DATA EVALUATION REPORT

Metolachlor OA (CGA-51202 TECHNICAL)

STUDY TYPE: DEVELOPMENTAL TOXICITY- RAT [870.3700 (§83-3a)]
MRID 44929510

Prepared for

4/25/01

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U.S. Environmental Protection Agency
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DATA EVALUATION RECORD

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

DP BARCODE: D260000
P.C. CODE: 108801 (parent)

SUBMISSION CODE: S569354
TOX. CHEM. NO.: 188DD

TEST MATERIAL (PURITY): CGA-51202 Technical (100% a.i.)

SYNONYMS: none; degradate of metolachlor

CITATION: Marty, J.H. (1992) CGA-51202 technical: Rat oral teratogenicity. Ciba-Geigy Limited, Reproduction Toxicology, 4332 Stein, Switzerland. Laboratory Study No. 911351. November 3, 1992. MRID 44929510. Unpublished.

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

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44929510), 24 presumed pregnant Tif: RAI f (SPF) (hybrids of RII/1 × RII/2) rats per group were administered CGA 51202 Technical (100%; Batch No. JD 7069/3) by gavage in 0.5% aqueous sodium carboxy-methylcellulose solution at doses of 0, 10, 100, or 1000 mg/kg/day on gestation days (GD) 6-15, inclusive. Controls were treated with 0.5% sodium carboxymethylcellulose (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.

One low-dose animal was sacrificed moribund on GD 20 with a urogenital infection. All other animals survived to terminal sacrifice. No clinical signs of toxicity were observed in any animal. Maternal body weights and body weight gains were similar between the treated and control groups throughout the study. Food consumption was not affected by treatment. 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.

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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-51202 Technical

Description: beige crystals
Batch No.: JD 7069/3
Purity: 100% a.i.
Stability of compound: not stated
CAS No.: not given
Structure: not given

2. Vehicle and/or positive control

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

3. Test animals

Species: rat
Strain: Tif: RAI f (SPF), hybrids of RII/1 × RII/2
Age and weight at study initiation: minimum of 8 weeks; 173.7-220.4 g
Source: Animal Production, WST-455, Ciba-Geigy Limited, 4332 Stein, 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 production (in house) and the first day of treatment

B. PROCEDURES AND STUDY DESIGN

This study was designed to assess the developmental toxicity potential of CGA-51202 Technical when administered by gavage to rats on GD 6-15, inclusive.

1. In life dates

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Start: April 7, 1992; end: April 28, 1992 (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 3 a.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	24
Low Dose	10	24
Mid Dose	100	24
High Dose	1000	24

Data taken from text tables pp. 16 and 17, MRID 44929510.

4. Dose selection rationale

Doses were selected on the basis of a range-finding study (Laboratory No. 911361) in pregnant rats. In this study, no maternal or developmental toxicity was observed at doses of 500 or 1000 mg/kg/day. 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 carboxymethyl-cellulose. 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 twice during the study. Samples from the top, middle, and bottom of the dosing solutions were analyzed for concentration and homogeneity. Stability was determined after 2 hours at room temperature from samples taken from the middle of the solutions.

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Results -

Concentration analysis: Absence of test article was confirmed in the vehicle. Concentrations of the dosing solutions ranged from 92.0% to 102.8% of nominal.

Homogeneity analysis: Concentrations of the top, middle, and bottom of the dosing solutions differed by <4%.

Stability analysis: After 2 hours, concentrations of the dosing solutions ranged from 94.4% to 105.9% of their initial measured concentrations.

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 daily for clinical signs and 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, early and late resorptions, and abortion sites. Uteri that appeared nongravid were placed in ammonium sulfide to visualize possible implantation 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 was 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 January 1, 1988 to March 1, 1992 on 624 mated females were provided to allow comparison with concurrent controls and treatment groups.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and clinical signs

One low-dose dam was sacrificed on GD 20 following observations of weight loss and inflammation of the vulva. All remaining animals survived to scheduled sacrifice. Necropsy showed a congested, dilated bladder and a white-yellowish discharge indicative of a uro-genital infection. 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	10 mg/kg/day	100 mg/kg/day	1000 mg/kg/day
0	196.3 ± 10.6	195.8 ± 11.5	195.1 ± 10.5	196.1 ± 12.8
6	225.2 ± 13.6	226.3 ± 13.6	226.9 ± 11.9	227.4 ± 13.4
10	245.3 ± 13.2	246.7 ± 14.6	249.7 ± 14.0	246.1 ± 15.9
16	289.3 ± 15.0	295.4 ± 17.3	296.4 ± 18.0	288.0 ± 19.8
21	360.9 ± 25.1	372.8 ± 27.6	369.4 ± 33.0	364.6 ± 31.4
Adjusted body wt.[a]	263.2	265.5	274.1	263.1

Data taken from Tables 2 and 7, pp. 32-34 and 47, respectively, MRID 44929510.
[a]Adjusted body weight = terminal body weight - gravid uterine weight.

