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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

001051

Metolachlor Technical Prenatal Developmental Toxicity (Rabbit) (83-3b; OPPTS 870.3700)

Supplement to Document #001051- DER for MRID No.00041283: Prenatal Developmental Toxicity Study in Rabbits. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 7/10/01
Reregistration Branch I, Health Effects Division (7509C)

Branch Senior Scientist: Whang Phang, Ph.D. 7/26/01
Reregistration Branch I, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity - Rabbit
OPPTS Number: 870. 3700 OPP Guideline Number: 83-3b

PC CODE: 108801

TEST MATERIAL (PURITY): CGA-24705 (Metolachlor) (95.4% a.i.)

Chemical Name: 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl) acetamide

CITATION: Lightkep, G.E. (1980) Teratogenic Potential of CGA-24705 in New Zealand White Rabbits Segment II Evaluation. Argus Research Laboratories, Inc., Horsham, PA. Argus Project 203-001, July 16, 1980. MRID No. 00041283. Unpublished.

SPONSOR: CIBA-GEIGY Corporation

EXECUTIVE SUMMARY:

In a prenatal developmental toxicity study (MRID 00041283), CGA-24705 (metolachlor) (95.4% a.i.) in 0.75% aqueous hydroxy methylcellulose was administered by gavage (10 ml/kg) to 16 pregnant New Zealand White rabbits/group from gestation days (GD) 6 through 18, inclusive, at dose levels of 0, 36, 120 or 360 mg/kg/day. The animals were sacrificed on GD 30 and the fetuses examined for evidence of developmental effects.

One doe at 36 mg/kg/day and another at 360 mg/kg/day died on GDs 24 and 29, respectively. The cause of death in both animals was attributed to persistent anorexia. Two rabbits aborted, one at 120 mg/kg/day (GD 25) and another at 360 mg/kg/day (GD 17). The high-dose animal had persistent anorexia. One rabbit in each group delivered prior to GD 30; the control, low- and

high-dose animals on GD 29 and the mid-dose animal on GD 30. There was a treatment-related increase in the incidence of persistent anorexia in the does treated at 360 mg/kg/day, which was defined as less than one-half of the daily food allotment consumed. However, food consumption data were not provided to support this finding. There was a treatment-related decrease in body weight gain in the 360 mg/kg/day group for GD 6-18 (-0.16 kg vs +0.04 kg in controls; $p<0.01$) and GD 6-30 (-0.01kg vs +0.03 kg in controls). There was no treatment-related increase in gross pathological findings in maternal animals at necropsy.

No treatment-related increase in external, visceral or skeletal developmental effects was observed.

The maternal toxicity LOAEL was 360 mg/kg/day based on an increased incidence of clinical observations (persistent anorexia) and decreased body weight gain. The NOAEL was 120 mg/kg/day.

The developmental toxicity LOAEL was not established. The NOAEL was 360 mg/kg/day.

The study is classified as **Acceptable/guideline** and **satisfies** the guideline requirements for a prenatal developmental toxicity study in rabbits (83-3b; OPPTS 870.3700).

DER #6

Metolachlor: Developmental Toxicity Study in Rabbits
Ciba-Geigy Corporation. 1980. MRID No. 00041283. HED Doc. No. 001051, 010088

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 3/9/93
Senior Pharmacologist, Review Section I, TB II/HED H7509C
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Section Head, Review Section I, TB II/HED H7509C

DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity
Species: Rabbit Guideline: 83-3 b

EPA Identification No.s:
EPA MRID No. 00041283
EPA Pesticide Chemical Code 108801
Toxicology Chemical Code 188DD
DP Barcode: D182880

Test Material: CGA-24705, 95.4% a.i. (an odorless, colorless liquid)

Synonyms: Technical Metolachlor, FL-791174, 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl) acetamide

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: Teratogenic Potential of CGA-24705 in New Zealand White Rabbits Segment II Evaluation - Project 203-001

Study Number(s): Argus Project 203-001

Author(s): Gerald E. Lightkep

Report Issued: July 16, 1980

Conclusions: CGA-24705 was administered by oral gavage to pregnant New Zealand White Rabbits from Dutchland Lab. at dose levels of 0, 36, 120, and 360 mg/kg/day from gestation days 6 through 18 inclusive. Maternal Toxicity was noted in the high dose group in the form of an increase in clinical observations and lower body weight gain. No Developmental Toxicity was noted in the dose levels tested.
Core Classification: Core Minimum Data.

