DATA EVALUATION REPORT

Metolachlor ESA (CGA-354743 TECHNICAL)

STUDY TYPE: DEVELOPMENTAL TOXICITY- RAT [870.3700 (83-3a)]
MRID 44931711

Prepared for

4/25/01

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Office of Pesticide Programs
U.S. Environmental Protection Agency
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Prepared by

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DATA EVALUATION RECORD

STUDY TYPE: Developmental Toxicity - Rat;OPPTS 870.3700 (§83-3a)]

DP BARCODE: D260393 SUBMISSION CODE: S570059
P.C. CODE: 108801 (parent) TOX. CHEM. NO.: 188DD

TEST MATERIAL (PURITY): CGA-354743 Technical (98% a.i.)

SYNONYMS: none; degradate of metolachlor

CITATION: Doubovetzky, M. (1999) CGA-354743 technical: Rat oral teratogenicity. Novartis Crop Protection AG, Toxicology, 4332 Stein, Switzerland. Laboratory Study No. 981009. January 25, 1999. MRID 44931711. Unpublished.

SPONSOR: Novartis Crop Protection, Inc., 410 Swing Road, Post Office Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44931711), 28 presumed pregnant Wistar B: Hanlbm:WIST rats per group were administered CGA 354743 Technical (98%; Batch No. KI-5408/6) by gavage in 0.5% aqueous sodium carboxymethylcellulose in 0.1% aqueous polysorbate 80 at doses of 0, 250, 500, or 1000 mg/kg/day on gestation days (GD) 6-15, inclusive. Controls were treated with 0.5% sodium carboxymethylcellulose in 0.1% aqueous polysorbate 80 (vehicle). On GD 21, dams were sacrificed, subjected to gross necropsy, and all fetuses examined externally. Approximately one-half of each litter was processed for visceral examination and the remaining one-half was processed for skeletal examination.

All animals survived to terminal sacrifice. No clinical signs of toxicity were observed in any animal. Maternal body weights, body weight gains, and food consumption were similar between the treated and control groups throughout the study. Maternal necropsy was unremarkable.

Therefore, the maternal toxicity NOAEL is ≥1000 mg/kg/day and the maternal toxicity LOAEL was not identified.

No differences were observed between the treated and control groups for number of corpora lutea, number of implantation sites, live fetuses/dam, pre- and post-implantation losses, fetal body weights, or fetal sex ratios.

No treatment-related external, visceral, or skeletal malformations/variations were observed in any fetus from any group.

The high dose is equivalent to the limit dose for developmental toxicity studies.

Therefore, the developmental toxicity NOAEL is ≥1000 mg/kg/day and the developmental toxicity LOAEL was not identified.

This study is classified as **Acceptable/Guideline** and satisfies the requirements for a developmental toxicity study [870.3700 (§83-3a)] in rats.

COMPLIANCE: Signed and dated Quality Assurance, Good Laboratory Practice, Flagging, and Data Confidentiality statements were included.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: CGA-354743 Technical

Description: solid
Batch No.: KI-5408/6
Purity: 98% a.i.
Stability of compound: not stated
CAS No.: not given
Structure: not given

2. Vehicle and/or positive control

A 0.5% (w/w) aqueous solution of sodium carboxymethylcellulose (CMC, Hercules Powder Company, Pharmacopeia quality, high viscosity, Prod. 7HF) in 0.1% aqueous polysorbate 80 was used as the vehicle and negative control. No positive control was used in this study.

3. Test animals

Species: rat
Strain: Wistar B: Hanlbm:WIST
Age and weight at study initiation: minimum of 8 weeks; 170.0-216.4 g
Source: BRL, Biological Research Laboratories Ltd., Woelferstrasse 4, CH-4414 Fuellinsdorf, Switzerland
Housing: Animals were individually housed in Macrolon cages with wire mesh tops and standardized granulated soft wood bedding material.
Diet: Pelleted certified standard feed (Nafag No. 890, Tox; Nafag, Naehr- und Futtermittel AG, Gossau, Switzerland) was available *ad libitum*.
Water: Tap water was available *ad libitum*.
Environmental conditions:
Temperature: 22 ± 3°C
Humidity: 50 ± 20%
Air changes: about 16/hour
Photoperiod: 12 hr light/dark
Acclimation period: at least 7 days between delivery from animal breeder and the first day of treatment

B. PROCEDURES AND STUDY DESIGN

This study was designed to assess the developmental toxicity potential of CGA-354743 Technical when administered by gavage to rats on GD 6-15, inclusive.

