OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SEP FS 361

REVIEWER

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

009509

MAY 20 1992

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Rat teratology study with metolachlor. EPA Pesticide Chemical Code 108801, Toxicology Chemical Code 188DD, HED Project No. 2-1738.

TO: George Ghali, Ph.D.
RfD/Mini Peer Review Committee
SACB/HED (H7509C)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/8/92
Senior Pharmacologist, Review Section I
Toxicology Branch II/HED (H7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y.M. Ioannou 5/11/92
Section Head, Review Section I
and
Marcia van Gemert, Ph.D. Marcia van Gemert 5/18/92
Branch Chief, Toxicology Branch II
Health Effects Division (H7509C)

Action Requested: The HED-RfD Peer Review Committee requested the review of a previously unreviewed rat teratology study with metolachlor (Embryo/Fetal Toxicity and Teratogenic Potential Study of CGA-24705 (FL-841697) Administered Orally via Gavage to Crl:COBS®CD®(SD)BR Presumed Pregnant Rats, Argus Project 203-004, August 6, 1985, MRID # 00151941).

Conclusions: CGA-24705 was administered by oral gavage to pregnant Crl:COBS®CD®(SD)BR rats from Charles River Kingston Breeding Laboratories, Inc. at dose levels of 0, 30, 100, 300, or 1000 mg/kg/day. Maternal toxicity was noted in the high dose in the form of deaths, increased incidence of clinical signs, lower body weight gains and decreased food consumption. Developmental toxicity was noted in the high dose group as reduced number of implantations per dam, with a resulting reduced litter size, a slight increase in resorptions per dam and the resultant slight increase in postimplantation loss. Also, a statistically significant decrease in mean fetal body weight was noted in the high dose group.

Core Classification: Core Minimum Data.

Maternal NOEL = 300 mg/kg/day
Maternal LOEL = 1000 mg/kg/day
Developmental Toxicity NOEL = 300 mg/kg/day
Developmental Toxicity LOEL = 1000 mg/kg/day

This study satisfies the guideline requirements (§83-3a) for a teratology study in rats.

Printed on Recycled Paper

000509

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C Dapson 5/8/92
Senior Pharmacologist, Review Section I, TB II/HED H7509C
Secondary Review by: Yinnakis M. Ioannou, Ph.D., D.A.B.T. JMI 5/8/92
Section Head, Review Section I, TB II/HED H7509C

DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity
Species: Rat Guideline: 83-3 a

EPA Identification No.s: EPA MRID No. 00151941
EPA Pesticide Chemical Code 108801
Toxicology Chemical Code 188DD
HED Project No. 2-1738

Test Material: CGA-24705 (Metolachlor, FL-841697), 96.4% a.i., a brown, slightly viscous liquid, Lot No. B-203-004-A

Sponsor: CIBA-GEIGY Corporation, CIBA-GEIGY Agricultural Division
P.O. Box 18300, Greensboro, North Carolina 27419

Testing Facility: Argus Research Laboratories, Inc.
935 Horsham Road
Horsham, Pennsylvania 19044

Title of Report: Embryo/Fetal Toxicity and Teratogenic Potential Study of CGA-24705 (FL-841697) Administered Orally via Gavage to Crl:COBS®CD®(SD)BR Presumed Pregnant Rats

Study Number(s): Argus Project 203-004

Author(s): Elizabeth A. Lochry, Ph.D.

Report Issued: August 6, 1985

Conclusions: CGA-24705 was administered by oral gavage to pregnant Crl:COBS®CD®(SD)BR rats from Charles River Kingston Breeding Laboratories, Inc. at dose levels of 0, 30, 100, 300, or 1000 mg/kg/day. Maternal toxicity was noted in the high dose in the form of deaths, increased incidence of clinical signs, lower body weight gains and decreased food consumption. Developmental toxicity was noted in the high dose group as reduced number of implantations per dam, with a resulting reduced litter size, a slight increase in resorptions per dam and the resultant slight increase in postimplantation loss. Also, a statistically significant decrease in mean fetal body weight was noted in the high dose group.

Core Classification: Core Minimum Data.

