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

010251

MAY 12 1993

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

**MEMORANDUM**

**SUBJECT:** METOLACHLOR: Rat chronic toxicity/carcinogenicity study and subchronic dog study - rereview of data. EPA DP Barcode: D191071; EPA Pesticide Chemical Code 108801, Toxicology Chemical Code 188DD.

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

**FROM:** Stephen C. Dapson, Ph.D. *Stephen C. Dapson 5/10/93*  
Senior Pharmacologist, Review Section I  
Toxicology Branch II/HED (H7509C)

**THRU:** Yiannakis M. Ioannou, Ph.D., D.A.B.T. *Y M Ioannou 5/10/93*  
Section Head, Review Section I  
and  
Marcia van Gemert, Ph.D. *in van Gemert 5/11/93*  
Branch Chief, Toxicology Branch II  
Health Effects Division (H7509C)

**Action Requested:** The HED-RfD Peer Review Committee requested the rereview of a previously reviewed chronic toxicity/carcinogenicity study in the rat (§83-1a and §83-2a) with metolachlor (*Two-Year Chronic Oral Toxicity and Oncogenicity Study with Metolachlor in Albino Rats*, Hazleton-Raltech, Inc. for CIBA-GEIGY Corporation, Agricultural Division, Study # 80030, May 2, 1983, MRID # 00129377) for chronic effects only. Also, in support of the chronic dog study the Committee requested the rereview of a previously reviewed subchronic toxicity study in the dog (§82-1b) with metolachlor (*6-Month Chronic Oral Toxicity Study in Beagle Dogs*, International Research and Development Corporation (IRDC) for CIBA-GEIGY Corporation, Agricultural Division, Study # 382-054, May 21, 1980 (revised), MRID # 00032174).

**Conclusions:** The following are the conclusions from those reviews:

chronic toxicity/carcinogenicity study in the rat (§83-1a & §83-2a)

Metolachlor (95.3 % a.i., Batch No. FL-800362) dose levels of 0, 30, 300, and 3000 ppm were administered in the diet to CD-Crl:CD (SD)BR albino rats from Charles River for 2 years. A very slight effect was noted on body weight gain in the high dose males with a

*10/40*

significant effect noted in high dose females from about week 4 to the end of the study. There was an apparent increase in liver absolute (7%) and relative (13%) weights compared to controls for the high dose males (although these changes were not statistically significant).

Systemic Toxicity NOEL = 300 ppm  
Systemic Toxicity LOEL = 2000 ppm

This study is classified as **Core Minimum Data** and satisfies the guideline requirements (§83-1a) for a chronic toxicity study in rats.

**subchronic toxicity study in the dog (§82-1b)**

CGA-24705 Technical (Metolachlor) was administered at dose levels of 0, 100, 300, and 1000 ppm in the diet to Beagle dogs from Ridglan Research Farms, Inc. for 6 months. Reduced body weight gains and food consumption was noted in the high dose males and females. An effect was noted on the APTT in the mid and high dose males and females (not statistically significant in high dose females) at the end of the study; however, the biological relevance of these observations is unknown. Also, a statistically significant increase in alkaline phosphatase activity was noted in the mid dose males and high dose males and females, again the biological relevance of this observation is unknown as it is not accompanied by gross or histopathological observations. This study is acceptable as a range finding study for a chronic toxicity study in the dog.

Systemic Toxicity NOEL = 300 ppm  
Systemic Toxicity LOEL = 1000 ppm

This study is classified as **Core Supplementary Data** and does not satisfy the guideline requirements (§82-1b) for a subchronic toxicity study in nonrodents. Major deficiency: the purity of the test article was not provided.

The reason for the rereview of the subchronic dog study was based on the Committee's disagreement with the conclusions of the review of the chronic dog study (*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) in terms of the body weight gains and the decrease in alkaline phosphatase activity. The conclusions from that review are as follows:

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

The registrant had disagreed with a previous review of this study where the systemic NOEL for female dogs was determined to be 100 ppm based on decreased body weight gains. They submitted additional data to support the above conclusions. TB II agreed that the body weight gain table from the original review incorrectly included animals sacrificed at 13 weeks. When the data were properly presented, showed 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 appeared to be due to 2 animals (1 sacrificed at 13 weeks) with a lower body weight gain than the other animals. 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. Therefore, it was concluded that the NOEL for Systemic Toxicity in both males 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. However, since the increased alkaline phosphatase activity has been discounted by the Committee, the NOEL would be based on the body weight gain decrement in females alone.

