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

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MAR 17 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Metolachlor: Rereview of chronic dog study, 2-generation reproduction study, and rabbit developmental toxicity (teratology) study.
DP Barcode 182880; MRID No's. 409807-01,411645-01, 422186-01, 422186-02, 00080897, 00041283; EPA Pesticide Chemical Code 108801; Toxicology Chemical Number 188DD.

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

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 3/11/93
Senior Pharmacologist, Review Section I
Toxicology Branch II/HED (H7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y.M. Ioannou 3/11/93
Section Head, Review Section I
and
Marcia van Gemert, Ph.D.
Branch Chief, Toxicology Branch II Marcia van Gemert 3/12/93
Health Effects Division (H7509C)

Action Requested: The HED-RfD Peer Review Committee requested the rereview of a previously reviewed chronic dog study, 2-generation reproduction study, and rabbit developmental toxicity (teratology) study with metolachlor.

Conclusions:

For the study: "Metolachlor Technical, 13/52-Week Oral Toxicity Study in Dogs" (Ciba-Geigy Corporation, Study No. 862253, MRID No's. 409807-01, 411645-01, 422186-01 and 422186-02, 1/23/89), a table of food efficiency data for the study is attached. The following are the conclusions from the original review, no changes were made:

> Metolachlor was fed to male and female dogs at dietary levels of 0, 100, 300, or 1000 ppm for 13 or 52 weeks. The mean daily compound intake for male dogs receiving 100, 300, and 1000 ppm was 3.5, 9.7, and 32.7 mg/kg/day, respectively, and the doses for females receiving the same dietary levels were 3.6, 9.7, and 33.0 mg/kg/day, respectively. A decrease in body weight gain (compared with controls) was noted in the

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high-dose males and females at week 13 and in high dose females at week 52. Transient reductions in food consumption were noted at several time points during the treatment period, but the reductions were not considered to be of toxicological significance. A treatment-related increase in mean alkaline phosphatase activity was seen in the high-dose males and females at weeks 12, 26, 40, and 52. There was no effect of treatment on organ weights, mortality, ophthalmology, hematology, gross pathology, or histopathology. The systemic NOEL for male dogs is 300 ppm (9.7 mg/kg/day) and the LOEL is 1000 ppm (32.7 mg/kg/day) based on the increase in alkaline phosphatase activity. The systemic NOEL for female dogs is 300 ppm (9.7 mg/kg/day) and the LOEL is 1000 ppm (33 mg/kg/day) based on decreased body weight gains.

This study is classified as Core-Guideline Data and satisfies the guideline requirement (§83-1(b)) for a chronic toxicity study in dogs.

For the study: "Two-Generation Reproduction Study in Albino Rats with Metolachlor Technical" (Toxigenics, Inc. for Ciba-Geigy Corp., Study Number 450-0272, 8/31/81, MRID No. 00080897) the following are the conclusions from the review:

Metolachlor Technical, 94.5% a.i., was administered in the diet to two consecutive generations of male and female CD strain albino rats at dosage levels of 0, 30, 300 and 1000 ppm. There was no evidence of treatment-related effects on clinical parameters, reproductive indices, progeny indices or post-mortem findings for the F_0 generation. The 1000 ppm group of the F_{1A} litter did have statistically significant decreases in body weight on day 14 and 21 of lactation. A decrease in food consumption in the 1000 ppm group females was observed in the F_1 parental animals; body weight and body weight gain were unaffected. Reproductive and progeny indices of the treated animals in this generation were comparable to the controls. The 1000 ppm group of the F_{2A} litter had statistically significant decreases in body weight on days 4, 7, 14 and 21 of lactation. There was no evidence of a treatment-related effect on the necropsy findings of either the F_1 parental animals or the F_{2A} litter. Based on the absence of clinical signs of maternal toxicity, the **systemic NOEL is ≥ 1000 ppm; the LEL is > 1000 ppm.** Based on the reduction in body weight of the progeny in both the F_{1A} and F_{2A} litters, the **reproductive NOEL is 300 ppm; the LEL is 1000 ppm.**

The study is classified as Core-Guideline Data and satisfies the guideline requirements (§83-4) for a multigeneration reproduction study in rats. 2

For the study: "Teratogenic Potential of CGA-24705 in New Zealand White Rabbits Segment II Evaluation - Project 203-001" (Argus Research Laboratories, Inc. for Ciba-Geigy Corp., Argus Project 203-001, MRID No. 00041283) the following are the conclusions from the review:

> 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.

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

The study is classified as Core Minimum Data and satisfies the guideline requirements (§83-3b) for a developmental toxicity (teratology) study in rabbits.

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Metolachor Technical, 13/52-Week Oral Toxicity Study in Dogs (Ciba-Geigy Corp. Study # 862253, 1/23/90 MRID # 409807-01, 411645-01, 422186-01, 422186-02).

Food Efficiency Data (%)

Week:	13	28	48	52
Dose (ppm)				
		Males		
Control	6.2	3.0		2.2
100	8.4	4.8		3.1
300	8.9	3.6		2.3
1000	6.7	4.2		2.6
		Females		
Control	7.0	3.7	2.5	2.4
100	7.2	4.1	2.6	2.4
300	7.2	3.7	3.1	2.6
1000	5.5	3.6	2.1	2.0

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 3/3/93
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Stephen Dapson, Ph.D. Stephen C. Dapson 3/5/93
Section I, Toxicology Branch II (H7509C)

DATA EVALUATION RECORD

STUDY TYPE: Multigeneration Reproduction/Rat (Guideline 83-4)

P. C. CODE: 108801

TEST MATERIAL: Metolachlor Technical, 95.4% a.i.

STUDY NUMBER: 450-0272 MRID # 00080897

TESTING FACILITY: Toxigenics, Inc.
Decatur, IL

SPONSOR: Ciba-Geigy Corporation
Greensboro, NC

TITLE OF REPORT: Two-Generation Reproduction Study in Albino Rats with Metolachlor Technical

AUTHOR(S): John G. Page, Ph.D., D.A.B.T.

REPORT ISSUED: August 31, 1981

CONCLUSIONS: Metolachlor Technical, 95.4% a.i., was administered in the diet to two consecutive generations of male and female CD strain albino rats at dosage levels of 0, 30, 300 and 1000 ppm (see page 11 of DER for mean mg/kg/day intake for each dosage level for each generation for each sex). There was no evidence of treatment-related effects on the clinical parameters, reproductive indices, progeny indices or post-mortem findings for the F_0 generation. The 1000 ppm group of the F_{1A} litter did have statistically significant decreases in body weight on days 14 and 21 of lactation. A decrease in food consumption in the 1000 ppm group females was observed in the F_1 parental animals; body weight and body weight gain were not affected. Reproductive and progeny indices of the treated animals in this generation were comparable to the controls. The 1000 ppm group of the F_{2A} litter had statistically significant decreases in body weight on days 4, 7, 14 and 21 of lactation. There was no evidence of a treatment-related effect on the necropsy findings of either the F_1 parental animals or

the F_{2A} litter. Based on the absence of clinical signs of maternal toxicity, the **systemic NOEL is ≥ 1000ppm; the LEL is > 1000 ppm.** Based on the reduction in body weight of the progeny in both the F_{1A} and F_{2A} litters, the **reproductive NOEL is 300 ppm ; the LEL is 1000 ppm.**

CLASSIFICATION: Guideline - This study satisfies the guideline requirements (83-4) for a multigeneration reproduction study in rats.