Maternal NOEL = 300 mg/kg/day
Maternal LOEL = 1000 mg/kg/day
Developmental Toxicity NOEL = 300 mg/kg/day
Developmental Toxicity LOEL = 1000 mg/kg/day

This study satisfies the guideline requirements (§83-3a) for a teratology study in rats.

2

A. Materials and Methods

A copy of the "materials and methods" section from the investigators report is appended.

Test Compound: Purity: 96.4 %
Density: not provided
Description: a brown, slightly viscous liquid
Lot No.: B-203-004-A
Receipt date: 2/14/85
Other provided information: supplier - CIBA-GEIGY
Contaminants: not provided

Vehicle(s): 0.5% w/v aqueous methyl cellulose, Sigma Chemical Company, Lot No. 14F-0544 and R.O water

Test Animal(s): Species: albino rat
Strain: Crl:COBS®CD®(SD)BR
Source: Charles River Kingston Breeding Laboratories, Inc. Kingston, New York
Age: 71 days at receipt
Body Weight: 204-277 g at start of study (148-250 g at receipt)
Males used: 73 days old at receipt, 240-338 g at receipt, at start of study - 100 days old and 351-554 g

B. Study Design

This study was designed to assess the developmental toxicity potential of CGA-24705 (metolachlor) when administered by oral gavage on gestation days 6 through 15, inclusive.

Mating Procedure

One male and 1 female were placed together in wire-bottomed cages. "Upon observation of either spermatozoa in a vaginal smear or a vaginal plug *in situ* or in the cage pan...", this was considered day 0 of gestation.

Animal Husbandry

Animals were kept under standard animal care conditions and received Certified Rodent Meal® #5002 (Ralston Purina) and processed local water (by automatic system) *ad libitum*.

3

Group Arrangement:

Test Group	Dose Level (mg/kg/day)	Number Assigned
Control	Vehicle	25
Low Dose	30	25
Low Mid Dose	100	25
High Mid Dose	300	25
High Dose	1000	25

Animals were randomized using computer-generated randomization by body weight.

Dose Administration:

All doses were administered in a volume of 10 ml/kg of body weight/day prepared weekly during the dosing period. The dosing solutions were analyzed for concentration and stability. Dosing was based on daily gestation day body weight. Dose levels were based on a pilot study (Argus Research Project 203-004P) where presumed pregnant rats received either 0, 30, 100, 300, or 1000 mg/kg/day by oral gavage for gestation days 6-15 inclusive. No other information on the pilot study was provided.

Observations

The animals were checked twice daily for "viability" and for "clinical signs and or general appearance" several times prior to study initiation, during the predosage period, several times a day during the dosing period (gestation days 6 to 15) and daily after the dosing period. The body weights were recorded 3 times prior to mating and then on a daily basis through gestation day 20. Food consumption was recorded for gestation day 0-6 and then daily from gestation days 6 through 20. All animals found dead were autopsied with pregnancy status determined and uterine contents recorded. Any gross lesions were retained for further examination if necessary.

Dams were sacrificed on day 20 of gestation. Examinations at sacrifice consisted of opening of the abdomen, examination of the uterus for pregnancy, number and placement of implantations, early and late resorptions, live and dead fetuses, and number of corpora lutea; any gross lesions were preserved for further examination if necessary.

Each fetus was weighted examined for sex and gross external observations. According to the investigators: "Approximately one-half of the fetuses in each litter were examined for soft tissue variations, using a modification of Wilson's sectioning technique. The remaining fetuses in each litter were eviscerated, cleared, stained with alizarin red-S and examined for skeletal variations."

Historical control data were provided to allow comparison with concurrent controls.

4

Statistical analysis

The following statistical analysis methods were employed (from the investigators report):

For all evaluations, the minimum level of statistical significance reported was $P \leq 0.05$.

Maternal physical sign data and maternal and fetal incidence data were analyzed using the variance test for homogeneity of the binomial distribution(5).

Maternal body weight and feed consumption data averages and litter averages for fetal body weight, fetal ossification sites, percent dead or resorbed conceptuses, percent male fetuses and percent fetuses with variations were analyzed using Bartlett's test of homogeneity of variances(6) and the Analysis of Variance(7). If the Analysis of Variance was significant and appropriate, i.e., it passed Bartlett's test, then Dunnett's test(8) was used to identify the statistical significance of individual groups. If the Analysis of Variance was not appropriate, the Kruskal-Wallis test(9) was used; in cases where statistical significance occurred, Dunn's method of multiple comparisons(10) was used to identify the statistical significance of individual groups.