The following table presents the body weight gains for the 13/52 week dog study:

## Body Weight Gain Data for All Animals:

Dose Group (ppm):	Control	100	300	1000	HC
<b>Males</b>					
Week:					
0-13	1.9 <sup>a</sup>	2.4	2.5	1.7 (10) <sup>b</sup>	2.0
0-26/28	2.0	3.2	2.1	2.2	2.9
0-52	2.8	4.0	2.6 (7)	2.8	3.5
<b>Females</b>					
Week:					
0-13	1.8	1.7 (7)	1.6 (13)	1.5 (16)	
0-26/28	2.0	2.2	1.8 (10)	1.9 (5)	
0-48	2.4	2.5	2.5	2.2 (8)	
0-52	2.5	2.6	2.2 (15)	2.1 (17)	

Body Weight Gain Data for 52 Week Animals only:  
Females

Week:	Control	100	300	1000	HC
0-13	1.8	1.8	1.7 (6)	1.5 (17)	1.6
0-26	1.9	2.1	1.8 (5)	1.8 (5)	2.2
0-48	2.3	2.5	2.6	2.0 (13)	
0-52	2.4	2.5	2.3 (4)	2.0 (17)	2.8

<sup>a</sup> = in kilograms; <sup>b</sup> = % difference from control; HC = historical control

As can be seen in the above data the high dose females gained less body weight than the controls. This was for both the 13+52 week animals and for those kept on study for the entire 52 weeks.

## Food Efficiency Data (%)

Week:	13	28	48	52
<b>Males</b>				
Dose (ppm)				
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
<b>Females</b>				
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

Food efficiency for the first 13 weeks was reduced for the high dose females which is indicative of toxicity and this remained reduced throughout the study. Therefore, the NOEL for systemic toxicity should remain at 300 ppm with a LOEL of 1000 ppm based on body weight gain decrements in the high dose females.

Primary Review by: Stephen C. Dapson, Ph.D. *Stephen C. Dapson 4/14/93*  
Senior Pharmacologist, Review Section I, TB II/HED H7509C  
Secondary Review by: Yiannakis M. Ioannou, Ph.D., D.A.B.T. *Y. Ioannou 4/14/93*  
Section Head, Review Section I, TB II/HED H7509C

DATA EVALUATION RECORD

010251

**NOTE: This DER covers only chronic toxicity**

**Study Type:** Chronic Toxicity/Carcinogenicity  
**Species:** Rat **Guideline:** §83-1a and §83-2a

**EPA Identification No.:** EPA MRID No. 00129377  
EPA Pesticide Chemical Code 108801  
Toxicology Chemical Code 188DD

**Test Material:** Metolachlor, 95.3 % a.i., Batch No. FL-800362

**Sponsor:** CIBA-GEIGY Corporation, Agricultural Division  
Greensboro, North Carolina 27419

**Testing Facility:** Hazleton-Raltech, Inc., 3301 Kinsman Boulevard  
Madison, Wisconsin 53704

**Title of Report:** Two-Year Chronic Oral Toxicity and Oncogenicity  
Study with Metolachlor in Albino Rats

**Study Number(s):** 80030

**Author(s):** Merril Tisdell

**Report Issued:** May 2, 1983

**Conclusions:** Metolachlor - dose levels of 0, 30, 300, and 3000 ppm were administered in the diet to CD-Crl:CD (SD)BR albino rats from Charles River for 2 years. A very slight effect was noted on body weight gain in the high dose males with a significant effect noted in high dose females from about week 4 to the end of the study. There was an apparent increase in liver absolute (7%) and relative (13%) weights for the high dose males (although these differences were not statistically significant).

