THE RFD/PEER REVIEW MEETING FOR ALPHA-METOLACHLOR WILL BE HELD ON THURSDAY, APRIL 10 IN ROOM 817 FROM 10:00 TO 12:00.

Alpha-Metolachlor: New chemical. This chemical requires RfD and developmental toxicity assessments. Mutagenicity studies have been given to Nancy McCarroll for review.

K. Baetcke
W. Burnam
K. Farwell
G. Ghali
M. Ioannou
S. Makris
N. McCarroll
G. Reddy
W. Sette
H. Spencer

Alpha-Metolachlor:

Reviewer: S. Dapson
Section Head: J. Rowland

UNDATED
PC 108800

CHEMICAL: ALPHA-METOLACHLOR
PC CODE: 108800

DER #	STUDY TYPE - DOSE LEVELS	NOEL (mg/kg/day)	LEL (mg/kg/yay)
1	DEVELOPMENTAL TOX RAT (1995) 0, 5, 50, 500 & 1000 mg/kg/day	50 (Maternal) 1000 (Development) [Acceptable - Guideline]	500 (Maternal) --- (Developmental)
2	DEVELOPMENTAL TOX RABBIT (1995) 0, 20, 100 & 5000 mg/kg/day	20 (Maternal) 500 (Developmental) [Acceptable - Guideline]	100 (Maternal) --- (Developmental)
3	13-WEEK FEEDING RAT (1995) 0, 30, 300, 3000 & 10000 ppm 0, 1.5, 15, 150 & 500 mg/kg/day	15 [Acceptable - Guideline]	150
4	13-WEEK FEEDING DOG (1995) 0, 300, 500, 1000 & 2000 ppm M: 0, 9, 15.1, 31.1 & 62 mg/kg F: 0, 10, 17.2, 31.5 & 74 mg/kg	62 (Male) 74 (Female) [Acceptable - Nonguideline]	--- (Male) --- (Female)

CGA-77102 (A CHIRAL METOLACHLOR)

I. INTRODUCTION

The subject of this **Reduced Risk Document** is CGA-77102 (proposed common name of alpha-metolachlor pending ISO approval). Registration of this product will have a favorable environmental impact as it will result in a reduction of between 22-26 MM pounds of active ingredient being introduced annually into the environment compared to the continued use of metolachlor.

CGA-77102 is the [RS,1S]isomer pair in metolachlor that is responsible for most of the herbicidal activity demonstrated with use of metolachlor. Metolachlor is the most widely used herbicide in the chloroacetamide family of herbicides and is the second most widely used herbicide in the U.S. in terms of pounds applied. It was first registered in 1976 and introduced for use on corn in 1977. Since that time, metolachlor usage has expanded into many additional crops, including soybeans, peanuts, sorghum, potatoes, cotton, safflower, and legume vegetables, as well as several other minor use crops.

Most recently, in 1995, EPA issued a **Reregistration Eligibility Decision (RED)** for metolachlor. That decision shows the data base for metolachlor is essentially complete with only a few outstanding studies to be submitted (2 small-scale prospective ground water studies, one of which is to be proposed to be conducted with CGA-77102, avian reproduction studies in the bobwhite quail and mallard duck, and residue storage stability).

In developing CGA-77102, Ciba used a "bridging data" concept. Data were developed which would demonstrate the equivalency or enhanced safety profile for CGA-77102 when compared to metolachlor. Ciba believes the data package for CGA-77102 is quite complete and provides ample data for the Agency to make a decision on its registrability. For those data not generated for CGA-77102 alone, Ciba wishes to rely on metolachlor's acceptable data base cited in the **RED** which in essence reflects CGA-77102 as well, as it is the active part of metolachlor and comprises 50 percent of metolachlor.

Many of the labeling requirements of the **Metolachlor RED** are included on the labels of the CGA-77102-containing end-use products. A technical and three end-use products are proposed for registration at this time. The end-use product labels are equivalent to existing metolachlor end-use products, except that the use rate will be reduced as discussed below. Further discussion of the end use products follows in the **Reduced Risk Rationale** section.

Metolachlor is a 1:1 mixture of CGA-77101 and CGA-77102. CGA-77102's herbicidal properties have been known since 1983, however, due to manufacturing and cost constraints, commercialization of CGA-77102 was not possible at that time.

Recent innovations by Ciba chemists and engineers have resulted in an economical method by which to produce a higher ratio of CGA-77102:CGA-77101 (88:12).

Efficacy studies completed with CGA-77102 and metolachlor show that no weed control properties are sacrificed when CGA-77102 is applied at approximately 62.5% of the metolachlor rate. A more complete discussion of the biology of CGA-77102 compared to metolachlor and other chloroacetamides is presented in **Section F** of this document.

CGA-77102 is proposed for use on the same crops for which metolachlor is currently registered (40CFR180.368). As stated previously, CGA-77102 will be used at approximately 62.5% of the metolachlor rate. Residue data generated for CGA-77102 on corn and soybeans, the two crops metolachlor is used most widely on, shows that residues of CGA-77102 are equivalent to or less than that of tolerances already established for metolachlor. Therefore, the accompanying submission does not petition the Agency for separate tolerances for CGA-77102, as Ciba wishes to rely on the already established tolerances for metolachlor.

Because of the more than one-third rate reduction across all crops, commercialization of CGA-77102 will result in reduced environmental loading, both in terms of the amount of pesticide used per acre and the packaging used to deliver it to the customer. This rate reduction is expected to result in reduced residues in groundwater, which is a stated Agency concern for metolachlor, as it is one of the five pesticides under consideration for the implementation of State Management Plans. A more detailed discussion of reduced environmental loading is presented in **Section G** of this document.

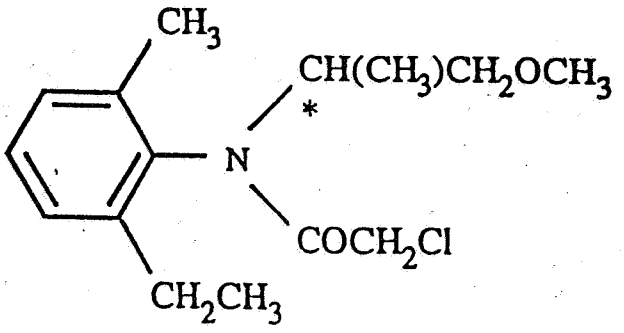
As you will see from the in-depth discussions of CGA-77102's safety profile, it closely parallels that of metolachlor. And when it is compared to the other chloroacetamide family members, a favorable risk reduction picture develops.

Ciba believes the registration of CGA-77102 demonstrates its commitment to developing and commercializing pesticides under the Agency's reduced risk initiative. The registration will also meet the Agency's stated goals of reducing pesticide use.

Because metolachlor is currently the second most widely used herbicide in the U.S., Ciba is not prepared at this time to cancel its registration in favor of CGA-77102. The magnitude of the conversion in logistical terms coupled with production capacities for CGA-77102 make a phase-in of CGA-77102 over a three to five year period more practical, resulting in the conversion of greater than 90 percent of metolachlor use to CGA-77102 by the year 2001. Ciba wishes to introduce CGA-77102 in limited quantities for the 1997 use season and continue with the phase-in as presented to the Agency in meetings with Dr. Goldman in August, 1995 and OPP staff in December, 1995. In order to achieve this goal, an accelerated

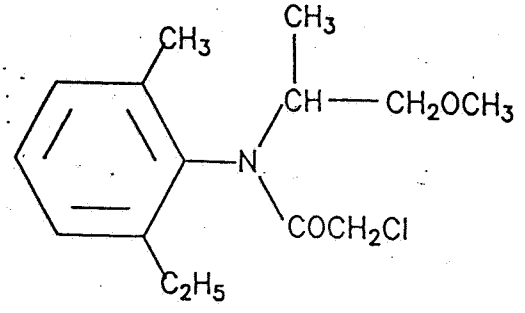
review will be needed due to the Agency's budgetary and other resource constraints. A reduced risk determination by the Agency will allow this accelerated review to get underway. Ciba believes this proposal is one which does meet the criteria for a reduced risk determination and one which will benefit the environment, the agricultural community, and the consuming public as well.

ATTACHMENT 3 - STRUCTURE OF CGA-77102



$C_{15}H_{22}ClNO_2$

ATTACHMENT 4 - STRUCTURE OF CGA-77102



$C_{15}H_{22}ClNO_3$

Metolachlor

BP: Ciba (Dual*, Dual II*, Pennant*)
Ciba, Ltd. (Dual*, Dual S*, Dualor*)

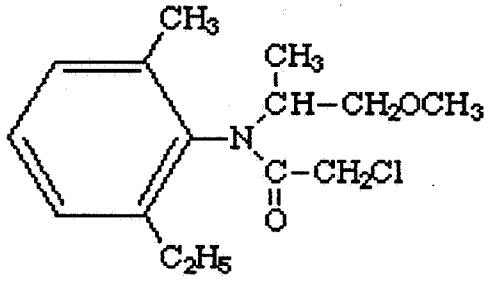
Identification

COMMON NAME: Metolachlor (ISO, ANSI, BSI, WSSA); métolachlore (ISO-F).
EXP. CODE NUMBERS: CGA-24705 (Ciba-Geigy).
OTHER CODE NUMBERS: CAS 51218-45-2; SHA 108801; EINECS 257-060-8.
DISCONTINUED NAMES: Pyracur* L (+ chloridazon + lenacil) (BASF AG); Cycle* (+ cyanazine) (Ciba); Milocep* (+ propazine), Ontrack* (Ciba-Geigy).
Chemistry

COMPOSITION: 2-chloro-N-(2-ethyl-6-methylphenyl) -N-(2-methoxy-1-methylethyl) acetamide (CAS). Dual II* contains the safener benoxacor.

CLASS: Chloracetanilide.

PROPERTIES: Odorless white to tan liquid, boiling point 100°C at 0.001 mm/Hg. Miscible with most organic solvents.
Metolachlor - Chemical Structure



Action/Use
ACTION: Selective herbicide.
USE: Preemergence and preplant incorporated weed control in corn, soybeans, peanuts, grain sorghum (seed treated with safener Concep* II or III), potatoes, pod crops, cotton, safflower, and woody ornamentals.

FORMULATIONS: Emulsifiable concentrate, granules.

PREMIXES: Pyracur* (+ chloridazon) (BASF AG); Turbo* (+ metribuzin) (Bayer); Bicep*, Bicep II*, Bicep Lite II* (+ atrazine), Derby* (+ simazine) (Ciba); Codal* (+ prometryn), Primagram*, Primextra* (+ atrazine), Cotoran Multi* (+ fluometuron) (Ciba, Ltd.); Broadstrike*+Dual* (+ flumetsulam) (DowElanco); Galex* (+ metobromuron).

Registration Notes
OUTSIDE U.S.: Dual S* for use outside of North America; Dualor* for use in France.
Environmental Guidelines

HAZARDS: Bird: Oral LD50 >2510 mg/kg (mallard). Dietary LC50 >10,000 ppm (mallard).

SOIL PARTICLE ADSORPTION: Data incomplete, but indicates essentially stable in loamy sand over 64 days. Mobile in sandy clay loam, loam soil.
SOLUBILITY: Solubility in water, 530 ppm at 20°C.

Safety Guidelines
SIGNAL WORD: CAUTION.
TOXICITY CLASS: III.

TOXICITY: Tech (Rat): Oral LD50 2780 mg/kg. Inhalation LC50 (4 h) >1.75 mg/l. (Rabbit): Dermal LD50 >10,000 mg/kg. Nonirritating to eye, mildly irritating to skin.
Dual* 8E: 2534 mg/kg. Inhalation (4 h) >6.0 mg/l. (Rabbit): >5009 mg/kg. Moderately irritating to eye, skin.

SPILL CONTROL/CLEANUP: Large spillages should be dammed-off and pumped into containers; soak up remainder with absorbent material and dispose of in accordance with local regulations.

PRODUCT/WASTE DISPOSAL: Must be disposed of by special means, e.g., suitable incineration, in accordance with local regulations.

Dr. G. Ghali

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

25 AUG 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: RfD/Peer Review Report of Metolachlor
EPA Chem Code: 108801
CAS No. 51218-45-2
Reg. Group: List A

FROM: George Z. Ghali, Ph.D. G. Ghali 7/27/93
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (H7509C)

TO: Richard Mountfort, PM 23
Herbicide-Fungicide Branch
Registration Division (H7505C)

Walter Waldrop/Connie Childress, PM 71
Special Review Branch
Special review and Re-registration Division
(H7508W)

Lois Rossi, Chief
Re-registration Branch
Special review and Re-registration Division
(H7508W)

The Health Effects Division RfD/Peer Review Committee met on September 17, 1992 and again on April 1, and May 27, 1993 to evaluate data available in support of Metolachlor re-registration. Material available for review included an RfD summary document, and data evaluation records for chronic and subchronic feeding studies in rats and dogs, carcinogenicity studies in rats and mice, developmental toxicity studies in rats and rabbits and a two-generation reproduction study in rats.

A Reference Dose (RfD) for Metolachlor was assessed by the Health Effects Division RfD Committee on March 21, 1986 and verified by the Agency RfD Work Group on April 22, 1986. The RfD was then reassessed by the Health Effects Division RfD Committee on April 7, 1988 and verified by the Agency Work Group on June 22, 1988. The current RfD value on IRIS is 0.15 mg/kg/day based on a NOEL of 15 mg/kg/day for decreased body weight gain observed at 150 mg/kg/day in a long-term feeding study in rats using an uncertainty factor of 100.

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Subsequently, a long-term feeding study in dogs, with a lower no-observable effect level, was submitted to the Agency. This information was considered, along with all other data, in reassessing the RfD for Metolachlor. In the meeting of May 27, 1993, the Committee recommended that an RfD should be established based upon a NOEL of 9.7 mg/kg/day for decreased body weight gain observed at 32.7 mg/kg/day in the long-term feeding study in dogs using an uncertainty factor of 100 to account for the interspecies extrapolation and the intraspecies variability.

The Committee considered the long-term toxicity study in dogs (83-1b), the chronic toxicity phase of the rat study (83-1a), the developmental toxicity studies in rats and rabbits (83-3a and -3b) and the reproduction study in rats (83-4) to be acceptable. In the meeting of September 17, 1992 the Committee recommended revisions and/or updates to the data evaluation records of the long-term study in dogs, the reproduction study in rats and the developmental toxicity studies in rats and rabbits. These revisions and updates were completed and the revised and updated data evaluation records were made available to the Committee in the subsequent meeting.

The RfD Committee did not discuss the carcinogenicity phase of the rat study and the mouse carcinogenicity study since the carcinogenicity issue had already been addressed by the Health Effects Division Carcinogenicity Peer Review Committee (CPRC). According to the CPRC, the chemical was classified as a "group C", possible human carcinogen. Quantification of carcinogenicity risk using a low dose extrapolation (Q^{*1}) was recommended by the same committee.

There was no evidence, based on the available data, that the chemical was associated with significant reproductive or developmental toxicity under the testing conditions.

There were limited data available for review to address or characterize the hazard of a one-time or one-day exposure. However, data available for review did not indicate that a one-day exposure to the chemical would be of such concern as to warrant the need for acute exposure studies to be used in an acute dietary risk assessment.

A. Individual in Attendance

1. Peer Review Committee Members and Associates (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Reto Engler

Marcia Van Gemert

Karl Baetcke

Henry Spencer

William Sette

Roger Gardner

James Rowe

Esther Rinde

John Tice

George Ghali

Rick Whiting

2. Scientific Reviewer(s) (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Stephen Dapson

Mike Ioannou

3. Others:

Kerry Dearfield, Flora Chow, Linda Kutney and Virginia Dobozy of the Health Effects Division as observers

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia Van Gemert
Mike Ioannou/Stephen Dapson
Rick Whiting
Flora Chow
James Kariya

B. Material Reviewed

Material available for review in one or more of the three meetings held on Metolachlor included chronic toxicity/ carcinogenicity study in rats (83-5 or 83-1a and -2a), long-term toxicity study in dogs (83-1b), carcinogenicity study in mice (83-2b), developmental toxicity study in rats (83-3a), developmental toxicity study in rabbit (83-3b), a reproduction study in rats (83-4), an RfD summary document and a tox. one-liner. The Committee focused on the following studies

1. Hazellete, J. R. and Arthur, A. T. (1989). Metolachlor technical: 52-week oral toxicity study in dogs. MRID No. 40980701, 41164501, 42218601, 42218602, MRID No. 008442, 01088.

Core Classification: This study is classified Core-Guideline according to the data evaluation record.

Committee's Conclusions and Recommendations:

The chemical was tested at 100, 300 and 1000 ppm (equivalent to 3.5, 9.7 and 32.7 mg/kg/day and 3.6, 9.7 and 33.0 mg/kg/day for males and females respectively). The committee generally agreed with the reviewer's evaluation and interpretation of the data. However, in the meeting of September 17, 1992 the Committee questioned the significance of body weight gain decrease since it was minimal and was accompanied by decrease in food consumption. The Committee requested food efficiency information. The Committee questioned also the increase in alkaline phosphatase in both males and females. The reviewer indicated that this increase was relative to the decrease of alkaline phosphatase in the concurrent controls and this fluctuation was within the normal biological range. The study was considered acceptable and the data evaluation record, except for minor revisions, i. e. inclusion of food efficiency data, was considered adequate. This study fulfills data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in a non-rodent species.

2. Estes, F. L. (1980). 6-Month chronic oral toxicity study in Beagle dogs. MRID No. 00032174, HED Doc. No. 000000

Core Classification: This study is classified Core-supplementary according to the data evaluation record.

Committee's Conclusions and Recommendations:

The chemical was tested at 100, 300 and 1000 ppm. This study provided useful supplemental information. The committee generally agreed with the reviewer's evaluation and interpretation of the data. When the long-term toxicity study in dogs (above) is viewed in light of the results of this six-month feeding study in dogs, they both provided a some what reasonable basis to establish a no-

observable effect level for what appeared to be marginal effects seen in the long-term study. The results of this study support a no-observable effect level of 9.7 mg/kg/day in the long-term study.

3. Tisdel, M. (1983). Two-year chronic oral toxicity and oncogenicity study with metolachlor in Albino rats. MRID No. 00129377, HED Doc. No. 000000.

Core Classification: This study is classified Core-minimum according to the data evaluation record.

Committee's Conclusions and Recommendations:

The chemical was tested at 30, 300 and 3000 ppm (equivalent to 1.5, 15 and 150 mg/kg/day). This study was not evaluated by the Committee in the Meeting of September 17, 1992. In the April 1, 1993 meeting the Committee requested the respective branch to update the chronic toxicity phase of the rat study because of possible impact on the reference dose assessment. In the meeting of May 27, 1993 the committee examined the updated data evaluation record of the chronic toxicity phase of the rat study and generally agreed with the reviewer's evaluation and interpretation of the data. The effects observed in this study were limited to increase relative (7%) and absolute (13%) liver weights in males. This liver changes were also observed after the four weeks recovery period. This study fulfills data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.

4. Lochry, E. A. (1985). Embryo-fetal toxicity and teratogenic potential study of CGA-24705 (FL-841697) administered orally via gavage to rats. MRID No. 00151941, HED Doc. No. 009509.

Core Classification: This study is classified as Core-minimum according to the data evaluation record.

Committee's Conclusions and Recommendations:

The chemical was tested at 30, 100, 300 and 1000 mg/kg/day. In the meeting of September 17, 1992 the Committee recommended to the respective branch to reevaluate the study and update the data evaluation record. The updated data evaluation records were submitted to the Committee for consideration in the meeting of April 27, 1993. The committee generally agreed with the reviewer's evaluation and interpretation of the data. However, the Committee recommended to revise the NOEL/LOEL for maternal toxicity to be 100 and 300 mg/kg/day based on increased salivation in a significant number of animals. The NOEL/LOEL for developmental toxicity were considered to be 300 and 1000 mg/kg/day respectively. This study fulfills data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

5. Lightkep, G. E. (1980). Teratogenic potential of CGA-24705 in New Zealand white rabbits. MRID No. 00041283, HED Doc. No. 010088.

Core Classification: This study is classified as Core-minimum according to the data evaluation record.

Committee's Conclusions and Recommendations:

The chemical was tested at 36, 120 and 360 mg/kg/day. In the meeting of September 17, 1992 the Committee recommended to the respective branch to reevaluate the study and update the data evaluation record. The updated data evaluation records were submitted to the Committee for consideration in the meeting of April 27, 1993. The committee generally agreed with the reviewer's evaluation and interpretation of the data. The NOEL/LOEL for maternal toxicity were considered to be 120 and 360 mg/kg/day, respectively. The developmental toxicity NOEL/LOEL were considered to be > 360 mg/kg/day. This study fulfills data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

6. Page, J. G. (1981). Two-generation reproduction study in Albino rats with metolachlor technical. MRID No. 00080897, HED Doc. No. 010088.

