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DATA EVALUATION REPORT

CGA-51202
(METOCHLOR OA) (DEGREDATE OF METOCHLOR)

STUDY TYPE: SUBCHRONIC ORAL TOXICITY FEEDING - RAT [OPPTS 870.3100 (82-1)]
MRID 44929509

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

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Prepared by

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Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

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DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Toxicity Feeding - Rat [OPPTS 870.3100 (§82-1)]

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

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

TEST MATERIAL (PURITY): CGA-51202 (Metochlor OA, degredate of metochlor, 100% a.i.)

SYNONYMS: Not provided

CITATION: Schneider, M. (1992) CGA-51202: Final Report. 3-Month oral toxicity study in rats (Administration in food). CIBA-GEIGY Limited, Short/Long-term Toxicology, 4332 Stein, Switzerland. Laboratory Study ID: 911344, July 23, 1992. MRID 44929509. Unpublished.

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

EXECUTIVE SUMMARY: In a subchronic oral feeding study, (MRID 44929509), CGA-51202 technical (100% a.i.; batch No. JD 7069/3) was fed to groups of 10 male and 10 female albino rats at dose levels of 0, 300, 1000, or 15,000 ppm for 3 months. The average achieved doses for the corresponding groups were 0, 18.7, 62.1, and 1000 mg/kg bodyweight for males, and 0, 20.6, 67.3, and 1020 mg/kg for females.

All animals survived to study termination and no treatment-related clinical signs were observed. There were no treatment-related effects on body weight, food consumption, ophthalmoscopic parameters, or urinalysis. Platelet counts were decreased 16% ($p<0.01$) in high-dose males. Total protein in high-dose males (5% decrease, $p<0.01$) and females (4% decrease, N.S.) was slightly decreased due to decreased globulin in males and decreased albumin and globulin fractions in females. These effects were not considered biologically significant. There were no treatment-related organ weight effects or macroscopic or microscopic lesions. **Under the conditions of this study, the NOAEL is 15,000 ppm in the diet (1000 mg/kg for males, 1020 mg/kg for females, limit dose) based on no biologically significant effects. A LOAEL was not identified.**

This subchronic toxicity study in rats (82-1) is classified as **Acceptable/Guideline.** It satisfies the guideline requirement for a subchronic dietary toxicity study in rodents.

COMPLIANCE: Signed and dated GLP, Data Confidentiality, and Quality Assurance, and Flagging statements were provided.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: CGA- 51202 technical

Description: beige, crystalline
Lot/Batch #: JD 7069/3
Purity: 100%
Stability of compound: study report states "September, 1995"
CAS #: not provided

2. Vehicle and/or positive control

Vehicle: Diet, Nafag No. 890 Tox.

3. Test animals

Species: albino rat
Strain: Tif: RAIf (SPF) hybrids of RII/1 x RII/2
Age and weight at study initiation: approximately 5-6 weeks old; males: 112.5-132.0 g; females: 105.2-124.3 g
Source: CIBA-GEIGY Limited, 4332 Stein, Switzerland
Housing: housed 5/macrolon type 4 cage with wire mesh tops
Diet: Nafag No. 890 Tox., *ad libitum*
Water: drinking water (tap) available, *ad libitum*
Environmental conditions:
Temperature: 22 ± 2°C
Humidity: 55 ± 10
Air changes: 16-20 changes/hour
Photoperiod: 12 hours light/dark cycle
Acclimation period: 7 days

B. STUDY DESIGN

1. In life dates

Start: December 10, 1991; end: March 11, 1992

2. Animal assignment

Rats were assigned randomly to the study using a computer-generated program. The study design is shown in Table 1.

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TABLE 1. Study design					
Test group	Conc. in diet (ppm)	Achieved dose (mg/kg)		Number of animals	
		Male	Female	Male	Female
Control	0	0	0	10	10
low-dose	300	18.7	20.6	10	10
mid-dose	1000	62.1	67.3	10	10
high-dose	15,000	1000	1020	10	10

Data taken from pp. 17 and 34-35, MRID 44929509.

3. Test material preparation and analysis

CGA-51202 technical was weighed and appropriate amounts were homogeneously mixed with pulverized food. The food was pelleted by adding ~25% drinking water to ensure necessary quality. Pellets were then air dried. Test diets were prepared at monthly intervals and stored in stainless steel containers at room temperature. Homogeneity analysis was performed by HPLC on food samples containing the test article at concentrations of 100, 1000 and 15000 ppm from three different segments of feed preparation (beginning, middle, end). Stability analyses of test diets were performed by HPLC on days 0 and 35. Concentration analyses were performed by HPLC on test diets prepared on December 4, 1991 and January 27, 1992.

Results -
Homogeneity analysis: The range of the test compound concentration from the sample's beginning, middle, and end varied in the range of -3% to +4% of the mean concentration.

Stability analysis: The CGA 51202 was found to be stable in rodent feed at room temperature over a period of 5 weeks. Percentages of the initial values after 35 days were: 102.6% at 100 ppm, 99.2% at 1000 ppm, and 97.7% at 15000 ppm.