These same tests were used to analyze the average maternal body weight change for days 16 to 17 through 20 of gestation because average maternal body weights significantly differed ($P \leq 0.05$ to $P \leq 0.01$) on day 16 of gestation.

The Analysis of Covariance(11) was used to evaluate maternal body weight change data for days 0 to 6 and 6 through 16 of gestation. This analysis was performed using day 0 as the covariate with days 6 and 20 and using day 6 as the covariate with days 7 through 16, 19 and 20 of gestation.

Count data obtained at Caesarean-sectioning were evaluated using the Kruskal-Wallis test(9); in cases where statistical significance occurred, Dunn's method of multiple comparisons(10) was used to identify the statistical significance of individual groups.

5

Compliance

A signed statement of Confidentiality Claims **was not** provided.

A signed Statement of compliance with EPA GLP's (two statements) was provided.

A signed Quality Assurance Statement was provided.

A signed Flagging Statement for Potential Adverse Effects under 40 CFR 158.34 **was not** provided. However, the study neither meets nor exceeds any of the applicable criteria.

6

B. Results

1. Maternal Toxicity:

Mortality

Four animals of the high dose group (1000 mg/kg/day) died on gestation days 7, 8, and 10 (2 rats), 3 of the animals were pregnant. The investigators noted: Clonic and/or tonic convulsions immediately.." prior to death. "The rats ...had excess salivation, urine-stained abdominal fur and/or excess lacrimation..." which they observed 1 or more days prior to death of the animal. They attributed the deaths to treatment with the test substance. No gross lesions were found. No other animals were reported to have died.

Clinical Observations

The following table presents the summary of selected clinical observations from gestation days 6 through 20.

Table 1
Clinical Signs (total incidence days/total # animals)[a]

Dose Group: Observation:	Control	LDT	LMDT	HMDT	HDT
Excess Salivation	0/0	0/0	0/0	61/16**	214**/25**
Urine-stained abdominal fur	0/0	0/0	0/0	0/0	140**/19**
Excess Lacrimation	0/0	0/0	0/0	0/0	21**/8**
Convulsions:					
Clonic/tonic	0/0	0/0	0/0	0/0	6**/6**
Clonic	0/0	0/0	0/0	0/0	5**/5**

** = $p < 0.01$ as compared to vehicle control
[a] = Data extracted from Report 203-004, Table 2.

As shown on Table 1, there is a treatment related increase in clinical observations of the 300 mg/kg/day dose group and above. Other clinical observations did not appear to be treatment related.

7

Body Weight

The investigators supplied the following group summary and individual animal data. The following table presents body weight gains.

Table II: Body Weight Gains (grams)[a]

Gest. Days:	0-6	6-16	16-20	0-20	6-20
Control	35.8	61.3	65.0	162.2	126.3
LDT	35.2	66.5	67.4	169.2	134.0
LMDT	35.3	59.4	67.2	161.9	126.6
HMDT	35.7	58.4	62.1	156.2	120.5
HDT	32.2	50.9*	60.4	142.1**	111.2*

* = $p < 0.05$; ** = $p < 0.01$; as compared to vehicle control
[a] = Data extracted from Report 203-004, Table 4.

Corrected body weight gains were not calculated. There is a lower body weight gain at the high dose as compared to the vehicle control for the dosing period, the days following dosing and for both combined entire gestation period and dosing plus post dosing periods.

Food Consumption

The investigators supplied the following group summary and individual animal data. The following table presents food consumption data for similar periods as for the body weight gains table above.

Table III: Food Consumption Data (g/kg bw/day)[a]

Gest. Days:	0-6	6-16	16-20	0-20	6-20
Control	93.2	85.9	77.0	81.0	82.0
LDT	89.0	85.5	76.9	79.5	81.8
LMDT	88.9	83.4	76.2	78.5	80.0
HMDT	87.4	83.2	77.3	78.3	80.1
HDT	88.7	81.4	81.5	78.5	79.8

[a] = Data extracted from Report 203-004, Table 5.