Core Classification: This study is classified as Core-Guideline according to the data evaluation record.

Committee's Conclusions and Recommendations:

The chemical was tested at 30, 100 and 1000 ppm. In the meeting of September 17, 1992 the Committee recommended to the respective branch to reevaluate the study and update the data evaluation record. The updated data evaluation records were submitted to the Committee for consideration in the meeting of April 27, 1993. The committee generally agreed with the reviewer's evaluation and interpretation of the data. The NOEL for maternal/systemic toxicity was considered to be > 1000 ppm. Based on the reduction of body weight of the progeny in both F1a and F2a, the reproductive toxicity NOEL/LOEL were considered to be 300 and 1000 ppm respectively. This study fulfills data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

C. Conclusions and Recommendations

1. Reference Dose

A Reference Dose (RfD) for Metolachlor was assessed by the Health Effects Division RfD Committee on March 21, 1986 and verified by the Agency RfD Work Group on April 22, 1986. The RfD was then reassessed by the Health Effects Division RfD Committee on April 7, 1988 and verified by the Agency Work Group on June 22, 1988. The current RfD value on IRIS is 0.15 mg/kg/day based on a NOEL of 15 mg/kg/day for decreased body weight gain observed at 150 mg/kg/day in a long-term feeding study in rats using an uncertainty factor of 100.

Subsequently, a long-term feeding study in dogs, with a lower no-observable effect level, was submitted to the Agency. This information was considered, along with all other data, in reassessing the RfD for Metolachlor. In the meeting of May 27, 1993, the Committee recommended that an RfD should be established based upon a NOEL of 9.7 mg/kg/day for decreased body weight gain observed at 32.7 mg/kg/day in the long-term feeding study in dogs using an uncertainty factor of 100 to account for the interspecies extrapolation and the intraspecies variability.

2. Data Base

The Committee considered the long-term toxicity study in dogs (83-1b), the chronic toxicity phase of the rat study (83-1a), the developmental toxicity studies in rats and rabbits (83-3a and -3b) and the reproduction study in rats (83-4) to be acceptable. In the meeting of September 17, 1992 the Committee recommended revisions and/or updates to the data evaluation records of the long-term study in dogs, the reproduction study in rats and the developmental toxicity studies in rats and rabbits. These revisions and updates were completed and the revised and updated data evaluation records were made available to the Committee in the subsequent meeting.

3. Carcinogenicity

The RfD Committee did not discuss the carcinogenicity phase of the rat study and the mouse carcinogenicity study since the carcinogenicity issue had already been addressed by the Health Effects Division Carcinogenicity Peer Review Committee (CPRC). According to the CPRC, the chemical was classified as a "group C", possible human carcinogen. Quantification of carcinogenicity risk using a low dose extrapolation (Q^{*1}) was recommended by the same committee.

4. Acute and Subchronic Toxicity Concern

There was no evidence, based on the available data, that the

chemical was associated with significant reproductive or developmental toxicity under the testing conditions.

There were no data available for review to address or characterize the hazard of a one-time or one-day exposure. However, other data available for review did not indicate that a one-day exposure to the chemical would be of such concern as to warrant the need for acute exposure studies to be used in an acute dietary risk assessment.

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

Chemical Name: Metolachlor

PC Code: 108801

Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

Reviewer: Mike Ioannou J M Ioannou Date: 1/4/95

Branch Chief: Marcia van Gemert M van Gemert Date: 1/4/95

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Dermal Absorption Data (If available)

MRID: 418331-02

% absorbed: 62.8% after 24 hours in a rat dermal penetration study in which 0.01 mg/cm^2 was applied.

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Acute Dietary Endpoint (One Day)

Study Selected - Guideline No.: None

MRID No.: None

Summary (Enter Standard Executive Summary or equivalent):

None

Endpoint and dose for use in risk assessment.

None

Comments about study and/or endpoint:

None

This risk assessment is not required. No study was identified from the database which indicated the potential for adverse effects after a single dietary exposure.

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Short Term Occupational or Residential Exposure (1 to 7 Days)

Study Selected - Guideline No.: None

MRID No.: None

Summary (Enter Standard Executive Summary or equivalent):

None

Endpoint and dose for use in risk assessment.

None

Comments about study and/or endpoint:

None

This risk assessment is not required. No study was identified that indicated the potential for adverse effects after a short term (less than 1 week) occupational or residential exposure.

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Intermediate Term Occupational or Residential (1 Week to Several Months)

Study Selected - Guideline No.: 21-Day Dermal Toxicity Study - Rabbit (82-2)

MRID No.: 418331-01

Summary: A 21-day dermal toxicity study was performed in New Zealand white rabbits with 0, 10, 100 or 1000 mg/kg/day of metolachlor. Very slilght or moderate erythema was observed in all groups. There were dose-related increases in minor histopathological alterations of the skin, in total bilirubin for females*, in absolute and relative liver weights for males, and in relative kidney weights for females. The systemic NOEL was 100 mg/kg/day for females and males. The systemic LOEL was 1000 mg/kg/day for males and females.

Endpoint and dose for use in risk assessment: NOEL = 100 mg/kg/day. See summary above.

Comments about study and/or endpoint:

This risk assessment is not required.

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Cancer Classification and Basis: C (Possible Human Carcinogen) based upon liver tumors in female rats.

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R_fD and basis: 0.097 mg/kg/day based upon the results of a one-year toxicity study in dogs.

NOEL for critical study: 9.7 mg/kg/day; LOEL = 32.7 mg/kg/day based upon decreased body weight gain in females.

Study Type - Guideline No.: One-year Oral Toxicity Study - Dog (83-1)

MRID: 411645-01

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*The increase in total bilirubin in female rabbits was considered by the Committee (on 12/14/94) to be of no biological significance and it was most probably due to an unusually low value of bilirubin in the control group. Thus, the NOEL of 100 mg/kg/day was established for male and female rabbits based on the systemic effects (see summary) observed at the 1000 mg/kg/day dose level.

CHEMICAL: METOLACHLOR
PC CODE: 108801

DER #	STUDY TYPE - DOSE LEVELS	NOEL (mg/kg/day)	LEL (mg/kg/day)
1	1-YR FEEDING DOG (1989) 0, 100, 300 & 1000 ppm M: 0, 3.5, 9.7 & 32.7 mg/kg/day F: 0, 3.6, 9.7 & 33.0 mg/kg/day	9.7 (Female) [Core grade Guideline]	33 (Female)
2	2-YR FEEDING/ONCOGENICITY RAT 0, 30, 300 & 3000 ppm 0, 1.5, 15 & 150 mg/kg/day	15 [Core grade Minimum]	150
3	2-GEN REPRODUCTION RAT 0, 30, 300, or 1000 ppm M: 0, 2.3, 23.6 & 76.2 mg/kg/dy F: 0, 2.5, 25.9 & 85.1 mg/kg/dy	76.2 (M - Systemic) 85.1 (F - Systemic) 23.6 (M - Reprod) 25.9 (F - Reprod) [Core grade Guideline]	--- --- 76.2 (M - Reprod) 85.1 (F - Reprod)
4	DEVELOPMENTAL TOX RAT (1985) 0, 30, 100, 300 & 1000 mg/kg/dy	300 (Maternal) 300 (Development) [Core grade Minimum]	1000 (Maternal) 1000 (Development)
5	DEVELOPMENTAL TOX RAT (1976) 0, 60, 180 & 360 mg/kg/day	360 (Maternal) 360 (Developmental) [No core grade]	--- ---
6	DEVELOPMENTAL TOX RABBIT (1980) 0, 36, 120 & 360 mg/kg/day	120 (Maternal) 360 (Developmental) [Core grade Minimum]	360 (Maternal) ---
7	CARCINOGENICITY MOUSE (1982) 0, 300, 1000 & 3000 ppm M: 0, 50, 170 & 526 mg/kg/day F: 0, 64, 224 & 704 mg/kg/day	178 (Male) 224 (Female) [Core grade Minimum]	526 (Male) 704 (Female)
8	6-MONTH FEEDING DOG (1980) 0, 100, 300 & 1000 ppm M: 0, 2.92, 9.71 & 29.61 mg/kg F: 0, 2.97, 8.77 & 29.42 mg/kg	9.71 (Male) 8.77 (Female) [Core grade Supplementary]	29.61 (Male) 29.42 (Female)

CHEMICAL: METOLACHLOR
PC CODE: 108801

DER #	STUDY TYPE - DOSE LEVELS	NOEL (mg/kg/day)	LEL (mg/kg/day)
8	13-WEEK FEEDING RAT (1974)	50	---
	0, 100, 300 & 1000 ppm		
	0, 5, 15 & 50 mg/kg/day	[No core grade]	

Alpha-Metolachlor: Developmental Toxicity Study in Rats
Ciba-Geigy Corporation. 1995. MRID No. 43928925.
HED Doc. No. ?.

C O M P U T E R I N V E N T O R Y P R I N T O U T

First Name: UNASSIGNED Branch: TOX1 Phone #:
Last Name: BAETCKE Room #:

CPU INFORMATION

Brand: DELL 433/L
8088:
80286:
80386:
80486: X
Mac:
Laptop:
Network: X
3.5 Drive: X
5.25 Drive: X
Math Coproc:
Serial #: 3ZHXY
Prop. #: 949788

MONITOR INFORMATION

Brand:
Color:
Mono:
Serial #:
Prop. #:

KEYBOARD INFORMATION

AT Style: X
XT Style:
Serial #:

PRINTER INFORMATION

Brand:
Laser:
Dot:
Other:
Network:
Serial #:
Prop. #:
Font Cart:

Was computer purchased with FIFRA funds (Y/N)? N
Was printer purchased with FIFRA funds (Y/N)? N

Unique Software Found Only on CPU

PROGRAMMATIC FUNDS

Date record was last updated: 10/24/94

C O M P U T E R I N V E N T O R Y P R I N T O U T

First Name: UNASSIGNED Branch: TOX1 Phone #:
Last Name: BAETCKE Room #:

CPU INFORMATION

Brand: DELL 433/L
8088:
80286:
80386:
80486: X
Mac:
Laptop:
Network: X
3.5 Drive: X
5.25 Drive: X
Math Coproc:
Serial #: 37J42
Prop. #: 949787

MONITOR INFORMATION

Brand:
Color:
Mono:
Serial #:
Prop. #:

KEYBOARD INFORMATION

AT Style: X
XT Style:
Serial #:

PRINTER INFORMATION

Brand:
Laser:
Dot:
Other:
Network:
Serial #:
Prop. #:
Font Cart:

Was computer purchased with FIFRA funds (Y/N)? N
Was printer purchased with FIFRA funds (Y/N)? N

Unique Software Found Only on CPU

PROGRAMMATIC FUNDS

Date record was last updated: 10/24/94

ALPHA-METOLACHLOR **RAT TERATOLOGY(OPPTS 870.3700; OPP 83-3A)**

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 3/27/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Jess Rowland, M.S. Jess Rowland 3/27/97
Acting Section Head, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity
Species: Rat Guideline: OPPTS 870.3700; OPP 83-3a

EPA ID No.s: EPA MRID No. 43928925
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 Technical
Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S. KHALIL (1995): CGA-77102 RAT ORAL TERATOLOGY; CIBA-GEIGY LIMITED, BASLE SWITZERLAND FOR CIBA CROP PROTECTION, CIBA-GEIGY CORPORATION; LABORATORY STUDY NUMBER 941058; AUGUST 21, 1995; EPA MRID No. 43928925

Executive Summary: In a developmental (teratology) study (MRID# 43928925), rats (Strain: Tif: RAI f (SPF), hybrids of RII/1 x RII/2 from Animal Production, WST-455, CIBA-GEIGY Limited, 4332 Stein, Switzerland) received either 0, 5, 50, 500, or 1000 mg/kg/day CGA-77102 Technical (Batch No.: v. 4673/7 with a purity of 95.6%) suspension in 0.5% (w/w) aqueous solution of sodium carboxymethylcellulose by oral gavage from gestation days 6 through 15.

No treatment related mortality was noted. There was a dose related increase in clinical signs seen as all 500 and 1000 mg/kg/day animals and 9/24 of the 50 mg/kg/day animals exhibited as pushing head through bedding for about one hour. This was noted throughout the dosing period and may be an indication of neurotoxicity. The 500 and 1000 mg/kg/day dose groups had lower overall body weights at gestation days 15 and 21 and gained less weight than the control during the dosing period (gestation days 6-16) and for the calculated periods of gestation days 6-21 and 0-21, also for corrected body weight gains from gestation days 6-21. Also the 500 and 1000 mg/kg/day dose groups had reduced food consumption during the dosing period (gestation days 6-16, statistically significantly different), reduced food consumption following the dosing period and for the overall periods (gestation days 6-21 and 0-21). This is also reflected in reduced food efficiency for the same periods (6-16, 6-21, 6-21, and 0-21). **The**

maternal toxicity NOEL was 50 mg/kg/day with a LOEL of 500 mg/kg/day based on increased clinical signs of toxicity, decreased body weights and body weight gains and reduced food consumption and reduced food efficiency.

No significant treatment related developmental toxicity was noted at the dose levels tests. **The developmental toxicity was equal to or greater than 1000 mg/kg/day, a LOEL was not reached.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§ 83-3a) for a teratology study in rats.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, Certification of Good Laboratory Practices, FLAGGING STATEMENT (according to the investigators: This study neither meets nor exceeds any of the applicable criteria.) and Quality Assurance Statement was provided.

THIS REVIEW CONTAINS TEXT INFORMATION SCANNED BY THE REVIEWER INTO ELECTRONIC FORMAT (USED IN MATERIALS AND METHODS, STUDY DESIGN AND CONCLUSIONS-INVESTIGATORS SUMMARY SECTIONS).

A. Materials and Methods

Test Compound: CGA-77102 Technical
Purity: 95.6%
Description: oily liquid
Batch No.: v. 4673/7
other provided information:
The test material was stable at room temperature and was stored at room temperature.

Vehicle(s): 0.5% (w/w) aqueous solution of sodium carboxymethylcellulose: CMC, Pharmacopeia quality, high viscosity (HERCULES POWDER Company, Product No. 7HF)

Test Animal(s): Species: rat
Strain: Tif: RAI f (SPF), hybrids of RII/1 x RII/2 (An outbred cross between two genetically stable inbred Sprague-Dawley derived strains, with high fecundity and extensive historical data)
Source: Animal Production, WST-455, CIBA-GEIGY Limited, 4332 Stein, Switzerland
Age: at mating approximately 8 weeks
Body Weight: 195.2-196.4 g at gd 0
males of the same strain were used

B. Study Design

According to the investigators (from page 12 of the report):
This study was conducted in order to determine possible adverse effects of the test substance [CGA 77102 Technical] on embryonic and fetal development following daily maternal administration from day 6 through 15 of gestation.

Mating Procedure

From page 15 of the report:
Nulliparous females were mated overnight with males of the same stock and proven fertility at an initial ratio of three females to one male in mating cages. Each cage is divided into two parts by a guillotine door, separating the sexes until 3 a.m. on the mating day, when the door opens automatically.

Three to six hours later, successful mating is assessed by the presence of a vaginal plug or of spermatozoa in a vaginal smear. This day is designated as day 0 (of pregnancy) = day 0 post coitum (p.c.). Pregnant females were removed from the mating cages and the procedure repeated for remaining females until sufficient dams were produced.

Appendix 12 identifies the animals used for mating in this study.

Nulliparous females were mated overnight with males of the same stock and proven fertility at an initial ratio of three females to one male in mating cages. Each cage is divided into two parts by a guillotine door, separating the sexes until 3 a.m. on the mating day, when the door opens automatically.

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Appendix 12 identifies the animals used for mating in this study.

Animal Husbandry

From page 15 of the report: The study was conducted under optimal hygienic conditions (OHC). The animals were housed individually in Macrolon cages with wire mesh tops and standardized granulated soft wood bedding material (Societe Parisienne des Sciures Pantin, Paris, France), with the following environmental conditions:

Temperature (°C): 22±3
Relative Humidity (%): 50±20
Ventilation: about 16 air changes/hour
Light Cycle: 12 hours of light per day

Neither insecticides nor other chemicals were applied in the animal room with the exception of the disinfectant BRADOPHEN (TM) (CIBA-GEIGY Limited, Basle, Switzerland).

Pelleted, certified standard feed (Nafag No. 890, Tox; Nafag, Naehr- und Futtermittel AG, Gossau, Switzerland) was provided ad libitum; all batches of feed were analyzed for composition and contaminant levels. Tap water was provided ad libitum in plastic bottles; the water quality is routinely checked to standard specifications. Data on diet and water specifications were provided in study appendix 2.

From page 16 of the report: Acclimation under test conditions was for at least seven days, between delivery from animal production (WST-455, in-house) and the first treatment on day 6 post coitum.

Group Arrangement:

From page 16 of the report: Mated females were allocated to experimental and control groups using a method of randomization by weight stratification, as shown in Appendix 13. Animals were identified by a color code on the tail (a dash-dot code, painted with a felt-tipped waterproof marker) and placed one per cage in Macrolon cages. The cages were identified by a label colored according to dose group. Each cage label also showed the study number, test substance code, animal number (=cage number), dose level (mg/kg), dose volume (ml/kg), and dates of treatment and necropsy.

Test Group	Dose Level (mg/kg)	Number Assigned
Control	0	24
Low Dose	5	24
Low Mid Dose	50	24
High Mid Dose	500	24
High Dose	1000	24

According to the investigators (from page 17 of the report): The following dose levels were selected based on the results of a previous rangefinding study no. 941057 in pregnant rat [not provided]. The limit dose of 1000 mg/kg was utilized because in the range finding study it was demonstrated that this dose would be tolerated by the pregnant rat during gestation days 6-15. The 500 mg/kg dose group was included to assess the dose-response relationship and doses of 50 and 5 mg/kg were included to establish the no observable adverse effect level.

Dosing Suspension Preparation

From page 17 of the report:

Preparation Dates: fresh every day

Preparation Method: Test substance-vehicle mixtures were prepared with a high-speed homogenizer (Polytron PT6000, Kinematica AG, 6014 Littau, Switzerland). Homogeneity of the mixtures during administration was maintained with a magnetic stirrer.

Dose Administration:

From page 17 of the report:
Administration Schedule: Daily from day 6 to day 15 of gestation.

Administration Route: Intragastrically by gavage. The oral route was used because it is a potential route of human exposure.

Administration Volume: 10 ml mixture/kg actual body weight

Test Substance Content: 0, 0.5, 5, 50 and 100 mg/ml mixture

Dosing Suspension Analysis

From page 18 of the report: In order to permit determination of content, homogeneity and stability of the test substance under the actual conditions of administration during the study, samples of test substance-vehicle mixtures were taken on the date(s) designated below, once before and once after dosing. The samples from before dosing were taken from the top, middle and bottom of the container; the samples from after dosing were taken from the middle of the container.

Samples were taken in duplicate. Together with 10 ml of vehicle and approximately 2.0 g of test substance they were transported frozen to the analytical laboratory for analysis.

Date(s) of Sampling: June 21 and 27, 1994

The results of these analyses were provided in Appendix 1 of the report and indicate that the mean concentrations of the homogeneity samples were 93.5, 97.7, 98.1 and 98.1% on the nominal concentration for the 0.5, 5, 50, and 100 mg/ml solutions, respectively. The homogeneity ranged from -1 to 1% of the mean concentration for the samples analyzed. The test substance in 0.5% CMC was also found to be stable at room temperature.

Observations

Maternal examinations:

From pages 19-20 of the report:

Mortality:	daily
Cage-side Observations:	daily
Body Weight:	daily
Feed Consumption:	days 6, 11, 16 and 21

Mean daily feed consumption per animal was calculated according to the following formula:

$$\frac{\text{feed consumption (g) per period}}{\text{days per period}}$$

Dams were killed on day 21 by carbon dioxide inhalation, and fetuses removed by hysterectomy.

The following were recorded at necropsy:
- Macroscopic pathological examination of the main organs of the thoracic and abdominal cavities, in particular the genitals
- Number of corpora lutea in each ovary
- Weight of the uterus including contents

- Uterine contents:

In dams at scheduled necropsy
- number and location of live and dead fetuses
- number and location of early and late embryonic/fetal) losses
- total postimplantation loss (dead + early + late)

In dams sacrificed or dying before scheduled necropsy
- number and location of implantation sites

Classification of Uterine Findings

Early Resorption: any implantation site without visible fetal remains: the embryo may be visible; placental remains may or may not be present, occasionally only placenta is present

Late Resorption: implantation site with fetal remains,visible (usually head, hands and feet can be seen)

Implantation Site: used to describe implantations in animals dying or killed before scheduled sacrifice, when it is not possible to establish whether and what form of losses have occurred

Fetal examinations:

From pages 21-23 of the report: Following removal from the uterus, the fetuses were numbered, sexed (on the basis of ano-genital distance), externally examined and weighed. They were then killed by subcutaneous injection of an appropriate barbiturate anesthetic in the scruff of the neck and processed for visceral or skeletal examination.