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I. MATERIALS AND METHODS

A. Materials

1. Test Compound

   Purity: 95.4% a.i.
   Description: Not stated
   Lot Number: FL-800362, code 36083

2. Test Species: 21-day old male and female CD strain of albino rats were obtained for the first parental generation of the study from Charles River Breeding Laboratories, Portage, MI. The rats were acclimated for a period of 10 days before they were placed into the study. During this period, they were group housed. For the remainder of the study, they were housed individually in stainless steel, wire-bottom cages in rooms where the temperature and humidity levels ranged from 60 to 82° and 38 to 82%, respectively, and there was a 12 hour light/dark cycle. Food (Certified Purina Rodent Chow #5002) and water were provided *ad libitum*.

3. Diet Preparation: Diets containing the test article were prepared weekly and stored under refrigeration. Fresh diets were offered to the animals daily. The diets were analyzed for homogeneity and chemical stability prior to the initiation of the study. The percent of metolachlor in the diets was determined prior to the initiation of the study and then at three-month intervals.

B. Procedures and Study Design

1. Mating: 15 males were caged with 30 females from the same test group until a copulatory plug in the vagina or sperm positive results of vaginal smears were observed. "Polygamous cohabitation was employed (1 male: 2 females, when possible) with the animal pairings conducted randomly employing computer generated male/female random assignments within the treatment groups. Males were rotated among the females at 5 day intervals. Each female was paired with a maximum of 3 different males." Mating trials were continued for 15 days. After successful mating, each pregnant female was individually placed into a cage with a solid bottom and bedding where they were kept through gestation and lactation. Nesting material was provided from approximately the fifteenth day of gestation until the progeny were seven days old. Litters were weaned at 21 days of age.

2. Mating Schedule: The F_0 parental animals were given test diets for 14 weeks before they were mated, and the F_1 parental animals were not mated until 17 weeks after they were selected

from the F_{1A} litters. On day 4 of lactation of the F_1 generation, the litters were standardized to 10 pups; 15 males and 30 females were then randomly selected from each treatment group to serve as F_1 parents. (See attached Flow Chart from the study report.)

3. Animal Assignment: F_0 animals were randomly assigned to test groups as follows:

Test groups No.	Designation	Dose (ppm)*	Animals per group** Males	Females
VC	Control	None	15	30
T-I	Low (LDT)	30	15	30
T-II	Mid	300	15	30
T-III	High (HDT)	1,000	15	30

* Diets were administered from the beginning of the study until the animals were sacrificed.

** The same number of animals were picked from the F_1 litters as parents for the F_2 generation.

C. Observation Schedule

1. Parental Animals: Observations and the schedule for those observations is summarized from the report as follows:

Type of observation	Number of animals per sex per group	Frequency
Mortality and signs of toxicity	All	Twice daily during premating and growth periods
Detailed clinical observations	All	Once a week during growth and breeding periods
Body weight	All	Weekly during the premating period
	Maternal animals	Days 0, 6, 15 and 20 of gestation; days 0, 4, 7, 14 and 21 of lactation and at sacrifice
	Paternal animals	Monthly until sacrifice
Food consumption	All	Weekly during the premating period

2. Reproductive Performance: Parental reproductive performance was assessed from breeding and parturition records of animals in the study. A mating was successful if a copulatory plug was

observed or the presence of sperm was detected in vaginal smears.

The following indices were calculated:

$$\text{Mating Index} = \frac{\text{Number of Copulations}}{\text{Number of Estrus Cycles* Utilized}} \times 100$$

$$\text{Fertility Index} = \frac{\text{Number of Pregnancies}}{\text{Number of Copulations}} \times 100$$

$$\text{Gestation Index} = \frac{\text{Number of Parturitions}}{\text{Number of Pregnancies}} \times 100$$

$$\text{Female Fertility Index} = \frac{\text{Number of Pregnancies}}{\text{Number of Females Mated}} \times 100$$

$$\text{Male Fertility Index} = \frac{\text{Number of Sires}}{\text{Number of Males Mated}} \times 100$$

* Five days equals 1 estrus cycle

3. Litter Observations: According to the report, the following litter observations were made:

	Time of observation (lactation day)				
Observation	Birth	Day 4	Day 7	Day 14	Day 21
Number of pups delivered	X				
Number of live pups	X				
Number stillborn	X				
Number cannibalized	X				
Pup weight	X	X	X	X	X
Developmental abnormalities	X				X

Dead pups were examined grossly for external and internal abnormalities, and a possible cause of death was determined for pups born or found dead.

The following indices were calculated:

$$\text{Born Viable (Live Birth Index)} = \frac{\text{No. of Pups Delivered Viable}}{\text{Total No. of Pups Delivered}} \times 100$$

$$\text{Born Dead} = \frac{\text{No. of Stillbirths}}{\text{Total No. of Pups Delivered}} \times 100$$

$$\text{Born \& Cannibalized} = \frac{\text{No. of Pups Partially Cannibalized at Birth}}{\text{Total No. of Pups Delivered}} \times 100$$

$$\text{1 Day} = \frac{\text{No. of Pups Viable at Lactation Day 1}}{\text{No. of Pups Born Viable}} \times 100$$

4 Day (Viability Index)	=	No. of Pups Viable at Lactation Day 4 / No. of Pups Born Viable X 100
7 Day	=	No. of Pups Viable at Lactation Day 7 / No. of Pups Retained at Lactation Day 4 X 100
14 Day	=	No. of Pups Viable at Lactation Day 14 / No. of Pups Retained at Lactation Day 4 X 100
21 Day (Weaning Index)	=	No. of Pups Viable at Lactation Day 21 / No. of Pups Retained at Lactation Day 4 X 100

4. Necropsy

a. Parental Animals: The F_0 parental males were sacrificed at 167 days of age; the females were sacrificed at 196 days of age (after the last litter was weaned). These animals were subjected to post mortem examinations as follows:

Animals Examined	Macroscopic	Microscopic
Found dead	X	X
Unscheduled sacrifice	X	X
Scheduled sacrifice (males)	X	testes & abnormal organs
Scheduled sacrifice (females)	X (if abnormal)	X (if abnormal)
	sacrificed and discarded if normal	

b. Offspring: The F_1 parental males were sacrificed at 157 to 167 days of age; the parental females were 197 to 208 days. The F_2 offspring were sacrificed at weaning. These animals were subjected to post mortem examinations as follows:

Animals Examined	Macroscopic	Microscopic
Found dead	X	X
F_1 (scheduled sacrifice)	X	X
F_2 (5 males & 5 females from each treatment group at scheduled sacrifice)	X	X

c. Necropsy Observations: "The necropsy included examination of the external body surface and all orifices; cranial cavity, external and cut surfaces of the brain and spinal cord; thoracic, abdominal and pelvic cavities and their viscera; cervical tissues and organs; and the carcass."