**Systemic Toxicity NOEL = 300 ppm**  
**Systemic Toxicity LOEL = 3000 ppm**

**Core Classification:** Core Minimum Data.

**This study satisfies the guideline requirements (§83-1a) for a chronic toxicity study in rats.**

## A. Materials and Methods

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

1. **Test Compound:** Purity: 95.3 %  
 Density: not provided  
 Description: not provided  
 Batch No.: FL-800362  
 Receipt date: not provided  
 Contaminants: not provided
2. **Test Animal(s):** Species: Albino Rat  
 Strain: CD-Crl:CD(SD)BR  
 Source: Charles River Breeding Laboratories  
 Wilmington Massachusetts  
 Age: 3 weeks  
 Body Weight: 139 mg for males; 121 g for  
 females at study initiation

### 3. Animal Assignment

Animals were randomly assigned by a computer generated model to the following test groups:

Test Group	Dose in diet (ppm)	Main Study 24 months		Interim Sac. 12/13 months	
		male	female	male	female
1 Control	0	70*	70*	10	10
2 Low (LDT)	30	60	60		
3 Mid (MDT)	300	60	60		
4 High (HDT)	3000	70*	70*	10	10
5. Prestudy clinical	-	10	10		

\* = 10 animals were assigned to a "recovery" period

### 4. Diet preparation

Diet was prepared weekly and stored at 4°C. Samples of treated food were analyzed for stability (at room temperature), homogeneity and concentration during weeks 1, 2, 3, and 4 with random sampling during weeks 5-104.

### 5. Animal Husbandry

Animals were kept under standard animal care conditions and received Purina Certified Rodent Chow® #5002 and tap (by an automatic watering system) *ad libitum*.

## 6. Observations

Animals were inspected twice daily for signs of moribundity, mortality and signs of toxicity and once a week for abnormal appearance or behavior with a palpation for tissues masses beginning study week 14.

## 7. Body Weight

Animals were weighed at study initiation, weekly through week 13, then biweekly starting on week 16.

## 8. Food Consumption and Compound Intake

Individual food consumption was recorded weekly through week 13, then biweekly starting on week 16 from a randomly determined group (used at each time point). Food efficiency and compound intake were not calculated.

## 9. Ophthalmological Examination

Ophthalmological examinations were not performed.

## 10. Clinical Laboratory Studies

Clinical laboratory studies including hematology, serum chemistry, and urinalysis were conducted at 3, 6, 12, 18, and 24 months on the same 8 animals per dose group. At 18 months, an additional 10 animals per dose group were added. Urine was collected overnight from fasted (food only) animals in metabolism cages, these animals were then anesthetized with ether and blood was collected from the orbital sinus.

### a. Hematology

Total erythrocyte count (RBC)*	Total leukocyte count (WBC)*
Differential leukocyte count*	Hematocrit (HCT)*
Hemoglobin (HGB)*	Platelet count*
Reticulocyte count and Heinz Body determination - if anemia present	
* required for subchronic and chronic studies	

### b. Clinical Chemistry

Lactate dehydrogenase (LDH)	AST (formerly SGOT)
ALT (formerly SGPT)*	Alkaline phosphatase (ALP)
Blood urea nitrogen (BUN)*	Glucose (fasting)*
Total protein (TP)* - if abnormal A/G ratio calculated	Direct and total bilirubin
Total cholesterol*	Potassium
Calcium*	
not measured: Chloride*, Phosphorus*, Blood creatinine*, Sodium*, Creatinine phosphokinase*	
* required for subchronic and chronic studies	

### c. Urinalysis

Ames Multistix (pH, Protein\*, Glucose\*, Ketones\*, Bilirubin\*, Blood\*, Urobilinogen), Specific gravity\*, Sediment (microscopic)\* assume both Appearance\* and Volume\* were determined  
 \* required for subchronic and chronic studies

### 11. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and tissues were collected for histological examination. The organs with a \* were weighed.

Adrenal gland*	Optic nerve*
Bone marrow section (femur)*	Pancreas*
Brain (cerebrum, cerebellum and pons)**	Parathyroids*
Cecum*	Pituitary* fixed in situ
Colon*	Prostate
Esophagus*	Salivary glands (submaxillary)*
Eyes*	Peripheral nerve (sciatic)*
Gonads (Ovaries**, Testes**, etc).	Skin*#
Heart**	Small intestine (Duodenum*, Jejunum*, Ileum*)
Kidneys**	Spinal cord (2 levels, should be 3)*
Liver (2 lobes)**	Spleen*
Lungs (including bronchi)*	Stomach*
Lymph nodes (cervical & mesenteric)*	Thymus*
Mammary gland*	Thyroids*
Skeletal muscle*	Urinary bladder*
Uterus*	All gross lesions & masses*

the following required organs were not preserved: Aorta\*, Rectum\*, Bone\*, Trachea\*

\* Required for subchronic and chronic studies.

\* Organ weight required in subchronic and chronic studies (except heart and spleen).