Fetuses were assigned to either visceral or skeletal evaluation at an approximate 1:1 ratio within each litter, independent of sex (starting with skeletal). In the case of gross external anomaly or malformation, fetuses were allocated to one technique depending on the type and incidence of finding.

Classification of Fetal observations

Malformation:	Very rare, permanent structural change that may adversely affect fetal survival, development or function.
Anomaly:	Rare, slight to moderate, permanent or reversible structural change that is not considered to impair fetal survival, development or function.
Variation:	Relatively frequent, transient structural deviation from normal development that is considered not to have any detrimental effect on fetal survival, development or function. Variations occur regularly in control fetuses.
Incidental:	Finding of no biological relevance, e.g. due to processing (hemorrhage, mottled lung).

In the fetal external examination, special attention was paid to possible alterations in the following body regions:

- Body surface (e.g. generalized or localized edema, hemorrhage)
- Head (e.g. cranioschisis, encephalocele, cleft palate)
- Trunk (e.g. rachischisis, atresia of a body orifice, omphalocele)
- Extremities (e.g. deformed, limb position anomaly, kinked tail)

The viscera of approximately half of the fetuses per litter were fixed whole in Bouin's solution for at least two weeks and then micro-dissected as follows: limbs, tail and skin are removed, leaving the cranial skin in situ. The fetus is placed ventral surface up on a cork board and the head cut between upper and lower Jaws downwards in a line towards the ears. After removal of the tongue, the head is sectioned transversely (perpendicular to the palate) through eyes and brain, including a central lenticular section [1]. The trunk is cut, just penetrating the body wall, down both sides in a line from shoulder blade to hind limb, along a line across the diaphragm region, and from jaw to diaphragm along the line of the sternum (penetrating the sternum). The body walls and ribs are peeled back and pinned down to reveal the abdominal and thoracic organs. Heart and kidneys are examined by slicing.

Visceral examination included, in particular, morphology and position of the following organs and organ systems:

- Skin
- Central Nervous System: brain (olfactory bulbs, cerebrum, lateral and medial ventricles), spinal cord
- Eyes: lens, vitreous, retina
- Body Cavities: thorax and abdomen, including diaphragm
- Respiratory System: nasal cavity (nasal septum, turbinates, choanae), trachea, bronchi, lungs, pleura
- Digestive System: oral cavity, palate, tongue, esophagus, stomach, intestine, rectum, liver, peritoneum
- Endocrine System: thyroid, pancreas, adrenals, thymus, pituitary
- Circulatory System spleen, pericardium, heart (atria, ventricles, septae), major vessels
- Excretory System: kidneys (renal papillae, renal pelvis), ureters, urinary bladder
- Genital System: testes, epididymides, vas deferens, seminal vesicles; ovaries, oviducts, uterus

Skeletal assessment in approximately half of the fetuses per litter was done according to the staining technique of Dawson [2]; after clearing with potassium hydroxide and staining with alizarin red S. the specimens were stored in glycerol.

Routine investigation of these fetuses included the following skeletal elements:

- Facial bones: nasal, premaxillary, maxillary and zygomatic bones, mandibula
- Cranial bones: frontal, parietal, interparietal, occipital and exoccipital bones, fontanel
- Sternum: sternebrae 1 to 6
- Shoulder girdle: scapula and clavicle
- Forelimbs: humerus, ulna, radius, metacarpals 2 to 5, proximal and distal phalanges of anterior digits 1 to 5 (except proximal phalanx 1: not present)
- Pelvic girdle: ilium, ischium, pubis
- Hindlimbs: femur, tibia, fibula, calcaneus, metatarsals 1 to 5, proximal and distal phalanges of posterior digits 1 to 5 (except proximal phalanx 1: not present)
- Ribs: anteroposterior 1 to 13
- Spinal column: cervical vertebral centers and arches 1 to 7
  thoracic vertebral centers and arches 1 to 13
  lumbar vertebral centers and arches 1 to 6
  sacral vertebral centers and arches 1 to 4

Historical control data were not provided to allow comparison with concurrent controls.

Statistical analysis

From page 24 of the report: Data were collected by hand and on a Digital Equipment Corporation (DEC) VAX computer with SCC Reprotoxicology System software (Scientific Computer Consultants Inc., Ringwood, NJ 07456, USA; customized for CIBA-GEIGY Reproduction Toxicology Stein by SCC). Validation Certificate on of the SCC Reprotoxicology System was issued by Weinberg Associates Inc., Boothwyn, PA 19061, U.S.A. (Project Code 91041, December 1991).

The SCC Reprotoxicology System is protocol driven and allows authorized personnel to create a study protocol, including related work schedules, diets and dosages. The system prompts for appropriate data input (feed consumption, body weight, dosing, clinical signs, C-section data, and fetal visceral and skeletal observations), and checks that input is reasonable and complete. Weight data are input directly from balances to the on-line database. The system allows loading of proper historical data and produces data tables with statistical analyses on request.

This report, consisting of text, figures, and formatted SCC tables, was produced with LEX-WP and LEX-GRAPH software (Ace Microsystems Ltd., London W5 4EH, England) running on a DEC VAX computer.

The following statistical analysis methods were employed (From pages 24-25 of the report):

Statistical analysis of continuous data (e.g. body weight, feed consumption) was performed using the Analysis of Variance Procedure (ANOVA) [3] followed by Dunnett's t-Test [4] in case of a significant result in the ANOVA.

Categorical data (e.g. malformation counts) were analyzed using Chi-Square test [5] followed by Fisher's Exact test [6] in case of a significant result in the Chi-Square test.

Non-parametric data (e.g. mean percent affected fetuses/litter) were analyzed using the Kruskal-Wallis nonparametric analysis of variance test [7] followed by Mann-Whitney U-test [8].
In all summary tables with statistics, the p value for the blocking test (ANOVA, Chi-square or Kruskal-Wallis) is given in the control column. P values for subsequent comparisons against controls (Dunnett's, Fisher's Exact or Mann-Whitney U) are given in the appropriate group column, if the blocking test is significant.

Statistical analyses are performed to draw attention to distinctive values. The responsible scientist may consider statistically significant values lying within the historical control range as not relevant, and may also comment on values which are not statistically significant but which differ substantially from the expected normal values.

The statistics used are indicated by footnotes in the tables; no statistics are performed when the number of observations is insufficient (normally n<2).

Censoring of Data: Positively mated females which were not pregnant are excluded from summary tables for body weight, body weight gain, and feed consumption during gestation.

References (from page 27 of the report):

[1] Wilson J.G., in: Teratology: Principles and Techniques. Wilson J.G. and Warkany J., The University of Chicago Press, Chicago and London, 1965, pp. 251-278.

[2] Dawson A.B., Stain Tech. 1, 123-124, 1926.

[3] Winer B.J., Statistical Principles in Experimental Design. McGraw-Hill, New York, 2nd edition, 1971

[4] Dunnett C.W., J. Am. Stat. Assoc. 50, 1096-1121, 1955

[5] Gad S. and Weil C.S., Statistics and Experimental Design for Toxicologists. The Telford Press, Caldwell, New Jersey, 1986, p. 57

[6] Dixon W.J., Fisher's Exact Probability, in: BMDP Statistical Software, University of California Press, 1981, p. 663

[7] Kruskal W.H. and Wallis W.A., J. Am. Stat. Assoc. 47, 583-621, 1952

[8] Mann H.B. and Whitney D.R., Ann. Math. Stat. 18, 50-60, 1947

C. Results

Maternal Toxicity:

Mortality

No deaths were reported in this study.

Clinical Observations

All 500 and 1000 mg/kg/day animals and 9/24 of the 50 mg/kg/day animals exhibited *discomfort after test article administration* which was described as pushing head through bedding for about one hour. This was noted throughout the dosing period (following each dose) and may be an indicator of neurotoxicity. The following table presents the individual day observations:

Table I: Clinical Observation (pushing head through bedding)[a]

Gestation Day	7	8	9	10	11	12	13	14	15	16	Total
Dose (mg/kg/day):											
Control	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	6	9	8	1	9
500	3	5	10	14	15	19	24	24	22	1	24
1000	6	17	24	24	23	23	24	24	24	0	24

[a] = data from Table 1, page 30 of the report.

Body Weight

The investigators supplied group mean and individual animal data. The following tables present selected body weights and body weight gains:

Table II: Body Weights (grams)[a]

Gestation Day Dose (mg/kg/day):	0	6	15	21
0	195.3±8.9	226.5±10.3	284.1±15.3	375.2±25.6
5	195.5±8.2	225.5±10.5	283.7±15.6	369.8±27.7
50	195.2±8.8	229.5±12.0	285.4±15.1	377.3±29.4
500	196.4±8.0	227.7±9.5	274.0±14.3	357.9±28.1
1000	195.2±8.7	225.0±9.9	265.4**±13.5	345.3**±29.0

[a] = data from Tables 2, 3 and 7, pages 33-35, 37, and 48 of the report; ** = $p < 0.01$

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

Gestation Day Dose (mg/kg/day):	0-6	6-16	16-21	6-21	0-21[1]	C6-21[2]
0	31.2±5.6	70.0±9.4	78.7±13.3	148.7±20.2	179.9	41.4±13.3
5	30.0±6.0	69.6±10.5	74.8±12.5	144.2±21.3	174.3	46.7±13.5
50	34.3±5.5	67.1±9.6	81.2±18.3	148.0±25.1	182.1	43.3±11.5
500	31.3±5.5	56.8**±9.5	73.4±19.3	130.2*±23.5	161.5	36.9±11.3
1000	29.8±5.4	50.5**±11.9	69.9±18.1	120.4**±27.5	150.1	28.6**±9.0

[a] = data from Tables 2, 3 and 7, pages 33-35, 37, and 48 of the report; [1] = calculated by reviewer from mean data on Table II above; [2] = corrected body weight gain (minus uterine weight); * = $p < 0.05$; ** = $p < 0.01$

The 500 and 1000 mg/kg/day dose groups had lower overall body weights at gestation days 15 and 21 and gained less weight than the control during the dosing period (gestation days 6-16) and for the calculated periods of gestation days 6-21 and 0-21, also for corrected body weight gains from gestation days 6-21.

37

Food Consumption

The investigators supplied group mean and individual animal data. The following table presents selected food consumption data in grams/animal and food efficiency data:

Table IV: Food Consumption (grams)[a]

Gestation Days Dose (mg/kg/day):	0-6	6-11	11-16	16-21
0	22.7	26.0	27.8	26.9
5	22.5	25.9	27.8	27.5
50	23.2	25.3	27.1	28.2
500	22.9	22.5**	25.6*	28.4
1000	22.7	20.3**	25.1**	27.3

[a] = data from Table 4, page 40 of the report.

Table V: Food Efficiency Data (%)[a]

Gestation Days Dose (mg/kg/day):	0-76	6-16	16-21	6-21	0-21
0	19.6	23.6	48.8	34.6	31.8
5	19.1	23.5	45.3	33.3	30.7
50	21.1	23.2	48.0	34.3	31.9
500	19.5	21.4	43.1	31.7	29.5
1000	18.8	20.0	42.7	30.8	28.5

[a] = calculated by the reviewer.

As seen with the body weights and body weight gains, the 500 and 1000 mg/kg/day dose groups had reduced food consumption during the dosing period (gestation days 6-16, statistically significantly different), reduced food consumption following the dosing period and for the overall periods (gestation days 6-21 and 0-21). This is also reflected in reduced food efficiency for the same periods (6-16, 6-21, 6-21, and 0-21).

Gross Pathological Observations

No treatment related effects were noted.

Cesarean Section Observations

There was a decrease in litter size at 1000 mg/kg/day; however, the variability in litter size within this group was high, therefore the biological relevance of this observation is unclear. The following table presents the cesarean section observations:

Table VI: Cesarean Section Observations

Dose (mg/kg/day):	0	5	50	500	1000
#Animals Assigned	24	24	24	24	24
#Animals Mated/Inseminated	24	24	24	24	24
#Animals Pregnant	22	23	23	21	22
Pregnancy Rate (%)	100	95.8	95.8	87.5	91.6
Maternal Wastage					
#Died/Sacrificed	0	0	0	0	0
#Died/pregnant	0	0	0	0	0
#Non pregnant	2	1	1	3	2
#Aborted	0	0	0	0	0
#Premature Delivery	0	0	0	0	0
Total litters examined	22	23	23	21	22
Total Corpora Lutea	377	414	388	332	355
Corpora Lutea/dam	17.1±2.4	18.0±3.3	16.9±2.3	15.8±3.1	16.1±2.9
Total Implantations	352	348	369	302	295
Implantations/Dam	16.0±2.4	15.1±2.8	16.0±2.5	14.4±4.3	13.4±4.8
Total Live Fetuses	329	315	342	275	282
Live Fetuses/Dam	15.0±2.6	13.7±2.8	14.9±3.0	13.1±4.0	12.8±4.8
Total Resorptions	23	33	27	27	13
Early	23	33	27	27	13
Late	0	0	0	0	0
Resorptions/Dam	1.0±0.9	1.4±1.5	1.2±1.3	1.3±1.2	0.6±0.6
Total Dead Fetuses	0	0	0	0	0
Mean Fetal Weight (gm)	5.2±0.5	5.3±0.3	5.3±0.3	5.4±0.6	5.3±0.3
Preimplantation Loss(%)	6.6	15.9	4.9	9.0	16.9
Postimplantation Loss(%)	6.5	9.5	7.3	8.9	4.4
Sex Ratio (% Male)	49.5	51.7	53.5	48.4	51.4

* = data from Tables 5 and 6, pages 42 and 44-46 of the report.

2. Developmental Toxicity

No treatment related effects were noted in external, visceral or skeletal examination data.

a. External Examinations

The following table presents the external examination data:

Table VII: External Examinations[a]

Dose (mg/kg/day):	0	5	50	500	1000
Observations					
#pups/litters examined	329/22	315/23	342/23	275/21	282/22
Runt	1/1	0/0	0/0	0/0	0/0
Umbilical hernia	0/0	0/0	1/1	0/0	0/0
Position anomaly hindlimb	1/1	0/0	0/0	0/0	0/0
Polyscelia	0/0	0/0	0/0	1/1	0/0
Kinked tail	1/1	0/0	0/0	0/0	0/0
Total External Observations	1/1	0/0	1/1	1/1	0/0

[a] = data from Tables 9, pages 52-54 of the report.

b. Visceral Examinations

The following table presents the soft tissue examination data:

Table VIII: Visceral Examinations[a]

Dose (mg/kg/day):	0	5	50	500	1000
Observations					
#pups/litters examined	329/22	315/23	342/23	275/21	282/22
Umbilical hernia	0/0	0/0	1/1	0/0	0/0
Enlarged thymus	5/4	3/3	4/3	1/1	8/7
Liver: accessory lobulet	3/2	4/3	1/1	1/1	1/1
Renal pelvic dilatation	3/3	3/2	0/0	2/2	1/1
Ureteral dilatation	1/1	0/0	0/0	0/0	0/0
Total Visceral Observations	10/7	9/7	7/6	5/5	10/8

[a] = data from Table 10, pages 55-58 of the report.

c. Skeletal Examinations

The following table presents the skeletal examination data:

Table VII: Skeletal Examinations[a]

Dose (mg/kg/day):	0	5	50	500	1000
Observations					
#pups/litters examined	329/22	315/23	342/23	275/21	282/22
Sternebra(e):					
Fused					
#1&#2	4/3	3/3	5/3	2/2	1/1
#4&#5	0/0	0/0	0/0	1/1	0/0
all	1/1	0/0	0/0	0/0	0/0
Bipartite					
#1	1/1	0/0	0/0	0/0	0/0
#2	1/1	0/0	0/0	0/0	0/0
#1 fragmented	0/0	0/0	0/0	1/1	0/0
Asymmetrically shaped					
#1	0/0	1/1	0/0	0/0	0/0
#2	0/0	0/0	0/0	1/1	0/0
#3	0/0	1/1	0/0	1/1	0/0
#4	1/1	1/1	1/1	3/3	0/0
#5	1/1	4/4	2/2	4/4	1/1
#6	3/2	1/1	2/1	2/2	1/1
all	1/1	0/0	0/0	0/0	0/0
#1 reduced	0/0	1/1	1/1	2/2	2/2
Absent ossification					
#2	1/1	0/0	0/0	0/0	0/0
#5	0/0	0/0	0/0	1/1	0/0
#6	1/1	0/0	0/0	0/0	0/0
Poor ossification					
#1	0/0	1/1	0/0	0/0	0/0
#2	0/0	0/0	0/0	1/1	0/0
#5	1/1	0/0	0/0	0/0	0/0
#6	2/1	0/0	0/0	0/0	0/0
Cranial bones:					
Wide fontanel	6/2	1/1	0*/0	1/1	1/1
Irregular ossification of occipital bone	7/3	0/0	1*/1	3/2	0/0
Metacarpals #5: ossification					
absent	5/2	0/0	0/0	0/0	0/0
poor	1/1	0/0	0/0	0/0	0/0
Metatarsals #1: ossification					
absent	22/9	16/10	23/8	31/10	23/10
poor	6/4	2/2	2/2	4/4	4/3

Continued

Table VII: Skeletal Examinations continued

Dose:	0	5	50	500	1000
Observations					
#pups/litters examined	329/22	315/23	342/23	275/21	282/22
Pelvic girdle:					
Displaced pubis	2/1	0/0	0/0	0/0	1/1
Thoracic vertebral center:					
Bipartite	1/1	1/1	1/1	0/0	0/0
Displaced	1/1	0/0	0/0	0/0	0/0
Dumbbell-shaped	4/4	3/3	11/9	4/4	0/0
Absent ossificat.	1/1	0/0	0/0	0/0	0/0
Lumbar vertebral center:					
Displaced	1/1	0/0	0/0	0/0	0/0
Dumbbell-shaped	1/1	0/0	0/0	0/0	0/0
Absent ossificat.	1/1	0/0	0/0	0/0	0/0
Cervical vertebral center:					
ossification					
absent	167/22	162/23	176/23	138/21	141/22
poor	17/11	26/14	35/19	25/15	18/13
Bipartite	9/7	11/8	13/9	9/7	20/10
Dumbbell-shaped	1/1	1/1	2/2	3/3	7*/6
Ribs:					
Ossification					
Absent	1/1	0/0	0/0	0/0	0/0
#13 absent	2/2	1/1	0/0	1/1	0/0
Shortened	14/8	20/9	6/4	13/9	3*/3
Hind limb:					
Calcaneus: ossification					
absent	156/22	161/23	154/23	132/19	140/21
poor	4/4	1/1	0/0*	0/0	0/0
Anterior digit: Distal phalanx: ossification					
Absent					
#1	1/1	0/0	1/1	0/0	0/0
#2	1/1	0/0	0/0	0/0	0/0
#4	0/0	0/0	1/1	0/0	0/0
#5	3/3	3/2	4/3	8/5	2/2
Poor					
#1	1/1	0/0	0/0	0/0	0/0
#2	0/0	0/0	1/1	0/0	0/0
#3	1/1	0/0	0/0	0/0	0/0
#5	1/1	1/1	0/0	1/1	0/0

Continued

Table VII: Skeletal Examinations continued

Dose:	0	5	50	500	1000
Observations					
#pups/litters examined	329/22	315/23	342/23	275/21	282/22
Anterior digit: Proximal phalanx: ossification					
Absent					
#2	10/3	2*/1	4/4	11/4	2*/2
#3	4/1	0/0	0/0	0/0	0/0
#4	7/2	0*/0	0**/0	1/1	0*/0
#5	18/10	13/9	13/9	21/7	6*/6
Poor					
#2	1/1	2/2	2/2	6/3	1/1
#5	6/5	4/2	7/3	13/9	3/3
Posterior digit: Distal phalanx: ossification					
Absent					
#1	1/1	2/1	1/1	0/0	0/0
#5	0/0	0/0	1/1	0/0	0/0
Poor					
#1	7/1	2/2	1*/1	1/1	0*/0
#2	8/1	1*/1	1*/1	1*/1	0**/0
#3	6/1	1/1	1/1	1/1	0*/0
#4	8/1	1*/1	1*/1	1*/1	0**/0
#5	9/1	1*/1	1*/1	1*/1	0**/0
Posterior digit: Proximal phalanx: ossification					
Absent					
#2	60/18	58/19	69/17	55/14	52/18
#3	38/16	38/14	51/15	52/14	40/17
#4	38/15	34/12	44/16	47/13	44/18
#5	98/22	93/21	98/21	86/16	81/21
Poor					
#2	14/11	10/8	15/11	7/6	9/8
#3	9/7	8/7	13/10	10/9	12/9
#4	9/7	9/6	12/8	8/6	8/6
#5	15/10	14/10	16/11	13/9	12/8
Total Skeletal Observations					
Malformations	**0/0**	**0/0**	**0/0**	**0/0**	**0/0**
Anomalies	**16/9**	**10/8**	**10/6**	**12/10**	**5/5**
Variations	**168/22**	**163/23**	**176/23**	**142/21**	**148/22**

a = data from Tables 11-13, pages 59-99 of the report; * = $p < 0.05$; ** $p < 0.01$

D. Discussion/Conclusions

i. Investigators Summary:

From page 10 of the report: In this study, CGA 77102 Technical (Batch NO. V.4673/7, Purity: 95.6%) was tested for its embryotoxic, fetotoxic, and teratogenic potential in rats. The test substance was administered by gavage in an aqueous solution of carboxymethylcellulose (0.5% w/w) at daily doses Of 0, 5, 50, 500 and 1000 mg/kg body weight to 24 mated rats per group from day 6 through day 15 post-coitum (=p.c.) inclusive. Dams were killed on day 21 p.c. and fetuses removed by cesarean section for examination.