The following checked tissues of those required by EPA guidelines were prepared for microscopic examination.

X Ovaries	X Epididymides
X Uterus	X Prostate
X Unusual lesions	___Seminal vesicles
X Vagina/cervix	X Testes

Additional tissues prepared for microscopic examination included the following:

adrenals	pituitary
aorta	salivary gland
bone (with marrow)	sciatic nerve
brain (3 levels)	skeletal muscle
esophagus	skin
eyes	small intestine
heart	spinal cord (2 levels)
kidneys	spleen
large intestine	stomach
liver (2 lobes)	trachea
lung (with mainstem bronchi)	thymus
lymph nodes (mesenteric)	thyroid (with parathyroid)
lymph nodes (non-mesenteric)	urinary bladder
mammary gland	
pancreas	

D. Data Analyses

1. Statistical Analyses: The study report states, "Quantitative continuous variables, i.e., body weights, food consumption, were analyzed by Analysis of Variance with significant differences described by that treatment further studied by multiple comparison (Tukey's or Scheffe's, dependent upon "N" values). Organ weight ratios were studied employing Kruskal-Wallis analyses. Chi-Square analysis was performed where appropriate."

2. Compliance: Signed statements of Quality Assurance and compliance with the Good Laboratory Practices regulations were submitted by the testing facility.

II. REPORTED RESULTS

A. Analysis of Test Diets: The mean and range of values for the concentrations of metolachlor in the test diets for each group are as follows:

Theoretical conc.	Mean (ppm)	Range (ppm)
30 ppm	32	26.2 - 39.3
300 ppm	294	239 - 324
1,000 ppm	959	774 - 1030

The diet was analyzed for homogeneity at three time periods, five days apart, prior to the initiation of the study. It was also analyzed for stability at 0, 7 and 14 days after preparation. The data from these analyses have been presented but the study report draws no conclusions about either homogeneity or stability. On examination of the data, the concentrations of metolachlor appear to be homogeneous and stable after 14 days.

B. Parental Animals

1. Mortality and clinical signs: The F_0 males and females were exposed to the test substance for 135 and 164 days, respectively. No deaths occurred prior to sacrifice. The F_1 males and females were 157-167 and 197-208 days old, respectively, at the time of sacrifice. All of the F_1 males survived to the final sacrifice. Two of the F_1 females died during the pre-mating period, one (300 ppm) at 32 days of age and the other (1000 ppm) at 52 days. One female in the 300 ppm group was found dead on gestation day 19 at 170 days of age and another in the control group was sacrificed in a moribund condition on lactation day 1 at 170 days of age. The cause of death of these animals is discussed under Pathology.

There were no clinical signs attributable to the test material in either the F_0 or F_1 generations. Table 9: Summary of Antemortem Observations from the study report is attached to the DER.

2. Body weight and food consumption: Food consumption was comparable between the treated and control groups of the F_0 generation. For the F_1 treated males, there was one statistically significant decrease in food consumption in the 1000 ppm group during week 6. For the F_1 treated females, there were reductions for the 30 ppm group (week 16), the 300 ppm group (weeks 6, 7, and 10) and the 1000 ppm group (weeks 1, 6, 7, 8, 10, 12, 13 and 15). Body weight and body weight gain of the treated animals were comparable to the control animals except for a statistically significant decrease in body weight in the 1000 ppm males and an increase in the 30 ppm females of the F_1 generation during Week 0. Reported body weight, body weight gain and selected food consumption results are summarized as follows:

Observation and study week	Dose Group (ppm) 0	30	300	1000
F_0 Generation Males - Pre-mating				
Mean body weight (g)				
0	127.0	126.8	126.6	126.9
14	494.2	482.8	493.0	489.7
Pre-mating mean weight gain (g)				
0-14	367.2	356.0	366.4	362.8
Mean food consumption (g/rat/day)				
week 1	21.3	22.1	21.4	20.4
week 8	27.1	27.3	27.9	26.5
week 14	25.7	27.1	27.5	26.1
F_0 Generation Females - Premating				
Mean body weight (g)				
0	110.4	110.2	110.4	110.3
14	274.4	273.0	277.7	268.2
Pre-mating mean weight gain (g)				
0-14	164.0	162.8	167.3	157.9
Mean food consumption (g/rat/day)				
week 1	17.6	17.9	17.8	16.6
week 8	19.2	19.1	18.5	18.4
week 14	19.4	19.3	19.2	18.0
F_1 Generation Males - Pre-mating				
Mean body weight (g)				
0	48.1	44.2	47.4	41.1*
17	543.2	492.4	540.2	502.0
Pre-mating mean weight gain (g)				
0-17	495.2	448.2	492.8	460.8
Mean food consumption (g/rat/day)				
week 1	13.5	13.0	13.3	12.3
week 8	25.4	25.2	27.8	24.6
week 17	24.0	23.1	24.9	22.2

Observation and Study Week	Dose Group (ppm) 0	30	300	1000
F_1 Generation Females - Pre-mating				
Mean body weight (g)				
0	42.6	46.5*	42.7	40.9
17	287.2	277.0	278.1	270.1
Pre-mating mean weight gain (g)				
0-17	244.6	230.5	235.4	229.2
Mean food consumption (g/rat/day)				
week 1	11.8	11.7	10.9	10.6*
week 8	18.8	18.2	17.9	16.5**
week 15	17.5	16.7	16.4	15.7*
week 17	15.9	15.9	16.4	15.0

* statistically significant differences at $p < .05$
** statistically significant differences at $p < .01$
extracted from Tables 4 and 7 of the study report

Selected group mean body weights for pregnant or nursing dams were summarized in the report as follows:

Observation and study time	Dose Group (ppm) 0	30	300	1000
F_0 Generation - F_{1A} Litter				
Mean body weight (g)				
Gestation day 0	280.	274.	282.	268.
Gestation day 20	394.	384.	399.	386.
Lactation day 0	308.	301.	315.	297.
Lactation day 21	336.	321.	333.	323.
Mean body weight gain (g)				
Gestation days 0-20	114	110	117	118
Lactation days 0-21	28	20	18	26
F_1 Generation - F_{2A} Litter				
Mean body weight (g)				
Gestation day 0	285.	278.	275.	271.
Gestation day 20	392.	382.	395.	381.
Lactation day 0	314.	300.	310.	297.
Lactation day 21	318.	320.	332.	327.
Mean body weight gain (g)				
Gestation days 0-20	107	104	120	110
Lactation days 0-21	4	20	15	30

extracted from Table 5 of the study report.

