

US EPA ARCHIVE DOCUMENT

007682
007632



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

JAN 16 1990

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Ametryn. Review of an Acute Battery and a Mutagenicity Assay.

EPA No. 080801
Record No. 240673

Project No. 9-0924
Tox. Chem. No. 431

TO: Franklin D. Rubis, PM #50
Registration Division (H7505C)

FROM: John E. Whalan, D.P.B.T., Toxicologist
Section 1, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

John Whalan
1-12-90

THROUGH: Roger L. Gardner, Acting Section Head
Section 1, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

Roger Gardner
1-12-90

In response to a Data-Call-In, Ciba Geigy Corporation has submitted a battery of acute studies and a Mutagenicity study (Ames Assay) of Ametryn technical. All of the acute studies were acceptable except for the acute inhalation study. The aerosol used in this study contained large, nonrespirable particles, and there was no apparent attempt to generate the test article in a respirable particle range (at least 25% of the particles <1 um). The Mutagenicity study was acceptable.

The Toxicity Categories for Ametryn technical are III for acute oral, acute dermal, and primary eye irritation; and IV for primary dermal irritation. No category can be assigned for acute inhalation.

1 of 16

Reviewed by: John E. Whelan JW 1-12-90
Section I, Tox. Branch I (IRS) (H7509C)
Secondary reviewer: Roger L. Gardner 1-15-90
Section I, Tox Branch I (IRS) (H7509C)

81-1

07682

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity Study in Rats

ACCESSION NUMBER: N/A

TOX. CHEM. NO.: 431

TEST MATERIAL: Ametryn technical (96.7% pure)
Batch No. 16133
White powder

MRID NO.: 409958-14

SYNONYMS: Evik, Ametrex, Crisatrine, G-34162, Gesapax

STUDY NUMBER(S): 5566-88

SUBMITTED BY: Ciba Geigy Corporation

TESTING FACILITY: Stillmeadow, Inc.

TITLE OF REPORT: Acute Oral Toxicity Study in Rats

AUTHOR(S): Janice O. Kuhn

REPORT ISSUED: September 15, 1988

CONCLUSIONS: The defined doses and slopes were as follows:

Male LD₅₀ = 1356 (1164-1581) mg/kg; slope = 8.1
Female LD₅₀ = 1009 (829-1228) mg/kg; slope = 4.5
Combined LD₅₀ = 1162 (966-1398) mg/kg; slope = 3.3

STUDY CLASSIFICATION: This study is ACCEPTABLE. Toxicity Category III. Test article purity was not reported; it was obtained from the Registrant. This study received Quality Assurance review. This study satisfied data requirement 81-1 for an acute oral toxicity study.

Special Review Criteria (40 CFR 154.7): N/A

PROTOCOL: Groups of 5 male (210-320 g) and 5 female (176-217 g) fasted HSD:(SD) BR rats were orally intubated with a 25% w/v formulation of ametryn in 0.5% carboxymethylcellulose at doses of 850 (females only), 1000, 1400, and 5050 mg/kg. The rats were observed three times on the day of dosing and daily during the 14-day recovery period. Body weights were measured prior to dosing, and on days 7 and 14. All animals were necropsied. Food and water were available ad libitum.

RESULTS: The mortality patterns were as follows:

<u>Dose (mg/kg)</u>	<u>Males</u>	<u>Females</u>	<u>Combined</u>
850	-	2/5	2/5
1000	0/5	1/5	1/10
1400	3/5	5/5	8/10
5050	5/5	5/5	10/10

All deaths occurred on days 0 and 1. Dose-related clinical signs observed on the day of dosing included piloerection, decreased activity, lacrimation, nasal discharge, epistaxis, ptosis, salivation, polyuria, dyspnea, tremors, dilated pupils, constricted pupils, and death. Many of these signs were seen within 30 minutes after dosing. The only clinical sign seen during the recovery period was piloerection which reversed within several days except in two 1400 mg/kg males which had piloerection throughout the recovery period. Normal body weight gain was seen in the survivors.

Dose-related gross lesions were found only in the animals which died on study and included salivation, lacrimation, chromodacryorrhea, nasal discharge, epistaxis, gas and grey or white slurry in stomach, yellow paste or red-orange mucoid material in small intestines, and testes drawn into abdominal cavity.