Maternal Data

There were no premature deaths.

All dams in the 500 and 1000 mg/kg dose groups and nine dams in the 50 mg/kg group displayed discomfort after test article application (pushing head through bedding for about one hour). This behavior was initially noted on day 7 p.c.and was no longer present at the end of the dosing period.

Maternal weight gain during treatment (days 6-15) was reduced by 19 and 28%, respectively, in the 500 and 1000 mg/kg dose groups compared to controls; this was accompanied by an 11 and 16% reduction in food consumption, respectively, in these groups. There were no effects of treatment on body weight gain or food consumption at doses of 5 and 50 mg/kg/day.

Carcass weight and net body weight change from day 6 to 21 was significantly reduced in the 1000 mg/kg group. There were no treatment-related necropsy findings in dams.

Reproduction and Cesarean Section Data

There were no treatment-related effects on the number of corpora lutea, implantation sites or early resorptions. The mean number of live fetuses per animal was comparable for all groups. There were no late resorptions or dead fetuses.

Fetal Examination

Fetal sex ratios and body weights were not affected by treatment
There were no treatment-related fetal external, skeletal abnormalities.

Conclusion

Maternal toxicity (reduced feed consumption and body weight gain) was seen in the 500 and 1000 mg/kg groups. There were no evidence for embryotoxic or teratogenic potential.

The no observed adverse effect level (NOAEL) for CGA 77102 Technical in the rat dam was 50 mg/kg body weight/day and the no observed effect level (NOEL) was 5 mg/kg/day.

The no observed effect level (NOEL) for CGA 77102 Technical for fetuses was 1000 mg/kg body weight/day.

ii. Reviewers Conclusions:

a. Maternal Toxicity:

No treatment related mortality was noted. There was a dose related increase in clinical signs seen as all 500 and 1000 mg/kg/day animals and 9/24 of the 50 mg/kg/day animals exhibited as pushing head through bedding for about one hour. This was noted throughout the dosing period and may be an indication of neurotoxicity. The 500 and 1000 mg/kg/day dose groups had lower overall body weights at gestation days 15 and 21 and gained less weight than the control during the dosing period (gestation days 6-16) and for the calculated periods of gestation days 6-21 and 0-21, also for corrected body weight gains from gestation days 6-21. Also the 500 and 1000 mg/kg/day dose groups had reduced food consumption during the dosing period (gestation days 6-16, statistically significantly different), reduced food consumption following the dosing period and for the overall periods (gestation days 6-21 and 0-21). This is also reflected in reduced food efficiency for the same periods (6-16, 6-21, 6-21, and 0-21).

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.

c. Conclusions:

Maternal Toxicity NOEL = 50 mg/kg/day
Maternal Toxicity LOEL = 500 mg/kg/day
Developmental Toxicity NOEL => 1000 mg/kg/day
Developmental Toxicity LOEL > 1000 mg/kg/day

d. Study Deficiencies:

No major deficiencies were noted.

e. Classification: Acceptable-Guideline.

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Alpha-Metolachlor: Developmental Toxicity Study in Rats [RABBIT]
Ciba-Geigy Corporation. 1995. MRID No. 43928924.
HED Doc. No. ?.

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 3/26/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Jess Rowland, M.S. Jess Rowland 3/26/97
Acting Section Head, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity
Species: Rabbit Guideline: OPPTS 870.3700; OPP 83-3b

EPA ID No.s: EPA MRID No. 43928924
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 Technical

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: P.A. GILLES AND M.L.A. GIKNIS (1995): A TERATOLOGY STUDY OF CGA-77102 TECHNICAL IN NEW ZEALAND WHITE RABBITS; CIBA-GEIGY CORPORATION, CROP PROTECTION DIVISION, ENVIRONMENTAL HEALTH CENTER; LABORATORY STUDY NUMBER F-00192; 4/27/95; EPA MRID No. 43928924, unpublished.

Executive Summary: In a developmental (teratology) study (MRID# 43928924), sexually mature virgin female New Zealand White, S.P.F. Rabbits (Strain: Har:PF/CF(NZW)BR) from H.A.R.E., Rabbits for Research, Hewitt, N.J. Received either 0, 20, 100, or 500 mg/kg/day CGA-77102 Technical (Lot No. FL-830813 with a purity of 89.6% (93.7% S isomer) suspension in 3% corn starch containing 0.5% Tween 80 by oral gavage from gestation days 7 through 19.

No treatment related mortality was noted. There was a dose related increase in little/none/soft stool observations at the 100 and 500 mg/kg/day dose levels. The 500 mg/kg/day dose group had lower overall body weights at gestation days 19, 29 and corrected body weights at day 29 gained less weight than the control during the dosing period (gestation days 7-19) with a rebound weight gain following the dosing period (gestation days 19-29), an indicator of toxicity. This group also had lower overall weight gain for the calculated periods of gestation days 7-29, 0-29 and corrected body weight gains for 0-29. This was supported by reduced food consumption during the dosing period (gestation days 7-19) and for the overall periods (gestation days 7-28 and 0-28) with a rebound in food consumption following dosing (gestation days 19-28) at the 500 mg/kg/day dose level. This is also reflected in reduced food efficiency for the same periods (7-

19, 7-28, and 0-28) and increased food efficiency following dosing (19-28) at the 500 mg/kg/day dose level. **The maternal toxicity NOEL was 20 mg/kg/day with a LOEL of 100 mg/kg/day based on clinical signs of toxicity.**

No significant treatment related developmental toxicity was noted at the dose levels tests. **The developmental toxicity was equal to or greater than 500 mg/kg/day, a LOEL was not reached.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§83-3b) for a teratology study in rabbits.

Compliance: A signed and data STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, CERTIFICATION OF GOOD LABORATORY PRACTICES, FLAGGING STATEMENT (according to the investigators: This study neither meets nor exceeds any of the applicable criteria.) and QUALITY ASSURANCE STATEMENT was provided.

THIS REVIEW CONTAINS TEXT INFORMATION PROVIDED BY THE REGISTRANT IN ELECTRONIC FORMAT (USED IN MATERIALS AND METHODS, STUDY DESIGN AND CONCLUSIONS-INVESTIGATORS SUMMARY SECTIONS).

A. Materials and Methods

Test Compound: CGA-77102 Technical

Purity: Lot No. FL-830813 with a purity of 89.6% (93.7% S isomer) was used for dosing of animals.
Lot No. FL-941255 with a purity of 94.4% and a reassay date of 7/15/96 was used for retrospective preparation and analyses of CGA-77102 suspensions in 3% corn starch containing 0.5% Tween 80 vehicle.

Description: amber-brown (FL-830813) or amber (FL-941255) liquid

Lot No.: above

other provided information: The test article was supplied by Ciba Crop Protection (formerly Agricultural Division), Ciba-Geigy Corporation, Greensboro, N.C.

The test material was stable at room temperature and was stored at room temperature.

Vehicle(s): suspension in 3% corn starch containing 0.5% Tween 80

Test Animal(s): Species: sexually mature virgin female New Zealand White, S.P.F. rabbits

Strain: Har:PF/CF(NZW)BR

Source: H.A.R.E., Rabbits for Research, Hewitt, N.J.

Age: "sexually mature"

Body Weight: Gestation day 0 body weights ranged from 3.28 to 4.66 kg.

males of the same strain were used

B. Study Design

According to the investigators (from page 12 of the report): This study was sponsored by Ciba Crop Protection (then known as the Agricultural Division), Ciba-Geigy Corporation, and conducted at the Safety Evaluation Facility (SEF) of the Ciba-Geigy Pharmaceutical Division in Summit, New Jersey. The purpose of the study was to determine whether CGA-77102 Technical has embryotoxic, fetotoxic and/or teratogenic effects when administered orally to pregnant rabbits from gestational day 7 through gestational day 19.

NOTE: This study was initiated on May 30, 1983 and completed on June 24, 1983.

Mating Procedure

From page 15 of the report: Following a period of at least 3 weeks for acclimation to the facility environment, a total of 76 sexually mature (date of birth 12/24/82-1/7/83) virgin female New Zealand White, S.P.F. rabbits (Har:PF/CF(NZW)BR) (obtained from H.A.R.E., Rabbits for Research, Hewitt, N.J.) were artificially inseminated using semen collected from the buck colony of the same strain maintained at the SEF in Summit, N.J. The day of artificial insemination was designated as day "0" of presumed gestation. Gestation day 0 body weights ranged from 3.28 to 4.66 kg.

Animal Husbandry

From page 15 of the report: During the study, all animals received Purina Certified Rabbit Chow and water ad libitum (via an automatic watering system). The rabbits were caged individually in mesh bottomed stainless steel cages which were changed bi-weekly. Paper liners below the cages were changed 2-3 times each week. The animals were maintained in a room equipped to control temperature (65 ± 5°F/18 ± 3°C) and relative humidity (50 ± 20%) and were automatically regulated for 14-hour periods of light and 10-hour periods of darkness (whenever possible).

Group Arrangement:

From page 15 of the report: Each animal was assigned a unique alpha-numeric number and identified by ear tag. Seventy-six inseminated females were distributed, using randomization tables, into 4 groups of 19 animals each.

Nineteen presumed pregnant females were assigned to each of the four treatment groups: 0 (group 1), 20 (group 2), 100 (group 3) and 500 (group 4) mg/kg/day.

Test Group	Dose Level (mg/kg)	Number Assigned
Control	0	19
Low Dose	20	19
Mid Dose	100	19
High Dose	500	500

According to the investigators (from page 16 of the report): The results of a previously conducted oral dose-rangefinding study (Arthur, 1983) in pregnant rabbits conducted at doses of 20, 100 or 500 mg/kg/day were reviewed before selecting the same doses for this study. Dose-related decreases in stool were observed at both 100 and 500 mg/kg/day, while pronounced reductions in food consumption, body weight and body weight gain were observed at 500 mg/kg/day. There were no deaths attributed to the administration of CGA-77102 in this study. Therefore, based on these results, the same doses were used in this definitive teratology study. The high dose of 500 mg/kg/day was selected to achieve signs of maternal toxicity without

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mortality. The selected low dose, 20 mg/kg/day, was anticipated to be asymptomatic and the selected intermediate dose, 100 mg/kg/day, was expected to produce effects between the low and high doses. The route of administration was oral by gavage. The oral route is the potential route of exposure in humans.

Dosing Suspension Preparation

From page 16 of the report: CGA-77102 Technical was mixed with aqueous 3% corn starch containing 0.5% Tween 80 on a weight per volume basis to prepare the intended concentrations of 2.0 (0.20%), 10 (1.00%) or 50.0 (5.00%) mg/ml. No corrections were made for impurities. Suspensions were stored in amber glass containers at 2°-8°C. Suspensions were prepared five times and were used within four days of preparation.

Dose Administration:

From page 16 of the report: CGA-77102 (Lot No. FL-830813) was administered to groups 2 (20 mg/kg/day), 3 (100 mg/kg/day), and 4 (500 mg/kg/day) (Note: mg/kg/day refers to milligrams of compound administered per kilogram of body weight, once daily). CGA-77102 was administered once daily by gastric intubation as a 0.20%, 1.00% or 5.00% suspension in 3% corn starch containing 0.5% Tween 80. The does in group 1 received an equivalent volume (10 ml/kg) of 3% corn starch with Tween 80 and served as controls. The volume of suspension of compound or vehicle to be administered to each animal was determined by the animal's most recent body weight recorded on gestational days 7 and 14. Does were treated from day 7 through 19 of presumed gestation, the period of organogenesis in the rabbit.

Dosing Suspension Analysis

From page 17 of the report: The concentration and homogeneity (uniformity) of the dose suspensions (Lot No. FL-830813), 2.0 (0.20%), 10.0 (1.00%) and 50.0 (5.00%) mg/ml, were determined by the SEF Analytical Chemistry Laboratory. Determination of concentration was based on two samples from each suspension. Determination of concentration and homogeneity (uniformity) was based on three samples, top (T), middle (M) and bottom (B), from each suspension. A sample of the vehicle was obtained both at the time of sampling for concentration determination and at the time of sampling for concentration and homogeneity determinations. Each sample was diluted with methanol and analyzed by gas chromatography using a 3% HI-EFF-8BP on Gas Chrom Q (100/120 mesh) column (3' x 2 mm) with a helium carrier and N-P detection in an isothermal separation of 195°C.

Stability of CGA-77102 in the vehicle was not determined when this study was conducted. Suspensions of CGA-77102 Technical (Lot No. FL-941255) in aqueous 3% corn starch containing 0.5% Tween 80 were prepared and analyzed by the EHC Analytical Chemistry Laboratory in 1995. Suspensions were prepared at intended concentrations of 2.0 mg/ml (low dose) and 50.0 mg/ml (high dose).

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Each suspension was dispensed into four amber glass containers (A, B, C and D). Six samples were taken from each container. One sample was taken from the center and side of the top (T), middle (M) and bottom (B) of each container and analyzed. A single sample of the vehicle was obtained and analyzed. Samples were also taken after four days of storage at ≈4°C for determination of stability in the vehicle. Each sample was diluted with acetonitrile and analyzed by HPLC using a YMC-AQ ODS column with an acetonitrile/water mobile phase and UV detection at 215 nm. Samples were quantitated using an external standard calibration curve. These retrospective procedures were done to demonstrate that the preparation procedure and storage conditions used in the conduct of this study would provide stable, homogeneous suspensions over the range of the intended concentrations.

From page 22 of the report: Results of chemical analyses of dose suspensions and of retrospectively prepared suspensions of CGA-77102 are summarized in Table 11 (of the study report). Concentration and homogeneity (uniformity), and concentration determinations of dose suspensions are presented in Table 11A and 11B (of the study report), respectively. Concentration and homogeneity, and bulk stability determinations for retrospectively prepared suspensions are presented in Table 11C and 11D (of the study report), respectively. Test substance was not detected in control vehicle. The mean concentrations and relative standard deviations for suspensions of CGA-77102 Technical were within acceptable limits for concentration (≤± 10% of the target concentration) and homogeneity (r.s.d. ≤ 10%).

Test article concentration of CGA-77102 was not reduced (101.5% recovery) in the 2.0 mg/ml suspension and was reduced only 1.6% (98.4% recovery) in the 50.0 mg/ml suspension after 4 days of refrigerated storage (≈4°C). Therefore, suspensions of CGA-77102 over the range of intended concentrations administered to rabbits in this study were considered homogeneous and stable under the conditions of use.

Observations

From pages 17-19 of the report: The does were observed daily for changes in appearance and behavior. Females were weighed on days 0, 7, 14, 19, 21, 25 and 29 of gestation. Feed consumption measurements were taken daily from the time of insemination to the time of necropsy (days 0-28 of gestation).

The does were necropsied on day 29 of presumed gestation after CO_2 asphyxiation. The ovaries were examined and corpora lutea counted. The uteri including their contents were weighed and live fetuses, dead fetuses and intrauterine resorptions were counted. The fetuses were numbered in order of their positions in the uterus from the ovarian end of the left horn to the ovarian end of the right horn. Apparently viable fetuses and their placentas were weighed and the fetuses examined for gross abnormalities.

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On the day of necropsy (if possible) each fetus was examined viscerally according to a modification of the Staples technique (Staples, 1974) and its sex determined. The fetuses were then prepared for a subsequent skeletal examination after clearing in potassium hydroxide and staining with Alizarin Red S (Staples and Schnell, 1964). The procedures utilized in reporting rabbit gross, skeletal and visceral observations are summarized in Appendix 16 [of the study report].

Following a gross external examination at the time of necropsy, the fetuses were placed in 70% ethanol. The visceral examination was conducted on all fetuses as soon as possible following necropsy (within 24 hours). Visceral examination included the following systems, organs and glands which were examined using dissection and slicing under appropriate magnification:

Central Nervous System:	brain (including eyes)
Cardiovascular System:	heart, major blood vessels
Respiratory System:	trachea, lungs, diaphragm
Gastro-intestinal System:	oral cavity, tongue, esophagus, stomach, intestines, liver, gall-bladder, pancreas
Lymphoid Structures:	thymus, spleen
Urinary System:	kidneys, ureters, bladder
Endocrine System:	adrenals
Genital System:	ovaries, uterus or testicles

Following the visceral examination, all fetuses were stained and subjected to skeletal examination using appropriate magnification. All ossification centers that are characteristically present at day 29 of gestation in this strain of rabbit (Appendix 16 (of the study report)) were examined for: presence/absence, size, shape, location and relationship to adjacent ossification centers. Results of the skeletal and visceral exams were recorded as normal or abnormal in the raw data; whereas, only abnormal data are presented and summarized in this report.

All does were killed by CO_2 asphyxia and examined for gross pathologic changes. A single maternal gross lesion was excised, stored in formalin and submitted to the Pathology Section for microscopic evaluation.

From page 22 of the report: Review of the accumulated data revealed that all animals were healthy and suitable for use in this study. Two dosing errors occurred during the course of the study. One intermediate dose doe (BK19) did not retain the full intended dose volume administered on the first day of treatment. Another intermediate dose doe (BO16) received 4 ml in excess of the correct dose on the seventh day of treatment. As these were singular isolated incidents, they had no impact on the final outcome or data interpretation of this study.

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Historical control data were not provided to allow comparison with concurrent controls.

Statistical analysis

The following statistical analysis methods were employed (From page 22 of the report):

Statistical analyses of the data were performed as indicated below or as indicated in the individual reports from the Statistics Section:

Parametric Analysis On:	Body Weight, Body Weight Gain, Feed Consumption, and Fetal Weight
Statistical Methods:	Test for Outliers (Pearson and Hartley, 1966) Bartlett's Test for Homogeneity of Variance (Snedecor and Cochran, 1968) For Homogeneous Variances - One-Way Analysis of Variance (Snedecor and Cochran, 1968) with Dunnett's (Dunnett, 1964) Method of Multiple Comparisons For Heterogeneous Variances - Behren's T-Test with Cochran's Approximation (Cochran, 1964)
Nonparametric Analysis On:	Number of corpora lutea, implantations, viable fetuses, calculated pre-implantation loss, and number of resorptions; % pre-implantation loss, % post-implantation loss.
Statistical Methods:	Dunn's Method of Multiple Comparisons Using Rank Sums (Dunn, 1964) Rank Analysis of Covariance (Quade, 1967)

REFERENCES

Arthur, A. CGA 77102 Rabbit-Segment II Dose Range Teratology Study Pilot (P-1) (MIN 832062), (1983).

Cochran, W.G., Biometrics, 20:191 (1964).

Dunn, D.J. Technometrics, 6: 241 (1964).

Dunnett, C.W. Biometrics, 20:482 (1964).

Pearson, E.S. and Hartley, H.O., Biometrika Tables For Statisticians, Vol. 1, P. 200 (1966).

Quade, D., Journal of the American Statistical Association, Vol. 62, P. 1187 (1967).

Snedecor, G.W. and Cochran, W.G., Statistical Methods, PP 296, 258 (1968).

Staples, R.E., Teratology 9(3): A-37 (1974).

Staples, R.E. and Schnell, V.L., Stain Technology 39: 62 (1964).