Organ to body weight and organ to brain weight ratios were calculated. The necropsy consisted of an examination of the external body surface, all orifices, the cranial cavity, the external and cut surfaces of the brain, spinal cord, the nasal cavity and paranasal sinuses, the abdominal, thoracic, and pelvic cavities and related viscera, and the animal carcass.

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## 12. The "Recovery" Segment

The following procedure was followed (from the investigators report):

After 12 months on test, 10 males and 10 females from the survivors on each test diet were selected at random for the recovery study. Five of the 10 animals were sacrificed at 12 months on test (Week 53). The remaining 5 of each 10 selected animals were placed (or continued) on the negative control diet for 4 weeks. Body weights were recorded for Weeks 52, 54, 55, and 56, and feed consumption for Weeks 52 and 56. During Week 57 the remaining 5 selected animals of each group were sacrificed. All animals in the recovery study were subjected to clinical laboratory studies, had terminal organ weights recorded, and underwent gross and histopathologic examination.

## 13. Statistical Analysis

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

Body weight and feed consumption data, clinical pathology data, and terminal organ weight data were analyzed using analysis of variance. When significant F ratios were found, Dunnett's t-test was used to determine significant differences between control and other treatment means. Incidences of pathologic lesions, where indicated, were analyzed using a 2 x 4 contingency Chi-square analysis, and when significant, followed by Fisher's Exact test techniques. Survival data were analyzed using Cox's test for linear trends. Means that were statistically different from those of the control at significance levels of 0.05 and 0.01 are indicated on the summary tables.

## 14. Compliance

This study was a 1983 submission, and has not been resubmitted since that time.

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 Statement was provided.

A signed Flagging Statement for Potential Adverse Effects under 40 CFR 158.34 was not provided.

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## B. Results

### 1. Diet Analyses

Data provided indicated that the diet preparations were homogenous, were stable for at least 4 weeks at room temperature, and the investigators achieved an average of 97, 91 and 95 % of theoretical for the 30, 300 and 3000 ppm dietary mixtures, respectively.

### 2. Clinical Observations

#### a. Mortality

The following table (Table 4 of Study No. 80030) presents the mortality data. No effect of treatment was noted.

#### Males

Type of Death	Group 1 0 ppm	Group 2 30 ppm	Group 3 300 ppm	Group 4 3000 ppm
Found dead	20	15	20	17
Moribund sacrifice	7	11	15	9
Interim sacrifice 12 months	5	-	-	5
Interim sacrifice 13 months	5	-	-	5
Terminal sacrifice	33	34	25	34
Total	70	60	60	70

#### Females

Type of Death	Group 5 0 ppm	Group 6 30 ppm	Group 7 300 ppm	Group 8 3000 ppm
Found dead	16	12	11	11
Moribund sacrifice	11	18	20	9
Interim sacrifice 12 months	5	-	-	5
Interim sacrifice 13 months	5	-	-	5
Terminal sacrifice	33	30	29	40
Total	70	60	60	70

### b. Clinical Signs

Signs of sialodacryoadenitis virus (SDAV) were noted in a number of animals in all groups. According to the table of data provided signs of SDAV were seen in 39/70, 26/60, 28/60, and 40/70 for the males, and 39/70, 30/70, 19/60, and 24/70 for the females for the 0, 30, 300, and 3000 ppm dose groups, respectively. No treatment related effects were noted in other clinical sign data. Palpable tissue masses were noted in 16/70, 19/60, 14/60, and 28/70 for the males, and 41/70, 34/60, 39/60, and 43/70 for the females for the 0, 30, 300, and 3000 ppm dose groups, respectively. The investigators stated that The incidences are typical for 2-year-old CD rats...

### 3. Body Weight

The following table presents body weight gains at selected intervals (calculated by the reviewer from Tables 20 and 23 of Study No. 80030, tables did not give unit of measure):

Dose Group (ppm):	Control	30	300	3000
		<b>Males</b>		
<b>Week:</b>				
1	58a	59	58	54 (7)
13	357	368	372	351 (2)
26	460	474	484	447 (3)
52	587	599	609	562 (4)
78	649	652	669	605 (7)
104	666	705	649 (2)	619 (7)
		<b>Females</b>		
1	36	37	36	34 (6)
13	174	171 (2)	172 (1)	158 (9)
26	223	222	225	198 (11)
52	314	317	319	270 (14)
78	372	354 (5)	380	309 (17)
104	416	431	434	363 (13)

\* - assume grams

A very slight effect was noted on body weight gain in the high dose males with a significant effect noted in high dose females from about week 4 to the end of the study (according to the investigators, statistical significance was noted; however, the data they presented were for body weight gain per week).