Reviewed by: John E. Whalan JW 1-12-90
Section I, Tox. Branch I (IRS) (H7509C) Roy L. Gardner
Secondary reviewer: Roger L. Gardner 1-15-96
Section I, Tox. Branch I (IRS) (H7509C)

81-2

007682

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity Study in Rabbits

ACCESSION NUMBER: N/A

TOX. CHEM. NO.: 431

TEST MATERIAL: Ametryn technical (96.7% pure)
Batch No. 16133
White powder

MRID NO.: 409958-15

SYNONYMS: Evik, Ametrex, Crisatrine, G-34162, Gesapax

STUDY NUMBER(S): 5567-88

SUBMITTED BY: Ciba Geigy Corporation

TESTING FACILITY: Stillmeadow, Inc.

TITLE OF REPORT: Acute Dermal Toxicity Study in Rabbits

AUTHOR(S): Janice O. Kuhn

REPORT ISSUED: September 16, 1988

CONCLUSIONS: No toxicity was observed in rabbits dosed with 2020 mg/kg of ametryn.

STUDY CLASSIFICATION: This study is ACCEPTABLE. Toxicity Category III. Test article purity was not reported; it was obtained from the Registrant. This study received Quality Assurance review. This study satisfied data requirement 81-2 for an acute dermal toxicity study.

Special Review Criteria (40 CFR 154.7): N/A

PROTOCOL: Groups of 5 male (2.550-3.075 kg) and 5 female (2.375-3.250 kg) New Zealand White rabbits were dermally dosed with 2020 mg/kg of ametryn moistened with 2.2 ml of deionized water. The doses were applied to nonabraded clipped areas of the dorsal trunk (>10% of the body surface area). The doses were covered with gauze, held in place with nonirritating adhesive tape, and occluded with semi-permeable dressings (orthopedic stockinette). The dressings were removed after 24 hours, and the dosing sites were washed with water and a clean cloth.

The rabbits were observed three times on the day of dosing and daily during the 14-day recovery period. Body weights were measured prior to dosing, and on days 7 and 14. All animals were necropsied. Food and water were available ad libitum.

RESULTS: No rabbits died during this study. One male had very slight to moderate diarrhea during much of the recovery period. This finding cannot be ascribed to the treatment. No other clinical signs or gross lesions were observed. Body weight gain was normal.

Reviewed by: John E. Whalan JW 1-12-70
Section I, Tox. Branch I (IRS) (H7503C)
Secondary reviewer: Roger L. Gardner Ross Gardner
Section I, Tox. Branch I (IRS) (H7509C) 1-15-76

81-3

007682

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation Toxicity Study in Rats

ACCESSION NUMBER: N/A

TOX. CHEM. NO.: 431

TEST MATERIAL: Ametryn technical (96.7% pure)
Batch No. 16133
White powder

MRID NO.: 409958-16

SYNONYMS: Evik, Ametrex, Crisatrine, G-34162, Gesapax

STUDY NUMBER(S): 5571-88

SUBMITTED BY: Ciba Geigy Corporation

TESTING FACILITY: Stillmeadow, Inc.

TITLE OF REPORT: Acute Inhalation Toxicity Study in Rats

AUTHOR(S): Mark S. Holbert

REPORT ISSUED: October 14, 1988

CONCLUSIONS: A group of male and female rats was exposed to an analytical (gravimetric) concentration of 5.17 mg/l of Ametryn (MMAD of 5.188-7.069 μ m) in a dynamic inhalation chamber. Although there were no deaths, no conclusions can be made about toxicity since so few particles were respirable.

STUDY CLASSIFICATION: This study is UNACCEPTABLE and cannot be assigned a toxicity category since there were almost no respirable particles (<1 μ m), and no apparent attempt to generate particles in a respirable range. Test article purity was not reported; it was obtained from the Registrant. This study received Quality Assurance review. This study does not satisfy data requirement 81-3 for acute inhalation toxicity.

Special Review Criteria (40 CFR 154.7): N/A

PROTOCOL: Groups of 5 male (322-361 g) and 5 female (200-212 g) HSD:(SD) BR rats were dynamically exposed for four hours to an ametryn aerosol in a 200 liter stainless steel inhalation chamber. An aerosol was generated by passing dry filtered air through a series of four glass flasks containing the powdered test material. The aerosol was diluted with dry filtered air prior to chamber introduction in order to yield a nominal concentration of 25.6 mg/l. There was no mention of milling the powder prior to generation.