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1. In life dates

   Start: April 7, 1998; end: April 28, 1998 (start of necropsy)

2. Mating

   Females were mated to a male of the same stock and proven fertility at a ratio of three females to one male. Each cage was divided into two parts by a guillotine door, separating the sexes until 4 p.m. on the mating day, when the door opened automatically. Successful mating was assessed by the presence of a vaginal plug or of spermatozoa in a vaginal smear. The day of successful mating was designated as gestation day (GD) 0.

3. Animal assignment and dose selection are presented in Table 1. Animals were assigned to a control or treatment group using a method of randomization based on weight stratification.

TABLE 1. Animal assignment

Test Group	Dose Level (mg/kg/day)	Number Assigned
Control	0	28
Low Dose	250	28
Mid Dose	500	28
High Dose	1000	28

Data taken from text tables pp. 15 and 16, MRID 44931711.

4. Dose selection rationale

   Doses were selected on the basis of a range-finding study (Laboratory Study No. 981008) in which pregnant rats were administered 250, 500, or 1000 mg/kg/day. No maternal or developmental toxicity was observed at any dose. Further details of this study were not included in the report.

5. Dose solution preparation and analysis

   The test substance was mixed in a 0.5% aqueous solution of sodium carboxymethylcellulose in 0.1% aqueous polysorbate 80. Solutions were prepared daily with a high-speed homogenizer. Homogeneity during administration was maintained with a magnetic stirrer. Samples of the dosing solutions were analyzed for concentration, homogeneity, and stability three times during the study. Samples from the top, middle, and bottom of the dosing solutions were analyzed for concentration and homogeneity.

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Stability was determined after storage at room temperature for the duration of dosing from samples taken from the middle of the solutions.

Results -
Concentration analysis: Absence of test article was confirmed in the vehicle. Mean concentrations of the dosing solutions ranged from 99.5% to 104% of nominal.

Homogeneity analysis: Concentrations of the top, middle, and bottom of the dosing solutions differed by <10%.

Stability analysis: Samples taken after the period of dosing differed from their initial measured concentrations by <6%.

Analyses of the dosing solutions indicated that the test article could be adequately mixed in the vehicle, was stable for the duration of use, and that actual doses to the animals were acceptable.

6. Dosing

All doses were administered in a volume of 10 mL/kg of body weight.

C. OBSERVATIONS

1. Maternal observations and evaluations

The animals were checked once daily for clinical signs and twice daily for mortality. Body weights were measured daily and food consumption was measured on days 6, 11, 16, and 21. Dams were sacrificed on GD 21 by carbon dioxide inhalation and examined grossly. The number of corpora lutea on each ovary was counted. Gravid uteri were weighed and examined for number and location of live and dead fetuses and number and location of early and late resorptions and abortion sites. Dams found dead or sacrificed early were subjected to gross necropsy.

2. Fetal evaluations

At necropsy, each live fetus was weighed, sexed, and examined for external abnormalities. Fetuses were killed by subcutaneous injection of a barbiturate anesthetic. Approximately one-half of each litter was processed for visceral examination and the remaining one-half processed for skeletal examination. In the case of a gross external anomaly or malformation, fetuses were allocated to one technique depending on the type and incidence of the finding. For the visceral examinations, fetuses were fixed in Bouin's solution for at least two weeks and then micro-dissected. For the skeletal examinations, fetuses were cleared with potassium hydroxide and stained with alizarin red S.