#### 4. Food Consumption and Compound Intake

The following table presents body weight gains at selected intervals (calculated by the reviewer from Tables 20 and 23 of Study No. 80030, tables did not give unit of measure):

Dose Group (ppm):	Control	30	300	3000	
		<b>Males</b>			
<b>Week:</b>					
1	158 <sup>a</sup>	157	165	160	
13	190	194	205	187	
26	197	193	186	189	
52	187	187	188	185	
78	186	185	189	183	
104	193	189	195	193	
		<b>Females</b>			
1	131	129	120	123	
13	150	135	143	136	
26	147	137	142	141	
52	148	144	147	140	
78	150	146	147	142	
104	155	157	165	154	

<sup>a</sup> = assume grams/animal/week

No effects on food consumption were noted in males, the females of all treated groups tended to consume less food than that of the controls. Compound intake was not calculated by the investigators.

#### 5. Ophthalmological Examinations

Ophthalmological examinations were not performed.

#### 6. Clinical Laboratory Studies

##### a. Hematology

No biologically relevant differences were noted.

##### b. Clinical Chemistry

No biologically relevant differences were noted.

##### c. Urinalysis

No biologically relevant differences were noted.

## 7. Pathology

## a. organ weights

The following is selected data for the liver from the investigators report (Tables 34-36 of Study No. 80030):

Dose Group:	Control	30	300	3000
	<b>Males</b>			
Liver (g)	17.8	18.8	19.1	19.0
Liver to Body Weight (%)	2.342	2.332	2.552	2.643
Liver to Brain Weight (%)	784.4	810.2	815.5	821.7
	<b>Females</b>			
Liver (g)	14.0	13.7	13.7	13.7
Liver to Body Weight (%)	2.826	2.670	2.591	3.078
Liver to Brain Weight (%)	676.9	653.8	655.0	675.1

The investigators stated that they believed there was an increase in liver absolute (7%) and relative (13%) weights and liver to brain weight (5%) for the high dose males, although these differences were not statistically significant. This is supported by the above data. No biologically relevant differences were noted in other organ weights or for the females.

Gross pathology and Microscopic pathology (both non-neoplastic and neoplastic) were adequately covered in previous DER's and this data has been evaluated by the HED Peer Review Committee for Carcinogenicity and by the SAP.

## 8. The "Recovery" Segment

Data from the control and high dose animals used for a 4 week "recovery" segment did not show any biologically relevant differences in body weights, food consumption, or clinical analyses. There was an increase in liver weight noted in the males.

Dose Group:	Control	3000
	<b>12 month sacrifice</b>	
	<b>Males</b>	
Liver (g)	18.8	19.2
Liver to Body Weight (%)	2.411	3.012**
Liver to Brain Weight (%)	829	840
	<b>Females</b>	
Liver (g)	10.2	10.3
Liver to Body Weight (%)	2.637	2.808
Liver to Brain Weight (%)	496	483
	<b>13 month sacrifice</b>	
	<b>Males</b>	
Liver (g)	16.2	18.4
Liver to Body Weight (%)	2.439	2.663
Liver to Brain Weight (%)	703	819
	<b>Females</b>	
Liver (g)	10.4	10.8
Liver to Body Weight (%)	2.605	2.990
Liver to Brain Weight (%)	491	527

\*\* =  $p < 0.01$  by Dunnett's procedure

**C. Discussion/Conclusions**

A very slight effect was noted on body weight gain in the high dose males with a significant effect noted in high dose females from about week 4 to the end of the study. There was an apparent increase in liver absolute (7%) and relative (13%) weights for the high dose males (although these differences were not statistically significant).

Systemic Toxicity NOEL = 300 ppm  
Systemic Toxicity LOEL = 3000 ppm

Core Classification: Core Minimum Data.

This study satisfies the guideline requirements (§83-1a) for a chronic toxicity study in rats.

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Pages 16 through 24 are not included.

