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

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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Alpha-Metolachlor: Review of Bridging Data Studies and Acute Toxicity Studies with Formulations.

EPA DP Barcodes: D226782, D226830, D232249, D235664; EPA Submission Barcodes: S501353, S501350, S515306; EPA MRID Numbers: 43928404, -05, -06, -07, -08, 43928503, -04, -05, -06, -07, -08, 43928915, -16, -17, -18, -19, -20, -21, -23, -22, -24, -25, 43928303, -04, -05, -06, -07, -08, 44126802, -03, -04, -05, -06, -07, 44172203, -04, -05, -06, -07, -08, -09, -10, 44128003, -04, -05, -06, -07, -08; EPA Pesticide Chemical Code: 108800; CAS# 87392-12-9.

FROM: Stephen C. Dapson, Ph.D.
Branch Senior Scientist
Toxicology Branch II/HED (7509C)

THRU: K. Clark Swentzel
Branch Chief
Toxicology Branch II/HED (7509C)

TO: Karen Whitby, Ph.D.
Branch Chief
RCAB/HED (7509C)

and

Joanne Miller/Eugene Wilson, PM 23
Registration Division (7505C)

Registrant: Ciba Crop Protection
Ciba-Geigy Corporation
Post Office Box 18300
Greensboro, NC 27419

Recommendations: Toxicology Branch II reviewed the studies submitted in support of Alpha-Metolachlor (S-enantiomer, CGA 77102) registration, with the proposed use of the toxicology data base, submitted in support of the registration of technical grade Metolachlor, to support the registration of Alpha-metolachlor. This request was based on the fact that the S-enantiomer, Alpha-Metolachlor, has already been subject to extensive toxicological testing during the course of the development of Metolachlor.

The HED RfD/QA Peer Review Committee compared data available on Alpha-Metolachlor with those submitted in support of Metolachlor registration and concluded that without metabolism studies and side-by-side subchronic studies conducted in the same strain of rat using comparable dose levels of the two subject test substances, the identification of any possible qualitative or quantitative differences between the toxicological properties of CGA-77102 and Metolachlor would not be possible. **Therefore these studies should be recommended to the registrant for submission for further consideration of the use of the Metolachlor database to support registration of Alpha-Metolachlor.**

Based on the available information, the Committee could not determine whether the use of the toxicology data base, submitted in support of the registration of technical grade Metolachlor, to support the registration of Alpha-Metolachlor would be appropriate at this time.

A. Background

From the registrant's document *CGA 77102 Technical, Summary of Toxicity Studies Supporting the Registration of CGA 77102 Technical*, pages 4 and 5:

CGA 77102 has a low order of acute toxicity; it is slightly irritating to the eyes and is a skin sensitizer. Acute studies on proposed commercial formulations of CGA 77102 are comparable to those of existing metolachlor formulations. CGA 77102 is not genotoxic or developmentally toxic and subchronic studies in the rat and dog indicate that CGA 77102 has a hazard profile comparable to that of metolachlor, with liver being the principal target organ. The metabolic profile for metolachlor in plants and animals is well understood and it is expected to be similar for CGA 77102.

Based on the similarity of the hazard profile of CGA 77102 to that of metolachlor in acute and subchronic studies, it is expected that CGA 77102 would also have a similar profile in chronic studies. Thus it that CGA 77102 would not adversely affect reproductive performance and that it would exhibit similar high-dose toxic effects on the liver in lifetime feeding studies. The reference dose for CGA 77102 is therefore expected to be the same as that of metolachlor (RfD = 0.1 mg/kg)

An evaluation of potential exposure to CGA 77102 indicates that acceptable margins of exposure exist for all sources of exposure including diet, water, and dermal and inhalation exposure of agricultural workers. Exposure to CGA 77102 is expected to be less than that of metolachlor because of the approximate 1/3 reduction in use rate.

This evaluation presents the current assessment of the toxicological

properties of technical grade CGA 77102, the S-enantiomer of the racemic compound metolachlor (CGA 24705). Technical grade metolachlor consists of 50% of each of the R-enatiomer (CGA 77101) and the S-enantiomer (CGA 77102). Consequently, as an intrinsic part of the racemate, CGA 77102 was already subject to extensive toxicological testing during the course of the development of metolachlor. The specific investigation of the enantiomer CGA 77102 was therefore confined to selected endpoints in the fields of acute and subchronic toxicity, mutagenicity and reproductive toxicity with the aim of identifying possible qualitative or quantitative differences between the toxicological properties of CGA 77102 and metolachlor.
As will be shown in the following sections, none of the studies revealed any unexpected effects of CGA 77102 and also the quantitative dose-effect relationships of the racemate and the S-enantiomer were very similar. The applicability of the database established for metolachlor in the safety evaluation of the S-enantiomer, CGA 77102 can therefore be justified because both compounds have identical toxicological profiles.

From the registrant document *Reduced-Risk Document Prepared in Accordance with PR Notice 93-9 Supporting the Registration of CGA-77102 Technical (A Chiral Metolachlor)*, pages 5-9, 12 and 13

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 the reduced risk 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 the reduced risk 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.

Mechanism of Action:

Metolachlor (CGA-77102) has a complex and multi-site mechanism of action in plants. Known inhibitions include biosynthesis of fatty acids and lipids, protein, isoprenoids, and flavonoids. These effects may be linked with conjugation of acetyl coenzyme A and other sulfhydryl-containing biomolecules. This complex mechanism is a factor in why weed resistance to metolachlor (CGA-77102) has not developed.

Proposed Use Pattern:

CGA-77102 is proposed for the same crops as metolachlor is currently registered on, i.e. corn, cotton, peanuts, pod crops, potatoes, safflower, grain or forage sorghum and soybeans. Initially, it will not be marketed for uses which are sold under 24(c) registrations with indemnification. It will be applied either preplant surface, preplant incorporated, preemergence or postemergence by ground or by air. It will be marketed initially via three end-use formulations (registration and conversion of other metolachlor end-use formulations will take place according to the phase-in schedule):

Dual® Magnum - (8.0 lb. ai/gal. emulsifiable concentrate)- CGA-77102 as the sole active ingredient

Dual II® Magnum - (7.6 lb. ai/gal. emulsifiable concentrate) - CGA-77102 as the sole active ingredient and benoxacor (CGA-154281), a herbicidal safener registered by the Agency in June, 1992

Bicep® Magnum - (5.5 lb. ai/gal. flowable) - CGA-77102/atrazine (2.4 lbs. ai per gallon/3.1 lbs. ai/gal) in combination with benoxacor

The product labels will parallel the corresponding existing registrations except that the recommended application rates will be approximately 62.5% of the metolachlor rate.

Dual Magnum will parallel **Dual Herbicide** - EPA Reg. No. 100-673

Dual II Magnum will parallel **Dual II Herbicide** - EPA Reg. No. 100-711

Bicep Magnum will parallel **Bicep II Herbicide** - EPA Reg. No. 100-710

Reduced-Risk Statement:

The following provides a summary of the major points supporting this application for a reduced risk designation for CGA-77102:

Reduced application rates will result in:

- Reduced environmental loading of between 22-26 MM lbs of active ingredient per year when full introduction is achieved
- Reduced amount of pesticide subject to surface runoff into surface water bodies
- Reduced amount of pesticide available for leaching into ground water
- Reduced amount of pesticide in the trade supply chain
- Reduced worker exposure
- Reduced exposure to nontarget sites
- Reduced number of packaging containers entering the wastestream

Residue data show that a reduction in dietary exposure will occur with the registration of CGA-77102 compared with metolachlor, being mainly derived from reduced residues in corn forage.

There is a low order of acute and chronic toxicity associated with CGA-77102 as demonstrated by the enclosed toxicology studies and by the previously reviewed and EPA-accepted database for metolachlor:

- Generally a low order of acute and dermal toxicity
- Rapid excretion, no tendency to accumulate in the body
- Not mutagenic

- Not fetotoxic, embryolethal or teratogenic in the rat or rabbit
- Not a reproductive toxin
- Not oncogenic in the mouse
- Weak oncogenic response in female rats

Compared to other members of the chloroacetamide family:

CGA-77102, in general, has a more favorable safety profile, in terms of mammalian toxicity, ecological effects parameters, and environmental fate characteristics.

Weed resistance has not developed to metolachlor, nor is it expected to develop with CGA-77102 because of the complex multi-site mode-of-action in plants.

Conversion of metolachlor to CGA-77102 does not alter the flexibility and biological characteristics and maintains the biological advantages over competitive products.

B. Reviews of submitted studies:

1. Acute Toxicity on the Technical

Table I: Summary of Acute Toxicity

TEST	RESULTS	CATEGORY	% a.i.
Oral LD_{50}--rat	Males: 3267 (2299-4642) mg/kg Females: 2577 (1980-3354) mg/kg	III	95.4%
Dermal LD_{50}--rabbit	Male & Female > 2000 mg/kg	III	95.4%
Inhalation LC_{50}--rat	Male & Female > 2.91 mg/L	IV	97.6%
Eye irritation--rabbit	slight to moderate conjunctival irritation to washed and unwashed eyes	III	95.4%
Dermal irritation--rabbit	mean PIS for the 4, 24, 48, and 72-hour scores was 1.8	IV	95.4%
Dermal sensitization--guinea pig	I. dermal sensitizer with the closed patch technique II. dermal sensitizer with the guinea pig maximization test	NA NA	95.4% 95.6%

a. §81-1 Acute Oral Toxicity

S.M. Glaza (1994): CGA-77102 Technical FINAL REPORT Acute Oral Toxicity Study of CGA-77102 Technical in Rats, Hazleton Wisconsin, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: HWI 40702449, November 23, 1994 (Unpublished); EPA MRID Number 43928915.

In an acute oral toxicity study (MRID# 43928915), groups of 5 male and 5 female young adult albino rats (Strain: Crl:CD®(SD)BR from Charles River Laboratories, Inc., Portage, Michigan) received either 2000, 3000, or 5000 mg/kg CGA-77102 Technical (Purity: 95.4% purity; Lot Number FL-941255 (Batch Code V.4673/7)) as a single gavage dose.

The Acute Oral LD_{50} for CGA-77102 Technical is:

Males - 3267 mg/kg bw
95% Confidence Limits - 2299 to 4642 mg/kg bw

Females - 2577 mg/kg bw
95% Confidence Limits - 1980 to 3354 mg/kg bw

Combined - 2672 mg/kg bw
95% Confidence Limits - 2149 to 3322 mg/kg bw

Toxicity Category III.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

b. §81-2 Acute Dermal Toxicity

S.M. Glaza (1994): CGA-77102 Technical FINAL REPORT Acute Dermal Toxicity Study of CGA-77102 Technical in Rabbits, Hazleton Wisconsin, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation; Laboratory Project Identification: HWI-40702450; October 7, 1994 (Unpublished); EPA MRID Number 43928916.

In an acute dermal toxicity study (MRID# 43928916), 5 male and 5 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received a single topical application of 2000 mg/kg CGA-77102 Technical (Purity: 95.4% purity; Lot Number FL-941255 (Batch Code V.4673/7)).

The Acute Dermal LD_{50} for CGA-77102 Technical is greater than 2000 mg/kg for both sexes. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

c. §81-3 Acute Inhalation Toxicity

M.S. Holbert (1995): CGA-77102 Technical, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Study Number 1970-95, August 22, 1995 (Unpublished); EPA MRID Number 43928917.

In an acute inhalation toxicity study (MRID# 43928917), 5 male and

5 female rats (females were nulliparous and non-pregnant, Strain: HSD:Sprague-Dawley; Source: Harlan Sprague Dawley, Inc., Houston, Texas) were exposed by the nose only route to a generated aerosol of CGA-77102 Technical from undiluted liquid at a level of 2.91 mg/L (Purity: 97.6%; Batch 408001).

The Acute Inhalation LC_{50} for CGA-77102 Technical is greater than 2.91 mg/L for both sexes. The particle size distribution (MMAD) was 3.456 µm. **Toxicity Category IV.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

d. §81-4 Primary Eye Irritation

S.M. Glaza (1994): CGA-77102 Technical, FINAL REPORT, Primary Eye Irritation Study of CGA-77102 Technical in Rabbits, Hazleton Wisconsin, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: HWI 40702452, October 5, 1994 (Unpublished); EPA MRID Number 43928918.

In a primary eye irritation study (MRID# 43928918), 6 male and 3 female (nonwashed) and 3 female ("washed") albino rabbits (Strain: New Zealand White from Ray Nichols Rabbitry, Lumberton, Texas) received 0.1 mL CGA-77102 Technical (Purity: 95.4% active ingredient; Lot Number FL-941255; Batch Code V.4673/7) to one eye (the other serving as untreated control). Two groups were used, one group (6 animals) with the eyes unwashed, the other group (3 animals) had the eyes washed for 1 minute with lukewarm water 30 seconds after test compound instillation.

CGA-77102 Technical produced slight to moderate conjunctival irritation to washed and unwashed eyes. Irritation cleared by 48 hours after treatment. **Toxicity Category III.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

e. §81-5 Primary Dermal Irritation

S.M. Glaza (1994): CGA-77102 Technical FINAL REPORT Primary Dermal Irritation Study of CGA-77102 Technical in Rabbits, Hazleton Wisconsin, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation; Laboratory Project Identification: HWI 40702451, October 5, 1994

(Unpublished); EPA MRID Number 43928919.

In a primary dermal irritation study (MRID# 43928919), 3 male and 3 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.5 mL CGA-77102 Technical (Purity: 95.4% purity; Lot Number FL-941255 (Batch Code V.4673/7)) to the shaved backs of each animal.

CGA-77102 Technical produced very slight to well-defined erythema and very slight to slight edema reactions at the application site. Desquamation was also observed in one animal. The mean PIS for the 4, 24, 48, and 72-hour scores was 1.8. No irritation was seen by observation day 7. **Toxicity Category IV.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

f. §81-6 Dermal Sensitization

S.M. Glaza (1994): CGA-77102 Technical FINAL REPORT Dermal Sensitization Study of CGA-77102 Technical in Guinea Pigs - Closed Patch Technique, Hazleton Wisconsin, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: HWI 40702453, November 18, 1994 (Unpublished); EPA MRID Number 43928920.

In a dermal sensitization study (MRID# 43928920), 10 young adult albino guinea pigs (Strain: Crl:(HA)BR from Charles River Laboratories, Inc., Portage, Michigan) received three induction doses and one challenge dose of 0.4 mL CGA-77102 Technical (Purity: 95.4% purity; Lot Number FL-941255 (Batch Code V.4673/7)) applied to an adhesive patch and placed on the shaved backs of each animal.

CGA-77102 Technical was a dermal sensitizer in guinea pigs tested with the closed patch technique.

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

g. §81-6 Dermal Sensitization

J.H. Marty (1994): CGA-77102 TECHNICAL SKIN SENSITIZATION TEST IN THE GUINEA PIG MAXIMIZATION TEST, Ciba Geigy Limited for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Study Number

941069, September 16, 1994 (Unpublished); EPA MRID Number 43928921.

In a dermal sensitization study (MRID# 43928921), 10 male and 10 female albino Pirbright White Strain guinea pigs (Strain: Tif: DHP from CIBA-GEIGY Limited, Animal Production, 4332 Stein / Switzerland) received CGA-77102 Technical (Purity: 95.6% purity; Batch No. V.4673/7)) in a guinea pig maximization test.

CGA-77102 Technical was a dermal sensitizer in guinea pigs tested with the guinea pig maximization test.

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

2. Subchronic Toxicity

a. §82-1a Subchronic Feeding - Rodent

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.

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 Acceptable-Guideline and satisfies the guideline requirements (§82-1a) for a subchronic feeding study in rats.

b. §82-1b Subchronic Feeding - Nonrodent

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.

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 to the test compound than the rat.

3. Developmental Toxicity

a. §83-3a Developmental (Teratology) Toxicity - Rat

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

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.

b. §83-3b Developmental (Teratology) Toxicity - Rabbit

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.

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.

4. Mutagenicity

a. Gene Mutation

T. Hertner (1995): CGA-77102 Technical Salmonella and Escherichia/Mammalian-Microsome Mutagenicity Test, CIBA-GEIGY Ltd for CIBA-GEIGY Corp., Study No. 941060, June 9, 1995; EPA MRID Number 43928927.

In independently performed microbial mutagenicity assays (MRID# 43928927), *Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and TA102 and *Escherichia coli* WP2 *uvr*A were initially exposed to 312.5-5000.0 µg/plate CGA-77102 technical (95.6%) in the presence and absence of S9 activation. For the confirmatory trial, doses of 78.13-1250.0 µg/plate ±S9 were evaluated with *S. typhimurium* strains TA1535, TA1537, TA100 and TA102; concentrations of 312.5-5000.0 µg/plate ±S9 were examined with *S. typhimurium* TA 98 and *E.coli* WP2 *uvr*A. The S9 fraction was derived from Aroclor 1254 induced rat livers and the test material was delivered to the test system in dimethyl sulfoxide.

In general, doses ≥1250.0 µg/plate ±S9 were cytotoxic for *S. typhimurium* TA1535, TA1537, TA100 and TA102 and 5000.0 µg/plate ±S9 was slightly cytotoxic for *S. typhimurium* TA98 and *E. coli* WP2 uvrA. The nonactivated and S9-activated positive controls induced the expected mutagenic response in the corresponding tester strain. **There was, however, no indication that CGA-77102 technical induced of a mutagenic effect in any tester strain either in the presence or the absence of S9 activation.**

The study is classified as Acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for microbial gene mutation mutagenicity data.

b. Chromosome Aberrations

T. Hertner (1995): CGA-77102 Technical Micronucleus Test, Mouse (OECD Conform), CIBA-GEIGY Ltd for CIBA-GEIGY Corp., Study No. 941061, May 22, 1995; EPA MRID Number 43928926.

In a mouse micronucleus assay (MRID# 43928926), groups of five male and five female Tif:MAGf(SPF) mice received single oral gavage administrations of 500, 1000 or 2000 mg/kg CGA 77102 technical (95.6%). The test material was delivered to the animals as suspensions prepared in arachis oil. Animals in the vehicle and high-dose group were sacrificed at 16, 24 and 48 hours postadministration and mid- and low-dose mice were sacrificed at 24 hours. Bone marrow cells were harvested from all experimental

groups and examined for the incidence of micronucleated polychromatic erythrocytes (MPEs).

Toxic signs, similar to those seen in the preliminary range-finding studies (i.e., ataxia, tremors and/or hunched posture) were recorded for high-dose males and females throughout the 48-hour postexposure. No bone marrow cytotoxicity was seen at any dose or sacrifice time. The positive control induced the expected high yield of MPEs in males and females. **There was, however, no evidence that CGA 77102 technical induced a clastogenic or aneugenic effect in either sex at any dose or sacrifice time.**

The study is classified as Acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for <u>in vivo</u> cytogenetic mutagenicity data.

c. Other mutagenic mechanism

T. Hertner (1995): CGA-77102 Technical In Vivo/In Vitro Unscheduled DNA Synthesis In Rat Hepatocytes, CIBA-GEIGY Ltd for CIBA-GEIGY Corp., Study No. 941062, June 8, 1995; EPA MRID Number 43928928.

In an <u>in vivo/in vitro</u> replicative DNA synthesis (RDS)-unscheduled DNA synthesis (UDS) assay (MRID# 43928928), groups consisting of three to four rats per sex received single oral gavage administrations of CGA-77102 Technical (95.6%) at doses of 500, 1500 or 5000 mg/kg (males) or 500, 1500 or 3200 mg/kg (females). Hepatocytes harvested at 15 and 38 hours were evaluated for viability and replicative DNA synthesis (RDS). For the UDS determination, additional groups (3/sex/dose) were exposed to 500 or 1500 mg/kg and the recovered hepatocytes were scored at 2 or 15 hours postexposure. The test material was delivered to the animals as suspensions prepared in arachis oil.

Two of four females in the 3200-mg/kg group and 2 of 4 males in the 5000-mg/kg group died prior to the scheduled sacrifice at 38 hours. Severe cytotoxicity was seen in the hepatocytes recovered from 1 of 2 surviving males and both female survivors in the high-dose groups. Lower levels were neither toxic to the animals nor cytotoxic to the target cells. The positive controls induced the expected marked increases in RDS or UDS. **A clear dose-related increase in the percentage of cells in S-phase (RDS) was obtained from hepatocytes harvested 38 hours posttreatment of the male rats. The response ranged from a 5.3-fold increase at 1500 mg/kg to a 16.1-fold increase at the high dose (5000 mg/kg). In females, a marked increase in RDS was initially seen at 1500 mg/kg**

but the response declined over time with a 24.4-fold increase at 15 hours and a 12.2-fold increase at 38 hours. There was, however, no evidence that the CGA 77102 Technical at doses of 500 or 1500 mg/kg induced a genotoxic response at 2 or 15 hours posttreatment. We conclude, therefore, that the data indicate that CGA 77102 Technical was negative for genotoxicity but positive for cellular proliferation when tested up to overtly toxic and cytotoxic doses in this in vivo/in vitro rat hepatocyte RDS/UDS assay.

This study is classified as Acceptable and satisfies the guideline requirement for a UDS assay (84-4).

NOTE: Comparison with Technical Metolachlor can be made from table (extracted from HED RED Document for Metolachlor) presented at end of document in section referenced as Toxicological Profile of Metolachlor.

5. Acute Toxicity on the CGA-77102 960 EC

(this chemical will not be registered by the registrant, it is replaced with the CGA-77102 915EC-B formulation discussed following, these reviews are for information only)

Table II: Summary of Acute Toxicity

TEST	RESULTS	CATEGORY	% a.i.
Oral LD_{50}--rat	Males: 3937 (2548-6085) mg/kg Females: 2149 (1506-3068) mg/kg	III	87.2%
Dermal LD_{50}--rabbit	Male & Female > 2020 mg/kg	III	87.2%
Inhalation LC_{50}--rat	Males: 5.86 mg/L (undefined confidence limits) Females: 3.80 (3.50-4.12) mg/L	IV	87.2%
Eye irritation--rabbit	moderately irritating in unwashed eyes and minimally irritating to washed eyes	III	87.0%
Dermal irritation--rabbit	slightly irritating, mean PIS was 0.2	IV	87.0%
Dermal sensitization--guinea pig	not a dermal sensitizer with the closed patch technique	NA	87.2%

a. §81-1 Acute Oral Toxicity

J.O. Kuhn (1995): CGA-77102 960 EC, FINAL REPORT, ACUTE ORAL TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2317-95, December 1, 1995 (Unpublished); EPA MRID Number 43928303.

In an acute oral toxicity study (MRID# 43928303), groups of 5 male and 5 female young adult albino rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley SD from Harlan Sprague

Dawley, Inc., Houston, TX) received either 1500, 2000, 2500, 4000, or 5050 mg/kg in females and either 2500, 4000, or 5050 mg/kg in males of CGA-77102 960 EC-A (Purity: 87.2% active ingredient; Lot Number FL-951199) as a single gavage dose.

The Acute Oral LD_{50} for CGA-77102 960 EC-A is:

Males - 3937 mg/kg bw
95% Confidence Limits - 2548 to 6085 mg/kg bw

Females - 2149 mg/kg bw
95% Confidence Limits - 1506 to 3068 mg/kg bw

Combined - 2267 mg/kg bw
95% Confidence Limits - 1299 to 3956 mg/kg bw

Toxicity Category III.

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

b. §81-2 Acute Dermal Toxicity

J.O. Kuhn (1995): CGA-77102 960 EC, FINAL REPORT, ACUTE DERMAL TOXICITY STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2318-95, October 13, 1995, EPA MRID No. 43928304.

In an acute dermal toxicity study (MRID# 43928304), 5 male and 5 female albino rabbits (females were nulliparous and non-pregnant; Strain: New Zealand White from Ray Nichols Rabbitry; Lumberton, Texas) received 2020 mg/kg CGA-77102 960 EC-A (Purity: 87.2% active ingredient; Lot Number FL-951199) by the dermal route.

The Acute Dermal LD_{50} for CGA-77102 960 EC is greater than 2020 mg/kg for both sexes. **Toxicity Category III.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

c. §81-3 Acute Inhalation Toxicity

J. Bennick (1996): CGA-77102 960 EC, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2319-95, January 15, 1996; EPA MRID No. 43928305.
In an acute inhalation toxicity study (MRID# 43928305), groups of 5 male and 5 female rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley; Source: Harlan Sprague Dawley, Inc., Houston, Texas) were exposed by the nose only route to a generated aerosol of CGA-77102 920 EC from undiluted liquid at levels of 3.15, 3.60, and 3.79 mg/L mean exposure concentrations (Purity: 87.2% active ingredient; Lot Number: FL-951199).

The Acute Inhalation LC_{50} for CGA-77102 920 EC was calculated to be:

		95% confidence limits
Males:	5.86 mg/L	undefined
Females:	3.80 mg/L	3.50 to 4.12 mg/L
Combined:	4.06 mg/L	3.62 to 4.56 mg/L

The particle size distribution (MMAD) was 3.764, 3.563, and 3.532 µm for the 3.15, 3.60, and 3.79 mg/L mean exposure concentrations, respectively. **Toxicity Category IV.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

d. §81-4 Primary Eye Irritation

J.O. Kuhn (1995): CGA-77102 960EC, FINAL REPORT, PRIMARY EYE IRRITATION STUDY IN RABBITS, STILLMEADOW, Inc. For Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2036-95, June 27, 1995; EPA MRID Number 43928306.

In a primary eye irritation study (MRID# 43928306), 3 male and 3 female (nonwashed) and 3 female ("washed") albino rabbits (Strain: New Zealand White from Ray Nichols Rabbitry, Lumberton, Texas) received 0.1 mL CGA-77102 960EC (Purity: 87.0% active ingredient; Lot Number FL-950296) to one eye (the other serving as untreated control). Two groups were used, one group with the eyes unwashed, the other group had the eyes washed for 1 minute with lukewarm water 30 seconds after test compound instillation.

CGA-77102 960EC was moderately irritating in unwashed eyes and minimally irritating to washed eyes. Irritation cleared by 72

hours after treatment. **Toxicity Category III.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

e. §81-5 Primary Dermal Irritation

J.O. Kuhn (1995): CGA-77102 960EC, FINAL REPORT, PRIMARY DERMAL IRRITATION STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2037-95, June 27, 1995; EPA MRID Number 43928307.

In a primary dermal irritation study (MRID# 43928307), 3 male and 3 female albino rabbits (New Zealand White from Ray Nichols Rabbitry, Lumberton, Texas) received 0.5 mL CGA-77102 960EC (Purity: 87.0% active ingredient; Lot Number FL-950296) to the shaved back of each animal.

CGA-77102 960EC was slightly irritating. The mean PIS was 0.2. No irritation was seen by observation 48 hours. **Toxicity Category IV.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

f. §81-6 Dermal Sensitization

J.O. Kuhn (1995): CGA-77102 960 EC, FINAL REPORT, DERMAL SENSITIZATION STUDY IN GUINEA PIGS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2320-95, November 10, 1995; EPA MRID Number 43928308.

In a dermal sensitization study (MRID# 43928308), 2 male and 2 female (Irritation Screening) and 10 male and 10 female (Definitive Study) guinea pigs (Strain: Hartley- Albino from SASCO Inc., Madison, WI.) received 0.4 mL in 3 induction and 1 challenge application of CGA-77102 960 EC-A (Purity: 87.2% active ingredient; Lot Number FL-951199) to the shaved back of the animals using the closed patch technique.

CGA-77102 960 EC was not a dermal sensitizer in guinea pigs tested with the closed patch technique.

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

6. Acute Toxicity on the CGA-77102 915EC-B (Dual-Magnum™ Herbicide)

Table III: Summary of Acute Toxicity

TEST	RESULTS	CATEGORY	% a.i.
Oral LD_{50}--rat	Males: > 5000 mg/kg Females: 2515 (1205-5249) mg/kg	III	83.3%
Dermal LD_{50}--rabbit	Male & Female > 2000 mg/kg	III	83.3%
Inhalation LC_{50}--rat	Male & Female > 2.61 mg/L	IV	83.9%
Eye irritation--rabbit	moderately to severely irritating in unwashed eyes and moderately irritating to washed eyes	II	83.3%
Dermal irritation--rabbit	mean dermal PIS for the 4, 24, 48, and 72-hour scores was 0.8	IV	83.3%
Dermal sensitization--guinea pig	dermal sensitizer with the closed patch technique	NA	83.3%

a. §81-1 Acute Oral Toxicity

S.M. Glaza (1996): CGA-77102 915EC-B, FINAL REPORT, Study Title: Acute Oral Toxicity Study of CGA-77102 915EC-B in Rats, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504750, September 20, 1996; EPA MRID Number 44126802.

In an acute oral toxicity study (MRID# 44126802), groups of 5 male and 5 female young adult albino rats (Strain: Crl:CD®(SD)BR from Charles River Laboratories, Inc., Portage, Michigan) received either 500, 1000, 2000, or 5000 mg/kg to females and 2000 or 5000 mg/kg to males of CGA-77102 915EC-B [Purity: 83.3% CGA-77102; Lot Number FL-960621 (Batch Code 1098-21-04)] as a single gavage dose.

The Acute Oral LD_{50} for CGA-77102 915EC-B is:

Males - greater than 5000 mg/kg bw

Females - 2515 mg/kg bw
95% Confidence Limits - 1205 to 5249 mg/kg bw

Combined - 3425 mg/kg bw
95% Confidence Limits - 1772 to 6619 mg/kg bw

Toxicity Category III.

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

b. §81-2 Acute Dermal Toxicity

S.M. Glaza (1996): CGA-77102 915EC-B, FINAL REPORT, Study Title: Acute Dermal Toxicity Study of CGA-77102 915EC-B in Rabbits, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504751, August 15, 1996, EPA MRID Number 44126803.

In an acute dermal toxicity study (MRID# 44126803), 5 male and 5 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 2000 mg/kg CGA-77102 915EC-B [Purity: Active ingredient - 83.3% CGA-77102; Lot Number FL-960621 (Batch Code 1098-21-04)] as a single topical application to the shaved skin of each animal's back.

The Acute Dermal LD_{50} for CGA-77102 915EC-B is greater than 2000 mg/kg for both sexes. **Toxicity Category III.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

c. §81-3 Acute Inhalation Toxicity

J. Bennick (1996): CGA-77102 915EC-B, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2982-96, August 20, 1996; EPA MRID Number 44126804.

In an acute inhalation toxicity study (MRID# 44126804), 5 male and

5 female rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley; Source: Harlan Sprague Dawley, Inc., Indianapolis, IN) were exposed by the nose only route to a generated aerosol of CGA-77102 915EC-B (Purity: 83.9% active ingredient; Lot No. FL-961327) for 4 hours.

The Acute Inhalation LC_{50} for CGA-77102 Technical is greater than 2.61 mg/L for both sexes. The particle size distribution (MMAD) was 3.434 µm. **Toxicity Category IV.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

d. §81-4 Primary Eye Irritation

S.M. Glaza (1996): CGA-77102 915EC-B, FINAL REPORT, Study Title: Primary Eye Irritation Study of CGA-77102 915EC-B in Rabbits, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60401688, June 20, 1996; EPA MRID Number 44126805.

In a primary eye irritation study (MRID# 44126805), 3 male and 3 female (nonwashed) and 3 female ("washed") adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.1 mL CGA-77102 915EC-B [Purity: 83.3% CGA-77102 active ingredient; Lot Number FL-960621 (Batch Code 1098-21-04)] to one eye (the other serving as untreated control. Two groups were used, one group with the eyes unwashed, the other group had the eyes washed with lukewarm water for 1 minute beginning 30 seconds after test compound instillation.

CGA-77102 915EC-B was moderately to severely irritating in unwashed eyes and moderately irritating to washed eyes. Irritation cleared by 14 days in unwashed eyes and 48 hours in washed eyes after treatment. **Toxicity Category II.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

e. §81-5 Primary Dermal Irritation

S.M. Glaza (1996): CGA-77102 915EC-B, FINAL REPORT, Study Title: Primary Dermal Irritation Study of CGA-77102 915EC-B in Rabbits, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy

Corporation, Laboratory Project Identification: CHW 60401687, June 26, 1996; EPA MRID Number 44126806.

In a primary dermal irritation study (MRID# 44126806), 3 male and 3 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.5 mL CGA-77102 915EC-B [Purity: 83.3% CGA-77102 active ingredient; Lot Number FL-960621 (Batch Code 1098-21-04)] to the shaved back of each animal.

CGA-77102 915EC-B produced very slight (barely perceptible) erythema and edema reactions at the application site. The mean dermal PIS for the 4, 24, 48, and 72-hour scores was 0.8. No irritation was seen by observation Day 14. **Toxicity Category IV.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

f. §81-6 Dermal Sensitization

S.M. Glaza (1996): CGA-77102 915EC-B, FINAL REPORT, Study Title: Dermal Sensitization Study of CGA-77102 915EC-B in Guinea Pigs - Closed Patch Technique, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504752, September 17, 1996; EPA MRID Number 44126807.

In a dermal sensitization study (MRID# 44126807), 24 (4 for irritation screening and 2 groups of 10 for the definitive study) young adult male albino guinea pigs (Strain: Crl:(HA)BR from Charles River Laboratories, Inc., Portage, Michigan and Kingston, New York) received 0.4 mL CGA-77102 915EC-B (Purity: 83.3% CGA-77102; Lot Number FL-960621 [Batch Code 1098-21-04)] to the shaved back of each animal by the closed patch technique.

CGA-77102 915EC-B was a dermal sensitizer in guinea pigs tested with the closed patch technique.

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-5) for a dermal sensitization study in guinea pigs.

7. Acute Toxicity on the CGA-77102 II 915 EC (Dual II® Magnum Herbicide)

Table IV: Summary of Acute Toxicity

TEST	RESULTS	CATEGORY	% a.i.
Oral LD_{50}--rat	Males: 2675 (1722-4156) mg/kg bw Females: 2952 (2492-3498) mg/kg	III	82.4%
Dermal LD_{50}--rabbit	Male & Female > 2020 mg/kg	III	82.4%
Inhalation LC_{50}--rat	Male & Female > 3.06 mg/L	IV	82.4%
Eye irritation--rabbit	mildly irritating in unwashed eyes and mildly irritating to washed eyes	III	82.4%
Dermal irritation--rabbit	mean PIS for the 1/2, 24, and 48-hour scores was 0.5	IV	82.4%
Dermal sensitization--guinea pig	Not a dermal sensitizer with the closed patch technique	NA	82.4%

a. §81-1 Acute Oral Toxicity

J.O. Kuhn (1995): CGA-77102 II 915 EC, FINAL REPORT, ACUTE ORAL TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2321-95, November 10, 1995: EPA MRID Number 43928403.

In an acute oral toxicity study (MRID# 43928403), 20 male and 15 female young adult albino rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley SD from Harlan Sprague Dawley, Inc., Houston, TX) received either 2000, 0, 3500, 4000, or 5050 mg/kg in males and either 2500, 3500, or 5050 mg/kg in females of CGA-77102 II 915 EC-A (Purity: 82.4% CGA-77102; 4.03% CGA-154281; Lot Number FL-951200) as a single gavage dose.

The Acute Oral LD_{50} for CGA-77102 II 915 EC is:

Calculated Oral LD_{50} :
Males - 2675 mg/kg bw
95% Confidence Limits - 1722 to 4156 mg/kg bw

Females - 2952 mg/kg bw
95% Confidence Limits - 2492 to 3498 mg/kg bw

Toxicity Category III.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

b. §81-2 Acute Dermal Toxicity

J.O. Kuhn (1995): CGA-77102 II 915 EC, FINAL REPORT, ACUTE DERMAL TOXICITY STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2322-95, October 13, 1995; EPA MRID Number 43928404.

In an acute dermal toxicity study (MRID# 43928404), 5 male and 5 female albino rabbits (females were nulliparous and non-pregnant; Strain: New Zealand White from Ray Nichols Rabbitry; Lumberton, Texas) received 2020 mg/kg CGA-77102 II 915 EC-A (Purity: 82.4% CGA-77102; 4.03% CGA-154281; Lot Number FL-951200) by the dermal route.

The Acute Dermal LD_{50} for CGA-77102 II 915 EC is greater than 2020 mg/kg for both sexes. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

c. §81-3 Acute Inhalation Toxicity

J. Bennick (1995): CGA-77102 II 915 EC, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2323-95, November 22, 1995; EPA MRID Number 43928405.

In an acute inhalation toxicity study (MRID# 43928405),5 male and 5 female rats (females were nulliparous and non-pregnant, (Strain:

HSD:Sprague-Dawley; Source: Harlan Sprague Dawley, Inc., Houston, Texas) were exposed by the nose only route to a generated aerosol of CGA-77102 II 915 EC (Purity: 82.4% CGA-77102; 4.03% CGA-154281; Lot Number: FL-951200) at a concentration of 3.06 mg/L.

The Acute Inhalation LC_{50} for CGA-77102 II 915 EC is greater than 3.06 mg/L for both sexes. The particle size distribution (MMAD) was 3.092 µm. **Toxicity Category IV.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

d. §81-4 Primary Eye Irritation

J.O. Kuhn (1995): CGA-77102 II 915EC, FINAL REPORT, PRIMARY EYE IRRITATION STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2043-95, August 21, 1995; EPA MRID Number 43928406.

In a primary eye irritation study (MRID# 43928406, 3 male and 3 female (nonwashed) and 3 female ("washed") albino rabbits (Strain: New Zealand White from Ray Nichols Rabbitry, Lumberton, Texas) received 0.1 mL CGA-77102 II 915EC (Purity: 82.4% CGA-77102; 4.07% CGA-154281; Lot Number FL-950295) to one eye (the other serving as untreated control). Two groups were used, one group with the eyes unwashed, the other group had the eyes washed with lukewarm water for 1 minute beginning 30 seconds after test compound instillation.

CGA-77102 II 915 EC was mildly irritating in unwashed eyes and mildly irritating to washed eyes. Irritation cleared by 7 days in unwashed eyes and 72 hours in washed eyes after treatment. **Toxicity Category III.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

e. §81-5 Primary Dermal Irritation

J.O. Kuhn (1995): CGA-77102 II 915EC, FINAL REPORT, PRIMARY DERMAL IRRITATION STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2044-95, June 27, 1995; EPA MRID Number 43928407.

In a primary dermal irritation study (MRID# 43928407), 3 male and 3 female albino rabbits (Strain: New Zealand White from Ray Nichols Rabbitry; Lumberton, Texas) received 0.5 mL CGA-77102 II 915EC (Purity: 82.4% CGA-77102; 4.07% CGA-154281; Lot Number FL-950295) to the shaved back of the animals.

CGA-77102 II 915 EC produced erythema through 48 hours and edema in one male and one female at the 1/2 hour observation. No other signs of dermal irritation were observed during the study. The mean PIS for the 1/2, 24, and 48-hour scores was 0.5. No irritation was seen by 72 hours. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

f. §81-6 Dermal Sensitization

J.O. Kuhn (1995): CGA-77102 II 915 EC, FINAL REPORT, DERMAL SENSITIZATION STUDY IN GUINEA PIGS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2324-95, November 13, 1995; EPA MRID Number 43928408.

In a dermal sensitization study (MRID# 43928408), 2 male and 2 female (Irritation Screening) and 10 male and 10 female (Definitive Study) guinea pigs (Strain: Hartley- Albino from SASCO Inc., Madison, WI.) received 0.4 mL CGA-77102 II 915 EC-A (Purity: 82.4% CGA-77102; 4.03% CGA-154281; Lot Number FL-951200) to the shaved back of each animal with the closed patch technique.

CGA-77102 II 915 EC did not induce dermal sensitization in guinea pigs tested with the closed patch technique.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

8. Acute Toxicity on the CGA-77102 720

Table V: Summary of Acute Toxicity

TEST	RESULTS	CATEGORY	% a.i.
Oral LD_{50}--rat	Males: 3921 (2805-5479) mg/kg Females: 1782 (979-3242) mg/kg	III	70.3%
Dermal LD_{50}--rabbit	Male & Female > 2000 mg/kg	III	70.3%
Inhalation LC_{50}--rat	Male & Female > 2.62 mg/L	IV	70.3%
Eye irritation--rabbit	I. slight to moderate conjunctival irritation to washed and unwashed eyes II. slight to moderate conjunctival irritation to washed and unwashed eyes	III III	70.3% 70.4%
Dermal irritation--rabbit	I. average primary irritation score (PIS) for the 4, 24, 48, 72 and 96-hour & Day 7 scores was 1.4 II. average primary irritation score (PIS) for the 4, 24, 48, 72 & 6-hour scores was 1.0	IV IV	70.3% 70.4%
Dermal sensitization--guinea pig	dermal sensitizer with the closed patch technique	NA	70.3%

a. §81-1 Acute Oral Toxicity

S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Acute Oral Toxicity Study of CGA-77102 720 in Rats, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504273, October 17, 1996 (Unpublished); EPA MRID Number 44172203.

In an acute oral toxicity study (MRID# 44172203), groups of 5 male and 5 female young adult albino rats (Strain: Crl:CD®(SD)BR from Charles River Laboratories, Inc., Portage, Michigan) received either 2000, 3500, or 5000 mg/kg in males and 1000, 2000, or 5000 mg/kg in females of CGA-77102 120 (Purity: 70.3% CGA-77102 and 3.53% CGA-154281; Lot No. FL-961187; Batch Code 1098-26) as a single gavage dose.

The Acute Oral LD_{50} for CGA-77102 720 is:

Males - 3921 mg/kg bw
95% Confidence Limits - 2805 to 5479 mg/kg bw

Females - 1782 mg/kg bw
95% Confidence Limits - 979 to 3242 mg/kg bw

Combined - 3500 mg/kg bw
95% Confidence Limits - 2396 to 5113 mg/kg bw

Toxicity Category III.

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

b. §81-2 Acute Dermal Toxicity

S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Acute Dermal Toxicity Study of CGA-77102 720 in Rabbits, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504274, September 5, 1996 (Unpublished); EPA MRID Number 44172204.

In an acute dermal toxicity study (MRID# 441722047), 5 male and 5 female Adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 2000 mg/kg CGA-77102 720 (Purity: 70.3% CGA-77102 and 3.53% CGA-154281; Lot No. FL-961187; Batch Code 1098-26) by the dermal route.

The Acute Dermal LD_{50} for CGA-77102 720 is greater than 2000 mg/kg. Toxicity Category III.

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

c. §81-3 Acute Inhalation Toxicity

J. Bennick (1996): CGA-77102 720, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Study Number 2917-96, August 9, 1996 (Unpublished); EPA MRID Number 44172205.

In an acute inhalation toxicity study (MRID# 44172205), 5 male and 5 female Rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley from Harlan Sprague Dawley, Inc., Indianapolis, IN) were exposed by the nose only route to a generated aerosol of CGA-77102 720 from undiluted liquid at a level of 2.62 mg/L (Purity: 70.3% CGA-77102; 3.53% CGA-154281).

The Acute Inhalation LC_{50} for CGA-77102 720 is greater than 2.62 mg/L for both sexes. The particle size distribution (MMAD) was 2.980 µm. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

d. §81-4 Primary Eye Irritation

S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Study Title: Primary Eye Irritation Study of CGA-77102 720 in Rabbits, Corning Hazleton Inc. For Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504276, September 6, 1996 (Unpublished); EPA MRID Number 44172206.

In a primary eye irritation study (MRID# 44172206), male and female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.1 mL CGA-77102 720 (Purity: 70.3% CGA-77102 and 3.53% CGA-154281; Lot Number FL-961187 (Batch Code 1098-26) to one eye (the other serving as untreated control. Two groups were used, one group of 3 males and 3 females with their eyes unwashed, the other group of 3 females had their eyes washed for 1 minute with lukewarm water 30 seconds after test compound instillation.

CGA-77102 720 produced slight to moderate conjunctival irritation to washed and unwashed eyes. Irritation cleared by 96 hours after treatment. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

e. §81-4 Primary Eye Irritation

S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Study Title: Primary Eye Irritation Study of CGA-77102 720 in Rabbits, Corning Hazleton Inc. For Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504272, August 13, 1996 (Unpublished); EPA MRID Number 44172207.

In a primary eye irritation study (MRID# 44172207), male and female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.1 mL CGA-77102 720 (Purity: 70.4% CGA-77102 and 3.58% CGA-154281; Lot Number FL-961208 (Batch Code 1098-27)) to one eye (the other serving as untreated control. Two groups were used, one group of 3 males and 3 females with their eyes unwashed, the other group of 3 females had their eyes washed for 1 minute with lukewarm water 30 seconds after test compound instillation.

CGA-77102 720 produced slight to moderate conjunctival irritation to washed and unwashed eyes. Irritation cleared by 96 hours after treatment. **Toxicity Category III.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

g. §81-5 Primary Dermal Irritation

S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Study Title: Primary Dermal Irritation Study of CGA-77102 720 in Rabbits, Corning Hazleton, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504275, August 13, 1996 (Unpublished); EPA MRID Number 44172208.

In a primary dermal irritation study (MRID# 44172208), 3 male and 3 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.5 mL CGA-77102 720 (Purity: 70.3% CGA-77102 and 3.53% CGA-154281; Lot Number FL-961187 (Batch Code 1098-26)) to the shaved back of each animal.

CGA-77102 720 produced very slight to well-defined erythema and very slight to slight edema reactions at the application site. The average primary irritation score (PIS) for the 4, 24, 48, 72 and 96-hour and Day 7 scores was 1.4. No irritation was seen by observation Day 14. **Toxicity Category IV.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-5) for a primary

dermal irritation study in rabbits.

h. §81-5 Primary Dermal Irritation

S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Study Title: Primary Dermal Irritation Study of CGA-77102 720 in Rabbits, Corning Hazleton, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation; Laboratory Project Identification: CHW 60504271, August 13, 1996 (Unpublished); EPA MRID Number 44572209.

In a primary dermal irritation study (MRID# 44572209), 3 male and 3 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.5 mL CGA-77102 720 (Purity: 70.4% CGA-77102 and 3.58% CGA-154281; Lot Number FL-961208 (Batch Code 1098-27)) to the shaved back of each animal.

CGA-77102 720 produced very slight erythema reactions and very slight to slight edema reactions at the application site. The average primary irritation score (PIS) for the 4, 24, 48, 72 and 96-hour scores was 1.0. No irritation was seen by observation Day 7. **Toxicity Category IV.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

i. §81-6 Dermal Sensitization

S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Study Title: Dermal Sensitization Study of CGA-77102 720 in Guinea Pigs - Closed Patch Technique, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504277, September 17, 1996 (Unpublished); EPA MRID Number 44172210.

In a dermal sensitization study (MRID# 44172210), 10 young male adult albino guinea pigs (Strain: Crl:(HA)BR from Charles River Laboratories, Inc., Portage, Michigan) received 0.4 mL (3 induction and 1 challenge application) CGA-77102 720 (Purity: 70.3% CGA-77102 and 3.53% CGA-154281; Lot Number: FL-961187 (Batch Code 1098-26)) to the shaved back of each animal.

CGA-77102 720 was a dermal sensitizer in guinea pigs tested with the closed patch technique.

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

9. Acute Toxicity on the CGA-77102/G30027 II

Table VI: Summary of Acute Toxicity

TEST	RESULTS	TOX CAT	% a.i.
Oral LD_{50}--rat	Males: 3372 (2430-4680) mg/kg Females: 3251 (2917-3623) mg/kg	III	26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT)
Dermal LD_{50}--rabbit	Male & Female > 2020 mg/kg	III	26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT)
Inhalation LC_{50}--rat	Male & Female > 1.60 mg/L	III	26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT)
Eye irritation--rabbit	mildly irritating in unwashed eyes and minimally irritating to washed eyes	III	26.6% CGA-77102; 1.34% CGA-154281; 33.0% Atrazine (33.4% TCT)
Dermal irritation--rabbit	average primary irritation score (PIS) for the 4 and 24 hour scores was 0.2, no irritation was seen by the 48 hour observation period.	IV	26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT)
Dermal sensitization--guinea pig	not a dermal sensitizer with the closed patch technique	NA	26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT)

a. §81-1 Acute Oral Toxicity

J.O. Kuhn (1995): CGA-77102/G30027 II, FINAL REPORT, ACUTE ORAL TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2429-95, December 21, 1995; EPA MRID No. 43928503.

In an acute oral toxicity study (MRID# 43928503), groups of 5 male

and 5 female young adult albino rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley SD from Harlan Sprague Dawley, Inc., Houston, TX) received either 2500, 3500, or 5163 mg/kg of CGA-77102/G30027 II 660SC-EXP [Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT); Lot Number FL-951649] as a single gavage dose.

The Acute Oral LD_{50} for CGA-77102/G30027 II is:

Males - 3372 mg/kg bw
95% Confidence Limits - 2430 to 4680 mg/kg bw

Females - 3251 mg/kg bw
95% Confidence Limits - 2917 to 3623 mg/kg bw

Combined - 3271 mg/kg bw
95% Confidence Limits - 2755 to 3882 mg/kg bw

Toxicity Category III.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

b. §81-2 Acute Dermal Toxicity

J.O. Kuhn (1995): CGA-77102/G30027 II, FINAL REPORT, ACUTE DERMAL TOXICITY STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2430-95, November 22, 1995; EPA MRID Number 43928504.

In an acute dermal toxicity study (MRID# 43928504), 5 male and 5 female albino rabbits (females were nulliparous and non-pregnant; Strain: New Zealand White from Ray Nichols Rabbitry; Lumberton, Texas) received 2020 mg/kg CGA-77102/G30027 II 660SC-EXP [Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT); Lot Number FL-951649] by the dermal route.

The Acute Dermal LD_{50} for CGA-77102/G30027 II is greater than 2020 mg/kg for both sexes. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

c. §81-3 Acute Inhalation Toxicity

J. Bennick (1996): CGA-77102/G30027 II, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2431-95, January 11, 1996; EPA MRID Number 43928505.

In an acute inhalation toxicity study (MRID# 43928505), groups of 5 male and 5 female rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley; Source: Harlan Sprague Dawley, Inc., Houston, Texas) were exposed by the nose only route to a generated aerosol of CGA-77102/G30027 II from undiluted liquid at levels of 0.619 or 1.60 mg/L mean exposure concentrations [Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT); Lot Number FL-951649].

The Acute Inhalation LC_{50} for CGA-77102/G30027 II was greater than 1.60 mg/L. The particle size distribution (MMAD) was 4.512 and 13.982 µm for the 0.619 and 1.60 mg/L mean exposure concentrations, respectively. **Toxicity Category III.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

d. §81-4 Primary Eye Irritation

J.O. Kuhn (1995): CGA-77102/G-30027 II, FINAL REPORT, PRIMARY EYE IRRITATION STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2365-95, November 13, 1995; EPA MRID Number 43928506.

In a primary eye irritation study (MRID# 43928506), 3 male and 3 female (nonwashed) and 3 male ("washed") albino rabbits (Strain: New Zealand White from Ray Nichols Rabbitry, Lumberton, Texas) received 0.1 mL CGA-77102/G30027 II 660SC-EXP [Purity: 26.6% CGA-77102; 1.34% CGA-154281; 33.0% Atrazine (33.4% TCT); Lot Number FL-951423] to one eye (the other serving as untreated control). Two groups were used, one group with the eyes unwashed, the other group had the eyes washed with room temperature deionized water for 1 minute beginning 30 seconds after test compound instillation.

CGA-77102/G30027 II was mildly irritating in unwashed eyes and minimally irritating to washed eyes. Irritation cleared by 4 days after treatment. **Toxicity Category III.**

This study is classified as <u>Acceptable-Guideline</u> and

satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

e. §81-5 Primary Dermal Irritation

J.O. Kuhn (1995): CGA-77102/G30027 II, FINAL REPORT, PRIMARY DERMAL IRRITATION STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2432-95, November 30, 1995; EPA MRID Number 43928507.

In a primary dermal irritation study (MRID# 43928507), 3 male and 3 female albino rabbits (New Zealand White from Ray Nichols Rabbitry, Lumberton, Texas) received 0.5 mL CGA-77102/G30027 II 660SC-EXP [Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT); Lot Number FL-951649] to the shaved back of each animal.

CGA-77102/G30027 II was slightly irritating. The mean PIS was 0.2. No irritation was seen by the 48 hour observation period. **Toxicity Category IV.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

f. §81-6 Dermal Sensitization

J.O. Kuhn (1996): CGA-77102/G30027 II, FINAL REPORT, DERMAL SENSITIZATION STUDY IN GUINEA PIGS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2433-95, January 11, 1996; EPA MRID Number 43928508.

In a dermal sensitization study (MRID# 43928508), 2 male and 2 female (Irritation Screening) and 5 male and 5 female (Definitive Study) guinea pigs (Strain: Hartley-Albino from SASCO Inc., Madison, WI) received 0.4 mL CGA-77102/G30027 II 660SC-EXP [Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT); Lot Number FL-951649] to the shaved back of each animal using the closed patch technique.

CGA-77102/G30027 II was not a dermal sensitizer in guinea pigs tested with the closed patch technique.

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-5) for a dermal sensitization study in guinea pigs.

10. Acute Toxicity on the CGA-77102/G-30027 II [illegible]

Table VII: Summary of Acute Toxicity

[illegible]	RESULTS	TOX CAT	[illegible]
Oral LD_{50}	Males: 5477 (4374-6858) mg/kg bw Females: 3633 (2516-5248) mg/kg bw	III	35.8% CGA-77102, 28.7% Atrazine (29.0% TCT), 1.79% CGA-154281
Dermal LD_{50}--rabbit	Male & Female > 2000 mg/kg	III	35.8% CGA-77102, 28.7% Atrazine (29.0% TCT), 1.79% CGA-154281
Inhalation LC_{50}--rat	Male & Female > 0.640 mg/L	III	35.8% CGA-77102, 28.7% Atrazine (29.0% TCT), 1.79% CGA-154281
Eye irritation--rabbit	Moderate conjunctival irritation to washed and unwashed eyes. Unwashed eyes had corneal involvement and both groups had iridal involvement.	III	35.8% CGA-77102, 28.7% Atrazine (29.1% TCT), 1.79% CGA-154281
Dermal irritation--rabbit	Average primary irritation score (PIS) for the 4, 24, 48, 72 and 96-hour and Day 7 scores was 1.2.	IV	35.8% CGA-77102, 28.7% Atrazine (29.1% TCT), 1.79% CGA-154281
Dermal sensitization--guinea pig	A dermal sensitizer with the closed patch technique.	NA	35.8% CGA-77102, 28.7% Atrazine (29.0% TCT), 1.79% CGA-154281

a. §81-1 Acute Oral Toxicity

S.M. Glaza (1996): CGA-77102/G-30027 II 720SC-Exp, FINAL REPORT [illegible] Acute Oral Toxicity Study of CGA-77102/G-30027 720SC Exp in Rats, (EPA Guidelines 81-1), Conducted Hazleton [illegible] Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504756, September 20, 1996

(Unpublished); EPA MRID Number 44128003.

In an acute oral toxicity study (MRID# 44128003), groups of 5 male and 5 female young adult albino rats (Strain: Crl:CD®(SD)BR from Charles River Laboratories, Inc., Portage, Michigan) received either 3000, 5000, or 6000 mg/kg in males and 1000, 3000, or 5000 mg/kg in females of CGA-77102/G-30027 II 720 SC-Exp (Purity: 35.8% CGA-77102, 28.7% Atrazine (29.0% TCT) and 1.79% CGA-154281; Lot No.: FL-961156, Batch Code 1098-25-1) as a single gavage dose. A range-finding study was conducted using 500, 1000, 3000 or 5000 mg/kg as a single gavage dose in 1 male and 1 female at each dose level.

The Acute Oral LD_{50} for CGA-77102/G-30027 II 720 SC-Exp is:

Males - 5477 mg/kg bw
95% Confidence Limits - 4374 to 6858 mg/kg bw

Females - 3633 mg/kg bw
95% Confidence Limits - 2516 to 5248 mg/kg bw

Combined - 4824 mg/kg bw
95% Confidence Limits - 3660 to 6358 mg/kg bw

Toxicity Category III.

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

b. §81-2 Acute Dermal Toxicity

S.M. Glaza (1996): CGA-77102/G-30027 II 720SC-Exp, FINAL REPORT, Study Title: Acute Dermal Toxicity Study of CGA-77102/G-30027 II 720SC-Exp in Rabbits, (EPA Guidelines 81-2), Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504757, September 13, 1996 (Unpublished); EPA MRID Number 44128004.

In an acute dermal toxicity study (MRID# 441722047), 5 male and 5 female Adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 2000 mg/kg CGA-77102/G-30027 II 720SC-Exp (Purity: 35.8% CGA-77102, 28.7% Atrazine (29.0% TCT) and 1.79% CGA-154281; Lot No.: FL-961156, Batch Code 1098-25-1) by the dermal route.