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D. DATA ANALYSIS

1. Statistical analysis

Continuous data were analyzed by the Analysis of Variance (ANOVA) followed by Dunnett's t-test to separate the means. The Chi-Square and Fisher's Exact tests were used for the analysis of categorical data. Non-parametric data were analyzed with the Kruskal-Wallis test followed by the Mann-Whitney U test.

2. Historical control data from September 19, 1970 to December 31, 1998 on 432 mated females were provided to allow comparison with concurrent controls and treatment groups.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and clinical signs

All animals survived to scheduled sacrifice. No treatment-related clinical signs of toxicity were observed in any animal.

2. Body weight

Selected maternal body weights during gestation are given in Table 2. No statistically significant differences in absolute body weights occurred at any time between the treated groups and the control group. Body weight gains were also similar between the treated and control groups throughout the study.

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TABLE 2: Maternal body weights during gestation (g)				
GD	**0 mg/kg/day**	**250 mg/kg/day**	**500 mg/kg/day**	**1000 mg/kg/day**
0	190.6 ± 9.8	190.2 ± 10.0	189.8 ± 9.2	190.0 ± 9.2
6	212.9 ± 9.7	211.6 ± 8.6	211.3 ± 8.4	212.4 ± 9.9
10	228.4 ± 10.5	227.2 ± 9.4	227.0 ± 10.4	229.1 ± 10.6
16	262.9 ± 13.5	262.9 ± 12.6	262.4 ± 14.5	265.1 ± 14.3
21	315.6 ± 19.3	320.5 ± 18.1	317.4 ± 19.1	318.8 ± 20.7
Adjusted body wt.[a]	245.2	246.8	245.8	245.8

Data taken from Tables 2 and 7, pp. 31-33 and 46, respectively, MRID 44931711.
[a]Adjusted body weight = terminal body weight - gravid uterine weight.

3. Food consumption

Maternal food consumption was similar between the treated and control groups throughout the study.

4. Gross pathology

No treatment-related gross abnormalities were observed at maternal necropsy.

5. Cesarean section data

Data collected at cesarean section are summarized in Table 3. No differences were observed between the treated and control groups for number of corpora lutea, number of implantation sites, live fetuses/dam, resorptions, pre- and post-implantation losses, fetal body weights, or fetal sex ratios. No dam had complete litter resorption or contained dead fetuses.

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TABLE 3: Cesarean section observations				
Observation	0 mg/kg/day	250 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
No. Animals Assigned	28	28	28	28
No. Animals Pregnant	27	25	27	28
Pregnancy Rate (%)[a]	96.4	89.3	96.4	100
Maternal Mortality	0	0	0	0
Delivered Early/Aborted	0	0	0	0
Gravid Uterine Wt (g)	70.4	73.7	71.7	73.0
Corpora Lutea/Dam	11.1	11.3	11.1	11.5
Implantation/Dam	10.7	11.0	10.6	11.1
Preimplantaion Loss (mean %)	4.1	2.8	4.7	4.4
Postimplantaion Loss (mean %)	4.0	1.3	1.4	4.1
Total Live Fetuses	279	272	282	302
Live Fetuses/Litter	10.3	10.9	10.4	10.8
Mean Fetal Weight (g)	4.9	5.0	5.0	5.0
Sex Ratio (% Male)	48.7	45.2	46.1	48.7
Total Dead Fetuses	0	0	0	0
Dams With All Resorptions	0	0	0	0
Resorptions/Dam				
Early Resorptions	0.4	0.2	0.1	0.4
Late Resorptions	0.0	0.0	0.0	0.0

Data taken from Tables 5, 6, and 7, pp. 40, 42-44, and 46, respectively, MRID 44931711.
[a]Calculated by reviewer.

B. DEVELOPMENTAL TOXICITY

No treatment-related external, visceral, or skeletal malformations/variations were observed in any fetus from any group. A summary of findings is given in Table 4.

1. External examination

The number of fetuses(litters) examined for external malformations/variations in the 0, 250, 500, and 1000 mg/kg/day groups was 279(27), 272(25), 282(27), and 302(28), respectively. One high-dose litter contained a fetus with an umbilical hernia.