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Primary Review by: Stephen C. Dapson, Ph.D. *Stephen C. Dapson 5/6/93*  
Senior Pharmacologist, Review Section I, TB II/HED H7509C  
Secondary Review by: Yiannakis M. Ioannou, Ph.D., D.A.B.T. *Y.M.I. 5/7/93*  
Section Head, Review Section I, TB II/HED H7509C

**DATA EVALUATION RECORD**

010251

Study Type: Subchronic Toxicity - nonrodent  
Species: Dog Guideline: §82-1b

EPA Identification No.s: EPA MRID No. 00032174  
EPA Pesticide Chemical Code 108801  
Toxicology Chemical Code 188DD

Test Material: CGA-24705 Technical (Metolachlor)

Sponsor: CIBA-GEIGY Corporation, Agricultural Division, Greensboro, NC 27419

Testing Facility: International Research and Development Corporation (IRDC),  
Mattawan, Michigan

Title of Report: 6-Month Chronic Oral Toxicity Study in Beagle Dogs

Study Number(s): 382-054

Author(s): Frances L. Estes

Report Issued: May 21, 1980 (revised)

Conclusions: CGA-24705 was administered at dose levels of 0, 100, 300, and 1000 ppm in the diet to Beagle dogs from Ridgman Research Farms, Inc. for 6 months. Reduced body weight gains and food consumption was noted in the high dose males and females. An effect was noted on the APTT in the mid and high dose males and females (not statistically significant in high dose females) at the end of the study; however, the biological relevance of these observations is unknown. Also, a statistically significant increase in alkaline phosphatase activity was noted in the mid dose males and high dose males and females, again the biological relevance of this observation is unknown as it is not accompanied by gross or histopathological observations. This study is acceptable as a range finding study for a chronic toxicity study in the dog.

Systemic Toxicity NOEL = 300 ppm  
Systemic Toxicity LOEL = 1000 ppm

Core Classification: Core Supplementary Data.  
This study does not satisfy the guideline requirements (§82-1b) for a subchronic toxicity study in nonrodents. Major deficiency: the purity of the test article was not provided.

## A. Materials and Methods

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

1. **Test Compound:** Purity: not provided  
Density: not provided  
Description: Amber liquid  
Batch No.: FL-781314  
Receipt date: October 10, 1978  
Contaminants: not provided
2. **Test Animal(s):** Species: Dog  
Strain: Beagle  
Source: Ridglan Research Farms, Inc., Mt. Horeb, Wisconsin  
Age: 4-6 months  
Body Weight: 11.6-11.8 kg for males: 8.4-8.7 kg for females at study initiation

### 3. Animal Assignment

Animals were randomly assigned by a computer generated model to the following test groups:

Group	Dose Level	# Males	# Females
Control	0	8*	8*
Low	100	6	6
Mid	300	6	6
High	1000	8*	8*

\* = extra animals used for "recovery" period for 4 weeks on basal diet after the 6 month treatment period

### 4. Diet preparation

CGA-24705 was dissolved in ethanol to prepared a 50% (w/v) solution which was adrixted to ground Purina Dog Chow®. Diet was prepared weekly and stored at 4°C. Prior to study initiation and at weekly intervals the concentration of the test article was analyzed. Also the sponsor "analyzed" samples at 3 and 6 months.

### 5. Animal Husbandry

Animals were kept under standard animal care conditions and received ground Purina Dog Chow® and tap water *ad libitum*. The dogs were vaccinated for hepatitis, distemper, leptospirosis, treated for intestinal worms, checked for presence of heart worms and given an ophthalmologic examination.

## 6. Observations

Animals were inspected daily for general physical appearance and behavior and daily for mortality. Incidence of tissue masses was checked weekly.

## 7. Body Weight

Animals were weighed weekly.

## 8. Food Consumption and Compound Intake

Individual food consumption was recorded weekly. Compound consumption was calculated weekly. Food efficiency was not calculated.

## 9. Ophthalmological Examination

Ophthalmological examinations were performed pretest and at 6 months of study for each dog.

## 10. Clinical Laboratory Studies

Blood was collected from all dogs (fasted overnight) during pretest and at monthly intervals including the "recovery" period. Urine samples were collected from all dogs during the pretest period, at 2, 4, and 6 months on study and at month 7 for those dogs in the "recovery" period.

