9-27-94

FILE

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

SEP 27 1994

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SEP 27 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Subject: AC 303,630 2SC Insecticide-Miticide: Application for Experimental Use Permit for Use on Greenhouse and Shadehouse Ornamentals

P.C.#: 129093
Submission #s: S468291
Project No. D204626
EPA ID#: 000241-EUP-REI

From: Guruva B. Reddy, D.V.M., Ph. D.
Section 4
Toxicology Branch I
Health Effects Division (7509C)

9/21/94

To: Dennis Edwards/Meredith Johnson
Project Manager 19
Registration Division (7505C)

Thru: Marion P. Copley, D.V.M., D.A.B.T.
Section Head
Section 4, Toxicology Branch I
Health Effects Division (7509C)

9/21/94

KB 9/23/94

I. **CONCLUSIONS:**

The data base supports the requested EUP for use on greenhouse and shadehouse crnamentals. All reviewed studies are acceptable. The cross reference to inhalation toxicity (81-3, MRID 427702-15) and dermal sensitization study (81-6, MRID 427702-18) in support of AC 303,630 2SC Formulation is appropriate and acceptable, since the active and inactive ingredients were the same, except for minor changes in the concentrations. However, it should be noted that HED files remain incomplete for the chromosomal aberration assay which was a **NON-TEST.**

A copy of the DERs are attached.

cc: CCB, OREB (Dorsey)

There is no acute toxicity endpoint of concern based on current data. **Based on the Toxicity Category of the technical the restricted entry interval (REI) of 12 hours is adequate.**

II. **ACTION REQUESTED:**

American Cyanamid Company, has submitted an application for an Experimental Use Permit for AC 303,630 2SC Insecticide-Miticide. The studies included in this package are listed below and the * by the studies indicate that the DERs are attached.

Technical:

Data requirements on the Technical AC 303,630 have been satisfied (see HED Doc. 010651).

Formulation: AC 303,630 2SC Insecticide-Miticide

Guideline #	Study Type	MRID #
81-1*	Acute Oral Toxicity	432682-04
81-2*	Acute Dermal Toxicity	432682-05
81-3	Acute Inhalation Toxicity	Satisfied by study using 3SC Formulation - MRID 427702-15
81-4*	Primary Eye Irritation	432682-06
81-5*	Primary Dermal Irritation	432682-07
81-6	Dermal Sensitization	Satisfied by studies using Technical and 3SC Formulations (MRID #s 427702-12 and 427702-18, respectively)

The sponsor's preliminary data indicate that AC 303,630 2SC is effective when applied (0.02 to 0.32 lb ai/100 gallons) as foliar spray against a number of problem insects and mites on greenhouse and shadehouse ornamentals. The experimental use program proposes to evaluate product efficacy against target pests, when applied to larger plots, shadehouses and entire greenhouse buildings. The petitioner is requesting an authorization for the use of 300 lbs of active ingredient to treat a maximum of 150 acres (about 100 acres in greenhouses and 50 acres in shadehouses) during the next two years. The objective of this EUP is to fine tune the rates of AC 303,630 2SC against the target pests.

The proposed EUP is for nonfood use; no residue tolerance is required.

Registrant has requested use of 81-3 and 81-6 studies on 3SC Formulation to be used instead of studies on the 2SC Formulation. This appears reasonable because the active and inactive ingredients are same, except for minor changes in the

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concentrations.