The Acute Dermal LD_{50} for CGA-77102/G-30027 II 720SC-Exp is greater

than 2000 mg/kg. **Toxicity Category III.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

c. §81-3 Acute Inhalation Toxicity

J. Bennick (1996): CGA-77102/G-30027 II 720SC, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, EPA GUIDELINE NO. 81-3, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2886-96, August 9, 1996 (Unpublished); EPA MRID Number 44128005.

In an acute inhalation toxicity study (MRID# 44128005), groups of 5 male and 5 female rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley from Harlan Sprague Dawley, Inc., Indianapolis, IN) were exposed by the nose only route to a generated aerosol of CGA-77102/G-30027 II 720SC from undiluted liquid at levels of 0.640 and 2.93 mg/L (Purity: 35.8% CGA-77102, 28.7% Atrazine (29.0% TCT), 1.79% CGA-154281; Lot No.: FL-961156).

The Acute Inhalation LC_{50} for CGA-77102/G-30027 II 720SC is greater than 0.640 mg/L for both sexes. The particle size distribution (MMAD) was 3.484 µm. **Toxicity Category III.**

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

d. §81-4 Primary Eye Irritation

S.M. Glaza (1996): CGA-77102/G-30027 II 720SC-Exp, FINAL REPORT, Study Title: Primary Eye Irritation Study of CGA-77102/G-30027 II 720SC-Exp in Rabbits, (EPA Guideline 81-4), Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60304557, June 13, 1996 (Unpublished); EPA MRID Number 44128006.

In a primary eye irritation study (MRID# 44128006), male and female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.1 mL CGA-77102/G-30027 II 720SC-Exp (Purity: 35.8% CGA-77102, 28.7% Atrazine (29.1% TCT) and 1.76% CGA-154281; Lot Number: FL-960542, Batch Code 1098-20-4) to one eye (the other serving as untreated control. Two groups were

used, one group of 3 males and 3 females with their eyes unwashed, the other group of 3 females had their eyes washed for 1 minute with lukewarm water 30 seconds after test compound instillation.

In a Primary Eye Irritation study, CGA-77102/G-30027 II 720SC-Exp produced moderate conjunctival irritation to washed and unwashed eyes. Unwashed eyes had corneal involvement and both groups had iridal involvement. Irritation cleared by 96 hours after treatment. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

e. §81-5 Primary Dermal Irritation

S.M. Glaza (1996): CGA-77102/G-30027 II 720SC-Exp, FINAL REPORT, Study Title: Primary Dermal Irritation Study of CGA-77102/G-30027 II 720SC-Exp in Rabbit, (EPA Guideline 81-5), Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60304556, June 13, 1996 (Unpublished); EPA MRID Number 44128007.

In a primary dermal irritation study (MRID# 44128007), 3 male and 3 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.5 mL CGA-77102/G-30027 II 720SC-Exp (35.8% CGA-77102, 28.7% Atrazine (29.1% TCT) and 1.76% CGA-154281; Lot Number: FL-960542, Batch Code 1098-20-4) to the shaved back of each animal.

In a Primary Dermal Irritation study, CGA-77102/G-30027 II 720SC-Exp produced very slight to well-defined erythema reactions 5/6 animals and very slight edema reaction in 3 animals. Desquamation was also observed at 1 test site. The average primary irritation score (PIS) for the 4, 24, 48, 72 and 96-hour and Day 7 scores was 1.2 (considered to be slightly irritating). All irritation was cleared by study day 14. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

f. §81-6 Dermal Sensitization

S.M. Glaza (1996): CGA-77102/G-30027 II 720SC-Exp, FINAL REPORT, Study Title: Dermal Sensitization Study of CGA-77102/G-30027 II 720SC-Exp in Guinea Pigs - Closed Patch Technique, (EPA Guideline 81-6), Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504758, September 17, 1996 (Unpublished); EPA MRID Number 44128008.

In a dermal sensitization study (MRID# 44128008), 10 young male adult albino guinea pigs (Strain: Crl:(HA)BR from Charles River Laboratories, Inc., Portage, Michigan) received 0.4 mL (3 induction and 1 challenge application) CGA-77102/G-30027 II 720SC-Exp (Purity: 35.8% CGA-77102, 28.7% Atrazine (29.0% TCT), 1.79% CGA-154281; Lot Number: FL-961156, Batch Code 1098-25-1) to the shaved back of each animal, an additional 10 animals served as naive control (only received a challenge dose). An irritation screening group of 4 animals was also used.

In a Dermal Sensitization study, CGA-77102/G-30027 II 720SC-Exp was a dermal sensitizer in guinea pigs tested with the closed patch technique.

This study is classified as <u>Acceptable-Guideline</u> and satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

C. RfD:

The Health Effects Division-RfD/Peer Review Committee met on April 10, 1997 to discuss and evaluate recently submitted toxicology data in support of Alpha-Metolachlor (S-enantiomer, CGA 77102) registration, (Final document date stamped: 07/16/97), based on the proposed the use of the toxicology data base, submitted in support of the registration of technical grade Metolachlor, to support the registration of Alpha-metolachlor. The registrant's request was based on the fact that the S-enantiomer, Alpha-metolachlor, has already been subject to extensive toxicological testing during the course of the development of Metolachlor.

Therefore, the specific investigation of Alpha-metolachlor submitted to the Agency was confined to selected endpoints in the area of acute and subchronic toxicity, mutagenicity and reproductive toxicity for the purpose of identifying possible qualitative or quantitative differences between the toxicological properties of Alpha-Metolachlor and Metolachlor.

The Committee was asked to determine whether the limited toxicological investigation submitted on behalf of Alpha-metolachlor is adequate to demonstrate that both alpha-metolachlor and Metolachlor itself have identical toxicological properties, and if so, the applicability of the data base established for Metolachlor in the safety evaluation of the Alpha-metolachlor, and whether or not a separate Reference Dose (RfD) for this chemical should be established in this case.

a. Chronic and Subchronic Toxicity:

i. Alpha-Metolachlor:

There were no chronic toxicity data in rats (83-1a) or dogs (83-1b) available for review by the Committee. Two subchronic studies in rats and dogs (82-1a, 1995, MRID No. 43928923 and 82-1b, 1995, MRID No. 43928922) were available for review by the Committee. The Committee considered the subchronic toxicity study in rats (82-1a, 1995, MRID No. 43928923) and the subchronic toxicity study in dogs (82-1b, 1995, MRID No. 43928922) to be acceptable and the data evaluation record to be adequate.

ii. Metolachlor:

In a subchronic study conducted with Metolachlor, groups of Sprague-Dawley rats were administered Metolachlor in diets at 100, 300 or 1000 ppm (5, 50 or 50 mg/kg/day) for three months. Since no toxic manifestations were evident in any group at week ten, it was decided to increase the dose from 100 ppm to 2000 ppm for the remaining three weeks of the study. Ten rats per sex from the high- dose group also received increased levels of 2000 ppm for the remaining three weeks of the study and then sacrificed after a recovery period of 4 weeks. No significant systemic effects were noted at any dose tested. Therefore, the NOEL was established at 1000 ppm (50 mg/kg/day), the highest dose level tested.

b. Reproductive and Developmental Toxicity:

i. Alpha-Metolachlor:

The Committee considered the developmental toxicity study in rats (83-3a, 1995, MRID 43928925) and the developmental toxicity study in rabbits (83-3b, 1995, MRID 43928924) to be acceptable and the data evaluation record to be adequate.

ii. Metolachlor:

In a two-generation reproduction study in Sprague-Dawley rats, 94.5% metolachlor was administered at dietary levels of 30,

300, or 1000 ppm (2.3, 23.6, or 76.2 mg/kg/day for males; 2.5, 25.9, or 85.1 mg/kg/day for females). The parental systemic NOEL was 1000 ppm (76.2/85.1 mg/kg/day for M/F), the highest dose tested. The reproductive NOEL was 300 ppm (25.9 mg/kg/day for dams) and the reproductive LOEL was 1000 ppm (85.1 mg/kg/day for dams), based on decreased offspring postnatal body weights on days 14 and 21 for F1a litters and days 4, 7, 14, and 21 for F1b litters (Page, 1981; MRID 00080897).

In a prenatal developmental toxicity study in Sprague-Dawley rats (25/group), metolachlor (96.4%) was administered by gavage in aqueous 0.5% carboxymethylcellulose at a dose volume of 10 ml/kg on gestation days 6-15. Dose levels were 30, 100, 300, or 1000 mg/kg/day. The maternal NOEL was 100 mg/kg/day, and the maternal LOEL was 300 mg/kg/day, based on clinical observations of salivation. At 1000 mg/kg/day, the following were observed: mortality (4/25), more extensive clinical signs (salivation, urine stained abdominal fur, excess lacrimation, and clonic or clonic/tonic convulsions), and reductions in body weight gain and food consumption. The developmental NOEL was 300 mg/kg/day, and the developmental LOEL was 1000 mg/kg/day, based on decreased implantations/dam, reduced litter size, increased postimplantation loss (resorptions/dam), and decreased mean fetal body weight (Lochry, 1985; MRID 00151941).

In a previously-conducted prenatal developmental toxicity study in Sprague-Dawley rats (25/group), metolachlor (unspecified purity) was administered by gavage in 2% carboxymethylcellulose at dose levels of 60, 180, or 360 mg/kg/day on gestation days 6-15. No evidence of maternal or developmental toxicity was observed at any dose level. (Fritz, 1976; MRID 00015396)

In a prenatal developmental toxicity study in New Zealand White rabbits (16/group), 95.4% metolachlor was administered by gavage at doses of 36, 120, or 360 mg/kg/day on D 7-18. The test substance was delivered in 0.75% aqueous hydroxymethylcellulose at a dose volume of 10 ml/kg. The maternal NOEL was 120 mg/kg/day. The maternal LOEL, 360 mg/kg/day, was based on increased clinical observations (blood in pan and anorexia) and reduced body weight gain. No evidence of developmental toxicity was noted. Therefore, the developmental toxicity NOEL was considered to be $\geq$360 mg/kg/day (Lightkep, 1980; MRID 00041283).

iii. Developmental Neurotoxicity:

Based upon a review of the currently available data base for alpha-metolachlor, a developmental neurotoxicity study in rats is not recommended at this time.

iv. Conclusions (Reproductive and Developmental Toxicity):

In the prenatal developmental toxicity studies, administration of Alpha-metolachlor at limit dose levels (1000 mg/kg/day) did not result in any evidence of developmental toxicity. Studies conducted with Metolachlor were not sufficiently equivalent in dose spacing to allow a comparison of the study findings. Furthermore, the results of the two-generation study in rats with metolachlor can not be extrapolated to alpha metolachlor due to the lack of available supporting or bridging toxicity information.

d. FQPA Considerations:

The data package for Metolachlor included acceptable prenatal developmental toxicity studies in rats and rabbits with alpha-metolachlor. In addition, an acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits were submitted for metolachlor. The completeness of this data package, specifically in regard to the evaluation of Alpha-metolachlor for reproductive toxicity, is dependant upon the adequacy of standard "bridging" data; these data were not addressed by the Committee.

The data provided no indication of increased sensitivity of rats or rabbits to *in utero* exposure to alpha-metolachlor. No evidence of developmental toxicity was observed in either species, at dose levels which were demonstrated to be maternally toxic. In the prenatal developmental toxicity study in rats, the developmental NOEL was $\geq$1000 mg/kg/day, the limit dose, although maternal toxicity was observed at 500 mg/kg/day (maternal NOEL = 50 mg/kg/day). In the prenatal developmental toxicity study in rabbits, the developmental NOEL was $\geq$500 mg/kg/day, while the maternal NOEL was 20 mg/kg/day, based on clinical signs of toxicity (soft stool) at the LOEL of 100 mg/kg/day.

Additionally, the data provided no indication of increased sensitivity of rats or rabbits to *in utero* exposure to metolachlor. In the prenatal developmental toxicity study in rats, the maternal NOEL (100 mg/kg/day) was less than the developmental NOEL (300 mg/kg/day). Developmental toxicity noted at the highest dose tested, 1000 mg/kg/day, occurred in the presence of severe maternal toxicity. In the prenatal developmental toxicity study in rabbits, no developmental toxicity was observed, although maternal toxicity was noted at the LOEL of 360 mg/kg/day (increased clinical signs and reduced weight gain).

However, in the two-generation reproduction study in rats, a

possible sensitivity of the offspring to *in utero* and/or postnatal exposure to metolachlor is suggested by the data. Although no parental systemic toxicity was identified, a reproductive NOEL (300 ppm; 25.9 mg/kg/day for dams) was based on decreased offspring postnatal body weights (days 14 and 21 for F1a litters and days 4, 7, 14, and 21 for F1b litters) at the reproductive LOEL of 1000 ppm (85.1 mg/kg/day for dams).

e. Mutagenicity:

Three acceptable mutagenicity studies (§84-2) with alpha-metolachlor were available for review by the Committee. The following are the Committee's conclusions for each study:

Results from the three studies indicated that alpha-metolachlor was neither mutagenic to microbial cells nor clastogenic in whole animals. Similarly, there was no evidence of DNA damage/repair in the hepatocytes recovered from treated rats. In contrast, treatment with alpha-metolachlor induced marked increase in cell proliferation indicating that the test substance reached the target organ and induced a hepatotoxic but not genotoxic effect. Overall, the findings with alpha-metolachlor are in good agreement with the genetic toxicology profile for metolachlor. It was noted that an in vitro mammalian cell gene mutation assay was not included in the data package. However, an acceptable and negative mouse lymphoma assay with metolachlor was previously submitted to the Agency. Based on the chemical equivalency and similarity of the genetic toxicology profiles for alpha-metolachlor and metolachlor, we concluded that the requirement to conduct a mammalian cell gene mutation assay can be waived.

The Committee further concluded that the submitted test battery satisfies the new mutagenicity initial testing Guidelines. No other genetic toxicology data requirements have been identified at this time.

f. Reference Dose (RfD):

The Committee deferred the decision on whether or not a separate Reference Dose (RfD) for Alpha-metolachlor should be established until a final decision is made regarding the adequacy of the toxicology data base and whether it is appropriate to use toxicology data generated with Metolachlor to support the registration of Alpha-metolachlor.

g. Committee's Conclusions and Recommendations:

The Committee compared data available on Alpha metolachlor with those submitted in support of Metolachlor registration and concluded that without metabolism studies and side-by-side subchronic studies conducted in the same strain of rat using comparable dose levels of the subject test substances, the identification of any possible qualitative or quantitative differences between the toxicological properties of CGA 77102 and metolachlor would not be possible.

Therefore, the Committee could not determine whether the use of the toxicology data base, submitted in support of the registration of technical grade metolachlor, to support the registration of Alpha-metolachlor would be appropriate at this time.

D. Toxicology Profile for Metolachlor (40 CFR 158.340)

Technical: Metolachlor
Use Pattern: food

This compound is a registered active ingredient. The following data are required for technical metolachlor. This compound is on reregistration List A.

THIS INFORMATION DOES NOT NECESSARILY REFLECT THE DATA REQUIREMENTS FOR REREGISTRATION.

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes
§82-1(a) 90 day feeding study - rat	Yes	No[1]
§82-1(b) 90 day feeding study - nonrodent	Yes	Yes
§82-2 21 day dermal - rabbit	Yes	Yes
§83-1(a) 2-year feeding - rodent	Yes	Yes
§83-1(b) 1 year feeding - nonrodent	Yes	Yes
§83-2(a) Carcinogenicity - rat	Yes	Yes
§83-2(b) Carcinogenicity - mouse	Yes	Yes
§83-3(a) Teratology - rat	Yes	Yes
§83-3(b) Teratology - rabbit	Yes	Yes
§83-4 Multigeneration reproduction-rat	Yes	Yes
§84-2(a) Mutagenicity Gene Mutation	Yes	Yes
§84-2(b) Muta - Struct.Chromosome Aberr.	Yes	Yes
§84-4 Muta - Other Genotoxic Effects	Yes	Yes
§85-1 General metabolism - rat	Yes	Yes
§85-2 Dermal Penetration	Yes	Yes

[1] = satisfied by 2-year chronic feeding study in the rat

Formulation: Dual 8E

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	**NO**

Formulation: Metolachlor 15%

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	**NO**

Formulation: Metolachlor 25.9% (DUAL II G)

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes

Formulation: Metolachlor 84.4% (DUAL II)

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes

Formulation: CGA 24705 6EC

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	DA
§81-2 Acute dermal toxicity in rabbits	Yes	DA
§81-3 Acute inhalation toxicity in rats	Yes	DA
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	DA
§81-6 Dermal sensitization - guinea pig	Yes	**NO**

DA = Data available, needs to be reviewed

Formulation: Bicep 4.5 F-G

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	**NO**
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	**NO**

Formulation: Bicep 4.5 F-H

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	**NO**
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	**NO**

Formulation: Atrazine 51%/Metolachlor 30.6%

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	DA
§81-2 Acute dermal toxicity in rabbits	Yes	DA
§81-3 Acute inhalation toxicity in rats	Yes	DA
§81-4 Primary eye irritation in rabbits	Yes	DA
§81-5 Primary dermal irritation in rabbits	Yes	DA
§81-6 Dermal sensitization - guinea pig	Yes	**NO**

DA = Data available, needs to be reviewed

Formulation: Atrazine 18%/Metolachlor 31.8%

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes

Formulation: Bicep III (Atrazine 27.4%/Metolachlor 36.1%)

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes

Formulation: Paraquat 7.86%/Linuron 2.84%/Metolachlor 22.75%

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	**NO**
§81-2 Acute dermal toxicity in rabbits	Yes	**NO**
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	**NO**
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes

Formulation: Metolachlor 73.6%/Metribuzin 17.2%

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	**NO**

Formulation: Metolachlor 30.3%/Glufosinate 13.45%

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	**NO**
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes

Formulation: Metolachlor 44.3%/Linuron 17.7%

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	**NO**
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes

Formulation: Dual 6E/Banvel 4S

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	**NO**

Formulation: Dual (Bladex 22.0%/Metolachlor 22.0%)

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes

Formulation: NAF-9 (Broadstrike)/Dual (Metolachlor 79.9%)

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes

Formulation: Milocep

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	NO

IV. Data Gaps

The database for technical Metolachlor is complete. There are acute toxicity study data gaps with the registered formulations. These must be resolved before further permanent food use tolerances with these products are granted.

V. Actions Being Taken to Obtain Additional Information or Clarification:

None at this time.

VI. Reference Dose

The RfD is 0.1 mg/kg/day (0.097) based on the chronic feeding study in the dog with a NOEL of 9.7 mg/kg/day and a LOEL of 32.7 mg/kg/day based upon decreased body weight gain in females and an uncertainty factor (UF) of 100 [revised 5/27/93].

Metolachlor was fed to beagle dogs at dose levels of 0, 100, 300, or 1000 ppm for up to 52 weeks (Guideline §83-1b; MRID# 40980701). The systemic NOEL for male dogs was 1000 ppm (32.7 mg/kg/day). The systemic NOEL for female dogs was 300 ppm (9.7 mg/kg/day) and the LOEL was 1000 ppm (33 mg/kg/day) based on decreased body weight gain (Document Number 010088).

VII. Pending Regulatory Actions

None at this time.

VIII: Toxicological Issues Pertinent to this Request

This chemical was a registration standard in 1986 and is a **List A** chemical for reregistration.

A. New toxicology Data on Metolachlor

No new studies were submitted.

B. Carcinogenicity

The HED Carcinogenicity Peer Review Committee (CPRC) recommended that metolachlor be classified as a Group C (possible human) carcinogen, with a Q_1^* of 9.2×10^{-3} $(mg/kg/day)^{-1}$. The classification of Group C was based on increases in liver tumors in the female rat, by both pair-wise and trend analysis and the replication of the finding of tumors in the female rat in a second study. However, the CPRC conducted July 27, 1994, recommended an MOE approach since there was no supportable mutagenicity concern and in light of new information on the relative metabolism of metolachlor quinone imine is presumed to be the ultimate carcinogen for 2,6-dimethylaniline. Because of stearic hindrance (provided by the additional alkyl group about the nitrogen atom) is significantly less susceptible to amide dealkylation and extremely stable to metabolic hydrolysis of the amide so that formation of the disubstituted aniline is presumably very low (if any).

C. Toxicology End Point Selection

I. Dermal Absorption Data

% absorbed: 62.8% after 24 hours in a rat dermal penetration study in which 0.01 mg/cm2 was applied. MRID No: 41833102

II. Acute Dietary Endpoint (One Day)

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.

III. Short Term Occupational or Residential Exposure (1 to 7 days)

This risk assessment is not required. No study was identified from the database which indicated the potential for adverse effects after a short term (1 week to 7 days) exposure.

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

21-Day Dermal Toxicity Study - Rabbit (§82-2); MRID No.: 41833101

A 21-day dermal toxicity study was performed in New Zealand rabbits with 0, 10, 100 or 1000 mg/kg/day of metolachlor. Very slight 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 (endpoint for risk assessment). The systemic LOEL was 1000 mg/kg/day for males and females. **This risk assessment is required.**

* 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 observed at the 1000 mg/kg/day.

Acute Toxicity with Technical Metolachlor

TEST	RESULTS	TOX CAT
Oral LD_{50}--rat MRID# 00015523	2780 mg/kg	III
Dermal LD_{50}--rabbit MRID# 00015526	> 10 g/kg	III
Inhalation LC_{50}--rat MRID# 00015535	> 1.75 mg/L	III
Eye irritation--rabbit MRID# 00015528	Non-irritating	IV
Dermal irritation--rabbit MRID# 00015530	Non-irritating	IV
Dermal sensitization--guinea pig MRID# 00015631	A dermal sensitizer	NA

012310

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/2/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)
Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 5/9/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Oral Toxicity - Rat
Species: Rat Guideline: §81-1

EPA ID No.s: EPA MRID No. 43928915
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.M. Glaza (1994): CGA-77102 Technical FINAL REPORT Acute Oral Toxicity Study of CGA-77102 Technical in Rats, Hazleton Wisconsin, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: HWI 40702449, November 23, 1994 (Unpublished); EPA MRID Number 43928915.

Executive Summary: In an acute oral toxicity study (MRID# 43928915), groups of 5 male and 5 female young adult albino rats (Strain: Crl:CD®(SD)BR from Charles River Laboratories, Inc., Portage, Michigan) received either 2000, 3000, or 5000 mg/kg CGA-77102 Technical (Purity: 95.4% purity; Lot Number FL-941255 (Batch Code V.4673/7)) as a single gavage dose.

The Acute Oral LD_{50} for CGA-77102 Technical is:

Males - 3267 mg/kg bw
95% Confidence Limits - 2299 to 4642 mg/kg bw
Females - 2577 mg/kg bw
95% Confidence Limits - 1980 to 3354 mg/kg bw
Combined - 2672 mg/kg bw
95% Confidence Limits - 2149 to 3322 mg/kg bw

Toxicity Category III.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

Compliance: A signed and dated STATEMENT OF NO DATA, CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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: 95.4% purity
Description: Brown liquid
Lot Number: FL-941255 (Batch Code V.4673/7)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Young adult albino rats
Strain: Crl:CD®(SD)BR
Source: Charles River Laboratories, Inc., Portage, Michigan
Age: Not provided, "young adult"
Body Weight: 230-295 g

B. Study Design

From pages 5 and 8 of the report:

The objective of this study was to assess the acute oral toxicity produced when the test material was administered by the oral route (gavage) to rats.

Study Timetable

In-life Start Date	July 28, 1994
In-life Termination Date	September 12, 1994

1. Animal Husbandry and Assignment

From page 9 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were separated by sex and group housed in screen-bottom stainless steel cages in temperature- and humidity-controlled quarters. Environmental controls for the animal room were set to maintain a temperature of 19° to 25°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from the required temperature and humidity conditions existed, they were documented and considered to have had no adverse effect on the study outcome. Animal husbandry and housing at HWI comply with the standards outlined in the "Guide for the Care and Use of Laboratory Animals."

The animals were provided continuous access to Laboratory Rodent Diet #5001, PMI Feeds, Inc., and water except for approximately 17 to 20 hours before test material administration when food, but not water, was withheld. The feed is routinely analyzed by the manufacturer for nutritional components and

58

environmental contaminants. Samples of the water are periodically analyzed by HWI. There were no known contaminants in the feed or water at levels that would have interfered with or affected the results of the study.

Fifteen male and fifteen female healthy, acclimated rats, weighing from 230 to 295 g, were assigned to three treatment groups of 2,000, 3,000, and 5,000 mg/kg of body weight. Each dose level consisted of five male and five female rats.

2. Dose Preparation and Administration

From page 10 of the report:

The undiluted test material was administered at room temperature by gavage using a bulk density determination of 1.10 g/mL to determine the dose volume for each dose level. An individual dose was calculated for each animal based on its fasted body weight.

3. Observations

From page 10 of the report:

Body weights were determined before test material administration (Day 0). Additional body weights were determined at Day 7, at termination of the experimental phase (Day 14), or at death when survival exceeded 1 day.

Clinical observations and mortality checks were conducted at approximately 1, 2.5, and 4 hours after test material administration. Additional clinical observations and twice a day mortality checks (morning and afternoon) were conducted daily thereafter for 14 days.

At termination of the experimental phase all animals were euthanized. All animals, whether dying during the study or euthanized at termination were subjected to an abbreviated gross necropsy examination and any abnormalities were recorded. After necropsy, the animals were discarded and only those tissues with lesions were collected for possible histopathological evaluation.

4. Statistical Analyses

From pages 10 and 13 of the report:

The LD_{50} values for males, females, and the sexes combined was determined by a computer program using a modified Behren-Reed-Muench cumulant method. No other statistical analyses were required by the protocol.

Reference: Thakur, A. K. and Fezio, W. L., "A computer Program for Estimating LD_{50} and it Confidence Limits Using a Modified Behren-Reed-Muench Cumulant Method," Drug and Chemical Toxicology, 4(3):297-305 (1981).

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-1.

C. Results:

1. Mortality

The investigators provided a group summary of the observed mortality. One 2000 mg/kg female, six 3000 mg/kg animals (2 males and 4 females) and all 5000 mg/kg animals died within 1 day of the test compound administration. No other mortality was observed. The following table (extracted from Table 1, page 15 of the report) summarizes the mortality findings:

Table I: Mortality Summary

Dose Level (mg/kg)	Mortality, Day Died*
Males	
2000	0/5
3000	2/5, Day 1^2
5000	5/5, Day 1^5
Females	
2000	1/5, Day 1^1
3000	4/5, Days 0^2 and 1^2
5000	5/5, Day 1^5

* = Superscript number indicates number of animals found dead on that day.

Calculated Oral LD_{50} :

Males - 3267 mg/kg bw
95% Confidence Limits - 2299 to 4642 mg/kg bw

Females - 2577 mg/kg bw
95% Confidence Limits - 1980 to 3354 mg/kg bw

Combined - 2672 mg/kg bw
95% Confidence Limits - 2149 to 3322 mg/kg bw

2. Clinical Signs

The investigators provided individual clinical signs. The clinical signs of toxicity included soft stool; excessive salivation; hunched posture; hypoactivity; red-stained face; dark and/or yellow-stained urogenital area; dark staining around the eyes; hypersensitive to touch; miosis; wet urogenital area; tremors; lacrimation; and staggered gait. The investigators also observed dyspnea, tonic convulsions, generalized erythema, squinting of the eyes when exposed to light, and/or lack of righting reflex were observed in the animals treated at 3,000 and/or 5,000 mg/kg. All surviving animals were noted to have returned to a normal appearance by Day 9 after treatment.

60

3. Body Weights

The investigators provided individual and mean body weights. No treatment related effects were noted on body weight gain in surviving animals. The following table presents the body weights and body weight gains (extracted from Table 2, pages 16-18 of the report):

Table II: Mean Body Weights (grams)

Day: / Dose (mg/kg):	0	7	0-7 Gain	14	0-14 Gain
			Males		
2000	290(5)[n]	349(5)	59(5)	395(5)	106(5)
3000	278(5)	348(3)	70(3)	409(3)	131(3)
5000	234(5)				
			Females		
2000	247(5)	280(4)	32(4)	279(4)	31(4)
3000	252(5)	325(1)	49(1)	342(1)	66(1)
5000	248(5)				

[n] = number of animals

4. Pathology

The investigators provided individual gross necropsy pathology findings and a summary report by the study pathologist. According to the pathologist: *The only test material-related finding were limited to those animals dying during the study and pertained to the contents of the gastrointestinal tract. The stomach and small intestine contained an oily tan or a yellowish-white mucoid semifluid which possibly represented test material mixed with ingesta.*

D. Conclusions

1. Investigators Summary:

From page 8 of the report:

The test material, CGA-77102 Technical, was evaluated for its acute oral toxicity potential in male and female rats when administered as a single gavage dose at levels of 2,000, 3,000, and 5,000 mg/kg of body weight. The estimated oral LD_{50} in rats was determined to be 3,267, 2,577 and 2,672 mg/kg for males, females, and the sexes combined, respectively. All mortality occurred within 1 day of test material administration. Clinical signs of toxicity included soft stool; excessive salivation; hunched posture; dyspnea; hypoactivity; red-stained face; dark and/or yellow-stained urogenital area; dark staining around the eyes; tonic convulsions; hypersensitive to touch; miosis; wet urogenital area; tremors; lacrimation; staggered gait; generalized erythema, squinting of eyes when exposed to light; and righting reflex absent. All surviving animals returned to a normal appearance by Day 9 after treatment. There was no meaningful effect on body weight gain in surviving animals. Test material-related findings observed at necropsy were limited to those animals dying during the study and pertained to the contents of the gastrointestinal tract.

2. Reviewers' Conclusions:

The Acute Oral LD_{50} for CGA-77102 Technical is:

Males - 3267 mg/kg bw
95% Confidence Limits - 2299 to 4642 mg/kg bw

Females - 2577 mg/kg bw
95% Confidence Limits - 1980 to 3354 mg/kg bw

Combined - 2672 mg/kg bw
95% Confidence Limits - 2149 to 3322 mg/kg bw

Toxicity Category III.

012310

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/7/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 5/9/94
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Dermal Toxicity - Rabbit
Species: Rabbit Guideline: §81-2

EPA ID No.s: EPA MRID No. 43928916
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.M. Glaza (1994): CGA-77102 Technical FINAL REPORT Acute Dermal Toxicity Study of CGA-77102 Technical in Rabbits, Hazleton Wisconsin, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation; Laboratory Project Identification: HWI 40702450; October 7, 1994 (Unpublished); EPA MRID Number 43928916.

Executive Summary: In an acute dermal toxicity study (MRID# 43928916), 5 male and 5 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received a single topical application of 2000 mg/kg CGA-77102 Technical (Purity: 95.4% purity; Lot Number FL-941255 (Batch Code V.4673/7)).

The Acute Dermal LD_{50} for CGA-77102 Technical is greater than 2000 mg/kg for both sexes. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA, CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

63

A. Materials and Methods

Test Compound: CGA-77102 Technical
Purity: 95.4% purity
Description: Brown liquid
Lot Number: FL-941255 (Batch Code V.4673/7)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbits
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: Not provided, "adult"
Body Weight: 2008-2532 g

B. Study Design

From pages 5 and 8 of the report:

The objective of this study was to assess the systemic toxicity and relative skin irritancy of a test material when applied to the skin of rabbits.

Study Timetable

In-life Start Date	August 4, 1994
In-life Termination Date	August 18, 1994

1. Animal Husbandry and Assignment

From page 9 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in screen-bottom stainless steel cages in temperature- and humidity-controlled quarters. Environmental controls for the animal room were set to maintain a temperature of 19° to 23°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from the required temperature and humidity conditions existed, they were documented and considered to have had no adverse effect on the study outcome. Animal husbandry and housing at HWI complied with the standards outlined in the "Guide for the Care and Use of Laboratory Animals.

The animals were provided access to water *ad libitum* and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed by HWI. There were no known contaminants in the feed or water at levels that would have

interfered with or affected the results of the study.

Five male and five female healthy, acclimated rabbits, weighing from 2,008 to 2,532 g, were used for a single dose level of 2,000 mg/kg of body weight. This dose level was chosen based on the requirements of the regulatory test guidelines.

2. Dose Preparation and Administration

From page 10 of the report:

The test material was administered as received. An individual dose was calculated and weighed out based on each animal's body weight on the day of test material administration.

On the day before test material application, each rabbit's back was clipped free of hair with an electric clipper. The clipped area made up not less than 10% of the total body surface.

The test material was applied to the intact skin on each animal's back at a dose level of 2,000 mg/kg of body weight. The test material was applied to the test site at a rate of approximately 0.05 g/cm^2 in a thin and uniform layer. The area of application was covered with a 10-cm x 10-cm gauze patch secured with paper tape and overwrapped with Saran Wrap® and Elastoplast® tape to provide an occlusive dressing. Collars were used to restrain the test animals during the 24-hour exposure period.

At the end of the 24-hour exposure period, the restraining collars and bandages were removed and the test sites were washed using tap water and disposable paper towels.

3. Observations

From pages 10-11 of the report:

Body weights were determined before test material application (Day 0), at Day 7, and at termination of the experimental phase (Day 14).

Clinical observations and mortality checks were conducted at approximately 1, 2.5, and 4 hours after test material administration. Additional clinical observations (including dermal effects) and twice a day mortality checks (morning and afternoon) were conducted daily thereafter for 14 days.

At termination of the experimental phase, all animals were euthanized, subjected to an abbreviated gross necropsy examination, and any abnormalities were recorded. After necropsy, the animals were discarded and no tissues were saved.

4. Statistical Analyses

From page 11 of the report:

No statistical analyses were required by the protocol.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-2.

C. Results:

1. Mortality

The investigators provided group summary of the survival rate. No mortality was observed during the study. The estimated dermal LD_{50} for male and female rabbits was determined to be greater than 2000 mg/kg bw.

2. Clinical Signs

The investigators provided individual animal clinical signs and dermal reactions. No adverse clinical sings were noted. There was slight to moderate dermal irritation observed.

3. Body Weights

The investigators provided individual animal and mean body weights. No treatment related effects were noted. The following table presents the body weights and body weight gains (from Table 2, page 15 of the report):

Table I: Mean Body Weights and Body Weight Gains (grams)

Males Day: Dose (mg/kg):	0	7	0-7 gain	14	0-14 gain
			Males		
2000	2219(5)[n]	2375(5)	156(5)	2450(5)	232(5)
			Females		
2000	2375(5)	2544(5)	169(5)	2638(5)	263(5)

n = number of animals

66

4. Pathology

The investigators provided individual animal gross necropsy pathology findings. No treatment related effects were noted.

D. Conclusions

1. Investigators Summary:

From page 8 of the report:

The test material, CGA-77102 Technical, was evaluated for its acute dermal toxicity potential in male and female rabbits when administered as a single topical application at a level of 2,000 mg/kg of body weight. The estimated dermal LD_{50} for male and female rabbits was determined to be greater than 2,000 mg/kg. All animals appeared normal and exhibited body weight gain throughout the study. The test material produced slight to moderate dermal irritation. The gross necropsy at termination revealed no visible lesions.

2. Reviewers' Conclusions:

The Acute Dermal LD_{50} for CGA-77102 Technical is greater than 2000 mg/kg for both sexes. **Toxicity Category III.**

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/7/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 5/9/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Inhalation Toxicity - Rat
Species: Rat Guideline: §81-3

EPA ID No.s: EPA MRID No. 43928917
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: M.S. Holbert (1995): CGA-77102 Technical, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Study Number 1970-95, August 22, 1995 (Unpublished); EPA MRID Number 43928917.

Executive Summary: In an acute inhalation toxicity study (MRID# 43928917), 5 male and 5 female rats (females were nulliparous and non-pregnant, Strain: HSD:Sprague-Dawley; Source: Harlan Sprague Dawley, Inc., Houston, Texas) were exposed by the nose only route to a generated aerosol of CGA-77102 Technical from undiluted liquid at a level of 2.91 mg/L (Purity: 97.6%; Batch 408001).

The Acute Inhalation LC_{50} for CGA-77102 Technical is greater than 2.91 mg/L for both sexes. The particle size distribution (MMAD) was 3.456 µm. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

68

A. Materials and Methods

Test Compound: CGA-77102 Technical
Purity: 97.6% purity
Description: Brown liquid
Lot No.: FL-950233; Batch 408001
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Male and Female Rats (females were nulliparous and non-pregnant)
Strain: HSD:Sprague-Dawley
Source: Harlan Sprague Dawley, Inc., Houston, Texas
Age: Young adult (8-12 wks)
Body Weight: Males (192-218 g); Females (205-232 g)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the acute inhalation toxicity potential of the test material in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-3, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No. S9-FF81-3.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study.

The study was initiated on April 7, 1995, and the animals were exposed to the test material on June 2, 1995, at 11:20 A.M. The in-life portion of the study was terminated on June 16, 1995.

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	One per cage
Environmental Controls Set to Maintain:	Temperature Range: 72° ± 5°F Humidity Range: 30-80% 12-hour light/dark cycle 10-12 air changes/hour
Transfer to Clean Cages:	Weekly
Litter Pan Lining:	Paper and aspen bedding
Litter Pan Lining Change:	Three times weekly
Food:	Purina Formulab Chow #5008, available *ad libitum* except during the exposure period
Water Type:	Municipal water supply from automatic water system, available *ad libitum* except during the exposure period

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Procedures

From page 7-9 of the report:

Prestudy Testing
Trial assays were conducted to determine which method(s) of aerosolizing the test material into the exposure chamber would produce an acceptable concentration and mass median aerodynamic diameter (MMAD).

Exposure Chamber
A 500 L nose-only stainless steel, dynamic flow inhalation chamber was utilized in this experiment [provided in a diagram in the report]. The body of the chamber has 25 ports in 5 rows. Polycarbonate cones are inserted into 10 designated individual ports. The test material is introduced through the opening in the top of the chamber. The bottom section has a corresponding air outlet and a drain valve for cleaning the chamber. The individual polycarbonate cones (tubes) are tapered at one end to fit the shape of the animal's head and the back portion is sealed with a polycarbonate cap. The cones containing the animals fit tightly into the ports, and are sealed with "O" rings.

Generation of Test Atmosphere
The aerosol was generated by pumping the test material into a pressure operated Spraying System Company air atomizer (1/4 JSS) and then spraying the resulting aerosol directly into the exposure chamber. Air flow into the chamber was maintained through the use of a calibrated critical orifice at a rate of 13.6 air changes per hour. Air flow was recorded at 30 minute intervals during the exposure period, and was sufficient to ensure an oxygen content of at least 19% of the exposure atmosphere. Temperature and humidity were recorded at 30 minute intervals during the exposure period from a Taylor wet bulb/dry bulb hygrometer located in the exposure chamber.

Test Material Administration
Healthy albino rats were released from quarantine, and five males and five females were selected for testing. The animals were exposed to an aerosol generated from the undiluted liquid test material for a period of four hours. During the exposure period, the animals were individually housed in polycarbonate containers inserted into a 500 L stainless steel nose-only chamber when 99% concentration (T-99) was attained. At the termination of the exposure period, the animals were returned to their stock laboratory cages.

Determination of Concentration
The concentration of test material in the exposure atmosphere (taken from the breathing zone of the animals) was determined analytically once per hour, and nominally at the end of the exposure. The analytical determination was made using a Beckman System Gold HPLC with Autoinjector [HPLC operating parameters provided in Appendix A of the report]. The nominal concentration was determined by dividing the loss in weight of the test material after the exposure by the total volume of air which passed through the chamber.

Particle Size Distribution
Particle size, taken from the breathing zone of the animals, was determined twice during the exposure, using an Andersen cascade impactor, at a rate of 28.3 L/minute for a duration of 2 minutes. The MMAD and particle size distributions are calculated from these data.

In-life Observations
Observations for mortality and signs of pharmacologic and/or toxicologic effects were made frequently on the day of exposure and at least once daily thereafter for 14 days (day of exposure considered Day 0). Individual body weights were recorded just prior to the inhalation exposure and on Days 7 and 14, or at the time of discovery after death.

Postmortem Observations
At study termination, each surviving animal was euthanized by an injection of Fatal Plus (Vortech Pharmaceuticals, Dearborn, Michigan 48126). All study animals were subjected to gross necropsy and all abnormalities were recorded.

Statistical Analysis
In order to calculate a mean exposure, the Mean Value Theorem of Calculus was used to properly weight the concentration, since the concentrations could not be measured continuously [data provided]. This method weights concentrations based on the time span of each concentration. A concentration can be calculated for each minute, which better represents the exposure concentration received by each animal.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-3.

C. Results:

1. Mortality

The investigators provided individual animal survival. One male and one female were reported to have died during the study, the male at 2.5 hours and the female on study day 3. At necropsy both animals had signs of nasal discharge, salivation and polyuria. The acute inhalation LC_{50} for CGA-77102 Technical is greater than 2.91 mg/L.

2. Clinical Signs

The investigators provided group summary and individual animal data. Clinical signs included nasal discharge noted at 4.5 hours to Day 4 in males and 4.5 hours to Day 6 in females. Polyuria was noted at 4.5 hours to Day 1 in both sexes, ptosis was noted at Day 1 in males and Days 1 to 4 in females, respiratory gurgle was noted at 4.5 and 6 hours in both sexes, salivation was noted at 4.5 hours to Day 1 in males and at 4.5 and 6 hours in females, fur coated with urine/feces was noted at 0.5 hours to Day 6 in both sexes, and activity decrease and piloerection were noted at 4.5 hours to Day 11 in both sexes.

3. Body Weights

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

4. Pathology

The investigators provided individual animal gross necropsy findings. No treatment related effects were noted. The only findings noted were in the animals that died (see mortality section above).

5. Inhalation Chamber Conditions

The investigators provided individual half-hour chamber operating parameters. The mean chamber operating parameters were 75°F, 72% relative humidity and the airflow was 113 Lpm. The investigators provided analytical concentration determinations and calculations and particle size distribution determinations. The mean exposure concentration was 2.91 mg/L, the nominal concentration was 11.1 mg/L. The particle size distribution (MMAD) was 3.456 µm.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

CGA-77102 Technical was evaluated for its acute inhalation toxicity potential in albino rats. Five males and five females were exposed for four hours in a nose-only inhalation system to an aerosol generated from the undiluted liquid test material at a level of 2.91 mg/L. One male and one female died during the study. Clinical signs of toxicity included activity decrease, nasal discharge, piloerection, polyuria, ptosis, respiratory gurgle and salivation, which were no longer evident by Day 12. Body weights of surviving animals were unaffected by exposure. Abnormal necropsy findings were exhibited only in the animals that died, and pertained to the lungs and contents of the stomach. As indicated by the data, the acute inhalation LC_{50} for CGA-77102 Technical is greater than 2.91 mg/L.

2. Reviewers' Conclusions:

The Acute Inhalation LC_{50} for CGA-77102 Technical is greater than 2.91 mg/L for both sexes. The particle size distribution (MMAD) was 3.456 µm. **Toxicity Category IV.**

ALPHA METOLACHLOR **PRIMARY EYE IRRITATION - RABBITS §81-4**

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/2/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)
Secondary Review by: Nancy E. McCarroll Nancy E McCarroll 5/9/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Eye Irritation - Rabbit
Species: Rabbit Guideline: §81-4

EPA ID No.s: EPA MRID No. 43928918
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.M. Glaza (1994): CGA-77102 Technical, FINAL REPORT, Primary Eye Irritation Study of CGA-77102 Technical in Rabbits, Hazleton Wisconsin, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: HWI 40702452, October 5, 1994 (Unpublished); EPA MRID Number 43928918.

Executive Summary: In a primary eye irritation study (MRID# 43928918), 6 male and 3 female (nonwashed) and 3 female ("washed") albino rabbits (Strain: New Zealand White from Ray Nichols Rabbitry, Lumberton, Texas) received 0.1 mL CGA-77102 Technical (Purity: 95.4% active ingredient; Lot Number FL-941255; Batch Code V.4673/7) to one eye (the other serving as untreated control). Two groups were used, one group (6 animals) with the eyes unwashed, the other group (3 animals) had the eyes washed for 1 minute with lukewarm water 30 seconds after test compound instillation.

CGA-77102 Technical produced slight to moderate conjunctival irritation to washed and unwashed eyes. Irritation cleared by 48 hours after treatment. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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: 95.4% active ingredient
Description: Brown liquid
Lot Number: FL-941255; Batch Code V.4673/7
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbits
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: Not provided, "young adult"
Body Weight: 2317-2811 g
Acclimation Period: At least five days

B. Study Design

From pages 5 and 8 of the report:

The objective of this study was to assess the relative level of irritation produced following a single exposure of the test material to one eye of albino rabbits.

Study Timetable

In-life Start Date	August 1, 1994
In-life Termination Date	August 4, 1994

1. Animal Husbandry and Assignment

From page 9 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in screen-bottom stainless steel cages in temperature- and humidity-controlled quarters. Environmental controls for the animal room were set to maintain a temperature of 19° to 23°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from the required temperature and humidity conditions existed, they were documented and considered to have had no adverse effect on the study outcome. Animal husbandry and housing at HWI complied with the standards outlined in the "Guide for the Care and Use of Laboratory Animals."

The animals were provided access to water ad libitum and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental

contaminants. Samples of the water are periodically analyzed by HWI. There were no known contaminants in the feed or water at levels that would have interfered with or affected the results of the study.

Six male and three female healthy, acclimated rabbits, weighing from 2,317 to 2,811 g, were selected at random and identified by animal number and corresponding ear tag. The animals' eyes were examined on the day before test material administration using sodium fluorescein dye procedures. Only those animals with no sign of ocular injury or irritation were used. The rabbits were divided into two groups consisting of six rabbits in Group 1 and three rabbits in Group 2.

2. Dose Preparation and Administration

From page 10 of the report:

The test material was administered as received. The pH of the test material was not able to be determined.

Each rabbit received 0.1 mL of the undiluted test material placed into the everted lower lid of the right eye, with the left eye serving as the untreated control. The upper and lower lids were gently held together for 1 second to prevent loss of material and then released. The eyes of the Group 1 rabbits remained unflushed following instillation of the test material. The eyes of the Group 2 animals were flushed with lukewarm tap water for 1 minute starting 30 seconds after test material instillation.

3. Observations

From page 10 of the report:

Animals were weighed just before test material administration.

The treated eyes of both groups were observed for ocular irritation at 1, 24, 48, and 72 hours after treatment. Irritation was graded and scored according to the Draize technique. A sodium fluorescein examination was used to aid in revealing possible corneal injury at 72 hours. The investigators provided an ocular irritation scoring scale based on the method of Draize as an appendix to the report.

At termination of the experimental phase, all animals were euthanized and discarded.

4. Statistical Analyses

From page 10 of the report:

No statistical analyses were required by the protocol.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-2.

C. Results:

1. Eye Irritation

The investigators provided group summary and individual animal data for eye irritation. No sodium fluorescein staining was noted in either group. The following table presents the summarized eye irritation scores (from Table 1, page 13 of the report):

Table I: Average Primary Eye Irritation Scores[a]

Observation Period (hour)	Average Score (out of 20) Group 1	Group 2
1	4.0	4.7
24	1.0	0.7
48	0.0	0.0
72	0.0	0.0

[a] = The average primary eye irritation score is the total eye irritation score for all the animals divided by the number of animals in each group (6 for Group 1 or 3 for Group 2) at each observation period out of a total of 20.

2. Body Weights

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

D. Conclusions

1. Investigators Summary:

From page 8 of the report:

The primary eye irritation potential of CGA-77102 Technical was evaluated when instilled into the eyes of nine rabbits, six with treated eyes unwashed and three with treated eyes washed approximately 30 seconds after instillation. The test material produced slight to moderate conjunctival irritation in washed and unwashed eyes which cleared in all animals by 48 hours after treatment.

2. Reviewers' Conclusions

In a Primary Eye Irritation study, CGA-77102 Technical produced slight to moderate conjunctival irritation to washed and unwashed eyes. Irritation cleared by 48 hours after treatment. Toxicity Category III.

ALPHA METOLACHLOR **PRIMARY DERMAL IRRITATION - RABBITS §81-5**

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/2/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 5/9/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Dermal Irritation - Rabbit
Species: Rabbit Guideline: §81-5

EPA ID No.s: EPA MRID No. 43928919
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.M. Glaza (1994): CGA-77102 Technical FINAL REPORT Primary Dermal Irritation Study of CGA-77102 Technical in Rabbits, Hazleton Wisconsin, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation; Laboratory Project Identification: HWI 40702451, October 5, 1994 (Unpublished); EPA MRID Number 43928919.

Executive Summary: In a primary dermal irritation study (MRID# 43928919), 3 male and 3 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.5 mL CGA-77102 Technical (Purity: 95.4% purity; Lot Number FL-941255 (Batch Code V.4673/7)) to the shaved backs of each animal.

CGA-77102 Technical produced very slight to well-defined erythema and very slight to slight edema reactions at the application site. Desquamation was also observed in one animal. The mean PIS for the 4, 24, 48, and 72-hour scores was 1.8. No irritation was seen by observation day 7. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA, CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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: 95.4% purity
Description: Brown liquid
Lot Number: FL-941255 (Batch Code V.4673/7)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbits
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: Not provided, "young adult"
Body Weight: 2417 to 2481 g

B. Study Design

From pages 5 and 8 of the report:

The objective of this study was to assess the relative level of primary skin irritation of a test material on rabbits under semioccluded conditions.

Study Timetable

In-life Start Date	July 28, 1994
In-life Termination Date	August 4, 1994

1. Animal Husbandry and Assignment

From page 9 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in screen-bottom stainless steel cages in temperature- and humidity-controlled quarters. Environmental controls for the animal room were set to maintain a temperature of 19° to 23°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from the required temperature and humidity conditions existed, they were documented and considered to have had no adverse effect on the study outcome. Animal husbandry and housing at HWI complied with the standards outlined in the "Guide for the Care and Use of Laboratory Animals.

The animals were provided access to water *ad libitum* and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed by HWI. There were no known contaminants in the feed or water at levels that would have

interfered with or affected the results of the study.

Three male and three female healthy, acclimated rabbits, weighing from 2,417 to 2,481 g, were selected at random and identified by animal number and corresponding ear tag. On the day before treatment, the back and/or flanks of each animal were clipped free of hair to obtain an unblemished skin site.

2. Dose Preparation and Administration

From page 10 of the report:

The test material was administered as received. The pH of the test material was not able to be determined.

The test material was applied to the intact skin on each animal's back (approximate exposure area of 6.25 cm^2) in the amount of 0.5 mL. The area of application was covered with a 2.5 cm X 2.5 cm gauze patch secured with paper tape, loosely overwrapped with Saran Wrap® and secured with Elastoplast® tape to provide a semiocclusive dressing. Collars were not used to restrain the test animals during the 4-hour exposure period.

At the end of the 4-hour exposure period, the patches were removed and the test sites were washed using liquid Ivory® soap mixed with warm tap water, rinsed with clean tap water, and dried with disposable paper towels. The test material was removed from the test sites as thoroughly as possible without irritating the skin.

3. Observations

From page 10 of the report:

Animals were weighed just before test material administration and at Day 7.

Approximately 30 minutes after removal of the test material, the degree of erythema and edema at each test site was read according to the Draize technique (recorded as the 4-hour score). Subsequent examinations were made at 24, 48, 72, and 96 hours and Day 7. The untreated skin of each animal was used for comparison.

The investigators provided an ocular irritation scoring scale which is based on the method of Draize as an appendix to the report.

4. Statistical Analyses

From page 11 of the report:

No statistical analyses were required by the protocol.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-5.

C. Results:

1. Dermal Irritation

The investigators provided group summary and individual animal data for erythema and edema dermal irritation. The following table presents the summarized dermal irritation scores (from Table 3, page 14 of the report):

Table I: Mean Primary Dermal Irritation Scores[a]

Observation Period	Average Score (PIS)
4 Hour	2.7
24 Hour	1.8
48 Hour	1.3
72 Hour	1.3
96 Hour	0.5
Day 7	0.0

[a] = The average primary dermal irritation score is the total dermal irritation score for all the animals (erythema and edema) divided by the number of test sites (6) at each observation period.

2. Body Weights

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

D. Conclusions

1. Investigators Summary:

From page 8 of the report:

The primary dermal irritation potential of CGA-77102 Technical was evaluated in rabbits under 4-hour semioccluded conditions. The test material produced very slight to well-defined erythema and very slight to slight edema reactions. Desquamation was also observed at one test site. The average of the 4-, 24-, 48-, and 72-hour scores is 1.8 (considered to be slightly irritating). All irritation cleared by the Day 7 observation.

2. Reviewers' Conclusions

In a Primary Dermal Irritation study, CGA-77102 Technical produced very slight to well-defined erythema and very slight to slight edema reactions at the application site. Desquamation was also observed in one animal. The mean PIS for the 4, 24, 48, and 72-hour scores was 1.8. No irritation was seen by observation day 7. **Toxicity Category IV.**

012310

ALPHA METOLACHLOR **DERMAL SENSITIZATION - GUINEA PIGS §81-6**

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/7/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 5/9/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Dermal Sensitization - Guinea Pigs
Species: Guinea Pigs Guideline: §81-6

EPA ID No.s: EPA MRID No. 43928920
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.M. Glaza (1994): CGA-77102 Technical FINAL REPORT Dermal Sensitization Study of CGA-77102 Technical in Guinea Pigs - Closed Patch Technique, Hazleton Wisconsin, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: HWI 40702453, November 18, 1994 (Unpublished); EPA MRID Number 43928920.

Executive Summary: In a dermal sensitization study (MRID# 43928920), 10 young adult albino guinea pigs (Strain: Crl:(HA)BR from Charles River Laboratories, Inc., Portage, Michigan) received three induction doses and one challenge dose of 0.4 mL CGA-77102 Technical (Purity: 95.4% purity; Lot Number FL-941255 (Batch Code V.4673/7)) applied to an adhesive patch and placed on the shaved backs of each animal.

CGA-77102 Technical was a dermal sensitizer in guinea pigs tested with the closed patch technique.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

Compliance: A signed and dated STATEMENT OF NO DATA, CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

87

A. Materials and Methods

Test Compound: CGA-77102 Technical
Purity: 95.4% purity
Description: Brown liquid
Lot Number: FL-941255 (Batch Code V.4673/7)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Positive Control: 2,4-dinitrochlorobenzene
Source: Sigma Chemical Company, St. Louis, Missouri; Lot 41H08112; described as a yellow, crystalline powder. Purity of the material was 98.4%. The stability of the positive control mixtures under conditions of the test was determined by the investigators from a previous study. Analysis of the positive control mixtures for concentration, homogeneity/solubility, and stability was not done. The material was stored at room temperature.

Test Animal(s): Species: Young adult albino guinea pig
Strain: Crl:(HA)BR
Source: Charles River Laboratories, Inc., Portage, Michigan
Age: Not provided, "young adult"
Body Weight: 356-522 g

B. Study Design

From pages 5 and 8 of the report:

The objective of this study was to assess the delayed contact hypersensitivity potential of a test material in guinea pigs.

Study Timetable

In-life Start Date	July 27, 1994
In-life Termination Date	September 4, 1994

1. Animal Husbandry and Assignment

From pages 9-10 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in screen-bottom stainless steel cages in temperature- and humidity-controlled quarters. Environmental controls for the animal room were set to maintain a temperature of 19° to 25°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations

83

from the required temperature and humidity conditions existed, they were documented and considered to have had no adverse effect on the study outcome. Animal husbandry and housing at HWI complied with standards outlined in the "Guide for the Care and Use of Laboratory Animals."

The animals were provided continuous access to Certified Guinea Pig Diet #5026, PMI Feeds, Inc., and water. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed by HWI. There were no known contaminants in the feed or water at levels that would have interfered with or affected the results of the study.

Twenty-eight healthy, acclimated male albino guinea pigs, identified by animal number and corresponding ear tag and weighing from 356 to 522 g, were selected and divided into four groups consisting of an irritation screening group of four animals, a test group of 10 animals, a naive control group of 10 animals, and a positive control group of four animals.

2. Study Protocol

From pages 10-11 of the report:

Irritation Screening Study
An irritation screening study using four animals was conducted to determine the irritation threshold of the test material. The test material was administered undiluted and at concentrations of 25%, 50%, and 75% w/v in mineral oil with each animal receiving two different concentrations of the test material. The appropriate test material concentrations, in the amount of 0.4 mL, were applied to Hill Top Chamber® patches. The patches were then placed on two shaved sites (one on the right and one on the left dorsal quadrants) on each animal, covered with an overlapping strip of dental dam, and overwrapped with Elastoplast® tape. The patches remained in place for 6 hours after which they were removed and the sites washed with lukewarm tap water and patted dry with a disposable paper towel. The application sites were observed for dermal reactions at approximately 24 and 48 hours after patch removal. The test material concentrations, dose volume and the method, frequency, and duration of administration were chosen based on the requirements of the test guidelines which are designed to mimic potential human exposure.

Definitive Study
Based on the results of the irritation screening study, the test material was administered undiluted for the induction phase and for the challenge application. All test and positive control mixtures used in the irritation screening or definitive phases of the study were stored at room temperature until administered.