### a. Hematology

Hemoglobin (HGB)*	Hematocrit value (HCT)*
Erythrocyte count (RBC)*	Total leukocyte count (WBC)*
Differential leukocyte count*	Platelet count*
Reticulocyte count (determined at various intervals during study)	
Prothrombin time	Activated partial thromboplastin time (APPT)
Methemoglobin	Heinz bodies

\* required for subchronic and chronic studies

### b. Clinical Chemistry

Blood urea nitrogen (BUN)*	Glucose (fasting)*
Total cholesterol*	Total protein (TP)*
Serum calcium*	Serum potassium
Serum sodium*	Serum chloride*
Direct and total bilirubin	SGOT*
Serum alkaline phosphatase (ALP)	SGPT*
Lactate dehydrogenase (LDH)	

not measured: Phosphorus\*, Blood creatinine\*, Creatinine phosphokinase\*

\* required for subchronic and chronic studies

## c. Urinalysis

Specific gravity\*, Sediment (microscopic)\* with multistix determination of Protein\*, Glucose\*, Ketones\*, Bilirubin\*, Urobilinogen, pH, Nitrates, Blood. assume both Appearance\* and Volume\* were determined

\* required for subchronic and chronic studies

## 11. Sacrifice and Pathology

Animals were sacrificed at 6 months on study and necropsied. An examination was made of the external body surfaces and orifices. The animal was then opened and the contents of the cranial, thoracic, abdominal and pelvic cavities and their viscera were examined. The following tissues were prepared for histological examination (\* = tissues that were weighed).

Adrenal gland**w	Eyes & optic nerve**	Aorta*
Pancreas*	Bone marrow*	Parathyroids***
Brain**w	Peripheral nerve (sciatic)**	Cecum*
Pituitary**w	Colon*	Prostate
Esophagus*	Salivary glands (submaxillary)*	Skin**
Skeletal muscle**	Gall bladder*	Heart**w
Testes**w/Ovaries**w	Duodenum*/Jejunum*/Ileum*	Spleen <sup>w</sup>
Spinal cord (2 levels)**	Kidneys**w	Lung (w/bronchi)*
Liver**w	Stomach (3 levels)*	Mammary gland**
Thyroids (w/parat)***w	Lymph nodes (cervical & mesenteric)*	Thymus*
Trachea*	Urinary bladder*	
Uterus (corpus & cervix)*	"muscle"	
All gross lesions and masses*		

did not examine: Rectum\*, Bone\*\*

\* Required for subchronic and chronic studies.

# In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement.

\* Organ weight required in subchronic and chronic studies.

\*\* Organ weight required for non-rodent studies.

12. The "Recovery" Segment

Other than what was mentioned in the beginning under study conduct, no further information was provided.

13. Statistical Analysis

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

All statistical analyses compared the treatment groups with the control group, by sex.

Body weight gains (weeks 1 to 13 and 1 to 26), absolute and relative (to both body and brain) organ weights (terminal and withdrawal sacrifice), hematological, biochemical and urinalysis parameters (Control, 1, 2, 3, 4, 5, 6 months and 1 month withdrawal) except 1, 3 and 5 months on urinalysis were compared by analysis of variance (one-way classification), Bartlett's test for homogeneity of variances and the appropriate t-test (for equal or unequal variances) as described by Steel and Torrie<sup>13</sup> using Dunnett's<sup>19</sup> multiple comparison tables to judge significance of differences.

~~In addition the relative organ weights (from sacrifice only) were compared by the Mann-Whitney U-test as described by Siegel<sup>21</sup> to judge significance of differences.~~

14. Compliance

This study was a 1983 submission, and has not been resubmitted since that time.

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 Statement was provided.

A signed Flagging Statement for Potential Adverse Effects under 40 CFR 158.34 was not provided.

**B. Results****1. Diet Analyses**

Data were not provided.

**2. Observations****a. Mortality**

No deaths were reported in this study.

**b. Clinical Signs**

No treatment related effects were noted in the data provided.

**3. Body Weight**

The following table presents body weight gains at selected intervals (calculated by the reviewer from group means in text table under V.A.3. and Table 2 of Study No. 382-054):

Dose Gr	(ppm):	Control	100	300	1000
		<b>Males</b>			
<b>Week:</b>					
0-1		0.3 <sup>a</sup>	0.4	0.5	0 (-)
0-13		1.9	1.6(16) <sup>b</sup>	2.0	0.7 (63)
0-26		2.9	2.2(17)	2.6 (10)	1.3 (55)
		<b>Females</b>			
0-1		0.4	0.6	0.5	0 (-)
0-13		1.8	1.7 (6)	1.8	0.9 (50)
0-26		2.5	2.7	2.1 (16)	1.4 (44)

<sup>a</sup> = in kilograms, <sup>b</sup> = % difference from control

An effect was noted on body weight gain in the high dose males and females from the beginning of the study with the low and mid dose males and mid dose females showing reduced body weight gain at study termination. Body weight gain was also decreased in the low dose males at 13 weeks but not in the mid dose group.