3. Test Substance Intake: The study report (page 42) states, "The mean total amount of test article consumed per animal per test

group was calculated employing the pre-mating period food consumption determinations. The total amount of feed consumed was estimated by determining the average daily food consumption during the periods of food intake measurements and multiplying this figure by the total number of days the animals were offered the test diets." The doses expressed as mg test substance/kg body weight were as follows during the pre-mating period:

	Dose Levels (mg/kg/day)					
		Males (ppm)			Females (ppm)	
Week	30	300	1000	30	300	1000
		F_0 Generation				
1	5.0	47.9	152.6	4.7	46.5	145.4
5	2.4	24.3	76.7	2.6	26.7	86.7
10	1.8	17.7	54.9	2.3	21.3	71.5
15	1.7	15.9	50.8	1.9	19.5	63.7
		F_1 Generation				
1	4.8	50.6	163.6	4.7	47.7	155.5
5	2.8	29.4	96.6	3.1	31.5	104.4
10	1.8	18.1	57.8	2.2	19.8	69.8
17	1.4	13.8	44.3	1.7	17.8	55.6

extracted from Table 8 of the study report

The mean mg/kg/day Metolachlor intake over the 15 and 17 weeks of the pre-mating period for the F_0 and F_1 generations, respectively, was as follows.

	Males (ppm)			Females (ppm)		
	30	300	1000	30	300	1000
F_0	2.4	23.5	75.8	2.5	26.0	85.7
F_1	2.3	23.7	76.6	2.6	25.7	84.5

4. Reproductive performance: No statistically significant differences were noted in the treated and control reproductive performance indices for either the F_0 or the F_1 generation. Results for the parental animals are summarized from the study report as follows:

	Dose Levels (ppm) 0	30	300	1000
F_0 Generation - F_{1A} Litter				
Mating Index (%)	81.1	90.9	69.0	63.6
Fertility Index (%)	76.7	90.0	79.3	71.4
Gestation Index (%)	100	100	100	100
Female Fertility Index (%)	76.7	90.0	76.7	66.7
Male Fertility Index (%)	86.7	100	80	80
Average Gestation Length (Days)	22	22	22	22
F_1 Generation - F_{2A} Litter				
Mating Index (%)	60.0	54.9	74.4	60.9
Fertility Index (%)	88.9	85.7	89.7	89.3
Gestation Index (%)	100	87.5	96.0	100
Female Fertility Index(%)	80	80	89.7	86.2
Male Fertility Index (%)	80	73.3	93.3	93.3
Average Gestation Length (Days)	23	22	22	22

extracted from Table 16

5. Litter Observations: The study report states that no untoward maternal behavior during the lactation periods could be correlated with exposure to Metolachlor Technical. No statistically significant differences were noted in the treated and control offspring indices for either the F_1 or the F_2 generations. Statistically significant differences in body weights of offspring were found between the control and treated groups. The weight of the F_1 progeny in the 1000 ppm group were reduced at days 14 and 21 of lactation. In the F_{2A} litter, the weights of the 1000 ppm group were reduced at days 4, 7, 14 and 21. The 30 ppm progeny were reduced at day 4 and the females in the 1000 ppm group were reduced on day 21 of lactation. The latter two findings were not considered to be treatment-related. Viability and body weight results from pups during lactation are summarized from the study report as follows:

	Dose Levels (ppm) 0	30	300	1000
F_0 Generation - F_{1A} Litter				
Mean number of pups/ litter delivered	12.8	12.6	13.0	14.0
Mean number of live pups/litter	12.7	12.5	12.8	13.7
Live Birth Index	99.7	99.1	99.0	97.9
Number of stillborn	0	3	3	5
Number cannibalized	1	0	0	1
Offspring survival (%)				
Day 1	99.3	99.7	98.6	100.
Day 4 (Viability Index)	98.0	98.2	97.3	99.3
Day 21 (Weaning Index)	99.5	96.5	95.0	99.0
Offspring mean body weights (g)				
Day 4	9.7	9.7	9.8	9.6
Day 7	15.3	14.9	15.1	14.6
Day 14	27.6	27.8	27.7	26.4*
Day 21				
Male	46.2	45.9	45.1	41.9**
Female	43.9	43.9	41.6	40.5**

	Dose Levels (ppm) 0	30	300	1000
	F_1 Generation - F_{2A} Litter			
Mean number of pups/ litter delivered	12.0	13.0	12.2	12.7
Mean number of live pups/litter	11.7	12.9	11.8	12.5
Live Birth Index	97.9	99.6	96.6	98.4
Number of stillborn	5	1	9	5
Number of cannibalized	1	0	1	0
Offspring survival (%)				
Day 1	91.8	98.9	99.3	98.4
Day 4 (Viability Index)	90.2	93.7	98.6	97.4
Day 21 (Weaning Index)	94.8	98.0	99.1	97.9
Offspring mean body weights (g)				
Day 4	9.9	9.4*	9.7	9.2**
Day 7	14.8	14.4	14.7	13.9**
Day 14	27.3	26.4	26.5	25.9**
Day 21				
Male	44.2	42.6	42.6	41.0**
Female	42.7	41.8	40.3*	39.2**

* statistically significant differences noted at $p < .05$
** statistically significant differences noted at $p < .05$
statistical evaluations conducted utilizing the mean pup weights/litter revealed no significant differences.
extracted from Tables 12, 13 and 14 of the study report

6. Necropsy Results

a. Organ weights

F_1 Parental Animals - Some of the organ weights in the treated groups were statistically different from the controls but the differences were not considered to be biologically significant. The absolute brain weights in the males in the 30 and 1000 ppm groups were smaller; the liver/body ratios were larger in the 1000 ppm male and female groups; the thyroid/body and thyroid/brain ratios were higher in the 1000 ppm males as compared to the controls.

F_{1A} Weanlings - There was a statistically significant decrease in the absolute brain weight for the females in the 1000 ppm group; there was no difference in the brain/body weight ratio.

F_{2A} Weanlings - The study report states that the statistically significant differences in the mean weight of the brain, brain/body ratios, heart/body ratios, kidney/body ratios and the mean spleen weight for the 1000 ppm females was due to the extremely small size of one animal and these differences were not present if this animal was eliminated from the calculations.

b. Pathology

1. Macroscopic Examination

F_0 Generation - There were no significant findings on macroscopic examination of the males from this generation. Two females had clinically apparent lesions at sacrifice and were therefore necropsied. One animal in the 300 ppm group had a mass in the axillary region and another in the 1000 ppm group had an opacity of the right eye and multiple red depressions of the lung.

F_{1A} Weanlings (5/sex/group, 31-41 days old) - There were random findings on gross examination in most groups. One female in the 300 ppm group had multiple cystic calculi and dilated renal pelvises. One stillborn pup born to a female in the 30 ppm group had micrognathia.

F_1 Parental Rats - There were random findings on gross examination of most groups with the exception of a diffuse thickening of the pinna which occurred in 17 of 116 females, most frequently in the 300 ppm group. Two females in the 300 ppm group had renal and cystic calculi with accompanying bladder and kidney changes.

F_{2A} Weanlings (5/sex/group) - One female rat in the 1000 ppm group was extremely small (17 g) and had bilateral opacities in the eyes. Twelve male and female rats (distributed across all groups) had small cysts in the kidneys.

2. Microscopic Examination

F_0 Generation - Microscopic examination of the two females revealed a mammary gland fibroadenoma in the 300 ppm female and unilateral atrophy of the retina and chronic respiratory disease in the 1000 ppm female. On microscopic examination of the testes, two males in the 300 ppm group had atrophy of spermatic cells.