3. Food consumption

There were no dose- or treatment-related differences in food consumption between treated and control groups at any time during gestation. High-dose dams ate significantly (91.9% of control; $p \leq 0.05$) less food than the controls on GD 6-11, but no other differences were noted either during or after the treatment interval.

4. Gross pathology

No treatment-related gross abnormalities were observed at maternal necropsy. Evidence of a urogenital infection was seen in the low-dose dam sacrificed on GD 20.

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. All pregnant dams had live fetuses at necropsy.

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TABLE 3: Cesarean section observations				
Observation	**0 mg/kg/day**	**10 mg/kg/day**	**100 mg/kg/day**	**1000 mg/kg/day**
No. Animals Assigned	24	24	24	24
No. Animals Pregnant	21	22	22	23
Pregnancy Rate (%)[a]	87.5	91.7	91.7	95.8
Maternal Mortality	0	1	0	0
Delivered Early/Aborted	0	0	0	0
Gravid Uterine Wt (g)	97.6	107.3	95.3	101.4
Corpora Lutea/Dam	14.3	16.5	14.8	15.3
Implantation/Dam	13.3	15.2	13.6	14.0
Preimplantaion Loss (mean %)	7.5	8.0	9.0	10.2
Postimplantaion Loss (mean %)	3.9	4.7	8.7	2.9
Total Live Fetuses	268	321	279	312
Live Fetuses/Litter	12.8	14.6	12.7	13.6
Mean Fetal Weight (g)	5.5	5.4	5.3	5.6
Sex Ratio (% Male)	50.4	49.8	44.1	51.6
Total Dead Fetuses	0	1	0	0
Dams With All Resorptions	0	0	0	0
Resorptions/Dam				
Early Resorptions	0.6	0.5	1.0	0.4
Late Resorptions	0.0	0.0	0.0	0.0

Data taken from Tables 5, 6, and 7, pp. 41, 43-45, and 47, respectively, MRID 44929510.
[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 these findings is given in Table 4.

1. External examination

The number of fetuses(litters) examined for external malformations/variations in the 0, 10, 100, and 1000 mg/kg/day groups was 268(21), 321(22), 279(22), and 312(23), respectively. A protruding tongue was seen in one control fetus. One low-dose litter

contained a fetus with a position anomaly of the hindlimb and another fetus with generalized edema.

2. Visceral examination

The number of fetuses(litters) examined for visceral malformations/variations in the 0, 10, 100, and 1000 mg/kg/day groups was 129(21), 153(22), 135(22), and 150(23), respectively. Anomalies such as hypertrophy of the left heart ventricle, renal pelvic dilatation, blood stained fluid in the abdominal cavity, enlarged thymus, and accessory lobulets on the liver were seen in one to two fetuses per group including controls.

3. Skeletal examination

The number of fetuses(litters) examined for skeletal malformations/variations in the 0, 10, 100, and 1000 mg/kg/day groups was 139(21), 167(22), 144(22), and 162(23), respectively. 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.

TABLE 4: Fetal external, visceral, and skeletal observations (no. fetuses [no. litters] affected)

Observation	0 mg/kg/day	10 mg/kg/day	100 mg/kg/day	1000 mg/kg/day
External				
Total external findings	1 (1)	2 (1)	0 (0)	0 (0)
Visceral				
Total visceral findings	4 (3)	1 (1)	2 (2)	2 (2)
Enlarged thymus	1 (1)	0 (0)	1 (1)	1 (1)
Hypertrophy left ventricle	1 (1)	0 (0)	0 (0)	0 (0)
Blood stained fluid in abdominal cavity	0 (0)	0 (0)	0 (0)	1 (1)
Renal pelvic dilatation	0 (0)	1 (1)	0 (0)	0 (0)
Accessory liver lobulet	2 (2)	0 (0)	1 (1)	0 (0)
Skeletal				
Total skeletal malformations	0 (0)	0 (0)	0 (0)	0 (0)
Total skeletal anomalies	5 (5)	2 (2)	7 (7)	7 (6)
Total skeletal variations	139 (21)	167 (22)	144 (22)	162 (23)

Data taken from Tables 9, 10, and 14, pp. 51-52, 54-55, and 78, respectively, MRID 44931710.

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III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS

The study author concluded that CGA 51202 Technical resulted in maternal toxicity as evidenced by reduced food consumption in the 1000 mg/kg/day group on GD 6-11. The maternal toxicity NOEL was 100 mg/kg/day.

No test article related effects in the reproductive parameters were noted. No evidence of a "teratogenic potential" was apparent. Therefore, the developmental toxicity NOEL 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 and body weight gains were similar between the treated and control groups. The lower food consumption by the high-dose group during GD 6-11 was within 9% of the control level, was not accompanied by reductions in body weight gains by these dams, was not dose-related, and is not considered to be biologically significant. Therefore, the transient reduction in food consumption by the high-dose dams is not considered by the reviewer to be an adverse affect of treatment.

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. The only major malformation described was generalized edema in one low-dose fetus.

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

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.

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.