#### 4. Food Consumption and Compound Intake

The following table presents food consumption at selected intervals (from Table 3 of Study No. 382-054):

Dose group (ppm):	Control	100	300	1000
<b>Males</b>				
<b>Week:</b>				
1	369 <sup>a</sup>	415	450	335
13	353	375	383	312
26	379	345	373	330
Average food consumption	355	376 (6) <sup>b</sup>	386 (9)	349 (-2)
Average compound consum. (mg/kg/day)	2.92		9.71	29.61
<b>Females</b>				
1	370	347	338	296
13	310	290	278	290
26	288	294	242	245
Average food consumption	308	289 (-6)	292 (-5)	279 (-9)
Average compound consum. (mg/kg/day)	2.97		8.77	29.42

<sup>a</sup> = grams/animal/day; <sup>b</sup> = % difference from control

Reduced food consumption was noted in high dose males and females; also the mid dose females tended to consume less food than of the controls.

#### 5. Ophthalmological Examinations

No treatment related ophthalmological observations were noted.

#### 6. Clinical Laboratory Studies

##### a. Hematology

The following table presents data for the measurement of activated partial thromboplastin time (APTT, from Table 5, Study No. 382-054):

Dose Group (ppm):	Control	100	300	1000
<b>Males</b>				
<b>Week:</b>				
Pretest	15.0	15.0	15.0	16.0
1	12.0	12.0	12.0	12.0
13	11.5	10.5	11.6	11.6
26	11.5	12.4	9.6**	9.7**
<b>Females</b>				
Pretest	15.0	14.0	15.0	16.0
1	12.0	12.0	12.0	12.0
13	11.4	10.7	11.5	11.2
26	11.3	11.6	9.9*	10.3

\* =  $p < 0.05$ ; \*\* =  $p < 0.01$ ; both by t-test as compared to control

An effect was noted on the APTT in the mid and high dose males and females (not statistically significant in high dose females) at the end of the study. The investigators claimed that these values for treated dogs were within the normal range for the controls. However, from the individual animal data, more animals presented with lower values than were noted in the control animals (more variation in high dose). No other biologically relevant differences were noted.

#### b. Clinical Chemistry

The following table presents data for the measurement of alkaline phosphatase activity (from Table 14, Study No. 382-054):

Dose Group (ppm):	Control	100	300	1000
<b>Males</b>				
<b>Week:</b>				
Pretest	118	127	129	118
1	109	109	117	109
13	81	86	90	105
26	56	77	78**	87*
Recovery	64			86
<b>Females</b>				
Pretest	137	136	142	128
1	126	121	128	134
13	87	98	106	108
26	69	86	83	100*
Recovery	67			53*

\* =  $p < 0.05$ ; \*\* =  $p < 0.01$ ; both by t-test as compared to control

A statistically significant increase was noted in the mid dose males and high dose males and females in alkaline phosphatase activities. The increase continued in high dose males but decreased in high dose females during the recovery period. No other biologically relevant differences were noted.

#### c. Urinalysis

No biologically relevant differences were noted.

### 7. Pathology

#### a. Organ Weights

No biologically relevant differences were noted.

#### b. Gross Observations

No biologically relevant differences were noted.

#### c. Histopathology

No biologically relevant differences were noted.

**C. Discussion/Conclusions**

Reduced body weight gains and food consumption was noted in the high dose males and females. An effect was noted on the APTT in the mid and high dose males and females (not statistically significant in high dose females) at the end of the study; however, the biological relevance of these observations is unknown. Also, a statistically significant increase in alkaline phosphatase activity was noted in the mid dose males and high dose males and females, again the biological relevance of this observation is unknown as it is not accompanied by gross or histopathological observations. This study is acceptable as a range finding study for a chronic toxicity study in the dog.

Systemic Toxicity NOEL = 300 ppm  
Systemic Toxicity LOEL = 1000 ppm

Core Classification: Core Supplementary Data.

This study does not satisfy the guideline requirements (§82-1b) for a subchronic toxicity study in nonrodents. Major deficiency: the purity of the test article was not provided, this study can be upgraded if data is supplied and found acceptable to the Agency.

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