The study protocol and four protocol amendments are in Appendix 22 (of the study report and amendments 3 & 4 are at end of this DER). The first protocol amendment documents a correction to the Master Index Number. The second protocol amendment documents corrections to the sponsor's P.O. Box and Zip Code. These corrections did not affect the study. The third protocol amendment describes the preparation and analysis of suspensions of CGA-77102 Technical in the 3% corn starch containing 0.5% Tween 80 vehicle. These procedures were conducted in the EHC Analytical Chemistry Laboratory in 1995. Stability of CGA-77102 in this vehicle had not been determined when the study was conducted at the SEF in 1983. These retrospective procedures were done to demonstrate acceptable concentration and homogeneity and stability under conditions described for the use in 1983. The fourth protocol amendment documents a correction to the third protocol amendment that stated that concentration and homogeneity of the dose suspensions had not been determined for the study when it was conduced in 1983. These determinations were made at the time of study conduct and were sent to the EHC on April 13, 1995. These data had not been included in the transfer of study material from the SEF on April 15, 1994.

C. Results

Maternal Toxicity:

Mortality

One 20 mg/kg/day (gd 28) died possibly due to aborting and one 500 mg/kg/day (gd 25) animal died following several days of anorexia and body weight reductions, this was considered by the investigators to be related to treatment. Also a 20 mg/kg/day animal was sacrificed on gd 21 after aborting and a 100 mg/kg/day animal was sacrificed for humane reasons after breaking a hindlimb.

Clinical Observations

There was a dose related increase in little/none/soft stool observations:

Table I: Clinical Sign (stool)[a]

Dose(mg/kg/day):	0	20	100	500
Incidence	6/19[b]	11/19	14/19*	19/19*
Incidence Days	15/6[c]	36/11	61/14	271/19

[a] = data from Table 1, page 30 of the report; [b] = number of animals with observation over number of animals in group; [c] = number of days with observation over number of animals with observation; * = statistically significant by a Mantel's trend test (multiple comparisons).

The incidence of little/none/soft stool at 0 and 20 mg/kg/day occurred towards the end of the study whereas the incidences at 100 and 500 mg/kg/day occurred earlier and were most likely related to treatment. This was supported by the individual animal data and by considering the incidence in terms of total incidence days.

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Body Weight

The following tables present selected body weights and body weight gains):

Table II: Body Weights (grams)[a]

Gestation Day	0	7	19	29	C-29[b]
Dose (mg/kg/day):					
0	3832±74	3952±75	4101±86	4225±92	3694±76
20	3785±94	3956±101	4142±110	4213±94	3759±85
100	3933±93	4080±90	4226±95	4330±97	3813±104
500	3817±61	3963±62	3782±68*	4097±74	3615±58

[a] = data from Tables 3 and 4, pages 35-36 of the report; b = corrected body weight (body weight - gravid uterus weight); * = $p < 0.05$.

Table III: Body Weight Gains (grams)

Gestation Days	0-7	7-19[1]	19-29[1]	7-29[1]	0-29[1]	C0-29[b]
Dose (mg/kg/day):						
0	120±17	149	124	273	393	-138±45
20	171±27	186	71	257	428	-26±62
100	147±22	146	104	250	397	-120±55
500	146±25	-181	315	134	280	-202±53

[a] = data from Tables 3 and 4, pages 35-36 of the report; b = corrected body weight gain (body weight gain - gravid uterus weight); [1] = calculated by reviewer from group mean body weight data above (Table II); * = $p < 0.05$.

The 500 mg/kg/day dose group had lower overall body weights at gestation days 19, 29, corrected body weights at day 29 and gained less weight than the control during the dosing period (gestation days 7-19) with a rebound weight gain following the dosing period (gestation days 19-29), an indicator of toxicity. This group also had lower overall weight gain for the calculated periods of gestation days 7-29, 0-29 and corrected body weight gains for 0-29.

Food Consumption

The following tables present selected food consumption data in grams/animal and food efficiency data:

Table IV: Food Consumption (total grams/time period)[a]

Gestation Days	0-7	7-19	19-28	7-28	0-28
Dose (mg/kg/day):					
0	1439	2094	1171	3116	4388
20	1500	2268	1210	3313	4637
100	1483	2151	1253	3251	4551
500	1319	972	1371	2265	3509

[a] = data from Table 2, pages 31-34 of the report.

Table V: Food Efficiency Data (%)[a]

Gestation Days	0-7	7-19	19-28	7-28	0-28
Dose (mg/kg/day):					
0	8.3	7.1	10.6	8.8	9.0
20	11.4	8.2	5.9	7.8	9.2
100	9.9	6.8	8.3	7.7	8.7
500	11.1	-17.9	23.0	5.9	8.0

[a] = calculated by the reviewer.

As seen with the body weights and body weight gains, the 500 mg/kg/day dose group had reduced food consumption during the dosing period (gestation days 7-19) and for the overall periods (gestation days 7-28 and 0-28) with a rebound in food consumption following dosing (gestation days 19-28). This is also reflected in reduced food efficiency for the same periods (7-19, 7-28, and 0-28) and increased food efficiency following dosing (19-28).

Gross Pathological Observations

No treatment related effects were noted.

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Cesarean Section Observations

The following table presents the cesarean section observations:

Table VI: Cesarean Section Observations[a]

Dose (mg/kg/day):		0	20	100	500
#Animals Assigned		19	19	19	19
#Animals Mated/Inseminated		19	19	19	19
#Animals Pregnant		19	17	17	19
Pregnancy Rate (%)		100	89.5	89.5	100
Maternal Wastage					
#Died/Sacrificed		0	1	1	0
#Died/pregnant		0	1	0	1
#Non pregnant		0	2	2	0
#Aborted		0	1	1	0
#Premature Delivery		0	0	0	0
Total litter examined		19	15	16	18
Total Corpora Lutea		251	192	210	238
Corpora Lutea/dam		13.2	12.8	13.1	13.2
Total Implantations		187	118	144	169
Implantations/Dam		9.8	7.9	9.0	9.4
Total Live Fetuses		161	107	129	143
Live Fetuses/Dam		8.5	7.1	8.1	7.9
Total Resorptions		26	11	15	26
Early, Late			not provided		
Resorptions/Dam		1.4	0.7	0.9	1.4
Total Dead Fetuses		0	0	0	0
Mean Fetal Weight (gm)	M	43.0	43.5	44.4	39.8
	F	41.8	44.4	42.3	40.3
Preimplantation Loss(%)		25.5	38.5	31.5	29.0
Postimplantation Loss(%)		13.9	9.3	10.4	15.4
Sex Ratio (% Male)		50.3	54.2	51.9	50.3

[a] = data from Tables 5 and 6, pages 37-38 and Appendix 9, pages 101-104 of the report.

No treatment related effects were noted.

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2. Developmental Toxicity

a. External Examinations

The following table presents the external examination data:

Table VII: External Examinations[a]

Dose (mg/kg/day):	0	20	100	500
Observations				
#pups/litters examined	161/19	107/15	129/16	143/18
Abnormal limb flexure	0/0	0/0	0/0	4°/1

[a] = data from Table 7, page 39 of the report; ° = observations from same litter.

b. Visceral Examinations

The following table presents the soft tissue examination data:

Table VIII: Visceral Examinations[a]

Dose (mg/kg/day):	0	20	100	500
Observations				
#pups/litters examined	161/19	107/15	129/16	143/18
Cleft palate	0/0	0/0	0/0	4/1°
Hydrocephaly	0/0	0/0	0/0	2/2(1°)
Thymus enlarged	1/1	0/0	0/0	0/0
Gonad malpositioned	0/0	1/1	0/0	0/0
Pale kidney	0/0	0/0	0/0	1/1
Trachea reduced in size	0/0	0/0	0/0	1/1°
Tongue curled	0/0	0/0	0/0	3/1°

[a] = data from Tables 7 and 8, pages 39-40 of the report; ° = observations from same litter.

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c. Skeletal Examinations

Table VII: Skeletal Examinations[a]

The following table presents the skeletal examination data:

Dose (mg/kg/day): Observations	0	20	100	500
#pups/litters examined	161/19	107/15	129/16	143/18
Centrum/vertebrae/rib agenesis	0/0	0/0	1/1	0/0
Zygomas/squamosals short	0/0	0/0	0/0	5/1°
Clavicle wavy	0/0	0/0	0/0	4/1°
Ulna/radius short & bowed	0/0	0/0	0/0	5/1°
Scapular bowed	0/0	0/0	0/0	1/1°
Cleft palate	0/0	0/0	0/0	1/1°
Hyoid: bipartite	2/2	0/0	0/0	0/0
Widened sutures	0/0	0/0	0/0	4/1
Centrum/vertebra:				
additional	4/4	1/1	3/3	9/2
bipartite	0/0	0/0	1/1	0/0
Rib:				
rudimentary	22/12	27/8	19/10	16/11
fully formed	49/15	18/7	29/12	72*/15*
floating	3/3	0/0	2/2	0/0
wavy	0/0	0/0	0/0	2/1
bifurcation	0/0	0/0	1/1	0/0
Sternebra:				
not ossified	40/13	29/9	51/12	28/12
misaligned	25/10	7/5	12/7	9/4
bipartite	1/1	3/3	3/3	3/2
fused	1/1	0/0	0/0	0/0
Forepaw:				
metacarpal not ossified	1/1	0/0	0/0	1/1
middle phalanx not ossified	0/0	0/0	0/0	2/1
Hindpaw:				
talus/calcaneus not ossified	0/0	0/0	2/2	1/1
patella not ossified	14/4	11/4	16/7	17/6
middle phalanx not ossified	0/0	0/0	0/0	2/1

[a] = data from Tables 7-10, pages 39, 41-42 of the report; ° = observations from same litter; * = $p < 0.007$.

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No treatment related effects were noted in external, visceral or skeletal examination data. Most of the severe observations occurred only in one high dose litter and were likely due to chance. Although there was a statistically significant increase in fully formed ribs, there was no biologically relevant difference from control.

D. Discussion/Conclusions

i. Investigators Summary:

From page 11 of the report:

CGA-77102 Technical, a chloroacetamide herbicide, was evaluated for maternal toxicity as well as embryotoxicity, fetotoxicity and teratogenic potential in pregnant New Zealand White rabbits. The compound (89.6% purity, Lot No. FL-830813) was administered orally by gavage, as suspensions in aqueous 3% corn starch containing 0.5% Tween 80, to three groups (N=19/group) of artificially inseminated rabbits at daily doses of 20, 100, or 500 mg/kg/day on gestational days 7 through 19. A fourth group (N=19) of inseminated female rabbits received equivalent volumes (10 ml/kg) of aqueous 3% corn starch containing 0.5% Tween 80 and served as the control. The volume of suspension of compound or vehicle administered to each animal was based on the animal's most recent body weight recorded on gestational days 7 and 14. All animals were observed daily for mortality and clinical signs. Feed consumption was determined daily (gestational days 0-28) and body weights were taken on gestational days 0, 7, 14, 19, 21, 25 and 29. Following necropsy on gestational day 29, gravid uterine weights and reproductive parameters were recorded and each fetus was subsequently sexed, weighed and examined for external, visceral and skeletal abnormalities. There was one compound-related death in this study. A doe from the 500 mg/kg/day dose group was found dead on gestational day 25 following a period of anorexia and subsequent body weight loss. Death was considered to be secondary to the anorexia. Treatment-related changes were observed at doses ≥ 100 mg/kg/day and consisted of 1) stool alterations at ≥ 100 mg/kg/day; and 2) pronounced reductions in maternal feed consumption with concomitant reductions in maternal body weight and body weight gain (including actual body weight losses) at 500 mg/kg/day. There were no effects of compound administration on necropsy findings, reproductive parameters, fetal sex ratios, placental weights or fetal weights, and no compound-related fetal external, visceral or skeletal malformations or variations at any dose level.

In conclusion, oral administration of CGA-77102 produced compound-related maternal effects at daily doses of 100 and 500 mg/kg/day. While these maternal effects were pronounced and included mortality at 500 mg/kg/day, the compound was not embryotoxic, fetotoxic or teratogenic at any dose level. The no-observed-effect level for maternal toxicity was at least 20 mg/kg/day and for developmental toxicity was at least 500 mg/kg/day of CGA-77102 Technical.

ii. Reviewers Conclusions:

a. Maternal Toxicity:

No treatment related mortality was noted. There was a dose related increase in little/none/soft stool observations at the 100 and 500 mg/kg/day dose levels. The 500 mg/kg/day dose group had lower overall body weights at gestation days 19, 29 and corrected body weights at day 29 gained less weight than the control during the dosing period (gestation days 7-19) with a rebound weight gain following the dosing period (gestation days 19-29), an indicator of toxicity. This group also had lower overall weight gain for the calculated periods of gestation days 7-29, 0-29 and corrected body weight gains for 0-29. This was supported by reduced food consumption during the dosing period (gestation days 7-19) and for the overall periods (gestation days 7-28 and 0-28) with a rebound in food consumption following dosing (gestation days 19-28) at the 500 mg/kg/day dose level. This is also reflected in reduced food efficiency for the same periods (7-19, 7-28, and 0-28) and increased food efficiency following dosing (19-28) at the 500 mg/kg/day dose level.

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. Conclusions

Maternal Toxicity NOEL = 20 mg/kg/day
Maternal Toxicity LOEL = 100 mg/kg/day
Developmental Toxicity NOEL = 500 mg/kg/day
Developmental Toxicity LOEL > 500 mg/kg/day

E. Study Deficiencies:
No major deficiencies were noted.

F. Classification: Acceptable-Guideline.

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Protocol deviations:

The following are protocol amendments from pages 270-271 of the report:

Amendment from Protocol: CGA-77102 Technical (Lot No. FL-941255) will be mixed with aqueous 3% corn starch containing 0.5% Tween 80 on a weight per volume basis to prepare intended concentrations of 2.0 mg/ml and 50.0 mg/ml. No corrections will be made for impurities. Suspensions will be stored in amber glass containers at 2°-8°C. The preparation procedure and storage conditions are the same as those used in 1983 for the dose suspensions in study F-00192 (MIN 832076). The concentration, homogeneity, and stability of each suspension will be determined by the Analytical Laboratory at Ciba's Environmental Health Center. Two aliquot from the top, middle, and bottom of both suspension and a single sample of the vehicle will be obtained and analyzed. Samples will also be taken after four days of storage at 2°-8°C for determination of stability in the vehicle. A sample of CGA-77102 Technical will be retained in the Ciba Crop Protection test substance archives in Greensboro, N.C.
Justification: Concentration and homogeneity of the dose suspensions and stability of CGA-77102 in the aqueous 3% corn starch containing 0.5% Tween 80 vehicle had not been determined for the study when it was conducted in 1983. Suspensions of CGA-77102 in 3% corn starch containing 0.5% Tween 80 are being prepared and analyzed to demonstrate that the preparation procedure and storage conditions used in the conduct of this study would provide stable, homogeneous suspensions at the intended concentrations 2.0 mg/ml (0.2%) and 50 mg/ml (5.00%). These were the concentrations of the dose suspensions administered to animals in the low and high dose groups, respectively.

Amendment from Protocol: Concentration and homogeneity of the dose suspensions of CGA-77102 in the aqueous 3% corn starch containing 0.5% Tween 80 vehicle were determined for the study when it was conducted in 1983.
Justification: The third protocol amendment dated March 16, 1995 stated that these determinations had not been performed. This analytical data had not been included in the transfer of the study file from the SEF to the EHC on April 15, 1994. These data were sent to the EHC on April 13, 1995.

Alpha-Metolachlor: 13-Week Feeding Study in Rats
Ciba-Geigy Corporation. 1995. MRID No. 43928923.
HED Doc. No. ?.

C O M P U T E R I N V E N T O R Y P R I N T O U T

First Name: UNASSIGNED Branch: TOX1 Phone #:
Last Name: BAETCKE Room #:

CPU INFORMATION

Brand: DELL 433/L
8088:
80286:
80386:
80486: X
Mac:
Laptop:
Network: X
3.5 Drive: X
5.25 Drive: X
Math Coproc:
Serial #: 3ZHYY
Prop. #: 949786

MONITOR INFORMATION

Brand:
Color:
Mono:
Serial #:
Prop. #:

KEYBOARD INFORMATION

AT Style: X
XT Style:
Serial #:

PRINTER INFORMATION

Brand:
Laser:
Dot:
Other:
Network:
Serial #:
Prop. #:
Font Cart:

Was computer purchased with FIFRA funds (Y/N)? N
Was printer purchased with FIFRA funds (Y/N)? N

Unique Software Found Only on CPU

PROGRAMMATIC FUNDS

Date record was last updated: 10/24/94

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 3/27/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Jess Rowland, M.S. Jess Rowland 3/27/97
Acting Section Head, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Subchronic Oral Toxicity - Rodent
Species: Rat Guideline: OPPTS 870.3100; OPP 82-1a

EPA ID No.s: EPA MRID No. 43928923
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 Technical

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.C.F. CHANG (1995): CGA-77102 TECHNICAL 13-WEEK ORAL TOXICITY IN RATS; CIBA-GEIGY CORPORATION, CROP PROTECTION DIVISION, ENVIRONMENTAL HEALTH CENTER, 400 FARMINGTON AVENUE, FARMINGTON, CT 06032 FOR CIBA CROP PROTECTION, CIBA-GEIGY CORPORATION; LABORATORY STUDY NUMBER F-000191; FEBRUARY 21, 1995; EPA MRID No. 43928923, unpublished.

Executive Summary: In a subchronic oral study (MRID# 43928923), Sprague-Dawley rats (Strain: Crl: COBS® CD® (SD)BR from Source: Charles River Breeding Laboratories, Kingston, New York) received either 0, 30, 300, 3000, or 10000 ppm CGA-77102 Technical (Purity: 89.6% Dual content (93.7% S-Isomer); Batch No.: FL-830813 (SL-649)) in the diet for 13 weeks.

Treatment related systemic toxicity was noted at 3000 ppm and above as lower body weights and body weight gains in both sexes along with lower food consumption and reduced food efficiency. The 3000 and 10000 ppm males had increased absolute and relative kidney weights (statistically significantly different), this was a trend in the females also but only the relative organ weights were statistically significantly different. The 10000 ppm dose groups had increased gamma-GT activities and the males alone had increased eosinophilic intracytoplasmic inclusions bodies (of unknown etiology). **The Systemic Toxicity NOEL was 300 ppm and the LOEL was 3000 ppm based on lower body weights and body weight gains, reduced food consumption and reduced food efficiency in both sexes and increased kidney weights in males.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§82-1a) for a subchronic feeding study in rats.

<u>Compliance</u>: A signed and dated STATEMENT OF <u>NO</u> DATA CONFIDENTIALITY CLAIMS, CERTIFICATION OF GOOD LABORATORY PRACTICES, EPA FLAGGING CRITERIA STATEMENT (according to the investigators: This study neither meets nor exceeds any of the applicable criteria.) and QUALITY ASSURANCE STATEMENT was provided.

THIS REVIEW CONTAINS TEXT INFORMATION SCANNED BY THE REVIEWER INTO ELECTRONIC FORMAT (USED IN MATERIALS AND METHODS, STUDY DESIGN AND CONCLUSIONS-INVESTIGATORS SUMMARY SECTIONS).

A. Materials and Methods

Test Compound: CGA-77102 Technical
Purity: 89.6% Dual content (93.7% S-Isomer)
Description: Amber liquid
Batch No.: FL-830813 (SL-649)
other provided information:
Source: CIBA-GEIGY Corporation
The test material admixture were stable at 14 days at room temperature and was stored at room temperature.

Vehicle(s): Acetone (ACS); Control No: L-7680 and M-1048; Source: J.T. Baker Chemical Company; Purity: 100%

Test Animal(s): Species: Sprague-Dawley rat
Strain: Crl: COBS® CD® (SD)BR
Source: Charles River Breeding Laboratories, Kingston, New York
Age: Date of Birth: April 20 1983
Body Weight: males: 230.4-234.7 g; females: 166.3-171.8 g at study initiation

B. Study Design

From page 14 of the report: This study was sponsored by the Ciba Crop Protection Division (then known as the Agricultural Division) and conducted at the Safety Evaluation Facility (SEF) of the Ciba-Geigy Pharmaceutical Division in Summit, New Jersey. The purpose of the study was to determine the subchronic toxicity of CGA-77102 Technical in rats after 90 days of exposure.

NOTE: This study was initiated on June 10, 1983 and completed on October 13, 1983.

1. Animal Husbandry and Assignment

From pages 20-21 of the report:

Pretreatment: The animals were acclimated to the SEF environment and diet for 23 days prior to study initiation.

Housing: The animals were housed individually in wire-bottom cages suspended on racks which were kept in a sanitized room maintained at a mean daily temperature of 73 ± 5°F a relative humidity of 50 ± 20% and having an artificial light cycle of 12 hours. Racks and cages were cleaned monthly.

Diet: Certified Purina Rodent Chow® No. 5002 (powdered) and water (automatic delivery system) were available in excess ad libitum throughout the study period. The drinking water was monitored for contaminants at periodic intervals. An analysis of the diet was obtained from the supplier for monitoring acceptable nutrients and contaminants.