Induction Phase. On the day of test material application, the hair was removed from the backs of each animal in the test and positive

control groups with electric clippers. The undiluted test material was applied to each animal in the test group by placing 0.4 mL on an adhesive patch (Hill Top Chamber®, 25-mm diameter) and placing the patch on the induction site along the dorsal anterior left quadrant. The patch was covered with dental dam and overwrapped with Elastoplast® tape. The dressing remained in place for a period of 6 hours after which it was removed and the induction site was washed with lukewarm tap water and patted dry with a disposable paper towel. The positive control material, 0.3% w/v 2,4-dinitrochlorobenzene (DNCB) in 80% v/v ethanol in deionized water, was administered to the positive control animals in the same manner used for the test material. The animals in the test and positive control groups received one application per week for 3 weeks for a total of three applications. Due to the strong irritation present in the induction site of the positive control animals, the third induction dose for these animals was applied to an induction site slightly posterior to the initial site. The naive control animals were not treated during this phase of the study.

Challenge Phase. Two weeks following the administration of the third induction dose, a challenge dose of 0.4 mL of the undiluted test material was administered along the dorsal anterior right quadrant of the test group animals in the same manner as during the induction phase of the study. At this time the 10 naive (previously untreated) control animals were also treated in the same manner with a challenge application of the test material. The positive control material was administered at a concentration of 0.1% w/v in acetone. The method used for the positive control group was the same as that of the test group.

3. Observations

From pages 11-12 of the report:

Approximately 3 hours before the 24-hour examination following the irritation screening and challenge applications, the application sites of the respective animals were depilated by applying Neet® depilatory for approximately 20 minutes, which was then washed off with lukewarm water.

The respective application sites were examined and scored for dermal reactions according to the Buehler scoring scale at approximately 24 and 48 hours following the irritation screening, induction, and challenge applications.

Buehler Sensitization Scoring Scale

No reaction	0
Very faint erythema, usually nonconfluent	0.5
Faint erythema, usually confluent	1.0
Moderate erythema	2.0
Strong erythema, with or without edema	3.0

Clinical observations were conducted daily throughout the study. Body weights on the irritation screening animals were determined only on the day of treatment. Body weights on the definitive animals were taken on Day 1, at weekly intervals throughout the study, and at termination of the experimental phase.

The animal that died during the study was subjected to an abbreviated gross necropsy examination and any abnormalities were recorded. After necropsy, the animal was discarded and no tissues were saved. At termination of the experimental phase, surviving animals were designated to be euthanized and discarded.

Evaluation of Challenge Responses
Determination of sensitization was based on the dermal reactions to the challenge dose. Grades of 1 or greater in the test animals may indicate evidence of sensitization, provided grades of less than 1 are seen in the naive control animals.

4. Statistical Analyses

From page 12 of the report:

No statistical analyses were required by the protocol.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-6.

C. Results:

1. Irritation Screening Phase

The investigators provided individual body weights and dermal reactions data. No dermal irritation was reported with any test compound concentration. No treatment related effects were noted in the animals of the irritation screening phase of the study.

2. Definitive Phase

a. Clinical Observations

The investigators provided individual clinical signs data, no relevant treatment related effects were noted. The single death occurring in the naive control group was not related to the test material.

b. Body Weights

The investigators provided individual body weights. Both the control group and treated animals lost weight during the last 2 day of the study. The investigators attributed this to...*the slight stress that the animals experienced due to the extra handling and procedures associated with the challenge dose.*

c. Dermal Reactions

i. Test Compound

The investigators provided individual dermal reaction scores for the test and naive control animals. No effect was noted after the first dose of the induction phase at 24 or 48 hours in the test animals. The second and third dose produced "very faint erythema, usually nonconfluent to moderate erythema" reactions in all test animals at 24 and 48 hours. The challenge phase produced "very faint erythema, usually nonconfluent" reactions in 3 control animals at 24 hours and 3 control animals (one different animal) at 48 hours. In the test animals, all exhibited "very faint erythema, usually nonconfluent to moderate erythema" reactions at 24 hours with 8 of the animals exceeding the control animal reactions and 9 out of 10 animals exhibiting "very faint erythema, usually nonconfluent to faint erythema, usually confluent" reactions at 48 hours with 3 of the animals exceeding the control animal reactions.

ii. Positive Control (DNCB)

The investigators provided individual dermal reaction scores for the positive control animals. The positive control animals exhibited reactions from "faint erythema, usually confluent to strong erythema, with or without edema" including some animals with "possible necrotic areas at all induction phase dosings and at challenge. According to the investigators: Historical data compiled at HWI have indicated that a 0.1% w/v concentration of DNCB in acetone does not produce irritation or causes very slight irritation in previously untreated animals when treated in the same manner as for the challenge application.

D. Conclusions

1. Investigators Summary:

From page 8 of the report:

The delayed contact hypersensitivity potential of CGA-77102 Technical was evaluated in albino guinea pigs. Very faint to moderate erythema reactions were observed in all 10 test animals when the test material was administered undiluted at challenge. Four of the nine surviving animals in the naive control group exhibited very faint erythema reactions to the challenge application of the undiluted test material. Eight of the challenge reactions in the test group exceeded the highest naive control reaction. Based on these results, this test material is considered to be a dermal sensitizer in guinea pigs. The death of the one naive control animal was not test material related.

2. Reviewers' Conclusions:

In a Dermal Sensitization study, CGA-77102 Technical was a dermal sensitizer in guinea pigs tested with the closed patch technique.

012310

ALPHA METOLACHLOR

DERMAL SENSITIZATION - GUINEA PIGS §81-6

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/2/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 5/9/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Dermal Sensitization - Guinea Pigs
Species: Guinea Pigs Guideline: §81-6

EPA ID No.s: EPA MRID No. 43928921
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.H. Marty (1994): CGA-77102 TECHNICAL SKIN SENSITIZATION TEST IN THE GUINEA PIG MAXIMIZATION TEST, Ciba Geigy Limited for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Study Number 941069, September 16, 1994 (Unpublished); EPA MRID Number 43928921.

Executive Summary: In a dermal sensitization study (MRID# 43928921), 10 male and 10 female albino Pirbright White Strain guinea pigs (Strain: Tif: DHP from CIBA-GEIGY Limited, Animal Production, 4332 Stein / Switzerland) received CGA-77102 Technical (Purity: 95.6% purity; Batch No. V.4673/7)) in a guinea pig maximization test.

CGA-77102 Technical was a dermal sensitizer in guinea pigs tested with the guinea pig maximization test.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

Compliance: A signed and dated STATEMENT OF NO DATA, CONFIDENTIALITY CLAIMS, CERTIFICATION OF GOOD LABORATORY PRACTICES Statement and Quality Assurance Statement were 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% purity
Description: Oily liquid
Batch No.: V.4673/7
Other provided information:
The test material was stored at room temperature.

Vehicle(s), etc.: Physiological saline (0.9 %), sterile solution (Hausmann, St. Gallen, Switzerland).
Bacto Adjuvant, Complete, Freund (Difco Lab. Detroit, Michigan USA)
Vaseline (white petrolatum) Ph. H. VI (Siegfried AG, Zofingen, Switzerland)
Oleum arachidis Ph. H. VI (Siegfried AG, Zofingen, Switzerland

Positive Control: Positive control studies were conduced 1-2 times a year, data were provided.

Test Animal(s): Species: Albino guinea pig
Strain: Pirbright White Strain (Tif: DHP)
Source: CIBA-GEIGY Limited, Animal Production, 4332 Stein / Switzerland
Age: Not provided
Body Weight: 335 to 431 g

B. Study Design

From page 11 of the report:

At the request of the Ciba Crop Protection of CIBA-GEIGY Limited, a sensitization test in albino guinea pigs was performed to determine the contact allergenic potency of CGA 77102 tech. in albino guinea pigs.

Experimental starting date: August 2, 1994
Experimental termination date: August 25, 1994

1. Animal Husbandry and Assignment

From pages 12-13 of the report:

The test was performed on a total of 10 male and 10 female guinea pigs in the test group and 5 males and 5 females in the control group, respectively, initially weighing between 335 to 431 g.

The animals were housed individually in Macrolon cages (Type 3), assigned to the different groups by means of random numbers generated by the random number generator, identified by individual ear tags, kept at a constant room temperature of 22±3°C, at a relative humidity of 30 to 70% and a 12 hours light cycle day.

The animals received ad libitum standard guinea pig pellets NAFAG No. 845, Gossau SG and fresh water.

All batches of the diet are assayed for nutritive ingredients and contamination level by the manufacturer. Analytical results are available at the animal supply office.

The drinking water quality fulfilled the critical parameters in the specifications of the "Schweizerisches Lebensmittelbuch" (Edition 1972). The results of the routine chemical examination of water at source (Grundwasserfassung stein) as conducted periodically by the water authority (Baudepartement des Kantons Aargau, Abteilung Gewaesserschutz) are available to CIBA-GEIGY Limited, as well as the results of in house chemical analysis by the analytical laboratories of the Pharmaceutical Division, CIBA-GEIGY Limited.

2. Study Protocol

From pages 14-15 of the report:

Intradermal Induction

The concentration for the intradermal injections was selected on account of the solubility of the test article in standard vehicles and its local and systemic tolerability in a pretest. The following concentration of test article has been used for intradermal injection:

5% in Oleum arachidis (w/v).

Since 5% CGA 77102 tech. in Oleum arachidis could be injected and was well tolerated, this concentration was used for the intradermal induction.

Epidermal Applications (induction and challenge)

The concentrations for the epidermal applications were selected on account of the primary irritation potential of the test article. The following concentrations of CGA 77102 tech. have been examined on separate animals for the determination of the maximum subirritant concentration [data provided]:

50, 60, and 80% in vaseline and the undiluted test article.

80% was the highest possible concentration of the test article in vaseline.

Reactions were observed with 60 and 80% CGA 77102 tech. in vaseline and with the undiluted test article.

DAY 0: INDUCTION, intradermal injections

Three pairs of intradermal injections (0.1 ml per injection) were made simultaneously into the left and right side of the shaved neck of the test and control group animals.

Test group:
- adjuvant/saline mixture 1:1 (v/v)
- 5% CGA 77102 tech. in Oleum arachidis (w/v)
- 5% CGA 77102 tech. in the adjuvant/saline mixture (w/v)

Control group:
- adjuvant/saline mixture 1:1 (v/v)
- adjuvant/saline mixture 1:1 (v/v)
- Oleum arachidis

DAY 8: INDUCTION, epidermal application

In the test group CGA 77102 tech: was applied on a filter paper patch to the neck of the animals (patch 2x4 cm; approx. 0.4 g per patch; occluded administration for 48 hours). The control group was treated with vaseline only.

Test group:
- 100% CGA 77102 tech.

Control group:
- vaseline only

DAY 21: Challenge

The test and control group animals were tested on one flank with CGA 77102 tech. in vaseline (w/w) and on the other flank with the vehicle alone (patch 2x2 cm; approx. 0.2 g per patch; occluded administration for 24 hours).

Test and control groups:
- 50% CGA 77102 tech. in vaseline
- vaseline only

3. Observations

From pages 15-16 of the report:

Induction reactions

After removal of the dressing on day 10, irritation of the epidermal application site was observed in 20/20 test group animals.

92

Challenge reactions

Twenty four and forty eight hours after removing the dressings, the challenge reactions were graded according to the Draize scoring scale [provided in the report].

General

The body weight was recorded at start and end of the test.

Interpretation of results

The sensitizing potential of CGA 77102 tech. was classified according to the grading of Magnusson and Kligman [provided in the report].

According to the guide to the labelling of dangerous substances and the criteria for the choice of sentences indicating particular hazards (R sentences) attributed to dangerous substances (Commission Directive 93/21/EEC, April 27, 1993) a test article was classified as a sensitizer in the case where a positive response was noted in at least 30 % of the animals.

4. Statistical Analyses

No statistical analyses were performed.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-6.

C. Results:

1. Induction (occlusive epidermal application)

No effects were noted in the control group at 24 and 48 hours for either vehicle control or test article. No effects were noted in the vehicle control of the test group at either 24 or 48 hours, while 18 out of 20 animals in the test article group had positive reactions at 24 hours and 20 out of 20 animals of the test article group with positive reactions at 48 hours.

2. Challenge (epidermal application)

No effects were noted in either vehicle control or test article control at 24 or 48 hours after removal of the dressing. The vehicle control of the test group showed no reactions at 24 and 48 hours after removal of the dressing while the test article group of the test group had 9/10 animals with erythema (grades 1-2) and edema (grades 1-2) in males and 9/10 females with erythema (grades 1-3) and 8/10 females with edema (grades 1-2) at 24 hours and all males and females with erythema (some with scaling) and 7/10 males with edema and 8/20 females with edema at 48 hours.

93

3. Primary skin irritation potential

Skin irritation occurred with the undiluted CGA 77102 technical at 60% concentrations and above while in vaseline, only the 100% was irritating to the skin.

4. Body Weights

The investigators provided individual body weights. No treatment related effects were noted.

D. Conclusions

1. Investigators Summary:

From page 11 of the report:

Under the experimental conditions employed, 90% and 100% of the animals of the test group showed skin reactions 24 and 48 hours after removing the dressings, respectively.

According to the maximization grading of Magnusson and Kligman CGA 77102 tech. showed an extreme grade of skin-sensitizing (contact allergenic) potential in albino guinea pigs.

2. Reviewers' Conclusions

In a Dermal Sensitization study, CGA-77102 Technical was a dermal sensitizer in guinea pigs tested with the guinea pig maximization test.

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 Acceptable-Guideline and satisfies the guideline requirements (§82-1a) for a subchronic feeding study in rats.

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: 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.

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

98

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:

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

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.

100

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			
Reticulocyte count*			

*Conducted on controls and high-dose groups although blood smears were prepared for all animals.

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.

101

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

102

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

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)

105

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

Dose (ppm):	0		10000	
Week				
		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.

106

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

107

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.

108

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.

110

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

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.

112

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.**

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. 4/11/97
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).

116

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

117

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

119

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.

120

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.

121

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

137

Urinalysis

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

*Semiquantitative

123

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

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

125

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):

127

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):

128

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	293.7±48.6

** = $p < 0.01$

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).

129

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.

ALPHA-METOLACHLOR **RABBIT TERATOLOGY**

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).

134

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

136

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).

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.

138

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.

139

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)

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

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

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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.

142

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.

144

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.

14

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.

c. Skeletal Examinations

Table VII: Skeletal Examinations[a]

The following table presents the skeletal examination data:

Dose (mg/kg/day):	0	20	100	500
Observations				
#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; * = $p < 0.007$.

14-7

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.

146

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.**

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 **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).

152

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.

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.

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.

154

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.

153

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

156

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.

159

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.

158

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.

160

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

161

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.

167

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	0	6	15	21
Dose (mg/kg/day):				
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	0-6	6-16	16-21	6-21	0-21[1]	C6-21[2]
Dose (mg/kg/day):						
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.

163

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

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

163

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

167

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

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

160

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.

171

CGA-77102 TECHNICAL **MICRONUCLEUS**

Principal Reviewer: Nancy E. McCarroll
Review Section III, Toxicology Branch
II/HED (7509C)
Signature: Nancy E. McCarroll
Date: 4/2/97

Secondary Reviewer: Stephen C. Dapson, Ph.D.
Review Section I,
Toxicology Branch II/HED (7509C)
Signature: Stephen C. Dapson
Date: 4/3/97

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: Mouse micronucleus assay; OPPTS 870.5395 [§84-2]

DP BARCODE: D226782 SUBMISSION NO.: S501353

PG CODE: 108800 TOX. CHEM. NO.: MRID NO: 43928926

TEST MATERIAL (PURITY): CGA-77102 Technical (95.6%)

SYNONYM(S): (S)-2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl) acetamide

CITATION: Hertner, Th. (1995) CGA-77102 Technical Micronucleus Test, Mouse (OECD Conform); CIBA-GEIGY Ltd, Basle, Switzerland; Study No. 941061; Study Completion Date: May 22, 1995. (Unpublished) MRID NUMBER: 43928926

SPONSOR: CIBA-GEIGY Corp., Greensboro, NC

EXECUTIVE SUMMARY: In a mouse micronucleus assay (MRID No: 43928926), groups of five male and five female Tif:MAGf(SPF) mice received single oral gavage administrations of 500, 1000 or 2000 mg/kg CGA 77102 technical (95.6%). The test material was delivered to the animals as suspensions prepared in arachis oil. Animals in the vehicle and high-dose group were sacrificed at 16, 24 and 48 hours postadministration and mid- and low-dose mice were sacrificed at 24 hours. Bone marrow cells were harvested from all experimental groups and examined for the incidence of micronucleated polychromatic erythrocytes (MPEs).

Toxic signs, similar to those seen in the preliminary range-finding studies (i.e., ataxia, tremors and/or hunched posture) were recorded for high-dose males and females throughout the 48-hour postexposure. No bone marrow cytotoxicity was seen at any dose or sacrifice time. The positive control induced the expected high yield of MPEs in males and females. There was, however, no evidence that CGA 77102 technical induced a clastogenic or aneugenic effect in either sex at any dose or sacrifice time.

The study is classified as Acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for in vivo cytogenetic mutagenicity data.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: CGA-77102 technical

Description: Oily liquid
Lot/batch number: V.4673/7
Purity: 95.6%
Receipt date: Not reported
Stability: Reported to be stable
CAS number: 87392-12-9
Structure: Not provided
Vehicle used: Arachis oil
Other provided information: The test material was stored at room temperature. Samples of the high and low dosing suspensions prepared for the micronucleus assay were analyzed to verify actual concentrations.

2. Control Materials:

Negative/Route of administration: None

Vehicle/Final concentration/Route of administration: Arachis oil was administered once by oral gavage at a dosing volume of 10 mL/kg.

Positive/Final concentration/Route of administration:
Cyclophosphamide (CP) was dissolved in double-distilled water and was administered once by oral gavage at 64 mg/kg.

3. Test Compound:

Route of administration: Oral gavage

Dose levels used:

(a) Range-finding studies:

Study I: 2000 and 3200 mg/kg (one male and one female)
Study II: 2000 mg/kg (one male and one female)

(b) Micronucleus assay: 500, 1000 and 2000 mg/kg

4. Test Animals:

(a) Species: Mouse; Strain: Tif:MAGf(SPF); Age (at dosing): 7-8 weeks

Weight range at dosing:
- range-finding studies: 30-39 g (males) 24-28 g (females);
- micronucleus assay: 27-34 g (males) 23-28 g (females)

Source: Animal Farm of CIBA-GEIGY, Sisseln, Switzerland

(b) Number of animals used per dose:

Range-finding studies: 1 male and 1 female per group

Micronucleus assay:

- Vehicle and high-treatment group: 15 ♂ 15 ♀
- Positive control and mid- and low-treatment groups: 5 ♂ 5 ♀

Note: A secondary group of 3 males and 3 females received the high dose of the test material and were used to replace animal in the primary groups that died prior to the scheduled sacrifice.

(c) Were test animals properly maintained? Yes.

B. TEST PERFORMANCE:

1. Range-finding Assay: Groups containing one male and one female mouse received single oral gavage administrations of the selected doses of the test substance. Animals were monitored for mortality and other clinical signs for 3 days. Body weights were recorded hourly for the first few hours and daily, thereafter, until termination. The findings were confirmed in a repeat study using one male and one female per dose as described.

2. Micronucleus Assay:

(a) Treatment and sampling times:

1. Test compound (high dose) and vehicle control:
Dosing: x once _____ twice (24 hours apart)
_____ other (describe):

Sampling (after last dose): _____ 6 hours x 16 hours
x 24 hours x 48 hours ___ 72 hours

2. Test compound (mid and low dose) and positive control:
Dosing: x once _____ twice (24 hours apart)
_____ other (describe):

Sampling (after last dose):

__x__ 24 hours ____ 48 hours ____ 72 hours

3. Tissues and Cells Examined:

__x__ bone marrow ____ other (list):
Number of polychromatic erythrocytes (PCEs) examined per animal: 1000
Number of normochromatic erythrocytes (NCEs, more mature RBCs) examined per animal: 1000 total erythrocytes.

4. Details of Cell Harvest and Slide Preparation: At 16, 24 and 48 hours after the administration of the high dose or the vehicle control, the appropriate groups of animals were euthanized by CO_2 asphyxiation. Animals in the mid- and low-treatment groups and the positive control group were sacrificed 24 hours postexposure. Bone marrow was harvested from both femurs of each animal with fetal calf serum (FCS). Cells were centrifuged, resuspended in FCS and dropped onto slides. Slides were stained with May-Grunwald/Giemsa and coded prior to scoring for micronuclei in polychromatic erythrocytes (MPEs) and determining the ratio of PCEs to NCEs.

5. Statistical Methods: The data were analyzed by the Chi-squared contingency test at F=1, $p<0.05$.

6. Evaluation Criteria:

Assay validity: The assay was considered acceptable if: 1) the mean number of MPEs in the vehicle control group was ≤0.2%; 2) the positive control was genotoxic and 3) the highest applied concentration represented the maximum tolerated dose (MTD), the solubility limit of the test substance or a limit dose of 2000 mg/kg.

Positive response: The test material results were considered positive if the mean number of MPEs in any group exceeded 0.2% and if there was a statistically significant ($\chi^2 \leq 3.84$) increase in MPEs compared to the concurrent vehicle control.

C. REPORTED RESULTS:

1. Range-finding Studies: In the initial study, the test material was administered once to groups of one male and one female mouse at 2000 or 3200 mg/kg. Both high-dose animals succumbed to treatment one day postdosing. Signs of ataxia, tonic spasm and tremors, which were recorded for the female administered 2000 mg/kg, were resolved within one day. No clinical signs were noted in the males. Ataxia, tremors and hunched posture were also observed in the single male and female treated with 2000 mg/kg in the confirmatory study. Based on the overall results, 2000 mg/kg was chosen as the high dose for the micronucleus assay. Lower concentrations of 500 and 1000 mg/kg were also processed.

2. Micronucleus Assay:

a. Analytical determinations: High and low dosing suspensions prepared for the micronucleus assay were found to contain ≥90% of the target concentrations.

b. Animal observations: Signs of compound toxicity similar to those seen in the preliminary studies (i.e., ataxia, tremors and/or hunched posture) were recorded for high-dose males and females throughout the 48-hour postexposure period. Lower doses were not toxic.

c. Bone marrow analysis: Representative data are presented in Table 1. As shown, PCE:NCE ratios for males and females of the treatment groups were generally comparable to the values for vehicle control at all harvest times. No significant increase in the incidence of MPEs either by sex or combined for both sexes was seen in bone marrow cells harvested 16, 24 or 48 hours following adminstration of 2000 mg/kg. Results for the lower dose groups were also negative. By contrast, the positive control (64 mg/kg CP) induced significant ($p<0.05$) genotoxic effects in both sexes.

Based on the overall results, the study author concluded that CGA-77102 technical was negative in this in vivo mouse micronucleus assay.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We agree with the study author's conclusion that CGA-77102 technical was neither clastogenic nor aneugenic in this mouse micronucleus assay. The clear demonstration of a reproducible toxic response at the high dose (2000 mg/kg) indicates that a adequate range of treatment levels were evaluated. There was, however, no evidence that the test material reached the target organ in a potentially genotoxic concentration. Nevertheless, the response induced by the positive control demonstrated that an adequate level of assay sensitivity was achieved. Based on the above considerations, we assess that the data support the conclusion that CGA-77102 technical was negative in this in vivo test system.

E. STUDY DEFICIENCIES: NONE.

176

TABLE 1. Representative Results of the Micronucleus Assay in Mice Treated with CGA-77102 Technical

Substance	Dose/kg	Exposure Time[a] (hours)	Sex	Number of Animals Analyzed per Group	Number of MPEs per Group	Percent MPEs per group	PCE/NCE Ratio
Vehicle Control							
Arachis oil	10 mL	16	M	5	5	0.10	0.87
			F	5	3 (8)[b]	0.06 (0.08)[b]	0.92
		24	M	5	2	0.04	0.83
			F	5	4 (6)	0.08 (0.06)	0.79
		48	M	5	2	0.04	0.77
			F	5	5 (7)	0.10 (0.07)	0.80
Positive Control							
Cyclophosphamide	64 mg	24	M	5	79	1.58*	0.86
			F	5	75 (154)	1.50*(1.54)*	0.89
Test Material							
CGA-18809 technical	2000 mg[c]	16	M	5	4	0.08	0.84
			F	5	3 (7)	0.06 (0.07)	0.74
		24	M	5	4	0.08	0.84
			F	5	4 (8)	0.08 (0.08)	0.82
		48	M	5	4	0.08	0.79
			F	5	4 (8)	0.08 (0.08)	0.82

[a] Time after compound administration by oral gavage
[b] Values in ( ) are the combined results for both sexes.
[c] Results for the low- (500 mg/kg) and mid-(1000 mg/kg) dose groups did not suggest a positive effect.

*Significantly higher ($p<0.05$) than the corresponding vehicle control by the χ^2 test.

Abbreviations used:

PCE = Polychromatic erythrocytes
MPE = Micronucleated polychromatic erythrocytes
NCE = Normochromatic erythrocytes

Note: Data were extracted from the study report, Tables 3-5, pp 29-31.

CGA-77102 TECHNICAL **SALMONELLA/ESCHERICHIA COLI**

Principal Reviewer: Nancy E. McCarroll
Review Section III, Toxicology Branch
II/HED (7509C)
Signature: Nancy E. McCarroll
Date: 3/28/97
Secondary Reviewer: Stephen C. Dapson, Ph.D.
Review Section I,
Toxicology Branch II/HED (7509C)
Signature: Stephen C. Dapson
Date: 3/28/97

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: Salmonella typhimurium / Escherichia coli--mammalian microsome mutagenicity assay; OPPTS 870.5100/5265 [§84-2]

DP BARCODE: D226782 SUBMISSION NO.: S501353

PC CODE: 108800 TOX. CHEM. NO.: MRID NO: 43928927

TEST MATERIAL (PURITY): CGA-77102 Technical (95.6%)

SYNONYM(S): (S)-2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl) acetamide

CITATION: Hertner, Th. (1995) CGA-77102 Technical Salmonella and Escherichia/Mammalian-Microsome Mutagenicity Test; CIBA-GEIGY Ltd, Basle, Switzerland; Study No. 941060; Study Completion Date: June 9, 1995. (Unpublished) MRID NUMBER: 43928927

SPONSOR: CIBA-GEIGY Corp., Greensboro, NC

EXECUTIVE SUMMARY: In independently performed microbial mutagenicity assays (MRID No. 43928927), Salmonella typhimurium TA1535, TA1537, TA98, TA100 and TA102 and Escherichia coli WP2 uvrA were initially exposed to 312.5-5000.0 µg/plate CGA-77102 technical (95.6%) in the presence and absence of S9 activation. For the confirmatory trial, doses of 78.13-1250.0 µg/plate +/-S9 were evaluated with S. typhimurium strains TA1535, TA1537, TA100 and TA102; concentrations of 312.5-5000.0 µg/plate +/-S9 were examined with S. typhimurium TA 98 and E.coli WP2 uvrA. The S9 fraction was derived from Aroclor 1254 induced rat livers and the test material was delivered to the test system in dimethyl sulfoxide.

In general, doses ≥1250.0 µg/plate +/-S9 were cytotoxic for S. typhimurium TA1535, TA1537, TA100 and TA102 and 5000.0 µg/plate +/-S9 was slightly cytotoxic for S. typhimurium TA98 and E. coli WP2 uvrA. The nonactivated and S9-activated positive controls induced the expected mutagenic response in the corresponding tester strain. **There was, however, no indication that CGA-77102 technical induced of a mutagenic effect in any tester strain either in the presence or the absence of S9 activation.**

The study is classified as Acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for microbial gene mutation mutagenicity data.

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

178

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: CGA-77102 technical

Description: Oily liquid
Lot/batch number: V.4673/7
Purity: 95.6%
Receipt date: Not reported
Stability: Reported to be stable under the conditions of use.
CAS number: 87392-12-9
Structure: Not provided
Solvent used: Dimethyl sulfoxide (DMSO)
Other provided information: Storage conditions for the test material were not reported. Samples of the lowest dosing solutions used in each mutagenicity assay were analyzed to verify actual concentrations.

2. Control Materials:

Negative: None

Solvent/final concentration: DMSO/0.1 mL per plate

Positive:

Nonactivation:

Sodium azide	5.0	µg/plate TA1535, TA100
2-Nitrofluorene (2-NF)	20.0	µg/plate TA98
9-Aminoacridine (9-AA)	150.0	µg/plate TA1537
Mitomycin C (Mit C)	2.0	µg/plate TA102
4-Nitroquinoline (4-NQO)	2.0	µg/plate WP2 uvrA

Activation:

2-Aminoanthracene (2-AA)	2.5	µg/plate TA1537, TA98, TA100
	20.0	µg/plate TA102
	50.0	µg/plate E. coli WP2 uvrA
Cyclophosphamide (CP)	400.0	µg/plate TA1535

3. Activation: S9 derived from male Tif:RAIf[SPF]

x Aroclor 1254	x induced	x rat	x liver
_____ phenobarbital	_____ noninduced	_____ mouse	_____ lung
_____ none		_____ hamster	_____ other
_____ other		_____ other	

The S9 homogenate was prepared by the testing laboratory and was found to contain 32.22 mg/mL protein.

179

S9 mix composition:

Component:	Concentration/mL
Na phosphate buffer, pH 7.4	100 μM
Glucose-6-phosphate	5 μM
NADP	4 μM
KCl	33 μM
$MgCl_2$	8 μM
S9	10%

4. Test Organism Used: S. typhimurium strains
_____ TA97 __x__ TA98 __x__ TA100 __x__ TA102 _____ TA104
__x__ TA1535 __x__ TA1537 ___ TA1538
list any others: ~~E. coli~~ WP2 uvrA

Test organisms were properly maintained? Yes.
Checked for appropriate genetic markers (rfa mutation, R factor)? Yes.

5. Test Compound Concentrations Used:

(a) Preliminary Cytotoxicity assay: Six doses (20.58, 61.73, 185.19, 555.56, 1666.67 and 5,000.00 μg/plate) were evaluated with strains TA100 and WP2 uvrA in the presence and absence of S9 activation; single plates were used per dose, per strain, per condition.

(b) Mutation assays:

Initial Trial: Five doses (312.5, 625.0, 1250.0, 2500.0 and 5000.0 μg/plate) were evaluated in the presence and absence of S9 activation with all Salmonella tester strains and the E. coli strain.

Confirmatory Trial: Nonactivated and S9-activated doses comparable to those listed above for the initial mutation assay trial were investigated with S. typhimurium TA98 and the E. coli strain. For strains TA1535, TA1537, TA100 and TA102, doses of 78.13, 156.25, 312.50, 625.00 and 1250.00 μg/plate +/-S9 were evaluated.

B. TEST PERFORMANCE:

1. Type of Salmonella Assay: __x__ Standard plate test
_____ Pre-incubation (_____) minutes
_____ "Prival" modification
_____ Spot test
_____ Other (describe)

2. Protocol: Similar procedures were used for the preliminary cytotoxicity and the mutation assays. A 0.1 mL aliquot of overnight broth cultures of the appropriate tester strain, 0.1 mL of the appropriate test material dose, solvent, or positive control and either 0.5 mL of phosphate buffer (nonactivated series) or 0.5 mL of the S9-cofactor mix

(S9-activated series) were mixed with 2.0 mL volumes of molten top agar supplemented with L-histidine and biotin (S. typhimurium strains) or tryptophan (E. coli strain). The contents of the tubes were mixed, poured over Vogel-Bonner Medium E plates and incubated at 37±1.5°C for ≈48 hours. At the end of incubation, revertant colonies were counted and the condition of the background lawn of growth was examined. Means and standard deviations for the mutation tests were determined from the counts of triplicate plates per strain, per dose, per condition.

3. Evaluation Criteria:

(a) Assay validity: The assay was considered acceptable if (1) the number of spontaneous revertants for each tester strain was within the provided historical control ranges and (2) the nonactivated and S9-activated positive controls induced responses that met the criteria for a positive effect (see below).

(b) Positive response: The test material was considered positive if it caused a reproducible dose-related increase in the mean number of revertants per plate of at least one strain. This increase must be at least 2-fold in strains TA1535, TA1537, TA98 or WP2 uvrA or at least 1.5-fold in strains TA100 or TA102.

C. REPORTED RESULTS:

1. Solubility Determination: The test substance was found to be soluble in DMSO at 50 mg/mL; accordingly, this concentration was selected as the maximum dose to be evaluated in the preliminary study.

2. Preliminary Cytotoxicity Assay: Six doses of the test material ranging from 20.58 to 5,000.00 µg/plate were evaluated with and without S9 activation using strains TA100 and WP2 uvrA. No compound precipitation was seen at any level. At 5000 µg/plate +/-S9, reductions in revertant colonies and/or the background lawn of growth were recorded for both strains. Cytotoxicity was not evident at lower doses with or without S9 activation. Based on these findings, the initial mutation assay was conducted with a dose range of 312.50-5000.0 µg/plate +/-S9.

3. Mutation assays:

Initial trial: Summarized results of the initial trial are presented in Study Report Tables 5 and 6, pp. 27 and 28 (see Addendum I). As shown, CGA 77102 technical at ≥2500.0 µg/plate +/-S9 caused a marked reduction in the revertant colonies of S. typhimurium strains TA1535, TA1537, TA100 and TA102. With the exception of TA1535, cytotoxicity was also observed in the above strains at 1250 µg/plate +/-S9. Cytotoxicity was less pronounced in S. typhimurium TA98 and E. coli WP2 uvrA, with reduced mutant colonies in the E. coli strain at 5000.0 µg/plate +S9 and in TA98 at ≥2500.00 µg/plate -S9 and 5000 µg/plate +S9. There was, however, no evidence of a mutagenic effect at any noncytotoxic dose in any strain or under any assay condition.

Confirmatory trial: Based on the above findings, concentrations of 78.13-1250.00 µg/plate +/-S9 were investigated with S. typhimurium strains TA1535, TA1537, TA100 and TA102. E. coli WP2 uvrA and TA98 were exposed to a dose range of 312.5-5000.0 µg/plate +/-S9. A slight decrease in revertant colonies and/or the background lawn of growth was achieved in the majority of strains at the corresponding high nonactivated or S9-activated dose (see Study Report Tables 7 and 8, pp. 29 and 30, Addendum II). In agreement with the earlier results, CGA-77102 technical was not mutagenic. By contrast to the lack of a mutagenic effect with the test material, all strains responded to the genotoxic action of the appropriate nonactivated and S9-activated positive controls.

Analytical determinations: The lowest dosing solutions prepared for the mutation assays were analyzed for actual concentrations and found to contain ≥95% of the intended concentrations.

Based on the overall findings, the study author concluded that CGA-77102 technical was not mutagenic in this test system.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We assess that the study was properly conducted and we concur with the study author's conclusion that CGA-77102 technical did not induced a mutagenic response in the S. typhimurium or E. coli strains up to cytotoxic levels. Additionally, the sensitivity of the test system to detect mutagenesis was adequately demonstrated by the responses induces in all tester strains. We conclude, therefore, that the study provided acceptable evidence that CGA-77102 technical was negative in this microbial test system.

E. STUDY DEFICIENCIES: None.

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ADDENDUM I

STUDY REPORT TABLES 5 AND 6; PP. 27 AND 28

183

RIA # 0785-01

DERs S-Metolachlor

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ADDENDUM II

STUDY REPORT TABLES 7 AND 8; PP. 29 AND 30

186

RIN# 0785-01

DERs 5-MeTolachlor

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CGA-77102 TECHNICAL **IN VIVO RDS/UDS**

Principal Reviewer: Nancy E. McCarroll
Review Section III, Toxicology Branch
II/HED (7509C)
Signature: Nancy E. McCarroll
Date: 4/2/97
Secondary Reviewer: Stephen C. Dapson, Ph.D.
Review Section I,
Toxicology Branch II/HED (7509C)
Signature: Stephen C. Dapson
Date: 4/3/97

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: Mutagenicity: In vivo/in vitro unscheduled DNA synthesis assay in primary rat hepatocytes assay; OPPTS 870.5550 [§84-2]

DP BARCODE: D226782 SUBMISSION NO.: S501353

PC CODE: 108800 TOX. CHEM. NO.: MRID NO: 43928928

TEST MATERIAL (PURITY): CGA-77102 Technical (95.6%)

SYNONYM(S): (S)-2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl) acetamide

CITATION: Hertner, Th. (1995) CGA-77102 Technical In Vivo/In Vitro Unscheduled DNA Synthesis In Rat Hepatocytes; CIBA-GEIGY Ltd, Basle, Switzerland; Study No. 941062; Study Completion Date: June 8, 1995. (Unpublished) MRID NUMBER: 43928928

SPONSOR: CIBA-GEIGY Corp., Greensboro, NC

EXECUTIVE SUMMARY: In an in vivo/in vitro replicative DNA synthesis (RDS)-unscheduled DNA synthesis (UDS) assay (MRID No. 43928928, groups consisting of three to four rats per sex received single oral gavage administrations of CGA-77102 Technical (95.6%) at doses of 500, 1500 or 5000 mg/kg (males) or 500, 1500 or 3200 mg/kg (females). Hepatocytes harvested at 15 and 38 hours were evaluated for viability and replicative DNA synthesis (RDS). For the UDS determination, additional groups (3/sex/dose) were exposed to 500 or 1500 mg/kg and the recovered hepatocytes were scored at 2 or 15 hours postexposure. The test material was delivered to the animals as suspensions prepared in arachis oil.

Two of four females in the 3200-mg/kg group and 2 of 4 males in the 5000-mg/kg group died prior to the scheduled sacrifice at 38 hours. Severe cytotoxicity was seen in the hepatocytes recovered from 1 of 2 surviving males and both female survivors in the high-dose groups. Lower levels were neither toxic to the animals nor cytotoxic to the target cells. The positive controls induced the expected marked increases in RDS or UDS. **A clear dose-related increase in the percentage of cells in S-phase (RDS) was obtained from hepatocytes harvested 38 hours posttreatment of the male rats. The response ranged from a 5.3-fold increase at 1500 mg/kg to a 16.1-fold increase at the high dose (5000 mg/kg). In females, a marked increase in RDS was initially seen at 1500 mg/kg but the response declined over time with a 24.4-fold increase at 15 hours and a 12.2-fold increase at 38 hours. There was, however, no evidence that the CGA 77102 Technical at doses of 500 or 1500 mg/kg induced a genotoxic response at 2 or 15 hours posttreatment. We conclude, therefore, that the data indicate that CGA 77102 Technical was negative for genotoxicity but positive for cellular proliferation when tested up to overtly toxic and cytotoxic doses in this in vivo/in vitro rat hepatocyte RDS/UDS assay.**

This study is classified as Acceptable and satisfies the guideline requirement for a UDS assay (84-4).

189

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

190

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: CGA-77102 technical

Description: Oily liquid
Lot/batch number: V.4673/7
Purity: 95.6%
Receipt date: Not reported
Stability: Reported to be stable under the conditions of use.
CAS number: 87392-12-9
Structure: Not provided
Vehicle used: Arachis oil
Other provided information: The test material was stored at room temperature and dosing suspensions were prepared fresh for each administration. Samples of the high and low dosing suspensions prepared for the RDS/UDS assay were analyzed to verify actual concentrations.

2. Control Materials:

Negative/Route of administration: None

Vehicle/Final concentration/Route of administration: Arachis oil was administered once by oral gavage at a dosing volume of 10 mL/kg.

Positive/Final concentration/Route of administration:

Unscheduled DNA synthesis (UDS) control: Dimethylnitrosamine (DMN) was dissolved in water and was administered once by oral gavage at 15 mg/kg (2-hour sacrifice).

Replicative DNA synthesis (RDS) control: 4-Acetylaminofluorene (4-AAF) was dissolved in arachis oil and was administered once by oral gavage at 1000 mg/kg (38-hour sacrifice).

3. Medium: Williams' Medium E (WME) containing 10% fetal bovine serum (FBS) and antibiotics.

4. Test Compound:

Route of administration: Oral gavage

19

Dose levels used:

(a) Range-finding studies:

Study I: 1250, 2000 and 3200 mg/kg (1 ♂ and 1 ♀)
Study II: 3200 mg/kg (1 ♂ and 1 ♀)
Study III: 4000 mg/kg (3 ♀); 5000 mg/kg (1 ♂ and 1 ♀)

(b) RDS assay: 500, 1500 and 5000 mg/kg (3 ♂/group + 1 additional high-dose animal)

500, 1500 and 3200 mg/kg (3 ♀/group + 1 additional high-dose animal)

(c) UDS assay: 500 and 1500 mg/kg (3 ♂ and 3 ♀/group)

5. Test Animals:

(a) Species: Rat; Strain: Tif:RAIf(SPF); Sprague-Dawley derived ;
Age: 6-12 weeks; Weight range: 152-348 g ;
Source: Animal Farm of CIBA-GEIGY, Sisseln, Switzerland

(b) Number of animals used per dose: See Section I A.4 a,b,c.
(c) Were test animals properly maintained? Yes.

B. TEST PERFORMANCE:

1. Range-finding Assays: Groups containing one male and one female mouse received single oral gavage administrations of the selected doses of the test substance. Animals were monitored for mortality and other clinical signs for 2 days. Body weights were recorded hourly for the first few hours and daily, thereafter, until termination. The findings were confirmed in two repeat studies (See above for the number of animals).

2. RDS/UDS Assays:

(a) Perfusion techniques/hepatocyte harvest: At ≈2, 15 or 38 hours postdosing, animals in the appropriate test material, vehicle or positive control groups were sacrificed and livers were perfused with Hanks' buffer solution (BSS) and with BSS containing 0.05% collagenase, 2 mM $CaCl_2$ and $NaHCO_3$. Livers were excised, placed into culture dishes containing BSS, antibiotics, 2 mM $CaCl_2$, 0.4 mM $MgSO_4$, 0.5% bovine serum albumin and $NaHCO_3$ and shaken to disperse the hepatocytes.

(b) Hepatocyte harvest/culture preparation: Recovered cells were filtered, resuspended in WME and counted, and aliquots (10^5 cells/mL) were seeded onto plastic coverslips in multi-well culture dishes. The cultures were allowed a 1.5-2-hour attachment period. Unattached cells were removed and viable cells were refed WME. Viable cells were incubated in fresh WME with 6-^{3}H-thymidine (10 μCi/mL) for 4 hours, washed and reincubated overnight in WME containing unlabeled thymidine. Cells were washed and fixed in ethanol:acetic acid (3:1); coverslips were mounted and autoradiographies were prepared from four slides per animal.

(c) Preparation of autoradiographies/grain development: Slides were coated with Ilford K.5 emulsion, exposed for 5 days at 4°C in air-

142

and light-proof boxes containing desiccants, developed in KodaK D-19, fixed in Hypam solution and stained with hematoxylin and eosin. The slides were coded prior to analysis.

(d) Grain counting:

RDS: The percentage of cells in S-phase (i.e., cells with >120 grains/nucleus) was determined from the count of 3000 cells/animal (1000 cells/coverslip). RDS was evaluated in hepatocytes recovered from animals 15 or 38 hours postexposure to the appropriate treatment levels, vehicle and positive control.

UDS: The nuclear grains of 100 cells (50/coverslip) harvested from animals sacrificed 2 and 15 hours postexposure to the appropriate test material doses, the vehicle or positive control were counted. Net nuclear grains (NNG) were calculated by subtracting the average cytoplasmic grain count of three nuclear-sized areas adjacent to each nucleus from the nuclear grain count of each cell. In addition, the percentage of cells in repair (i.e., cells with NNG ≥2 grains/nucleus) was calculated.

(e) Statistical methods: The data were not evaluated for statistical significance.

3. Evaluation Criteria:

(a) Assay validity: The assay was considered valid if: (1) the gross labelling of the vehicle control cultures did not exceed an average of 8 total grains per nucleus; (2) the net values in the vehicle control did not exceed an average of 2 NNG; (3) the positive control fulfilled all criteria for a positive response; and (4) grain count data for a given treatment were obtained from at least two replicate cultures and at least 50 cells per culture.

(b) Positive response: The test material was considered positive if both the mean gross and NNG counts were higher than the vehicle control with the mean net value being ≥2.0 NNG, and the percentage of nuclei in repair was higher than the vehicle control.

C. REPORTED RESULTS:

1. Range-finding Studies: In the initial study, the test material was administered once to groups of one male and one female rat at 1250, 2000 or 3200 mg/kg. All animals survived the 2-day observation period. However, reduced locomotor activity, diarrhoea, hunched posture and reduced body weight were recorded for the two high-dose animals. With the exception of reduced body weight in the male receiving 2000 mg/kg, no signs of compound toxicity were observed in the remaining rats. In the confirmatory trial, no clinical signs were noted in the male or female administered 3200 mg/kg. Accordingly, an additional trial was conducted with three females exposed to 4000 mg/kg and one male and one female dosed with 5000 mg/kg. Females in both treatment groups either died within one day of dosing or were sacrificed moribund. The surviving 5000-mg/kg male showed signs of reduced locomotor activity, diarrhoea, hunched posture and reduced body weight. Based on the overall results, high doses of 3200 mg/kg (females) or 5000 mg/kg (males) were selected for further investigation. Lower concentrations of 500 and 1500 mg/kg were processed in both sexes.

193

2. RDS/UDS Assays:

a. Analytical determinations: High and/or low dosing suspensions prepared for the RDS and UDS assays were analyzed for actual concentrations and found to contain 101.3-121.6% of the target concentrations.

b. Animal observations: Two of four females in the 3200-mg/kg group and two of four males in the 5000-mg/kg group succumbed to treatment prior to the scheduled sacrifice at 38 hours. No symptoms of compound toxicity were noted in the surviving high-dose females and clinical signs similar to those seen in the preliminary studies (i.e., reduced locomotor activity and reduced body weight) were recorded for surviving high-dose males. Lower doses were not toxic.

c. RDS analysis: Less than 10% of the hepatocytes harvested from one of the surviving high-dose males were viable; therefore, autoradiographies were not prepared for this animal. For the remaining high-dose male, 71% of the harvested cells were viable. Initial viability of hepatocytes recovered from the surviving females was also high (77 and 90%); however, no scorable cells were found following autoradiography. The study author stated that effects on cell recovery and viability in the high-doses groups were assumed to be related to treatment with CGA 77102 technical. Hepatocyte viability for the lower treatment groups at either 15 or 38 hours was ≥71%. Summarized results presented in Table 1 show that a clear dose-related increase in the percentage of cells in S-phase was obtained from hepatocytes harvested 38 hours posttreatment of the male rats (3.01% at 1500 mg/kg and 9.17% at 5000 mg/kg versus 0.57% in the vehicle control group). The response ranged from a 5.3-fold increase at 1500 mg/kg to a 16.1-fold increase at the high dose (5000 mg/kg). In females, the marked increase seen in RDS at 1500 mg/kg (4.4%) declined over time (24.4-fold increase at 15 hours and a 12.2-fold increase at 38 hours). No response was detected at 500 mg/kg in either sex or at either harvest time. We conclude, therefore, that the results indicate that CGA 77102 technical is hepatotoxic and had a proliferative effect on hepatocytes isolated from the treated rats.

d. UDS analysis: In contrast to the clear evidence of an RDS response, the summarized data presented in Table 1 provided no evidence that the test article induced UDS at either dose or harvest time.

Based on the overall data, the study author concluded that CGA 77102 technical failed to induce UDS but did have a cytotoxic effect on the harvested cells.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We assess that the study was properly conducted and that the study author correctly interpreted the data. CGA 77102 technical was tested up to levels (3200 mg/kg - ♀; 5000 mg/kg - ♂) that produced mortality in the treated animals and cytotoxicity in the target cells but failed to induce a genotoxic response. The demonstration of target cell cytotoxicity in the absence of genotoxicity heightens our confidence in this negative conclusion. Finally, the increased frequency in RDS noted for both males and females supports our assessment that CGA 77102 technical has a proliferative effect on rat liver. Results with the positive controls (15 mg/kg DMN or 1000 mg/kg 4-AAF) demonstrated that the assay was sufficiently sensitive to detect genotoxicity and cell proliferation. We noted that the RDS response elicited by 4-AAF in the male

194

rats (≈10-fold) was less that the peak response induced by the test material (16.1-fold at 5000 mg/kg); albeit in a single male. We conclude, therefore, that the data are acceptable and indicate that CGA 77102 technical was negative for genotoxicity but positive for cellular proliferation when tested up to overtly toxic and cytotoxic doses in this in vivo/in vitro rat hepatocyte RDS/UDS assay.

E. STUDY DEFICIENCIES: NONE.

195

TABLE 1. Representative Results of the In Vivo Replicative/Unscheduled DNA Synthesis (RDS/UDS) Assays in Rats Administered CGA 77102 Technical by Oral Gavage

Treatment	Dose/kg	No. of Animals Treated	Harvest Time (Hours)	Percent Viable Cells	% Cells in S-phase[a]	Mean Net Nuclear Grains[a]	Mean % Cells with ≥2 NNG
Vehicle Control							
Arachis oil	10 mL	3M	2	82	--	-0.0±0.1	13.7
		3F	2	79	--	0.0±0.2	14.0
	10 mL	3M	15	84	0.07	-0.8±0.7	7.3
		3F	15	80	0.18	-0.0±0.2	8.3
	10 mL	3M	38	82	0.57	--	--
		3F	38	71	0.37	--	--
Positive Control							
Dimethylnitrosamine	15 mg	3M	2	65	--	31.8±3.9	99.7
		3F	2	86	--	13.2±0.5	99.3
4-Acetylaminofluorene	1000 mg	3M	38	69	5.66	--	--
		3F	38	82	10.15	--	--
Test Material							
CGA 77102	1500 mg[b]	3M	2	67	--	-0.3±0.5	13.7
		3F	2	87	--	0.3±0.3	19.0
	1500 mg	3M	15	67	0.07	-1.3±0.4	9.3
		3F	15	84	4.40	0.2±0.3	13.0
	1500 mg	3M	38	83	3.01	--	--
		3F	38	87	4.52	--	--
	5000 mg	4M	38	71[c]	9.17	Cytotoxic dose - no cells scored	
	3200 mg	4F	38	84[d]	--	Cytotoxic dose - no cells scored	

[a] Mean values from the count of 100 cells/animal (50 cells/slide) for individual animals were presented.
[b] Results for the lowest dose (500 mg/kg) were negative.
[c] Two of the four males died prior to sacrifice at 38 hours. Cell viability for one of the two survivors was <10%; presented results are from the single male with 71% hepatocyte viability. Owing to the high incidence of cells in S-phase, this level was not scored for unscheduled DNA synthesis.
[d] Two of the four females died prior to sacrifice at 38 hours; cell viability for the two survivors was initially high but no scorable preparations were obtained for RDS or UDS analysis.

Note: Data were extracted from the study report, Tables 3-9; pp. 28-33.

012310

CGA-77102 960 EC ACUTE ORAL TOXICITY - RATS §81-1

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/7/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 5/9/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Oral Toxicity - Rat
Species: Rat Guideline: §81-1

EPA ID No.s: EPA MRID No. 43928303
EPA Pesticide ~~Chemical~~ Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 960 EC-A

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102 960 EC, FINAL REPORT, ACUTE ORAL TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2317-95, December 1, 1995 (Unpublished); EPA MRID Number 43928303.

Executive Summary: In an acute oral toxicity study (MRID# 43928303), groups of 5 male and 5 female young adult albino rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley SD from Harlan Sprague Dawley, Inc., Houston, TX) received either 1500, 2000, 2500, 4000, or 5050 mg/kg in females and either 2500, 4000, or 5050 mg/kg in males of CGA-77102 960 EC-A (Purity: 87.2% active ingredient; Lot Number FL-951199) as a single gavage dose.

The Acute Oral LD_{50} for CGA-77102 960 EC-A is:

Males - 3937 mg/kg bw
95% Confidence Limits - 2548 to 6085 mg/kg bw

Females - 2149 mg/kg bw
95% Confidence Limits - 1506 to 3068 mg/kg bw

Combined - 2267 mg/kg bw
95% Confidence Limits - 1299 to 3956 mg/kg bw

Toxicity Category III.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-1) for an acute

oral toxicity study in rats.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT, and QUALITY ASSURANCE STATEMENT were 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 960 EC-A
Purity: 87.2% active ingredient
Description: Dark amber-brown, clear liquid
Lot Number: FL-951199
Other provided information:
Density: 1.0876 g/mL
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Albino rat (females were nulliparous and non-pregnant)
Strain: HSD:Sprague-Dawley SD
Source: Harlan Sprague Dawley, Inc., Houston, TX
Age: Not provided, "young adult"
Body Weight: Males (253-299 g); Females (179-232 g)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the acute oral toxicity potential of the test material when administered to rats in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-1, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No. S9-FF81-1.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the Sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are on file in the STILLMEADOW, Inc. archives. The study was initiated on August 24, 1995, and the animals were treated as follows:

198

Dose		Male Treatment		Female Treatment		Termination Date	
mg/kg	mL/kg	Date	Time	Date	Time	Males	Females
1500	1.38			09/20/95	9:26 A.M.		10/04/95
2000	1.84			10/04/95	10:16 A.M.		10/18/95
2500	2.30	09/13/95	11:17 A.M.	09/13/95	11:26 A.M.	09/27/95	09/27/95
4000	3.68	09/05/95	9:37 A.M.	09/05/95	9:43 A.M.	09/20/95	09/08/95
5050	4.64	08/30/95	9:53 A.M.	08/30/95	10:00 A.M.	09/13/95	09/13/95

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type: Suspended, wire bottom, stainless steel
Housing: 1 per cage
Environmental Controls Set to Maintain:
- Temperature Range of 72° ±5°F
- Humidity Range of 30-80%
- 12-hour light/dark cycle
- 10-12 air changes per hour

Litter Pan Lining: Paper and aspen bedding; changed three times/week
Food: Purina Formulab Chow #5008; available *ad libitum* except for approximately 16 hours before dosing
Water Type: Municipal water supply, available *ad libitum* from automatic water system

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Dose Preparation and Administration

From page 8 of the report:

The test material was administered as received and was not diluted. An individual dose was calculated for each animal based on its fasted body weight and administered by gavage at a volume ranging from 1.38 mL/kg at the 1500 mg/kg level to 4.64 mL/kg at the 5050 mg/kg level. Each dose was administered using an appropriately sized syringe and stainless steel ball-tipped intubation needle. The animals were returned to their cages immediately after dosing.

3. Observations

From page 8 of the report:

Observations for mortality and clinical/behavioral signs of toxicity were made at least three times on the day of dosing (Day 0) and at least once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing and on Days 7 and 14, or at the time of discovery after death.

At study termination, each surviving animal was euthanized by an overdose of CO_2. All study animals were subjected to gross necropsy and all abnormalities were recorded.

4. Statistical Analyses

From pages 8 and 37 of the report:

The LD_{50} value was calculated by a computer program utilizing probit analysis. No other statistical analyses were required by the protocol.

Reference: Litchfield, J.T., Jr., and Wilcoxon, F.: A Simplified Method of Evaluating Dose-Effect Experiments, J. Pharm. & Exp. Ther., 96, 99-115, 1949.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-1.

C. Results:

1. Mortality

The investigators provided a group summary of the observed mortality along with individual animal data. Three 2000-mg/kg females, five 2500-mg/kg animals (1 male and 4 females), eight 4000-mg/kg animals (3 males and all 5 females) and seven 5050-mg/kg animals (3 males and 4 females), with 2 exceptions, died within 1 day of the test compound administration. No other mortality was observed. The following table (from the table on page 9 and Table 1, pages 11-15 of the report) presents a summary of the mortality data:

200

Table I: Mortality Summary

Dose Level (mg/kg)	Mortality, Day Died*
Males	
2500	1/5, Day 1^1
4000	3/5, Day 1^3
5050	3/5, Day 1^3
Females	
1500	0/5
2000	3/5, Day 1^3
2500	4/5, Days 1^3 and 3^1
4000	5/5, Days 1^4 and 2^1
5050	4/5, Day 1^4

* = Superscript number indicates number of animals found dead on that day.

Calculated Oral LD_{50} :

Males - 3937 mg/kg bw
95% Confidence Limits - 2548 to 6085 mg/kg bw

Females - 2149 mg/kg bw
95% Confidence Limits - 1506 to 3068 mg/kg bw

Combined - 2267 mg/kg bw
95% Confidence Limits - 1299 to 3956 mg/kg bw

2. Clinical Signs

The investigators provided summary and individual animal clinical signs data. The clinical signs of toxicity included piloerection, salivation, ptosis, activity decrease, diarrhea, respiratory gurgle and chirp, gasping, staining of the muzzle hair and around eyes, clear nasal discharge, crust around eyes and nose, and polyuria. The investigators observed convulsions, body tremors, lateral recumbency and rapid breathing in those animals which died. All surviving animals were noted to have returned to a normal appearance by study Day 7 after treatment except for one 1500-mg/kg female that expressed no symptoms from study Day 4 through 8 then displayed piloerection, ptosis and gasping, and one 2500-mg/kg female with respiratory gurgle through Day 14.