F_{1A} Weanlings - The female in the 300 ppm group which had cystic calculi had moderate pyelonephritis and cystitis on histopathology. The study report states that, "Forty to 100 percent of the rats exhibited a minimal form of chronic respiratory disease of the type commonly associated with Mycoplasma pulmonis infection in the laboratory rats." Other lesions occurred sporadically across all dosage groups.

F_1 Parental Rats - On microscopic examination, the gross thickening of the pinna in many of the female rats of this generation appeared to be a degeneration of the auricular cartilage which was followed by an inflammatory response and then a hyperplasia and fibroplasia of the cartilage and the

overlying epidermis. The study report states, "Although this lesion occurred with a high frequency in treated animals, its occurrence was not dose related, was observed in one vehicle control female rat, and was therefore not considered to be treatment related." The etiology of the lesion was unknown. Chronic respiratory disease in the form of lymphocytic infiltrates in the bronchial wall and in the peribronchial and perivascular areas was present in essentially all the animals. Lesions in the kidneys consisting of glomerulonephrosis, pyelonephritis, mineralization, hydronephrosis and tubular cysts were present in 20 to 40% of the rats in all the groups. Other microscopic lesions also not considered as treatment-related were mononuclear cellular infiltrates in the liver in 34 - 71% of the animals, a hepatocellular neoplastic nodule in a 300 ppm group male and thyroid cysts in animals from all groups.

Four females in this generation died or were sacrificed in a moribund condition before the terminal sacrifice. One rat in the 300 ppm group died of pyelonephritis and cystic calculi one day after being selected as a parental animal. Another in the 1000 ppm group died on day 31 of the study from bacterial nephritis and cystitis. A control female was sacrificed on day 149 due to endometritis with centrilobular necrosis of the liver and cortical necrosis of the kidneys and adrenals. A 300 ppm group female also died on day 149 of thrombosis of the glomerular capillaries and diffuse centrilobular necrosis of the liver.

F_{2A} Weanlings - The female rat in the 1000 ppm group which was extremely underweight had lesions in multiple organs. The renal cysts in the kidneys of the 12 animals were tubular in origin and were accompanied by chronic nephritis in many of the animals. Mononuclear cellular infiltrates in the liver and chronic respiratory disease were observed in all four groups.

III. CONCLUSIONS

Metolachlor Technical, 95.4% a.i., was administered in the diet to two consecutive generations of male and female CD strain albino rats at dosage levels of 0, 30, 300 and 1000 ppm. There was no evidence of treatment-related effects on the clinical parameters, reproductive indices, progeny indices or post-mortem findings for the F_0 generation. The 1000 ppm group of the F_{1A} litter did have statistically significant decreases in body weight on days 14 and 21 of lactation. A decrease in food consumption in the 1000 ppm group females was observed in the F_1 parental animals; body weight and body weight gain were not affected. Reproductive and progeny indices of the treated animals in this generation were comparable to the controls. The 1000 ppm group of the F_{2A} litter had statistically significant decreases in body weight on days 4, 7, 14 and 21

of lactation. There was no evidence of a treatment-related effect on the necropsy findings of either the F_1 parental animals or the F_{2A} litter. Based on the absence of clinical signs of maternal toxicity, the **systemic NOEL is ≥ 1000ppm; the LEL is > 1000 ppm.** Based on the reduction in body weight of the progeny in both the F_{1A} and F_{2A} litters, the **reproductive NOEL is 300 ppm ; the LEL is 1000 ppm.**

METOLACHLOR Tox review 010088

Page_____ is not included in this copy.

Pages 21 through 25 are not included.

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.

X FIFRA registration data.

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

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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.

010088

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 3/9/93
Senior Pharmacologist, Review Section I, TB II/HED H7509C
Secondary Review by: Yiannakis M. Ioannou, Ph.D., D.A.B.T. 3/9/93
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.

010088

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 x 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 comparisom 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:	Control	LDT	MDT	HDT
Observation:				
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.

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.

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.

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.

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.

METOLACHLOR Tox review 010088

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Pages 36 through 45 are not included.

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____ 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.

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____ A draft product label.

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

AUG 27 1992

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Metolachlor - additional data on chronic feeding study in the dog (MRID # 409807-01). EPA DP Code D176237, EPA Submission # S414932, MRID #'s 422186-01 and 422186-02, EPA Pesticide Chemical Code 108801, Toxicology Chemical Code 188DD, HED Project No. 2-1885.

TO: Walter Waldrop/Connie Childress, PM 71
SRRD (H7505W)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 8/17/92
Senior Pharmacologist, Review Section I
Toxicology Branch II/HED (H7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. E. A. Doyle for
Section Head, Review Section I
and
for Marcia van Gemert, Ph.D. James N. Rowe 8/17/92
Branch Chief, Toxicology Branch II 8/20/92
Health Effects Division (H7509C)

Registrant: CIBA-GEIGY Corp., Post Office Box 18300
Greensboro, NC 27419-8300

Action Requested: Review additional data submitted by registrant in support of a chronic feeding study in the dog with metolachlor (MRID # 409807-01).

Recommendations: TB II has reviewed the additional data provided for "Metolachlor Technical, 13/52-Week Oral Toxicity Study in Dogs" (Ciba-Geigy Corporation, Study No. 862253, MRID No's. 409807-01 and 411645-01, 1/23/89). Based on the additional information, the following are the conclusions of the rereview:

Metolachlor was fed to male and female dogs at dietary levels of 0, 100, 300, or 1000 ppm for 13 or 52 weeks. The mean daily compound intake for male dogs receiving 100, 300, and 1000 ppm was 3.5, 9.7, and 32.7 mg/kg/day, respectively, and the doses for females receiving the same dietary levels were 3.6, 9.7, and 33.0 mg/kg/day, respectively. A decrease in body weight gain (compared with controls) was noted in the high-dose males and females at

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300 ppm (9.7 mg/kg/day) based on decreased body weight gains.

This study was classified as Core-Supplementary Data and did not satisfy the guideline requirement (§83-1(b)) for a chronic toxicity study in dogs. The study deficiency was that the purity of the test article was not reported. It was stated that the study could be upgraded to Core-Minimum Data when the deficiency is resolved.

The registrant provided with this submission the purity of the test article (MRID# 422186-02) as 97% a.i. for metolachlor technical (FL 861768) with a certificate of analysis included.

The registrant disagreed with the systemic NOEL for female dogs of 100 ppm which was based on decreased body weight gains.

The following is presented from the registrant's submission (Tables are attached):

The purpose of this document is to provide purity data for the batch of test material used in the study (FL 861768) and to provide additional analysis and historical control data to support the conclusion in the final report that the NOEL is 300 ppm in both males and females.

Summary of Body Weight Data

Body weight and body weight gain data from the original 6-month dog study (MRID No. 00032174) and the new 12-month dog study (MRID No. 409807-01) are summarized for males in Table 1 and for females in Table 2. These tables are formatted similarly to the one prepared by the Dynamac reviewer (page 7 of the DER) for the 12-month study except that data for week 28 is presented to facilitate a comparison to data from the 6-month study.