The above data show a decrease in food consumption at the high dose (not statistically significant; although the first few days of dosing had statistically significant decreases), during the dosing period with a rebound in food consumption in the days following dosing. Food efficiency was not calculated.

Gross Pathological Observations

No data were reported.

8

Cesarean Section Observations

Table V: Cesarean Section Observations[a]

Dose:	Control	LDT	LMDT	HMDT	HDT
#Animals Assigned	25	25	25	25	25
#Animals Mated	25	25	25	25	25
#Animals Pregnant	24	24	21	24	23
Pregnancy Rate (%)	96	96	84	96	92
Maternal Wastage					
#Died	0	0	0	0	3
#Died/pregnant	0	0	0	0	3
#Non pregnant	1	1	4	1	2
#Aborted	0	0	0	0	0
#Premature Del.	0	0	0	0	0
Total Litters avail.	24	24	21	24	20
Total Corpora Lutea[1]	408	403	360	393	314
Corpora Lutea/dam	17.0	16.8	17.1	16.4	15.7
Total Implantations[1]	379	381	330	370	291
Implantations/Dam	15.8	15.9	15.7	15.4	14.6
Total Live Fetuses	366	374	320	353	275
Live Fetuses/Dam	15.2	15.6	15.2	14.7	13.8
Total Resorptions[1]	13	7	10	17	16
Early	13	7	9	17	15
Late	0	0	1	0	1
Resorptions/Dam[1]	0.5	0.3	0.5	0.7	0.8
Total Dead Fetuses	0	0	0	0	0
Dead Fetuses/Dam	0	0	0	0	0
Mean Fetal Wgt(g)	3.46	3.48	3.47	3.41	3.32*
Preimplant.Loss(%)[2]	7.1	5.5	8.3	5.9	7.3
Postimplant.Loss(%)[2]	3.4	1.8	3.0	4.6	5.5
Sex Ratio (% Male)	51.7	49.8	46.7	52.8	50.1

* = $p < 0.05$ as compared to vehicle control
[1] = calculated by reviewer; [2] = calculated by reviewer from means
[a] = Data extracted from Report 203-004, Table 6 & 7.

The high dose group presented with reduced number of implantations per dam, with a resulting reduced litter size; although both were not statistically significant, there was also a slight increase in resorptions per dam with a resultant slight increase in postimplantation loss; again not statistically significant. However, there was a statistically significant decrease in mean fetal body weight.

2. Developmental Toxicity

External Examinations

Table VI: External Examinations[a]

	Control	LDT	LMDT	HMDT	HDT
#pups/litters examined	366/24	374/24	320/21	353/24	275/20
Observations[1]					
Exencephaly; ears: low set; tongue: protruding	0/0[2]	0/0	0/0	1/1[3]	0/0
Micrognathia	0/0	0/0	0/0	0/0	1/1
Body:					
Shortened; spina bifida	0/0	0/0	0/0	1/1[3]	0/0
Tail:					
Thread-like	0/0	0/0	1/1	0/0	0/0

[1] = some observations may be grouped together; [2] = fetal/litter incidence; [3] = same fetus
[a] = Data extracted from Report 203-004, Table 9.

External examination data showed no treatment related effects.

Visceral Examinations

Table VII: Visceral Examinations[a]

	Control	LDT	LMDT	HMDT	HDT
#pups/litters examined	177/24	182/24	156/21	170/24	132/20
Observations[1]					
Brain: Lateral and third ventricles					
Slight dilation	1/1	0/0	0/0	1/1	1/1
Hydrocephalus	1/1[3]	0/0	0/0	0/0	0/0
Lungs:					
Apical or cardial, lobe, agenesis	2/2	0/0	2/2	1/1	0/0
Cardiac lobe, reduced in size	0/0	1/1	1/1	0/0	0/0
Total incidences of reduced lung formation	2/2	1/1	2/3	1/1	0/0
Kidneys:					
Pelvis, slight to moderate dilation, unilateral or bilateral	3/4	1/1	1/1	1/1	2/2

[1] = some observations may be grouped together; [2] = fetal/litter incidence; [3] = same fetus
[a] = Data extracted from Report 203-004, Table 10.