3. Body Weights

The investigators provided individual and mean body weights. No relevant treatment related effects were noted on body weights and body weight gains in surviving animals. The following table presents the body weights and body weight gains calculated by the reviewer (from Table 1, pages 11-15 of the report):

Table II: Mean Body Weights and Body Weight Gains (grams)

Day: / Dose (mg/kg):	0	7	0-7 Gain	14	0-14 Gain
			Males		
2500	272(5)[n]	307(4)	34(4)	336(4)	63(4)
4000	280(5)	307(2)	27(2)	335(2)	55(2)
5050	268(5)	286(2)	27(2)	318(2)	58(2)
			Females		
1500	183(5)	214(5)	31(5)	215(5)	32(5)
2000	198(5)	225(2)	31(2)	234(2)	41(2)
2500	189(5)	181(1)	2(1)	191(1)	12(1)
4000	216(5)				
5050	206(5)	225(1)	16(1)	258(1)	49(1)

[n] = number of animals.

4. Pathology

The investigators provided a summary and individual gross necropsy pathology findings and report. According to the investigators: *The gross necropsy findings primarily pertained to the contents of the gastrointestinal tract, and matting and staining of the muzzle and genital hair. Other findings included lungs extended in one 2000 mg/kg group female, discolored lungs in one high dose male, and discolored liver in two high dose females. Except for one animal at the 1500 mg/kg level, animals surviving to termination had no observable abnormalities.* This is supported by the individual animal data.

20

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

The test material, CGA-77102 960 EC, was evaluated for its acute oral toxicity potential in albino rats when administered as gavage doses at levels of 2500, 4000, and 5050 mg/kg to males and females, as well as levels of 1500 and 2000 mg/kg to females. No mortality occurred in females dosed at the 1500 mg/kg level. Clinical signs of toxicity included piloerection, salivation, ptosis, activity decrease, diarrhea, respiratory gurgle and chirp, gasping, staining of the muzzle hair and around eyes, clear nasal discharge, crust around eyes and nose, and polyuria; body tremors, convulsions, rapid breathing, and lateral recumbency were observed only in animals dying on test. There was no meaningful effect on body weight gain in animals surviving to termination. Gross necropsy findings pertained to the contents of the gastrointestinal tract, discoloration of the liver or lungs, and matting and staining of muzzle and genital hair, and occurred primarily in animals dying on test. The acute oral LD_{50}'s, as indicated by the data, were determined to be 3937 mg/kg in males, 2149 mg/kg in females, and 2267 mg/kg overall.

2. Reviewers' Conclusions

The Acute Oral LD_{50} for CGA-77102 960 EC is:

Males - 3937 mg/kg bw
95% Confidence Limits - 2448 to 6085 mg/kg bw

Females - 2149 mg/kg bw
95% Confidence Limits - 1506 to 3068 mg/kg bw

Combined - 2267 mg/kg bw
95% Confidence Limits - 1299 to 3956 mg/kg bw

Toxicity Category III.

CGA-77102 960 EC ACUTE DERMAL TOXICITY - RABBITS §81-2

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/7/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 5/9/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Dermal Toxicity - Rabbit
Species: Rabbit Guideline: §81-2

EPA ID No.s: EPA MRID No. 43928304
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 960 EC-A

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102 960 EC, FINAL REPORT, ACUTE DERMAL TOXICITY STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2318-95, October 13, 1995, EPA MRID No. 43928304.

Executive Summary: In an acute dermal toxicity study (MRID# 43928304), 5 male and 5 female albino rabbits (females were nulliparous and non-pregnant; Strain: New Zealand White from Ray Nichols Rabbitry; Lumberton, Texas) received 2020 mg/kg CGA-77102 960 EC-A (Purity: 87.2% active ingredient; Lot Number FL-951199) by the dermal route.

The Acute Dermal LD_{50} for CGA-77102 960 EC is greater than 2020 mg/kg for both sexes. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT, and QUALITY ASSURANCE STATEMENT were 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).

264

A. Materials and Methods

Test Compound: CGA-77102 960 EC-A
Purity: 87.2% active ingredient
Description: Dark amber-brown, clear liquid
Lot Number: FL-951199
Other provided information:
Density: 1.0876 g/mL
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Albino rabbit (females were nulliparous & non-pregnant)
Strain: New Zealand White
Source: Ray Nichols Rabbitry; Lumberton, Texas
Age: Not provided, "Young adult"
Body Weight: Males (2.450-2.950 kg); Females (2.350-2.525 kg)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the acute dermal toxicity potential of the test material when administered to rabbits in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-2, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No. S9-FF81-2.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations, effective October 30, 1989. In the opinion of the Sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are on file in the STILLMEADOW, Inc. archives. The study was initiated on August 24, 1995, and the animals were treated on August 31, 1995. The in-life portion of the study was terminated on September 14, 1995.

105

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Controls Set to Maintain:	·Temperature Range of 72° ±5°F ·Humidity Range of 30-80% ·12-hour light/dark cycle ·10-12 air changes per hour
Litter Pan Lining:	Paper; changed daily
Food:	Purina Rabbit Chow; available in measured amounts
Water Type:	Municipal water supply, available ad libitum from automatic water system

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Dose Preparation and Administration

From page 8 of the report:

Healthy albino rabbits were released from quarantine. Each animal was prepared on the day prior to treatment by clipping the dorsal surface of the trunk free of hair to expose not less than 10% of the total body surface area. Care was taken to avoid abrading the skin. Only those animals with exposure areas free of pre-existing skin irritation or defects were used for this study. All animals were treated with 2020 mg/kg (1.86 mL/kg) of undiluted test material. An individual dose was calculated for each animal based on its Day 0 body weight just before exposure. The test material was applied to each exposure area in a thin, uniform layer. The area of application was covered with an appropriately sized surgical gauze patch (8 x 4 in) and secured with non-irritating adhesive tape. The trunk of each animal was then wrapped with a plastic film and secured in place with non-irritating adhesive tape to prevent possible ingestion of the test material.

After 24 hours, the wrappings were removed. The test sites were gently washed with room temperature tap water and a clean wet cloth to remove as much residual test material as possible.

3. Observations

From page 8 of the report:

Observations for mortality and clinical/behavioral signs of toxicity were made

204

at least three times on the day of dosing (Day 0) and at least once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing and on Days 7 and 14.

Observations for evidence of dermal irritation were made at approximately 30 minutes after removal of wrappings, and on Days 3, 7, 10 and 14.

At study termination, animals were euthanized by an intracardiac injection of Fatal Plus (Vortech Pharmaceuticals, Dearborn, Michigan 48126). All study animals were subjected to gross necropsy and all abnormalities were recorded. After necropsy, the animal carcasses were discarded.

4. Statistical Analyses

No statistical analysis was conducted.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-2.

C. Results:

1. Mortality

The investigators provided individual animal and group summary of the survival rate. No mortality was observed during the study. The estimated dermal LD_{50} for male and female rabbits was determined to be greater than 2020 mg/kg bw.

2. Clinical Signs

The investigators provided group summary and individual animal clinical signs and dermal reactions. Clinical signs were diarrhea in 1 male from study Days 8 through 13, small feces in another male on study Day 13 and in 1 female on study Day 5. Dermal irritation signs included 1 male and 3 females with erythema on study Day 1, 1 male and 2 females with erythema and 1 female with desquamation on study Day 3, 1 male and 2 females with erythema, 1 male and 2 females with desquamation and 1 male (same one) with fissuring on study Day 7, 1 male and 2 females with desquamation and 1 females with atonia on study Day 10, and the same female with atonia and desquamation on study Day 14.

207

3. Body Weights

The investigators provided individual animal and mean body weights. No treatment related effects were noted. The following table presents the body weights and body weight gains (from Table 1, page 14 of the report):

Table I: Mean Body Weights and Body Weight Gains (grams)

Day: / Dose (mg/kg):	0	7	0-7 Gain	14	0-14 Gain
			Males		
2020	2605	2740	135	2885	280
			Females		
2000	2435	2620	185	2775	340

4. Pathology

The investigators provided individual animal gross necropsy pathology findings. No treatment related effects were noted.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

The test material, CGA-77102 960 EC, was evaluated for its dermal toxicity potential when a single undiluted dose, at a level of 2020 mg/kg, was applied to the intact skin of male and female albino rabbits. No mortality occurred during the study. Clinical signs included diarrhea and small feces which were no longer present by Day 14. There was no meaningful effect on body weight gain. The gross necropsy conducted at termination of the study revealed no treatment-related abnormalities. The estimated acute dermal LD50, as indicated by the data, was determined to be greater than 2020 mg/kg body weight.

2. Reviewers' Conclusions

The Acute Dermal LD_{50} for CGA-77102 960 EC is greater than 2020 mg/kg for both sexes. Toxicity Category III.

20

CGA-77102 960 EC ACUTE INHALATION TOXICITY - RATS §81-3

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Inhalation Toxicity - Rat
Species: Rat Guideline: §81-3

EPA ID No.s: EPA MRID No. 43928305
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 960 EC

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J. Bennick (1996): CGA-77102 960 EC, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2319-95, January 15, 1996; EPA MRID No. 43928305.

Executive Summary: In an acute inhalation toxicity study (MRID# 43928305), groups of 5 male and 5 female rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley; Source: Harlan Sprague Dawley, Inc., Houston, Texas) were exposed by the nose only route to a generated aerosol of CGA-77102 920 EC from undiluted liquid at levels of 3.15, 3.60, and 3.79 mg/L mean exposure concentrations (Purity: 87.2% active ingredient; Lot Number: FL-951199).

The Acute Inhalation LC_{50} for CGA-77102 920 EC was calculated to be:

		95% confidence limits
Males:	5.86 mg/L	undefined
Females:	3.80 mg/L	3.50 to 4.12 mg/L
Combined:	4.06 mg/L	3.62 to 4.56 mg/L

The particle size distribution (MMAD) was 3.764, 3.563, and 3.532 µm for the 3.15, 3.60, and 3.79 mg/L mean exposure concentrations, respectively. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

209

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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 960 EC-A
Purity: 87.2% active ingredient
Description: Dark amber-brown, clear liquid
Lot Number: FL-951199
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Male and Female Rat (females were nulliparous and non-pregnant)
Strain: HSD:Sprague-Dawley
Source: Harlan Sprague Dawley, Inc., Houston, Texas
Age: Not provided, "Young adults"
Body Weight: Males (241-290 g); Females (191-220 g)
Acclimation Period: At least five days

B. Study Design

From page 7 of the report:

The objective of this study was to determine the acute inhalation toxicity potential of the test material in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-3, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No. S9-FF81-3.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data and a copy of this report are kept on file permanently in the STILLMEADOW, Inc. archives. The study was initiated on August 24, 1995, and the animals were exposed as follows:

210

Beginning of 4 Hour Exposure					Termination of In-Life Observations	
Dose (mg/L)	Males		Females		Males	Females
	Date	Time	Date	Time	Date	Date
3.15	11/12/95	11:45 A.M.	11/12/95	11:45 A.M.	11/26/95	11/26/95
3.60	9/20/95	9:30 A.M.	9/20/95	9:30 A.M.	10/11/95	10/11/95
3.79	9/13/95	10:45 A.M.	9/13/95	10:45 A.M.	9/27/95	9/27/95

1. Animal Husbandry and Assignment

From page 8 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	One per cage
Environmental Controls Set to Maintain:	·Temperature Range: 72° ± 5°F ·Humidity Range: 30-80% ·12-hour light/dark cycle ·10-12 air changes/hour
Transfer to Clean Cages:	Weekly
Litter Pan Lining:	Paper and aspen bedding
Litter Pan Lining Change:	Three times weekly
Food:	Purina Formulab Chow #5008, available ad libitum except during the exposure period
Water Type:	Municipal water supply from automatic water system, available ad libitum except during the exposure period

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Procedures

From pages 8-10 of the report:

Prestudy Testing
Trial assays were conducted to determine which method(s) of aerosolizing the test material into the exposure chamber would produce an acceptable concentration and mass median aerodynamic diameter (MMAD).

Exposure Chamber
A 500 L nose-only stainless steel, dynamic flow inhalation chamber was utilized in this experiment [diagram provided]. The body of the chamber has 25 ports in 5 rows. Polycarbonate cones are inserted into 10 designated individual ports. The test material is introduced through the opening in the top of the chamber. The bottom section has a corresponding air outlet and a drain valve for cleaning the chamber. The individual polycarbonate cones (tubes) are tapered at one end to fit the shape of the animal's head and the back portion is sealed with a polycarbonate cap. The cones containing the animals fit tightly into the ports, and are sealed with "O" rings.

Generation of Test Atmosphere
The aerosol was generated by pumping the test material into a pressure operated Spraying System Company air atomizer (1/4 JSS) and then elutriating the resulting aerosol through a baffling chamber. The concentrated aerosol was then diluted with filtered air and drawn into the exposure chamber. Air flow into the chamber was maintained through the use of a calibrated orifice plate at a rate of 11.5 air changes per hour. Air flow was recorded at 30 minute intervals during the exposure period, and was sufficient to ensure an oxygen content of at least 19% of the exposure atmosphere. Temperature and relative humidity were recorded at 30 minute intervals during the exposure period from a Taylor wet bulb/dry bulb hygrometer located in the exposure chamber.

Test Material Administration
Healthy albino rats were released from quarantine. Five males and five females per each of three exposure levels were selected for testing. The animals were exposed to an aerosol generated from the undiluted liquid test material for a period of four hours. When 99% concentration (T-99) was attained, the animals which were individually housed in polycarbonate exposure tubes were inserted into a 500 L stainless steel nose-only inhalation chamber for the specified exposure period. A maximum of 10 animals were exposed during any given exposure period. At the termination of the exposure period, the animals at the two high dose levels were washed, and all animals were returned to their stock laboratory cages.

Determination of Concentration
The concentration of test material in the exposure atmosphere (taken from the breathing zone of the animals) was determined analytically once per hour, and nominally at the end of each exposure. The analytical determination was made using a Beckman System Gold HPLC with Autoinjector (Appendix A). The nominal concentration was determined by dividing the loss in weight of the test material after each exposure by the total volume of air which passed through the chamber.

Particle Size Distribution
Particle size, taken from the breathing zone of the animals, was determined twice during each exposure, using an Andersen cascade impactor, at a rate of 28.3 L/minute for a duration of 3/4-2 minutes. The MMAD and particle size distributions are calculated from these data.

In-life Observations
Observations for mortality and signs of pharmacologic and/or toxicologic effects were made frequently on the day of exposure and at least once daily thereafter for 14 to 21 days (day of exposure considered Day 0). Individual body weights were recorded just prior to the inhalation exposure and on Days 7, 14, and 21 (3.60 mg/L level only), or at the time of discovery after death.

Postmortem Observations
At study termination, each surviving animal was euthanized by an injection of Fatal Plus (Vortech Pharmaceuticals, Dearborn, Michigan 48126). All study animals were subjected to gross necropsy and all abnormalities were recorded. animals were subjected to gross necropsy and all abnormalities were recorded.

Statistical Analysis
In order to calculate a mean exposure, the Mean Value Theorem of Calculus was used to properly weight the concentration, since the concentrations could not be measured continuously (see Table 5). This method weights concentrations based on the time span of each concentration. A concentration can be calculated for each minute, which better represents the exposure concentration received by each animal. The LC50 value was calculated by a computer program utilizing probit analysis. No other statistical analyses were required by the protocol.

References (from pages 13 and 32 of the report):

Litchfield, J.T., Jr., and Wilcoxon, F.: A Simplified Method of Evaluating Dose-Effect Experiments, J. PHARM. & EXP. THER., 96, 99-115, 1949.

Finney, D.J.: PROBIT ANALYSIS, 3rd ed., Chapters 3 and 4, 1971, Cambridge University Press.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-3.

C. Results:

1. Mortality

The investigators provided group summary and individual animal survival data. The following table (from table on page 10 and Table 1, pages 16-18 of the report) presents the mortality data:

Concentration (mg/L)	Number Dead/Number Treated Males	Females	Combined
3.15	0/5	0/5	0/10
3.60	1/5, Day 14*	2/5, Days 6 & 9	3/10
3.79	0/5	2/5, Days 2 & 3	2/10

* Day found dead.

13

The acute inhalation LC_{50} for CGA-77102 920 EC was calculated to be:

		95% confidence limits
Males:	5.86 mg/L	undefined
Females:	3.80 mg/L	3.50 to 4.12 mg/L
Combined:	4.06 mg/L	3.62 to 4.56 mg/L

2. Clinical Signs

The investigators provided group summary and individual animal data. Clinical signs included activity decrease (3.60 mg/L: in males on study Days 12 and 13 and in females from 4.5 hours to study Day 2; 3.79 mg/L: in males on study Day 2 and in females on study Day 1), crust around eyes (3.15 mg/L: in males on and females on study Days 1 and 2; 3.60 mg/L: in males on study Days 4 to 6 and in females on study Days 3 to 15) and nose (3.60 mg/L: in males on study Days 3 to 6), diarrhea (3.60 mg/L in males on study Day 11; 3.79 mg/L in males on study Day 2), gasping (3.15 mg/L: in males on study Days 3 and 4; 3.60 mg/L: in females on study Days 1 to 3; 3.79 mg/L: in females on study Days 1 and 2), nasal discharge (3.15 mg/L: in males and females at 4.5 hours; 3.60 mg/L: in males at 4.5 hours to study Day 2 and in females from 6 hours to study Day 5; 3.79 mg/L: in males at 6.0 hours to study Day 2 and in females from study Day 1 and 2), respiratory gurgle (3.15 mg/L: in males and females at 4.5 hours to study Day 4 and then again in males from study Days 7 to 12 and in females from study Days 7 and 8; 3.60 mg/L: in males and females at 4.5 hours to study Day 16; 3.79 mg/L: in males at 4.5 hours to study Day 13 and in females from study Days 1 to 2) and chirp (3.79 mg/L: in females on study Day 1), piloerection (3.15 mg/L: in males and females at 6.0 hours to study Day 10 in males and study Day 9 in females; 3.60 mg/L: in males and females at 4.5 hours to study Day 13 in males and study Day 10 in females; 3.79 mg/L: in males and females at 4.5 hours to study Day 13 in males and study Day 5 in females, ptosis (3.60 mg/L: in females at 4.5 and 6.0 hours) and salivation (3.15 mg/L: in males and females at 4.5 hours). As noted the piloerection, activity decrease, respiratory gurgle and chirp, nasal discharge and ptosis were observed during the exposure period. Most of the animals were clear of signs by study Day 14 with 1 male and 2 females showing signs up to study Day 17.

214

3. Body Weights

The investigators provided individual animal body weights. No treatment-related effects were noted. The following table presents the mean body weights and body weight gains (from Table 1, pages 16-18 of the report):

Mean Body Weights and Body Weight Gains (grams)

Day:	0	7	0-7	14	0-14	21	0-21
Dose (mg/L):				Males			
3.15	281	276	-5	301	20		
3.60	267	253	-14	262	-5	303	36
3.79	256	266	10	308	52		
				Females			
3.15	204	204	0	214	10		
3.60	208	186	-22	213	5	222	14
3.79	205	197	-8	212	7		

4. Pathology

The investigators provided individual animal gross necropsy findings. The only findings noted were in the animals that died, sing included matted, stained hair around nose; discoloration of lungs, liver and contents of the gastrointestinal tract; swollen lungs and gas in the gastrointestinal tract. Surviving animals had no abnormal pathology.

5. Inhalation Chamber Conditions

The investigators provided individual half-hour chamber operating parameters. The mean chamber operating parameters are as follows (from Table 4, page 28 of the report):

Conc.(mg/L)	Temp.(°F)	RH(%)[1]	Air Flow (Lpm)
3.15	74	60	113
3.60	73	60	113
3.79	71	58	113

1 = RH = relative humidity

The investigators provided analytical concentration determinations and calculations and particle size distribution determinations.

215

The mean exposure concentration are as follows (from Tables 5 and 6, pages 29-38 of the report):

Conc.(mg/L)	MEC(mg/L)[1]	NC(mg/L)[2]	MMAD(μm)[3]
3.15	3.154	5.19	3.764
3.60	3.598	4.95	3.563
3.79	3.789	3.56	3.532

[1] = MEC = Mean Exposure Concentration; [2] = NC = Nominal Concentration; [3] = MMAD = Mass Mean Aerodynamic Diameter.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

CGA-77102 960 EC was evaluated for its acute inhalation toxicity potential in albino rats. The animals were exposed for four hours in a nose-only inhalation system to an aerosol generated from the undiluted liquid test material. Dose levels and deaths are as follows:

Conc.	Number Dead/Number Treated		
(mg/L)	Males	Females	Males & Females Combined
3.15	0/5	0/5	0/10
3.60	1/5	2/5	3/10
3.79	0/5	2/5	2/10

Clinical signs included activity decrease, crust around eyes and nose, diarrhea, gasping, nasal discharge, respiratory gurgle and chirp, piloerection, ptosis and salivation. Except for three animals at the 3.60 mg/L level, signs were no longer evident by Day 14 in surviving animals. Body weights of surviving animals were apparently affected by exposure; most males and females lost weight during the study. Abnormal necropsy findings primarily pertained to the lungs and contents of the gastrointestinal tract in animals that died on test. The acute inhalation LC50 with 95% confidence limits and the slope function (S) with 95% confidence limits for CGA-77102 960 EC were calculated to be:

	LC50 (mg/L)	95% Confidence Limits (mg/L)	Slope Function (S)	95% Confidence Limits
Males	5.86	Undefined	1.40	Undefined
Females	3.80	3.50-4.12	1.10	0.98-1.22
Overall	4.06	3.62-4.56	1.14	0.92-1.41

2/6

2. Reviewers' Conclusions

The acute inhalation LC_{50} for CGA-77102 920 EC was calculated to be:

		95% confidence limits
Males:	5.86 mg/L	undefined
Females:	3.80 mg/L	3.50 to 4.12 mg/L
Combined:	4.06 mg/L	3.62 to 4.56 mg/L

The particle size distribution (MMAD) was 3.764, 3.563, and 3.532 µm for the 3.15, 3.60, and 3.79 mg/L mean exposure concentrations, respectively. Toxicity Category IV.

CGA-77102 960 EC PRIMARY EYE IRRITATION - RABBITS §81-4

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/9/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 5/12/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Eye Irritation - Rabbit
Species: Rabbit Guideline: §81-4

EPA ID No.s: EPA MRID No. 43928306
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 960 EC

Synonyms: Alpha-metolachlor; A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102 960EC, FINAL REPORT, PRIMARY EYE IRRITATION STUDY IN RABBITS, STILLMEADOW, Inc. For Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2036-95, June 27, 1995; EPA MRID Number 43928306.

Executive Summary: In a primary eye irritation study (MRID# 43928306), 3 male and 3 female (nonwashed) and 3 female ("washed") albino rabbits (Strain: New Zealand White from Ray Nichols Rabbitry, Lumberton, Texas) received 0.1 mL CGA-77102 960EC (Purity: 87.0% active ingredient; Lot Number FL-950296) to one eye (the other serving as untreated control). Two groups were used, one group with the eyes unwashed, the other group had the eyes washed for 1 minute with lukewarm water 30 seconds after test compound instillation.

CGA-77102 960EC was moderately irritating in unwashed eyes and minimally irritating to washed eyes. Irritation cleared by 72 hours after treatment. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

218

A. Materials and Methods

Test Compound: CGA-77102 960EC
Purity: 87.0% active ingredient
Description: Dark amber-brown, clear liquid
Lot Number: FL-950296
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Albino rabbit
Strain: New Zealand White
Source: Ray Nichols Rabbitry, Lumberton, Texas
Age: Young adult (3-6 months)
Body Weight: Males (2.050-2.875 kg); Females (2.200-2.750 kg)
Acclimation Period: At least five days

B. Study Design

From page 7 of the report:

The objective of this study was to determine the eye irritation potential of the test material in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-4, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation, according to the approved protocol (No. S9-FF81-4.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the Sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are on file in the STILLMEADOW, Inc. archives. The study was initiated on April 27, 1995, and the animals were treated with the test material between 13:33 and 13:43 on May 8, 1995. The in-life portion of the study was terminated on May 19, 1995.

219

1. Animal Husbandry and Assignment

From page 8 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Conditions Set to Maintain:	·Temperature Range of 72° ± 5°F ·Humidity Range of 30-80% ·12-hour light/dark cycle ·10-12 air changes per hour
Litter Pan Lining:	Paper; changed daily
Food:	Purina Rabbit Chow; presented in measured amounts
Water Type:	Municipal water supply, available ad libitum from automatic water system

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Dose Preparation and Administration

From page 8 of the report:

Prior to starting the study, the pH of the test material was determined to be 4.67. Healthy albino rabbits were released from quarantine. Both eyes of each animal were carefully examined at least 24 hours prior to treatment with a fluorescein sodium ophthalmic solution. Both eyes of each animal were again carefully examined just prior to treatment, but without the fluorescein sodium ophthalmic solution. Only those animals without eye defects or irritation were selected for testing.

On Day 0, a dose of 0.1 mL of the undiluted test material was placed into the conjunctival sac of the right eye of each animal by gently pulling the lower lid away from the eyeball to form a cup into which the test material was dropped. The lids were gently held together for one second to prevent loss of material. Three of the treated eyes ("washed eyes") were each washed with room temperature deionized water for one minute beginning 30 seconds after treatment. The untreated left eyes served as comparative controls.

3. Observations

From pages 8-9 of the report:

The treated eyes of all animals were examined under normal room lighting without magnification, and the grades of ocular reaction were recorded at 1, 24, 48 and 72 hours, and at 4, 7 and 11 days after treatment. The corneas of

220

all treated eyes were examined immediately after the 24-hour observation with a fluorescein sodium ophthalmic solution. Any of the corneas which exhibited fluorescein staining at the 24-hour observation were re-examined with the fluorescein sodium ophthalmic solution at each consecutive observation until fluorescein staining of the cornea no longer occurred. All treated eyes were washed with room temperature deionized water for one minute immediately after recording the 24-hour observation.

Irritation Scoring Method
Individual irritation scores for each animal at each scheduled observation were determined using the grading scale given in the Legend to Table 1. An average irritation score for each scheduled observation for all nonwashed and washed eyes was then determined, based on the number of animals tested in those groups. A maximum average irritation score for nonwashed and washed eyes was derived from the observation yielding the highest average irritation score. The maximum average irritation scores were used to rate the test material according to the ratings presented in the Legend to Table 2 [the investigators provided an ocular irritation scoring scale]. Any corneal involvement or iridic irritation with a score of 1 or more is considered positive. Any conjunctival irritation (redness or chemosis) with a score of 2 or more is considered positive.

4. Statistical Analyses

No statistical analysis was performed.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-4.

221

C. Results:

1. Eye Irritation

The investigators provided group summary and individual animal data for eye irritation. The following table presents the average eye irritation scores (from Table 2, page 19 of the report). The investigators noted fluorescein staining in 3/6 eyes at 24, 48 and 72 hours, and 1/6 eye at 4 days after treatment in the unwashed eyes. No fluorescein staining was noted in the washed eyes.

Table I: Average Primary Eye Irritation Scores[a]

Observation Period	Average Score (out of 110) Unwashed	Washed
1 hour	13.3	12.0
24 hours	18.8	4.0
48 hours	15.3	2.0
72 hours	10.2	0.0
4 days	4.2	0.0
7 days	1.8	0.0
11 days	0.0	0.0

a = The average primary eye irritation score is the total eye irritation score for all the animals divided by the number of animals in each group (6 or 3) at each observation period out of a possible maximum score of 110.

2. Body Weights

No data were provided.

222

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

A primary eye irritation study was conducted on nine albino rabbits using test material CGA-77102 960EC. The undiluted test material (0.1 mL) was placed into the conjunctival sac of the right eye of each animal selected for testing. Three of the treated eyes ("washed eyes") were each washed with room temperature deionized water for one minute beginning 30 seconds after treatment. All treated eyes were washed with room temperature deionized water for one minute immediately after recording the 24-hour observation. The number of animals testing "positive" for each parameter (according to the Legend to Table 1) over the number of animals tested is presented below.

	Time After Treatment						
	Hours				Day		
	1	24	48	72	4	7	11
	NONWASHED EYES						
Cornea Opacity	0/6	3/6	3/6	3/6	2/6	1/6	0/6
Iritis	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Conjunctivae Redness	6/6	6/6	6/6	3/6	0/6	0/6	0/6
Chemosis	1/6	3/6	2/6	0/6	0/6	0/6	0/6
	WASHED EYES						
Cornea Opacity	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Conjunctivae Redness	3/3	0/3	0/3	0/3	0/3	0/3	0/3
Chemosis	0/3	0/3	0/3	0/3	0/3	0/3	0/3

There were no "positive" effects exhibited in nonwashed eyes on Day 11 after treatment. There were no "positive" effects exhibited in washed eyes at 24 hours after treatment.

2. Reviewers conclusions

In a Primary Eye Irritation study, CGA-77102 960EC was moderately irritating in unwashed eyes and minimally irritating to washed eyes. Irritation cleared by 72 hours after treatment. Toxicity Category III.

223

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/9/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 5/12/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Dermal Irritation - Rabbit
Species: Rabbit Guideline: §81-5

EPA ID No.s: EPA MRID No. 43928307
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 960 EC

Synonyms: Alpha-metolachlor; A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102 960EC, FINAL REPORT, PRIMARY DERMAL IRRITATION STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2037-95, June 27, 1995; EPA MRID Number 43928307.

Executive Summary: In a primary dermal irritation study (MRID# 43928307), 3 male and 3 female albino rabbits (New Zealand White from Ray Nichols Rabbitry, Lumberton, Texas) received 0.5 mL CGA-77102 960EC (Purity: 87.0% active ingredient; Lot Number FL-950296) to the shaved back of each animal.

CGA-77102 960EC was slightly irritating. The mean PIS was 0.2. No irritation was seen by observation 48 hours. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT, and QUALITY ASSURANCE STATEMENT were 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 960EC
Purity: 87.0% active ingredient
Description: Dark amber-brown, clear liquid
Lot Number: FL-950296
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Albino rabbits
Strain: New Zealand White
Source: Ray Nichols Rabbitry, Lumberton, Texas
Age: Young adult (3-6 months)
Body Weight: Males (2.050-2.100 kg); Females (2.550-2.950 kg)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the dermal irritation potential of the test material in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-5, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation, according to the approved protocol (No. S9-FF81-5.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the Sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are on file in the STILLMEADOW, Inc. archives. The study was initiated on April 27, 1995, and the animals were treated with the test material between 9:32 and 9:42 A.M. on May 9, 1995. The in-life portion of the study was terminated on May 12, 1995.

225

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Conditions Set to Maintain:	·Temperature Range of 72° ± 5°F ·Humidity Range of 30-80% ·12-hour light/dark cycle ·10-12 air changes per hour
Litter Pan Lining:	Paper; changed daily
Food:	Purina Rabbit Chow; presented in measured amounts
Water Type:	Municipal water supply, available ad libitum from automatic water system

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Dose Preparation and Administration

From page 8 of the report:

Prior to starting the study, the pH of the test material was determined to be 4.67. Each animal was prepared on the day prior to treatment by clipping the dorsal area of the trunk free of hair to expose an area at least 8 x 8 cm. Only those animals with exposure areas free of pre-existing skin irritation or defects were selected for testing. A single intact exposure site was selected as the test site while the contralateral intact site served as a control site.

On Day 0, 0.5 mL of the undiluted test material was applied to each test site and covered with a surgical gauze patch measuring 2.5 x 2.5 cm and two single layers thick. Each patch was secured in place with a strip of non-irritating adhesive tape. The entire trunk of each animal was loosely wrapped with a semi-permeable dressing (orthopedic stockinette) and secured on both edges with strips of tape to retard evaporation of volatile substances and to prevent possible ingestion of the test material.

After four hours, the patches and wrappings were removed. The test sites were gently washed with room temperature tap water and a clean wet cloth to remove as much residual test material as possible.

226

3. Observations

From page 8 of the report:

The test sites were observed for erythema formation, edema formation, and any other dermal defects or irritation at 1/2, 24, 48 and 72 hours after washing. [The investigators provided a dermal irritation scoring scale]. For each animal, all of the erythema and edema scores through 72 hours were added, and the sum was divided by 4 to obtain an individual irritation score. The primary irritation index was determined by calculating the mean of the irritation scores for the six animals and was used to obtain a rating for the test material.

4. Statistical Analyses

No statistical analysis was performed.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-5.

C. Results:

1. Dermal Irritation

The investigators provided group summary and individual animal data for erythema and edema dermal irritation. The primary irritation score (called primary irritation index by the investigators) for all 6 animals through 72 hours was 0.2 out of a possible maximum of 8.0.

2. Body Weights

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

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

A primary dermal irritation study was conducted on six albino rabbits using test material CGA-77102 960EC. There was one intact test site per animal. Each test site was treated with 0.5 mL of undiluted test material and covered with a semipermeable dressing for 4 hours. Observations for dermal irritation and defects were made at 1/2, 24, 48 and 72 hours after removal of the dressings.

Irritation scores derived from the respective erythema and edema scores through the 72 hour observations for each animal are presented below.

Animal Number	Erythema Hours after Unwrap 1/2	24	48	72	Edema Hours after Unwrap 1/2	24	48	72	Irritation Scores
9854-M	1	1	0	0	0	0	0	0	0.50
9858-M	0	0	0	0	0	0	0	0	0.00
9860-M	0	1	0	0	0	0	0	0	0.25
9845-F	0	0	0	0	0	0	0	0	0.00
9847-F	1	0	0	0	0	0	0	0	0.25
9849-F	0	0	0	0	0	0	0	0	0.00

Based on the scores for the above observations, the Primary Irritation Index (PII) is 0.2. The test material is therefore rated slightly irritating.

2. Reviewers conclusions

In a Primary Dermal Irritation study, CGA-77102 960EC was slightly irritating. The mean PIS was 0.2. No irritation was seen by observation 48 hours. Toxicity Category IV.

228

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/9/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 5/12/97
Acting Section Head, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Dermal Sensitization - Guinea Pigs
Species: Guinea Pigs Guideline: §81-6

EPA ID No.s: EPA MRID No. 43928308
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 960 EC

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102 960 EC, FINAL REPORT, DERMAL SENSITIZATION STUDY IN GUINEA PIGS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2320-95, November 10, 1995; EPA MRID Number 43928308.

Executive Summary: In a dermal sensitization study (MRID# 43928308), 2 male and 2 female (Irritation Screening) and 10 male and 10 female (Definitive Study) guinea pigs (Strain: Hartley-Albino from SASCO Inc., Madison, WI.) received 0.4 mL in 3 induction and 1 challenge application of CGA-77102 960 EC-A (Purity: 87.2% active ingredient; Lot Number FL-951199) to the shaved back of the animals using the closed patch technique.

CGA-77102 960 EC was not a dermal sensitizer in guinea pigs tested with the closed patch technique.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT, and QUALITY ASSURANCE STATEMENT were 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 960 EC-A
Purity: 87.2% active ingredient
Description: Dark amber-brown, clear liquid
Lot Number: FL-951199
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Positive Control: from page 8 of the report:

Label:	C-3762 Lot 52H00471 Grade II: Approx. 95% SIGMA 1-CHLORO-2,4-DINITROBENZENE
Manufacturer:	SIGMA Chemical Company
Physical Description:	Light brown crystals
Storage:	Room temperature
Concentration Administered:	
	Induction: 0.45% w/v solution in 80% ethanol
	Challenge: 0.1% w/v solution in 80% ethanol
Purity, Composition and Stability:	Available from manufacturer
Vehicle Material:	Alcohol Dehydrated, USP Absolute 200 Proof Lot 94117

Positive Control Testing
The sensitivity of guinea pigs to a positive control material (1-chloro-2,4-dinitrobenzene) is confirmed in this laboratory periodically. The positive control animals used to conduct this study were supplied by SASCO Inc., and were tested according to the Buehler Method (Ritz, H.L. and E.V. Buehler, "Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests", Current Concepts in Cutaneous Toxicity, p.28, Academic Press, NY, 1980).

STILLMEADOW, Inc. Study No. 2061-95
In-life start: May 24, 1995; In-life completed: June 23, 1995

Test Animal(s): Species: Guinea Pig
Strain: Hartley-Albino
Source: SASCO Inc., Madison, WI.
Age: Not provided, "young adult"
Body Weight: Males (336-373 g); Females (335-371 g)
Acclimation Period: At least five days

230

B. Study Design

From page 6 of the report:

The objective of this study was to determine the sensitizing potential of the test material using a modification of the Buehler method (Ritz, H. L. and E.V. Buehler, "Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests," Current Concepts in Cutaneous Toxicity, p. 28, Academic Press, NY, 1980), in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-6, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation, according to the approved protocol (No. S9-FF81-6.C3) and STILLMEADOW, INC SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with the Animal Welfare Act Regulations, effective October 30, 1989. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are kept on file in the STILLMEADOW, Inc. archives. The protocol was initiated on August 24, 1995, and the animals were treated as follows:

	Induction Treatments		
Group	First	Last	Challenge Treatment
I Naive Control	--	--	10/11/95
II Test	09/13/95	09/27/95	10/11/95

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1-4 per cage (males separate from females)
Transfer to Clean Cages:	Weekly
Litter Pan Lining:	Paper
Litter Pan Lining Change:	Three times weekly
Food:	Purina Guinea Pig Chow; available ad libitum
Water Type:	Tap; available ad libitum
Water System:	Water bowls

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Study Protocol

From pages 8-9 of the report:

Irritation Screening
Two male and two female albino guinea pigs were selected for irritation screening [diagram provided] to determine both the maximum dose producing no more than slight irritation, and the maximum non-irritating dose. Concentrations tested in the screening were 100% (undiluted), and 50%, 20% and 5% v/v dilutions in deionized water, with each animal receiving 0.4 mL of each concentration at different test sites.

Preparation of Animals
Five males and five females were selected for each of two treatment groups. Group I animals served as a naive control group and Group II animals were designated as the test group. On the day prior to each treatment, the animals were prepared by clipping the back of the trunk free of hair to expose a longitudinal area at least 8 x 10 cm on each animal. Individual body weights were recorded on Days 0 and 28.

Test Material Preparation and Administration
Based on the results of the irritation screening, the test material was administered by application of 0.4 mL of undiluted test material. For each induction treatment, Group II animals were treated by introducing the test material beneath a 3.8 x 5 cm patch (a 1.6 x 2.8 cm gauze pad secured to a 3.8 x 5 cm piece of adhesive) known as a Coverlet adhesive dressing (Mfg. by Beiersdorf, Inc., South Norwalk, Conn.). Each adhesive coverlet patch was placed laterally from the midline of the back on the left front quadrant of the exposure area with the edge of the gauze pad adjacent to, but not overlapping the midline of the back [diagram provided]. The entire trunk of each animal was then wrapped with clear polyethylene film to secure the patch in place. Each animal was then placed in a restrainer for approximately six hours. At the end of the exposure period, the animals were removed from the restrainers, the wrappings and patches were removed, and the animals were returned to their cages. Group II animals were treated once weekly for three weeks with 0.4 mL of undiluted test material. Induction treatments were on Days 1, 8 and 15. The same treatment regimen and test site location was used for all three induction treatments. Group I animals remained untreated during the induction phase of the study.

Challenge Treatment
After a two week rest period, all animals (Groups I and II) were each challenged at a virgin test site with an application of 0.4 mL of undiluted test material. The challenge treatment was on Day 29. The dose was applied in a manner identical to the induction treatments, except the test site was placed laterally on the right rear quadrant of the exposure area with the edge of the gauze pad adjacent to the midline of the back [diagram provided].

230

3. Observations

From page 9 of the report:

Observations for skin reactions at each test site were made approximately 24 hours after each treatment. In addition, observations for skin reactions were made approximately 48 hours after the first induction treatment and 48 hours after the challenge treatment.

[The investigators provided a dermal irritation scoring scale]. An average score for each time period was obtained by adding all of the scores for each time period and dividing by the number of test sites scored for that time period. The test material is considered a sensitizer if the mean irritation scores, the total number of animals with scores, and/or the total number of scores for the virgin test site in the test group after the challenge treatment are appreciably greater than those for the naive challenge group.

4. Statistical Analyses

No statistical analysis was conducted.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-6.

C. Results:

1. Irritation Screening Phase

The investigators provided individual dermal reactions data. Two animals had a slight reaction at 24 hours (very faint, usually nonconfluent), no other dermal irritation was reported with any test compound concentration.

2. Definitive Phase

i. Test Compound

The investigators provided individual dermal reaction scores for the test and naive control animals. One test animal had a slight reaction at 24 and 48 hours after first treatment (very faint, usually nonconfluent) and another at 24 hours only after second treatment on day 8, again very faint, usually nonconfluent. No effect was noted after the third dose of the induction phase at 24 hours in the test animals. No effects were noted during the challenge phase. No effect on body weights were noted.

232

ii. Positive Control (DNCB)

The data provided indicated a mean score of 1.3 for the test group after challenge treatment. The naive control group had a mean challenge score of 0.5.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

A skin sensitization study was conducted on 10 male and 10 female short-haired albino guinea pigs to determine if test material CGA-77102 960 EC produced a sensitizing reaction. Five males and five females were assigned to each of two groups, designated Groups I and II. Group I animals remained untreated during the induction phase of the study and served as a naive control group. Group II animals, the test group, were treated with 0.4 mL of undiluted test material (selected from previous screening). The animals were treated once weekly for three weeks, for a total of three treatments. After a two week rest period, all animals (Groups I and II) were challenged at a virgin test site with an application of 0.4 mL of undiluted test material.

The test material produced no irritation in animals of the naive control group (Group I) after the single treatment at challenge. The test material likewise produced no irritation in animals of the test group (Group II) after the challenge and therefore did not elicit a sensitizing reaction in guinea pigs.

2. Reviewers conclusions

In a Dermal Sensitization study, CGA-77102 960 EC was not a dermal sensitizer in guinea pigs tested with the closed patch technique.

234

CGA-77102 915 EC-B ACUTE ORAL TOXICITY - RATS §81-1

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)
Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Oral Toxicity - Rat
Species: Rat Guideline: §81-1

EPA ID No.s: EPA MRID No. 44126802
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 915EC-B
Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102 915EC-B, FINAL REPORT, Study Title: Acute Oral Toxicity Study of CGA-77102 915EC-B in Rats, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504750, September 20, 1996; EPA MRID Number 44126802.

Executive Summary: In an acute oral toxicity study (MRID# 44126802), groups of 5 male and 5 female young adult albino rats (Strain: Crl:CD®(SD)BR from Charles River Laboratories, Inc., Portage, Michigan) received either 500, 1000, 2000, or 5000 mg/kg to females and 2000 or 5000 mg/kg to males of CGA-77102 915EC-B [Purity: 83.3% CGA-77102; Lot Number FL-960621 (Batch Code 1098-21-04)] as a single gavage dose.

The Acute Oral LD_{50} for CGA-77102 915EC-B is:

Males - greater than 5000 mg/kg bw

Females - 2515 mg/kg bw
95% Confidence Limits - 1205 to 5249 mg/kg bw

Combined - 3425 mg/kg bw
95% Confidence Limits - 1772 to 6619 mg/kg bw

Toxicity Category III.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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 915EC-B
Purity: 83.3% CGA-77102
Description: Dark brown liquid
Lot Number: FL-960621 (Batch Code 1098-21-04)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Young adult albino rats
Strain: Crl:CD®(SD)BR
Source: Charles River Laboratories, Inc., Portage, Michigan
Age: Males-6-11 weeks, females-9-16 weeks
Body Weight: 218-299 g

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the acute oral toxicity produced when the test material is administered by the oral route (gavage) to rats.

The dose levels, method, frequency, and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton (CHW) Inc. Standard Operating Procedure (SOP).

Study Timetable

Study Initiation Date	June 5, 1996
Experimental (In-life) Start Date	June 11, 1996
In-life End Date	September 9, 1996
Experimental Termination Date	September 20, 1996
Study Completion Date	September 20, 1996

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were separated by sex and group housed in screen-bottom stainless steel cages. Environmental controls for the animal room were set to maintain a temperature of 19° to 25°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they

236

were documented and considered to have had no adverse effect on the study outcome.

The animals were provided continuous access to Laboratory Rodent Diet #5001, PMI Feeds, Inc., and water except for 17 to 20 hours before test material administration when food, but not water, was withheld. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed. There were no known contaminants in the feed or water at levels that could be expected to interfere with or affect the results of the study.

Ten male and 20 female healthy, acclimated rats, weighing from 218 to 299 g, were utilized in this study. Males were approximately 6 to 11 weeks of age and females were approximately 9 to 16 weeks of age at initiation of treatment. Five males per level were treated at 2,000 and 5,000 mg/kg of body weight. Five females per level were treated at 500, 1,000, 2,000 and 5,000 mg/kg of body weight. The animals were identified by animal number and corresponding ear tag throughout the study.

2. Dose Preparation and Administration

From page 11 of the report:

The undiluted test material was administered by gavage using an average bulk density determination of 1.08 g/mL to determine the dose volume for each dose level. An individual dose was calculated for each animal based on its fasted body weight.

3. Observations

From page 11 of the report:

Body weights were determined before test material administration (Day 0). Additional body weights were determined at Day 7, at termination of the respective in-life phase (Day 14), or at death when survival exceeded 1 day.

Clinical observations were conducted at 1, 2.5, and 4 hours after test material administration and daily thereafter for 14 days. Mortality checks were conducted twice a day (morning and afternoon) for 13 days after test material administration and again the morning of Day 14.

At termination of the respective in-life phase for each dose level, surviving animals were euthanized. All animals, whether found dead during the study or euthanized, were subjected to an abbreviated gross necropsy examination and any abnormalities were recorded. After necropsy, the animals were discarded and no tissues were saved.

237

4. Statistical Analyses

From pages 12 and 14 of the report:

The LD50 values for females and the sexes combined were determined by a computer program using a modified Behren-Reed-Muench cumulant method. No other statistical analysis were required by the protocol.

Reference: Thakur, A. K. and Fezio, W. L., "A Computer Program for Estimating LD50 and its Confidence Limits Using a Modified Behrens-Reed-Muench Cumulant Method," Drug and Chemical Toxicology, 4(3):297-305 (1981).

PROTOCOL DEVIATIONS (from page 30 of the report):

Protocol	Actual Procedure
Page 4, 5. Test Material, B., Reserve Samples. Reserve samples will not be required for this study.	Because this study was over four weeks in length a reserve sample was taken. In order to comply with MAFF requirements, the reserve sample of the test material will be stored at CHW in a freezer set to maintain a temperature of -20°C ±10°C for 10 years.
Page 9, 8. Location of Raw Data, Records, and Final Report, Second and Third Sentences. When the final report is completed, all original paper data, including those items listed below will be retained in the archives of CHW for a period of one year following signing of the final report. One year after signing of the final report, all of the aforementioned materials will be sent to the Sponsor and a return fee will be charged.	In order to comply with MAFF requirements, the final report and all original paper data will be retained in the archives of CHW for 10 years.

These deviations are not considered to have had an adverse effect on the outcome of the study.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-1.

235

C. Results:

1. Mortality

The investigators provided a group summary of the observed mortality. The following table presents the mortality summary (from Table 1, page 16 of the report):

Table I: Mortality Summary

Dose Level (mg/kg)	Mortality, Day Died*
Males	
2000	0/5
5000	1/5, Day 2^1
Females	
500	0/5
1000	2/5, Day 0^2
2000	1/5, Day 0^1
5000	4/5, Days 0^2, 1^2

* = Superscript number indicates number of animals found dead on that day.

Calculated Oral LD_{50} :

Males - greater than 5000 mg/kg bw

Females - 2515 mg/kg bw
95% Confidence Limits - 1205 to 5249 mg/kg bw

Combined - 3425 mg/kg bw
95% Confidence Limits - 1772 to 6619 mg/kg bw

2. Clinical Signs

The investigators provided individual clinical signs. No effects were noted in females at 500 mg/kg. The clinical signs of toxicity for females (3/5) at 1000 mg/kg included staggered gait, tremors, hypoactivity, tonic convulsions, prostration, mydriasis, and/or dyspnea. For animals (9/10) at 2000 mg/kg the clinical signs of toxicity included hypoactivity, excessive salivation, lacrimation, red-stained face, soft stool and/or watery stool with all surviving animals appearing normal by study Day 2. The clinical signs of toxicity in animals at 5000 mg/kg included staggered gait, tremors, hypoactivity, red-stained face, excessive salivation, dyspnea, soft/watery stool and/or dark- or yellow-stained urogenital area with all surviving animals appearing normal by study Day 8.

234

3. Body Weights

The investigators provided individual and average body weights. No relevant treatment related effects were noted on body weight gain in surviving animals. The following table presents the body weights and body weight gains (from Table 2, pages 17-20 of the report):

Table II: Average Body Weights (grams)

Day: / Dose (mg/kg):	0	7	0-7 gain	14	0-14 gain
			Males		
2000	250	330	80	380	130
5000	293	332	40	377	85
			Females		
500	222	259	37	273	51
1000	266	304	35	318	49
2000	225	264	39	273	48
5000	279	289	18	286	15

4. Pathology

The investigators provided individual gross necropsy pathology findings and a summary report by the study pathologist. According to the pathologist (from page 15 of the report): At necropsy, the only findings were in the DOTs [died on test] and pertained to content of the gastrointestinal tract, and pertained to a oral or nasal discharge. The stomach and the small intestines contained material of variable color and consistency which possibly represented test material mixed with ingesta. The oral and nasal discharge was red and of variable consistency. These observations were considered incidental findings and unrelated to the test material. There were no visible lesions in the animals surviving to study termination.

240

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The test material, CGA-77102 915EC-B, was evaluated for its acute oral toxicity potential in male and female rats when administered as a single gavage dose at levels of 2,000 and 5,000 mg/kg of body weight for males and 500, 1,000, 2,000, and 5,000 mg/kg of body weight for females. The estimated oral LD50 values in rats were determined to be greater than 5,000 mg/kg for males, 2,515 mg/kg for females, and 3,425 mg/kg of body weight for the sexes combined. All mortality occurred within 2 days of test material administration. The females treated at 500 mg/kg appeared normal during the study. Clinical signs of toxicity observed in the other dose levels included staggered gait, tremors, hypoactivity, tonic convulsions, prostration, red-stained face, mydriasis, excessive salivation, dyspnea, lacrimation, soft/watery stool, and dark- or yellow-stained urogenital area. The clinical signs of tonic convulsions, tremors, prostration, mydriasis and dyspnea were seen only in those females treated at 1,000 or 5,000 mg/kg that died during the test period. All surviving animals returned to a normal appearance by Day 8 after treatment. Animals surviving to the end of the observation period exhibited body weight gain with the exception of one female treated at 5,000 mg/kg which exhibited an insignificant weight loss during the last week of the study. The only test material related findings observed at necropsy were in those animals dying during the study and pertained primarily to the content of the gastrointestinal tract (possibly representing test material mixed with ingesta).

2. Reviewers conclusions

The Acute Oral LD_{50} for CGA-77102 915EC-B is:

Males - greater than 5000 mg/kg bw

Females - 2515 mg/kg bw
95% Confidence Limits - 1205 to 5249 mg/kg bw

Combined - 3425 mg/kg bw
95% Confidence Limits - 1772 to 6619 mg/kg bw

CGA-77102 915 EC-B ACUTE DERMAL TOXICITY - RABBITS §81-2

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 6/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Dermal Toxicity - Rabbit
Species: Rabbit Guideline: §81-2

EPA ID No.s: EPA MRID No. 44126803
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 915EC-B

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102 915EC-B, FINAL REPORT, Study Title: Acute Dermal Toxicity Study of CGA-77102 915EC-B in Rabbits, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504751, August 15, 1996, EPA MRID Number 44126803.

Executive Summary: In an acute dermal toxicity study (MRID# 44126803), 5 male and 5 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 2000 mg/kg CGA-77102 915EC-B [Purity: Active ingredient - 83.3% CGA-77102; Lot Number FL-960621 (Batch Code 1098-21-04)] as a single topical application to the shaved skin of each animal's back.

The Acute Dermal LD_{50} for CGA-77102 915EC-B is greater than 2000 mg/kg for both sexes. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

242

A. Materials and Methods

Test Compound: CGA-77102 915EC-B
Purity: Active ingredient - 83.3% CGA-77102
Description: Dark brown liquid
Lot Number: FL-960621, (Batch Code 1098-21-04)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbits
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: Approximately 14 to 18 weeks
Body Weight: 2260-2528 g

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the systemic toxicity and relative skin irritancy of a test material when applied to the skin of rabbits.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose level, method, frequency, and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

Study Timetable

Study Initiation Date	May 31, 1996
Experimental (In-life) Start Date	June 13, 1996
In-life End Date	June 27, 1996
Experimental Termination Date	August 15, 1996
Study Completion Date	August 15, 1996

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in suspended stainless steel cages. Environmental controls for the animal room were set to maintain a temperature of 19° to 23°C, a relative

243

humidity of 50% ±20%, and a 12-hour light/ 12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided access to water *ad libitum* and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed. There were no known contaminants in the feed or water at levels that could be expected to interfere with or affect the results of the study.

Five male and five female healthy, acclimated rabbits, weighing from 2,260 to 2,528 g and approximately 14 to 18 weeks of age, were used for a single dose level of 2,000 mg/kg of body weight. The animals were identified by animal number and corresponding ear tag throughout the study. On the day before test material application, each rabbit's back was clipped free of hair. The clipped area made up not less than 20% of total body surface.

2. Dose Preparation and Administration

From page 11 of the report:

The test material was administered as received. An individual dose was calculated and weighed out based on each animal's body weight on the day of test material administration.

The test material was applied to the intact skin on each animals' back at a dose level of 2,000 mg/kg of body weight. The test material was applied to the test site at a rate of approximately 0.03 g/cm^2 in a thin and uniform layer. The area of application (approximately 180 cm^2) was covered with a 4-ply 9.5-cm x 19-cm gauze patch secured with paper tape and overwrapped with Saran Wrap® and Elastoplast® tape to provide an occlusive dressing. Collars were used to restrain the test animals during the 24-hour exposure period.

At the end of the 24-hour exposure period, the restraining collars and bandages were removed and the test sites were washed using tap water and disposable paper towels.

3. Observations

From page 12 of the report:

Body weights were determined before test material administration (Day 0), at Day 7, and at termination of the in-life phase (Day 14).

Clinical observations were conducted at 1, 2.5, and 4 hours after test material administration. Additional clinical observations (including dermal effects) were conducted daily thereafter for 14 days. Mortality checks were conducted twice a day (morning and afternoon) for 13 days after test material

administration and again the morning of Day 14.

At termination of the in-life phase, all animals were euthanized, subjected to an abbreviated gross necropsy examination, and any abnormalities were recorded. After necropsy, the animals were discarded and no tissues were saved.

4. Statistical Analyses

From page 12 of the report:

No statistical analyses were required by the protocol.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-2.

C. Results:

1. Mortality

The investigators provided group summary of the survival rate. No mortality was observed during the study. The estimated dermal LD_{50} for male and female rabbits was determined to be greater than 2000 mg/kg bw.

2. Clinical Signs and Dermal Irritation

The investigators provided individual animal clinical signs and dermal reactions. No adverse clinical signs were noted. There was moderate to severe dermal irritation observed.

34

3. Body Weights

The investigators provided individual animal and average body weights. No relevant treatment related effects were noted. The following table presents the body weights and body weight gains (from Table 2, page 17 of the report):

Table I: Average Body Weights and Body Weight Gains (grams)

Day: / Dose (mg/kg):	0	7	0-7 gain	14	0-4 gain
			Males		
2000	2470	2504	34	2550	80
			Females		
2000	2360	2434	74	2434	74

4. Pathology

The investigators provided individual animal gross necropsy pathology findings and the pathologists summary. No treatment related effects were noted.

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The test material, CGA-77102 915EC-B, was evaluated for its acute dermal toxicity potential in male and female rabbits when administered as a single topical application at a level of 2,000 mg/kg of body weight. The estimated dermal LD_{50} values for male and female rabbits were determined to be greater than 2,000 mg/kg. All animals appeared normal throughout the study. All animals exhibited body weight gain during the study with the exception of two females which exhibited slight weight losses of 4 to 34 g during the second week. The test material produced moderate to severe dermal irritation. The gross necropsy at termination revealed no visible lesions.

2. Reviewers conclusions

The Acute Dermal LD_{50} for CGA-77102 915EC-B is greater than 2000 mg/kg for both sexes.