2. Visceral examination

The number of fetuses(litters) examined for visceral malformations/variations in the 0, 250, 500, and 1000 mg/kg/day groups was 130(27), 128(25), 135(27), and 143(27), respectively. One mid-dose fetus had most organs in situs inversus. Anophthalmia and hemorrhagic liver were also observed in the high-dose fetus with the umbilical hernia. Anomalies such as thymic remnant in the neck and accessory lobulets on the liver were seen in one to five fetuses per group including controls.

3. Skeletal examination

The number of fetuses(litters) examined for skeletal malformations/variations in the 0, 250, 500, and 1000 mg/kg/day groups was 149(27), 143(25), 146(27), and 159(28), respectively. The only skeletal malformation was fused ribs in one low-dose fetus. Skeletal anomalies of the sternebrae, vertebrae, and ribs were observed at low incidences in fetuses from the treated and control groups. Variations in ossification rates of the cranial bones, metatarsals, sternebrae, calcaneus, vertebrae, ribs, and phalanges were also common to fetuses from all groups.

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TABLE 4: Fetal external, visceral, and skeletal observations no. fetuses (no. litters) affected				
Observation	**0 mg/kg/day**	**250 mg/kg/day**	**500 mg/kg/day**	**1000 mg/kg/day**
External				
Total external findings (umbilical hernia)	0 (0)	0 (0)	0 (0)	1 (1)
Visceral				
Umbilical hernia	0 (0)	0 (0)	0 (0)	1 (1)
Most organs in situs inversus	0 (0)	0 (0)	1 (1)	0 (0)
Anophthalmia	0 (0)	0 (0)	0 (0)	1 (1)
Hemorrhagic liver	0 (0)	0 (0)	0 (0)	1 (1)
Thymic remnant in the neck	1 (1)	1 (1)	3 (3)	1 (1)
Accessory liver lobulet	0 (0)	3 (3)	5 (5)	2 (2)
Total visceral observations	1 (1)	4 (3)	9 (7)	4 (4)
Skeletal				
Total skeletal malformations (fused ribs)	0 (0)	1 (1)	0 (0)	0 (0)
Total skeletal anomalies	9 (7)	10 (7)	17 (11)	11 (8)
Total skeletal variations	147 (27)	138 (25)	144 (27)	155 (27)

Data taken from Tables 9, 10, and 11-13, pp. 50, 52-55, and 58-96, respectively, MRID 44931711.

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III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS

The study author concluded that no signs of maternal or fetal toxicity and no evidence of teratogenicity were observed following maternal treatment with CGA 354743 Technical on GD 6-15; the NOEL for rat dams and fetuses was 1000 mg/kg/day.

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY

Maternal toxicity was not evident in any treated group. No clinical signs were observed and body weights, body weight gains, and food consumption were similar between the treated and control groups.

Therefore, the maternal toxicity NOAEL is ≥1000 mg/kg/day and the maternal toxicity LOAEL was not identified.

2. DEVELOPMENTAL TOXICITY

a. Deaths/resorptions

Maternal treatment with the test article did not result in increases in either pre- or postimplantation loss or fetal death.

b. Altered growth

No treatment-related effects on fetal body weights or ossification rates were observed.

c. Developmental variations

Developmental variations were common to both treated and control fetuses and the incidence rates of specific variations were not affected by treatment.

d. Malformations

Malformations did not increase with exposure to the test article.

It should be noted that although neither maternal nor developmental toxicity were apparent, the high dose is equivalent to the limit dose for developmental toxicity studies.

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Therefore, the developmental toxicity NOAEL is ≥1000 mg/kg/day and the developmental toxicity LOAEL was not identified.

C. STUDY DEFICIENCIES

No deficiencies were identified that would compromise the integrity of this study.

D. CORE CLASSIFICATION

This study is classified as **Acceptable/Guideline** and satisfies the requirements for a developmental toxicity study [870.3700 (§83-3a)] in rats.

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