The body weight and body weight gain data in Table 2 present an incorrect estimate of weight gain over the 12-month period because the animals which were sacrificed at 13 weeks were included in the mean body weight at week 0. Animals in the control group which were sacrificed at week 13 weighed 0.3 kg less at week 0 than the animals which were sacrificed at week 52 weighed at week 0. Including the lighter animals at week 0, then removing them at week 13, artificially increases the overall weight gain from week 0 through termination for the control group. Table 3 presents a comparison of mean body weights and weight gains using only those animals alive at week 0 which were alive at week 52 to the weights and weight gains when all animals are included (such as presented in Table 2). Appendix 2 provides the individual animal data underlying the calculations shown in Table 3.

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Tables 4 and 5 present the historical control data from the SEF, the conducting laboratory.

TB II agrees that the table from the DER (Table 1) that presented the data for body weight gain for females over the 52 weeks period incorrectly includes those animals sacrificed at 13 weeks. The proper presentation is on Table 3 (attached). This shows that for the entire study period the female high dose group had a treatment related decrease in body weight gain; however, it must be noted that during the first 13 weeks there was a dose related decrease in body weight gain for the mid and high dose groups. From inspection of the individual animal data it was noted that for the mid dose group, this decrease in body weight gain seemed to be due to 2 animals (1 sacrificed at 13 weeks) with a lower body weight gain than the other animals (seen in Appendix 2). For the males, although the 6 month dog study showed decreased body weight gains for the high dose group, this was not seen in the 52 week study; however, systemic toxicity was observed in the high dose males in the form of increased alkaline phosphatase activity.

TB II agrees with the registrant that the NOEL for Systemic Toxicity in both male and females for the "Metolachlor Technical, 13/52-Week Oral Toxicity Study in Dogs" (Ciba-Geigy Corporation, Study No. 862253, MRID No's. 409807-01 and 411645-01, 1/23/89) is 300 ppm with a LOEL of 1000 ppm based on reduced body weight gains in the females and increased alkaline phosphatase activity in the high dose males. Other additional data submitted where the final report was amended to include individual organ weights as a percentage of the brain weight for all animals necropsied at a scheduled sacrifice did not affect the conclusions of the study.

01008

III. Data Gaps

The database for technical Metolachlor is not complete, additional data on the following studies are required for the technical metolachlor database:

§85-1 General metabolism - rat

There are acute toxicity study data gaps with the registered formulations. These must be resolved before further permanent food use tolerances are granted.

IV. Actions Being Taken to Obtain Additional Information or Clarification

None at this time.

V. Reference Dose

The RfD is 0.15 mg/kg/day based on the chronic feeding study in the rat with a NOEL of 15 mg/kg/day and an uncertainty factor (UF) of 100.

VI. Pending Regulatory Actions

None at this time.

VII: Toxicological Issues Pertinent to this Request

This chemical was a registration standard in 1986.

A. New toxicology Data on Metolachlor

See previous discussion on the chronic feeding study in the dog.

B. Carcinogenicity

Prior to April 17, 1991, Metolachlor was reviewed but not classified by the HED Peer Review Committee (PRC) for Carcinogenicity. The PRC concluded (MEMO R. Engler to R. Mountfort, August 23, 1985) that the available data for Metolachlor provides weak evidence of carcinogenicity. However, they stated that before they can make a final conclusion on the carcinogenic potential of Metolachlor, additional information was required. The PRC reassessed the carcinogenic potential of Metolachlor in light of the additional data and the following

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Page_____ is not included in this copy.

Pages 50 through 54 are not included.

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.

X 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.

The database for technical Metolachlor is not complete, 21 day dermal toxicity and dermal penetration studies are required, although the registrant has indicated that they have completed these studies and will submit them for review.

DISCUSSION

I. Background Information:

Prior to April 17, 1991, Metolachlor was reviewed but not classified by the HED Peer Review Committee (PRC) for Carcinogenicity. The PRC concluded (MEMO R. Engler to R. Mountfort, August 23, 1985) that the available data for Metolachlor provides weak evidence of carcinogenicity. However, they stated that before they can make a final conclusion on the carcinogenic potential of Metolachlor, they required a full mutagenicity battery and metabolism studies. These studies have since been submitted by the registrant and reviewed by TB-II and were submitted to the PRC, they reassessed the carcinogenic potential of Metolachlor and will have a final document by the end of July, 1991.

II. Review of Additional Studies to Support Toxicology Database

Review of "Metolachlor Technical, 13/52-Week Oral Toxicity Study in Dogs" (Ciba-Geigy Corporation, Study No. 862253, MRID No's. 409807-01 and 411645-01, 1/23/89).

Metolachlor was fed to male and female dogs at dietary levels of 0, 100, 300, or 1000 ppm for 13 or 52 weeks. The mean daily compound intake for male dogs receiving 100, 300, and 1000 ppm was 3.5, 9.7, and 32.7 mg/kg/day, respectively, and the doses for females receiving the same dietary levels were 3.6, 9.7, and 33.0 mg/kg/day, respectively. A decrease in body weight gain (compared with controls) was noted in the high-dose males and females at week 13, whereas a decrease in this parameter was noted in the mid-dose and high-dose females at week 52. Transient reductions in food consumption were noted at several time points during the treatment period, but the reductions were not considered to be of toxicological significance. A treatment-related increase in mean alkaline phosphatase activity was seen in the high-dose males and females at weeks 12, 26, 40, and 52. There was no effect of treatment on organ weights, mortality, ophthalmology, hematology, gross pathology, or histopathology. The systemic NOEL for male dogs is 300 ppm (9.7 mg/kg/day) and the LOEL is 1000 ppm (32.7 mg/kg/day) based on the increase in alkaline phosphatase activity. The

carboxylic acid, as well as hydrolytic removal of the chlorine atom. Conjugation of the parent or metabolites with glucuronic acid or sulfate does not appear to occur.

The aqueous extractable urinary radioactivity contained 58% of the total urinary radioactivity and was composed of 5 different radioactive fractions which were not identified.

This study did not follow current guideline recommendations as to dose levels or the use of both sexes. Therefore, if the metabolic pattern is altered by dose or repeated exposure, this cannot be determined by these data. Further, the doses tested in this study were not equivalent to those tested in the previously discussed study (MRID No. 401144-01). The study is classified as Core-Supplementary Data and does not fulfill the data requirements (§85-1) for a general metabolism study in rats.

TB-II recommends that the registrant provide data on the identification of urinary and fecal metabolites from the submitted study, "Disposition of metolachlor in the rat (general metabolism)" (Ciba-Geigy Corporation, Study No. ABR-8611, MRID No. 401144-01, 2/17/87) to resolve this data gap.

IV. Data Gaps

The following are the studies reviewed in this document to resolve data gaps in the technical metolachlor database:

§83-1(b) 2 year feeding - nonrodent
§85-1 General metabolism - rat

The database for technical Metolachlor is not complete, the following studies are required for the technical metolachlor database:

§82-2 21 day dermal toxicity in rabbits
§83-1(b)1 year feeding - nonrodent
§85-1 General metabolism - rat
§85-2 Dermal penetration

There are acute toxicity study data gaps with the registered formulations. These must be resolved before further permanent tolerances are granted.