24

CGA-77102 915EC-B ACUTE INHALATION TOXICITY - RATS §81-3

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 6/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Inhalation Toxicity - Rat
Species: Rat Guideline: §81-3

EPA ID No.s: EPA MRID No. 44126804
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 915EC-B

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J. Bennick (1996): CGA-77102 915EC-B, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2982-96, August 20, 1996; EPA MRID Number 44126804.

Executive Summary: In an acute inhalation toxicity study (MRID# 44126804), 5 male and 5 female rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley; Source: Harlan Sprague Dawley, Inc., Indianapolis, IN) were exposed by the nose only route to a generated aerosol of CGA-77102 915EC-B (Purity: 83.9% active ingredient; Lot No. FL-961327) for 4 hours.

The Acute Inhalation LC_{50} for CGA-77102 Technical is greater than 2.61 mg/L for both sexes. The particle size distribution (MMAD) was 3.434 µm. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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 915EC-B
Purity: 83.9% active ingredient
Description: Brown liquid
Lot No.: FL-961327
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Male and Female Rats (nulliparous and non-pregnant)
Strain: HSD:Sprague-Dawley
Source: Harlan Sprague Dawley, Inc., Indianapolis, IN
Age: Young adult
Body Weight: Males (304-353 g); Females (206-230 g)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the acute inhalation toxicity potential of the test substance in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-3, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No. S9-FF81-3.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data and a copy of this report are kept on file permanently in the STILLMEADOW, Inc. archives. The study was initiated on June 28, 1996, and the animals were exposed on July 5, 1996, at 10:30. The in-life portion of the study was terminated on July 19, 1996.

248

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	One per cage
Environmental Controls Set to Maintain:	·Temperature Range: 72° ± 5°F ·Humidity Range: 30-80% ·12-hour light/dark cycle ·10-12 air changes/hour
Transfer to Clean Cages:	Weekly
Litter Pan Lining:	Paper and aspen bedding
Litter Pan Lining Change:	Three times weekly
Food:	Purina Mills Inc. Feeds, Lab Diet Formula #5008, available ad libitum except during the exposure period
Water Type:	Municipal water supply from automatic water system, available ad libitum except during the exposure period

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Procedures

From page 7-9 of the report:

Prestudy Testing
Trial assays were conducted to determine which method(s) of aerosolizing the test substance into the exposure chamber would produce an acceptable concentration and mass median aerodynamic diameter (MMAD).

Exposure Chamber
A 500 L nose-only stainless steel, dynamic flow inhalation chamber was utilized in this experiment [diagram was provided in the report]. The body of the chamber has 25 ports in 5 rows. Polycarbonate cones are inserted into 10 designated individual ports. The test substance is introduced through the opening in the top of the chamber. The bottom section has a corresponding air outlet and a drain valve for cleaning the chamber. The individual polycarbonate cones (tubes) are tapered at one end to fit the shape of the animal's head and the back portion is sealed with a polycarbonate cap. The cones containing the animals fit tightly into the ports, and are sealed with "O" rings.

Generation of Test Atmosphere
The aerosol was generated by pumping the test substance into a container from which the test substance was directly aspirated by a pressure operated Spraying System Company air atomizer (1/4 JSS) into a baffling chamber. The concentrated aerosol was then diluted with filtered air and drawn into the exposure chamber. Air flow into the chamber was maintained through the use of a calibrated orifice plate at a rate of 17.3 air changes per hour. Air flow was recorded at 30 minute intervals during the exposure period, and was sufficient to ensure an oxygen content of at least 19% of the exposure atmosphere. Temperature and relative humidity were recorded at 30 minute intervals during the exposure period from a Taylor wet bulb/dry bulb hygrometer located in the exposure chamber.

Test Substance Administration
Healthy albino rats were released from quarantine, and five males and five females were selected for testing. The animals were exposed to an aerosol generated from the undiluted liquid test substance for a period of four hours. When 99% concentration (T-99) was attained, the animals which were individually housed in polycarbonate exposure tubes were inserted into a 500 L stainless steel nose-only inhalation chamber for the specified exposure period. At the termination of the exposure period, the animals were returned to their stock laboratory cages.

Determination of Concentration
The concentration of test substance in the exposure atmosphere (taken from the breathing zone of the animals) was determined analytically once per hour, and nominally at the end of the exposure. The analytical determination was made using a Beckman System Gold HPLC with Autoinjector [provided in the report, Appendix A]. The nominal concentration was determined by dividing the loss in weight of the test substance after the exposure by the total volume of air which passed through the chamber.

Particle Size Distribution
Particle size, taken from the breathing zone of the animals, was determined twice during the exposure, using an Andersen cascade impactor, at a rate of 28.3 L/minute for a duration of 1 minute. The MMAD and particle size distributions are calculated from these data.

In-life Observations
Observations for mortality and signs of pharmacologic and/or toxicologic effects were made frequently on the day of exposure and at least once daily thereafter for 14 days (day of exposure considered Day 0). Individual body weights were recorded just prior to the inhalation exposure and on Days 7 and 14.

Postmortem Observations
At study termination, each animal was euthanized by an injection of Fatal Plus (Vortech Pharmaceuticals, Dearborn, Michigan 48126). All study animals were subjected to gross necropsy and all abnormalities were recorded.

250

Statistical Analysis

In order to calculate a mean exposure, the Mean Value Theorem of Calculus was used to properly weight the concentration, since the concentrations could not be measured continuously [provided in the report, Table 5]. This method weights concentrations based on the time span of each concentration. A concentration can be calculated for each minute, which better represents the exposure concentration received by each animal.

Reference (from page 19 of the report): Finney, D.J.: PROBIT ANALYSIS, 3rd ed., Chapters 3 and 4, 1971, Cambridge University Press.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-3.

C. Results:

1. Mortality

The investigators provided individual animal survival. No mortality was reported. The acute inhalation LC_{50} for CGA-77102 Technical is greater than 2.61 mg/L.

2. Clinical Signs

The investigators provided group summary and individual animal data. Clinical signs included activity decrease, nasal discharge, respiratory gurgle, piloerection, polyuria and salivation. No clinical signs were noted by study day 10.

3. Body Weights

The investigators provided individual animal body weights. No relevant treatment related effects were noted. The following table presents the body weight and body weight data (from Table 1, page 11 of the report):

Table 1: Average Body Weights & Body Weight Gains (grams)

Day: / Dose (mg/L):	0	7	0-7 gain	14	0-14 gain
			Males		
2.61	326	315	-11	344	18
			Females		
2.61	215	217	2	230	15

-251

4. Pathology

The investigators provided individual animal gross necropsy findings. No relevant treatment related effects were noted. The only findings noted were discolored lungs in 3 males and 2 females at study termination.

5. Inhalation Chamber Conditions

The investigators provided individual half hour chamber operating parameters. The mean chamber operating parameters were 75°F, 79% relative humidity and the airflow was 133 Lpm. The investigators provided analytical concentration determinations and calculations and particle size distribution determinations. The mean exposure concentration was 2.606 mg/L, the nominal concentration was 5.20 mg/L. The particle size distribution (MMAD) was 3.434 µm.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

CGA-77102 915EC-B was evaluated for its acute inhalation toxicity potential in albino rats. Five males and five females were exposed for four hours in a nose-only inhalation system to an aerosol generated from the undiluted liquid test substance at a level of 2.61 mg/L. There was no mortality during the study. Clinical signs included activity decrease, nasal discharge, respiratory gurgle, piloerection, polyuria and salivation, which were no longer evident by Day 10. Body weights in three males and one female were apparently affected during the first week after exposure. The gross necropsy revealed no observable abnormalities except for discolored lungs in five animals. As indicated by the data, the acute inhalation LC50 for CGA-77102 915EC-B is greater than 2.61 mg/L.

2. Reviewers conclusions

The Acute Inhalation LC_{50} for CGA-77102 Technical is greater than 2.61 mg/L for both sexes. The particle size distribution (MMAD) was 3.434 µm.

352

CGA-77102 915EC-B PRIMARY EYE IRRITATION - RABBITS §81-4

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 7/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)
Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Eye Irritation - Rabbit
Species: Rabbit Guideline: §81-4

EPA ID No.s: EPA MRID No. 44126805
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 915EC-B

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102 915EC-B, FINAL REPORT, Study Title: Primary Eye Irritation Study of CGA-77102 915EC-B in Rabbits, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60401688, June 20, 1996; EPA MRID Number 44126805.

Executive Summary: In a primary eye irritation study (MRID# 44126805), 3 male and 3 female (nonwashed) and 3 female ("washed") adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.1 mL CGA-77102 915EC-B [Purity: 83.3% CGA-77102 active ingredient; Lot Number FL-960621 (Batch Code 1098-21-04)] to one eye (the other serving as untreated control. Two groups were used, one group with the eyes unwashed, the other group had the eyes washed with lukewarm water for 1 minute beginning 30 seconds after test compound instillation.

CGA-77102 915EC-B was moderately to severely irritating in unwashed eyes and moderately irritating to washed eyes. Irritation cleared by 14 days in unwashed eyes and 48 hours in washed eyes after treatment. **Toxicity Category II.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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 915EC-B
Purity: 83.3% CGA-77102 active ingredient
Description: Dark brown liquid
Lot Number: FL-960621 (Batch Code 1098-21-04)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbit
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: Adult, 14-18 weeks
Body Weight: 2448-2798 g
Acclimation Period: At least 7 days

Test Material

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the relative level of irritation produced following a single exposure of a test material to one eye of albino rabbits.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose, method, frequency and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

Study Timetable

Study Initiation Date	April 17, 1996
Experimental (In-life) Start Date	April 18, 1996
In-life End Date	May 2, 1996
Experimental Termination Date	May 2, 1996
Study Completion Date	June 20, 1996

254

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in stainless steel cages. Environmental controls for the animal room were set to maintain a temperature of 19° to 23°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided access to water ad libitum and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed by CHW. There were no known contaminants in the feed or water at levels that would have interfered with or affected the results of the study.

Three male and six female healthy, acclimated rabbits, weighing from 2,448 to 2,798 g and approximately 14-18 weeks of age, were selected at random and identified by animal number and corresponding ear tag. The animals' eyes were examined on the day before test material administration using sodium fluorescein dye procedures. Only those animals with no sign of ocular injury or irritation were used.

2. Dose Preparation and Administration

From page 11 of the report:

The test material was administered as received. The pH of the test material was determined to be 4.9.

Each rabbit received 0.1 mL of the undiluted test material placed into the everted lower lid of the right eye, with the left eye serving as the untreated control. The upper and lower lids were gently held together for 1 second to prevent loss of material and then released. The eyes of the rabbits in Group 1 remained unflushed immediately after treatment while the treated eyes of the rabbits in Group 2 were flushed with lukewarm tap water for 60 seconds starting 30 seconds after test material instillation.

3. Observations

From page 12 of the report:

Animals were weighed before test material administration.

The treated eyes were observed for ocular irritation at 1, 24, 48, 72, and 96 hours after treatment. Additional observations were made at Days 7 and 14

after treatment for the animals in Group 1. Irritation was graded and scored according to the Draize technique using a penlight as the source of illumination. Sodium fluorescein examinations were used to aid in revealing possible corneal injury at the observations conducted at 24, 48, 72, and 96 hours when applicable. [The investigators provided an ocular scoring scale as an attachment]

At termination of the respective in-life phase for each group, all animals were euthanized and discarded.

4. Statistical Analyses

From page 12 of the report:

No statistical analyses were required by the protocol.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-4.

C. Results:

1. Eye Irritation

The investigators provided group summary and individual animal data for eye irritation. The following table presents the eye irritation scores (from Table 1, page 15 of the report): The investigators noted fluorescein staining in 6/6 eyes at 24 hours, 4/6 eyes at 48 hours and 1/6 eyes at 72 hours, none at 96 hours after treatment in the unwashed eyes. No fluorescein staining was noted in the washed eyes.

256

Table I: Average Primary Eye Irritation Scores[a]

Observation Period	Average Score (out of 20) Unwashed	Washed
1 hour	32.2	17.3
24 hours	27.3	7.7
48 hours	19.3	3.3
72 hours	10.3	0.7
4 days	5.3	0.0
7 days	1.7	-
14 days	0.0	-

[a] = The average primary eye irritation score is the total eye irritation score for all the animals divided by the number of animals in each group (6 or 3) at each observation period out of a possible 110.

2. Body Weights

The investigators provided individual animal body weight data only for study initiation.

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The primary eye irritation potential of CGA-77102 915EC-B was evaluated when instilled into the eyes of nine rabbits (six with treated eyes unwashed and three with treated eyes washed approximately 30 seconds after instillation). The test material produced corneal and iridal involvement and moderate to severe conjunctival irritation in unwashed eyes which cleared in all animals by Day 14 after treatment. Positive irritation reactions were observed in all six animals with unwashed eyes which cleared in all animals by the Day 7 observation. In treated eyes receiving a washout, the test material produced corneal and iridal involvement and moderate conjunctival irritation which cleared in all animals by 96 hours after treatment. Positive irritation reactions were observed in all three animals with washed eyes which cleared in all animals by the 48 hour observation.

2. Reviewers conclusions

In a Primary Eye Irritation study, CGA-77102 915EC-B was moderately to severely irritating in unwashed eyes and moderately irritating to washed eyes. Irritation cleared by 14 days in unwashed eyes and 48 hours in washed eyes after treatment. Toxicity Category II.

257

CGA-77102 915EC-B PRIMARY DERMAL IRRITATION - RABBITS §81-5

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)
Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Dermal Irritation - Rabbit
Species: Rabbit Guideline: §81-5

EPA ID No.s: EPA MRID No. 44126806
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 915EC-B
Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102 915EC-B, FINAL REPORT, Study Title: Primary Dermal Irritation Study of CGA-77102 915EC-B in Rabbits, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60401687, June 26, 1996; EPA MRID Number 44126806.

Executive Summary: In a primary dermal irritation study (MRID# 44126806), 3 male and 3 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.5 mL CGA-77102 915EC-B [Purity: 83.3% CGA-77102 active ingredient; Lot Number FL-960621 (Batch Code 1098-21-04)] to the shaved back of each animal.

CGA-77102 915EC-B produced very slight (barely perceptible) erythema and edema reactions at the application site. The mean dermal PIS for the 4, 24, 48, and 72-hour scores was 0.8. No irritation was seen by observation Day 14. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

258

A. Materials and Methods

Test Compound: CGA-77102 915EC-B
Purity: 83.3% CGA-77102 active ingredient
Description: Dark brown liquid
Lot Number: FL-960621 (Batch Code 1098-21-04)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbits
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: 14-18 weeks
Body Weight: 2283 to 2666 g
Acclimation Period: At least 7 days

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the relative level of primary skin irritation of a test material on rabbits under semioccluded conditions.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose, method, frequency, and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

Study Timetable

Study Initiation Date	April 15, 1996
Experimental (In-life) Start Date	April 16, 1996
In-life End Date	April 30, 1996
Experimental Termination Date	April 30, 1996
Study Completion Date	June 26, 1996

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in suspended stainless steel cages. Environmental controls for the

259

animal room were set to maintain a temperature of 19° to 23°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided access to water ad libitum and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed by CHW. There were no known contaminants in the feed or water at levels that could be expected to interfere with or affect the results of the study.

Three male and three female healthy, acclimated rabbits, weighing from 2,283 to 2,666 g and approximately 14-18 weeks of age, were selected at random and identified by animal number and corresponding ear tag. On the day before treatment, the back and/or flanks of each animal were clipped free of hair to obtain an unblemished skin site.

2. Dose Preparation and Administration

From page 11 of the report:

The test material was administered as received. The pH of the test material was determined to be 4.9.

The undiluted test material was applied to the intact skin site on each animal's back (approximate exposure area of 6.25 cm2) in the amount of 0.5 mL. The area of application was covered with an 8-ply 2.5-cm x 2.5-cm gauze patch secured with paper tape, loosely overwrapped with Saran Wrap®, and secured with Elastoplast® tape to provide a semiocclusive dressing.

At the end of the 4-hour exposure period, the patches were removed and the test sites were washed using liquid Ivory® soap mixed with warm tap water, rinsed with clean tap water, and dried with disposable paper towels. The test material was removed from the test sites as thoroughly as possible without irritating the skin.

3. Observations

From page 12 of the report:

Animals were weighed before test material administration.

Thirty minutes after removal of the test material, the degree of erythema and edema at each test site was read according to the Draize technique (recorded as the 4-hour score). Subsequent examinations were made at 24, 48, 72, and 96 hours and Days 7 and 14. [The investigators provided an dermal irritation scoring scale as an attachment]

260

At termination of the in-life phase, all animals were euthanized and discarded.

4. Statistical Analyses

From page 12 of the report:

No statistical analyses were required by the protocol.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-5.

C. Results:

1. Dermal Irritation

The investigators provided group summary and individual animal data for erythema and edema dermal irritation. The following table presents the dermal irritation scores (from Table 3, page 17 of the report):

Table I: Average Primary Dermal Irritation Scores[a]

Observation Period	Average Score (PIS)
4 Hour	1.3
24 Hour	0.7
48 Hour	0.5
72 Hour	0.5
96 Hour	0.3
Day 7	0.2
Day 14	0.0

[a] = The average primary dermal irritation score is the total dermal irritation score for all the animals (erythema and edema) divided by the number of test sites (6) at each observation period.

2. Body Weights

The investigators provided individual animal body weights only for study initiation.

261

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The primary dermal irritation potential of CGA-77102 915EC-B was evaluated in rabbits under 4-hour semioccluded conditions. The test material produced very slight erythema and edema reactions. No other dermal irritation was observed. All irritation cleared by the Day 14 observation. The average of the individual animal index scores is 0.8 (considered to be slightly irritating).

2. Reviewers conclusions

In a Primary Dermal Irritation study, CGA-77102 915EC-B produced very slight (barely perceptible) erythema and edema reactions at the application site. The mean dermal PIS for the 4, 24, 48, and 72-hour scores was 0.8. No irritation was seen by observation Day 14. Toxicity Category IV.

262

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)
Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Dermal Sensitization - Guinea Pigs
Species: Guinea Pigs Guideline: §81-6

EPA ID No.s: EPA MRID No. 44126807
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 915EC-B
Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102 915EC-B, FINAL REPORT, Study Title: Dermal Sensitization Study of CGA-77102 915EC-B in Guinea Pigs - Closed Patch Technique, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504752, September 17, 1996; EPA MRID Number 44126807.

Executive Summary: In a dermal sensitization study (MRID# 44126807), 24 (4 for irritation screeening and 2 groups of 10 for the definitive study) young adult male albino guinea pigs (Strain: Crl:(HA)BR from Charles River Laboratories, Inc., Portage, Michigan and Kingston, New York) received 0.4 mL CGA-77102 915EC-B (Purity: 83.3% CGA-77102; Lot Number FL-960621 [Batch Code 1098-21-04)] to the shaved back of each animal by the closed patch technique.

CGA-77102 915EC-B was a dermal sensitizer in guinea pigs tested with the closed patch technique.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-5) for a dermal sensitization study in guinea pigs.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

263

A. Materials and Methods

Test Compound: CGA-77102 915EC-B
Purity: 83.3% CGA-77102
Description: Dark brown liquid
Lot Number: FL-960621 (Batch Code 1098-21-04)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Positive Control: 2,4-dinitrochlorobenzene
From page 14 of the report:

A study report detailing the results of sensitization testing of 2,4-dinitrochlorobenzene (a known skin sensitizer) using the same sensitization method was appended to the report. This positive control study was conducted within 6 months of the conduct of this study [March 26, 1996, Corning Hazleton, Inc., Laboratory Project Identification: CHW 51104718].

Test Animal(s): Species: Young adult albino guinea pig
Strain: Crl:(HA)BR
Source: Charles River Laboratories, Inc., Portage, Michigan & Kingston, NY
Age: 4-8 weeks
Body Weight: 429-533 g
Acclimation Period: At least 7 days

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the delayed contact hypersensitivity potential of a test material in guinea pigs.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose levels, method, frequency, and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

264

Study Timetable

Study Initiation Date	June 6, 1996
Experimental (In-life) Start Date	June 11, 1996
In-life End Date	July 19, 1996
Experimental Termination Date	July 19, 1996
Study Completion Date	September 17, 1996

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in screen-bottom stainless steel cages. Environmental controls for the animal room were set to maintain a temperature of 19° to 25°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided continuous access to Certified Guinea Pig Diet #5026, PMI Feeds, Inc., and water. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed. There were no known contaminants in the feed or water at levels that could be expected to interfere with or affect the results of the study.

Twenty-four healthy, acclimated male albino guinea pigs, weighing from 429 to 533 g and approximately 4 to 8 weeks of age, were selected and divided into three groups consisting of an irritation screening group of four animals, a test group of 10 animals, and a naive control group of 10 animals. The animals were identified by animal number and corresponding ear tag throughout the study.

2. Study Protocol

From pages 11-12 of the report:

Irritation Screening Study

An irritation screening study using four animals was conducted to determine the irritation threshold of the test material. The test material was administered undiluted and at concentrations of 25%, 50%, and 75% w/v in sterile water with each animal receiving two different concentrations of the test material. All test material mixtures used in the irritation screening phase of the study were stored at room temperature until administered. The appropriate test material concentrations, in the amount of 0.4 mL, were applied to adhesive patches (Hill Top Chamber®, 25-mm diameter). The patches were then placed on two shaved sites (one on the right and one on the left anterior dorsal quadrants) on each animal, covered with an overlapping strip

of dental dam, and overwrapped with Elastoplast® tape. The patches remained in place for 6 hours after which they were removed and the sites were wiped with wet disposable paper towels. The application sites were observed for dermal reactions at 24 and 48 hours after test material application.

Definitive Study
Based on the results of the irritation screening study, the test material was administered undiluted for the induction phase and for the challenge application.

Induction Phase. On the day of test material application, the hair was removed from the back of each animal in the test group with electric clippers. The undiluted test material was applied to each animal by placing 0.4 mL on an adhesive patch (Hill Top Chamber®, 25-mm in diameter) and placing the patch on the induction site along the dorsal anterior left quadrant. The patch was covered with dental dam and overwrapped with Elastoplast® tape. The dressing remained in place for a period of 6 hours after which it was removed and the induction site wiped with wet disposable paper towels. The animals in the test group received one application per week for 3 weeks for a total of three applications. The naive control animals were not treated during this phase of the study.

Challenge Phase. Two weeks following the administration of the third induction dose, a challenge dose of 0.4 mL of the undiluted test material was administered along the dorsal anterior right quadrant of the test group animals in the same manner as during the induction phase of the study. At this time the 10 naive (previously untreated) control animals were also treated in the same manner with a challenge application of the test material.

3. Observations

From pages 12-13 of the report:

On the day of the 24-hour examination following the irritation screening and challenge applications, the application sites of the respective animals were depilated by applying Neet® depilatory. After approximately 15 to 20 minutes, the depilatory was washed from the application sites. The 24-hour observation occurred at least 2 hours after removal of the depilatory.

The respective application sites were examined and scored for dermal reactions according to the following Buehler scoring scale at 24 and 48 hours following the irritation screening, induction, and challenge applications:

264

Buehler Sensitization Scoring Scale

No reaction	0.0
Very faint erythema, usually nonconfluent	0.5
Faint erythema, usually confluent	1.0
Moderate erythema	2.0
Strong erythema, with or without edema	3.0

Clinical observations were conducted daily throughout the study. Body weights on the irritation screening animals were determined only on the day of treatment. Body weights on the definitive study animals were determined before test material administration and at termination of the in-life phase.

At termination of the respective in-life phase for each group, all animals were euthanized and discarded.

Evaluation of Challenge Responses
Determination of sensitization was based on the dermal reactions to the challenge dose. Grades of 1.0 or greater in the test animals may indicate evidence of sensitization, provided grades of less than 1.0 are seen in the naive control animals.

4. Statistical Analyses

From page 13 of the report:

No statistical analyses were required by the protocol.

Protocol Deviations from page 20 of the report:

Protocol	Actual Procedure
Page 4, 5. Test Material, E. Reserve Samples, Second Sentence. The test material reserve samples will be stored at CHW in a freezer set to maintain a temperature of -20°C ±10°C until returned to the Sponsor after completion of the in-life phase of the study.	In order to comply with MAFF requirements, the reserve sample of the test material will be stored at CHW in a freezer set to maintain a temperature of -20°C ±10°C for 10 years.

Page 8, 6. Experimental Design, C. Observation of Animals, (3) Body weights. Before test material administration and at the termination of the experimental phase.	Body weights for the irritation screening animals were determined only on the day of treatment.
Page 9, 8. Location of Raw Data, Records, and Final Report, Second and Third Sentences. When the final report is completed, all original paper data, including those items listed below will be retained in the archives of CHW for a period of one year following signing of the final report. One year after signing of the final report, all of the aforementioned materials will be sent to the Sponsor and a return fee will be charged.	In order to comply with MAFF requirements, the final report and all original paper data will be retained in the archives of CHW for 10 years.

These deviations are not considered to have had an adverse effect on the outcome of the study.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-6.

C. Results:

1. Irritation Screening Phase

The investigators provided individual body weights and dermal reactions data. A very faint erythema reaction was seen in 1 site with the 25% w/v mixture, 1 site with 50% w/v mixture, and 1 site with the 75% w/v mixture with sterile water. No other sites showed dermal irritation. No clinical signs of toxicity were noted.

2. Definitive Phase

a. Clinical Observations

The investigators provided individual clinical signs data, no relevant treatment related effects were noted.

268

b. Body Weights

The investigators provided individual body weights. No treatment related effects were noted.

c. Dermal Reactions

i. Test Compound

The investigators provided individual dermal reaction scores for the test and naive control animals. No effect was noted after the first or second dose of the induction phase at 24 or 48 hours in the test animals. The third dose produced a "moderate erythema" reaction at 24 hours in 1 test animal and a "very faint erythema, usually nonconfluent" reaction in 1 test animal and a "moderate erythema" reaction in another test animal at 48 hours. The challenge phase produced a "very faint erythema, usually nonconfluent" reaction in 1 control animal at 24 hours and no reactions in control animals at 48 hours. In the test group at both 24 and 48 hours, 2 animals exhibited a "very faint erythema, usually nonconfluent reaction, 1 animal exhibited a "faint erythema, usually confluent" reaction and 1 animal exhibited a "moderate erythema" reaction.

D. Conclusions

1. Investigators Summary:

From page 8 of the report:

The delayed contact hypersensitivity potential of CGA-77102 915EC-B was evaluated in albino guinea pigs. The test material was administered undiluted to each animal in the test group during the induction phase of the study. Very faint to moderate erythema reactions (scores of 0.5 to 2.0) were observed in four of the 10 test animals while a very faint erythema reaction (score of 0.5) was seen in one of the 10 naive control animals when the test material was administered undiluted at challenge. Two of the reactions in the test group exceeded the highest naive control reaction. Based on these results, this test material is considered to be a dermal sensitizer in guinea pigs.

2. Reviewers conclusions

In a Dermal Sensitization study, CGA-77102 915EC-B was a dermal sensitizer in guinea pigs tested with the closed patch technique.

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C Dapson 6/4/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/4/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Oral Toxicity - Rat
Species: Rat Guideline: §81-1

EPA ID No.s: EPA MRID No. 43928403
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 II 915 EC

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102 II 915 EC, FINAL REPORT, ACUTE ORAL TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2321-95, November 10, 1995: EPA MRID Number 43928403.

Executive Summary: In an acute oral toxicity study (MRID# 43928403), 20 male and 15 female young adult albino rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley SD from Harlan Sprague Dawley, Inc., Houston, TX) received either 2000, 0, 3500, 4000, or 5050 mg/kg in males and either 2500, 3500, or 5050 mg/kg in females of CGA-77102 II 915 EC-A (Purity: 82.4% CGA-77102; 4.03% CGA-154281; Lot Number FL-951200) as a single gavage dose.

The Acute Oral LD_{50} for CGA-77102 II 915 EC is:

Calculated Oral LD_{50} :
Males - 2675 mg/kg bw
95% Confidence Limits - 1722 to 4156 mg/kg bw

Females - 2952 mg/kg bw
95% Confidence Limits - 2492 to 3498 mg/kg bw

Toxicity Category III.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

270

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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 II 915 EC-A
Purity: 82.4% CGA-77102; 4.03% CGA-154281
Description: Dark amber-brown, clear liquid
Lot Number: FL-951200
Other provided information:
Density: 1.0880 g/mL
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Albino rat (females were nulliparous and non-pregnant)
Strain: HSD:Sprague-Dawley SD
Source: Harlan Sprague Dawley, Inc., Houston, TX
Age: Not provided, "young adult"
Body Weight: Males (226-283 g); Females (172-212 g)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the acute oral toxicity potential of the test material when administered to rats in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-1, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No. S9-FF81-1.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the Sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are on file in the STILLMEADOW, Inc. archives. The study was initiated on August 24, 1995, and the animals were treated as follows:

211

Dose		Male Treatment		Female Treatment		Termination Date	
mg/kg	mL/kg	Date	Time	Date	Time	Males	Females
2000	1.84	09/20/95	9:16 A.M.			10/04/95	
2500	2.30			09/06/95	9:57 A.M.		09/20/95
3500	3.22	09/13/95	11:38 A.M	09/13/95	11:45 A.M	09/27/95	09/27/95
4000	3.68	09/06/95	9:49 A.M.			09/07/95	
5050	4.64	08/30/95	10:08 A.M	08/30/95	10:16 A.M	09/13/95	08/31/95

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Controls Set to Maintain:	·Temperature Range of 72° ± 5°F ·Humidity Range of 30-80% ·12-hour light/dark cycle ·10-12 air changes per hour
Litter Pan Lining:	Paper and aspen bedding; changed three times/week
Food:	Purina Formulab Chow #5008; available ad libitum except for approximately 16 hours before dosing
Water Type:	Municipal water supply, available ad libitum from automatic water system

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Dose Preparation and Administration

From page 8 of the report:

The test material was administered as received and was not diluted. An individual dose was calculated for each animal based on its fasted body weight and administered by gavage at a volume ranging from 1.84 mL/kg at the 2000 mg/kg level to 4.64 mL/kg at the 5050 mg/kg level. Each dose was administered using an appropriately sized syringe and stainless steel ball-tipped intubation needle. The animals were returned to their cages immediately after dosing.

272

3. Observations

From page 8 of the report:

Observations for mortality and clinical/behavioral signs of toxicity were made at least three times on the day of dosing (Day 0) and at least once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing and on Days 7 and 14, or at the time of discovery after death.

At study termination, each surviving animal was euthanized by an overdose of CO_2. All study animals were subjected to gross necropsy and all abnormalities were recorded.

4. Statistical Analyses

From pages 8 and 33 of the report:

The LD_{50} value was calculated by a computer program utilizing probit analysis. No other statistical analyses were required by the protocol.

Reference: Litchfield, J.T., Jr., and Wilcoxon, F.: A Simplified Method of Evaluating Dose-Effect Experiments, J. Pharm. & Exp. Ther., 96, 99-115, 1949.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-1.

C. Results:

1. Mortality

The investigators provided a group summary of the observed mortality along with individual animal data. The following table summarizes the mortality data (from the table on page 9 and Table 1, pages 11-15 of the report):

273

Table I: Mortality Summary

Dose Level (mg/kg)	Mortality, Day Died*
Males	
2000	1/5, Day 1^1
3500	4/5, Days 1^3 and 2^1
4000	5/5, Day 1^5
5050	3/5, Days 1^2 and 2^1
Females	
2500	1/5, Day 1^1
3500	4/5, Day 1^4
5050	5/5, Day 1^5

*** = Superscript number indicates number of animals found dead on that day.**

Calculated Oral LD_{50} :

Males - 2675 mg/kg bw
95% Confidence Limits - 1722 to 4156 mg/kg bw

Females - 2952 mg/kg bw
95% Confidence Limits - 2492 to 3498 mg/kg bw

2. Clinical Signs

The investigators provided summary and individual animal clinical signs data. The clinical signs of toxicity included piloerection (from 1 hour to study Day 4 in males at 2000 mg/kg and females at 3500 mg/kg, to study Day 5 in females at 2500 mg/kg and males at 3500 and 5050 mg/kg), salivation (from 1 to 4 hours in males at 2000 mg/kg and females at 2500 mg/kg, on day 1 in males and females at 3500 mg/kg, from 1 hour to study Day 2 in males at 5050 mg/kg), ptosis (from 4 hours to study Day 2 in males at 2000 mg/kg, from 1 to 4 hours in females at 2500 and 3500 mg/kg, from 1 hours to study Day 1 in males at 3500 mg/kg, from 1 to 2 hours in females at 4000 mg/kg, from 1 hour to study Day 2 in males at 5050 mg/kg), polyuria (from study Day 1 to 4 in females at 2500 mg/kg, on study Day 1 in males and females at 3500 mg/kg, at 2 hours in females at 4000 mg/kg), activity decrease (from study Day 1 to 2 in males at 2000 mg/kg, from 1 to 4 hours in females at 2500 and 3500 mg/kg, from 1 hour to study Day 1 in males at 3500 mg/kg, from 1 hour to study Day 4 in males at 5050 mg/kg), diarrhea (on study Days 1 and 2 in males at 2000 mg/kg, from 1 to 4 hours in females at 2500 mg/kg and males at 3500 mg/kg, from 1 hour to study Day 4 in males at 5050 mg/kg), gasping (from 1 to 4 hours in females at 3500 mg/kg, from 1 to 2 hours in females at 4000 mg/kg, at 2 hours in females at 5050 mg/kg), staining around muzzle (at 2 hours and at study Days 1 and 2 in males at 2000 mg/kg, at 2 hours to study Day 1 in females at 2500 mg/kg, at study day 1 in males at 3500 mg/kg), crust around the

274

nose and eyes (from 1 hours to study Day 3 in females at 2500 mg/kg, at study Day 1 and 2 in males and females at 3500 mg/kg) and respiratory gurgle (from 4 hours to study Day 2 in males at 2000 mg/kg, from 1 to 4 hours in males and females at 3500 mg/kg, from 1 to 2 hours in females at 4000 and 5050 mg/kg). The investigators observed respiratory chirp, clear nasal discharge, convulsions, body tremors, sensitivity to touch, and lateral recumbency in those animals which died. All surviving animals were noted to have returned to a normal appearance by Day 6 after treatment.

3. Body Weights

The investigators provided individual and mean body weights. No relevant treatment-related effects were noted on body weights and body weight gains in surviving animals. The following table presents the body weights and body weight gains calculated by the reviewer (from Table 1, pages 11-15 of the report):

Table II: Mean Body Weights and Body Weight Gains (grams)

Day: / Dose (mg/kg):	0	7	0-7 gain	14	0-14 gain
			Males		
2000	243 (5)[1]	293 (4)	50 (4)	332 (4)	89 (4)
3500	242 (5)	269 (1)	27 (1)	316 (1)	74 (1)
4000	274 (5)				
5050	243 (5)	266 (2)	23 (2)	316 (2)	73 (2)
			Females		
2500	204 (5)	226 (4)	22 (4)	232 (4)	28 (4)
3500	187 (5)	226 (1)	39 (1)	229 (1)	42 (1)
5050	191 (5)				

[1] = number of animals at time point.

4. Pathology

The investigators provided a summary and individual gross necropsy pathology findings and report. According to the investigators: *Gross necropsy in animals that died on test revealed staining and/or matting of anal and muzzle hair, discoloration of the spleen and liver, and gas and discoloration of the contents of the stomach and intestinal tract. All animals surviving to termination revealed no observable abnormalities.* This is supported by the data provided.

275

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

The test material, CGA-77102 II 915 EC, was evaluated for its acute oral toxicity potential in albino rats when administered as gavage doses at levels of 2000, 3500, 4000 and 5050 mg/kg to males, and at levels of 2500, 3500 and 5050 mg/kg to females. Mortality occurred at all dose levels. Clinical signs of toxicity included piloerection, salivation, ptosis, polyuria, activity decrease, diarrhea, gasping, staining around muzzle, crust around the nose and eyes, and respiratory gurgle. Respiratory chirp, clear nasal discharge, convulsions, body tremors, sensitivity to touch, and lateral recumbency were observed only in animals dying on test. Animals surviving to termination of the study were asymptomatic by Day 6. There was no effect on body weight gain in animals surviving to termination. Gross necropsy findings primarily pertained to the contents of the gastrointestinal tract in animals dying on test.

The acute oral LD50's of CGA-77102 II 915 EC were determined to be 2675 mg/kg in males and 2952 mg/kg in females.

2. Reviewers' Conclusions

The Acute Oral LD_{50} for CGA-77102 II 915 EC is:

Calculated Oral LD_{50} :

Males - 2675 mg/kg bw
95% Confidence Limits - 1722 to 4156 mg/kg bw

Females - 2952 mg/kg bw
95% Confidence Limits - 2492 to 3498 mg/kg bw

Toxicity Category III

CGA-77102 II 915 EC ACUTE DERMAL TOXICITY - RABBITS §81-2

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Dermal Toxicity - Rabbit
Species: Rabbit Guideline: §81-2

EPA ID No.s: EPA MRID No. 43928404
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 II 915 EC

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102 II 915 EC, FINAL REPORT, ACUTE DERMAL TOXICITY STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2322-95, October 13, 1995; EPA MRID Number 43928304.

Executive Summary: In an acute dermal toxicity study (MRID# 43928404), 5 male and 5 female albino rabbits (females were nulliparous and non-pregnant; Strain: New Zealand White from Ray Nichols Rabbitry; Lumberton, Texas) received 2020 mg/kg CGA-77102 II 915 EC-A (Purity: 82.4% CGA-77102; 4.03% CGA-154281; Lot Number FL-951200) by the dermal route.

The Acute Dermal LD_{50} for CGA-77102 II 915 EC is greater than 2020 mg/kg for both sexes. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

277

A. Materials and Methods

Test Compound: CGA-77102 II 915 EC-A
Purity: 82.4% CGA-77102; 4.03% CGA-154281
Description: Dark amber-brown, clear liquid
Lot Number: FL-951200
Other provided information:
Density:1.0880 g/mL
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Albino rabbit. (females were nulliparous & non-pregnant)
Strain: New Zealand White
Source: Ray Nichols Rabbitry; Lumberton, Texas
Age: Not provided, "Young adult"
Body Weight: Males (2.750-2.975 kg); Females (2.325-2.700 kg)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the acute dermal toxicity potential of the test material when administered to rabbits in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-2, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No. S9-FF81-2.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations, effective October 30, 1989. In the opinion of the Sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are on file in the STILLMEADOW, Inc. archives. The study was initiated on August 24, 1995, and the animals were treated on September 7, 1995. The in-life portion of the study was terminated on September 21, 1995.

278

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Controls Set to Maintain:	·Temperature Range of 72° ± 5°F ·Humidity Range of 30-80% ·12-hour light/dark cycle ·10-12 air changes per hour
Litter Pan Lining:	Paper; changed daily
Food:	Purina Rabbit Chow; available in measured amounts
Water Type:	Municipal water supply, available ad libitum from automatic water system

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Dose Preparation and Administration

From page 8 of the report:

Healthy albino rabbits were released from quarantine. Each animal was prepared on the day prior to treatment by clipping the dorsal surface of the trunk free of hair to expose not less than 10% of the total body surface area. Care was taken to avoid abrading the skin. Only those animals with exposure areas free of pre-existing skin irritation or defects were used for this study. All animals were treated with 2020 mg/kg (1.86 mL/kg) of undiluted test material. An individual dose was calculated for each animal based on its Day 0 body weight just before exposure. The test material was applied evenly to each exposure area in a thin, uniform layer. The area of application was covered with an appropriately sized surgical gauze patch (8 x 4 in) and secured with non-irritating adhesive tape. The trunk of each animal was then wrapped with a semi-permeable dressing (orthopedic stockinette) and secured in place with non-irritating adhesive tape to prevent possible ingestion of the test material.

After 24 hours, the wrappings were removed. The test sites were gently washed with room temperature tap water and a clean wet cloth to remove as much residual test material as possible.

279

3. Observations

From page 8 of the report:

Observations for mortality and clinical/behavioral signs of toxicity were made at least three times on the day of dosing (Day 0) and at least once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing and on Days 7 and 14.

Observations for evidence of dermal irritation were made at approximately 30 minutes after removal of wrappings, and on Days 3, 7, 10 and 14.

At study termination, animals were euthanized by an intracardiac injection of Fatal Plus (Vortech Pharmaceuticals, Dearborn, Michigan 48126). All study animals were subjected to gross necropsy and all abnormalities were recorded. After necropsy, the animal carcasses were discarded.

4. Statistical Analyses

No statistical analysis was conducted.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-2.

C. Results:

1. Mortality

The investigators provided individual animal and group summary of the survival rate. No mortality was observed during the study. The estimated dermal LD_{50} for male and female rabbits was determined to be greater than 2020 mg/kg bw.

2. Clinical Signs

The investigators provided group summary and individual animal clinical signs and dermal reactions. Clinical signs were one male that had polyuria on study Day 1. Dermal irritation included erythema, edema, atonia, and desquamation with the signs of erythema, edema and atonia no longer present by study Day 10. Desquamation was noted through study Day 14 in all animals.

280

3. Body Weights

The investigators provided individual animal and mean body weights. No relevant treatment related effects were noted. The following table presents the body weights and body weight gains (from Table 1, page 11 of the report):

Table I: Mean Body Weights and Body Weight Gains (grams)

Males Day: Dose (mg/kg):	0	7	0-7 gain	14	0-14 gain
			Males		
2020	2815	2945	130	3045	230
			Females		
2000	2515	2645	130	2785	270

4. Pathology

The investigators provided individual animal gross necropsy pathology findings. No treatment related effects were noted.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

The test material, CGA-77102 II 915 EC, was evaluated for its dermal toxicity potential in albino rabbits when a single undiluted dose, at a level of 2020 mg/kg, was applied to the intact skin of albino rabbits. No mortality occurred during the study. The only clinical sign observed was polyuria in one male on Day 1. There was no effect on body weight gain with the exception of one male that exhibited weight loss during the second week of the study. The gross necropsy conducted at termination of the study revealed no observable abnormalities. The estimated acute dermal LD50, as indicated by the data, was determined to be greater than 2020 mg/kg body weight.

2. Reviewers conclusions

The Acute Dermal LD_{50} for CGA-77102 II 915 EC is greater than 2020 mg/kg for both sexes.

CGA-77102 II 915 EC ACUTE INHALATION TOXICITY - RATS §81-3

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Inhalation Toxicity - Rat
Species: Rat Guideline: §81-3

EPA ID No.s: EPA MRID No. 43928405
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 II 915 EC

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J. Bennick (1995): CGA-77102 II 915 EC, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2323-95, November 22, 1995; EPA MRID Number 4398405.

Executive Summary: In an acute inhalation toxicity study (MRID# 43928405),5 male and 5 female rats (females were nulliparous and non-pregnant, (Strain: HSD:Sprague-Dawley; Source: Harlan Sprague Dawley, Inc., Houston, Texas) were exposed by the nose only route to a generated aerosol of CGA-77102 II 915 EC (Purity: 82.4% CGA-77102; 4.03% CGA-154281; Lot Number: FL-951200) at a concentration of 3.06 mg/L.

The Acute Inhalation LC_{50} for CGA-77102 II 915 EC is greater than 3.058 mg/L for both sexes. The particle size distribution (MMAD) was 3.092 µm. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

282

A. Materials and Methods

Test Compound: CGA-77102 II 915 EC
Purity: 82.4% CGA-77102; 4.03% CGA-154281
Description: Dark amber-brown, clear liquid
Lot Number: FL-951200
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Rats (females were nulliparous and non-pregnant)
Strain: HSD:Sprague-Dawley
Source: Harlan Sprague Dawley, Inc., Houston, Texas
Age: Young adults
Body Weight: Males (285-320 g); Females (206-221 g)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the acute inhalation toxicity potential of the test material in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-3, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No. S9-FF81-3.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data and a copy of this report are kept on file permanently in the STILLMEADOW, Inc. archives. The study was initiated on August 24, 1995, and the animals were exposed on September 18, 1995, at 10:26 A.M. The in-life portion of the study was terminated on October 9, 1995.

283

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	One per cage
Environmental Controls Set to Maintain:	·Temperature Range: 72° ± 5°F ·Humidity Range: 30-80% ·12-hour light/dark cycle ·10-12 air changes/hour
Transfer to Clean Cages:	Weekly
Litter Pan Lining:	Paper and aspen bedding
Litter Pan Lining Change:	Three times weekly
Food:	Purina Formulab Chow #5008, available ad libitum except during the exposure period
Water Type:	Municipal water supply from automatic water system, available ad libitum except during the exposure period

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Procedures

From pages 7-9 of the report:

Prestudy Testing
Trial assays were conducted to determine which method(s) of aerosolizing the test material into the exposure chamber would produce an acceptable concentration and mass median aerodynamic diameter (MMAD).

Exposure Chamber
A 500 L nose-only stainless steel, dynamic flow inhalation chamber was utilized in this experiment (Diagram 1). The body of the chamber has 25 ports in 5 rows. Polycarbonate cones are inserted into 10 designated individual ports. The test material is introduced through the opening in the top of the chamber. The bottom section has a corresponding air outlet and a drain valve for cleaning the chamber. The individual polycarbonate cones (tubes) are tapered at one end to fit the shape of the animal's head and the back portion is sealed with a polycarbonate cap. The cones containing the animals fit tightly into the ports, and are sealed with "O" rings.

Generation of Test Atmosphere
The aerosol was generated by pumping the test material into a pressure operated Spraying System Company air atomizer (1/4 JSS) and then elutriating

284

the resulting aerosol through a baffling chamber. The concentrated aerosol was then diluted with filtered air and drawn into the exposure chamber. Air flow into the chamber was maintained through the use of a calibrated critical orifice at a rate of 11.5 air changes per hour. Air flow was recorded at 30 minute intervals during the exposure period, and was sufficient to ensure an oxygen content of at least 19% of the exposure atmosphere. Temperature and relative humidity were recorded at 30 minute intervals during the exposure period from a Taylor wet bulb/dry bulb hygrometer located in the exposure chamber.

Test Material Administration
Healthy albino rats were released from quarantine, and five males and five females were selected for testing. The animals were exposed to an aerosol generated from the undiluted liquid test material for a period of four hours. When 99% concentration (T-99) was attained, the animals which were individually housed in polycarbonate exposure tubes were inserted into a 500 L stainless steel nose-only inhalation chamber for the specified exposure period. At the termination of the exposure period, the animals were washed and returned to their stock laboratory cages.

Determination of Concentration
The concentration of test material in the exposure atmosphere (taken from the breathing zone of the animals) was determined analytically once per hour, and nominally at the end of the exposure. The analytical determination was made using a Beckman System Gold HPLC with Autoinjector (Appendix A). The nominal concentration was determined by dividing the loss in weight of the test material after the exposure by the total volume of air which passed through the chamber.

Particle Size Distribution
Particle size, taken from the breathing zone of the animals, was determined twice during the exposure, using an Andersen cascade impactor, at a rate of 28.3 L/minute for a duration of 1 minute. The MMAD and particle size distributions are calculated from these data.

In-life Observations
Observations for mortality and signs of pharmacologic and/or toxicologic effects were made frequently on the day of exposure and at least once daily thereafter for 21 days (day of exposure considered Day 0). Individual body weights were recorded just prior to the inhalation exposure and on Days 7, 14 and 21.

Postmortem Observations
At study termination, each animal was euthanized by an injection of Fatal Plus (Vortech Pharmaceuticals, Dearborn, Michigan 48126). All study animals were subjected to gross necropsy and all abnormalities were recorded.

Statistical Analysis
In order to calculate a mean exposure, the Mean Value Theorem of Calculus was

285

used to properly weight the concentration, since the concentrations could not be measured continuously [provided in Table 5 of the report]. This method weights concentrations based on the time span of each concentration. A concentration can be calculated for each minute, which better represents the exposure concentration received by each animal.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-3.

C. Results:

1. Mortality

The investigators provided individual animal survival. No mortality was report during the study. The acute inhalation LC_{50} for CGA-77102 II 915 EC is greater than 3.06 mg/L.

2. Clinical Signs

The investigators provided group summary and individual animal data. Clinical signs included gasping in males, polyuria in females, and activity decrease, crust around the nose, nasal discharge and ptosis in both sexes which was no longer observed in males by study day 13 and females by study day 6. Piloerection and respiratory gurgle was seen in both sexes through study day 21.

3. Body Weights

The investigators provided individual animal and mean body weights. All animals lost weight during the first 7 days and the males tended to recover over the 21 day observation period whereas the females did not gain any weight. The following table presents the body weights and body weight gains (from Table 1, page 11 of the report):

Table I: Mean Body Weights and Body Weight Gains (grams)

Males Day:	0	7	0-7gain	14	0-14gain	21	0-21gain
Dose:				Males			
3.06mg/L	297	278	-19	294	-3	319	22
				Females			
3.06mg/L	216	202	-14	214	-2	213	-3

286

4. Pathology

The investigators provided individual animal gross necropsy findings. Two males and 2 females had discolored lungs at necropsy. No other animals had significant observations.

5. Inhalation Chamber Conditions

The investigators provided individual half-hour chamber operating parameters. The mean chamber operating parameters were 72°F, 57% relative humidity and an airflow rate of 113 Lpm. The investigators provided analytical concentration determinations and calculations and particle size distribution determinations. The mean exposure concentration was 3.06 mg/L, the nominal concentration was 3.58 mg/L. The particle size distribution (MMAD) was 3.092 µm.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

CGA-77102 II 915 EC was evaluated for its acute inhalation toxicity potential in albino rats. Five males and five females were exposed for four hours in a nose-only inhalation system to an aerosol generated from the undiluted liquid test material at a level of 3.06 mg/L. There was no mortality during the study. Clinical signs included activity decrease, crust around the nose, gasping, nasal discharge, polyuria and ptosis, which were no longer evident by Day 13. Slight piloerection and respiratory gurgle persisted through Day 21. Body weights were apparently affected by exposure. Three males and four females lost weight during the first week; one of the males also lost weight during the second week, and one of the females lost weight through termination of the study. The gross necropsy revealed discolored lungs in two males and two females. As indicated by the data, the acute inhalation LC50 for CGA-77102 II 915 EC is greater than 3.06 mg/L.

2. Reviewers conclusions

The Acute Inhalation LC_{50} for CGA-77102 II 915 EC is greater than 3.06 mg/L for both sexes. The particle size distribution (MMAD) was 3.092 µm. Toxicity Category IV.

28?

CGA-77102 II 915 EC PRIMARY EYE IRRITATION - RABBITS §81-4

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

Secondary Review by: Nancy E. McCarroll Nancy McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Eye Irritation - Rabbit
Species: Rabbit Guideline: §81-4

EPA ID No.s: EPA MRID No. 43928406
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 II 915EC

Synonyms: Alpha-metolachlor; A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102 II 915EC, FINAL REPORT, PRIMARY EYE IRRITATION STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2043-95, August 21, 1995; EPA MRID Number 43928406.

Executive Summary: In a primary eye irritation study (MRID# 43928406, 3 male and 3 female (nonwashed) and 3 female ("washed") albino rabbits (Strain: New Zealand White from Ray Nichols Rabbitry, Lumberton, Texas) received 0.1 mL CGA-77102 II 915EC (Purity: 82.4% CGA-77102; 4.07% CGA-154281; Lot Number FL-950295) to one eye (the other serving as untreated control). Two groups were used, one group with the eyes unwashed, the other group had the eyes washed with lukewarm water for 1 minute beginning 30 seconds after test compound instillation.

CGA-77102 II 915 EC was mildly irritating in unwashed eyes and mildly irritating to washed eyes. Irritation cleared by 7 days in unwashed eyes and 72 hours in washed eyes after treatment. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

288

A. Materials and Methods

Test Compound: CGA-77102 II 915EC
Purity: 82.4% CGA-77102; 4.07% CGA-154281
Description: Dark amber-brown, clear liquid
Lot Number: FL-950295
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Albino rabbit
Strain: New Zealand White
Source: Ray Nichols Rabbitry, Lumberton, Texas
Age: Young adult (3-6 months)
Body Weight: Males (2.375-2.550 kg); Females (2.150-2.650 kg)
Acclimation Period: At least five days

B. Study Design

From page 7 of the report:

The objective of this study was to determine the eye irritation potential of the test material in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-4, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation, according to the approved protocol (No. S9-FF81-4.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the Sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are on file in the STILLMEADOW, Inc. archives. The study was initiated on April 27, 1995, and the animals were treated with the test material between 13:52 and 14:00 on May 15, 1995. The in-life portion of the study was terminated on May 25, 1995.

289

1. Animal Husbandry and Assignment

From page 8 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Conditions Set to Maintain:	·Temperature Range of 72° ± 5°F ·Humidity Range of 30-80% ·12-hour light/dark cycle ·10-12 air changes per hour
Litter Pan Lining:	Paper; changed daily
Food:	Purina Rabbit Chow; presented in measured amounts
Water Type:	Municipal water supply, available ad libitum from automatic water system

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Dose Preparation and Administration

From page 8 of the report:

Prior to starting the study, the pH of the test material was determined to be 3.57. Healthy albino rabbits were released from quarantine. Both eyes of each animal were carefully examined at least 24 hours prior to treatment with a fluorescein sodium ophthalmic solution. Both eyes of each animal were again carefully examined just prior to treatment, but without the fluorescein sodium ophthalmic solution. Only those animals without eye defects or irritation were selected for testing.

On Day 0, a dose of 0.1 mL of the undiluted test material was placed into the conjunctival sac of the right eye of each animal by gently pulling the lower lid away from the eyeball to form a cup into which the test material was dropped. The lids were gently held together for one second to prevent loss of material. Three of the treated eyes ("washed eyes") were each washed with room temperature deionized water for one minute beginning 30 seconds after treatment. The untreated left eyes served as comparative controls.

3. Observations

From page 9 of the report:

The treated eyes of all animals were examined under normal room lighting without magnification, and the grades of ocular reaction were recorded at 1,

240

24, 48 and 72 hours, and at 4, 7 and 10 days after treatment. The corneas of all treated eyes were examined immediately after the 24-hour observation with a fluorescein sodium ophthalmic solution. Any of the corneas which exhibited positive fluorescein staining at the 24-hour observation were re-examined with the fluorescein sodium ophthalmic solution at each consecutive observation until fluorescein staining of the cornea no longer occurred. All treated eyes were washed with room temperature deionized water for one minute immediately after recording the 24-hour observation.

Irritation Scoring Method
Individual irritation scores for each animal at each scheduled observation were determined using the grading scale given in the Legend to Table 1. An average irritation score for each scheduled observation for all nonwashed and washed eyes was then determined, based on the number of animals tested in those groups. A maximum average irritation score for nonwashed and washed eyes was derived from the observation yielding the highest average irritation score. The maximum average irritation scores were used to rate the test material according to the ratings presented in the Legend to Table 2 [the investigators provided an ocular irritation scoring scale]. Any corneal involvement or iridic irritation with a score of 1 or more is considered positive. Any conjunctival irritation (redness or chemosis) with a score of 2 or more is considered positive.

4. Statistical Analyses

No statistical analysis was performed.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-4.

C. Results:

1. Eye Irritation

The investigators provided group summary and individual animal data for eye irritation. The following table presents the eye irritation scores (from Table 2, page 19 of the report): The investigators noted fluorescein staining in 1/6 eyes through 72 hours after treatment in the unwashed eyes. No fluorescein staining was noted in the washed eyes.

Table I: Average Primary Eye Irritation Scores[a]

Observation Period	Average Score (out of 110) Unwashed	Washed
1 hour	12.0	10.7
24 hours	13.2	7.3
48 hours	10.2	3.3
72 hours	6.7	1.3
4 days	3.0	0.7
7 days	1.0	0.0
10 days	0.0	0.0
Max. Average	13.2	10.7

[a] = The average primary eye irritation score is the total eye irritation score for all the animals divided by the number of animals in each group (6 or 3) at each observation period out of a possible 110.

b. Body Weights

No data were reported.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

A primary eye irritation study was conducted on nine albino rabbits using test material CGA-77102 II 915EC. The undiluted test material (0.1 mL) was placed into the conjunctival sac of the right eye of each animal selected for testing. Three of the treated eyes ("washed eyes") were each washed with room temperature deionized water for one minute beginning 30 seconds after treatment. All treated eyes were washed with room temperature deionized water for one minute immediately after recording the 24-hour observation. The number of animals testing "positive" for each parameter (according to the Legend to Table 1) over the number of animals tested is presented below.

292

CGA-77102 II 915 EC PRIMARY EYE IRRITATION - RABBITS S81-4

	Time After Treatment - Hours				Day		
	1	24	48	72	4	7	10
	NONWASHED EYES						
Cornea Opacity	0/6	1/6	1/6	1/6	0/6	0/6	0/6
Iritis	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Conjunctivae Redness	6/6	6/6	6/6	3/6	2/6	0/6	0/6
Chemosis	0/6	2/6	1/6	1/6	0/6	0/6	0/6
	WASHED EYES						
Cornea Opacity	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Conjunctivae Redness	3/3	2/3	1/3	0/3	0/3	0/3	0/3
Chemosis	0/3	0/3	0/3	0/3	0/3	0/3	0/3

There were no "positive" effects exhibited in nonwashed eyes on Day 7 after treatment. There were no "positive" effects exhibited in washed eyes at 72 hours after treatment.