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Selection and Distribution of Animals: Normal, healthy rabbits [assumed they meant rats] that passed physical and ocular examinations were distributed randomly into 1 of 5 groups/sex. During acclimatization, a pool of normal healthy animals within an appropriate weight range of 200-250 g for males, and 130-180 g for females, were selected for randomization. Randomization tables supplied for each sex were generated by the Statistics Department for this study.

Group Dosing Schedule

Group No	Sex	No of Rats	Rat No	Accession No.	Daily Dietary Level (ppm)
1	M	15*	1-15	37001-37015	0
2	M	15	16-25	37016-37025	30
3	M	15	26-35	37026-37035	300
4	M	15	36-45	37036-37045	3,000
5	M	15*	46-60	37046-37060	10,000
1	F	15*	61-75	37061-37075	0
2	F	10	76-85	37076-37085	30
3	F	10	86-95	37086-37095	300
4	F	10	96-105	37096-37105	3,000
5	F	15*	106-120	37106-37120	10,000

Recovery Groups*: Five (5) rats/sex in each of the control and high dose groups were permitted a 28-day recovery period following a 13-week challenge with CGA 77102 Technical.

From pages 14-15 of the report: The feeding levels for this study were selected based on results from a three-week rangefinding study in rats. In that study, CGA-77102 was administered in diet at concentrations of 0, 10 (30000)[1], 30, 300, 3000 or 10000 ppm for 1 (10 ppm), 2 (30000 ppm) or 3 weeks (0, 30, 300, 3000 or 10000 ppm).

Two moribund sacrifices occurred during the first week of dosing at 3000 ppm. Body weight gains were sharply decreased in both sexes at 10000 ppm whereas weight loss occurred in both sexes at 30000 ppm during the first week of the dosing regime. Total body weight gains vs control were 87/82 and 68/67% (M/F) at 3000 and 10000 ppm, respectively. Decreased food consumption paralleled the body weight effect at > 10000 ppm.

[1] Increased from 10 to 30000 ppm starting week 2.

Reduced WBC counts (both sexes) and platelet counts (males) were noted at 30000 ppm. There were treatment-related increases at ≥ 10000 ppm in SGPT (females) and γ-GT (both sexes) activities. Serum total protein and albumin concentrations were decreased in males at 30000 ppm and in females at ≥ 10000 ppm. Absolute liver weight was increased in males at 10000 ppm, relative liver

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weights (% body weight and % brain weight) were increased at ≥ 10000 ppm. In females, absolute and relative liver weights were increased at ≥ 10000 ppm.

Based on the results mentioned above, 10000 ppm was selected as the top feeding level for the 13-week study. At 10000 ppm, body weight gain reduction and liver effects were expected. The 30 ppm was selected as a possible no-observable-effect level (NOEL).

2. Diet Preparation and Administration

From pages 21-22 of the report:

Preparation of Test Substance: Homogeneous blends of CGA 77102 Technical in the powdered diet were prepared weekly by TPSS [not defined] according to TPSS SOP's. The admixtures were used within 10 days and were stored at temperatures ≤ 30°C. Admixtures of the test substance in the powdered diet were prepared by dissolving the test substance in acetone and after mixing the resulting solution with the powdered diet, evaporating the acetone under a hood (Appendix VII)

Calculations:

Total Weight CGA 77102 Technical (mg) = Concentration CGA 77102 Technical in diet (mg/kg) x Total Amount Test Admixture Needed (kg)

Preparation of Control Substance: The control powdered diet was prepared following the same procedures as those used for the test substance except for the omission of the test substance. The amount of the control diet prepared for each control group was the same as that prepared for each test group (Appendix VII).

Administration of Test Substance: The test substance in powdered feed blends was available at libitum in excess at concentrations of 0, 30, 300, 3,000, or 10,000 ppm. Control groups received the acetone-treated diet (Certified Purina Chow® No. 5002) ad libitum in excess.

Duration of Treatment The test substance admixtures were administered for a minimum of 13 consecutive weeks (7 days/week) and thereafter until the day of scheduled sacrifice.

Dosing Calculations: Mean daily doses of test substance were calculated as follows:

$$\text{Mean Daily Dose per rat/group (mg/kg b.w./day)} = \frac{\text{Mean Daily Food consumed per rat/group (gm/day)} \times \text{Concentration of Test Substance in Feed (mg/kg)}}{\text{Mean (mid-period) Body Weight per rat/group (gm)}}$$

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From page 20 of report:

Chemical Analyses and Stability: The Ag Chem Division accepted all responsibilities related to the purity and stability of the test and control substances. The Ag Chem Division determined that the test substance admixtures with feed would be stable for 14 days when stored at room temperature. The homogeneity of test article admixtures was established at study initiation by TPSS. At initiation and monthly thereafter, TPSS validated the test substance concentration of each admixture level.

According to the investigators (Appendix VI, pages 293-300 of the report), the mean % differences (actual and expected diet concentrations) were -2.0, -1.0, -1.1, and -1.9 for the 30, 300, 3000, and 10000 ppm feed admixtures, respectively.

3. Observations

From pages 22-24 of the report:

Physical Examinations: Physical examinations were conducted on all rats by the Vivarium Subdivision upon arrival at the SEF to select normal, healthy animals. At study initiation and monthly thereafter, each animal on study was examined for gross physical changes/defects which included examination of all orifices and eyes and palpations for tissue masses.

Ocular Examinations: Both eyes of every rat were examined initially (and/ or during conditioning) and terminally using focal illumination, indirect ophthalmoscopy, and when indicated slit-lamp microscopy.

Clinical Signs: Each animal was monitored daily (at least twice - a.m. and p.m.) for appearance, mortality, toxicologic, and/or pharmacologic overt effects. On weekends and holidays, observations were made only once daily.

Food Consumption and Body Weights: Both parameters were recorded weekly. Body weights were also recorded at study initiation.

Clinical Laboratory Tests[1]: Blood was obtained after an overnight fast by periorbital bleeding under ether anesthesia. Serum was used for clinical chemistry; blood for hematology was collected with EDTA.
[1]References to all clinical laboratory tests are presented in Appendix II
The following Clinical Laboratory Tests were conducted on each animal at study termination:

Hematology	Biochemistry		Urinalysis
Hemoglobin	Total Protein	Na^+	Occult blood
Hematocrit	Albumin	K^+	Protein
RBC, WBC Counts	A/G Ratio	Ca^{++}	Glucose
Differentials	Glucose	Cl^-	Ketones
Clotting Time	BUN	SGOT	Bilirubin
Platelet count	Total Bilirubin	SGPT	pH
Heinz bodies	Creatinine	Gamma-GT	Spec.Gravity
Erythrocyte indices (MCV, MCH, and MCHC)	Total Cholesterol	LDH	Urobilinogen
	Inorganic phosphorus	Alk. Phosphatase	
Methemoglobin	*Conducted on controls and high-dose groups although blood smears were prepared for all animals.		
Reticulocyte count*			

NOTE FROM REVIEWER: All guideline recommended hematology and clinical chemistry parameters were determined.

From pages 22-24 of the report:

Postmortem Examinations: A necropsy was performed on each animal which survived the scheduled experimental period. The following list of tissues were harvested by Pathology from each animal, and placed in 10% neutral buffered formalin:

All gross lesions	Cecum	Nostrils (nasal cavity)
All tissue masses	Rectum	Lymph Nodes Submaxillary (2)
Brain	Colon	Lymph Nodes Mesenteric
Spinal Cord (two levels)	Thymus	Urinary Bladder
Pituitary	Heart	Gonads (♂/♀ X 2)
Eyes/Optic Nerves (X2)	Aorta	Prostate (♂)
Salivary Glands	Lungs	Epididymides (♂ X 2)
Thyroids	Liver	Seminal Vesicles (♂ X 2)
Parathyroids	Pancreas	Uterus (♀ horns, X 2)
Trachea	Kidneys (X2)	Uterus (♀ cervix)
Esophagus	Adrenals (X2)	Vagina
Stomach	Spleen	Bone Marrow (from femur)
Duodenum	Sciatic Nerve	Muscle (skeletal)
Jejunum	External Auditory Canal	Skin
Ileum	Tongue	Mammary Gland (♂/♀)
Larynx		

NOTE FROM REVIEWER: All guideline recommended tissue examination parameters were determined.

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From pages 22-24 of the report:

Histopathology: Histopathological examinations were performed according to the following criteria:

(1) On the tissues listed from all animals in control and high-dose groups.

(2) On the lungs, kidneys, livers, and gross lesions from every animal in all dose groups.

Organ Weights The organs listed below were weighed for every animal at scheduled terminal necropsies. Those organ identified with an asterisk (*) were fixed in 10% neutral buffered formalin before being weighed while paired organs were weighed as pairs.

Brain (including brain stem)	*Adrenals	Testes
*Ovaries	Kidneys	Liver
*Heart	Spleen	

Statistical Analysis

From Appendix I, page 54 of the report:

Nonpathology Data: All numerical data that were obtained in the course of the study were submitted to the Computer Math Section for storage and for generation of interim/or final reports on a program developed by the Research Statistics Section of CIBA-GEIGY. This program routinely lists individual animal data and provides summary tables, and when the design requirements are met, generates statistical analyses. These analyses were designed mainly to test each parameter for the possible trends existing between treatment groups that comprise different doses of the same compound and zero dose control. If a significant trend was found, the test procedure was applied again to the remaiming treatment groups, excluding the highest dose group, and so on, in order to examine the significance of comparisons of dose groups against controls.

References: 1) Scheffe, H. (1959). Analysis of Variance. John Wiley and Sons, New York, (pp 55-59).

2) Barlow, R.E.; Bartholomew, D.J.; Breoner, J.M.; and Brunk, D. (1972). Statistical Inference Under Order Restrictions. John Wiley and Sons, New York (pp 183-188, 198-207, 214-215).

Pathology Data: All data from microscopically investigated animals were recorded by the pathologists into the Pathology Data Base. The data were tabulated and tables were generated by the N032 pathology data system. If sample sizes were adequate, these data were analyzed separately for each sex by Fisher's exact tests (4) and for both sexes by computing the convolved probabilities. Additional analyses, such as trend tests and time-adjusted

analyses, were available and were performed when requested.

References: 1) Fisher, R.A. (1958). Statistical Methods for Research Workers, 13th Edition Hafner Publishing Co., Inc., New York (pg 356).

2) Feller, W. (1950). An Introduction for Probability Theory and Its Applications, 3rd Edition. John Wiley and Sons, New York (pp 266).

C. Results:

1. Observations:

a. Mortality

No animals died during the study period.

b. Clinical Signs

No treatment related effects on *appearance, behavioral patterns, and physical and ocular examinations* were noted in the data provided (group summary and individual animal data).

2. Body Weight

The investigators provided graphed mean, group summary and individual animal data. The following tables present body weights and body weight gains for the study:

Table I: Body Weights (grams)[a]

Dose (ppm):	0	30	300	3000	10000
Week					
			Males		
0	230.4±3.8	232.2±6.2	233.4±3.3	232.1±4.3	234.7±3.6
1	298.9±4.0	299.2±4.6	296.4±8.7	287.5±6.7	262.6**±5.8
2	344.1±5.2	344.9±6.4	339.1±9.6	318.1*±8.9	305.9**±6.5
3	381.8±6.1	383.4±7.4	377.8±11.0	355.7*±10.0	337.8**±7.5
4	403.0±7.2	403.9±9.3	395.1±12.4	369.7*±11.1	354.9**±7.4
5	429.1±7.8	431.6±9.9	421.7±12.6	393.4*±11.9	380.6**±7.4
6	455.3±8.3	454.9±10.6	444.0±13.4	417.0**±12.3	401.6**±7.3
7	469.2±9.4	470.7±11.5	456.8±14.0	428.1**±12.2	412.5**±7.9
8	495.0±10.0	494.4±12.3	481.7±16.5	449.8**±13.6	428.8**±8.7
9	506.0±10.0	507.4±12.7	495.5±16.9	458.3**±14.2	439.1**±8.3
10	520.5±10.3	519.3±13.0	509.0±17.5	470.7**±15.0	453.5**±9.1
11	527.4±10.8	529.9±12.4	520.3±17.7	483.8*±15.9	462.2**±9.1
12	541.2±11.8	546.0±13.4	531.9±18.3	492.4*±16.5	469.8**±9.4
13	551.5±12.3	553.4±13.4	543.6±19.4	502.8*±16.7	477.9**±9.8

continued

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Table I: Body Weights (grams) continued

Dose (ppm): 0	30	300	3000	10000
		Females		
0	171.8±2.5	166.3±3.8	168.0±3.4	167.1±2.9	170.7±2.1
1	187.8±3.5	183.1±5.3	187.0±3.6	180.0±3.0	178.9*±2.6
2	205.6±4.0	198.3±5.9	204.1±4.5	194.3±3.6	195.9±2.7
3	217.9±4.3	214.5±8.1	216.9±5.4	207.3±4.4	204.4*±3.1
4	219.1±4.7	211.8±7.4	216.8±5.3	208.6±4.2	205.7*±3.6
5	237.0±5.3	224.4±7.4	232.7±5.3	224.4±5.2	218.1**±4.2
6	243.2±5.4	237.2±7.8	238.9±5.4	229.9±5.4	223.6**±3.8
7	246.4±5.2	237.4±8.1	240.7±5.3	230.9±5.1	223.9**±4.2
8	264.6±5.4	253.2±8.1	257.4±5.8	242.2**±5.5	231.4**±3.6
9	266.4±6.1	256.9±8.7	260.6±5.6	243.9*±5.8	234.0**±3.9
10	272.3±6.0	259.4±8.4	264.9±6.1	247.2**±6.0	235.3**±4.4
11	279.6±6.1	267.6±9.2	270.0±6.4	253.0**±6.7	238.6**±4.3
12	285.5±6.1	271.3±8.7	273.9±7.0	256.6**±6.7	238.6**±4.0
13	290.0±6.2	273.3±8.6	279.3±6.7	260.4**±7.3	240.3**±5.5

[a] = data from Table 2 and 3 and Appendix III, pages 46-47 and 62-74; * = $p < 0.05$; ** = $p < 0.01$.

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

Dose (ppm): 0	30	300	3000	10000
Weeks				
		Males		
0-13	321.1	321.2	310.2	270.7	243.2
%[1]	140.1	140.3	133.0	117.3	104.2
% control	-	100	96.6	84.3	75.7
		Females		
0-13	118.2	107.0	111.3	93.3	69.6
%	68.7	64.4	66.6	55.8	40.7
% control	-	93.7	96.9	81.2	59.2

[a] = data from Table 2 and 3 and Appendix III, pages 46-47 and 62-74; [1] = baseline (week 0)

Table III: Body Weights & Body Weight Gains - Recovery Period (grams)[a]

Dose (ppm): Week	0		10000	
		Males		
14	556.7±28.4		480.3*±14.0	
15	575.8±29.8		498.9*±14.8	
16	585.5±32.0		508.5±14.9	
17	598.9±30.6		524.6±16.5	
18	605.0±30.6	48.3[1](8.7)[1]	533.3±16.6	53.0(11.0)
		Females		
14	277.5±16.0		248.7±9.0	
15	281.9±15.6		255.7±7.9	
16	284.5±16.1		256.0±9.1	
17	289.5±16.8		262.3±10.9	
18	293.8±17.1	16.3(5.9)	268.4±9.8	19.7(7.9)

[a] = data from Table 2 and 3 and Appendix III, pages 46-47 and 62-74; * = p < 0.05: [1] = body weight gain; [2] = percent relative to recovery initiation

The 3000 ppm males had statistically significantly lower body weights from week 2 and 10000 ppm males from week 1 and 3000 ppm females from week 8 and 10000 ppm females from week 3. The 3000 and 10000 ppm dose groups had lower body weight gains for the study period (decreases of 15.7% and 24.3% were seen in the 3000 and 10000 ppm males, respectively. Decreases of 18.8% and 40.8% were seen in the 3000 and 10000 ppm females, respectively). The 10000 ppm recovery group gained weight similar to the control group.

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3. Food Consumption and Compound Intake

The investigators provided graphed mean, group summary and individual animal data. The following tables present food consumption for the study and food efficiency calculated by the reviewer:

Table IV: Food Consumption (grams/day)[a]

Dose (ppm): Week	0	30	300	3000	10000
			Males		
1	25.3±0.6	25.7±0.7	24.7±0.9	23.2±1.0	20.7±1.2
2	26.6±0.6	26.7±0.9	25.6±0.7	23.9*±1.0	25.0*±0.7
3	26.1±0.5	26.9±0.6	26.3±0.8	25.4±0.9	24.1**±0.5
4	24.9±0.6	25.1±0.9	24.3±0.8	23.0±0.8	23.1*±0.7
5	26.4±0.5	27.2±0.6	25.8±0.7	24.3*±0.9	23.4**±0.3
6	26.4±0.6	27.0±0.8	25.7±0.7	25.0±0.7	23.4**±0.4
7	25.2±0.6	25.4±0.7	24.4±0.6	24.0±0.7	23.2**±0.4
8	28.2±0.5	29.0±0.6	27.7±0.9	26.3*±0.8	24.7**±0.5
9	26.7±0.6	27.9±0.9	26.8±0.9	24.8±1.0	23.5**±0.5
10	27.1±0.5	27.6±0.8	26.7±0.9	25.6±0.9	24.4**±0.5
11	26.2±0.7	26.7±0.7	26.2±0.6	25.6±0.7	24.3*±0.6
12	26.7±0.7	27.8±0.7	25.8±0.7	24.4*±1.0	22.5**±0.6
13	26.8±0.6	27.5±0.7	26.8±0.7	26.0±0.8	23.6**±0.5
Total (kg)	2.398	2.453	2.358	2.249	2.142
g/rat/day	26.4	27.0 (+2.3)[1]	25.9 (-1.9)	24.7 (-6.4)	23.5 (-11.0)
			Females		
1	16.8±1.0	16.9±0.6	17.8±0.6	16.8±0.8	14.9±0.7
2	18.7±0.6	16.9±0.6	18.1±0.5	17.4±0.4	17.8±0.4
3	18.8±0.7	17.7±0.9	18.8±0.5	17.8±0.5	16.4**±0.3
4	17.2±0.6	15.7±0.4	17.7±0.7	16.5±0.4	16.6±0.5
5	18.6±0.7	17.5±0.6	18.3±0.4	18.1±0.5	17.1±0.4
6	18.7±0.7	18.3±0.8	18.4±0.4	17.7±0.4	16.8**±0.4
7	17.3±0.5	16.4±0.6	17.3±0.6	16.4±0.5	16.1±0.4
8	20.7±0.8	19.5±0.6	21.1±0.7	18.6*±0.4	17.3**±0.4
9	19.2±0.7	18.6±0.8	19.3±0.5	17.4±0.5	16.9**±0.5
10	18.8±0.6	18.1±0.6	18.9±0.5	17.6±0.4	16.0**±0.3
11	19.8±0.7	18.7±0.7	19.0±0.6	18.1*±0.5	16.2**±0.3
12	19.4±0.6	18.2±0.6	18.8±0.6	17.8±0.5	15.3**±0.4
13	20.2±0.7	18.0±0.5	19.3±0.6	18.2*±0.6	15.4**±0.6
Total (kg)	1.710	1.613	1.699	1.598	1.490
g/rat/day	18.8	17.7 (-5.9)[1]	18.7 (-0.5)	17.6 (-6.4)	16.4 (-12.8)

[a] = data from Tables 4-5 and Appendix III, pages 48-49, 62-74); [1] = % change from control; * = $p < 0.05$; ** = $p < 0.01$.

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Table V: Food Consumption (grams/day) - Recovery Period[a]

Dose (ppm):	0		10000	
	Total	g/rat/day	Total	g/rat/day
Males	772.0	27.6	724.0	25.9(-6.2)[1]
Females	496.2	17.7	526.7	18.8(6.2)

[a] = data from Tables 4-5 and Appendix III, pages 48-49, 62-74); [1] = percent change relative to controls.

Table VI: Food Efficiency (weeks 1-13, %)

Dose:	0	30	300	3000	10000
Males	13.4	13.1	13.2	12.0	11.4
Females	6.9	6.6	6.6	5.8	4.7

The 300 and 10000 ppm group consumed statistically significantly less food during the study and had reduced food efficiency for the overall study period.

Compound intake

The investigators did not calculate actual compound intake, by standard conversion techniques, the calculated compound intake was 0, 1.5, 15, 150, and 500 mg/kg/day for the 0, 30, 300, 3000, and 10000 ppm dose groups, respectively.

4. Ophthalmological examination

As noted in 1b above, no treatment related effects were noted during ocular examinations.