Chamber concentration was measured gravimetrically twice hourly. Particle sizing was accomplished with an Andersen cascade impactor. The rats were observed for clinical signs after the exposure and daily during the 14-day recovery period. Only a few animals could be observed during the exposure due to the chamber design. Body weights were measured prior to exposure, and

on days 7 and 14. All animals were necropsied. Food and water were available ad libitum except during exposure.

RESULTS: The mean gravimetric concentration was 5.17 mg/l. The particle size data were as follows:

	<u>@ 1.75 hr.</u>	<u>@ 3.75 hr.</u>
Mass Median Aerodynamic Diameter	5.188 um	7.069 um
Geometric Standard Deviation	1.862	1.756
Percentage of Respirable Particles (<1 um)	0.51%	0.09%

EPA guidelines call for a minimum of 25% of the particles to be in the respirable range (<1 um), yet these data show that almost no particles were small enough to reach the alveoli. Most of the particles would have been captured in the nose. There was no mention of any attempt to generate respirable particles.

No animals died during the study. Clinical signs seen during the exposure included piloerection, decreased activity, ptosis, nasal discharge, and lacrimation. Clinical signs seen during the recovery period included piloerection, lacrimation, epistaxis, decreased activity, polyuria, and chromodacryorrhea. Weight gain was normal.

Reviewed by: John E. Whalan JW 1-12-90
Section I, Tox. Branch I (IRS) (H7509C)
Secondary reviewer: Roger L. Gardner *Roger Gardner*
Section I, Tox. Branch I (IRS) (H7509C) 1-15-90

81-4

307682

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation Study in Rabbits

ACCESSION NUMBER: N/A

TOX. CHEM. NO.: 431

TEST MATERIAL: Ametryn technical (96.7% pure)
Batch No. 16133
White powder

MRID NO.: 409958-17

SYNONYMS: Evik, Ametrex, Crisatrine, G-34162, Gesapax

STUDY NUMBER(S): 5568-88

SUBMITTED BY: Ciba Geigy Corporation

TESTING FACILITY: Stillmeadow, Inc.

TITLE OF REPORT: Primary Eye Irritation Study in Rabbits

AUTHOR(S): Janice O. Kuhn

REPORT ISSUED: September 2, 1988

CONCLUSIONS: Ametryn was mildly irritating to the conjunctiva, and caused mild redness, chemosis, and discharge. These signs reversed by 72 hours in the washed eyes and by day 4 in the unwashed eyes.

STUDY CLASSIFICATION: This study is ACCEPTABLE. Toxicity Category III. Test article purity was not reported; it was obtained from the Registrant. This study received Quality Assurance review. This study satisfies data requirement 81-4 for a primary eye irritation study.

Special Review Criteria (40 CFR 154.7): N/A

PROTOCOL: Six male and 3 female New Zealand White rabbits were verified to be free of ocular defects prior to treatment. The right eye of each rabbit was treated with ametryn by placing a 100 mg aliquot into the conjunctival sac. The lids were then held together for one second. The eyes of three males were washed with room temperature deionized water for 1 minute, while the eyes of the other 3 males and 3 females were not washed. The left eyes served as controls. The eyes were examined and graded for eye irritation at 1, 24, 48, and 72 hours, and at 4 and 7 days following treatment.

RESULTS: In the washed eyes, there was no corneal or iridic involvement, but there was mild conjunctival redness, chemosis, and discharge. These signs had reversed by 72 hours. The unwashed eyes had the same signs of irritation as the washed eyes, but these signs did not reverse until day 4. All of the unwashed eyes still had traces of test material in the conjunctival sac 24 hours after treatment.

Reviewed by: John E. Whalan JW 1-12-90
Section I, Tox. Branch I (IRS) (H7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner
Section I, Tox. Branch I (IRS) (H7509C) 1-15-90

81-5

007682

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation Study in Rabbits

ACCESSION NUMBER: N/A

TOX. CHEM. NO.: 431

TEST MATERIAL: Ametryn technical (96.7% pure)
Batch No. 16133
White powder

MRID NO.: 409958-18

SYNONYMS: Evik, Ametrex, Crisatrine, G-34162, Gesapax

STUDY NUMBER(S): 5569-88

SUBMITTED BY: Ciba Geigy Corporation

TESTING FACILITY: Stillmeadow, Inc.