2. Reviewers conclusions

In a Primary Eye Irritation study, CGA-77102 II 915 EC was mildly irritating in unwashed eyes and mildly irritating to washed eyes. Irritation cleared by 7 days in unwashed eyes and 72 hours in washed eyes after treatment. Toxicity Category III.

293

CGA-77102 II 915 EC PRIMARY DERMAL IRRITATION - RABBITS §81-5

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Dermal Irritation - Rabbit
Species: Rabbit Guideline: §81-5

EPA ID No.s: EPA MRID No. 43928407
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 II 915 EC

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102 II 915EC, FINAL REPORT, PRIMARY DERMAL IRRITATION STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2044-95, June 27, 1995; EPA MRID Number 43928407.

Executive Summary: In a primary dermal irritation study (MRID# 43928407), 3 male and 3 female albino rabbits (Strain: New Zealand White from Ray Nichols Rabbitry; Lumberton, Texas) received 0.5 mL CGA-77102 II 915EC (Purity: 82.4% CGA-77102; 4.07% CGA-154281; Lot Number FL-950295) to the shaved back of the animals.

CGA-77102 II 915 EC produced erythema through 48 hours and edema in one male and one female at the 1/2 hour observation. No other signs of dermal irritation were observed during the study. The mean PIS for the 1/2, 24, and 48-hour scores was 0.5. No irritation was seen by 72 hours. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

294

A. Materials and Methods

Test Compound: CGA-77102 II 915EC
Purity: 82.4% CGA-77102; 4.07% CGA-154281
Description: Dark amber-brown, clear liquid
Lot Number: FL-950295
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Albino rabbit
Strain: New Zealand White
Source: Ray Nichols Rabbitry; Lumberton, Texas
Age: Young adult (3-6 months)
Body Weight: Males (2.125-2.550 kg); Females (2.200-2.625 kg)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the dermal irritation potential of the test material in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-5, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation, according to the approved protocol (No. S9-FF81-5.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the Sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are on file in the STILLMEADOW, Inc. archives. The study was initiated on April 27, 1995, and the animals were treated with the test material between 9:47 and 9:56 A.M. on May 16, 1995. The in-life portion of the study was terminated on May 19, 1995.

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Controls Set to Maintain:	·Temperature Range of 72° ± 5°F ·Humidity Range of 30 - 80% ·12-hour light/dark cycle ·10-12 air changes per hour
Litter Pan Lining:	Paper; changed daily
Food:	Purina Rabbit Chow; presented in measured amounts
Water Type:	Municipal water supply, available ad libitum from automatic water system

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Dose Preparation and Administration

From page 8 of the report:

Prior to starting the study, the pH of the test material was determined to be 4.51. Each animal was prepared on the day prior to treatment by clipping the dorsal area of the trunk free of hair to expose an area at least 8 x 8 cm. Only those animals with exposure areas free of pre-existing skin irritation or defects were selected for testing. A single intact exposure site was selected as the test site while the contralateral intact site served as a control site.

On Day 0, 0.5 mL of the undiluted test material was applied to each test site and covered with a surgical gauze patch measuring 2.5 x 2.5 cm and two single layers thick. Each patch was covered with plastic film and secured in place with a strip of non-irritating adhesive tape. The entire trunk of each animal was loosely wrapped with a semi-permeable dressing (orthopedic stockinette) and secured on both edges with strips of tape to retard evaporation of volatile substances and to prevent possible ingestion of the test material.

After four hours, the patches and wrappings were removed. The test sites were gently washed with room temperature tap water and a clean wet cloth to remove as much residual test material as possible.

248

3. Observations

From page 8 of the report:

The test sites were observed for erythema formation, edema formation, and any other dermal defects or irritation at 1/2, 24, 48 and 72 hours after washing.

Irritation Scoring Method
The scoring scale used to rate dermal irritation was provided by the investigators based on the method of Draize as an appendix to the report. For each animal, all of the erythema and edema scores through 72 hours were added, and the sum was divided by 4 to obtain an individual irritation score. The primary irritation index was determined by calculating the mean of the irritation scores for the six animals and was used to obtain a rating for the test material.

4. Statistical Analyses

No statistical analysis was conducted.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-5.

C. Results:

1. Dermal Irritation

The investigators provided individual animal data for erythema and edema dermal irritation. Erythema was observed through 48 hours. Edema was observed in one male and one female at the 1/2 hour observation. No other signs of dermal irritation were observed during the study. The Primary Irritation Score was 0.5 (individual scores are presented in the Investigators Summary below).

2. Body Weights

No data were provided.

247

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

A primary dermal irritation study was conducted on six albino rabbits using test material CGA-77102 II 915EC. There was one intact test site per animal. Each test site was treated with 0.5 mL of undiluted test material and maintained in contact with the skin for 4 hours. Observations for dermal irritation and defects were made at 1/2, 24, 48 and 72 hours after removal of the dressings.

Irritation scores derived from the respective erythema and edema scores through the 72 hour observations for each animal are presented below.

	Erythema				Edema				
Animal	Hours after Unwrap				Hours after Unwrap				Irritation
Number	1/2	24	48	72	1/2	24	48	72	Scores
9930-M	1	1	0	0	1	0	0	0	0.75
9932-M	1	0	0	0	0	0	0	0	0.25
9934-M	1	0	0	0	0	0	0	0	0.25
9925-F	1	0	0	0	0	0	0	0	0.25
9927-F	1	0	0	0	1	0	0	0	0.50
9929-F	1	1	1	0	0	0	0	0	0.75

Based on the scores for the above observations, the Primary Irritation Index (PII) is 0.5. The test material is therefore rated slightly irritating.

2. Reviewers conclusions

In a Primary Dermal Irritation study, CGA-77102 II 915 EC produced erythema through 48 hours and edema in one male and one female at the 1/2 hour observation. No other signs of dermal irritation were observed during the study. The mean PIS for the 1/2, 24, and 48-hour scores was 0.5. No irritation was seen by 72 hours. Toxicity Category IV.

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Dermal Sensitization - Guinea Pigs
Species: Guinea Pigs Guideline: §81-6

EPA ID No.s: EPA MRID No. 43928408
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 II 915 EC

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102 II 915 EC, FINAL REPORT, DERMAL SENSITIZATION STUDY IN GUINEA PIGS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2324-95, November 13, 1995; EPA MRID Number 43928408.

Executive Summary: In a dermal sensitization study (MRID# 43928408), 2 male and 2 female (Irritation Screening) and 10 male and 10 female (Definitive Study) guinea pigs (Strain: Hartley-Albino from SASCO Inc., Madison, WI.) received 0.4 mL CGA-77102 II 915 EC-A (Purity: 82.4% CGA-77102; 4.03% CGA-154281; Lot Number FL-951200) to the shaved back of each animal with the closed patch technique.

CGA-77102 II 915 EC did not induce dermal sensitization in guinea pigs tested with the closed patch technique.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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 II 915 EC-A
Purity: 82.4% CGA-77102; 4.03% CGA-154281
Description: Dark amber-brown, clear liquid
Lot Number: FL-951200
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Positive Control: from page 8 of the report:

Label:	C-3762 Lot 52HO0471 Grade II: Approx. 95% SIGMA 1-CHLORO-2,4-DINITROBENZENE
Manufacturer:	SIGMA Chemical Company
Physical Description:	Light brown crystals
Storage:	Room temperature
Concentration Administered:	Induction: 0.45% w/v solution in 80% ethanol Challenge: 0.1% w/v solution in 80% ethanol
Purity, Composition and Stability:	Available from manufacturer
Vehicle Material:	Alcohol Dehydrated, USP Absolute 200 Proof Lot 94117

Positive Control Testing

The sensitivity of guinea pigs to a positive control material (1-chloro-2,4-dinitrobenzene) is confirmed in this laboratory periodically. The positive control animals used to conduct this study were supplied by SASCO Inc., and were tested according to the Buehler Method (Ritz, H.L. and E.V. Buehler, "Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests", Current Concepts in Cutaneous Toxicity, p.28, Academic Press, NY, 1980).

STILLMEADOW, Inc. Study No. 2061-95
In-life start: May 24, 1995; In-life completed: June 23, 1995

Results: Data from this study are presented in Appendix A. A mean score of 1.3 for the test group after challenge treatment, when compared with the naive control group mean challenge score of 0.5, confirmed the sensitivity of guinea pigs to the positive control material.

Test Animal(s): Species: Guinea Pig
Strain: Hartley-Albino
Source: SASCO Inc., Madison, WI.
Age: Not provided
Body Weight: Males (352-458 g); Females (330-467 g)
Acclimation Period: At least five days

300

B. Study Design

From page 6 of the report:

The objective of this study was to determine the sensitizing potential of the test material using a modification of the Buehler method (Ritz, H. L. and E.V. Buehler, "Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests," Current Concepts in Cutaneous Toxicity, p. 28, Academic Press, NY, 1980), in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-6, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation, according to the approved protocol (No. S9-FF81-6.C3) and STILLMEADOW, INC SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with the Animal Welfare Act Regulations, effective October 30, 1989. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are kept on file in the STILLMEADOW, Inc. archives. The protocol was initiated on August 24, 1995, and the animals were treated as follows:

	Induction Treatments		
Group	First	Last	Challenge Treatment
I Naive Control	--	--	10/11/95
II Test	09/13/95	09/27/95	10/11/95

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1-4 per cage (males separate from females)
Transfer to Clean Cages:	Weekly
Litter Pan Lining:	Paper
Litter Pan Lining Change:	Three times weekly
Food:	Purina Guinea Pig Chow; available ad libitum
Water Type:	Municipal Water Supply; available ad libitum
Water System:	Water bowls

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Study Protocol

From pages 8, 9 and 13 of the report:

Irritation Screening
Two male and two female albino guinea pigs were selected for irritation screening (Diagram 1) to determine both the maximum dose producing no more than slight irritation, and the maximum non-irritating dose. Concentrations tested in the screening were 100% (undiluted), and 50%, 20% and 5% v/v dilutions in deionized water, with each animal receiving 0.4 mL of each concentration at different test sites.

Preparation of Animals
Five males and five females were selected for each of two treatment groups. Group I animals served as a naive control group and Group II animals were designated as the test group. On the day prior to each treatment, the animals were prepared by clipping the back of the trunk free of hair to expose a longitudinal area at least 8 x 10 cm on each animal. Individual body weights were recorded on Days 0 and 28.

Test Material Administration
Based on the results of the irritation screening, the test material was administered by application of 0.4 mL of undiluted test material. For each induction treatment, Group II animals were treated by introducing the test material beneath a 3.8 x 5 cm patch (a 1.6 x 2.8 cm gauze pad secured to a 3.8 x 5 cm piece of adhesive) known as a Coverlet adhesive dressing (Mfg. by Beiersdorf, Inc., South Norwalk, Conn.). Each adhesive coverlet patch was placed laterally from the midline of the back on the left front quadrant of the exposure area with the edge of the gauze pad adjacent to, but not overlapping the midline of the back (Diagram 2). The entire trunk of each animal was then wrapped with clear polyethylene film to secure the patch in place. Each animal was then placed in a restrainer for approximately six hours. At the end of the exposure period, the animals were removed from the restrainers, the wrappings and patches were removed, and the animals were returned to their cages. Group II animals were treated once weekly for three weeks with 0.4 mL of undiluted test material. Induction treatments were on Days 1, 8 and 15. The same treatment regimen and test site location was used for all three induction treatments. Group I animals remained untreated during the induction phase of the study.

Challenge Treatment
After a two week rest period, all animals (Groups I and II) were each challenged at a virgin test site with an application of 0.4 mL of undiluted test material. The challenge treatment was on Day 29. The dose was applied in a manner identical to the induction treatments, except the test site was placed laterally on the right rear quadrant of the exposure area with the edge of the gauze pad adjacent to the midline of the back (Diagram 2).

Observations and Scoring Method
Observations for skin reactions at each test site were made approximately 24

302

hours after each treatment. In addition, observations for skin reactions were made approximately 48 hours after the first induction treatment and 48 hours after the challenge treatment.

The scoring scale used for grading skin reactions based on the Buehler Sensitization Scoring Scale was provided by in the report. An average score for each time period was obtained by adding all of the scores for each time period and dividing by the number of test sites scored for that time period. The test material is considered a sensitizer if the mean irritation scores, the total number of animals with scores, and/or the total number of scores for the virgin test site in the test group after the challenge treatment are appreciably greater than those for the naive challenge group.

Reference: Ritz, H. L. and E.V. Buehler, "Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests," Current Concepts in Cutaneous Toxicity, p. 28, Academic Press, NY, 1980

4. Statistical Analyses

No statistical analysis was conducted.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-6.

C. Results:

1. Irritation Screening Phase

The investigators provided individual dermal reactions data. No dermal irritation was reported with any test compound concentration.

2. Definitive Phase

a. Body Weights

The investigators provided individual body weights. No treatment related effects were noted.

b. Dermal Reactions

1. Test Compound

The investigators provided individual dermal reaction scores for the test and naive control animals. During induction, 1 male after first dose at 24 hours and another male after third dose at 24 hours and one female at 48 hours had a very faint, usually nonconfluent reaction. At challenge 1 naive group female at 24 hours and 1 male and 1 female at 24 hours had a very faint, usually nonconfluent reaction . No other reactions were noted.

2. Positive Control (DNCB)

The investigators provided individual dermal reaction scores for the positive control animals. The positive control animals exhibited reactions from a very faint, usually nonconfluent reaction at 24 and 48 hours after first dose, a very faint, usually nonconfluent reaction to a faint, usually confluent reaction at 24 hours after second dose and a faint, usually confluent to moderate at 24 hours following the third dose. At challenge the naive control exhibited a very faint, usually nonconfluent reaction at 24 and 48 hours and the test group exhibited a faint, usually confluent to moderate reaction at 24 and 48 hours.

304

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

A skin sensitization study was conducted on 10 male and 10 female short-haired albino guinea pigs to determine if test material CGA-77102 II 915 EC produced a sensitizing reaction. Five males and five females were assigned to each of two groups, designated Groups I and II. Group I animals remained untreated during the induction phase of the study and served as a naive control group. Group II animals, the test group, were treated with 0.4 mL of undiluted test material (selected from previous screening). The animals were treated once weekly for three weeks, for a total of three treatments. After a two week rest period, all animals (Groups I and II) were challenged at a virgin test site with an application of 0.4 mL of undiluted test material.

The test material produced very slight erythema in one of the ten animals of the naive control group (Group I) after the single treatment at challenge. The test material produced very slight erythema in two of the ten animals of the test group (Group II) after the challenge and therefore did not elicit a sensitizing reaction in guinea pigs.

2. Reviewers conclusions

In a Dermal Sensitization study, CGA-77102 II 915 EC did not induce dermal sensitization in guinea pigs tested with the closed patch technique.

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)
Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/2/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Oral Toxicity - Rat
Species: Rat Guideline: §81-1

EPA ID No.s: EPA MRID No. 43928503
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102/G30027 II
Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102/G30027 II, FINAL REPORT, ACUTE ORAL TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2429-95, December 21, 1995; EPA MRID No. 43928503.

Executive Summary: In an acute oral toxicity study (MRID# 43928503), groups of 5 male and 5 female young adult albino rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley SD from Harlan Sprague Dawley, Inc., Houston, TX) received either 2500, 3500, or 5163 mg/kg of CGA-77102/G30027 II 660SC-EXP [Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT); Lot Number FL-951649] as a single gavage dose.

The Acute Oral LD_{50} for CGA-77102/G30027 II is:

Males - 3372 mg/kg bw
95% Confidence Limits - 2430 to 4680 mg/kg bw
Females - 3251 mg/kg bw
95% Confidence Limits - 2917 to 3623 mg/kg bw
Combined - 3271 mg/kg bw
95% Confidence Limits - 2755 to 3882 mg/kg bw

Toxicity Category III.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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). 306

A. Materials and Methods

Test Compound: CGA-77102/G30027 II 660SC-EXP
Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT)
Description: White to off-white liquid
Lot Number: FL-951649
Other provided information:
Density: 1.0938 g/mL
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Albino rat (nulliparous and non-pregnant)
Strain: HSD:Sprague-Dawley SD
Source: Harlan Sprague Dawley, Inc., Houston, TX
Age: Not provided, "young adult"
Body Weight: Males (251-349 g); Females (175-224 g)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the acute oral toxicity potential of the test material when administered to rats in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-1, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No. S9-FF81-1.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the Sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are on file in the STILLMEADOW, Inc. archives. The study was initiated on October 18, 1995, and the animals were treated as follows:

Dose		Male Treatment		Female Treatment		Termination Date	
mg/kg	mL/kg	Date	Time	Date	Time	Males	Females
2500	2.28	10/25/95	10:50 A.M.	10/25/95	10:55 A.M.	11/08/95	11/08/95
3500	3.20	11/01/95	10:48 A.M.	11/01/95	10:55 A.M.	11/15/95	11/15/95
5163	4.72	10/18/95	10:18 A.M.	10/18/95	10:23 A.M.	10/20/95	10/20/95

307

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Controls Set to Maintain:	·Temperature Range of 72° ± 5°F ·Humidity Range of 30-80% ·12-hour light/dark cycle ·10-12 air changes per hour
Litter Pan Lining:	Paper and aspen bedding; changed three times/week
Food:	Purina Formulab Chow #5008; available ad libitum except for approximately 16 hours before dosing
Water Type:	Municipal water supply, available ad libitum from automatic water system

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Dose Preparation and Administration

From page 8 of the report:

The test material was administered as received and was not diluted. An individual dose was calculated for each animal based on its fasted body weight and administered by gavage at a volume ranging from 2.28 mL/kg at the 2500 mg/kg level to 4.72 mL/kg at the 5163 mg/kg level. Each dose was administered using an appropriately sized syringe and stainless steel ball-tipped intubation needle. The animals were returned to their cages immediately after dosing.

3. Observations

From page 8 of the report:

Observations for mortality and clinical/behavioral signs of toxicity were made at least three times on the day of dosing (Day 0) and at least once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing and on Days 7 and 14, or at the time of discovery after death.

At study termination, each surviving animal was euthanized by an overdose of CO2. All study animals were subjected to gross necropsy and all abnormalities were recorded.

308

4. Statistical Analyses

From pages 8 and 24 of the report:

The LD50 value was calculated by a computer program utilizing probit analysis. No other statistical analyses were required by the protocol.

Reference: Litchfield, J.T., Jr., and Wilcoxon, F.: A Simplified Method of Evaluating Dose-Effect Experiments, J. Pharm. & Exp. Ther., 96, 99-115, 1949.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-1.

C. Results:

1. Mortality

The investigators provided a group summary of the observed mortality along with individual animal data. The following table presents the mortality data (from the table on page 8 and Table 1, pages 11-13 of the report):

Table I: Mortality Summary

Dose Level (mg/kg)	Mortality, Day Died*
Males	
2500	1/5, Day 1^1
3500	2/5, Day 1^2
5163	5/5, Days 1^4 and 2^1
Females	
2500	0/5
3500	4/5, Day 1^4
5163	5/5, Days 1^3 and 2^2

*** = Superscript number indicates number of animals found dead on that day.**

Calculated Oral LD_{50} :

Males - 3372 mg/kg bw
95% Confidence Limits - 2430 to 4680 mg/kg bw

Females - 3251 mg/kg bw
95% Confidence Limits - 2917 to 3623 mg/kg bw

Combined - 3271 mg/kg bw
95% Confidence Limits - 2755 to 3882 mg/kg bw

309

2. Clinical Signs

The investigators provided summary and individual animal clinical signs data. The clinical signs of toxicity included activity decrease, crusted and stained muzzle, diarrhea, gasping, piloerection, ptosis, respiratory gurgle and salivation. The investigators observed ataxia, convulsions, nasal and ocular discharge in those animals which died. All surviving animals were noted to have returned to a normal appearance by Day 7 after treatment.

3. Body Weights

The investigators provided individual and average body weights. No treatment related effects were noted on body weights and body weight gains in surviving animals. The following table presents the body weights (from Table 1, pages 11-13 of the report) and body weight gains (calculated by the reviewer):

Table II: Average Body Weights & Body Weight Gains (grams)

Day: / Dose (mg/kg):	0	7	0-7 gain	14	0-14 gain
			Males		
2500	276	304	28	307	31
3500	271	290	19	324	53
5163	307				
			Females		
2500	194	214	20	227	33
3500	184	205	21	213	29
5163	215				

4. Pathology

The investigators provided a summary and individual gross necropsy pathology findings. According to the investigators: *Gross necropsy in animals that died on test revealed staining and/or matting of muzzle and anal hair; gas and discolored contents in the gastrointestinal tract.* One animal had evidence of an apparent gavage error. The above statement is supported by the individual animal data.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

The test material, CGA-77102/G30027 II, was evaluated for its acute oral toxicity potential in albino rats when administered as a single gavage dose at levels of 2500, 3500 and 5163 mg/kg to males and females. No mortality occurred in females dosed at the 2500 mg/kg level. Clinical signs in surviving animals included activity decrease, crusted and stained muzzle, diarrhea, gasping, piloerection, ptosis, respiratory gurgle and salivation, which were no longer evident by Day 7. There was no meaningful effect on body weight gain in animals surviving to termination. Abnormal necropsy findings occurred only in the animals dying on test, and pertained primarily to the contents of the gastrointestinal tract. The acute oral LD50's of CGA-77102/G30027 II were determined to be 3372 mg/kg in males, 3251 mg/kg in females, and 3271 mg/kg overall.

2. Reviewers' Conclusions

The Acute Oral LD_{50} for CGA-77102/G30027 II is:

Males - 3372 mg/kg bw
95% Confidence Limits - 2430 to 4680 mg/kg bw

Females - 3251 mg/kg bw
95% Confidence Limits - 2917 to 3623 mg/kg bw

Combined - 3271 mg/kg bw
95% Confidence Limits - 2755 to 3882 mg/kg bw

Toxicity Category III.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

CGA-77102/G-30027 II 720SC was evaluated for its acute inhalation toxicity potential in albino rats. Five animals/sex/group were exposed for four hours in a nose-only inhalation system to an aerosol generated from the undiluted liquid test substance at levels of 0.640 and 2.93 mg/L. One male and one female in the high dose group died during the study. Clinical signs included activity decrease, crust around eyes and nose, respiratory gurgle, piloerection, polyuria, ptosis and withdrawn testes, which were no longer evident in surviving animals by Day 7. Abdominal distention, body tremors, emaciation, gasping and unsteady gait were observed only in the animals that died on test. Body weights in surviving animals were largely unaffected by exposure. Abnormal necropsy findings occurred only in animals that died on test and pertained to muzzle, anal area and lungs. The acute inhalation LC50 for CGA-77102/G-30027 II 720SC is greater than 2.93 mg/L.

2. Reviewers' Conclusions

The Acute Inhalation LC_{50} for CGA-77102/G-30027 II 720SC is greater than 0.640 mg/L for both sexes. The particle size distribution (MMAD) was 3.484 µm. Toxicity Category III.

3/2

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/2/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Dermal Toxicity - Rabbit
Species: Rabbit Guideline: §81-2

EPA ID No.s: EPA MRID No. 43928504
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102/G30027 II

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102/G30027 II, FINAL REPORT, ACUTE DERMAL TOXICITY STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2430-95, November 22, 1995; EPA MRID Number 43928504.

Executive Summary: In an acute dermal toxicity study (MRID# 43928504), 5 male and 5 female albino rabbits (females were nulliparous and non-pregnant; Strain: New Zealand White from Ray Nichols Rabbitry; Lumberton, Texas) received 2020 mg/kg CGA-77102/G30027 II 660SC-EXP [Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT); Lot Number FL-951649] by the dermal route.

The Acute Dermal LD_{50} for CGA-77102/G30027 II is greater than 2020 mg/kg for both sexes. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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/G30027 II 660SC-EXP
Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT)
Description: White to off-white liquid
Lot Number: FL-951649
Other provided information:
Density: 1.0938 g/mL
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Albino rabbit (females were nulliparous & non-pregnant)
Strain: New Zealand White
Source: Ray Nichols Rabbitry; Lumberton, Texas
Age: Not provided, "Young adult"
Body Weight: Males (2.175-2.500 kg); Females (2.325-2.700 kg)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the acute dermal toxicity potential of the test material when administered to rabbits in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-2, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No. S9-FF81-2.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations, effective October 30, 1989. In the opinion of the Sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are on file in the STILLMEADOW, Inc. archives. The study was initiated on October 18, 1995, and the animals were treated with the test material on October 19, 1995. The in-life portion of the study was terminated on November 2, 1995.

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Controls Set to Maintain:	·Temperature Range of 72° ± 5°F ·Humidity Range of 30-80% ·12-hour light/dark cycle ·10-12 air changes per hour
Litter Pan Lining:	Paper; changed daily
Food: Purina	Rabbit Chow; available in measured amounts
Water Type:	Municipal water supply, available ad libitum from automatic water system

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Dose Preparation and Administration

From page 8 of the report:

Healthy albino rabbits were released from quarantine. Each animal was prepared on the day prior to treatment by clipping the dorsal surface of the trunk free of hair to expose not less than 10% of the total body surface area. Care was taken to avoid abrading the skin. Only those animals with exposure areas free of pre-existing skin irritation or defects were used for this study. All animals were treated with 2020 mg/kg (1.85 mL/kg) of undiluted test material. An individual dose was calculated for each animal based on its Day 0 body weight just before exposure. The test material was applied to each exposure area in a thin, uniform layer. The area of application was covered with an appropriately sized surgical gauze patch (8 x 4 in) and secured with non-irritating adhesive tape. The trunk of each animal was then wrapped with a semi-permeable dressing (orthopedic stockinette) and secured in place with non-irritating adhesive tape to prevent possible ingestion of the test material.

After 24 hours, the wrappings were removed. The test sites were gently washed with room temperature tap water and a clean wet cloth to remove as much residual test material as possible.

3. Observations

From page 8 of the report:

Observations for mortality and clinical/behavioral signs of toxicity were made at least three times on the day of dosing (Day 0) and at least once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing and on Days 7 and 14.

Observations for evidence of dermal irritation were made at approximately 30 minutes after removal of wrappings, and on Days 3, 7, 10 and 14.

At study termination, animals were euthanized by an intracardiac injection of Fatal Plus (Vortech Pharmaceuticals, Dearborn, Michigan 48126). All study animals were subjected to gross necropsy and all abnormalities were recorded. After necropsy, the animal carcasses were discarded.

4. Statistical Analyses

No statistical analysis was conducted.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-2.

C. Results:

1. Mortality

The investigators provided individual animal and group summary of the survival rate. No mortality was observed during the study. The estimated dermal LD_{50} for male and female rabbits was determined to be greater than 2020 mg/kg bw.

2. Clinical Signs

The investigators provided group summary and individual animal clinical signs and dermal reactions. No treatment related clinical signs were noted. Dermal irritation signs included all animals with erythema on study Day 1; 4 males and 3 females with erythema and 1 male and 1 female with coriaceousness and desquamation on study Day 3; 4 males and 2 females with erythema, 2 males and 1 females with edema, 1 female with desquamation and another female with coriaceousness and desquamation on study Day 7; 3 males and 2 females with erythema, 1 male with coriaceousness and desquamation and another male with desquamation and 2 females with desquamation on study Day 10; no reactions by study Day 14.

316

3. Body Weights

The investigators provided individual animal and mean body weights. No relevant treatment related effects were noted. The following table presents the body weights and body weight gains (from Table 1, page 11 of the report):

Table I: Average Body Weights & Body Weight Gains (grams)

Day: Dose (mg/kg):	0	7	0-7 gain	14	0-14 gain
			Males		
2020	2370	2540	170	2665	295
			Females		
2020	2470	2595	125	2755	285

d. Pathology

The investigators provided individual animal gross necropsy pathology findings. No relevant treatment related effects were noted.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

The test material, CGA-77102/G30027 II, was evaluated for its dermal toxicity potential when a single undiluted dose was applied to the intact skin of male and female albino rabbits, at a level of 2020 mg/kg. No mortality occurred during the study. There were no clinical signs of toxicity exhibited at any time throughout the study. Slight skin irritation was observed through Day 10. There was no meaningful effect on body weight gain. The gross necropsy conducted at termination of the study revealed no treatment-related abnormalities, except for staining of anal hair in one male. The estimated acute dermal LD50, as indicated by the data, was determined to be greater than 2020 mg/kg body weight.

2. Reviewers' Conclusions

The Acute Dermal LD_{50} for CGA-77102/G30027 II is greater than 2020 mg/kg for both sexes. Toxicity Category III.

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/2/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Inhalation Toxicity - Rat
Species: Rat Guideline: §81-3

EPA ID No.s: EPA MRID No. 43928505
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102/G30027 II

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J. Bennick (1996): CGA-77102/G30027 II, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2431-95, January 11, 1996; EPA MRID Number 43928505.

Executive Summary: In an acute inhalation toxicity study (MRID# 43928505), groups of 5 male and 5 female rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley; Source: Harlan Sprague Dawley, Inc., Houston, Texas) were exposed by the nose only route to a generated aerosol of CGA-77102/G30027 II from undiluted liquid at levels of 0.619 or 1.60 mg/L mean exposure concentrations [Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT); Lot Number FL-951649].

The Acute Inhalation LC_{50} for CGA-77102/G30027 II was greater than 1.60 mg/L. The particle size distribution (MMAD) was 4.512 and 13.982 μm for the 0.619 and 1.60 mg/L mean exposure concentrations, respectively. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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/G30027 II 660SC-EXP
Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT)
Description: White to off-white liquid
Lot Number: FL-951649
Other provided information:
Density: 1.0938 g/mL
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Rat (females were nulliparous and non-pregnant)
Strain: HSD:Sprague-Dawley
Source: Harlan Sprague Dawley, Inc., Houston, Texas
Age: Young adult
Body Weight: Males (260-319 g); Females (202-233 g)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the acute inhalation toxicity potential of the test material in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-3, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No. S9-FF81-3.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data and a copy of this report are kept on file permanently in the STILLMEADOW, Inc. archives. The study was initiated on October 18, 1995, and the animals were exposed as follows:

Beginning of 4 Hour Exposure					Termination of In-Life Observations	
Dose (mg/L)	Males		Females		Males	Females
	Date	Time	Date	Time	Date	Date
0.619	11/22/95	10:15 A.M.	11/22/95	10:15 A.M.	12/06/95	12/06/95

1.60	11/17/95	11:00 A.M.	11/17/95	11:00 A.M.	12/01/95	12/01/95

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	One per cage
Environmental Controls Set to Maintain:	·Temperature Range: 72° ± 5°F ·Humidity Range: 30-80% ·12-hour light/dark cycle ·10-12 air changes/hour
Transfer to Clean Cages:	Weekly
Litter Pan Lining:	Paper and aspen bedding
Litter Pan Lining Change:	Three times weekly
Food:	Purina Formulab Chow #5008, available ad libitum except during the exposure period
Water Type:	Municipal water supply from automatic water system, available ad libitum except during the exposure period

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Procedures

From page 8-9 of the report:

Prestudy Testing
Trial assays were conducted to determine which method(s) of aerosolizing the test material into the exposure chamber would produce an acceptable concentration and mass median aerodynamic diameter (MMAD).

Exposure Chamber
A 500 L nose-only stainless steel, dynamic flow inhalation chamber was utilized in this experiment (Diagram 1). The body of the chamber has 25 ports in 5 rows. Polycarbonate cones are inserted into 10 designated individual ports. The test material is introduced through the opening in the top of the chamber. The bottom section has a corresponding air outlet and a drain valve for cleaning the chamber. The individual polycarbonate cones (tubes) are tapered at one end to fit the shape of the animal's head and the back portion is sealed with a polycarbonate cap. The cones containing the animals fit tightly into the ports, and are sealed with "O" rings.

Generation of Test Atmosphere

330

The aerosol for the 0.619 mg/L level was generated by pumping the test material into a pressure operated Spraying System Company air atomizer (1/4 JSS) and then elutriating the resulting aerosol through a baffling chamber. The concentrated aerosol was then diluted with filtered air and drawn into the exposure chamber. The aerosol for the 1.60 mg/L level was generated by pumping the test material into a pressure operated Spraying System Company air atomizer (1/4 JSS) and then spraying the resulting aerosol directly into the exposure chamber.

Air flow into the exposure chamber was maintained through the use of a calibrated orifice plate at a rate of 11.5-13.6 air changes per hour. Air flow was recorded at 30 minute intervals during the exposure period, and was sufficient to ensure an oxygen content of at least 19% of the exposure atmosphere. Temperature and relative humidity were recorded at 30 minute intervals during the exposure period from a Taylor wet bulb/dry bulb hygrometer located in the exposure chamber.

Test Material Administration
Healthy albino rats were released from quarantine. Five males and five females per each of two exposure levels were selected for testing. The animals were exposed to an aerosol generated from the undiluted liquid test material for a period of four hours. When 99% concentration (T-99) was attained, the animals which were individually housed in polycarbonate exposure tubes were inserted into a 500 L stainless steel nose-only inhalation chamber for the specified exposure period. A maximum of 10 animals were exposed during any given exposure period. At the termination of the exposure period, the animals were washed and returned to their stock laboratory cages.

Determination of Concentration
The concentration of test material in the exposure atmosphere (taken from the breathing zone of the animals) was determined analytically once per hour, and nominally at the end of each exposure. The analytical determination was made using a BAUSCH & LOMB SPECTRONIC 2000 Spectrophotometer (Appendix A). The nominal concentration was determined by dividing the loss in weight of the test material after each exposure by the total volume of air which passed through the chamber.

Particle Size Distribution
Particle size, taken from the breathing zone of the animals, was determined twice during each exposure, using an Andersen cascade impactor, at a rate of 28.3 L/minute for a duration of 1 minute. The MMAD and particle size distributions are calculated from these data.

In-life Observations
Observations for mortality and signs of pharmacologic and/or toxicologic effects were made frequently on the day of exposure and at least once daily thereafter for 14 days (day of exposure considered Day 0). Individual body weights were recorded just prior to the inhalation exposure and on Days 7 and

14.

2,33

Postmortem Observations
At study termination, each animal was euthanized by an injection of Fatal Plus (Vortech Pharmaceuticals, Dearborn, Michigan 48126). All study animals were subjected to gross necropsy and all abnormalities were recorded.

Statistical Analysis
In order to calculate a mean exposure, the Mean Value Theorem of Calculus was used to properly weight the concentration, since the concentrations could not be measured continuously (see Table 5). This method weights concentrations based on the time span of each concentration. A concentration can be calculated for each minute, which better represents the exposure concentration received by each animal.

Reference (from page 23 of the report): Finney, D.J.: PROBIT ANALYSIS, 3rd ed., Chapters 3 and 4, 1971, Cambridge University Press.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-3.

C. Results:

1. Mortality

The investigators provided group summary and individual animal survival data. No mortality was reported. The acute inhalation LC_{50} for CGA-77102/G30027 II was greater than 1.60 mg/L.

2. Clinical Signs

The investigators provided group summary and individual animal data. Clinical signs included activity decrease, crust around eyes, nasal discharge, piloerection, ptosis and respiratory gurgle. No clinical signs were noted by study Day 8.

3. Body Weights

The investigators provided individual animal body weights. No relevant treatment related effects were noted. The following table presents the average body weights and body weight gains (from Table 1, pages 12-13 of the report):

Average Body Weights and Body Weight Gains (grams)

Day:	0	7	0-7 gain	14	0-14 gain
Dose (mg/L):			Males		
0.619	297	315	18	333	36
1.60	273	282	9	305	32
			Females		
0.619	224	231	7	244	20
1.60	214	220	6	226	12

4. Pathology

The investigators provided individual animal gross necropsy findings. No treatment related effects were noted.

5. Inhalation Chamber Conditions

The investigators provided individual half hour chamber operating parameters. The mean chamber operating parameters are as follows (from Table 4, page 20 of the report):

Conc.(mg/L)	Temp.(°F)	RH(%)[1]	Air Flow (Lpm)
0.619	68	88	113
1.60	65	93	113

[1] = RH = relative humidity

The investigators provided analytical concentration determinations and calculations and particle size distribution determinations.

The mean exposure concentration are as follows (from Tables 5 and 6, pages 22-26 of the report):

Conc.(mg/L)	MEC(mg/L)[1]	NC(mg/L)[2]	MMAD(μm)[3]
0.619	0.6190	22.2	4.512
1.60	1.602	86.0	13.982

[1] = MEC = Mean Exposure Concentration; [2] = NC = Nominal Concentration; [3] = MMAD = Mass Mean Aerodynamic Diameter.

324

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

CGA-77102/G30027 II was evaluated for its acute inhalation toxicity potential in albino rats. Five animals/sex/group were exposed for four hours in a nose-only inhalation system to an aerosol generated from the undiluted liquid test material at levels of 0.619 and 1.60 mg/L, the maximum attainable concentration. There was no mortality during the study. Clinical signs included activity decrease, crust around the eyes, nasal discharge, piloerection, ptosis and respiratory gurgle, which were no longer evident by Day 8. Body weights were essentially unaffected by exposure. The gross necropsy revealed no observable abnormalities. As indicated by the data, the acute inhalation LC50 for CGA-77102/G30027 II is greater than 1.60 mg/L.

2. Reviewers' Conclusions

The Acute Inhalation LC_{50} for CGA-77102/G30027 II was greater than 1.60 mg/L. The particle size distribution (MMAD) was 4.512 and 13.982 μm for the 0.619 and 1.60 mg/L mean exposure concentrations, respectively. Toxicity Category III.

325

SignOff Date:	9/4/1997
DP Barcode:	D226782
HED DOC Number:	012310
Toxicology Branch:	RAB3

CGA-77102/G30027 II PRIMARY EYE IRRITATION - RABBITS §81-4

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/2/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Eye Irritation - Rabbit
Species: Rabbit Guideline: §81-4

EPA ID No.s: EPA MRID No. 43928506
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102/G30027 II

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102/G-30027 II, FINAL REPORT, PRIMARY EYE IRRITATION STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2365-95, November 13, 1995; EPA MRID Number 43928506.

Executive Summary: In a primary eye irritation study (MRID# 43928506), 3 male and 3 female (nonwashed) and 3 male ("washed") albino rabbits (Strain: New Zealand White from Ray Nichols Rabbitry, Lumberton, Texas) received 0.1 mL CGA-77102/G30027 II 660SC-EXP [Purity: 26.6% CGA-77102; 1.34% CGA-154281; 33.0% Atrazine (33.4% TCT); Lot Number FL-951423] to one eye (the other serving as untreated control). Two groups were used, one group with the eyes unwashed, the other group had the eyes washed with room temperature deionized water for 1 minute beginning 30 seconds after test compound instillation.

CGA-77102/G30027 II was mildly irritating in unwashed eyes and minimally irritating to washed eyes. Irritation cleared by 4 days after treatment. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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/G30027 II 660SC-EXP
Purity: 26.6% CGA-77102; 1.34% CGA-154281; 33.0% Atrazine (33.4% TCT)
Description: Off-white liquid
Lot Number FL-951423
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Albino rabbit
Strain: New Zealand White
Source: Ray Nichols Rabbitry, Lumberton, Texas
Age: Young adult
Body Weight: Males (2.350-2.725 kg); Females (2.550-2.600 kg)
Acclimation Period: At least five days

B. Study Design

From page 7 of the report:

The objective of this study was to determine the eye irritation potential of the test material in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-4, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No. S9-FF81-4.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the Sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are on file in the STILLMEADOW, Inc. archives. The study was initiated on September 19, 1995, and the animals were treated with the test material between 12:12 and 12:21 on September 25, 1995. The in-life portion of the study was terminated on October 2, 1995.

328

1. Animal Husbandry and Assignment

From page 8 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Conditions Set to Maintain:	·Temperature Range of 72° ± 5°F ·Humidity Range of 30-80% ·12-hour light/dark cycle ·10-12 air changes per hour
Litter Pan Lining:	Paper; changed daily
Food:	Purina Rabbit Chow; presented in measured amounts
Water Type:	Municipal water supply, available ad libitum from automatic water system

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Dose Preparation and Administration

From page 8 of the report:

Prior to starting the study, the pH of the test material was determined to be 6.08. Healthy albino rabbits were released from quarantine. Both eyes of each animal were carefully examined at least 24 hours prior to treatment with a fluorescein sodium ophthalmic solution. Both eyes of each animal were again carefully examined just prior to treatment, but without the fluorescein sodium ophthalmic solution. Only those animals without eye defects or irritation were selected for testing.

On Day 0, a dose of 0.1 mL of the undiluted test material was placed into the conjunctival sac of the right eye of each animal by gently pulling the lower lid away from the eyeball to form a cup into which the test material was dropped. The lids were gently held together for one second to prevent loss of material. Three of the treated eyes ("washed eyes") were each washed with room temperature deionized water for one minute beginning 30 seconds after treatment. The untreated left eyes served as comparative controls.

3. Observations

From pages 8-9 of the report:

The treated eyes of all animals were examined under normal room lighting without magnification, and the grades of ocular reaction were recorded at 1, 24, 48 and 72 hours, and at 4 and 7 days after treatment. The corneas of all

treated eyes were examined immediately after the 24-hour observation with a fluorescein sodium ophthalmic solution. Any of the corneas which exhibited fluorescein staining at the 24-hour observation were re-examined with the fluorescein sodium ophthalmic solution at each consecutive observation until fluorescein staining of the cornea no longer occurred. All treated eyes were washed with room temperature deionized water for one minute immediately after recording the 24-hour observation.

Individual irritation scores for each animal at each scheduled observation were determined using the grading scale was presented in Table 1 of the report. An average irritation score for each scheduled observation for all nonwashed and washed eyes was then determined, based on the number of animals tested in those groups. A maximum average irritation score for nonwashed and washed eyes was derived from the observation yielding the highest average irritation score. The maximum average irritation scores were used to rate the test material according to the ratings was presented in Table 2 of the report. Any corneal involvement or iridic irritation with a score of 1 or more is considered positive. Any conjunctival irritation (redness or chemosis) with a score of 2 or more is considered positive.

4. Statistical Analyses

No statistical analysis was performed.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-4.

330

C. Results:

1. Eye Irritation

The investigators provided group summary and individual animal data for eye irritation. The following table presents the eye irritation scores (from Table 2, page 19 of the report): The investigators noted fluorescein staining in 3/6 eyes at 24 hours and 1/6 eyes at 72 hours after treatment in the unwashed eyes. No fluorescein staining was noted in the washed eyes.

Table I: Average Primary Eye Irritation Scores[a]

Observation Period	Average Score (out of 110) Unwashed	Washed
1 hour	11.7	2.7
24 hours	19.5	1.3
48 hours	14.3	1.3
72 hours	11.0	0.0
4 days	2.3	0.0
7 days	0.0	0.0

[a] = The average primary eye irritation score is the total eye irritation score for all the animals divided by the number of animals in each group (6 or 3) at each observation period out of a possible 110.

2. Body Weights

No data were noted.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

A primary eye irritation study was conducted on nine albino rabbits using test material CGA-77102/G-30027 II. The undiluted test material (0.1 mL) was placed into the conjunctival sac of the right eye of each animal selected for testing. Three of the treated eyes ("washed eyes") were each washed with room temperature deionized water for one minute beginning 30 seconds after treatment. All treated eyes were washed with room temperature deionized water for one minute immediately after recording the 24-hour observation.

The number of animals testing "positive" for each parameter (according to the Legend to Table 1) over the number of animals tested is presented below.

	Time After Treatment					
	Hours				Day	
	1	24	48	72	4	7
			NONWASHED EYES			
Cornea Opacity	1/6	3/6	3/6	3/6	0/6	0/6
Iritis	0/6	0/6	0/6	0/6	0/6	0/6
Conjunctivae						
Redness	1/6	6/6	4/6	3/6	0/6	0/6
Chemosis	6/6	3/6	1/6	1/6	0/6	0/6
			WASHED EYES			
Cornea Opacity	0/3	0/3	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3	0/3	0/3
Conjunctivae						
Redness	0/3	0/3	0/3	0/3	0/3	0/3
Chemosis	0/3	0/3	0/3	0/3	0/3	0/3

There were no "positive" effects exhibited in nonwashed eyes on Day 4 after treatment. There were no "positive" effects exhibited in washed eyes at any time during the study.

2. Reviewers' Conclusions

In a Primary Eye Irritation study, CGA-77102/G30027 II was mildly irritating in unwashed eyes and minimally irritating to washed eyes. Irritation cleared by 4 days after treatment. Toxicity Category III.

332

CGA-77102/G30027 II PRIMARY DERMAL IRRITATION - RABBITS §81-5

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 6/4/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/4/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Dermal Irritation - Rabbit
Species: Rabbit Guideline: §81-5

EPA ID No.s: EPA MRID No. 43928507
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102/G30027 II

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.O. Kuhn (1995): CGA-77102/G30027 II, FINAL REPORT, PRIMARY DERMAL IRRITATION STUDY IN RABBITS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER: 2432-95, November 30, 1995; EPA MRID Number 43928507.

Executive Summary: In a primary dermal irritation study (MRID# 43928507), 3 male and 3 female albino rabbits (New Zealand White from Ray Nichols Rabbitry, Lumberton, Texas) received 0.5 mL CGA-77102/G30027 II 660SC-EXP [Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT); Lot Number FL-951649] to the shaved back of each animal.

CGA-77102/G30027 II was slightly irritating. The mean PIS was 0.2. No irritation was seen by the 48 hour observation period. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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/G30027 II 660SC-EXP
Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT)
Description: White to off-white liquid
Lot Number: FL-951649
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Albino rabbits
Strain: New Zealand White
Source: Ray Nichols Rabbitry, Lumberton, Texas
Age: Young adult
Body Weight: Males (2.275-2.775 kg); Females (2.450-2.700 kg)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the dermal irritation potential of the test material in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-5, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No. S9-FF81-5.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the Sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are on file in the STILLMEADOW, Inc. archives. The study was initiated on October 18, 1995, and the animals were treated with the test material between 8:50 and 9:00 on October 24, 1995. The in-life portion of the study was terminated on October 27, 1995.

334

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Controls Set to Maintain:	·Temperature Range of 72° ± 5°F ·Humidity Range of 30-80% ·12-hour light/dark cycle ·10-12 air changes per hour
Litter Pan Lining:	Paper; changed daily
Food:	Purina Rabbit Chow; presented in measured amounts
Water Type:	Municipal water supply, available ad libitum from automatic water system

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Dose Preparation and Administration

From page 8 of the report:

Prior to starting the study, the pH of the test material was determined to be 5.94. Each animal was prepared on the day prior to treatment by clipping the dorsal area of the trunk free of hair to expose an area at least 8 x 8 cm. Only those animals with exposure areas free of pre-existing skin irritation or defects were selected for testing. A single intact exposure site was selected as the test site while the contralateral intact site served as a control site.

On Day 0, 0.5 mL of the undiluted test material was applied to each test site and covered with a surgical gauze patch measuring 2.5 x 2.5 cm and two single layers thick. Each patch was secured in place with a strip of non-irritating adhesive tape. The entire trunk of each animal was loosely wrapped with a semi-permeable dressing (orthopedic stockinette) and secured on both edges with strips of tape to retard evaporation of volatile substances and to prevent possible ingestion of the test material.

After four hours, the patches and wrappings were removed. The test sites were gently wiped with a clean cloth to remove as much residual test material as possible.

355

3. Observations

From page 8 of the report:

The test sites were observed for erythema and edema formation, and any other dermal defects or irritation at 1/2, 24, 48 and 72 hours after wiping.

The scoring scale used to rate dermal irritation is presented as part of Table 1 in the report. For each animal, all of the erythema and edema scores through 72 hours were added, and the sum was divided by 4 to obtain an individual irritation score. The primary irritation index was determined by calculating the mean of the irritation scores for the six animals and was used to obtain a rating for the test material.

4. Statistical Analyses

No statistical analysis was performed.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-5.

C. Results:

1. Dermal Irritation

The investigators provided group summary and individual animal data for erythema and edema dermal irritation. Erythema was noted in 2 animals at 1/2 hour and 2 animals (1 different) at 24 hours, no irritation was noted at 48 hours and no edema was noted at any observation time. The Primary Irritation Score (out of a possible 8) was 0.2.

2. Body Weights

No data were provided.

334

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

A primary dermal irritation study was conducted on six albino rabbits using test material CGA-77102/G30027 II. There was one intact test site per animal. Each test site was treated with 0.5 mL of undiluted test material and maintained in contact with the skin for 4 hours. Observations for dermal irritation and defects were made at 1/2, 24, 48 and 72 hours after removal of the dressings.

Irritation scores derived from the respective erythema and edema scores through the 72 hour observations for each animal are presented below.

	Erythema				Edema				
Animal	Hours after Unwrap				Hours after Unwrap				Irritation
Number	1/2	24	48	72	1/2	24	48	72	Scores
1448-M	1	0	0	0	0	0	0	0	0.25
1450-M	0	0	0	0	0	0	0	0	0.00
1452-M	1	1	0	0	0	0	0	0	0.50
1435-F	0	0	0	0	0	0	0	0	0.00
1437-F	0	0	0	0	0	0	0	0	0.00
1439-F	0	1	0	0	0	0	0	0	0.25

Based on the scores for the above observations, the Primary Irritation Index (PII) is 0.2. The test material is therefore rated slightly irritating.

2. Reviewers' Conclusions

In a Primary Dermal Irritation study, CGA-77102/G30027 II was slightly irritating. The mean PIS was 0.2. No irritation was seen by the 48 hour observation period. Toxicity Category IV.

337

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/2/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Dermal Sensitization - Guinea Pigs
Species: Guinea Pigs Guideline: §81-6

EPA ID No.s: EPA MRID No. 43928508
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102/G30027 II

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J.O. Kuhn (1996): CGA-77102/G30027 II, FINAL REPORT, DERMAL SENSITIZATION STUDY IN GUINEA PIGS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2433-95, January 11, 1996; EPA MRID Number 43928508.

Executive Summary: In a dermal sensitization study (MRID# 43928508), 2 male and 2 female (Irritation Screening) and 5 male and 5 female (Definitive Study) guinea pigs (Strain: Hartley-Albino from SASCO Inc., Madison, WI) received 0.4 mL CGA-77102/G30027 II 660SC-EXP [Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT); Lot Number FL-951649] to the shaved back of each animal using the closed patch technique.

CGA-77102/G30027 II was not a dermal sensitizer in guinea pigs tested with the closed patch technique.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-5) for a dermal sensitization study in guinea pigs.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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/G30027 II 660SC-EXP
Purity: 26.0% CGA-77102; 1.33% CGA-154281; 33.7% Atrazine (34.1% TCT)
Description: White to off-white liquid
Lot Number: FL-951649
Other provided information:
The test material was stored at room temperature.
Concentrations administered: both for induction and challenge: 100%

Vehicle(s): None used, test material is a liquid.

Positive Control: from page 8 of the report:

Label:	C-3762 Lot 52H00471 Grade II: Approx. 95% SIGMA 1-CHLORO-2,4-DINITROBENZENE
Manufacturer:	SIGMA Chemical Company
Physical Description:	Light brown crystals
Storage:	Room temperature
Concentration Administered:	Induction: 0.45% w/v solution in 80% ethanol Challenge: 0.1% w/v solution in acetone
Purity, Composition and Stability:	Available from manufacturer
Vehicle Materials:	Alcohol Dehydrated, USP Absolute 200 Proof and Acetone

Positive Control Testing
The sensitivity of guinea pigs to a positive control material (1-chloro-2,4-dinitrobenzene) is confirmed in this laboratory periodically. The positive control animals used to conduct this study were supplied by SASCO Inc., and were tested according to the Buehler Method (Ritz, H.L. and E.V. Buehler, "Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests", Current Concepts in Cutaneous Toxicity, p.28, Academic Press, NY, 1980).

STILLMEADOW, Inc. Study No. 2411-95
In-life start: October 18, 1995; In-life completed: November 17, 1995

Results: Data from this study were provided in the report as Appendix A. A mean score of 1.3 for the test group after challenge treatment, when compared with the naive control group mean challenge score of 0.0, confirmed the sensitivity of guinea pigs to the positive control material.

339

Test Animal(s): Species: Guinea Pig
Strain: Hartley-Albino
Source: SASCO Inc., Madison, WI.
Age: Not provided, "young adult"
Body Weight: Males (351-400 g); Females (333-371 g)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the sensitizing potential of the test material using a modification of the Buehler method (Ritz, H. L. and E.V. Buehler, "Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests," Current Concepts in Cutaneous Toxicity, p. 28, Academic Press, NY, 1980), in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-6, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation, according to the approved protocol (No. S9-FF81-6.C3) and STILLMEADOW, INC SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with the Animal Welfare Act Regulations, effective October 30, 1989. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The protocol, raw data, and a copy of this report are kept on file in the STILLMEADOW, Inc. archives. The study was initiated on October 18, 1995, and the animals were treated as follows:

	Induction Treatments		
Group	First	Last	Challenge Treatment
I Naive Control	--	--	11/22/95
II Test	10/25/95	11/08/95	11/22/95

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1-4 per cage (males separate from females)
Environmental Controls Set to Maintain:	·Temperature Range of 72°F ± 5° ·Humidity Range of 30 - 80% ·12-hour light/dark cycle ·10-12 air changes per hour
Transfer to Clean Cages:	Weekly
Litter Pan Lining:	Paper
Litter Pan Lining Change:	Three times weekly
Food:	Purina Guinea Pig Chow; available ad libitum
Water Type:	Municipal Water Supply; available ad libitum
Water System:	Water bowls

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Study Protocol

From pages 8-9 of the report:

Irritation Screening
Two male and two female albino guinea pigs were selected for irritation screening (Diagram 1) to determine both the maximum dose producing no more than slight irritation, and the maximum non-irritating dose. Concentrations tested in the screening were 100% (undiluted), and 50%, 20% and 5% v/v dilutions in deionized water, with each animal receiving 0.4 mL of each concentration at different test sites.

Preparation of Animals
Five males and five females were selected for each of two treatment groups. Group I animals served as a naive control group and Group II animals were designated as the test group. On the day prior to each treatment, the animals were prepared by clipping the back of the trunk free of hair to expose a longitudinal area at least 8 x 10 cm on each animal. Individual body weights were recorded on Days 0 and 28.

Test Material Administration
Based on the results of the irritation screening, the test material was administered by application of 0.4 mL of undiluted test material. For each

34

induction treatment, Group II animals were treated by introducing the test material beneath a 3.8 x 5 cm patch (a 1.6 x 2.8 cm gauze pad secured to a 3.8 x 5 cm piece of adhesive) known as a Coverlet adhesive dressing (Mfg. by Beiersdorf, Inc., South Norwalk, Conn.). Each adhesive coverlet patch was placed laterally from the midline of the back on the left front quadrant of the exposure area with the edge of the gauze pad adjacent to, but not overlapping the midline of the back [diagram provided]. The entire trunk of each animal was then wrapped with clear polyethylene film to secure the patch in place. Each animal was then placed in a restrainer for approximately six hours. At the end of the exposure period, the animals were removed from the restrainers, the wrappings and patches were removed, and the animals were returned to their cages. Group II animals were treated once weekly for three weeks with 0.4 mL of undiluted test material. Induction treatments were on Days 1, 8 and 15. The same treatment regimen and test site location was used for all three induction treatments. Group I animals remained untreated during the induction phase of the study.

Challenge Treatment
After a two week rest period, all animals (Groups I and II) were each challenged at a virgin test site with an application of 0.4 mL of undiluted test material. The challenge treatment was on Day 29. The dose was applied in a manner identical to the induction treatments, except the test site was placed laterally on the right rear quadrant of the exposure area with the edge of the gauze pad adjacent to the midline of the back [diagram provided].

3. Observations

From page 9 of the report:

Observations for skin reactions at each test site were made approximately 24 hours after each treatment. In addition, observations for skin reactions were made approximately 48 hours after the first induction treatment and 48 hours after the challenge treatment.

The scoring scale used for grading skin reactions was provided in Table 1. An average score for each time period was obtained by adding all of the scores for each time period and dividing by the number of test sites scored for that time period. The test material is considered a sensitizer if the mean irritation scores, the total number of animals with scores, and/or the total number of scores for the virgin test site in the test group after the challenge treatment are appreciably greater than those for the naive challenge group.

4. Statistical Analyses

No statistical analysis was conducted.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-6.

C. Results:

1. Irritation Screening Phase

The investigators provided individual dermal reactions data. No animals had any reaction at 24 or 48 hours with any test compound concentration.