Visceral examination data showed no treatment related effects.

10

Skeletal Examinations

Table VIII: Skeletal Examinations[a]

	Control	LDT	LMDT	HMDT	HDT
#pups/litters examined	189/24	192/24	164/21	183/24	143/20
Observations[1]					
Skull:					
Parietals, frontals, interparietals & supraoccipals, agenesis	0/0	0/0	0/0	1/1[3]	0/0
Nasals, shortened; mandibles, thickened, shortened & fused; sphenoid, contained a hole; tympanic bone, right, not ossified, unilateral	0/0	0/0	0/0	0/0	1/1[3]
Sphenoid, contained a hole	0/0	0/0	0/0	1/1[3]	0/0
Parietals, inc.oss.	1/1[3]	1/1	0/0	0/0	0/0
Vertebrae:					
Thoracic centra, one or more:					
Bifid	5/5[3]	3/3[3]	3/3	4/5[3]	1/1
Unilateral oss.	0/0	1/1[3]	0/0	1/1[3]	1/1[3]
Not ossified	0/0	1/1[3]	0/0	1/1[3]	1/1[3]
Asymmetric	0/0	1/1[3]	0/0	0/0	1/1[3]
Cervical, thoracic, lumbar & sacral arches, flattened	0/0	0/0	0/0	1/1[3]	0/0
Lumbar:					
3 centra bifid	0/0	0/0	0/0	1/1[3]	0/0
1 centrum asymm.	0/0	0/0	0/0	1/1[3]	0/0
Manubrium:					
Duplicated	1/1[3]	0/0	0/0	0/0	1/1[3]
Incompl.ossific.	1/1[3]	0/0	0/0	0/0	1/1[3]
Unilateral.oss.	0/0	0/0	0/0	1/1[3]	0/0
Sternebrae:					
Centra, duplicated & fused	1/1[3]	0/0	0/0	0/0	0/0
Inc.or not oss.	4/4[3]	2/2	2/2	3/3[3]	3/3[3]
Bifid	0/0	0/0	0/0	1/1[3]	0/0
Ribs:					
Fused	0/0	0/0	0/0	0/0	1/1[3]
Pelvis:					
Pubes, incompletely or not ossified, unilateral or bilateral	3/3[3]	1/1	0/0	2/2[3]	3/4[3]
Ischia, inc.oss.	0/0	0/0	0/0	0/0	2/2**[3]

*** = $p < 0.01$ as compared to vehicle control

[1] = some observations may be grouped together; [2] = fetal/litter incidences; [3] = part of multiple observations in some fetuses

[a] = Data extracted from Report 203-004, Table 11.

No treatment related effects were noted in skeletal variations.

C. Discussion/Conclusions

a. Maternal Toxicity: Maternal toxicity was noted in the high dose in the form of deaths (4 animals) related to treatment with the test article; increased clinical signs such as excess salivation and lacrimation, urine-stained abdominal fur, clonic/tonic and clonic convulsions; lower body weight gain for the dosing period, the days following dosing and for both combined entire gestation period and dosing plus post dosing periods; a decrease in food consumption (not statistically significant; although the first few days of dosing had statistically significant decreases), during the dosing period with a rebound in food consumption in the days following dosing.

b. Developmental Toxicity:

i. Deaths/Resorptions: The high dose group presented with reduced number of implantations per dam, with a resulting reduced litter size; although both were not statistically significant, there was also a slight increase in resorptions per dam with a resultant slight increase in postimplantation loss; again not statistically significant.

ii. Altered Growth: A statistically significant decrease in mean fetal body weight was noted in the high dose group.

iii. Developmental Anomalies:

No treatment related effects were noted.

iv. Malformations:

No treatment related effects were noted.

D. Study Deficiencies: No data were reported for gross pathological observations

E. Core Classification: Core Minimum Data.

Maternal NOEL = 300 mg/kg/day
Maternal LOEL = 1000 mg/kg/day
Developmental Toxicity NOEL = 300 mg/kg/day
Developmental Toxicity LOEL = 1000 mg/kg/day

This study satisfies the guideline requirements (§83-3a) for a teratology study in rats.

F. Risk Assessment: None at this time.

12

Page ___ is not included in this copy.

Pages 13 through 26 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.