V. Actions Being Taken to Obtain Additional Information or Clarification

None at this time.

VI. Reference Dose

The RfD is 0.15 mg/kg/day based on the chronic feeding study in the rat with a NOEL of 15 mg/kg/day and an uncertainty factor (UF) of 100.

VII. Pending Regulatory Actions

Rereview of the carcinogenicity potential of metolachlor, final document is expected at the end of July 1991.

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DATA EVALUATION RECORD

GUIDELINE § 83-1

STUDY TYPE: Chronic toxicity in dogs.

MRID NUMBER: 409807-01, 411645-01 (supplement).

TEST MATERIAL: Metolachlor.

SYNONYMS: CGA-24705; 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide.

STUDY NUMBER: 862253.

SPONSOR: CIBA-GEIGY Corporation, Agricultural Division, Greensboro, NC.

TESTING FACILITY: Division of Toxicology/Pathology, CIBA-GEIGY Corporation, Summit, NJ; and Metpath Laboratories, Rockville, MD.

TITLE OF REPORT: Metolachlor Technical, 13/52-Week Oral Toxicity Study in Dogs (MIN 862253).

AUTHOR: J. R. Hazellete and A. T. Arthur.

REPORT ISSUED: January 23, 1989.

Test group	Dose in diet (ppm)	Main study (52 weeks) Males	Main study (52 weeks) Females	Interim sacrifice (13 Weeks) Males	Interim sacrifice (13 Weeks) Females
1 Control	0	6[a]	6[a]	4	4
2 Low (LDT)	100	4	4	4	4
3 Mid (MDT)	300	4	4	4	4
4 High (HDT)	1000	6[b]	6[b]	4	4

[a]Two control males and two control females were designated as recovery controls (52-week treatment followed by 4-week recovery).

[b]Two high-dose males and two high-dose females designated as recovery high-dose animals were treated for 52 weeks and were then allowed a 4-week recovery period.

Animals were housed individually in cages within rooms with the temperature maintained at 69 ± 5°F, a relative humidity of 50 ± 20%, and a 12-hour light/dark cycle. Animals were identified by individual ear tatoo numbers.

2. Diet Preparation: The test substance was mixed with an appropriate amount of feed to form a premix. The premix was then utilized in preparing the diets, which were stored at room temperature.

Stability of the test substance (50 and 2000 ppm) in the feed was determined prior to initiation of the study and for a period of 26 days and 45 days. The homogeneity of test substance in the diet was determined at weeks 1 and 15. Concentration analyses of the test substance in the diet was performed at weeks 1, 2, 9, 10, 11, 13, 15, 22, 25, 26, 30, 31, 33, and 38.

Results: Results of samples analyzed to determine homogeneity of the test substance in the diet indicated a homogeneous mix. The relative standard deviations of homogeneity ranged from 1.2% to 3.2% for all groups. Mean concentrations in diets at dose levels of 100, 300, and 1000 ppm were 98.5 ± 3.3%, 99.9 ± 3.1%, and 99.8 ± 3.1% of target (14 intervals of analysis), respectively. Results of stability analysis indicated that the test substance was chemically stable for at least 45 days at room temperature.

TABLE 1. Mean Body Weights at Selected Intervals for Dogs Fed Metolachlor for 13/52 Weeks[a]

Dietary Level (ppm)	Mean Body Weights (kg ± S.E.) at Selected Study Weeks:					Total Body Weight Gains at Weeks:	
	0	1	13	32	52	13	52
				Males			
0	7.030 ± 0.230	7.170 ± 0.266	8.920 ± 0.413	9.617 ± 0.450	9.800 ± 0.535	1.890 (100.0)[b]	2.770 (100.0)
100	6.862 ± 0.267	7.087 ± 0.327	9.225 ± 0.424	11.125 ± 0.698	10.825 ± 0.703	2.363 (125.0)	3.963 (143.1)
300	7.187 ± 0.300	7.375 ± 0.288	9.637 ± 0.393	9.625 ± 0.591	9.750 ± 0.514	2.450 (129.6)	2.569 (92.5)
1000	6.770 ± 0.259	6.580 ± 0.256	8.450 ± 0.257	9.417 ± 0.464	9.583 ± 0.396	1.680 (90.0)	2.813 (101.6)
				Females			
0	6.450 ± 0.196	6.590 ± 0.197	8.230 ± 0.262	8.767 ± 0.415	8.983 ± 0.485	1.780 (100.0)	2.533 (100.0)
100	5.975 ± 0.268	6.125 ± 0.252	7.637 ± 0.299	8.525 ± 0.342	8.525 ± 0.338	1.662 (93.4)	2.550 (100.7)
300	6.237 ± 0.247	6.287 ± 0.240	7.787 ± 0.162	8.450 ± 0.266	8.400 ± 0.268	1.550 (87.1)	2.163 (85.4)
1000	6.340 ± 0.254	6.250 ± 0.300	7.830 ± 0.395	8.700 ± 0.614	8.450 ± 0.575	1.490 (84.0)	2.110 (83.3)

[a]Includes all animals treated for 13 weeks (interim sacrifice) and 52 weeks (including those scheduled for a recovery period).

[b]Numbers in parentheses indicate body weight gain relative to control calculated by the study author according to the following equation:

$$\% \text{ Gain} = \frac{\text{Weight change of group}}{\text{Weight change of control}} \times 100$$

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TABLE 2. Mean Food Consumption Data at Selected Intervals in Dogs Fed Metolachlor for 13/52 Weeks[a]

Dietary Level (ppm)	Mean Food Consumption (g/week ± S.E.) at Selected Study Weeks: 0	1	4	13	32	40	52
				Males			
0	1723.5 ± 167.2	1909.5 ± 148.6	2203.6 ± 127.3	2344.3 ± 128.9	2331.0 ± 138.4	2353.1 ± 126.9	2483.2 ± 183.1
100	1636.3 ± 177.2	1913.1 ± 177.2	2029.9 ± 150.0	2196.7 ± 126.4	2398.7 ± 169.0	2336.9 ± 227.9	2518.5 ± 274.2
300	1792.1 ± 151.9	1808.3 ± 93.2	2140.6 ± 82.6	2163.6 ± 127.5	1960.5 ± 109.8	1888.8 ± 103.2	2165.0 ± 153.5
1000	1591.6 ± 121.4	1176.8 ± 125.3**	1785.7 ± 100.1**	1954.4 ± 59.3*	1869.8 ± 66.8*	1980.2 ± 63.7	2071.2 ± 153.7
				Females			
0	1208.7 ± 55.0	1478.5 ± 76.9	1718.4 ± 107.4	1967.9 ± 130.5	1656.8 ± 115.6	1845.5 ± 91.1	1943.3 ± 119.5
100	1381.9 ± 90.3	1468.8 ± 91.8	1723.9 ± 93.6	1930.6 ± 169.1	2089.3 ± 136.2	2061.0 ± 164.5	2000.3 ± 232.6
300	1356.4 ± 61.5	1486.0 ± 63.6	1679.8 ± 57.0	1826.4 ± 93.5	1759.8 ± 141.5	1897.3 ± 63.5	1680.8 ± 187.9
1000	1575.6 ± 114.6	1250.7 ± 107.2**	1686.0 ± 76.4**	2108.8 ± 84.7	1874.7 ± 93.4	1658.2 ± 128.7*	1895.2 ± 134.9

[a]Data include all animals treated for 13 weeks (interim sacrifice) and 52 weeks (including 4-week recovery period).

