformations	2 (2)	0	0	2 (2)
Visceral Variations				
Distended renal pelvis, papilla present	3 (3)	0	0	3 (3)
Tortuous ureter	13 (8)	7 (6)	2 (2)	11 (8)
Distended ureter	2 (2)	3 (2)	3 (2)	2 (2)
Blood in the urinary tract	0	1	0	0
Total no. of fetuses with visceral variations	14 (8)	11 (8)	5 (3)	12 (9)

[a]Data extracted from study no. 89-3461, Appendices L and M

[b]More than one type of anomaly may be found in one fetus.

[c]Litter incidence within parentheses

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Table 5. Incidence of Fetal Skeletal Malformations[a,b,c]

Findings	Dose Level (mg/kg/day) 0	100	500	1,000
No. of fetuses examined	190 (30)	185 (28)	178 (27)	185 (27)
Absent mandibles	1	0	0	0
Zygomatic arch ossification(s)				
-absent	1	0	0	1
-small and thickened	1	0	0	0
Presence of discrete ossification	1	0	0	1
Absent palatine process	0	0	0	1
Misshapen frontals	1	0	0	0
Misshapen basiphenoid	1	0	0	0
Absent premaxilla(s)	1	0	0	0
Absent nasal(s)	1	0	0	0
Defect of the mandible	0	0	0	1
Mandible fused to maxillary process	0	0	0	1
Molar fused to squamosal	0	0	0	1
Fused nasals	0	0	0	1
Premaxilla(s)				
-fused	0	0	0	1
-misshapen	0	0	0	1
Maxillary process small and misshapen	0	0	0	1
Fused cervical transverse process	0	0	0	1
Misshapen lumbar centrum	1	0	0	0
Absent sacral vertebrae	1	0	0	0
Absent caudal vertebrae	1	0	0	0
Wavy rib(s)	3 (2)	0	0	1
Bent humerus	0	0	0	1
Bent radius	0	0	0	1
Bent ulna	0	0	0	1
Bent, shortened femur	0	0	0	1
Bent scapula	0	0	0	1
Total no. of fetuses with skeletal malformations	5 (4)	0	0	3 (3)

[a]Data extracted from study no. 89-3461, Appendix N

[b]More than one type of anomaly may be found in one fetus.

[c]Litter incidence within parentheses

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Table 6. Incidence of Selected Fetal Skeletal Variations[a,b,c]

Findings	Dose Level (mg/kg/day)			
	0	100	500	1,000
No. of fetuses examined	190 (30)	185 (28)	178 (27)	185 (27)
Incompletely ossified basiphenoid	0	0	1	0
Incompletely ossified cervical transverse process(es)	20 (8)	12 (8)	20 (12)	21 (12)
Incompletely ossified thoracic transverse process(es)	0	1	1	0
Thoracic centrum(a)				
-split	2 (2)	1	1	3 (3)
-incompletely ossified	76 (29)	79 (27)	84 (23)	76 (25)
-not ossified	1	1	2 (2)	1
Incompletely ossified lumbar transverse process(es)	0	1	1	0
Incompletely ossified lumbar centrum(a)	0	2 (2)	1	0
Unossified sacral transverse process(es)	13 (7)	13 (9)	14 (9)	8 (2)
Incompletely ossified caudal transverse process(es)	78 (28)	80 (26)	87 (25)	77 (21)
Incompletely ossified caudal centrum(a)	0	1	0	0
Incompletely ossified sternebra				
-1st	2 (2)	3 (2)	4 (4)	2 (2)
-3rd	8 (8)	4 (4)	10 (7)	11 (7)
-4th	41 (21)	43 (21)	59 (23)	44 (17)
Unossified sternebra				
-2nd	5 (5)	0	0	3 (3)
-4th	0	1	1	2 (2)
-6th	14 (7)	14 (10)	22 (15)	29 (11)
Split sternebra				
-4th	0	0	0	1
Misshapen sternebra(ae)	0	0	0	1
Short rib(s)	5 (3)	2 (2)	7 (4)	4 (4)
1st lumbar rudimentary rib(s)	3 (2)	1	1	6 (3)
Metatarsal(s)				
-incompletely ossified	2 (2)	4 (4)	3 (3)	6 (4)
-unossified	0	2 (2)	1	2 (2)
Total no. of fetuses with skeletal variations	167 (30)	158 (28)	165 (27)	158 (27)

[a]Data extracted from study no. 89-3461, Appendix II

[b]More than one type of anomaly may be found in one fetus.

[c]Litter incidence within parentheses

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D. REVIEWERS' DISCUSSION/CONCLUSIONS

Acceptance Criteria

The reviewers have completed an acceptance criteria check list (Attachment I) to be included in the evaluation of the study. All criteria were fulfilled.

Test Material Analyses

Purity of the test material and homogeneity and stability of the test material in the dosing solution were confirmed. Concentrations of the dosing solutions were within ±6% of target.

Maternal Toxicity

Compound-related maternal toxicity was seen in dams at 1,000 mg/kg/day and manifested by an increased occurrence of clinical signs and decreased body weight gain and food consumption during the dosing period (GD 6-16). Based on these findings, the NOEL and LOEL for maternal toxicity were 500 and 1,000 mg/kg/day, respectively.

Developmental Toxicity

Deaths/resorptions: No dead fetuses were recovered from control or treated dams. No compound-related effects were noted at any dose level in the number (or percentage) of resorbed fetuses per litter.

Altered growth: No compound-related effects were observed in fetal body weight at any dose level. In all dose groups, the number of fetuses/litter and number of litters with skeletal variations (i.e., incomplete/absent ossification) increased compared to controls, but this increase was not significant and no dose-response was evident.

Developmental anomalies: The sporadic occurrence of malformations in the control and high-dose groups was considered to be spontaneous in origin since no dose-related pattern was evident; no malformations were seen at 100 or 500 mg/kg/day.

Based on these results, the LOEL for developmental toxicity was >1,000 mg/kg/day, and the NOEL was 1,000 mg/kg/day.

E. CLASSIFICATION: Core Guideline Data

Maternal NOEL = 500 mg/kg/day
Maternal LOEL = 1,000 mg/kg/day based on clinical signs, decreased body weight gain, and decreased food consumption during the dosing period

Developmental NOEL = 1,000 mg/kg/day (limit dose) based on absence of developmental toxicity
Developmental LOEL = >1,000 mg/kg/day

F. RISK ASSESSMENT: Not applicable

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ATTACHMENT I

83-3 Teratology Studies 010202

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1. YES Technical form of the active ingredient tested.

2. YES At least 20 pregnant animals/dose group of rats are available (three test groups and control group).

3. YES At the high dose, overt maternal effects such as slight weight loss are reported (or a limit dose is given, 1,000 mg/kg).

4.* YES At the low dose, no developmental toxicity is reported.

5. YES Dosing duration is least during the period of major organogenesis, but may extend up to 1 day prior to term.

6.* YES Analysis for test material stability, homogeneity, and concentration in dosing medium.

7. YES Individual daily observations.

8. YES Individual body weights.

9. YES Individual food consumption.

10. YES Necropsy on all animals.

11. YES Individual uterine examination, including numbers of fetal deaths, early and late resorptions, and viable fetuses per sex.

12. YES All ovaries examined to determine number of corpora lutea.

13. YES Individual litter weights and/or individual fetal weights/sex/litter.

14. YES Individual fetal external examination.

15. YES Individual fetal skeletal examination for 1/3 to 1/2 of each litter for rodents and all for rabbits.

16. YES Individual fetal soft tissue examination.

Criteria marked with an * are supplemental, may not be required for every study.

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