Concentration analysis: CGA 51202 concentration ranges were 86.6-92.3% (300 ppm), 89.5-89.6% (1000 ppm), and 88.3-90.6% (15000 ppm). No test compound was detected in the control sample.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

4. Statistics

"For each time point and parameter an univariate statistical analysis was performed. Nonparametric methods were applied, to allow for non normal as well as normal data

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distribution. Each treated group was compared to the control group by Lepage's two-sample test and tested for increasing or decreasing trends from control up to the respective dose group by Jonckheere's test for ordered alternatives."

C. METHODS

1. Observations

All animals were observed twice daily (morning and afternoon) for mortality and signs of overt toxicity. All animals received a detailed physical at least weekly.

2. Body weight

All animals were weighed weekly beginning during the acclimation period.

3. Food consumption and compound intake

Food consumption was recorded weekly. Food consumption ratios were calculated as the mean of individual weekly ratios as follows:

$$\frac{\text{Weekly food consumption (g)}}{\text{midweek bodyweight (g)}} \times \frac{1000}{7} = \text{g food / kg bodyweight / day}$$

Compound intake was calculated (mg/kg/day) for corresponding food consumption intervals as follows:

4. Ophthalmoscopic examination

Ophthalmologic examinations were conducted on control and high-dose animals using an ophthalmoscope. Examinations were performed prior to study initiation (day -6) and after 85 days of treatment.

5. Blood was collected from the orbital sinus of ether anesthetized animals at the end of the study. The animals were fasted overnight prior to sample collection. The CHECKED (X) parameters were examined.

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a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)
x	Platelet count*		Reticulocyte count
	Blood clotting measurements*		Heinz body determination
	(Thromboplastin time)		RBC morphology
	(Clotting time)		
x	(Prothrombin time)		

* Required for subchronic studies based on Subdivision F Guidelines

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
	Magnesium	x	Blood urea nitrogen*
x	Phosphorus*	x	Total cholesterol
x	Potassium*	x	Globulins
x	Sodium*	x	Glucose*
		x	Total bilirubin
	ENZYMES	x	Total serum protein (TP)*
x	Alkaline phosphatase (ALK)		Triglycerides
	Cholinesterase (ChE)		Serum protein electrophoresis
	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
x	Serum alanine amino-transferase (also SGPT)*		
x	Serum aspartate amino-transferase (also SGOT)*		
x	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic studies based on Subdivision F Guidelines

6. Urinalysis*

Urine was collected from individual animals in metabolism cages overnight. Food and water were withheld during the sample collection period. The CHECKED (X) parameters were examined.

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

*Not required for subchronic studies by Subdivision F Guidelines.

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7. Sacrifice and pathology

All animals survived the treatment period and were sacrificed under ether anesthesia on schedule by exsanguination. Gross pathological examination was performed on all rats, and the CHECKED (X) tissues were preserved in 4% neutral buffered formalin. The (XX) organs were weighed. The X* organs were embedded in paraplast, sectioned at 3-5 microns, stained with hematoxylin and eosin, and examined microscopically.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT	X	NEUROLOGIC
x	Tongue	x*	Aorta**	xx	Brain**
x*	Salivary glands**	x*	Heart**	x*	Periph. nerve**
x*	Esophagus**	x*	Bone marrow**	x	Spinal cd. (3 levels)[T, 1]
x*	Stomach**	x*	Lymph nodes**	x*	Pituitary**
x*	Duodenum**	x*	Spleen**	x	Eyes (optic n.)[T]
x*	Jejunum**	x*	Thymus**		
x*	Ileum**				**GLANDULAR**
x*	Cecum**		**UROGENITAL**	xx	Adrenal gland**
x*	Colon**			x	Lacrimal gland[T]
	Rectum**	xx	Kidneys**[+]	x	Mammary gland[T]
xx*	Liver**[+*]	x*	Urinary bladder**	x*	Parathyroids**
	Gall bladder	xx	Testes**[+]	x*	Thyroids**
x*	Pancreas**	x	Epididymides		
		x	Prostate		
	RESPIRATORY	x	Seminal vesicle		**OTHER**
		xx	Ovaries	x	Bone
x*	Trachea**	x*	Uterus**	x	Skeletal muscle
x*	Lung**	x*	Vagina	x	Skin
x	Nose			x*	All gross lesions and masses**
	Pharynx				
	Larynx				

** = Required for subchronic studies based on Subdivision F Guidelines
[+] = Organ weight required in subchronic and chronic studies.
[T] = Required only when toxicity or target organ
[1] = Cervical spine only

II. RESULTS

A. OBSERVATIONS

1. Toxicity

There were no compound-related clinical observations observed.

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2. Mortality

All animals survived to study termination.

B. BODY WEIGHT

No treatment-related body weight effects were noted. Data are summarized in Table 2.