*Significantly different from control value, $p \leq 0.05$.

**Significantly different from control value, $p \leq 0.01$.

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Results: Mean alkaline phosphatase activities were significantly increased in the high-dose females at weeks 12, 26, and 40 (results summarized in Table 3). The activity of this enzyme in the high-dose females was also slightly but nonsignificantly increased at weeks 52 and 56. The increase in alkaline phosphatase activities in the females was considered by the study author to be treatment-related. However, the study author considered the toxicological significance of the increase to be minimal because there was no corresponding histomorphological change. Nonsignificant dose-related increases in mean alkaline phosphatase activities were also seen in the high-dose males at weeks 12, 26, 40, and 52. Other statistically significant clinical chemistry alterations were regarded by the study author to be incidental, since the changes were inconsistent, marginal, and/or occurred in a non-dose-response manner. These changes included increased SGOT levels in the high-dose males at the end of recovery, increased glucose levels in the mid-dose females at week 40, decreased total protein levels in the mid-dose females at weeks 40 to 52, increased calcium levels in the mid-dose females at week 12, decreased calcium levels in the mid-dose females at week 12, decreased calcium levels in the high-dose males at week 12, and increased sodium levels in the high-dose females at week 26.

6. Urinalysis: Urinalysis was performed on all animals at weeks 12, 25, 40, 52, and 56. The CHECKED (X) parameters were examined:

X	Appearance†	X	Glucose†
	Volume†	X	Ketones
X	Specific gravity†	X	Bilirubin†
X	pH		Blood†
X	Sediment (microscopic)†		Nitrate
X	Protein†	X	Urobilinogen

Results: No effects of treatment with metolachlor on urinary parameters were seen.

†Recommended by Subdivision F (November 1984) Guidelines.

7. **Sacrifice and Pathology**: All animals that died that were scheduled for sacrifice following 13 or 52 weeks of treatment and at the end of the recovery period were subjected to gross pathological examination, and the CHECKED (X) tissues were collected for histological examination. In addition, the (XX) organs were weighed:

Digestive System	Cardiovasc./Hemat.	Neurologic
X Tongue	X Aorta†	XX Brain
X Salivary glands†	XX Heart†	X Peripheral nerve (sciatic nerve)†
X Esophagus†	X Bone marrow† (femur and sternum)	X Spinal cord (3 levels)
X Stomach†	X Lymph nodes†	XX Pituitary†
X Duodenum†	XX Spleen	XEyes (optic nerve)†
X Jejunum†	XX Thymus	
X Ileum†	**Urogenital**	**Glandular**
X Cecum†	XX Kidneys†	XX Adrenals†
X Colon†	X Urinary bladder†	Lacrimal gland
X Rectum	XX Testes†	X Mammary gland†
XX Liver†	XX Epididymides	XX Thyroids†
X Gallbladder†	X Prostate	XX Parathyroids†
X Pancreas†	Seminal vesicle	Harderian glands
Respiratory	XX Ovaries	
X Trachea†	X Uterus	
X Lung†	X Vagina	
		Other
		X Bone (sternum and femur)†
		X Skeletal muscle†
		X Skin
		X All gross lesions and masses

Results:

a. Organ Weights: Table 4 summarizes organ weight data in dogs treated with the test substance for 52 weeks. No treatment-related changes in absolute or relative organ weights were observed. Slight decreases in the mean relative (to body weight and brain weight) kidney weights were noted in males receiving 100 ppm, while slight decreases in the mean relative (to brain weight only) kidney weights were seen in males receiving 300 ppm. The absolute and relative (to brain and body weight) kidney weights were slightly decreased in the high-dose males. The decreases in the kidney weights

†Recommended by Subdivision F (November 1984) Guidelines.

TABLE 4. (continued)

Dietary Level (ppm)	Organ Weight (GM)		Organ Weight/Brain Weight (%)		Organ Weight/Body Weight (%)	
	Males	Females	Males	Females	Males	Females
			Spleen			
0	65.335 ± 12.637	46.070 ± 7.719	74.934 ± 12.525	58.019 ± 6.443	0.653 ± 0.119	0.517 ± 0.092
100	28.767 ± 1.203	43.185 ± 6.516	33.837 ± 1.778	53.055 ± 7.355	0.271 ± 0.018	0.506 ± 0.066
300	55.572 ± 15.308	64.880 ± 20.114	66.064 ± 17.899	78.827 ± 23.651	0.611 ± 0.193	0.782 ± 0.235
1000	41.842 ± 7.799	30.967 ± 4.520	51.765 ± 10.865	38.622 ± 5.542	0.459 ± 0.103	0.373 ± 0.056
			Thymus			
0	5.092 ± 1.102	7.845 ± 1.133	5.852 ± 1.134	10.147 ± 1.473	0.052 ± 0.011	0.087 ± 0.010
100	5.297 ± 1.307	5.955 ± 0.767	6.253 ± 1.544	7.419 ± 1.155	0.048 ± 0.009	0.071 ± 0.010
300	4.087 ± 0.535	3.825 ± 0.503*	4.912 ± 0.765	4.728 ± 0.705*	0.043 ± 0.005	0.047 ± 0.008*
1000	5.070 ± 0.425	5.800 ± 0.968	6.139 ± 0.412	7.239 ± 1.202	0.054 ± 0.003	0.069 ± 0.011

[a]Data include all animals treated for 13 weeks (interim sacrifice) and 52 weeks (including 4-week recovery period).

*Significantly different from control value, $p \leq 0.05$.

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addition, a rationale for the selection of doses utilized in the study was not provided.

Administration of 1000 ppm metolachlor to dogs affected only body weight gain, food consumption, and alkaline phosphatase activity. Mean body weight gains were nonsignificantly decreased relative to baseline values (day 0) in the high dose males (at weeks 1 and 2) and in the high-dose females at week 1. Mean body weight gains in the high-dose males and females were lower than in controls at week 13, while the mean body weight gain at week 52 was lower in the mid- and high-dose females. At week 1, decreases in body weight gain of high-dose animals corresponded to decreases in food consumption in these animals. Reductions in food consumption at other times of the treatment period were transient and did not correspond with changes in body weight gain. A treatment-related increase in mean alkaline phosphatase activity was noted in the high-dose males and females at weeks 12, 26, 40 and 52. No treatment-related changes in organ weights, mortality, ophthalmology, hematology, gross pathology, or histopathology were observed.

Based on the aforementioned results, the systemic NOEL for female dogs is 100 ppm and the LOEL is 300 ppm. The NOEL for male dogs is 300 ppm and the LOEL is 1000 ppm.