Maternal NOEL = 120 mg/kg/day
Maternal LOEL = 360 mg/kg/day
Developmental Toxicity NOEL => 360 mg/kg/day
Developmental Toxicity LOEL > 360 mg/kg/day
This study satisfies the guideline requirements (§83-3b) for a teratology study in rabbits.

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A. Materials and Methods

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

Test Compound: Purity: 95.4 %
Density: not provided
Description: an odorless, colorless liquid
Lot No.: not provided
Receipt date: not provided
Other provided information: supplier - CIBA-GEIGY
Contaminants: not provided

Vehicle(s): 0.75% aqueous hydroxy methyl cellulose K 4M Premium (METHOCEL™), Dow Chemical Company, Lot # MN112093K and MM042693K.

Test Animal(s): Species: New Zealand White Rabbit
Strain: DLI:NZW
Source: Dutchland Laboratories, Inc. Swampbridge Road, Box 139A, Denver, PA 17517
Age: 175 days at receipt
Body Weight: 3.15-5.60 kg at 179 days of age; at 191 days of age, start of study, 3.34-5.34 kg
Males used: 4 bucks, same source and strain

B. Study Design

This study was designed to assess the developmental toxicity potential of CGA-24705 (metolachlor) when administered to pregnant rabbits by oral gavage (stomach tube) on gestation days 6 through 18, inclusive.

Mating Procedure

Artificial insemination was used: "Following an acclimation interval of approximately one month, 64 female rabbits which appeared to be in good health were selected for study assignment. Female rabbits were intravenously administered 20 USP Units/kg of HCG [PREGNYL™] approximately three hours prior to insemination with an estimated 0.25 ml of semen which had been diluted with normal saline to a concentration of 6.0×10^6 spermatozoa/ml. The day of artificial insemination was designated day 0 of presumed gestation."

Animal Husbandry

Animals were kept under standard animal care conditions and received 160 grams of Certified Rabbit Chow™ #5322 (Ralston Purina) and processed local water (individual bottles) *ad libitum*.

Group Arrangement:

Test Group	Dose Level (mg/kg/day)	Number Assigned
Control	Vehicle	16
Low Dose	36	16
Mid Dose	120	16
High Dose	360	16

Animals were randomized using a table of random numbers made for body weights.

Dose Administration:

All doses were administered in a volume of 10 ml/kg of body weight/day prepared daily (from vehicle prepared every 2-3 days) during the dosing period. The investigators stated that: "CGA-24705 had been determined by the sponsor to be relatively stable for up to three years." This of course does not take into account whether the dosing mixtures are stable. Apparently the dosing solutions were not analyzed for concentration and stability. It was not stated if dosing was based on daily gestation day body weight. Treatment was administered during the same time period every dosing day. Dose levels were based on "...available LD50 data."

Observations

The animals were checked several times for "physical signs" and/or "general appearance" several times prior to study initiation and on gestation day 0. During the exposure period, the animals were checked several times daily for "physical signs of drug effect" and/or "viability", observations for "general health" and/or "signs of abortion" were done several times a day after the dosing period. The body weights were recorded several times prior to study initiation and on gestation day 0 and then on a daily basis through gestation day 30. Food consumption was not recorded. All animals found dead or requiring termination were autopsied with pregnancy status determined and uterine contents recorded. Any gross lesions were retained for further examination if necessary. Any fetuses obtained after 26 or more days of gestation were evaluated if possible.

Dams were sacrificed on day 30 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.

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Each fetus was weighed, examined for gross external observations, sacrificed, examined for visceral abnormalities excluding the brain then eviscerated, stained with alizarin red S and examined for skeletal abnormalities.

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

Statistical analysis

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

Maternal body weight data were analyzed using Bartlett's test of homogeneity of variances (5), an Analysis of Variance (6) and an Analysis of Covariance (7).

Data obtained at Caesarean-sectioning were evaluated using the Kruskal-Wallis test (8), Fisher's Exact test (9), the normal approximation to the binomial distribution (10), and the variance test for homogeneity of the binomial distribution (11).