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TABLE 2. Group mean body weights (g) in rats fed CGA51202 for 13 weeks				
Week of study	Exposure concentration (ppm)			
	0	300	1000	15,000
	Males			
-1	122.0	123.6	122.2	122.0
1	184.4	184.6	181.1	179.4
2	248.7	245.3	242.2	240.9
3	309.0	302.2	297.6	302.7
4	353.8	340.6	344.0	344.4
5	384.8	377.5	382.8	381.4
6	416.3	406.4	412.2	410.1
7	444.1	431.2	438.2	434.1
8	468.1	453.1	460.1	458.2
9	485.1	466.7	476.6	474.1
10	503.1	480.4	489.4	481.8
11	515.4	495.5	503.2	492.4
12	526.5	507.4	516.0	504.5
13	539.8	520.9	531.1	518.1
	Females			
-1	114.6	113.9	114.4	114.5
1	154.9	153.5	154.3	152.3
2	181.7	188.0	186.7	185.3
3	205.7	215.7	217.4	210.9
4	234.3	239.6	245.5	237.3
5	249.3	260.3	262.8	254.4
6	257.5	269.9	267.4	268.8
7	269.4	287.1	282.7	278.4
8	283.0	301.9	294.5	288.6
9	288.1	310.6	305.6	293.4
10	294.7	312.4	309.8	297.2
11	300.4	321.8	320.1	306.0
12	305.2	325.3	320.4	312.9
13	312.6	327.9	323.1	312.0

Data taken from pp. 38-39, MRID 44929509.
No Statistical significance was achieved.

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C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. Food consumption

No treatment-related, biologically significant food consumption effects were observed. Food consumption was decreased ($p<0.05$) 6.8% in mid-dose males and 9.8% in high-dose males compared to controls during week 1 only. Food consumption was increased ($p<0.05$) 17% in mid-dose females compared to controls during week 3 only.

2. Compound consumption

Animals were offered diets containing the compound *ad libitum* for 90 days. Achieved doses are shown in Table 1.

3. Food consumption ratios

Food consumption ratios were 2.1-11.7% higher than controls in high-dose males from weeks 3 through 13. No other effects were noted.

D. OPHTHALMOSCOPIC EXAMINATION

There were no treatment-related findings.

E. BLOOD WORK

1. Hematology

Platelet counts were decreased ($p<0.01$) 16% in high-dose males compared to controls. This change is not considered biologically relevant.

2. Clinical chemistry

Clinical chemistry parameter effects were noted in high-dose animals. Total protein in high-dose males (5% decrease, $p<0.01$) and females (4% decrease, N.S.) was slightly decreased due to decreased globulin in males and decreased albumin and globulin fractions in females. Other observations ($p<0.01$) included a 23% decrease in total bilirubin and a 22% decrease in cholesterol in high-dose males, and a 21% decrease in alanine amino transferase in high-dose females compared to controls. These effects are not considered biologically relevant as they are all within historical control ranges.

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F. URINALYSIS

No treatment-related effects were noted.

G. SACRIFICE AND PATHOLOGY

1. Organ weight

No biologically significant, treatment-related effects were noted. Mean absolute liver weight was decreased ($p<0.01$) 10-16% in all male treatment groups compared to the control. However, a dose-response was not observed and the author attributes the apparent effect to a comparatively high mean value for the control group (compared to historical controls). The mean relative adrenal weight was increased ($p<0.01$) 6% in high-dose females and 11% in high-dose males compared to controls; however, no corroborative pathology was observed. No other organ weight effects were observed.

2. Gross pathology

There were no treatment-related gross lesions.

3. Microscopic pathology

There were no treatment-related microscopic lesions.

III. DISCUSSION

A. DISCUSSION

All animals survived to study termination and no treatment-related clinical signs were observed. There were no treatment-related effects on body weight, food consumption, opthlamological parameters, or urinalysis. Platelet counts were decreased 16% ($p<0.01$) in high-dose males. Total protein in high-dose males (5% decrease, $p<0.01$) and females (4% decrease, N.S.) was slightly decreased due to decreased globulin in males and decreased albumin and globulin fractions in females. The observed hematology and clinical chemistry changes are not considered biologically relevant since they are within historical control ranges and/or are of small magnitude. There were no treatment-related organ weight effects or macroscopic or microscopic lesions.

It is probable that the minor hematological and clinical chemistry changes in observed high-dose animals are treatment-related, and can be considered a LOEL. However, in light of the small magnitude and biological insignificance of the changes, they do not, in the reviewer's opinion, define a LOAEL. It should be noted that the study author did consider the high dose to be a LOAEL.

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Under the conditions of this study, the NOAEL is 15,000 ppm (1000 mg/kg for males, 1020 mg/kg for females, limit dose) based on a lack of biologically significant effects. A LOAEL was not identified.

This subchronic toxicity study in rats [870.3100 (82-1)] is classified as **Acceptable/Guideline.** It satisfies the guideline requirement for a subchronic dietary toxicity study in rodents.

B. STUDY DEFICIENCIES

Although a LOAEL was not determined, CGA-51202 was tested up to the limit dose. A minor deficiency is the lack of histopathological evaluation of the rectum. This does not compromise the study.

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