TITLE OF REPORT: Primary Dermal Irritation Study in Rabbits

AUTHOR(S): Janice O. Kuhn

REPORT ISSUED: September 2, 1988

CONCLUSIONS: Ametryn is essentially nonirritating at a dermal dose of 500 mg/rabbit.

STUDY CLASSIFICATION: This study is ACCEPTABLE. Toxicity Category IV. Test article purity was not reported; it was obtained from the Registrant. This study received Quality Assurance review. This study satisfies data requirement 81-5 for a primary dermal irritation study.

Special Review Criteria (40 CFR 154.7): N/A

PROTOCOL: The dosing sites on 3 male and 3 female New Zealand White rabbits were prepared by clipping hair from an 8 x 8 cm area on the dorsal trunk. The sites were not abraded. Each rabbit was treated with 500 mg of ametryn moistened with 0.7 ml of saline. The doses were covered with gauze, held in place with nonirritating adhesive tape, and occluded with semi-permeable dressings (orthopedic stockinette). The dressings were removed after 4 hours, and the dosing sites were washed with water and a wet cloth. The dosing sites were examined and graded for dermal irritation 1, 24, 48, and 72 hours after dose removal.

RESULTS: One female had very slight erythema at 1, 24, and 48 hours. No other evidence of dermal irritation was found in the other animals.

Reviewed: John E. Whalan JW 1-12-90
Section Tox. Branch I (IRS) (H7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner
Section Tox. Branch I (IRS) (H7509C) 1-15-90

81-6

007682

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization Study in Guinea Pigs

ACCESSION NUMBER: N/A

TOX. CHEM. NO.: 431

TEST MATERIAL: Ametryn technical (96.7% pure)
Batch No. 16133
White powder

MRID NO.: 409958-19

SYNONYMS: Evik, Ametrex, Crisatine, G-34162, Gesapax

STUDY NUMBER(S): 5570-88

SUBMITTED BY: Ciba Geigy Corporation

TESTING FACILITY: Stillmeadow, Inc.

TITLE OF REPORT: Dermal Sensitization Study in Guinea Pigs

AUTHOR(S): Janice O. Kuhn

REPORT ISSUED: ~~September~~ ^{October} 10, 1988

CONCLUSIONS: Ametryn was not a sensitizer.

STUDY CLASSIFICATION: This study is ACCEPTABLE. Test article purity was not reported; it was obtained from the Registrant. This study received Quality Assurance review. This study satisfies data requirement 81-6 for a dermal sensitization study.

Special Review Criteria (40 CFR 154.7): N/A

PROTOCOL: Twenty male Hartley guinea pigs (305-360 g) were assigned to two groups of 10 guinea pigs. One group was dosed with ametryn; the other group was dosed with the positive control article 2,4-dinitrochlorobenzene. Prior to each treatment the hair was clipped from an 8 x 10 cm patch on the dorsal trunk to provide a dosing site. All sensitizing doses were administered to the left front quadrant sites, and the challenge doses were administered both to the left front quadrant and the right rear quadrant sites.

The guinea pigs were sensitized with either 500 mg of ametryn moistened with 0.75 ml of deionized water (determined to be the highest non-irritating dose), or 0.5 ml of 0.25% w/v 2,4-dinitrochlorobenzene in ethanol. They were treated on days 1, 3, 6, 8, 10, 13, 15, 17, 20, and 22, then challenged on day 36. The doses were covered with a 3.5 x 5 cm Beiersdorf Coverlet adhesive dressing (gauze pad with adhesive patch), and the entire trunk was covered with a 4 mil clear polyethylene film. The rabbits were held in restrainers for approximately 6 hours, after which the dressings were removed. The dosing sites were observed 24 hours after each treatment and challenge, and 48 hours after treatments 1, 10, and the challenge. Skin irritation was graded at each interval.

007682

RESULTS: The guinea pigs treated with ametryn had only sporadic findings of very slight erythema, and there was no evidence of sensitization. The positive control guinea pigs had signs of irritation after the second treatment (day 3) including very slight to severe erythema and edema with eschar. Irritation gradually worsened with each treatment. Following a 2 week rest, the challenge resulted in very slight to well defined erythema with eschar and very slight to moderate edema. The irritation was similar both after 24 and 48 hours. The left site, which was used for sensitizing, was more severely irritated than the right site. Thus, 2,4-dinitrochlorobenzene was a positive sensitizer, and demonstrated the sensitivity of the test system.