5. Hematology and clinical chemistry

a. Hematology

The investigators provided group mean and individual animal data. No treatment related effects were noted in the data provided. At week 13, there was a statistically significant reduction in leukocyte counts in 3000 ppm females (5.89×10^3) when compared to control females (9.83×10^3); however, the biological relevance of this finding is unclear due to the lack of a dose-response and sex-response.

b. Clinical Chemistry

The investigators provided group mean and individual animal data. Statistically significant reductions in SGPT (3000 and 10000 ppm, both sexes), SGOT (10000 ppm, both sexes), LDH (10000 ppm, males), and SAP (3000 and 10000 ppm, males). Following the recovery period while SAP values were comparable to the controls, the SGPT, SGOT and LDH remained reduced. Historical control data was provided for these values (study Appendix V, not attached to this DER). In spite of the statistically significant increases the mean values from the study were within the background values for this strain and age of rats. Therefore, the biological significance of these findings is unclear. There were also increases in gamma-GT (10000 ppm, both sexes), BUN (10000 ppm, males), creatinine (3000 and 10000 ppm, males and 10000 ppm, females), A/G ratios (all treated males and 3000 and 10000 ppm, females), and total bilirubin (10000 ppm, males and all treated females). These parameters reverted to normal values following the 4 week recovery period and the mean values from the study were within the historical control ranges provided. Also, except for possibly the gamma-GT values, no related pathology was noted, therefore the biological relevance of these findings is unclear.

6. Urinalysis

The investigators provided individual animal data. No treatment related effects were noted.

7. Sacrifice and Pathology

a. Organ weight

The investigators provided group mean and individual animal data. The following table presents the organ weight data:

Table VII: Absolute Organ Weights (gm) and Relative Organ to Body Weights (%)[a]

Dose (ppm):	0	30	300	3000	10000
Organ			Males		
Adrenals	0.054±0.003[a]	0.057±0.002	0.052±0.002	0.049±0.002	0.042**±0.002
	0.010±0.001[r]	0.010±0.000	0.010±0.000	0.010±0.000	0.009±0.000
Kidneys	2.8±0.07	3.2±0.09	3.1±0.14	3.3**±0.11	3.3**±0.11
	0.521±0.014	0.577±0.009	0.570±0.0.16	0.654**±0.018	0.717**±0.030
Liver	13.8±0.50	17.2±0.80	18.3±0.99	14.3±0.57	15.2±0.68
	2.543±0.072	3.111*±0.153	3.347*±0.104	2.842*±0.058	3.274**±0.115
Spleen	0.698±0.042	0.761±0.020	0.830±0.046	0.687±0.026	0.643±0.042
	0.130o.009	0.138±0.004	0.152±0.005	0.137±0.005	0.138±0.008
Testes	5.3±0.19	5.4±0.16	5.2±0.17	4.9±0.19	5.0±0.26
	0.975±0.025	0.984±0.034	0.960±0.027	0.984±0.036	1.080*±0.042
Heart	1.422±0.021	1.527±0.053	1.476±0.059	1.350±0.038	1.279**±0.030
	0.262±0.004	0.278±0.014	0.271±0.005	0.269±0.006	0.277±0.009
Brain	2.0±0.03	2.1±0.03	2.1±0.05	2.1±0.04	2.0±0.03
	0.377±0.011	0.378±0.011	0.386±0.012	0.418**±0.011	0.432**±0.009
			Females		
Adrenals	0.064±0.003	0.065±0.004	0.064±0.002	0.061±0.004	0.053*±0.002
	0.022±0.001	0.024±0.001	0.023±0.001	0.024±0.002	0.023±0.001
Kidneys	1.9±0.05	1.9±0.11	1.8±0.05	2.0±0.08	1.8±0.06
	0.642±0.015	0.678±0.026	0.654±0.017	0.767**±0.034	0.773**±0.036
Liver	8.3±0.45	9.0±0.35	8.0±0.55	9.3±0.44	7.9±0.28
	2.834±0.137	3.288±0.071	2.870±0.160	3.579**±0.144	3.367**±0.083
Spleen	0.453±0.017	0.500±0.024	0.455±0.021	0.450±0.023	0.382*±0.013
	0.155±0.007	0.183±0.006	0.163±0.005	0.174±0.010	0.164±0.006
Ovaries	0.074±0.007	0.079±0.012	0.086±0.007	0.060±0.007	0.080±0.006
	0.025±0.002	0.029±0.004	0.031±0.003	0.023±0.002	0.034±0.002
Heart	0.914±0.023	0.890±0.021	0.882±0.031	0.900±0.018	0.776**±0.022
	0.313±0.009	0.327±0.009	0.317±0.012	0.347±0.008	0.332±0.008
Brain	2.0±0.03	2.0±0.02	1.9±0.03	1.9±0.01	1.9±0.04
	0.669±0.014	0.731±0.021	0.681±0.015	0.746*±0.020	0.824**±0.019

[a] = data from Table 8 and Appendix III, pages 53 and 117-133 of the report); * = $p < 0.05$; ** = $p < 0.01$; [a] = absolute organ weight; [r] = relative organ weight to body weight.

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Table VIII: Absolute Organ Weights (gm) and Relative Organ to Body Weights (%) - Recovery Period[a]

Dose (ppm):	0	10000
Organ	**Males**	
Adrenals	605.0±30.56	533.3±16.58
	0.055±0.003	0.054±0.004
Kidneys	3.3±0.10	3.2±0.13
	0.542±0.027	0.595±0.035
Liver	16.0±0.97	14.2±0.62
	2.645±0.126	2.673±0.161
Spleen	0.680±0.050	0.568±0.024
	0.112±0.006	0.107±0.005
Testes	5.3±0.21	5.5±0.28
	0.883±0.063	1.030±0.044
Heart	1.404±0.104	1.451±0.076
	0.236±0.022	0.272±0.010
Brain	2.0±0.05	2.1±0.05
	0.338±0.17	0.396*±0.14
	Females	
Adrenals	0.072±0.005	0.067±0.005
	0.025±0.003	0.025±0.001
Kidneys	1.8±0.05	1.9±0.12
	0.613±0.025	0.721*±0.77
Liver	7.4±0.31	7.8±0.77
	2.555±0.253	2.898±0.196
Spleen	0.398±0.029	0.368±0.031
	0.125±0.006	0.137±0.009
Ovaries	0.090±0.011	0.099±0.010
	0.032±0.005	0.037±0.004
Heart	0.874±0.027	0.917±0.057
	0.301±0.017	0.341±0.013
Brain	1.9±0.03	1.9±0.05
	0.637±0.036	0.699±0.021

[a] = data from Table 8 and Appendix III, pages 53 and 117-133 of the report); * = $p < 0.05$; ** = $p < 0.01$; [a] = absolute organ weight; [r] = relative organ weight to body weight.

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The 3000 and 10000 ppm males had increased absolute and relative kidney weights (statistically significantly different), there was a trend in the females also at these dose but only the relative organ weights were statistically significantly different. Following the recovery period the organ weights in males were similar to the controls while the weights in females were slightly elevated. There was indications that all treated males had slightly increased liver weights, not dose related.

b. Gross pathology

The investigators provided group mean and individual animal data. No treatment related effects were noted. The investigators pointed out that one 10000 ppm male had an enlarged kidney.

c. Microscopic pathology

The investigators provided individual animal data. The following table presents selected histopathological observations:

Table IX: Histopathologic Observations[a]

Dose (ppm)	0	30	300	3000	10000
Liver, Hepatocytes					
Vacuolation					
Males	1/10	6/10	9/10	0/10	1/10
Females	0/10	4/10	2/10	0/10	2/10
Inclusion bodies					
Males	0/10	0/10	0/10	1/10	6/10

[a] = data from Appendix VII, pages 338-378 of the report.

No similar observations were noted in the recovery group animals. The eosinophilic intracytoplasmic inclusions bodies were of unknown etiology according to the investigators and are considered a treatment related effect at 10000 ppm.

D. Discussion/Conclusions

i. Investigators Summary:

CGA 77102 Technical, a potential herbicide, was administered to rats of both sexes for 13 consecutive weeks in order to characterize any toxicity induced during subchronic ingestion. CGA 77102 Technical was presented in the diet ad libitum at concentrations of 0, 30, 300, 3000, or 10,000 ppm. To determine the reversibility of any toxicological insults, a 4-week recovery period was imposed upon some control and high dose animals of each sex.

All animals, regardless of sex or treatment, survived the 13-week study. No overt signs of intoxication were witnessed during daily observations or through periodic ocular and physical examinations.

At doses > 300 ppm, animals of both sexes experienced dose-dependent depressions in body weight gains, relative to controls; however, the effect was most pronounced at 3000 and 10,000 ppm. CGA 77102 Technical ingestion by rats of both sexes was generally associated with slightly smaller food consultations than controls; however, statistically significant differences ($p < 0.01$) occurred most consistently at the 10,000 ppm dose level. Following the 4-week recovery period, both parameters rebounded significantly.

Except for a significant ($p < 0.01$) reduction in WBC counts in female rats at 10,000 ppm, hematological profiles of treated and corresponding control rats were comparable. Statistically significant ($p < 0.01$), dose-dependent reductions in serum alkaline phosphatase occurred among male rats exposed to 3000 and 10,000 ppm, while slight, but significant ($p < 0.01$) increases in serum gamma-GT levels were observed among high-dose rats of both sexes. Following the recovery period, both parameters were comparable to those of controls.

Postmortem gross examinations were unremarkable. Among treated males, dose-related increases in mean kidney weights occurred which were statistically significant ($p < 0.01$) at the 3000 and 10,000 ppm dose levels. Both sexes experienced significant ($p < 0.01$) increases in mean liver/body weight ratios, relative to their controls. Among females, this was limited to the 3000 and 10,000 ppm dose levels, while among males it was dose-related and included all dose levels. Following the 4-week recovery period, both absolute and relative organ weights of former high-dose animals of both sexes were statistically comparable to those of their respective controls.

Histological evaluations revealed significant ($p < 0.05$) increases in glycogen deposits in hepatocytes of rats of both sexes at 30 ppm and in male rats at 300 ppm, relative to controls. Eosinophilic intracytoplasmic inclusion bodies of unknown etiology were observed in hepatocytes of 1 Dale rat at 3000 ppm and 7 male rats ($p < 0.05$) at 10,000 ppm. After the 4-week recovery period, these hepatic inclusion bodies were no longer observed in the former high-dose rats.

In summary, CGA 77102 Technical induced hepatotoxicity at or above 3000 ppm in male rats which was reversible when the rats were afforded a 4-week recovery period. Doses of up to 300 ppm were well tolerated without signs of toxicity.

ii. Reviewers Conclusions:

Treatment related systemic toxicity was noted at 3000 ppm and above as lower body weights and body weight gains in both sexes along with lower food consumption and reduced food efficiency. The 3000 and 10000 ppm males had increased absolute and relative kidney weights (statistically significantly different), the was a trend in the females also but only the relative organ weights were statistically significantly different. The 10000 ppm dose groups had increased gamma-GT activities and the males alone had increased eosinophilic intracytoplasmic inclusions bodies (of unknown etiology). **The Systemic Toxicity NOEL was 300 ppm and the LOEL was 3000 ppm based on lower body weights and body weight gains, reduced food consumption and reduced food efficiency in both sexes and increased kidney weights in males.**

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Alpha-Metolachlor: 13-Week Feeding Study in Dogs
Ciba-Geigy Corporation. 1995. MRID No. 43928922.
HED Doc. No. ?.

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 4/1/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Timothy F. McMahon, Ph.D. 4/1/97
Pharmacologist, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Subchronic Oral Toxicity - Nonrodent
Species: Dog Guideline: OPPTS 870.3100; OPP 82-1b

EPA ID No.s: EPA MRID No. 43928922
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 Technical

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.C.F. CHANG (1995): CGA-77102 TECHNICAL FINAL REPORT 90-DAY ORAL TOXICITY IN DOGS. CIBA-GEIGY CORPORATION, CROP PROTECTION DIVISION, ENVIRONMENTAL HEALTH CENTER, 400 FARMINGTON AVENUE, FARMINGTON, CT 06032 FOR CIBA CROP PROTECTION, CIBA-GEIGY CORPORATION; LABORATORY STUDY NUMBER F-000193; JUNE 14, 1995; EPA MRID No. 43928922.

Executive Summary: In a subchronic oral study (MRID# 43928922), male and female beagle dogs (Source: Marshall Farms, North Rose, NY.) received either 0, 300, 500, 1000, or 2000 ppm CGA-77102 Technical (95.4% purity; Lot Number FL-941255) in the diet or by capsule for 16 weeks. According to the investigators: "This study was initially designed to determine the toxicity of CGA-77102 via dietary exposure. However, during the first two weeks, very poor test diet consumption accompanied by weight loss were seen in both sexes given the top feeding level, 2000 ppm; the effect was worse in the females. Addition of corn oil or water to the test diet of the 2000-ppm females did not improve the palatability. Consequently, a decision was made to provide the test material orally to the high dose males and females via capsules; the daily dose (700 mg/dog) was calculated on the basis that all 350 grams of the test diet was consumed by each dog daily. Upon the initiation of capsule dosing, the 2000-ppm animals were switched to basal diet whereas the other dose groups continued to receive test diets. Because very little test diet was consumed by the 2000-ppm animals during the first two weeks, the whole duration of the study was extended by an additional three weeks to allow for a total of 14 weeks in capsule dosing and 16 weeks in test diet exposure. The overall study is best described as a 14/16 week

oral/dietary study."

Other than the palatability problems noted above in the 2000 ppm dose group, no biologically relevant treatment related systemic toxicity was noted at any dose level tested. **The Systemic Toxicity NOEL was equal to or greater than 2000 ppm (62 mg/kg/day for males and 74 mg/kg/day for females) and the LOEL was greater than 2000 ppm (62 mg/kg/day for males and 74 mg/kg/day for females).**

This study is classified as Acceptable-Nonguideline and dose not satisfy the guideline requirements (§82-1b) for a subchronic feeding study in non-rodents. This study needs to be repeated to fulfill this guideline requirement.

NOTE: Based on the results of the rat subchronic study (MRID# 43928923), the dog appears less sensitive tot he test compound than the rat.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, CERTIFICATION OF GOOD LABORATORY PRACTICES, EPA FLAGGING CRITERIA STATEMENT (according to the investigators: This study neither meets nor exceeds any of the applicable criteria.) and QUALITY ASSURANCE STATEMENT was provided.

THIS REVIEW CONTAINS TEXT INFORMATION SCANNED BY THE REVIEWER INTO ELECTRONIC FORMAT (USED IN MATERIALS AND METHODS, STUDY DESIGN AND CONCLUSIONS-INVESTIGATORS SUMMARY SECTIONS).

A. Materials and Methods

Test Compound: CGA-77102 Technical
Purity: 95.4% purity
Description: Amber liquid
Lot Number FL-941255
other provided information:
Source:Ciba Crop Protection Division,Greensboro, NC.
The test material was stable at room temperature and was stored at room temperature..

Vehicle(s): Acetone (ACS); Control No: L-7680 and M-1048;
Source: J.T. Baker Chemical Company; Purity: 100%

Test Animal(s): Species: Male and female beagle dogs
Strain: beagle
Source: Marshall Farms, North Rose, NY.
Age: 6-7 months old at the start of the study
Body Weight: 9.83-10.03 kg

B. Study Design

From page 13-14 of the report:

This study was conducted to determine the subchronic toxicity of CGA-77102 in beagle dogs.

This study was initially designed to determine the toxicity of CGA-77102 via dietary exposure. However, during the first two weeks, very poor test diet consumption accompanied by weight loss were seen in both sexes given the top feeding level, 2000 ppm; the effect was worse in the females. Addition of corn oil or water to the test diet of the 2000-ppm females did not improve the palatability. Consequently, a decision was made to provide the test material orally to the high dose males and females via capsules; the daily dose (700 mg/dog) was calculated on the basis that all 350 grams of the test diet was consumed by each dog daily. Upon the initiation of capsule dosing, the 2000-ppm animals were switched to basal diet whereas the other dose groups continued to receive test diets.

Because very little test diet was consumed by the 2000-ppm animals during the first two weeks, the whole duration of the study was extended by an additional three weeks to allow for a total of 14 weeks in capsule dosing and 16 weeks in test diet exposure. The overall study is best described as a 14/16 week oral/dietary study.

All changes and modifications in study design were documented in the protocol amendments (Appendix 10.1.2) .

Groups of 4 dogs/sex were fed approximately 350 grams daily of 0, 300, 500 or

1000 ppm of CGA-77102 test diet for 16 weeks. Four males and four females were fed the 2000-ppm test diet for two weeks followed by capsule dosing at 700 mg/day/dog for 14 weeks. Physical and ophthalmologic examinations were performed at pretest and termination. Hematology, clinical chemistry and urinalysis were performed during pretest, week 7 and study termination. Complete necropsy and histopathology were conducted.

1. Animal Husbandry and Assignment

From pages 15-21 of the report:

Upon arrival at the EHC, the dogs were randomly distributed to single cages, during which the sex of each animal was confirmed. The dogs, with the ear tattooed by the supplier, were assigned sequential quarantine numbers which were recorded on cage cards. During the quarantine/acclimation period (33 days), the dogs were examined by a veterinarian to see if they were suitable as test animals.

The dogs were housed and maintained in compliance with the Animal Welfare Act, (1985) and the NIH Guides for the Use and Care of Laboratory Animals (1985). They were housed in Room 350 during the quarantine/acclimation and study periods singly in stainless steel cages with approximately 8 ft^2 of floor space. Fecal and urine collection trays were mounted beneath the cages. Clean food bowls were used daily. Fecal collection trays were flushed daily and cages were disinfected monthly. Conventional disease controls were practiced and only authorized personnel were allowed in the study room. The dogs were exercised at least once weekly.

The animal room was provided with at least 15 air changes per hour; temperature was maintained at 19-24°C and relative humidity was kept at 40-60 % (exceptions were noted and recorded in study file). Fluorescent lighting was provided on a 12-hour light/dark cycle (light on at ≈ 6:00 am). Temperature and humidity were monitored continuously; a recording was made daily and the documents were archived weekly.

PMI® Feeds' Certified Canine Diet #5007 kibble was provided *ad libitum* during the first 6 days of quarantine, followed by 2-hr daily of a 50/50 mix of kibble and ground meal for 7 days and then ground meal alone 2 hr daily. PMI® Feeds' Certified Canine Diet #5007 was analyzed by the manufacturer for nutrients and contaminants. Contaminants listed in the analysis profile were at concentrations which were considered not sufficient to have affected the conduct or purpose of the study.

Water was provided ad libitum by an automatic watering system and in water bowls during feeding. The water supplied to the facility was analyzed periodically for contaminants and the reports were incorporated into the study file. Concentrations of the contaminants tested were below detection levels or were below the maximum allowable concentrations published by the state of Connecticut. The concentrations of the contaminants in the analysis profile

were considered not sufficient to have affected the conduct or purpose of the study.

Group arrangement:

From page 16 of the report:

The dogs were randomized by body weight and assigned to the groups via a computer. They were assigned such that all groups of the same sex had similar mean body weights and that littermates were not in the same group. The body weight of males ranged from 8.6 to 11.5 kilograms and the females ranged from 7.3 to 9.8 kilograms.

Feeding Level (ppm)	Males	Females
0	1-4	21-24
300	5-8	25-28
500	9-12	29-32
1000	13-16	33-36
2000@	17-20	37-40

@ For the purpose of identification, the 2000 ppm level will be used in this report for this group although the exposure was mostly via oral capsules

From page 14 of the report:

The feeding levels were selected based on results from a 1-week rangefinder study as well as 6- and 12-month toxicity studies with metolachlor technical which contained approximately 25% of CGA-77102, a stereoisomer.

In the 1-week rangefinder study (382-053), metolachlor was administered in feed at 1000, 3000 and 5000 ppm to 1 dog per sex per dose. Very poor food consumption and weight loss were seen at 3000 and 5000 ppm whereas at 1000 ppm, food consumption and weight gain were comparable to those of the controls.

The feeding levels of metolachlor in both long term studies were 100,300 and 1000 ppm. In the 6-month study (382-054), metolachlor was dissolved as a 50% solution in ethanol and blended in feed. The only treatment-related results were the decreased food consumption in females at 1000 ppm and a slight decrease in body weight gain in both sexes at 1000 ppm. No treatment-related findings in hematology, clinical chemistry, gross and microscopic pathology were noted. The no-observable-effect level (NOEL) was 300 ppm.