2. Definitive Phase

i. Test Compound

The investigators provided individual dermal reaction scores for the test and naive control animals. No test animals exhibited any reactions at 24 and 48 hours after the first treatment. One female exhibited a "very faint, usually nonconfluent" reaction after the second dose at 24 hours. Two males and one female exhibited a "very faint, usually nonconfluent" reactions after the third dose at 24 hours. No naive controls exhibited reaction after challenge at 24 hours and 2 males exhibited a "very faint, usually nonconfluent" reactions after challenge at 48 hours. One male test animal exhibited a "very faint, usually nonconfluent" reaction after the second dose at 24 and 48 hours. No effects were noted in body weight data.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

A skin sensitization study was conducted on 10 male and 10 female short-haired albino guinea pigs to determine if test material CGA-77102/G30027 II produced a sensitizing reaction. Five males and five females were assigned to each of two groups, designated Groups I and II. Group I animals remained untreated during the induction phase of the study and served as a naive control group. Group II animals, the test group, were treated with 0.4 mL of undiluted test material (selected from previous screening). The animals were treated once weekly for three weeks, for a total of three treatments. After a two week rest period, all animals (Groups I and II) were challenged at a virgin test site with an application of 0.4 mL of undiluted test material.

The test material produced very faint erythema in two of ten animals of the naive control group (Group I) after the single treatment at challenge. The test material produced very faint erythema in one of ten animals of the test group (Group II) after the challenge and therefore did not elicit a sensitizing reaction in guinea pigs.

2. Reviewers' Conclusions

In a Dermal Sensitization study, CGA-77102/G30027 II was not a dermal sensitizer in guinea pigs tested with the closed patch technique.

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Oral Toxicity - Rat
Species: Rat Guideline: §81-1

EPA ID No.s: EPA MRID No. 44172203
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 720

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Acute Oral Toxicity Study of CGA-77102 720 in Rats, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504273, October 17, 1996 (Unpublished); EPA MRID Number 44172203.

Executive Summary: In an acute oral toxicity study (MRID# 44172203), groups of 5 male and 5 female young adult albino rats (Strain: Crl:CD®(SD)BR from Charles River Laboratories, Inc., Portage, Michigan) received either 2000, 3500, or 5000 mg/kg in males and 1000, 2000, or 5000 mg/kg in females of CGA-77102 120 (Purity: 70.3% CGA-77102 and 3.53% CGA-154281; Lot No. FL-961187; Batch Code 1098-26) as a single gavage dose.

The Acute Oral LD_{50} for CGA-77102 720 is:

Males - 3921 mg/kg bw
95% Confidence Limits - 2805 to 5479 mg/kg bw

Females - 1782 mg/kg bw
95% Confidence Limits - 979 to 3242 mg/kg bw

Combined - 3500 mg/kg bw
95% Confidence Limits - 2396 to 5113 mg/kg bw

Toxicity Category III.

344

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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 720
Purity: 70.3% CGA-77102 and 3.53% CGA-154281
Description: Dark red liquid
Lot No.: FL-961187, Batch Code 1098-26
other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Young adult albino rats
Strain: Crl:CD®(SD)BR
Source: Charles River Laboratories, Inc., Portage, Michigan
Age: Males: 8-9 weeks; females: 10-16 weeks
Body Weight: 219-277 g

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the acute oral toxicity produced when the test material is administered by the oral route (gavage) to rats.

The dose levels, method, frequency, and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton (CHW) Inc. Standard Operating Procedure (SOP).

Study Timetable	
Study Initiation Date	June 5, 1996
Experimental (In-life) Start Date	June 13, 1996
In-life End Date	September 19, 1996
Experimental Termination Date	October 17, 1996
Study Completion Date	October 17, 1996

1. Animal Husbandry and Assignment

From page 10 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were separated by sex and group housed in suspended stainless steel cages. Environmental controls for the animal room were set to maintain a temperature of 19° to 25°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided continuous access to Laboratory Rodent Diet #5001, PMI Feeds, Inc., and water except for 17 to 20 hours before test material administration when food, but not water, was withheld. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed. There were no known contaminants in the feed or water at levels that could be expected to interfere with or affect the results of the study.

Fifteen male and 15 female healthy, acclimated rats, weighing from 219 to 277 g, were utilized in this study. Males were approximately 8 to 9 weeks of age and females were approximately 10 to 16 weeks of age at initiation of treatment. Five males per level were treated at 2,000, 3,500, and 5,000 mg/kg of body weight, Five females per level were treated at 1,000, 2,000, and 5,000 mg/kg of body weight. The animals were identified by animal number and corresponding ear tag throughout the study.

2. Dose Preparation and Administration

From page 11 of the report:

The undiluted test material was administered by gavage using an average bulk density determination of 1.07 g/mL to determine the dose volume for each dose level. An individual dose was calculated for each animal based on its fasted body weight.

3. Observations

From page 11 of the report:

Body weights were determined before test material administration (Day 0). Additional body weights were determined at Day 7, at termination of the respective in-life phase (Day 14), or at death when survival exceeded 1 day.

Clinical observations were conducted at 1, 2.5, and 4 hours after test material administration and daily thereafter for 14 days. Mortality checks were conducted twice a day (morning and afternoon) for 13 days after test material administration and again the morning of Day 14.
At termination of the respective in-life phase for each dose level, surviving animals were euthanized. All animals, whether found dead during the study or euthanized, were subjected to an abbreviated gross necropsy examination and any abnormalities were recorded. After necropsy, the animals were discarded and only those tissues with lesions were collected and saved.

4. Statistical Analyses

From pages 11 and 14 of the report:

The LD_{50} values for males, females, and the sexes combined were determined by a computer program using a modified Behren-Reed-Muench cumulant method. No other statistical analyses were required by the protocol.

Reference: Thakur, A. K. and Fezio, W. L., "A Computer Program for Estimating LD_{50} and its Confidence Limits Using a Modified Behrens-Reed-Muench Cumulant Method," *Drug and Chemical Toxicology*, 4(3):297-305 (1981).

PROTOCOL DEVIATIONS (from page 31 of the report):

Protocol	Actual Procedure
Page 4, 5. Test Material, E. Reserve Samples. Reserve samples will not be required for this study.	Because this study was over four weeks in length a reserve sample was taken. In order to comply with MAFF requirements, the reserve sample of the test material will be stored at CHW in a freezer set to maintain a temperature of -20°C ±10°C for 10 years.

347

Page 7, 8. Location of Raw Data, Records, and Final Report, Second and Third Sentences. When the final report is completed, all original paper data, including those items listed below will be retained in the archives of CHW for a period of one year following signing of the final report. One year after signing of the final report, all of the aforementioned materials will be sent to the Sponsor and a return fee will be charged.	In order to comply with MAFF requirements, the final report and all original paper data will be retained in the archives of CHW for 10 years.

These deviations are not considered to have had an adverse effect on the outcome of the study.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-1.

C. Results:

1. Mortality

The investigators provided a group summary of the observed mortality. Three 2000-mg/kg females, two 3500-mg/kg males and 4 males and 5 females of the 5000-mg/kg group died from test compound administration. No other mortality was observed. The following table (from Table 1, page 16 of the report) summarize the mortality data:

Table I: Mortality Summary

Dose Level (mg/kg)		Mortality, Day Died*
	Males	
2000		0/5
3500		2/5, Day 1^2
5000		4/5, Day 0^1, 1^3
	Females	
1000		0/5
2000		3/5, Day 1^3
5000		5/5, Day 0^2, 1^3

* = Superscript number indicates number of animals found dead on that day.

348

Calculated Oral LD_{50} :

Males - 3921 mg/kg bw
95% Confidence Limits - 2805 to 5479 mg/kg bw

Females - 1782 mg/kg bw
95% Confidence Limits - 979 to 3242 mg/kg bw

Combined - 3500 mg/kg bw
95% Confidence Limits - 2396 to 5113 mg/kg bw

2. Clinical Signs

The investigators provided group summary and individual clinical signs data. The clinical signs of toxicity included on the day of treatment in four of the five females dosed at 1000-mg/kg included staggered gait, hypoactivity, lacrimation, and/or red-stained face. Three of the females treated at 2000-mg/kg died on study Day 1. Clinical signs of toxicity observed in the 2000-mg/kg animals included hypoactivity, excessive salivation, red-stained face, red-stained tail and fur (anal area), with prostration and fasciculations noted in 1 female which died. Two 3500-mg/kg males died on study Day 1. The clinical signs observed in the 3500-mg/kg animals included hypoactivity, staggered gait, excessive salivation, lacrimation, dyspnea, miosis, soft stool and dark stained urogenital areas. Four males and 5 females in the 5000-mg/kg level died on study Day 1. The clinical signs observed in the 5000-mg/kg animals included staggered gait, hypoactivity, red-stained face, excessive salivation, and dyspnea. In the animals which died at 5000-mg/kg, lacrimation, miosis, tremors, hunched posture, tonic convulsions, and absence of righting reflex were noted. All surviving animals appeared normal by Day 4.

3. Body Weights

The investigators provided individual and mean body weights and body weight gains. No treatment related effects were noted on body weight gain in surviving animals. The following table presents the body weights and body weight gains (from Table 2, pages 17-20 of the report):

Table I: Mean Body Weights and Body Weight Gains (grams)

Day: Dose (mg/kg):	0	7	0-7 gain	14	0-14 gain
			Males		
2000	242(5)[n]	313(5)	71(5)	380(5)	138(5)
3500	243(5)	301(3)	60(3)	361(3)	120(3)
5000	253(5)	299(1)	47(1)	368(1)	116(1)
			Females		
1000	222(5)	260(5)	38(5)	273(5)	51(5)
2000	259(5)	288(2)	27(2)	310(2)	49(2)
5000	267(5)				

[n] = number of animals

4. Pathology

The investigators provided individual gross necropsy pathology findings and a summary report by the study pathologist. According to the pathologist: *The primary findings observed at necropsy were in those animals dying during the study and pertained to the coloration changes and content of the gastrointestinal tract, to perineal staining, and to an oral discharge.*

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The test material, CGA-77102 720, was evaluated for its acute oral toxicity potential in male and female rats when administered as a single gavage dose at levels of 2,000, 3,500, and 5,000 mg/kg of body weight for males and 1,000, 2,000, and 5,000 mg/kg of body weight for females. The estimated oral LD_{50} values in rats were determined to be 3,921, 1,782, and 3,500 mg/kg of body weight for males, females, and the sexes combined, respectively. All mortality occurred within 1 day of test material administration. Clinical signs of toxicity observed included staggered gait, hypoactivity, red-stained face, excessive salivation, lacrimation, soft stool, dark-stained urogenital area, red-stained tail, miosis, dyspnea, and red-stained fur (anal area). In addition, the clinical signs of prostration, fasciculations, hunched posture, absence of righting reflex, tonic convulsions, and tremors, were seen only in those animals that died during the study. All surviving animals returned to a normal appearance by Day 4 after treatment. Animals surviving to the end of the observation period exhibited body weight gain. The primary findings observed at necropsy were in those animals dying during the study and pertained to the coloration changes and content of the gastrointestinal tract, to perineal staining, and to an oral discharge. These findings were attributed to the acute death of the animals.

2. Reviewers' Conclusions

The Acute Oral LD_{50} for CGA-77102 720 is:

Males - 3921 mg/kg bw
95% Confidence Limits - 2805 to 5479 mg/kg bw

Females - 1782 mg/kg bw
95% Confidence Limits - 979 to 3242 mg/kg bw

Combined - 3500 mg/kg bw
95% Confidence Limits - 2396 to 5113 mg/kg bw

Toxicity Category III.

CGA-77102 720 ACUTE DERMAL TOXICITY - RATS §81-2

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/2/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Dermal Toxicity - Rabbit
Species: Rabbit Guideline: §81-2

EPA ID No.s: EPA MRID No. 44172204
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 720

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Acute Dermal Toxicity Study of CGA-77102 720 in Rabbits, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504274, September 5, 1996 (Unpublished); EPA MRID Number 44172204.

Executive Summary: In an acute dermal toxicity study (MRID# 441722047), 5 male and 5 female Adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 2000 mg/kg CGA-77102 720 (Purity: 70.3% CGA-77102 and 3.53% CGA-154281; Lot No. FL-961187; Batch Code 1098-26) by the dermal route.

The Acute Dermal LD_{50} for CGA-77102 720 is greater than 2000 mg/kg. Toxicity Category III.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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 720
Purity: 70.3% CGA-77102 and 3.53% CGA-154281
Description: Dark red liquid
Lot No.: FL-961187, Batch Code 1098-26
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbits
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: 14-18 weeks
Body Weight: 2375-2702 g

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the systemic toxicity and relative skin irritancy of a test material when applied to the skin of rabbits.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose level, method, frequency, and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

Study Timetable

Study Initiation Date	May 31, 1996
Experimental (In-life) Start Date	June 6, 1996
In-life End Date	June 20, 1996
Experimental Termination Date	September 5, 1996
Study Completion Date	September 5, 1996

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in suspended stainless steel cages. Environmental controls for the animal room were set to maintain a temperature of 19° to 23°C, a relative

353

humidity of 50% ±20%, and a 12-hour light/ 12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided access to water *ad libitum* and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed. There were no known contaminants in the feed or water at levels that could be expected to interfere with or affect the results of the study.

Five male and five female healthy, acclimated rabbits, weighing from 2,375 to 2,702 g and approximately 14 to 18 weeks of age, were used for a single dose level of 2,000 mg/kg of body weight. The animals were identified by animal number and corresponding ear tag throughout the study. On the day before test material application, each rabbit's back was clipped free of hair. The clipped area made up not less than 20% of total body surface.

2. Dose Preparation and Administration

From pages 11-12 of the report:

The test material was administered as received. An individual dose was calculated and weighed out based on each animal's body weight on the day of test material administration.

The test material was applied to the intact skin on each animals' back at a dose level of 2,000 mg/kg of body weight. The test material was applied to the test site at a rate of approximately 0.03 g/cm^2 in a thin and uniform layer. The area of application (approximately 180 cm^2) was covered with a 4-ply 9.5-cm x 19-cm gauze patch secured with paper tape and overwrapped with Saran Wrap® and Elastoplast® tape to provide an occlusive dressing. Collars were used to restrain the test animals during the 24-hour exposure period.

At the end of the 24-hour exposure period, the restraining collars and bandages were removed and the test sites were washed using liquid Ivory® soap mixed with warm tap water, rinsed with clean tap water, and dried with disposable paper towels.

3. Observations

From page 12 of the report:

Body weights were determined before test material administration (Day 0), at Day 7, and at termination of the in-life phase (Day 14).

Clinical observations were conducted at 1, 2.5, and 4 hours after test material administration. Additional clinical observations (including dermal effects) were conducted daily thereafter for 14 days. Mortality checks were

conducted twice a day (morning and afternoon) for 13 days after test material administration and again the morning of Day 14.

At termination of the in-life phase, all animals were euthanized, subjected to an abbreviated gross necropsy examination, and any abnormalities were recorded. After necropsy, the animals were discarded and only those tissues with lesions were saved and preserved in phosphate-buffered 10% formalin.

4. Statistical Analyses

From page 12 of the report:

No statistical analyses were required by the protocol.

PROTOCOL DEVIATIONS (from page 21 of the report):

Protocol	Actual Procedure
Page 8, 8. Location of Raw Data, Records, and Final Report, Second and Third Sentences. When the final report is completed, all original paper data, including those items listed below will be retained in the archives of CHW for a period of one year following signing of the final report. One year after signing of the final report, all of the aforementioned materials will be sent to the Sponsor and a return fee will be charged.	In order to comply with MAFF requirements, the final report and all original paper data will be retained in the archives of CHW for 10 years.

This deviation is not considered to have had an adverse effect on the outcome of the study.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-2.

C. Results:

1. Mortality

The investigators provided a group summary of the observed mortality. No mortality was observed. The estimated dermal LD_{50} values for male and female rabbits were determined to be greater than 2,000 mg/kg bw.

2. Clinical Signs and Dermal Irritation

The investigators provided individual clinical signs data. No adverse clinical signs were noted in the data provided. The dermal irritation ranged from "slight to severe".

3. Body Weights

The investigators provided individual and mean body weights and body weight gains. No significant treatment related effects were noted, although 2 females lost weight during the first week and had lower body weight gain for the 2 Week observation period compared to the other animals in the group. The following table presents the body weights and body weight gains (from Table 2, page 17 of the report):

Table I: Mean Body Weights and Body Weight Gains (grams)

Day: 0	7	0-7 gain	14	0-14 gain
Dose (mg/kg):		Males		
2000 2492	2540	48	2645	143
		Females		
2000 2512	2545	33	2682	170

4. Pathology

The investigators provided individual gross necropsy pathology findings and a summary report by the study pathologist. According to the pathologist: *At necropsy, the dermal application site of one male had crusted dry areas of variable size and the skin at the application site in two females was observed to be thickened. These lesions are indicative of irritation, possibly caused by the test material. The skin with lesions were collected and preserved in 10% formalin as required. There were no visible lesions in the remaining animals. The skin in the dorsal thoracic region of all animals, except for one female, was stained red and although the source of this staining was undetermined, it possibly represents test material.*

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The test material, CGA-77102 720, was evaluated for its acute dermal toxicity potential in male and female rabbits when administered as a single topical application at a level of 2,000 mg/kg of body weight. The estimated dermal LD_{50} values for male and female rabbits were determined to be greater than 2,000 mg/kg. All animals appeared normal throughout the study. All animals exhibited body weight gain during the study with the exception of two females which exhibited weight losses of 17 to 53 g during the first week. The test material produced slight to severe dermal irritation. The gross necropsy at termination revealed only those lesions associated with the dermal irritation caused by the test material.

2. Reviewers' Conclusions

The Acute Dermal LD_{50} for CGA-77102 720 is greater than 2000 mg/kg. Toxicity Category III.

CGA 77102 720 ACUTE INHALATION TOXICITY - RATS §81-3

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/2/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Inhalation Toxicity - Rat
Species: Rat Guideline: §81-3

EPA ID No.s: EPA MRID No. 44172205
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 720

Synonyms: Alpha-metolachlor; A Chiral Metolachlor

Citation: J. Bennick (1996): CGA-77102 720, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Study Number 2917-96, August 9, 1996 (Unpublished); EPA MRID Number 44172205.

Executive Summary: In an acute inhalation toxicity study (MRID# 44172205), 5 male and 5 female Rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley from Harlan Sprague Dawley, Inc., Indianapolis, IN) were exposed by the nose only route to a generated aerosol of CGA-77102 720 from undiluted liquid at a level of 2.62 mg/L (Purity: 70.3% CGA-77102; 3.53% CGA-154281).

The Acute Inhalation LC_{50} for CGA-77102 720 is greater than 2.62 mg/L for both sexes. The particle size distribution (MMAD) was 2.980 µm. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

358

A. Materials and Methods

Test Compound: CGA-77102 720
Purity: 70.3% CGA-77102; 3.53% CGA-154281
Description: Dark red brown liquid
Lot No.: FL-961187
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Male and Female Rats (nulliparous and non-pregnant)
Strain: HSD:Sprague-Dawley
Source:Harlan Sprague Dawley, Inc., Indianapolis, IN
Age: Young adult (8-12 wks)
Body Weight: Males (282-307 g); Females (209-251 g)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the acute inhalation toxicity potential of the test substance in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-3, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No.S9-FF81-3.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the sponsor, the study did not unnecessarily duplicate any previous work. The original protocol, raw data and this report are kept on file permanently in the STILLMEADOW, Inc. archives. The study was initiated on June 10, 1996, and the animals were exposed on June 18, 1996, at 13:00.

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	One per cage
Environmental Controls Set to Maintain:	·Temperature Range: 72°F± 5° ·Humidity Range: 30-80% ·12-hour light/dark cycle ·10-12 air changes/hour
Transfer to Clean Cages:	Weekly
Litter Pan Lining:	Paper and aspen bedding
Litter Pan Lining Change:	Three times weekly
Food:	PMI Feeds, Inc.™ Lab Diet Formulab #5008, available *ad libitum* except during the exposure period
Water Type:	Municipal water supply from automatic water system, available *ad libitum* except during the exposure period

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Procedures

From pages 7-9 of the report:

Prestudy Testing
A trial assay was conducted to determine which method(s) of aerosolizing the test substance into the exposure chamber would produce an acceptable concentration and mass median aerodynamic diameter (MMAD).

Exposure Chamber
A 500 L nose-only stainless steel, dynamic flow inhalation chamber was utilized in this experiment [Diagram was provided]. The body of the chamber has 25 ports in 5 rows. Polycarbonate cones are inserted into 10 designated individual ports. The test substance is introduced through the opening in the top of the chamber. The bottom section has a corresponding air outlet and a drain valve for cleaning the chamber. The individual polycarbonate cones (tubes) are tapered at one end to fit the shape of the animal's head and the back portion is sealed with a polycarbonate cap. The cones containing the animals fit tightly into the ports, and are sealed with "O" rings.

Generation of Test Atmosphere
The aerosol was generated by pumping the test substance into a pressure operated Spraying System Company air atomizer (1/4 JSS) and then elutriating the resulting aerosol through a baffling chamber. The concentrated aerosol was then diluted with filtered air and drawn into the exposure chamber. Air flow into the chamber was maintained through the use of a calibrated orifice plate at a rate of 14.9 air changes per hour. Air flow was recorded at 30 minute intervals during the exposure period, and was sufficient to ensure an oxygen content of at least 19% of the exposure atmosphere. Temperature and humidity were recorded at 30 minute intervals during the exposure period from a Taylor wet bulb/dry bulb hygrometer located in the exposure chamber.

Test Substance Administration
Healthy albino rats were released from quarantine, and five males and five females were selected for testing. The animals were exposed to an aerosol generated from the undiluted liquid test substance for a period of four hours. When 99% concentration (t-99) was attained, the animals which were individually housed in polycarbonate exposure tubes were inserted into a 500 L stainless steel nose-only inhalation chamber for the specified exposure period. At the termination of the exposure period, the animals were washed and returned to their stock laboratory cages.

Determination of Concentration
The concentration of test substance in the exposure atmosphere (taken from the breathing zone of the animals) was determined analytically once per hour and nominally at the end of the exposure. The analytical determination was made using a BAUSCH & LOMB SPECTRONIC 2000 Spectrophotometer [specifications were provided in a appendix to the study report]. The nominal concentration was determined by dividing the loss in weight of the test substance after the exposure by the total volume of air which passed through the chamber.

Particle Size Distribution
Particle size, taken from the breathing zone of the animals, was determined twice during the exposure, using an Andersen cascade impactor, at a rate of 28.3 L/minute for a duration of 1 minute. The MMAD and particle size distributions are calculated from these data.

In-life Observations
Observations for mortality and signs of pharmacologic and/or toxicologic effects were made frequently on the day of exposure and at least once daily thereafter for 14 days (day of exposure considered Day 0). Individual body weights were recorded just prior to the inhalation exposure and on Days 7 and 14.

Postmortem Observations
At study termination, each animal was euthanized by an intraperitoneal injection of Fatal Plus® (Vortech Pharmaceuticals, Dearborn, Michigan 48126). All study animals were subjected to gross necropsy, and all

abnormalities were recorded.

Statistical Analysis
In order to calculate a mean exposure, the Mean Value Theorem of Calculus was used to properly weight the concentration, since the concentrations could not be measured continuously [data provided in study]. This method weights concentrations based on the time span of each concentration. A concentration can be calculated for each minute, which better represents the exposure concentration received by each animal.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-3.

C. Results:

1. Mortality

The investigators provided individual animal survival data. No animals were reported to have died. The acute inhalation LC_{50} for CGA-77102 720 is greater than 2.62 mg/L.

2. Clinical Signs

The investigators provided group summary and individual animal data. Clinical signs included activity decrease (3/5 males at 4.5 hours, 1/5 males at 6.0 hours, 1 female from 4.5-6.0 hours), crust or stain around nose and mouth (all animals from 4.5 hours to day 2 with 1 male continuing to day 3) and piloerection (all animals at 4.5 to 6.0 hours). No clinical signs were noted by study day 4.

3. Body Weights

The investigators provided individual animal body weights. No treatment related effects were noted, although 1 female had a weight loss during the second week.

4. Pathology

The investigators provided individual animal gross necropsy findings. No treatment related effects were noted.

5. Inhalation Chamber Conditions

The investigators provided individual half hour chamber operating parameters. The mean chamber operating parameters were

74°F, 74% relative humidity and the airflow was 124 Lpm. The investigators provided analytical concentration determinations and calculations and particle size distribution determinations. The mean exposure concentration was 2.62 mg/L, the nominal concentration was 4.93 mg/L. The particle size distribution (MMAD) was 2.980 µm.

D. Conclusions

1. Investigators Summary:

From page 6 of the report:

CGA-77102 720 was evaluated for its acute inhalation toxicity potential in albino rats. Five males and five females were exposed for four hours in a nose-only inhalation system to an aerosol generated from the undiluted liquid test substance at a level of 2.62 mg/L. There was no mortality during the study. Clinical signs included activity decrease, crust or stain around nose and mouth, and piloerection, which were no longer evident by Day 4. Body weights were essentially unaffected by exposure. The gross necropsy revealed no observable abnormalities. As indicated by the data, the acute inhalation LC_{50} for CGA-77102 720 is greater than 2.62 mg/L.

2. Reviewers' Conclusions

The Acute Inhalation LC_{50} for CGA-77102 720 is greater than 2.62 mg/L for both sexes. The particle size distribution (MMAD) was 2.980 µm.

CGA 77102 720 PRIMARY EYE IRRITATION - RABBITS §81-4

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Eye Irritation - Rabbit
Species: Rabbit Guideline: §81-4

EPA ID No.s: EPA MRID No. 44172206
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 720

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Study Title: Primary Eye Irritation Study of CGA-77102 720 in Rabbits, Corning Hazleton Inc. For Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504276, September 6, 1996 (Unpublished); EPA MRID Number 44172206.

Executive Summary: In a primary eye irritation study (MRID# 44172206), male and female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.1 mL CGA-77102 720 (Purity: 70.3% CGA-77102 and 3.53% CGA-154281; Lot Number FL-961187 (Batch Code 1098-26) to one eye (the other serving as untreated control. Two groups were used, one group of 3 males and 3 females with their eyes unwashed, the other group of 3 females had their eyes washed for 1 minute with lukewarm water 30 seconds after test compound instillation.

CGA-77102 720 produced slight to moderate conjunctival irritation to washed and unwashed. Irritation cleared by 96 hours after treatment. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA, CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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 720
Purity: 70.3% CGA-77102 and 3.53% CGA-154281
Description: Dark-red liquid
Lot Number: FL-961187 (Batch Code 1098-26)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbits
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: 14-18 weeks
Body Weight: 2535-2728 g

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the relative level of irritation produced following a single exposure of a test material to one eye of albino rabbits.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose, method, frequency and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

Study Timetable

Study Initiation Date	May 31, 1996
Experimental (In-life) Start Date	June 7, 1996
In-life End Date	June 11, 1996
Experimental Termination Date	June 11, 1996
Study Completion Date	September 6, 1996

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in suspended stainless steel cages. Environmental controls for the

365

animal room were set to maintain a temperature of 19° to 23°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided access to water *ad libitum* and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed. There were no known contaminants in the feed or water at levels that would have interfered with or affected the results of the study.

Three male and six female healthy, acclimated rabbits, weighing from 2,535 to 2,728 g and approximately 14 to 18 weeks of age, were selected at random and identified by animal number and corresponding ear tag. The animals' eyes were examined on the day before test material administration using sodium fluorescein dye procedures. Only those animals with no sign of ocular injury or irritation were used. The rabbits were divided into two groups consisting of six rabbits in Group 1 and three rabbits in Group 2.

2. Dose Preparation and Administration

From page 11 of the report:

The test material was administered as received. The pH of the test material was not able to be determined.

Each rabbit received 0.1 mL of the undiluted test material placed into the everted lower lid of the right eye, with the left eye serving as the untreated control. The upper and lower lids were gently held together for 1 second to prevent loss of material and then released. The eyes of the rabbits in Group 1 remained unflushed immediately after treatment while the treated eyes of the rabbits in Group 2 were flushed with lukewarm tap water for 60 seconds starting 30 seconds after test material instillation.

3. Observations

From page 12 of the report:

Animals were weighed before test material administration.

The treated eyes were observed for ocular irritation at 1, 24, 48, and 72 hours after treatment. Additional observations were made at 96 hours after treatment for the animals in Group 1. Irritation was graded and scored according to the Draize technique using a penlight as the source of illumination. A sodium fluorescein examination was used to aid in revealing possible corneal injury at the observation conducted at 24 hours. An attachment was provided with the report referring to the ocular irritation scoring scale which is based on the method of Draize.

366

At termination of the in-life phase, all animals were euthanized and discarded.

4. Statistical Analyses

From page 12 of the report:

No statistical analyses were required by the protocol.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-4.

C. Results:

1. Eye Irritation

The investigators provided group summary and individual animal data for eye irritation. The following table presents the eye irritation scores (from Table 1, page 15 of the report): The test compound produced slight to moderate conjunctival irritation in all treated eyes that were unwashed after treatment. All treated eyes in the unwashed group appeared normal by 96 hours. Positive irritation reactions were observed in 1/6 unwashed eyes which appeared normal by 24 hours (Table II extracted from Tables 2 and 5, pages 16 and 21 of the report). In treated then washed eyes, the test compound produced iridal involvement with slight conjunctival irritation. All of the treated then washed eyes appeared normal by 72 hours. A positive irritation reaction was observed in 2/3 animals with treated then washed eyes which appeared normal by the 24 hours. The results of the sodium fluorescein examinations were negative for both groups.

Table I: Average Primary Eye Irritation Scores[a]

Observation Period (Hour)	Average Score Unwashed	Washed
1	7.7	7.3
24	3.3	2.0
48	0.7	0.7
72	0.3	0.0
96	0.0	-

a = The average primary eye irritation score is the total eye irritation score for all the animals divided by the number of animals in each group (6 or 3) at each observation period.

367

Table II: Positive Ocular Reactions[a]

Observation Period (Hour)	1		24		48		72		96
	UW[1]	W[2]	UW	W	UW	W	UW	W	UW
Cornea Opacity	0/6	0/3	0/6	0/3	0/6	0/3	0/6	0/3	0/6
Iritis	0/6	2/3	0/6	0/3	0/6	0/3	0/6	0/3	0/6
Conjunctivae Redness	1/6	0/3	0/6	0/3	0/6	0/3	0/6	0/3	0/6
Chemosis	0/6	0/3	0/6	0/3	0/6	0/3	0/6	0/3	0/6

[a] = a positive reaction for each parameter is defined as any corneal opacity, an iris score of 1.0 or greater, or any conjunctival redness or chemosis score of 2.0 or greater; [1] = UW = unwashed eyes; [2] = W = washed eyes.

2. Body Weights

The investigators provided individual animal body weights apparently only for prior to study initiation, no treatment period weights were provided.

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The primary eye irritation potential of CGA-77102 720 was evaluated when instilled into the eyes of nine rabbits (six with treated eyes unwashed and three with treated eyes washed approximately 30 seconds after instillation). The test material produced slight to moderate conjunctival irritation in unwashed eyes which cleared in all animals by 96 hours after treatment. A positive irritation reaction was observed in one of the six animals with unwashed eyes which cleared by the 24 hour observation. In treated eyes receiving a washout, the test material produced iridal involvement and slight conjunctival irritation which cleared in all animals by 72 hours after treatment. Positive irritation reactions were observed in two of the three animals with washed eyes which cleared in all animals by the 24 hour observation.

2. Reviewers' Conclusions

In a Primary Eye Irritation study, CGA-77102 720 produced slight to moderate conjunctival irritation to washed and unwashed eyes. Irritation cleared by 96 hours after treatment. Toxicity Category III.

368

CGA 77102 720 PRIMARY EYE IRRITATION - RABBITS §81-4

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C Dapson 5/2/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll. Nancy E McCarroll 5/5/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Eye Irritation - Rabbit
Species: Rabbit Guideline: §81-4

EPA ID No.s: EPA MRID No. 44172207
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 720

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Study Title: Primary Eye Irritation Study of CGA-77102 720 in Rabbits, Corning Hazleton Inc. For Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW · 60504272, August 13, 1996 (Unpublished); EPA MRID Number 44172207.

Executive Summary: In a primary eye irritation study (MRID# 44172207), male and female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.1 mL CGA-77102 720 (Purity: 70.4% CGA-77102 and 3.58% CGA-154281; Lot Number FL-961208 (Batch Code 1098-27)) to one eye (the other serving as untreated control. Two groups were used, one group of 3 males and 3 females with their eyes unwashed, the other group of 3 females had their eyes washed for 1 minute with lukewarm water 30 seconds after test compound instillation.

CGA-77102 720 produced slight to moderate conjunctival irritation to washed and unwashed. Irritation cleared by 96 hours after treatment. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA, CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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 720
Purity: 70.4% CGA-77102 and 3.58% CGA-154281
Description: Dark red liquid
Lot Number: FL-961208 (Batch Code 1098-27)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbits
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: 14-18 weeks
Body Weight: 2659-2917 g

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the relative level of irritation produced following a single exposure of a test material to one eye of albino rabbits.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose, method, frequency and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

Study Timetable

Study Initiation Date	May 31, 1996
Experimental (In-life) Start Date	June 14, 1996
In-life End Date	June 18, 1996
Experimental Termination Date	June 18, 1996
Study Completion Date	August 13, 1996

1. Animal Husbandry and Assignment

From page 10 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in suspended stainless steel cages. Environmental controls for the

3/10

animal room were set to maintain a temperature of 19% to 23%C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided access to water ad libitum and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed. There were no known contaminants in the feed or water at levels that would have interfered with or affected the results of the study.

Six male and three female healthy, acclimated rabbits, weighing from 2,659 to 2,917 g and approximately 14 to 18 weeks of age, were selected at random and identified by animal number and corresponding ear tag. The animals' eyes were examined on the day before test material administration using sodium fluorescein dye procedures. Only those animals with no sign of ocular injury or irritation were used.

2. Dose Preparation and Administration

From page 11 of the report:

The test material was administered as received. The pH of the test material was not able to be determined.

Each rabbit received 0.1 mL of the undiluted test material placed into the everted lower lid of the right eye, with the left eye serving as the untreated control. The upper and lower lids were gently held together for 1 second to prevent loss of material and then released. The eyes of the rabbits in Group 1 remained unflushed immediately after treatment while the treated eyes of the rabbits in Group 2 were flushed with lukewarm tap water for 60 seconds starting 30 seconds after test material instillation.

3. Observations

From page 12 of the report:

Animals were weighed before test material administration.

The treated eyes were observed for ocular irritation at 1, 24, 48, and 72 hours after treatment. Additional observations were made at 96 hours after treatment for the animals in Group 1. Irritation was graded and scored according to the Draize technique using a penlight as the source of illumination. A sodium fluorescein examination was used to aid in revealing possible corneal injury at the observation conducted at 24 hours. Refer to Attachment 1 (page 26) for the ocular irritation scoring scale which is based on the method of Draize.

37

At termination of the in-life phase, all animals were euthanized and discarded.

The investigators provided an ocular irritation scoring scale which is based on the method of Draize as an appendix to the report.

4. Statistical Analyses

From page 12 of the report:

No statistical analyses were required by the protocol.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-4.

C. Results:

1. Eye Irritation

The investigators provided group summary and individual animal data for eye irritation. The following table presents the average eye irritation scores (from Table 1, page 15 of the report). The test compound produced slight to moderate conjunctival irritation in all treated eyes that were unwashed after treatment. All treated eyes in the unwashed group appeared normal by 96 hours. Positive irritation reactions were observed in 4/6 unwashed eyes which appeared normal by 24 hours (Table II, extracted from Tables 2 and 5, pages 16 and 21 of the report). In treated then washed eyes, the test compound produced slight to moderate conjunctival irritation. All of the treated then washed eyes appeared normal by 72 hours. A positive irritation reaction was observed in 1/3 animals with treated then washed eyes which appeared normal by the 24 hours. The results of the sodium fluorescein examinations were negative for both groups.

372

Table I: Average Primary Eye Irritation Scores[a]

Observation Period (Hour)	Average Score Unwashed	Washed
1	5.0	4.7
24	3.0	3.3
48	1.3	0.7
72	0.7	0.0
96	0.0	-

[a] = The average primary eye irritation score is the total eye irritation score for all the animals divided by the number of animals in each group (6 or 3) at each observation period.

Table II: Positive Ocular Reactions[a]

Observation Period (Hour)	1		24		48		72		96
	UW[1]	W[2]	UW	W	UW	W	UW	W	UW
Cornea Opacity	0/6	0/3	0/6	0/3	0/6	0/3	0/6	0/3	0/6
Iritis	0/6	0/3	0/6	0/3	0/6	0/3	0/6	0/3	0/6
Conjunctivae Redness	4/6	1/3	0/6	0/3	0/6	0/3	0/6	0/3	0/6
Chemosis	0/6	0/3	0/6	0/3	0/6	0/3	0/6	0/3	0/6

[a] = a positive reaction for each parameter is defined as any corneal opacity, an iris score of 1.0 or greater, or any conjunctival redness or chemosis score of 2.0 or greater; [1] = UW = unwashed eyes; [2] = W = washed eyes.

2. Body Weights

The investigators provided individual animal body weights apparently only for prior to study initiation, no treatment period weights were provided.

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The primary eye irritation potential of CGA-77102 720 was evaluated when instilled into the eyes of nine rabbits (six with treated eyes unwashed and three with treated eyes washed approximately 30 seconds after instillation). The test material produced slight to moderate conjunctival irritation in unwashed eyes which cleared in all animals by 96 hours after treatment. Positive irritation reactions were observed in four of the six animals with unwashed eyes which cleared in all animals by the 24 hour observation. In treated eyes receiving a washout, the test material produced slight to moderate conjunctival irritation which cleared in all animals by 72 hours after treatment. A positive irritation reaction was observed in one of the three animals with washed eyes which cleared by the 24 hour observation.

2. Reviewers conclusions

In a Primary Eye Irritation study, CGA-77102 720 produced slight to moderate conjunctival irritation to washed and unwashed eyes. Irritation cleared by 96 hours after treatment. Toxicity Category III.

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/2/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 5/9/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Dermal Irritation - Rabbit
Species: Rabbit Guideline: §81-5

EPA ID No.s: EPA MRID No. 44172208
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 720

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Study Title: Primary Dermal Irritation Study of CGA-77102 720 in Rabbits, Corning Hazleton, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504275, August 13, 1996 (Unpublished); EPA MRID Number 44172208.

Executive Summary: In a primary dermal irritation study (MRID# 44172208), 3 male and 3 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.5 mL CGA-77102 720 (Purity: 70.3% CGA-77102 and 3.53% CGA-154281; Lot Number FL-961187 (Batch Code 1098-26)) to the shaved back of each animal.

CGA-77102 720 produced very slight to well-defined erythema and very slight to slight edema reactions at the application site. The average primary irritation score (PIS) for the 4, 24, 48, 72 and 96-hour and Day 7 scores was 1.4. No irritation was seen by observation Day 14. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA, CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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 720
Purity: 70.3% CGA-77102 and 3.53% CGA-154281
Description: Dark red liquid
Lot Number: FL-961187 (Batch Code 1098-26)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbits
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: 14-18 weeks
Body Weight: 2229 to 2678 g

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the relative level of primary skin irritation of a test material on rabbits under semioccluded conditions.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose, method, frequency, and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

Study Timetable

Study Initiation Date	May 31, 1996
Experimental (In-life) Start Date	June 4, 1996
In-life End Date	June 18, 1996
Experimental Termination Date	June 18, 1996
Study Completion Date	August 13, 1996

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in suspended stainless steel cages. Environmental controls for the animal room were set to maintain a temperature of 19° to 23°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

3-14

The animals were provided access to water ad libitum and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed. There were no known contaminants in the feed or water at levels that could be expected to interfere with or affect the results of the study.

Three male and three female healthy, acclimated rabbits, weighing from 2,229 to 2,678 g and approximately 14 to 18 weeks of age, were selected at random and identified by animal number and corresponding ear tag. On the day before treatment, the back and/or flanks of each animal were clipped free of hair to obtain an unblemished skin site.

2. Dose Preparation and Administration

From page 11 of the report:

The test material was administered as received. The pH of the test material was not able to be determined.

The undiluted test material was applied to the intact skin site on each animal's back (approximate exposure area of 6.25 cm2) in the amount of 0.5 mL. The area of application was covered with an 8-ply 2.5-cm x 2.5-cm gauze patch secured with paper tape, loosely overwrapped with Saran Wrap®, and secured with Elastoplast® tape to provide a semiocclusive dressing.

At the end of the 4-hour exposure period, the patches were removed and the test sites were washed using liquid Ivory® soap mixed with warm tap water, rinsed with clean tap water, and dried with disposable paper towels. The test material was removed from the test sites as thoroughly as possible without irritating the skin.

3. Observations

From page 12 of the report:

Animals were weighed before test material administration.

Thirty minutes after removal of the test material, the degree of erythema and edema at each test site was read according to the Draize technique (recorded as the 4-hour score). Subsequent examinations were made at 24, 48, 72, and 96 hours and Days 7 and 14. The untreated skin of each animal was used for comparison. The investigators provided an dermal irritation scoring scale which is based on the method of Draize as an appendix to the report.

At termination of the in-life phase, all animals were euthanized and discarded.

4. Statistical Analyses

From page 12 of the report:

No statistical analyses were required by the protocol.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-5.

C. Results:

1. Dermal Irritation

The investigators provided group summary and individual animal data for erythema and edema dermal irritation. The following table presents the dermal irritation scores (from Table 3, page 17 of the report):

Table I: Average Primary Dermal Irritation Scores[a]

Observation Period	Average Score (PIS)
4 Hour	0.0
24 Hour	2.0
48 Hour	1.8
72 Hour	1.8
96 Hour	1.5
Day 7	1.0
Day 14	0.0

[a] = The average primary dermal irritation score is the total dermal irritation score for all the animals (erythema and edema) divided by the number of test sites (6) at each observation period.

2. Body Weights

The investigators provided individual animal body weights apparently only for prior to study initiation, no treatment period weights were provided.

378

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The primary dermal irritation potential of CGA-77102 720 was evaluated in rabbits under 4-hour semioccluded conditions. The test material produced very slight to well-defined erythema and very slight to slight edema reactions. No other dermal irritation was observed. All irritation cleared by the Day 14 observation. The average of the individual animal index scores is 1.4 (considered to be slightly irritating).

2. Reviewers conclusions

In a Primary Dermal Irritation study, CGA-77102 720 produced very slight to well-defined erythema and very slight to slight edema reactions at the application site. The average primary irritation score (PIS) for the 4, 24, 48, 72 and 96-hour and Day 7 scores was 1.4. No irritation was seen by observation Day 14. Toxicity Category IV.

012310

CGA 77102 720 PRIMARY DERMAL IRRITATION - RABBITS §81-5

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/2/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 5/9/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Dermal Irritation - Rabbit
Species: Rabbit Guideline: §81-5

EPA ID No.s: EPA MRID No. 44572209
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 720

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Study Title: Primary Dermal Irritation Study of CGA-77102 720 in Rabbits, Corning Hazleton, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation; Laboratory Project Identification: CHW 60504271, August 13, 1996 (Unpublished); EPA MRID Number 44572209.

Executive Summary: In a primary dermal irritation study (MRID# 44572209), 3 male and 3 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.5 mL CGA-77102 720 (Purity: 70.4% CGA-77102 and 3.58% CGA-154281; Lot Number FL-961208 (Batch Code 1098-27)) to the shaved back of each animal.

CGA-77102 720 produced very slight erythema reactions and very slight to slight edema reactions at the application site. The average primary irritation score (PIS) for the 4, 24, 48, 72 and 96-hour scores was 1.0. No irritation was seen by observation Day 7. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA, CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

380

A. Materials and Methods

Test Compound: CGA-77102 720
Purity: 70.4% CGA-77102 and 3.58% CGA-154281
Description: Dark red liquid
Lot Number: FL-961208 (Batch Code 1098-27)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbits
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: Not provided, "young adult"
Body Weight: 2644 to 2987 g

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the relative level of primary skin irritation of a test material on rabbits under semioccluded conditions.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose, method, frequency, and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

Study Timetable

Study Initiation Date	May 31, 1996
Experimental (In-life) Start Date	June 12, 1996
In-life End Date	June 19, 1996
Experimental Termination Date	June 19, 1996
Study Completion Date	August 13, 1996

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in suspended stainless steel cages. Environmental controls for the animal room were set to maintain a temperature of 19° to 23°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

381

The animals were provided access to water *ad libitum* and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed. There were no known contaminants in the feed or water at levels that could be expected to interfere with or affect the results of the study.

Three male and three female healthy, acclimated rabbits, weighing from 2,644 to 2,987 g, were selected at random and identified by animal number and corresponding ear tag. On the day before treatment, the back and/or flanks of each animal were clipped free of hair to obtain an unblemished skin site.

2. Dose Preparation and Administration

From page 11 of the report:

The test material was administered as received. The pH of the test material was not able to be determined.

The undiluted test material was applied to the intact skin site on each animal's back (approximate exposure area of 6.25 cm^2) in the amount of 0.5 mL. The area of application was covered with an 8-ply 2.5-cm x 2.5-cm gauze patch secured with paper tape, loosely overwrapped with Saran Wrap®, and secured with Elastoplast® tape to provide a semiocclusive dressing.

At the end of the 4-hour exposure period, the patches were removed and the test sites were washed using liquid Ivory® soap mixed with warm tap water, rinsed with clean tap water, and dried with disposable paper towels. The test material was removed from the test sites as thoroughly as possible without irritating the skin.

3. Observations

From page 12 of the report:

Animals were weighed before test material administration.

Thirty minutes after removal of the test material, the degree of erythema and edema at each test site was read according to the Draize technique (recorded as the 4-hour score). Subsequent examinations were made at 24, 48, 72, and 96 hours and Day 7. The untreated skin of each animal was used for comparison. The investigators provided an dermal irritation scoring scale which is based on the method of Draize as an appendix to the report.

At termination of the in-life phase, all animals were euthanized and discarded.

4. Statistical Analyses

From page 12 of the report:

No statistical analyses were required by the protocol.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-5.

C. Results:

1. Dermal Irritation

The investigators provided group summary and individual animal data for erythema and edema dermal irritation. The following table presents the average dermal irritation scores (from Table 3, page 17 of the report):

Table I: Average Primary Dermal Irritation Scores[a]

Observation Period	Average Score (PIS)
4 Hour	1.3
24 Hour	1.3
48 Hour	1.0
72 Hour	0.5
96 Hour	0.3
Day 7	0.0

[a] = The average primary dermal irritation score is the total dermal irritation score for all the animals (erythema and edema) divided by the number of test sites (6) at each observation period.

2. Body Weights

The investigators provided individual animal body weights apparently only for prior to study initiation, no treatment period weights were provided.

383

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The primary dermal irritation potential of CGA-77102 720 was evaluated in rabbits under 4-hour semioccluded conditions. The test material produced very slight erythema reactions and very slight to slight edema reactions. All irritation cleared by the Day 7 observation. The average of the individual animal index scores is 1.0 (considered to be slightly irritating).

2. Reviewers conclusions

In a Primary Dermal Irritation study, CGA-77102 720 produced very slight erythema reactions and very slight to slight edema reactions at the application site. The average primary irritation score (PIS) for the 4, 24, 48, 72 and 96-hour scores was 1.0. No irritation was seen by observation day 7. Toxicity Category IV.

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/30/97
Senior Pharmacologist, Review Section I, TB II/HED (7509C)

Secondary Review by: Nancy E. McCarroll Nancy E. McCarroll 6/3/97
Secondary Reviewer, Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Dermal Sensitization - Guinea Pigs
Species: Guinea Pigs Guideline: §81-6

EPA ID No.s: EPA MRID No. 44172210
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D226782
EPA Submission No. S501353

Test Material: CGA-77102 720

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102 720, FINAL REPORT, Study Title: Dermal Sensitization Study of CGA-77102 720 in Guinea Pigs - Closed Patch Technique, Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504277, September 17, 1996 (Unpublished); EPA MRID Number 44172210.

Executive Summary: In a dermal sensitization study (MRID# 44172210), 10 young male adult albino guinea pigs (Strain: Crl:(HA)BR from Charles River Laboratories, Inc., Portage, Michigan) received 0.4 mL (3 induction and 1 challenge application) CGA-77102 720 (Purity: 70.3% CGA-77102 and 3.53% CGA-154281; Lot Number: FL-961187 (Batch Code 1098-26)) to the shaved back of each animal.

CGA-77102 720 was a dermal sensitizer in guinea pigs tested with the closed patch technique.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

Compliance: A signed and dated STATEMENT OF NO DATA, CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

35

A. Materials and Methods

Test Compound: CGA-77102 720
Purity: 70.3% CGA-77102 and 3.53% CGA-154281
Description: Dark-red liquid
Lot Number: FL-961187 (Batch Code 1098-26)
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Positive Control: 2,4-dinitrochlorobenzene

A study report detailing the results of sensitization testing of 2,4-dinitrochlorobenzene (a known skin sensitizer) using the same sensitization method was appended to the report. This positive control study was initiated within 6 months of the conduct of this study (Corning Hazleton, Inc. For Corning Hazleton, Inc., Protocol TP2008.P.1, Study Title: Dermal Sensitization Study of 2,4-dinitrochlorobenzene in Guinea Pigs - Closed Patch Technique, January 8, 1996, Laboratory Project Identification: CHW 51104718).

Test Animal(s): Species: Young adult albino guinea pig
Strain: Crl:(HA)BR
Source: Charles River Laboratories, Inc., Portage, Michigan
Age: 4-8 weeks
Body Weight: 374 to 521 g

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the delayed contact hypersensitivity potential of a test material in guinea pigs.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose levels, method, frequency, and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

386

Study Timetable

Study Initiation Date	June 6, 1996
Experimental (In-life) Start Date	June 10, 1996
In-life End Date	July 24, 1996
Experimental Termination Date	July 24, 1996
Study Completion Date	September 17, 1996

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in screen-bottom stainless steel cages. Environmental controls for the animal room were set to maintain a temperature of 19° to 25°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided continuous access to Certified Guinea Pig Diet #5026, PMI Feeds, Inc., and water. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed. There were no known contaminants in the feed or water at levels that could be expected to interfere with or affect the results of the study.

Twenty-four healthy, acclimated male albino guinea pigs, weighing from 374 to 521 g and approximately 4 to 8 weeks of age, were selected and divided into three groups consisting of an irritation screening group of four animals, a test group of 10 animals, and a naive control group of 10 animals. The animals were identified by animal number and corresponding ear tag throughout the study.

2. Study Protocol

From pages 11-12 of the report:

Irritation Screening Study

An irritation screening study using four animals was conducted to determine the irritation threshold of the test material. The test material was administered undiluted and at concentrations of 25%, 50%, and 75% w/v in mineral oil with each animal receiving two different concentrations of the test material. All test material mixtures used in the irritation screening phase of the study were stored at room temperature until administered. The appropriate test material concentrations, in the amount of 0.4 mL, were applied to adhesive patches (Hill Top Chamber®, 25-mm diameter). The patches were then placed on two shaved sites (one on the right and one on the left anterior dorsal quadrants) on each animal, covered with an overlapping strip of dental dam, and overwrapped with Elastoplast® tape. The patches remained

384

in place for 6 hours after which they were removed. To aid in removal of the test material, mineral oil was applied to the sites and wiped away with wet disposable paper towels. The sites were then rinsed with tap water and wiped dry with disposable paper towels. The application sites were observed for dermal reactions at 24 and 48 hours after test material application.

Definitive Study
Based on the results of the irritation screening study, the test material was administered undiluted for the induction phase and for the challenge application.
Induction Phase. On the day of test material application, the hair was removed from the back of each animal in the test group with electric clippers. The undiluted test material was applied to each animal by placing 0.4 mL on an adhesive patch (Hill Top Chamber®, 25-mm in diameter) and placing the patch on the induction site along the dorsal anterior left quadrant. The patch was covered with dental dam and overwrapped with Elastoplast® tape. The dressing remained in place for a period of 6 hours after which it was removed. To aid in removal of the test material, mineral oil was applied to the induction sites and wiped away with wet disposable paper towels. The sites were then rinsed with tap water and wiped dry with disposable paper towels. The animals in the test group received one application per week for 3 weeks for a total of three applications. The naive control animals were not treated during this phase of the study.

Challenge Phase. Two weeks following the administration of the third induction dose, a challenge dose of 0.4 mL of the undiluted test material was administered along the dorsal anterior right quadrant of the test group animals in the same manner as during the induction phase of the study. At this time the 10 naive (previously untreated) control animals were also treated with a challenge application of the test material in the same manner as the animals in the test group.

3. Observations

From pages 12-13 of the report:

On the day of the 24-hour examination following the irritation screening and challenge applications, the application sites of the respective animals were depilated by applying Neet® depilatory. After approximately 15 to 20 minutes, the depilatory was washed from the application sites. The 24-hour observation occurred at least 2 hours after removal of the depilatory.

The respective application sites were examined and scored for dermal reactions according to the following Buehler scoring scale at 24 and 48 hours following the irritation screening, induction, and challenge applications:

386

Buehler Sensitization Scoring Scale

No reaction	0.0
Very faint erythema, usually nonconfluent	0.5
Faint erythema, usually confluent	1.0
Moderate erythema	2.0
Strong erythema, with or without edema	3.0

Clinical observations were conducted daily throughout the study. Body weights on the irritation screening animals were determined only on the day of treatment. Body weights on the definitive study animals were determined before test material administration and at termination of the in-life phase.

At termination of the respective in-life phase for each group, all animals were euthanized and discarded.

Evaluation of Challenge Responses
Determination of sensitization was based on the dermal reactions to the challenge dose. Grades of 1.0 or greater in the test animals may indicate evidence of sensitization, provided grades of less than 1.0 are seen in the naive control animals. If reactions in the naive control group are 1.0 or greater, then only those reactions in the test group that exceed the highest naive control reaction are considered to be sensitization reactions.

4. Statistical Analyses

From page 13 of the report:

No statistical analyses were required by the protocol.

PROTOCOL DEVIATIONS: From page 20 of the report:

Protocol	Actual Procedure
Page 4, 5. Test Material, E. Reserve Samples, Second Sentence. The test material reserve samples will be stored at CHW in a freezer set to maintain a temperature of -20°C ±10°C until returned to the Sponsor after completion of the in-life phase of the study.	In order to comply with MAFF requirements, the reserve sample of the test material will be stored at CHW in a freezer set to maintain a temperature of -20°C ±10°C for 10 years.
Page 8, 6. Experimental Design, C. Observation of Animals, (3) Body weights. Before test material administration and at the termination of the experimental phase.	Body weights for the irritation screening animals were determined only on the day of treatment.

389

Page 9, 8. Location of Raw Data, Records, and Final Report, Second and Third Sentences. When the final report is completed, all original paper data, including those items listed below will be retained in the archives of CHW for a period of one year following signing of the final report. One year after signing of the final report, all of the aforementioned materials will be sent to the Sponsor and a return fee will be charged.	In order to comply with MAFF requirements, the final report and all original paper data will be retained in the archives of CHW for 10 years.

These deviations are not considered to have had an adverse effect on the outcome of the study.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-6.

C. Results:

1. Irritation Screening Phase

The investigators provided individual body weights and dermal reactions data. The investigators observed very faint to faint erythema reactions in animals treated with the 50% w/v mixture of the test compound in mineral oil at 24 hours. Also, very faint erythema reactions were observed in animals treated with the 75% w/v mixture of test compound in mineral oil at 24 hours as well as the undiluted test compound at 24 hours. No dermal irritation was reported at 48 hours or for the 25% w/v mixture of the test compound in mineral oil. No treatment related effects were noted in screening animals of the irritation screening phase of the study.

2. Definitive Phase

a. Clinical Observations

The investigators provided individual clinical signs data, no treatment related effects were noted (1 naive control had soft stool).

340

b. Body Weights

The investigators provided individual body weights. No treatment related effects were noted.

c. Dermal Reactions

i. Test Compound

The investigators provided individual dermal reaction scores for the test and naive control animals. During the induction phase of the study, 9/10 animals had faint to strong erythema reactions at 24 and 48 hours. During the challenge phase, the undiluted test compound produced faint to moderate erythema reactions in all test animals at 24 to 48 hours. Naive control animals had very faint erythema (5/10) to moderate (1/10) reactions at 24 hours and very faint erythema (1/10) at 48 hours following challenge application. The investigators noted that 8 of the reactions noted in the test group exceeded the highest naive control reaction during the challenge phase.

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The delayed contact hypersensitivity potential of CGA-77102 720 was evaluated in albino guinea pigs. The test material was administered undiluted to each animal in the test group during the induction phase of the study. At challenge, the undiluted test material produced faint to moderate erythema reactions [scores of 1.0 to 3.0 (moderate erythema reactions with edema were recorded as a score of 3.0)] in all 10 test animals. Very faint erythema reactions (score of 0.5) were observed in five of the 10 naive control animals at challenge. In addition, one naive control animal had a moderate erythema reaction at the 24-hour observation period. Eight of the challenge reactions in the test group are considered to have exceeded the highest naive control reaction. Based on these results, this test material is considered to be a dermal sensitizer in guinea pigs.