Reviewed by: John E. Whalan *JW* 1-12-90 84-2
Section I, Tox. Branch I (IRS) (H7509C)
Secondary reviewer: Roger L. Gardner *Roger Gardner* 1-15-90
Section I, Tox. Branch I (IRS) (H7509C)
Tertiary reviewer: Irving Mauer, Geneticist *Irving Mauer* 01-04-90
Section I, Tox. Branch I (IRS) (H7509C)

007682

DATA EVALUATION REPORT

STUDY TYPE: Ames Assay

ACCESSION NUMBER: N/A

TOX. CHEM. NO.: 431

TEST MATERIAL: G 34 162 technical (99.9% pure)
Ametryn technical
Batch No. P 15194
White powder

MRID NO.: 409958-20

SYNONYMS: Evik, Ametrex, Crisatrine, G-34162, Gesapax

STUDY NUMBER(S): 840802

SUBMITTED BY: Ciba Geigy Corporation

TESTING FACILITY: Ciba-Geigy Limited, Basle, Switzerland

TITLE OF REPORT: Salmonella/Mammalian-Microsome Mutagenicity Test

AUTHOR(S): E. DeParade

REPORT ISSUED: October 30, 1984

CONCLUSIONS: There was no evidence of mutagenicity in Salmonella strains TA 98, TA 100, TA 1535, and TA 1537 dosed with G 34 162, even at a toxic concentration.

STUDY CLASSIFICATION: This study is ACCEPTABLE. This study was inspected for Quality Assurance compliance. This study satisfies data requirement 84-2a for a gene mutation test.

Special Review Criteria (40 CFR 154.7): N/A

PROTOCOL: This study was performed using four Salmonella typhimurium strains - TA 98, TA 100, TA 1535, and TA 1537. These strains were added to a nutrient broth and soft agar, and 0.1 ml aliquots were placed in petri dishes containing minimum agar, Vogel-Bonner Medium E and glucose, and 0.1 ml of the test article formulations or vehicle. G 34 162 was formulated in methanol at concentrations of 0 (vehicle control), 20, 80, 320, 1280, and 5120 ug/0.1 ml. Three plates/concentration were used for each strain. A like number of plates were also dosed with 0.5 ml of an activation mixture containing S9 fraction of liver from prochlor-induced rats, and 0.7 ml of a solution of cofactors. Positive controls were dosed as follows:

Unactivated:

TA 98 daunorubicin-HCl (0, 5, and 10 ug/0.1 ml phosphate buffer)
 TA 100 4-nitroquinoline-N-oxide (0, 0.125, and 0.25 ug/0.1 ml phosphate buffer)
 TA 1535 sodium azide (0, 2.5, and 5.0 ug/0.1 ml bidistilled water)
 TA 1537 9(5)-aminoacridine hydrochloride monohydrate (0, 50, and 100 ug/0.1 ml DMSO)

Activated:

TA 1535 cyclophosphamide (0 and 250 ug/0.1 ml in phosphate buffer)
 TA 100 2-aminoanthracene (0 and 5 ug/0.1 ml in DMSO)

All plates were incubated at 37° C for 48 hours in darkness, after which the colonies were counted. An increase number of colonies would be evidence of an increased number of histidine-prototrophic mutants. The entire experiment was repeated once.

RESULTS: The two highest concentrations precipitated in the soft agar. No increases were seen in colony counts in any unactivated or activated strain dosed with G 34 162. The highest concentration, however, caused a decreased number of colonies due to toxicity. The unactivated and activated positive controls had marked increases in colony counts, which demonstrated the sensitivity of the assay. Attached are the following photocopied data tables from the report:

<u>Table</u>	<u>Trial</u>	<u>Activation</u>
1	1	-
2	1	+
5	2	-
6	2	+

Amesbury Tox Review

Page ___ is not included in this copy.

Pages 13 through 16 are not included in this copy.

The material not included contains the following type of information:

- Identity of product inert ingredients.
- Identity of product inert impurities.
- Description of the product manufacturing process.
- Description of quality control procedures.
- Identity of the source of product ingredients.
- Sales or other commercial/financial information.
- A draft product label.
- The product confidential statement of formula.
- Information about a pending registration action.
- FIFRA registration data.
- The document is a duplicate of page(s) _____.
- The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