Fetal body weights were analyzed using Bartlett's test of homogeneity of variances (5) and the Analysis of Variance (6).

Fetal anomaly data were analyzed using Fisher's Exact test (9), the normal approximation to the binomial distribution (10), and the variance test for homogeneity of the binomial distribution (11).

Ossification site data values were analyzed using Bartlett's test of homogeneity of variances (5) and the Analysis of Variance (6).

Compliance

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

A signed Statement of compliance with EPA GLP's **was not** provided.

A signed Quality Assurance Unit Final Report 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.

B. Results

1. Maternal Toxicity:

a. Mortality

No animals were reported to have died due to treatment. Two animals, one low dose (gestation day 24) and one high dose (gestation day 29) died during the study considered to be due to "prolonged anorexia."

b. Abortion

No abortions due to treatment were reported by the investigators. Two rabbits aborted, one mid dose (gestation day 25) and one high dose (gestation day 17). The high dose animal had "persistent anorexia."

c. Early Delivery

One rabbit in each treatment group delivered prior to gestation day 30. The control, low and high dose on gestation day 29; the mid dose on gestation day 30.

d. Clinical Observations

The following table presents the summary of selected clinical observations from gestation days 6 through 30.

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

Dose Group: Observation:	Control	LDT	MDT	HDT
Blood in pan	-	-	-	4/4
Anorexia	47/8	72/11	50/10	124/12
Pupils constricted	-	-	25/1	9/1
Excess lacrimation	-	-	25/1	9/1
Ptosis	-	-	1/1	2/2
Diarrhea	5/1	1/1	3/1	-

[a] = Data extracted from Report 203-001, Table 1.

As shown on Table 1, there was a treatment related increase in clinical observations in the 360 mg/kg/day dose group in the form of anorexia. This was described as less than 1/2 of the daily food allotment eaten; however, no food consumption data were provided to support this. Other clinical observations did not appear to be treatment related.

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e. 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 (kg)[a]

Gest. Days:	0-6	6-18	18-30[r]	0-30	6-30
Control	0.03	0.04	-0.04	0.06	0.03
LDT	0.02	0.03	0.03	0.07	0.04
MDT	0.03	0.02	0.18	0.21	0.15
HDT	0.05	-0.16**	0.16	0.05	-0.01

** = $p < 0.01$; as compared to vehicle control; [r] = calculated by reviewer
[a] = Data extracted from Report 203-001, Table 3.

Corrected body weight gains were not calculated. There was lower body weight gain at the high dose as compared to the vehicle control for the dosing period and for the combined dosing plus post dosing periods.

f. Food Consumption

Food consumption data were not provided.

g. Gross Pathological Observations

No treatment related observations were noted in the supplied data.

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h. Cesarean Section Observations

Table III: Cesarean Section Observations[a].

Dose:	Control	LDT	MDT	HDT
#Animals Assigned	16	16	16	16
#Animals Mated	16	16	16	16
#Animals Pregnant	14	14	13	14
Pregnancy Rate (%)	87.5	87.5	81.3	87.5
Maternal Wastage				
#Died	0	1	0	1
#Died/pregnant	0	1	0	1
#Non pregnant	2	2	3	2
#Aborted	0	0	1	1
#Premature Delivery	1	1	1	1
Total Litters available	13	12	11	11
Total Corpora Lutea[1]	136	136	117	124
Corpora Lutea/dam	11.2	11.3	10.6	10.3
Total Implantations[1]	84	99	81	71
Implantations/Dam	6.5	8.2	7.4	6.3
Total Live Fetuses	75	83	72	62
Live Fetuses/Dam	5.8	7.0	6.5	5.6
Total Resorptions[1]	6	15	9	8
Early	6	13	9	7
Late	0	2	0	1
Resorptions/Dam	0.5	1.2	0.8	0.7
Dams w/ total resorptions	0	0	0	1
Total Dead Fetuses	1	1	0	0
Dead Fetuses/Dam	0.1	0.1	0	0
Mean Fetal Wgt(g)	53.0	48.9	53.3	52.1
Preimplantation Loss(%)[2]	38.2	27.2	30.8	42.7
Postimplantation Loss(%)[2]	10.7	16.2	11.1	12.7
Sex Ratio (% Male)	49.33	55.42	56.94	48.39

[1] = calculated by reviewer; [2] = calculated by reviewer from means

[a] = Data extracted from Report 203-001, Tables 5, 6 & 7.