2. Reviewers' Conclusions

In a Dermal Sensitization study, CGA-77102 720 was a dermal sensitizer in guinea pigs tested with the closed patch technique.

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 8/15/97
Senior Pharmacologist, Toxicology Branch II/HED (7509C)

Secondary Review by: K. Clark Swentzel K. Clark Swentzel 8/22/97
Acting Branch Senior Scientist, Toxicology Branch II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Oral Toxicity - Rat
Species: Rat Guideline: §81-1

EPA ID No.s: EPA MRID No. 44128003
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D235664
EPA Submission No. S515306

Test Material: CGA-77102/G-30027 II 720 SC-Exp
Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102/G-30027 II 720SC-Exp, FINAL REPORT, Study Title: Acute Oral Toxicity Study of CGA-77102/G-30027 II 720SC-Exp in Rats, (EPA Guidelines 81-1), Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504756, September 20, 1996 (Unpublished); EPA MRID Number 44128003.

Executive Summary: In an acute oral toxicity study (MRID# 44128003), groups of 5 male and 5 female young adult albino rats (Strain: Crl:CD®(SD)BR from Charles River Laboratories, Inc., Portage, Michigan) received either 3000, 5000, or 6000 mg/kg in males and 1000, 3000, or 5000 mg/kg in females of CGA-77102/G-30027 II 720 SC-Exp (Purity: 35.8% CGA-77102, 28.7% Atrazine (29.0% TCT) and 1.79% CGA-154281; Lot No.: FL-961156, Batch Code 1098-25-1) as a single gavage dose. A range-finding study was conducted using 500, 1000, 3000 or 5000 mg/kg as a single gavage dose in 1 male and 1 female at each dose level.

The Acute Oral LD_{50} for CGA-77102/G-30027 II 720 SC-Exp is:

Males - 5477 mg/kg bw
95% Confidence Limits - 4374 to 6858 mg/kg bw

Females - 3633 mg/kg bw
95% Confidence Limits - 2516 to 5248 mg/kg bw

Combined - 4824 mg/kg bw
95% Confidence Limits - 3660 to 6358 mg/kg bw

Toxicity Category III.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-1) for an acute oral toxicity study in rats.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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/G-30027 II 720 SC-Exp
Purity: 35.8% CGA-77102, 28.7% Atrazine (29.0% TCT) and 1.79% CGA-154281
Description: Off-white liquid
Lot No.: FL-961156, Batch Code 1098-25-1
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Young adult albino rats
Strain: Crl:CD®(SD)BR
Source: Charles River Laboratories, Inc., Portage, Michigan
Age: approximately 6 to 15 weeks of age
Body Weight: 208 to 277 g (primary study)

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the acute oral toxicity produced when the test material is administered by the oral route (gavage) to rats.

The dose levels, method, frequency, and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

342

Study Timetable

Study Initiation Date	June 5, 1996
Experimental (In-life) Start Date	June 13, 1996
In-life End Date	September 5, 1996
Experimental Termination Date	September 20, 1996
Study Completion Date	September 20, 1996

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the definitive study, the animals were separated by sex and group housed in screen-bottom stainless steel cages. During the range-finding study, the animals were individually housed. Environmental controls for the animal room were set to maintain a temperature of 19° to 25°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided continuous access to Laboratory Rodent Diet #5001, PMI Feeds, Inc, and water except for 17 to 20 hours before test material administration when food, but not water, was withheld. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed. There were no known contaminants in the feed or water at levels that could be expected to interfere with or affect the results of the study.

Initially, eight healthy, acclimated rats (one/sex/dose level), weighing from 242 to 279 g and approximately 6 to 15 weeks of age, were used for each of four dose levels (500, 1,000, 3,000, and 5,000 mg/kg of body weight) in a range-finding study.

Based on the results of the range-finding study, fifteen male and fifteen female healthy, acclimated rats, weighing from 208 to 277 g and approximately 6 to 15 weeks of age, were assigned to treatment groups in the definitive study. Five males per level were treated at 3,000, 5,000, and 6,000 mg/kg of body weight. Five females per level were treated at 1,000, 3,000, and 5,000 mg/kg of body weight.

2. Dose Preparation and Administration

From page 11 of the report:

The undiluted test material was administered by gavage using an average bulk density determination of 1.09 g/mL to determine the dose volume of each dose level. An individual dose was calculated for each animal based on its fasted body weight.

3. Observations

From pages 11-12 of the report:

Body weights for both range-finding and definitive study animals were determined before test material administration (Day 0). Additional body weights were determined at Day 7, at termination of the respective in-life phase (Day 14), or at death when survival exceeded 1 day.

The range-finding animals were observed for mortality only on the day of treatment and for 14 days thereafter.

Clinical observations for the definitive study animals were conducted at 1, 2.5, and 4 hours after test material administration and daily thereafter for 14 days. Mortality checks for the definitive study animals were conducted twice a day (morning and afternoon) for 13 days after test material administration and again the morning of Day 14.

Range-finding animals that died during the study were discarded without necropsy. The range-finding animals surviving to Day 14 were euthanized and discarded without necropsy.

At termination of the respective in-life phase for each definitive study dose level, surviving animals were euthanized. All animals, whether found dead during the study or euthanized, were subjected to an abbreviated gross necropsy examination and any abnormalities were recorded. After necropsy, the animals were discarded and only those tissues with lesions were saved for possible future examination.

4. Statistical Analyses

From pages 12 and 14 of the report:

The LD50 values for males, females, and the sexes combined were determined by a computer program using a modified Behrens-Reed-Muench cumulant method. No other statistical analyses were required by the protocol.

Reference: Thakur, A. K. and Fezio, W. L., "A Computer Program for Estimating LD50 and its Confidence Limits Using a Modified Behrens-Reed-Muench Cumulant Method," Drug and Chemical Toxicology, 4(3):297-305 (1981).

PROTOCOL DEVIATIONS (from page 32 of the report):

Protocol	Actual Procedure
Page 4, 5. Test Material, E. Reserve Samples, Second Paragraph. The test material reserve samples (if applicable) will be stored at CHW in a freezer set to maintain a temperature of -20°C ±10°C until returned to the Sponsor after completion of the in-life phase of the study.	In order to comply with MAFF requirements, the reserve sample of the test material will be stored at CHW in a freezer set to maintain a temperature of -20°C ±10°C for 10 years.
Page 8, 8. Location of Raw Data, Records, and Final Report, Second and Third Sentences. When the final report is completed, all original paper data, including those items listed below will be retained in the archives of CHW for a period of one year following signing of the final report. One year after signing of the final report, all of the aforementioned materials will be sent to the Sponsor and a return fee will be charged.	In order to comply with MAFF requirements, the final report and all original paper data will be retained in the archives of CHW for 10 years.

These deviations are not considered to have had an adverse effect on the outcome of the study.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-1.

C. Results:

1. Mortality

The investigators provided a group summary of the observed mortality. For the Range-Finding Study, one 5000 mg/kg female died within two days of treatment. For the definitive study, one

314

3000 mg/kg female, six 5000 mg/kg animals (two males and four females) and three 6000 mg/kg males were found dead. All mortality was noted to have occurred within two days of test material administration. One 5000 mg/kg female was sacrificed moribund. No other mortality was observed. The following table (from Table 1, page 16 of the report) summarizes the mortality data:

Table I: Mortality Summary

Dose Level (mg/kg)	Mortality, Day Died*
Range-Finding Study	
Males	
500	0/1
1000	0/1
3000	0/1
5000	0/1
Females	
500	0/1
1000	0/1
3000	0/1
5000	1/1, Day 2^1
Primary (Definitive) Study	
Males	
3000	0/5
5000	2/5, Day 1^2
6000	3/5. Day 0^1, 1^1, 2^1
Females	
1000	0/5
3000	1/5, Day 1^1
5000	5/5, Day 0^1, 1^3, 5^{1**}

*** = Superscript number indicates number of animals found dead on that day; ** = sacrificed moribund, included in LD_{50} calculations.**

Calculated Oral LD_{50} :

Males - 5477 mg/kg bw
95% Confidence Limits - 4374 to 6858 mg/kg bw

Females - 3633 mg/kg bw
95% Confidence Limits - 2516 to 5248 mg/kg bw

Combined - 4824 mg/kg bw
95% Confidence Limits - 3660 to 6358 mg/kg bw

2. Clinical Signs

The investigators provided group summary and individual clinical signs data for the primary study. No effects were noted in the 1000 mg/kg females. The clinical signs of toxicity included hypoactivity (2.5 hours, 5000 mg/kg males; 4 hours in one 5000 mg/kg male, 1.0-4.0 hours in 5000 mg/kg females; 2.5 hours-1 day in 6000 mg/kg males), thin appearance (days 3 and 4, 3000 mg/kg males and days 1-5 in 3000 mg/kg females; days 2-6, 5000 mg/kg males, days 3 to sacrifice moribund in one 5000 mg/kg female; days 3-6, one 6000 mg/kg male), red-stained face (days 1-5 in 3000 mg/kg males, 1.0 hours to day 4 in 3000 mg/kg females; days 2-6 in 5000 mg/kg males, 2.5 hours to day 5 in 5000 mg/kg females. 1.0 hours and days 1-5 in 6000 mg/kg males), dark-staining around eyes (day 5 in 5000 mg/kg female sacrificed moribund), dyspnea (2.5 and 4.0 hours in 6000 mg/kg males), wet and/or yellow-stained urogenital area (days 2 and 3 and 4 and 5 in a 3000 mg/kg female; 2.5 hours to day 5 in 5000 mg/kg females), soft stool (4.0 hours in one 5000 mg/kg female and 4.0 hours in one 6000 mg/kg male), scabs on both front feet (days 3-5 in the 5000 mg/kg female sacrificed moribund), staggered gait (1.0 hours to day 1 in 5000 mg/kg females and 4.0 hours to day 1 in 6000 mg/kg males), hunched posture (4.0 hours to day 1 and days 3-5 in 5000 mg/kg females; 2.5 hours to day 1 in 6000 mg/kg males), excessive salivation (1.0-4.0 hours in 5000 mg/kg males, 2.5-4.0 hours in 5000 mg/kg females; 1.0-4.0 hours in a 6000 mg/kg male), miosis (4.0 hours in a 5000 mg/kg female), tremors (1.0-4.0 hours and day 5 in 5000 mg/kg females) and hypothermic to touch (day 5 in the 5000 mg/kg female sacrificed moribund). All surviving animals returned to a normal appearance by day 9 after treatment.

3. Body Weights

The investigators provided individual and mean body weights and body weight gains for animals in the range-finding and primary study. No treatment related effects were noted on body weight gain in surviving animals. The following table presents the body weights and body weight gains (from Table 2, pages 17-20 of the report):

318

Table I: Mean Body Weights and Body Weight Gains (grams)

Day:	0	7	0-7 gain	14	0-14 gain
Dose (mg/kg):					
			Males		
		Range-Finding Study			
500	242(1)[n]	321(1)	79(1)	360(1)	118(1)
1000	245(1)	328(1)	83(1)	382(1)	137(1)
3000	246(1)	265(1)	19(1)	356(1)	110(1)
5000	254(1)	302(1)	48(1)	360(1)	106(1)
			Females		
500	271(1)	302(1)	31(1)	305(1)	34(1)
1000	277(1)	291(1)	14(1)	300(1)	23(1)
3000	279(1)	295(1)	16(1)	323(1)	44(1)
5000	273(1)				
		Primary (Definitive) Study			
			Males		
3000	228(5)	293(5)	65(5)	358(5)	130(5)
3500	243(5)	301(3)	60(3)	361(3)	120(3)
5000	274(5)	291(3)	18(3)	363(3)	91(3)
6000	225(5)	250(2)	28(2)	310(2)	88(2)
			Females		
1000	217(5)	265(5)	48(5)	281(5)	64(5)
3000	233(5)	274(4)	42(4)	303(4)	71(4)
5000	212(5)				

[n] = number of animals

4. Pathology

The investigators provided individual gross necropsy pathology findings and a summary report by the study pathologist. According to the pathologist: *At necropsy, the most prominent findings were in the DOTs and pertained to coloration changes and content of the gastrointestinal tract, and pertained to a oral or nasal discharge. The stomach and the small intestines contained material of variable color and consistency which possibly represented test material mixed with ingesta, autolysis, or both. The oral and nasal discharge was of variable color and consistency. The perineum of some animals was stained brown. There were no visible lesions observed in the animals surviving to study termination except in one female given 3,000 mg/kg. In this latter animal, the walls of the stomach were diffusely thickened; there were multiple gray, fibrous adhesions between the spleen and the adipose tissue adjacent to the stomach; and the spleen had diffuse brown areas of variable size. The stomach and spleen lesions were collected and preserved in 10% formalin as required. All observations in this animal and in the DOTs were considered incidental findings and unrelated to the test material. There were no visible lesions in the remaining animals.*

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The test material, CGA-77102/G-30027 II 720SC-Exp, was evaluated for its acute oral toxicity potential in male and female rats when administered as a single gavage dose in the definitive study at levels of 3,000, 5,000, and 6,000 mg/kg of body weight for males and 1,000, 3,000, and 5,000 mg/kg of body weight for females. The estimated oral LD50 values in rats were determined to be 5,477, 3,633, and 4,824 mg/kg for males, females, and the sexes combined, respectively. All deaths occurred within 2 days of test material administration. One female treated at 5,000 mg/kg was sacrificed on Day 5 due to moribund condition. All females treated at 1,000 mg/kg appeared normal during the study. The incidence and onset of clinical signs of toxicity in the other dose levels was dose related and included hypoactivity, staggered gait, thin appearance, hunched posture, red-stained face, excessive salivation, dark staining around eyes, miosis, wet and/or yellow-stained urogenital area, soft stool, tremors, scabs on both front feet, and hypothermic to touch. All surviving animals returned to a normal appearance by Day 9 after treatment. Animals surviving to the end of the observation period exhibited body weight gain. The most prominent findings at necropsy were in the animals that died during the study and pertained to the contents of the gastrointestinal tract (possibly representing test material mixed with ingesta). An oral and/or nasal discharge and yellow or brown staining of the perineum was also seen in some of these animals.

2. Reviewers' Conclusions

The Acute Oral LD_{50} for CGA-77102/G-30027 II 720 SC-Exp is:

Males - 5477 mg/kg bw
95% Confidence Limits - 4374 to 6858 mg/kg bw

Females - 3633 mg/kg bw
95% Confidence Limits - 2516 to 5248 mg/kg bw

Combined - 4824 mg/kg bw
95% Confidence Limits - 3660 to 6358 mg/kg bw

Toxicity Category III.

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 8/15/97
Senior Pharmacologist, Toxicology Branch II/HED (7509C)

Secondary Review by: K. Clark Swentzel K. Clark Swentzel 8/22/97
Acting Branch Senior Scientist, Toxicology Branch II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Dermal Toxicity - Rabbit
Species: Rabbit Guideline: §81-2

EPA ID No.s: EPA MRID No. 44128004
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D235664
EPA Submission No. S515306

Test Material: CGA-77102/G-30027 II 720SC-Exp

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102/G-30027 II 720SC-Exp, FINAL REPORT, Study Title: Acute Dermal Toxicity Study of CGA-77102/G-30027 II 720SC-Exp in Rabbits, (EPA Guidelines 81-2), Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504757, September 13, 1996 (Unpublished); EPA MRID Number 44128004.

Executive Summary: In an acute dermal toxicity study (MRID# 441722047), 5 male and 5 female Adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 2000 mg/kg CGA-77102/G-30027 II 720SC-Exp (Purity: 35.8% CGA-77102, 28.7% Atrazine (29.0% TCT) and 1.79% CGA-154281; Lot No.: FL-961156, Batch Code 1098-25-1) by the dermal route.

The Acute Dermal LD_{50} for CGA-77102/G-30027 II 720SC-Exp is greater than 2000 mg/kg. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-2) for an acute dermal toxicity study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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/G-30027 II 720SC-Exp
Purity: 35.8% CGA-77102, 28.7% Atrazine (29.0% TCT) and 1.79% CGA-154281
Description: Off-white liquid
Lot No.: FL-961156, Batch Code 1098-25-1
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbits
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: 14-18 weeks
Body Weight: 2596 to 2866 g

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the systemic toxicity and relative skin irritancy of a test material when applied to the skin of rabbits.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose level, method, frequency, and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

Study Timetable

Study Initiation Date	May 31, 1996
Experimental (In-life) Start Date	June 12, 1996
In-life End Date	June 26, 1996
Experimental Termination Date	September 13, 1996
Study Completion Date	September 13, 1996

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in suspended stainless steel cages. Environmental controls for the

408

animal room were set to maintain a temperature of 19° to 23°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided access to water ad libitum and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed. There were no known contaminants in the feed or water at levels that could be expected to interfere with or affect the results of the study.

Five male and five female healthy, acclimated rabbits, weighing from 2,596 to 2,866 g and approximately 14 to 18 weeks of age, were used for a single dose level of 2,000 mg/kg of body weight. The animals were identified by animal number and corresponding ear tag throughout the study. On the day before test material application, each rabbit's back was clipped free of hair. The clipped area made up not less than 20% of total body surface.

2. Dose Preparation and Administration

From page 11 of the report:

The test material was administered as received. An individual dose was calculated and weighed out based on each animal's body weight on the day of test material administration.

The test material was applied to the intact skin on each animals' back at a dose level of 2,000 mg/kg of body weight. The test material was applied to the test site at a rate of approximately 0.03 g/cm2 in a thin and uniform layer. The area of application (approximately 180 cm2) was covered with a 4-ply 9.5-cm x 19-cm gauze patch secured with paper tape and overwrapped with Saran Wrap® and Elastoplast® tape to provide an occlusive dressing. Collars were used to restrain the test animals during the 24-hour exposure period.

At the end of the 24-hour exposure period, the restraining collars and bandages were removed and the test sites were washed using tap water and disposable paper towels.

3. Observations

From page 12 of the report:

Body weights were determined before test material administration (Day 0), at Day 7, and at termination of the in-life phase (Day 14).

Clinical observations were conducted at 1, 2.5, and 4 hours after test material administration. Additional clinical observations (including dermal effects) were conducted daily thereafter for 14 days. Mortality checks were

conducted twice a day (morning and afternoon) for 13 days after test material administration and again the morning of Day 14.

At termination of the in-life phase, all animals were euthanized, subjected to an abbreviated gross necropsy examination, and any abnormalities were recorded. After necropsy, the animals were discarded and only those tissues with lesions were saved and preserved in 10% phosphate-buffered formalin.

4. Statistical Analyses

From page 12 of the report:

No statistical analyses were required by the protocol.

PROTOCOL DEVIATIONS (from page 20 of the report):

Protocol	Actual Procedure
Page 8, 8. Location of Raw Data, Records, and Final Report, Second and Third Sentences. When the final report is completed, all original paper data, including those items listed below will be retained in the archives of CHW for a period of one year following signing of the final report. One year after signing of the final report, all of the aforementioned materials will be sent to the Sponsor and a return fee will be charged.	In order to comply with MAFF requirements, the final report and all original paper data will be retained in the archives of CHW for 10 years.

This deviation is not considered to have had an adverse effect on the outcome of the study.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-2.

404

C. Results:

1. Mortality

The investigators provided a group summary of the observed mortality. No mortality was observed. The estimated dermal LD_{50} values for male and female rabbits were determined to be greater than 2000 mg/kg bw.

2. Clinical Signs and Dermal Irritation

The investigators provided individual clinical signs data. No adverse clinical signs were noted in the data provided. The dermal irritation ranged from "slight to moderate".

3. Body Weights

The investigators provided individual and mean body weights and body weight gains. There were body weight losses of 30 to 60 grams in 4 males and of 42 to 192 grams in 4 females during the first 7 days of the study. The second week noted most animals with body weight gain except for 2 males The following table presents the body weights and body weight gains (from Table 2, page 17 of the report):

Table I: Mean Body Weights and Body Weight Gains (grams)

Day: Dose (mg/kg):	0	7	0-7 gain	14	0-14 gain
			Males		
2000	2800	2775	-24	2782	-18
			Females		
2000	2662	2593	-69	2679	17

4. Pathology

The investigators provided individual gross necropsy pathology findings and a summary report by the study pathologist. According to the pathologist: *At necropsy, the treated skin of three males and five females was diffusely red or had multiple red areas of variable size. These lesions are indicative of irritation caused by the test material. The skin with lesions were collected and preserved in 10% formalin as required. There were no visible lesions in the remaining animals.*

405

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The test material, CGA-77102/G-30027 II 720SC-Exp, was evaluated for its acute dermal toxicity potential in male and female rabbits when administered as a single topical application at a level of 2,000 mg/kg of body weight. The estimated dermal LD50 values for male and female rabbits were determined to be greater than 2,000 mg/kg. All animals appeared normal throughout the study. Body weight losses from 30 to 60 g were noted for 4 males and 3 females during the first week of the study. In addition, one female had a weight loss of 192 g during the first week. All animals exhibited body weight gain during the second week with the exception of 2 males which exhibited weight losses of 5 to 53 g. The test material produced slight to moderate dermal irritation. The gross necropsy at termination revealed only those lesions associated with the dermal irritation caused by the test material.

2. Reviewers' Conclusions

The Acute Dermal LD_{50} for CGA-77102/G-30027 II 720SC-Exp is greater than 2000 mg/kg.

Toxicity Category III.

406

012310

CGA-77102/G-30027 II 720SC ACUTE INHALATION TOXICITY - RATS §81-3

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 8/15/97
Senior Pharmacologist, Toxicology Branch II/HED (7509C)
Secondary Review by: K. Clark Swentzel K. Clark Swentzel 8/22/97
Acting Branch Senior Scientist, Toxicology Branch II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute Inhalation Toxicity - Rat
Species: Rat Guideline: §81-3

EPA ID No.s: EPA MRID No. 44128005
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D235664
EPA Submission No. S515306

Test Material: CGA-77102/G-30027 II 720SC
Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: J. Bennick (1996): CGA-77102/G-30027 II 720SC, FINAL REPORT, ACUTE INHALATION TOXICITY STUDY IN RATS, EPA GUIDELINE NO. 81-3, STILLMEADOW, Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, LABORATORY STUDY NUMBER 2886-96, August 9, 1996 (Unpublished); EPA MRID Number 44128005.

Executive Summary: In an acute inhalation toxicity study (MRID# 44128005), groups of 5 male and 5 female rats (females were nulliparous and non-pregnant; Strain: HSD:Sprague-Dawley from Harlan Sprague Dawley, Inc., Indianapolis, IN) were exposed by the nose only route to a generated aerosol of CGA-77102/G-30027 II 720SC from undiluted liquid at levels of 0.640 and 2.93 mg/L (Purity: 35.8% CGA-77102, 28.7% Atrazine (29.0% TCT), 1.79% CGA-154281; Lot No.: FL-961156).

The Acute Inhalation LC_{50} for CGA-77102/G-30027 II 720SC is greater than 0.640 mg/L for both sexes. The particle size distribution (MMAD) was 3.484 µm. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-3) for an acute inhalation toxicity study in rats.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, GLP COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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).

409

A. Materials and Methods

Test Compound: CGA-77102/G-30027 II 720SC
Purity: 35.8% CGA-77102, 28.7% Atrazine (29.0% TCT), 1.79% CGA-154281
Description: White liquid
Lot No.: FL-961156
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Male and female rats (females were nulliparous and non-pregnant)
Strain: HSD:Sprague-Dawley
Source: Harlan Sprague Dawley, Inc., Indianapolis, IN
Age: Young adult (8-12 weeks)
Body Weight: Males (270-308 g); Females (191-218 g)
Acclimation Period: At least five days

B. Study Design

From page 6 of the report:

The objective of this study was to determine the acute inhalation toxicity potential of the test substance in accordance with Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Series 81-3, EPA Publication, EPA 540/9-84-014, November, 1984. This study was conducted for Ciba-Geigy Corporation according to the approved protocol (No.S9-FF81-3.C3) and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures used in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the sponsor, the study did not unnecessarily duplicate any previous work. The original protocol, raw data and this report are kept on file permanently in the STILLMEADOW, Inc. archives. The study was initiated on May 16, 1996, and the animals were exposed as follows:

Beginning of 4 Hour Exposure					Termination of In-Life Observations	
Dose (mg/L)	Males		Females		Males	Females
	Date	Time	Date	Time	Date	Date
0.640	6/17/96	10:30	6/17/96	10:30	7/01/96	7/01/96
2.93	6/12/96	10:30	6/12/96	10:30	6/26/96	6/26/96

48

1. Animal Husbandry and Assignment

From page 7 of the report:

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	One per cage
Environmental Controls Set to Maintain:	·Temperature Range: 72°F± 5° ·Humidity Range: 30-80% ·12-hour light/dark cycle ·10-12 air changes/hour
Transfer to Clean Cages:	Weekly
Litter Pan Lining:	Paper and aspen bedding
Litter Pan Lining Change:	Three times weekly
Food:	PMI Feeds, Inc.™ Lab Diet Formulab #5008, available *ad libitum* except during the exposure period
Water Type:	Municipal water supply from automatic water system, available *ad libitum* except during the exposure period

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No 86-23, revised 1985). No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

2. Procedures

From pages 8-9 of the report:

Prestudy Testing
Trial assays were conducted to determine which method(s) of aerosolizing the test substance into the exposure chamber would produce an acceptable concentration and mass median aerodynamic diameter (MMAD).

Exposure Chamber
A 500 L nose-only stainless steel, dynamic flow inhalation chamber was utilized in this experiment [Diagram provided in report]. The body of the chamber has 25 ports in 5 rows. Polycarbonate cones are inserted into 10 designated individual ports. The test substance is introduced through the opening in the top of the chamber. The bottom section has a corresponding air outlet and a drain valve for cleaning the chamber. The individual polycarbonate cones (tubes) are tapered at one end to fit the shape of the animal's head and the back portion is sealed with a polycarbonate cap. The cones containing the animals fit tightly into the ports, and are sealed with "O" rings.

Generation of Test Atmosphere
The aerosol at the 0.640 mg/L level was generated by pumping the test substance into a pressure operated Spraying System Company air atomizer (1/4 JSS) and then elutriating the resulting aerosol through a baffling chamber. The concentrated aerosol was then diluted with filtered air and drawn into the exposure chamber. The aerosol at the 2.93 mg/L level was generated by pumping the test substance into a pressure operated air atomizer and then spraying the resulting aerosol directly into the exposure chamber.

Air flow into the chamber was maintained through the use of a calibrated orifice plate at a rate of 16.0-26.2 air changes per hour. Air flow was recorded at 30 minute intervals during the exposure period, and was sufficient to ensure an oxygen content of at least 19% of the exposure atmosphere. Temperature and humidity were recorded at 30 minute intervals during the exposure period from a Taylor wet bulb/dry bulb hygrometer located in the exposure chamber.

Test Substance Administration
Healthy albino rats were released from quarantine. Five males and five females per each of two exposure levels were selected for testing. The animals were exposed to an aerosol generated from the undiluted liquid test substance for a period of four hours. When 99% concentration (t-99) was attained, the animals which were individually housed in polycarbonate exposure tubes were inserted into a 500 L stainless steel nose-only inhalation chamber for the specified exposure period. A maximum of 10 animals were exposed during any given exposure period. At the termination of the exposure period, the animals were returned to their stock laboratory cages.

Determination of Concentration
The concentration of test substance in the exposure atmosphere (taken from the breathing zone of the animals) was determined gravimetrically twice per hour and nominally at the end of each exposure. The gravimetric concentration was determined by passing a known volume of exposure air through a pre-weighed filter and dividing the amount of test substance deposited on the filter by the volume of air which passed through the filter. The nominal concentration was determined by dividing the loss in weight of the test substance after each exposure by the total volume of air which passed through the chamber.

Particle Size Distribution
Particle size, taken from the breathing zone of the animals, was determined twice during each exposure, using an Andersen cascade impactor, at a rate of 28.3 L/minute for a duration of 0.5-1.0 minute. The MMAD and particle size distributions are calculated from these data.

In-life Observations
Observations for mortality and signs of pharmacologic and/or toxicologic effects were made frequently on the day of exposure and at least once daily thereafter for 14 days (day of exposure considered Day 0). Individual body weights were recorded just prior to the inhalation exposure and on Days 7 and

14, or at the time of discovery after death.

Postmortem Observations
At study termination, each surviving animal was euthanized by an intraperitoneal injection of Fatal Plus® (Vortech Pharmaceuticals, Dearborn, Michigan 48126). All study animals were subjected to gross necropsy, and all abnormalities were recorded.

Statistical Analysis
In order to calculate a mean exposure, the Mean Value Theorem of Calculus was used to properly weight the concentration, since the concentrations could not be measured continuously [data provided in report]. This method weights concentrations based on the time span of each concentration. A concentration can be calculated for each minute, which better represents the exposure concentration received by each animal.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-3.

C. Results:

1. Mortality

The investigators provided individual animal survival data. One high dose male and one high dose female died. The acute inhalation LC_{50} for CGA-77102/G-30027 II 720SC is greater than 2.93 mg/L.

2. Clinical Signs

The investigators provided group summary and individual animal data. Clinical signs included activity decrease (4.5 hours in low dose animals; 4.5 hours to day 6 in high dose animals), piloerection (2.5 hours to day 1 in low dose males, 4.5 hours to day 1 in low dose females; 2.5 hours to day 6 in high dose males and to day 7 in high dose females), polyuria (4.5 hours to day 1 in low dose males, 4.5-6.0 hours in low dose females; 2.5 hours to day 4 in high dose males and to day 1 in high dose females), crust around eyes and nose (days 2-5 in high dose animals), ptosis (4.5 hours to day 3 in high dose males and days 2-3 in high dose females), respiratory gurgle (4.5 hours to day 4 in high dose males and 4.5 hours to day 1 and day 5 in high dose females), withdrawn testes (4.5 hours to day 1). In animal that died abdominal distention, body tremors, emaciation, gasping and

411

unsteady gait were noted. No clinical signs were noted in the low dose group by study day 2 and in the high dose group by study day 7.

3. Body Weights

The investigators provided individual animal body weights. No treatment related effects were noted, although 1 low dose female failed to gain weight and one high dose male lost weight during the first week. The following table presents mean body weight and body weight gains (from Table 1, page 12-13 of the report):

Table I: Mean Body Weights and Body Weight Gains (grams)

Day: Dose (mg/L):	0	7	0-7 gain	14	0-14 gain
			Males		
0.640	291(5)[n]	308(5)	19(5)	329(5)	39(5)
2.93	274(5)	283(4)	9(4)	325(4)	51(4)
			Females		
0.640	209	217	8(5)	229(5)	20(5)
2.93	200(5)	213(4)	13(4)	221(4)	21(4)

[n] = number of animals

4. Pathology

The investigators provided individual animal gross necropsy findings. The only observations were in animals which died and included stained and/or matted muzzle and anal hair, discolored and swollen lungs.

5. Inhalation Chamber Conditions

The investigators provided individual half hour chamber operating parameters. The mean chamber operating parameters were 72°F, 73% relative humidity and the airflow was 218 Lpm at the 0.640 mg/L dose and 70°F, 85% relative humidity and the airflow was 133 Lpm at the 2.93 mg/L dose. The investigators provided analytical concentration determinations and calculations and particle size distribution determinations. The mean exposure concentrations were 0.640 and 2.93 mg/L, the nominal concentrations were 8.20 and 49.1 mg/L. The particle size distributions (MMAD) were 3.484 and 9.690 µm. The MMAD of 9.660 is not acceptable for an acute inhalation study, therefore the mean exposure concentration of 0.640 mg/L with a MMAD of 3.484 is the LC_{50} for this study.

412

CGA-77102/G-30027 II 720SC-Exp PRIMARY EYE IRRITATION - RABBITS §81-4

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 8/14/97
Senior Pharmacologist, Toxicology Branch II/HED (7509C)

Secondary Review by: K. Clark Swentzel K. Clark Swentzel 8/22/97
Acting Branch Senior Scientist, Toxicology Branch II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Eye Irritation - Rabbit
Species: Rabbit Guideline: §81-4

EPA ID No.s: EPA MRID No. 44128006
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D235664
EPA Submission No. S515306

Test Material: CGA-77102/G-30027 II 720SC-Exp

Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102/G-30027 II 720SC-Exp, FINAL REPORT, Study Title: Primary Eye Irritation Study of CGA-77102/G-30027 II 720SC-Exp in Rabbits, (EPA Guideline 81-4), Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60304557, June 13, 1996 (Unpublished); EPA MRID Number 44128006.

Executive Summary: In a primary eye irritation study (MRID# 44128006), male and female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.1 mL CGA-77102/G-30027 II 720SC-Exp (Purity: 35.8% CGA-77102, 28.7% Atrazine (29.1% TCT) and 1.76% CGA-154281; Lot Number: FL-960542, Batch Code 1098-20-4) to one eye (the other serving as untreated control. Two groups were used, one group of 3 males and 3 females with their eyes unwashed, the other group of 3 females had their eyes washed for 1 minute with lukewarm water 30 seconds after test compound instillation.

In a Primary Eye Irritation study, CGA-77102/G-30027 II 720SC-Exp produced moderate conjunctival irritation to washed and unwashed eyes. Unwashed eyes had corneal involvement and both groups had iridal involvement. Irritation cleared by 96 hours after treatment. **Toxicity Category III.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-4) for a primary eye irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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/G-30027 II 720SC-Exp
Purity: 35.8% CGA-77102, 28.7% Atrazine (29.1% TCT) and 1.76% CGA-154281
Description: Off-white liquid
Lot Number: FL-960542, Batch Code 1098-20-4
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbits
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: "adult"
Body Weight: 2568 to 2803 g

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the relative level of irritation produced following a single exposure of a test material to one eye of albino rabbits.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose, method, frequency and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

414

Study Timetable

Study Initiation Date	April 2, 1996
Experimental (In-life) Start Date	April 11, 1996
In-life End Date	April 18, 1996
Experimental Termination Date	April 18, 1996
Study Completion Date	June 13, 1996

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in stainless steel cages. Environmental controls for the animal room were set to maintain a temperature of 19° to 23°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided access to water ad libitum and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed by CHW. There were no known contaminants in the feed or water at levels that would have interfered with or affected the results of the study.

Six male and three female healthy, acclimated rabbits, weighing from 2,568 to 2,803 g, were selected at random and identified by animal number and corresponding ear tag. The animals' eyes were examined on the day before test material administration using sodium fluorescein dye procedures. Only those animals with no sign of ocular injury or irritation were used.

2. Dose Preparation and Administration

From page 11 of the report:

The test material was administered as received. The pH of the test material was determined to be 6.0.

Each rabbit received 0.1 mL of the undiluted test material placed into the everted lower lid of the right eye, with the left eye serving as the untreated control. The upper and lower lids were gently held together for 1 second to prevent loss of material and then released. The eyes of the rabbits in Group 1 remained unflushed immediately after treatment while the treated eyes of the rabbits in Group 2 were flushed with lukewarm tap water for 60 seconds starting 30 seconds after test material instillation.

3. Observations

From page 12 of the report:

Animals were weighed before test material administration.

The treated eyes were observed for ocular irritation at 1, 24, 48, 72, and 96 hours after treatment. Additional observations were made at Day 7 after treatment for the animals in Group 1. Irritation was graded and scored according to the Draize technique using a penlight as the source of illumination. Sodium fluorescein examinations were used to aid in revealing possible corneal injury at the observations conducted at 24, 48, and 72 hours when applicable. An attachment was provided (in the report) with the ocular irritation scoring scale, based on the method of Draize.

At termination of the in-life phase, all animals were euthanized and discarded.

4. Statistical Analyses

From page 12 of the report:

No statistical analyses were required by the protocol.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-4.

C. Results:

1. Eye Irritation

The investigators provided group summary and individual animal data for eye irritation. The following table presents the eye irritation scores (from Table 1, page 15 of the report): The test compound produced corneal and iridal involvement and moderate conjunctival irritation in all treated eyes that were unwashed after treatment. All treated eyes in the unwashed group appeared normal by 7 days. Positive irritation reactions were observed in 6/6 unwashed eyes which appeared normal by 96 hours (Table II extracted from Tables 2 and 5, pages 16 and 22 of the report). In treated then washed eyes, the test compound produced iridal involvement with moderate conjunctival irritation. All of the treated then washed eyes appeared normal by 96 hours. A positive irritation reaction was observed in 3/3 animals with treated then washed eyes which appeared normal by the 24 hours.

4/6

The results of the sodium fluorescein examinations found one animal in the unwashed eyes group with a positive (45%) stain retention at 24 and 48 (10%) hours, by 72 hours it was negative. All other animals were negative (both groups).

Table I: Average Primary Eye Irritation Scores (PIS)

Observation Period	Average Score* Group 1 (Unwashed)	Group 2 (Washed)
1 Hour	17.0	16.3
24 Hours	9.2	3.3
48 Hours	5.5	2.7
72 Hours	2.7	1.3
96 Hours	0.7	0.0
Day 7	0.0	**

*** The average primary eye irritation score is the total eye irritation score for all the animals divided by the number of animals for each group (6 or 3) at each observation period; ** Ocular scoring not conducted.**

Table II: Positive Ocular Reactions[a]

	Observation Period (Hour) 1		24		48		72		96
	UW[1]	W[2]	UW	W	UW	W	UW	W	UW
Cornea Opacity	3/6	0/3	1/6	0/3	1/6	0/3	0/6	0/3	0/6
Iritis	5/6	3/3	1/6	0/3	0/6	0/3	0/6	0/3	0/6
Conjunctivae Redness	6/6	3/3	6/6	0/3	3/6	0/3	1/6	0/3	0/6
Chemosis	2/6	2/3	1/6	0/3	0/6	0/3	0/6	0/3	0/6

[a] = a positive reaction for each parameter is defined as any corneal opacity, an iris score of 1.0 or greater, or any conjunctival redness or chemosis score of 2.0 or greater; [1] = UW = unwashed eyes; [2] = W = washed eyes.

2. Body Weights

The investigators provided individual animal body weights apparently only for prior to study initiation, no treatment period weights were provided.

41

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The primary eye irritation potential of CGA-77102/G-30027 II 720SC-Exp was evaluated when instilled into the eyes of nine rabbits (six with treated eyes unwashed and three with treated eyes washed approximately 30 seconds after instillation). The test material produced corneal and iridal involvement and moderate conjunctival irritation in unwashed eyes which cleared in all animals by Day 7 after treatment. Positive irritation reactions were observed in all six animals with unwashed eyes which cleared in all animals by the 96 hour observation. In treated eyes receiving a washout, the test material produced iridal involvement and moderate conjunctival irritation which cleared in all animals by 96 hours after treatment. Positive irritation reactions were observed in all three animals with washed eyes which cleared in all animals by the 24 hour observation.

2. Reviewers' Conclusions

In a Primary Eye Irritation study, CGA-77102/G-30027 II 720SC-Exp produced moderate conjunctival irritation to washed and unwashed eyes. Unwashed eyes had corneal involvement and both groups had iridal involvement. Irritation cleared by 96 hours after treatment. Toxicity Category III.

012310

CGA-77102/G-30027 II 720SC-Exp PRIMARY DERMAL IRRITATION - RABBITS §81-5

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 8/14/97
Senior Pharmacologist, Toxicology Branch II/HED (7509C)

Secondary Review by: K. Clark Swentzel K. Clark Swentzel 8/22/97
Acting Branch Senior Scientist, Toxicology Branch II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Dermal Irritation - Rabbit
Species: Rabbit Guideline: §81-5

EPA ID No.s: EPA MRID No. 44128007
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D235664
EPA Submission No. S515306

Test Material: CGA-77102/G-30027 II 720SC-Exp
Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102/G-30027 II 720SC-Exp, FINAL REPORT, Study Title: Primary Dermal Irritation Study of CGA-77102/G-30027 II 720SC-Exp in Rabbits, (EPA Guideline 81-5), Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60304556, June 13, 1996 (Unpublished); EPA MRID Number 44128007.

Executive Summary: In a primary dermal irritation study (MRID# 44128007), 3 male and 3 female adult albino rabbits (Strain: Hra:(NZW)SPF from HRP, Inc., Kalamazoo, Michigan) received 0.5 mL CGA-77102/G-30027 II 720SC-Exp (35.8% CGA-77102, 28.7% Atrazine (29.1% TCT) and 1.76% CGA-154281; Lot Number: FL-960542, Batch Code 1098-20-4) to the shaved back of each animal.

In a Primary Dermal Irritation study, CGA-77102/G-30027 II 720SC-Exp produced very slight to well-defined erythema reactions 5/6 animals and very slight edema reaction in 3 animals. Desquamation was also observed at 1 test site. The average primary irritation score (PIS) for the 4, 24, 48, 72 and 96-hour and Day 7 scores was 1.2 (considered to be slightly irritating). All irritation was cleared by study day 14. **Toxicity Category IV.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-5) for a primary dermal irritation study in rabbits.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were provided.

49

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/G-30027 II 720SC-Exp
Purity: 35.8% CGA-77102, 28.7% Atrazine (29.1% TCT) and 1.76% CGA-154281
Description: Off-white liquid
Lot Number: FL-960542, Batch Code 1098-20-4
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Test Animal(s): Species: Adult albino rabbits
Strain: Hra:(NZW)SPF
Source: HRP, Inc., Kalamazoo, Michigan
Age: "adult"
Body Weight: 2490 to 2776 g

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the relative level of primary skin irritation of a test material on rabbits under semioccluded conditions.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose, method, frequency, and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

Study Timetable

Study Initiation Date	April 2, 1996
Experimental (In-life) Start Date	April 5, 1996
In-life End Date	April 19, 1996
Experimental Termination Date	April 19, 1996
Study Completion Date	June 13, 1996

400

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in suspended stainless steel cages. Environmental controls for the animal room were set to maintain a temperature of 19° to 23°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided access to water ad libitum and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed by CHW. There were no known contaminants in the feed or water at levels that could be expected to interfere with or affect the results of the study.

Three male and three female healthy, acclimated rabbits, weighing from 2,490 to 2,776 g, were selected at random and identified by animal number and corresponding ear tag. On the day before treatment, the back and/or flanks of each animal were clipped free of hair to obtain an unblemished skin site.

2. Dose Preparation and Administration

From page 11 of the report:

The test material was administered as received. The pH of the test material was determined to be 6.0.

The undiluted test material was applied to the intact skin site on each animal's back (approximate exposure area of 6.25 cm2) in the amount of 0.5 mL. The area of application was covered with an 8-ply 2.5-cm x 2.5-cm gauze patch secured with paper tape, loosely overwrapped with Saran Wrap®, and secured with Elastoplast® tape to provide a semiocclusive dressing.

At the end of the 4-hour exposure period, the patches were removed and the test sites were washed using tap water and disposable paper towels. The test material was removed from the test sites as thoroughly as possible without irritating the skin.

3. Observations

From page 12 of the report:

Animals were weighed before test material administration.

Thirty minutes after removal of the test material, the degree of erythema and

421

edema at each test site was read according to the Draize technique (recorded as the 4-hour score). Subsequent examinations were made at 24, 48, 72, and 96 hours and Days 7 and 14. The untreated skin of each animal was used for comparison. An attachment was provided (in the report) with the dermal irritation scoring scale, based on the method of Draize.

At termination of the in-life phase, all animals were euthanized and discarded.

4. Statistical Analyses

From page 12 of the report:

No statistical analyses were required by the protocol.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-5.

C. Results:

1. Dermal Irritation

The investigators provided group summary and individual animal data for erythema and edema dermal irritation. The following table presents the dermal irritation scores (from Table 3, page 17 of the report):

Table I: Average Primary Dermal Irritation Scores[a]

Observation Period	Average Score (PIS)
4 Hour	1.5
24 Hour	1.3
48 Hour	1.0
72 Hour	0.8
96 Hour	0.7
Day 7	0.2
Day 14	0.0

[a] = The average primary dermal irritation score is the total dermal irritation score for all the animals (erythema and edema) divided by the number of test sites (6) at each observation period.

428

2. Body Weights

The investigators provided individual animal body weights apparently only for prior to study initiation, no treatment period weights were provided.

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The primary dermal irritation potential of CGA-77102/G-30027 II 720SC-Exp was evaluated in rabbits under 4-hour semioccluded conditions. The test material produced very slight erythema to well-defined erythema and very slight edema reactions. Desquamation was also observed at one test site. All irritation cleared by the Day 14 observation. The average of the individual index scores (the total of the erythema and edema scores at 4, 24, 48, and 72 hours divided by 4) is 1.2 (considered to be slightly irritating).

2. Reviewers conclusions

In a Primary Dermal Irritation study, CGA-77102/G-30027 II 720SC-Exp produced very slight to well-defined erythema reactions 5/6 animals and very slight edema reaction in 3 animals. Desquamation was also observed at 1 test site. The average primary irritation score (PIS) for the 4, 24, 48, 72 and 96-hour and Day 7 scores was 1.2 (considered to be slightly irritating). All irritation was cleared by study day 14. Toxicity Category IV.

423

CGA-77102/G-30027 II 720SC-Exp DERMAL SENSITIZATION - GUINEA PIGS §81-6

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 8/25/97
Senior Pharmacologist, Toxicology Branch II/HED (7509C)

Secondary Review by: K. Clark Swentzel K. Clark Swentzel 8/22/97
Acting Branch Senior Scientist, Toxicology Branch II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Dermal Sensitization - Guinea Pigs
Species: Guinea Pigs Guideline: §81-6

EPA ID No.s: EPA MRID No. 44128008
EPA Pesticide Chemical Code 108800
CAS# 87392-12-9
EPA DP Barcode D235664
EPA Submission No. S515306

Test Material: CGA-77102/G-30027 II 720SC-Exp
Synonyms: Alpha-metolachlor, A Chiral Metolachlor

Citation: S.M. Glaza (1996): CGA-77102/G-30027 II 720SC-Exp, FINAL REPORT, Study Title: Dermal Sensitization Study of CGA-77102/G-30027 II 720SC-Exp in Guinea Pigs - Closed Patch Technique, (EPA Guideline 81-6), Corning Hazleton Inc. for Ciba Crop Protection, Ciba-Geigy Corporation, Laboratory Project Identification: CHW 60504758, September 17, 1996 (Unpublished); EPA MRID Number 44128008.

Executive Summary: In a dermal sensitization study (MRID# 44128008), 10 young male adult albino guinea pigs (Strain: Crl:(HA)BR from Charles River Laboratories, Inc., Portage, Michigan) received 0.4 mL (3 induction and 1 challenge application) CGA-77102/G-30027 II 720SC-Exp (Purity: 35.8% CGA-77102, 28.7% Atrazine (29.0% TCT), 1.79% CGA-154281; Lot Number: FL-961156, Batch Code 1098-25-1) to the shaved back of each animal, an additional 10 animals served as naive control (only received a challenge dose). An irritation screening group of 4 animals was also used.

In a Dermal Sensitization study, CGA-77102/G-30027 II 720SC-Exp was a dermal sensitizer in guinea pigs tested with the closed patch technique.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

Compliance: A signed and dated STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS, COMPLIANCE STATEMENT and QUALITY ASSURANCE STATEMENT were 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/G-30027 II 720SC-Exp
Purity: 35.8% CGA-77102, 28.7% Atrazine (29.0% TCT), 1.79% CGA-154281
Description: Off-white liquid
Lot Number: FL-961156, Batch Code 1098-25-1
Other provided information:
The test material was stored at room temperature.

Vehicle(s): None used, test material is a liquid.

Positive Control: 2,4-dinitrochlorobenzene

A study report detailing the results of sensitization testing of 2,4-dinitrochlorobenzene (a known skin sensitizer) using the same sensitization method was appended to the report. This positive control study was initiated within 6 months of the conduct of this study (Corning Hazleton, Inc. For Corning Hazleton, Inc., Protocol TP2008.P.1, Study Title: Dermal Sensitization Study of 2,4-dinitrochlorobenzene in Guinea Pigs - Closed Patch Technique, January 8, 1996, Laboratory Project Identification: CHW 51104718).

Test Animal(s): Species: Young adult albino guinea pig
Strain: Crl:(HA)BR
Source: Charles River Laboratories, Inc., Portage, Michigan
Age: 4-8 weeks
Body Weight: 419 to 549 g

B. Study Design

From pages 5 and 9 of the report:

The objective of this study was to assess the delayed contact hypersensitivity potential of a test material in guinea pigs.

All procedures used in this study were in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work. The dose levels, method,

425

frequency, and duration of administration utilized in this study were chosen based on the requirements of the regulatory test guidelines. All procedural times presented in this report fall within the acceptable ranges as specified in the Wisconsin facility of Corning Hazleton Inc. (CHW) Standard Operating Procedure (SOP).

Study Timetable

Study Initiation Date	June 6, 1996
Experimental (In-life) Start Date	June 13, 1996
In-life End Date	July 24, 1996
Experimental Termination Date	July 24, 1996
Study Completion Date	September 17, 1996

1. Animal Husbandry and Assignment

From pages 10-11 of the report:

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in screen-bottom stainless steel cages. Environmental controls for the animal room were set to maintain a temperature of 19° to 25°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

The animals were provided continuous access to Certified Guinea Pig Diet #5026, PMI Feeds, Inc., and water. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed. There were no known contaminants in the feed or water at levels that could be expected to interfere with or affect the results of the study.

Twenty-four healthy, acclimated male albino guinea pigs, weighing from 419 to 549 g and approximately 4 to 8 weeks of age, were selected and divided into three groups consisting of an irritation screening group of four animals, a test group of 10 animals, and a naive control group of 10 animals. The animals were identified by animal number and corresponding ear tag throughout the study.

2. Study Protocol

From pages 11-12 of the report:

Irritation Screening Study

An irritation screening study using four animals was conducted to determine the irritation threshold of the test material. The test material was administered undiluted and at concentrations of 25%, 50%, and 75% w/v in sterile water with each animal receiving two different concentrations of the test material. All test material mixtures used in the irritation screening

426

phase of the study were stored at room temperature until administered. The appropriate test material concentrations, in the amount of 0.4 mL, were applied to adhesive patches (Hill Top Chamber®, 25-mm diameter). The patches were then placed on two shaved sites (one on the right and one on the left anterior dorsal quadrants) on each animal, covered with an overlapping strip of dental dam, and overwrapped with Elastoplast® tape. The patches remained in place for 6 hours after which they were removed and the sites were wiped with wet disposable paper towels. The application sites were observed for dermal reactions at 24 and 48 hours after test material application.

Definitive Study
Based on the results of the irritation screening study, the test material was administered undiluted for the induction phase and for the challenge application.

Induction Phase. On the day of test material application, the hair was removed from the back of each animal in the test group with electric clippers. The undiluted test material was applied to each animal by placing 0.4 mL on an adhesive patch (Hill Top Chamber®, 25-mm in diameter) and placing the patch on the induction site along the dorsal anterior left quadrant. The patch was covered with dental dam and overwrapped with Elastoplast® tape. The dressing remained in place for a period of 6 hours after which it was removed and the induction site wiped with wet disposable paper towels. The animals in the test group received one application per week for 3 weeks for a total of three applications. The naive control animals were not treated during this phase of the study.

Challenge Phase. Two weeks following the administration of the third induction dose, a challenge dose of 0.4 mL of the undiluted test material was administered along the dorsal anterior right quadrant of the test group animals in the same manner as during the induction phase of the study. At this time the nine surviving naive (previously untreated) control animals were also treated in the same manner with a challenge application of the test material.

3. Observations

From pages 12-13 of the report:

On the day of the 24-hour examination following the irritation screening and challenge applications, the application sites of the respective animals were depilated by applying Neet® depilatory. After approximately 11 to 20 minutes, the depilatory was washed from the application sites. The 24-hour observation occurred at least 2 hours after removal of the depilatory.

The respective application sites were examined and scored for dermal reactions according to the following Buehler scoring scale at 24 and 48 hours following the irritation screening, induction, and challenge applications:

427

Buehler Sensitization Scoring	Scale
No reaction	0.0
Very faint erythema, usually nonconfluent	0.5
Faint erythema, usually confluent	1.0
Moderate erythema	2.0
Strong erythema, with or without edema	3.0

Clinical observations were conducted daily throughout the study. Body weights on the irritation screening animals were determined only on the day of treatment. Body weights on the definitive study animals were determined before test material administration and at termination of the in-life phase.

The animal that was sacrificed during the study due to an apparent broken leg was discarded without an abbreviated gross necropsy examination. At termination of the in-life phase, surviving animals were euthanized and discarded.

Evaluation of Challenge Responses
Determination of sensitization was based on the dermal reactions to the challenge dose. Grades of 1.0 or greater in the test animals may indicate evidence of sensitization, provided grades of less than 1.0 are seen in the naive control animals.

4. Statistical Analyses

From page 13 of the report:

No statistical analyses were required by the protocol.

PROTOCOL DEVIATIONS: From page 20 of the report:

Protocol	Actual Procedure
Page 4, 5. Test Material, E. Reserve Samples, Second Sentence. The test material reserve samples will be stored at CHW in a freezer set to maintain a temperature of -20°C ±10°C until returned to the Sponsor after completion of the in-life phase of the study.	In order to comply with MAFF requirements, the reserve sample of the test material will be stored at CHW in a freezer set to maintain a temperature of -20°C ±10°C for 10 years.
Page 8, 6. Experimental Design, C. Observation of Animals, (2) Reading of Dermal Reactions, Second Paragraph, First Sentence. On the day of the 24-hour examination following the irritation screen and challenge applications, the respective test sites will be depilated by	The Neet® depilatory was removed from the application sites of the definitive study test group animals approximately 11 to 20 minutes after application. The depilatory was removed from the application sites of the animals in the irritation screen and the definitive

428

applying Neet® for approximately 20 minutes, then washed off with warm water.	study naive control group Approximately 15 to 20 minutes after application.
Page 8, 6. Experimental Design, C. Observation of Animals, (3) Body weights. Before test material administration and at the termination of the experimental phase.	Body weights for the irritation screening animals were determined only on the day of treatment.
Page 9, 8. Location of Raw Data, Records, and Final Report, Second and Third Sentences. When the final report is completed, all original paper data, including those items listed below will be retained in the archives of CHW for a period of one year following signing of the final report. One year after signing of the final report, all of the aforementioned materials will be sent to the Sponsor and a return fee will be charged.	In order to comply with MAFF requirements, the final report and all original paper data will be retained in the archives of CHW for 10 years.

These deviations are not considered to have had an adverse effect on the outcome of the study.

NOTE FROM THE REVIEWER: THE PROTOCOL DESCRIBED ABOVE IN THE MATERIALS AND METHODS SECTION IS ACCEPTABLE TO FULFILL THE GUIDELINE §81-6.

C. Results:

1. Irritation Screening Phase

The investigators provided individual body weights and dermal reactions data. No dermal irritation was reported with any test compound concentration. No treatment related effects were noted in screening animals of the irritation screening phase of the study.

489

2. Definitive Phase

a. Clinical Observations

The investigators provided individual clinical signs data, no treatment related effects were noted (1 naive control had soft stool and was later sacrificed with a broken leg; 2 test group animals had soft stool).

b. Body Weights

The investigators provided individual body weights. No treatment related effects were noted.

c. Dermal Reactions

i. Test Compound

The investigators provided individual dermal reaction scores for the test and naive control animals. During the induction phase of the study after the third dose, 2/10 animals had very faint erythema, usually nonconfluent reactions at 24 and one of those animals had moderate erythema at 48 hours. During the challenge phase, the undiluted test compound produced very faint erythema, usually nonconfluent reactions in 4/10 animals, faint erythema, usually confluent reactions in 1/10 animals and moderate erythema reactions in 1/10 animals at 24. At 48 hours, 6/10 animals had very faint erythema, usually nonconfluent reactions and 1/10 had faint erythema, usually confluent reactions. Naive control animals had no reported reactions to the test compound. The investigators noted that: *All seven of the reactions in the test group exceeded the highest naive control reaction during the challenge phase of the study.*

4/30

D. Conclusions

1. Investigators Summary:

From page 9 of the report:

The delayed contact hypersensitivity potential of CGA-77102/G-30027 II 720SC-Exp was evaluated in albino guinea pigs. The test material was administered undiluted to each animal in the test group during the induction phase of the study. Very faint to moderate erythema reactions (scores of 0.5 to 2.0) were observed in seven of the 10 test animals while no erythema reactions were seen in any of the nine surviving naive control animals when the test material was administered undiluted at challenge. Based on these results, this test material is considered to be a dermal sensitizer in guinea pigs.

2. Reviewers' Conclusions

In a Dermal Sensitization study, CGA-77102/G-30027 II 720SC-Exp was a dermal sensitizer in guinea pigs tested with the closed patch technique.

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