In the 1-year study (862253), metolachlor was dissolved in acetone as a premix and blended in diet. An interim sacrifice was performed on 4 dogs/sex/group after 13 weeks. The in-life results from the first 13 weeks showed generally decreased food consumption at 1000 ppm in maps and a significant decrease in females during week 1 only. No effects on body weight, body weight gain, hematology, clinical chemistry, or urinalysis were noted. There were no

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treatment-related findings in organ weights, gross necropsy or histopathology on the dogs that were sacrificed after 13 weeks. Overall results from the 1 - year study showed slightly elevated alkaline phosphatase in females at 1000 ppm, however, no liver pathologic changes were seen. The NOEL for the 1-year study was 300 ppm.

Because the effects observed with metolachlor at 1000 ppm were minimal over a 6-12 month period, the high dose for the present study was selected at 2000 ppm to help better define the toxicity. The low doses, 300 and 500 ppm, were selected as the anticipated NOELs.

2. Diet Preparation and Administration

From page 17 of the report:

The test diet was prepared by mixing CGA-77102 technical with the PMI® feeds' Certified Canine Diet #5007 ground meal. The identity of each lot of feed used was recorded. Appropriate amounts of CGA-77102, used as received without adjustment for purity, were blended with appropriate amounts of the basal diet in a Patterson-Kelly twin shell blender to achieve the desired concentrations. The preparation procedures were approved by the study director and documented in the study file. All prepared test diets were stored at 4°C until presented to the animals.

The dosing capsules were prepared by dispensing 700 mg (or 0.625 ml, based on a density of 1.12 g/ml) of CGA-77102 directly into gelatin capsules (size 000). The capsules were stored at room temperature.

The stability of CGA-77102 in the capsule and test diet was determined by the EHC Analytical Chemistry Laboratory. Stability of CGA-77102 test diet with the addition of water (2:1, W/V) or corn oil (1 %, W/W) was not determined as these modified test diets were not consumed by the high dose females and each procedure was tried only once.

From page 17 of the report:

The concentration and homogeneity of CGA-77102 in the test diet were measured for 7 of 18 blends. Multiple samples from each dose level and one sample from the control (0 ppm) diet were obtained and analyzed by the EHC Analytical Chemistry Laboratory. Thirty six batches of capsules were prepared Analysis for concentration and homogeneity was not performed.

CGA-77102 was analyzed by an HPLC method as described in Appendix 10.2.

From Table 9.1, pages 37-38 of the report indicate that the test diet concentrations ranged from -5.6 to 0.3% of nominal for the 300 ppm, -4.8 to 0.2% of nominal for the 500 ppm, -5.4 to 0.3% of nominal for the 1000 ppm and -3.1 to 0% of nominal for the 2000 ppm (first 2 weeks, then by capsule) doses. Homogeneity analysis showed a relative s.d. of not more than 3.4% for the dietary mixtures.

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From page 17 of the report:

Dogs were provided with approximately 350 ± 5 grams of the test or control diet daily for approximately 2 hours in the morning. Afterwards, the unconsumed feed was removed.

The capsules were administered daily to the high dose males and females. One capsule was given orally to each dog at the end of the 2-hr feeding period.

From page 24 of the report:

The EHC Analytical Chemistry Laboratory determined that CGA-77102 was stable in dietary mixtures (at 300 and 2000 ppm) for up to 35 days 4°C. CGA-77102 was also stable for any 8-day period within the 35-day expiration period when stored refrigerated in small plastic zip-lock bags. When stored at room temperature in an open food bowl, CGA-77102 was stable for at least 4 hours.

3. Observations

From pages 18-22 of the report:

All test animals were observed at least twice daily (a.m., before and after the feeding and p.m.) for general appearance, behavior, signs of toxicity and mortality. Dogs receiving capsules were observed immediately and two hours post dosing. Signs including salivation or emesis were recorded.

All test animals were given a weekly detailed physical examination, including palpation for the presence of tissue masses. Ophthalmologic examinations were performed at pretest and prior to termination for all dogs.

Daily food consumption was measured 5 days/week during the study. Individual body weights were determined weekly (i.e. every 7 days + 1 day). Termination body weights were also recorded.

Scheduled clinical laboratory tests were performed during pretest, week 7 and study termination. In addition, unscheduled clinical laboratory tests were performed as needed.

Blood and urine specimens for clinical laboratory tests were collected from dogs that were fasted at least 16 hours prior to sample collection. Blood samples were collected from the jugular vein. Urine and fecal samples were collected overnight using metabolism trays. The following parameters were evaluated.

Hematology

Hematocrit
Hemoglobin
Erythrocyte count
Total leukocyte count
Differential leukocyte count (absolute counts calculated)
Platelet count
Reticulocyte count (when hematocrit was ≤ 41% in males and ≤ 42% in females)
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)

Bone marrow smears were made from ribs taken from all dogs at necropsy. No specimens were examined.

Coagulation

Prothrombin time (PT)
Activated partial thromboplastin time (APTT)

Clinical Chemistry

Alkaline phosphatase
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Gamma glutamyl transferase
Sorbitol dehydrogenase
5' Nucleotidase
Glucose
Cholesterol
Triglycerides
Bile acids
Total bilirubin
Direct bilirubin (when total bilirubin was > 0.4 mg/dl)
Total protein
Albumin
Globulin (by subtraction), also, A/G ratio
Creatinine
Creatine kinase (CK)
Blood urea nitrogen
Calcium
Inorganic phosphorus
Sodium
Potassium
Chloride

Urinalysis

Appearance (color and transparency)
pH
Volume
Specific gravity
Glucose*
Bilirubin*
Protein*
Occult blood*
Ketone*
Urobilinogen*
Microscopic examination of sediment*

*Semiquantitative

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Fecal Analysis

Occult blood
Ova and parasites

NOTE FROM REVIEWER: All guideline recommended hematology and clinical chemistry parameters were determined.

The animals were anesthetized by sodium pentobarbital (i.v.) and euthanized by exsanguination. Necropsies were performed on all animals by trained technicians under the direction of a veterinary pathologist. All observations were recorded.

All tissues listed in the protocol were collected from all animals. The following organs, tissues or samples of them, were collected and preserved in either 10% neutral buffered formalin (NBF) or 2.5% buffered glutaraldehyde (BG).

Organ System	Tissue	Fixative
Cardiovascular	Heart	NBF
	Aorta (thoracic)	NBF
Digestive	Salivary gland - mandibular (R or L)	NBF
	Esophagus	NBF
	Stomach	NBF
	Duodenum	NBF
	Jejunum	NBF
	Ileum	NBF
	Cecum	NBF
	Colon	NBF
	Rectum	NBF
	Pancreas (R lobe)	NBF
	Liver (samples of R and L lateral lobes)	NBF
	Gallbladder	NBF
Endocrine	Pituitary	BG
	Thyroid and parathyroids	BG
	Adrenal glands	BG
Hemic/lymphatic	Thymus	NBF
	Spleen	NBF
	Retropharyngeal lymph node (medial), R or L	NBF
	Bone marrow section (sternum)	NBF
Integumentary	Inguinal skin	
	Mammary gland (female), R or L	NBF

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Organ System	Tissue	Fixative
Respiratory	Nasal turbinates	NBF
	Trachea	NBF
	Lungs (R middle and L caudal lobes)	NBF
Sensory	Eyes	BG
Urogenital	Kidneys	NBF
	Urinary bladder	NBF
	Testes	BG
	Epididymides	BG
	Prostate	NBF
	Ovaries	BG
	Vagina	NBF
	Uterus (horns, body and cervix)	NBF
Musculoskeletal	Semimembranosus muscle (R or L)	NBF
	Bone (femur with articular surface)	NBF
Nervous	Brain	NBF
	Spinal Cord	
	cervical	NBF
	mid-thoracic	NBF
	lumbar	NBF
	sacral	NBF
	Sciatic nerve (R or L)	NBF
Gross Lesions	All	NBF

Organ Weights

The following organs were weighed; paired organs were weighed together.

Liver	Testes (without epididymides)
Kidneys	Ovaries
Brain	Adrenals
Spleen	Thyroid (with parathyroids)
Heart	

All collected tissues from all study animals were examined by the consultant study pathologist with the knowledge of the exposure level for individual animals. The severity of the tissue lesions was graded as follows:

Grade 1 (1 +): Minimum . This corresponds to changes ranging from barely noticeable to noticeable but so minor, small, or infrequent as to warrant no more than the least assignable grade.

Grade 2 (2+): third. This corresponds to a histopathologic change that is a

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noticeable but not a prominent feature of the tissue.

Grade 3 (3+): Moderate. This corresponds to a histopathologic change that is a prominent but not a dominant feature of the tissue.

Grade 4 (4+): Severe or Marked. This corresponds to a histopathologic change that is a dominant but not an overwhelming feature of the tissue.

All processes with severity grade of mild (+ 2), moderate (+ 3) or severe/marked (+ 4) are indicated in the Project Summary Table (Appendix C). Processes with minimal severity were not identified in the table.

NOTE FROM REVIEWER: All guideline recommended tissue examination parameters were determined.

Statistical Analysis

From page 23 of the report:

The specific statistical methods used to analyze the test parameters are listed below. The probability of Type 1 error (alpha) was set at 0.05. Significance at the 0.01 level was also indicated.

Statistical Methods	Data Evaluated
Bartlett's test for homogeneity; Shift right and rank transformation performed on non-homogeneous data One way ANOVA; followed by two-tailed Dunnett's "t" test	Body weights, body weight gains Food Consumption
One way ANOVA; followed by two-tailed Dunnett's Sty test	Hematology, clinical chemistry Organ weights, urine pH, specific gravity and volume

Data Calculation and Presentation

Compound consumption for a given week was calculated by multiplying the mean food consumption for that week with the nominal concentration of the test diet and dividing by the mean body weight obtained at the beginning and the end of that week.

The string of numbers and letters that is found at the bottom of some tables and appendices is for version identification and is not related to study data.

C. Results:

1. Observations:

a. Mortality

No animals died during the study period.

b. Clinical Signs

The investigators provided group summary and individual animal data. The following table presents selected observations (from Table 9.3 and 9.4, pages 40-43 of the report):

Table I: Clinical Observation Data

Dose(ppm):	0	300	500	1000	2000
Salivation	0	0	0	0	1 (15)[1]
Stool:					
			Males		
Few	0	1 (31)	0	3 (3)	4 (3)
No	0	0	0	2 (3)	2 (3)
Loose	0	1 (28)	1 (6)	0	1 (6)
			Females		
Salivation	0	1 (1)	1 (1)	0	3 (15)
Stool:					
Few	1 (3)	0	1 (18)	1 (3)	4 (3)
No	0	0	0	1 (4)	4 (2)
Loose	0	0	1 (10)	4 (8)	2 (6)

[1] = first day clinical observation noted.

The 1000 males and the 2000 ppm dose groups had increased incidence of few or no stool starting early in the study. Occasional emesis was observed usually within 2 hours after capsule administration (high dose only).

2. Body Weight

The investigators provided graphed mean, group summary and individual animal data. The following tables present selected body weights and body weight gains (0-13 and 0-16 weeks calculated by the reviewer from group mean data) for the study (from Tables 9.5 - 9.8, pages 44-51):

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Table II: Body Weights (kilograms)

Dose(ppm): 0	300	500	1000	2000
Week				
		Males		
0	9.83±1.14	9.93±0.91	9.93±0.75	10.03±0.93	9.55±0.70
1	9.98±0.95	10.03±0.87	9.95±0.75	9.55±1.14	9.13±0.39
2	10.18±0.90	10.15±0.69	10.18±0.66	9.43±1.35	9.18±0.61
7	10.85±0.52	10.63±0.46	10.53±1.45	9.88±1.10	10.38±0.25
13	11.33±0.30	10.83±0.61	11.23±1.66	9.70±1.58	11.55±0.33
16	11.63±0.41	10.93±0.68	11.50±1.86	9.65±1.59	11.95±0.37
		Females		
0	8.00±0.67	7.93±0.59	7.85±0.33	8.13±0.99	7.90±0.42
1	8.38±0.63	8.18±0.67	7.95±0.49	8.15±0.96	6.98±0.70
2	8.60±0.64	8.35±0.73	8.05±0.37	8.33±1.06	7.45±0.76
7	9.15±0.79	8.63±0.67	8.50±0.52	8.90±0.94	8.55±0.86
13	9.88±0.69	9.45±0.91	9.10±0.62	9.25±0.97	9.25±1.02
16	10.20±0.81	9.43±0.98	9.18±0.67	9.18±1.30	9.48±1.10

Table III: Body Weight Gains (kilograms)

Dose: 0	300	500	1000	2000
Weeks				
		Males		
1	0.15	0.10	0.03	-0.48	-0.43
2	0.20	0.13	0.23	-0.13	0.05
0-13	1.50	0.90	1.30	-0.33	2.00
0-16	1.80	1.00	1.57	-0.38	2.40
		Females		
1	0.38	0.25	0.10	0.03	-0.93**
2	0.23	0.18	0.10	0.18	0.48*
0-13	1.88	1.52	1.25	1.12	1.35
0-16	2.00	1.50	1.33	1.05	1.58

*** = $p < 0.05$; ** = $p < 0.01$**

Outside of the initial slight palatability problems, no treatment related effects were noted.

3. Food Consumption and Compound Intake

The investigators provided graphed mean, group summary and individual animal data. The following tables present food consumption for the study and food efficiency calculated by the reviewer from food consumption data and body weight gains for selected weeks (from Tables 9.9 and 9.10, pages 52-55):

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Table IV: Food Consumption (grams/day)

Dose:	0	300	500	1000	2000
Week			Males		
1	331.9±24.2	251.6±42.0	223.5±47.8	182.6±135.9	182.7±152.3
2	337.9±13.5	301.1±21.7	295.4±33.2	213.2±123.0	250.5±117.4
7	336.5±16.3	322.2±54.0	302.3±32.7	313.3±40.4	311.0±67.0
13	328.5±42.0	317.9±64.5	342.7±15.3	316.6±39.7	349.7±0.4
16	350.4±1.0	333.5±34.9	340.3±18.9	316.8±47.6	351.1±0.6
			Females		
1	274.7±42.4	231.1±35.0	231.8±75.4	239.6±92.7	10.4**±6.0
2	314.6±44.2	277.0±28.3	280.2±29.6	266.4±12.0	213.5±92.8
7	303.7±31.7	253.2±33.0	283.5±31.1	267.2±45.1	290.8±74.1
13	333.4±33.9	315.3±31.8	305.4±39.2	280.8±48.5	322.1±31.6
16	322.7±46.5	319.7±39.9	297.7±41.9	251.8±75.7	293.748.6

** = $p < 0.01$

Table V: Weekly Food Efficiency (%)

Dose:	0	300	500	1000	2000
Weeks			Males		
1	6.5	5.7	1.9	<0	<0
7	4.2	4.4	<0	1.4	<0
13	<0	<0	3.5	1.4	0.8
16	7.3	6.4	4.2	2.3	11.4
			Females		
1	19.8	15.5	6.2	1.8	<0
7	2.4	<0	<0	<0	1.5
13	<0	9.1	1.4	<0	5.8
16	3.5	1.3	<0	<0	6.3

All treated animals consumed less food than the control group during the study period; however, no dose relationship was noted. Food efficiency data was too inconsistent for any determination.

Compound intake

The investigators calculated actual compound intake. Compound intake was 0, 9.0, 15.1, 31.1, and 62 mg/kg/day for males and 0, 10, 17.2, 31.5, and 74 g/kg/day for females, for the 0, 300, 500, 1000, and 2000 ppm dose groups, respectively.

4. Ophthalmological examination

No treatment related effects were noted during ocular examinations (individual animal data were provided).

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5. Hematology and clinical chemistry

a. Hematology

The investigators provided group mean and individual animal data. No treatment related effects were noted in the data provided. There was a statistically significant increase in 1000 ppm male platelet counts and increases in 500 ppm female hemoglobin and hematocrit at week 16; however, the biological relevance of these findings is unclear since no dose response was noted.

b. Clinical Chemistry

The investigators provided group mean and individual animal data. No treatment related effects were noted in the data provided. Statistically significant increased total protein and globulin in 1000 ppm males at week 7, decreased sorbitol dehydrogenase activity in 300 and 500 ppm males at week 16 and decreased γ-glutamyl transferase in 2000 ppm females at week 7 were noted; however, the biological relevance of these findings is unclear since no dose response and related pathology was noted.

6. Urinalysis and Fecal Analysis

The investigators provided group summary and individual animal data. No treatment related effects were noted.

7. Sacrifice and Pathology

a. Organ weight

The investigators provided group mean and individual animal data. The following table presents selected organ weight data (from Tables 9.21 and 9.22, pages 80-81 of the report):

Table VI: Absolute Organ Weights (gm) and Relative Organ to Body Weights and Brain Weights(%)

Dose:		0	300	500	1000	2000
Organ				Males		
Kidneys	A	57.6±2.0	48.2±4.1	53.8±5.3	52.4±6.8	58.4±3.5
	R	0.51±0.03	0.44±0.03	0.47±0.08	0.54±0.06	0.49±0.05
	RB	68.7±4.1	58.2±3.0	67.1±11.0	62.6±6.0	72.3±9.3
Liver	A	310.6±13.8	293.9±34.2	336.6±38.0	316.6±50.9	358.1±16.3
	R	2.69±0.18	2.68±0.17	2.92±0.22	3.26*±0.37	2.97±0.15
	RB	371.5±31.1	355.7±39.1	420.1±69.8	377.4±38.7	442.4±44.7
				Females		
Kidneys	A	47.0±4.7	43.2±4.2	43.4±4.1	41.0±3.7	43.0±1.2
	R	0.46±0.02	0.46±0.05	0.47±0.05	0.46±0.03	0.46±0.05
	RB	65.2±45.6	55.8±6.9	56.8±5.0	54.3±6.2	55.4±5.3
Liver	A	286.2±26.7	260.7±37.3	239.7±19.2	230.3*±21.5	295.2±35.1
	R	2.79±0.07	2.76±0.19	2.60±0.19	2.58±0.37	3.11±0.17
	RB	397.1±45.6	336.0±46.0	314.1*±27.9	305.1*±37.5	379.5±48.1

*** = $p < 0.05$; A = absolute organ weight; R = relative organ weight to body weight; RB = relative organ weight to brain weight**

No treatment related effects were noted.

b. Gross pathology

The investigators provided group mean and individual animal data. No treatment related effects were noted.

c. Microscopic pathology

The investigators provided individual animal data. No treatment related effects were noted.

D. Discussion/Conclusions

i. Investigators Summary:

From page 12 of the report:
This study was conducted to evaluate the toxicity of CGA-77102, a stereoisomer of metolachlor herbicide, in beagle dogs. Groups of 4 dogs/sex were fed constant dietary concentrations of 0, 300, 500, 1000 ppm CGA-77102 (lot no. FL-941255, an amber liquid with a 95.4% purity) for 16 weeks. Four dogs per sex were given 2000 ppm of test diet for 2 weeks followed by capsule dosing (700 mg/dog/day) for 14 weeks; the capsule dosing was done to overcome the palatability problem of the 2000-ppm test diet. Body weights, food consumption and clinical observations were recorded. Clinical laboratory tests were performed at pretest, week 7 and study termination. Complete necropsies and histopathologic evaluations were performed.

The grand mean daily dosages, based on nominal concentrations of CGA-77102 in the feed or the capsule dose were 9.0, 15.1, 31.1 and 62 mg/kg/day in males fed 300, 500, 1000 ppm or given 2000 ppm equivalent, respectively. Corresponding dose levels for females were 10, 17.2, 31.5 and 74 mg/kg/day.

Weight loss was seen in both sexes given the 2000-ppm diet due to inappetence. Food consumption and body weight rebounded when the animals were switched to basal diet and capsule dosing. The only treatment-related effect was seen in the 1000-ppm males which had a cumulative weight loss during the study. Emesis and salivation were seen in animals given the capsules, otherwise, no treatment-related clinical observations were noted.

There were no treatment-related effects in hematology, clinical chemistry or urinalysis. No treatment-related changes in organ weights or necropsy observations were recorded. Histopathologic evaluation revealed no treatment-related microscopic lesions in any of the organs.

In conclusion, CGA-77102 was not palatable at 2000 ppm in diet. When given in capsules at 2000 ppm equivalent for 14 weeks, no treatment-related effects were seen in any of the parameters examined. The only effect related to dietary administration was the cumulative weight loss in males at 1000 ppm. The no-observable-effect level (NOEL) was 500 ppm.

ii. Reviewers Conclusions:

Other than the palatability problems noted above in the 2000 ppm dose group, no biologically relevant treatment related systemic toxicity was noted at dose levels tested. **The Systemic Toxicity NOEL was equal to or greater than 2000 ppm (62 mg/kg/day for males and 74 mg/kg/day for females) and the LOEL was greater than 2000 ppm (62 mg/kg/day for males and 74 mg/kg/day for females).**
This study is classified as Acceptable-Nonguideline.