No treatment related effects were noted in the above data.

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2. Developmental Toxicity

a. External Examinations

Table IV: External Examinations[a]

	Control	LDT	MDT	HDT
#pups/litters examined	83/14	92/13	78/12	65/12
Observations[1]				
Spina bifida	1/1[2]	0/0	0/0	0/0
Small body size	3/1	0/0	1/1	0/0
Protruding tongue	1/1	0/0	0/0	0/0
Disarthrosis, forlimbs, digits flexed	0/0	0/0	1/1	0/0
Multiple developmental anomalies of genetic origin	0/0	0/0	1/1	0/0
Hydrocephalus w/small exencephaly	0/0	0/0	0/0	2/1
Lived less than 15 min.	1/1	0/0	0/0	1/1

[1] = some observations may be grouped together; [2] = fetal/litter incidence
[a] = Data extracted from Report 203-001, Table 11.

No treatment related external examination anomalies were noted in the data provided.

b. Visceral Examinations

Table V: Visceral Examinations[a]

	Control	LDT	MDT	HDT
#pups/litters examined	82/14	87/13	78/12	64/12
Observations[1]				
Accessory spleen	1/1[2]	0/0	0/0	0/0
Multiple developmental anomalies of genetic origin	0/0	0/0	1/1	0/0

[1] = some observations may be grouped together; [2] = fetal/litter incidence
[a] = Data extracted from Report 203-001, Table 12.

Visceral examination data showed no treatment related effects.

c. Skeletal Examinations

Table VI: Skeletal Examinations[a]

	Control	LDT	MDT	HDT
#pups/litters examined	83/14	93/13	78/12	65/12
Observations[1]				
Limbs flexed	0/0[2]	0/0	1/1	0/0
Vertebrae; 2 or more fused	3/1	1/1	1/1	1/1
Ribs:				
2 fused	0/0	1/1	0/0	0/0
Localized thickened areas	0/0	1/1	0/0	0/0
Sternebrae:				
2 or more fused	0/0	1/1	1/1	0/0
1 or more asymmetric	3/3	1/1	2/2	1/1
Manubrium incompletely ossif.	0/0	0/0	0/0	1/1
Xiphoid:				
incompletely ossified	3/2	0/0	4/3	3/3
not ossified	0/0	0/0	1/1	0/0
Clavicle; localized thickened areas	0/0	1/1	0/0	0/0
Pelvis; pubic bones incomplete ossification	0/0	1/1	0/0	0/0
Multiple developmental anomalies of genetic origin	0/0	0/0	1/1	0/0

[1] = some observations may be grouped together; [2] = fetal/litter incidence
[a] = Data extracted from Report 203-001, Table 13.

No treatment related effects were noted in skeletal variations.

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C. Discussion/Conclusions

a. Maternal Toxicity: Maternal toxicity was noted in the high dose in the form of an increase in clinical observations. The 360 mg/kg/day dose group had "anorexia", this was described as less than 1/2 of the daily food allotment eaten; however, no food consumption data were provided to support this. Other clinical observations did not appear to be treatment related. There was also lower body weight gain at the high dose as compared to the vehicle control for the dosing period and for the combined dosing plus post dosing periods.

b. Developmental Toxicity:

i. Deaths/Resorptions:

No treatment related effects were noted.

ii. Altered Growth:

No treatment related effects were noted.

iii. Developmental Anomalies:

No treatment related effects were noted.

iv. Malformations:

No treatment related effects were noted.

D. Study Deficiencies: The brains of the fetuses were apparently not examined for possible defects. No data were reported for support of reduced food consumption as part of the clinical observations

E. Core Classification: Core Minimum Data.

Maternal NOEL = 120 mg/kg/day
Maternal LOEL = 360 mg/kg/day
Developmental Toxicity NOEL => 360 mg/kg/day
Developmental Toxicity LOEL > 360 mg/kg/day

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

F. Risk Assessment: None at this time.

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