III. **DATA REQUIREMENTS:**

For nonfood EUP. Updated: 8/18/94

Technical: AC 303,630 (Pirate® Insecticide-Miticide, MP)
Use Pattern: Domestic outdoor and Indoor
Action Type: Experimental Use Permit

Guideline #	Study	Required	Satisfied
81-1	Acute Oral Toxicity	Yes	Yes
81-2	Acute Dermal Toxicity	Yes	Yes
81-3	Acute Inhalation Toxicity	Yes	Yes
81-4	Primary Eye Irritation	Yes	Yes
81-5	Primary Dermal Irritation	Yes	Yes
81-6	Dermal Sensitization	Yes	Yes
82-1(b)	Subchronic Oral (non-rodent)	Yes	Yes
83-3	Teratology (non-rodent)	Yes	Yes
84-2	Gene mutation (Ames)	Yes	Yes
84-2	Gene mutation (mammalian)	Yes	Yes
84-2	Structural chromosomal aberration	Yes	No

Formulation: AC 303,630 2SC Insecticide-Miticide

Guideline #	Study Type	Required	Satisfied
81-1	Acute Oral Toxicity	Yes	Yes
81-2	Acute Dermal Toxicity	Yes	Yes
81-3	Acute Inhalation Toxicity	Yes	Yes
81-4	Primary Eye Irritation	Yes	Yes
81-5	Primary Dermal Irritation	Yes	Yes
81-6	Primary Dermal Sensitization	Yes	Yes

IV. TOXICOLOGY PROFILE Updated: 8/13/94

Guideline #	Study Identification and Classification	Results
Technical		
81-1	Acute Oral Toxicity in Rats MRID 427702-07/428842-01 Study #:T-0417 7/20/1992 Acceptable	LD_{50} (95% C.I.) = 441 (196 - 832) mg/kg, males LD_{50} (95% C.I.) = 1152 mg/kg, females LD_{50} (95% C.I.) = 628 (274 - 1085) mg/kg, combined TOXICITY CATEGORY: II, based on most sensitive sex
81-2	Acute Dermal Toxicity in Rabbits MRID 427702-08 Study #:T-0406 7/20/1992 Acceptable	LD_{50} > 2000 mg/kg (Limit Dose) TOXICITY CATEGORY: III
81-3	Acute Inhalation Toxicity in Rats MRID 427702-09 Study (american Cyanamid)#:91-8351 3/25/1993 Acceptable	Doses 0, 0.34, 0.71, 1.8 or 2.7 mg/l in SD rats. LC_{50} (95% C.I.) = 0.83 (0.48 - 1.4) mg/L, (males) LC_{50} (95% C.I.) = > 2.7 mg/L, females) LC_{50} (95% C.I.) = 1.9 (1.1 - 3.3) mg/L, combined TOXICITY CATEGORY: III, based on most sensitive sex
81-4	Primary Eye Irritation in Rabbits MRID 427702-10 Study #:T-0404 7/20/1992 Acceptable	Corneal opacity (4/6), iritis (2/6) and conjunctivitis (6/6) present at 48 hours. At 72 hours iritis was resolved. All rabbits were normal by Day-7. TOXICITY CATEGORY: III
81-5	Primary Dermal Irritation in Rabbits MRID 427702-11 Study #:T-0405 7/20/1992 Acceptable	Non-irritating. TOXICITY CATEGORY: IV
81-6	Dermal Sensitization in Guinea Pigs MRID 427702-12 Study #:T-0439 3/26/1993 Acceptable	Not a skin sensitizer (Closed-Patch Repeated Insult)

82-1(b)	Subchronic Feeding in Dogs (90-Day) MRID 427702-20 Study (American Cyanamid)#:971-92-118 4/8/1993 Minimum	Doses in beagles: 0, 60, 120 or 247 ppm (0, 2.16, 4.23 or 6.1 mg/kg/day) in feed. The 247 ppm was based on concentration of AC 303,630 in the diet of 300 ppm from Day 1 - 14, 240 ppm from Day 15 - 25 and 200 ppm from Day 25 - 93 (5.2, 5.9 and 7.2 mg/kg/day, respectively). NOEL = 120 ppm (4.23 mg/kg/day) LOEL = 247 ppm (6.1 mg/kg/day), based on reduced body weight gain and feed efficiency and emaciation.
83-3(b)	Teratology Study in Rabbits MRID 427702-22 Study (American Cyanamid)#:971-90-179 3/2/1993 Minimum	Doses of 0, 5, 15 or 30 mg/kg/day administered by gavage in 0.5% carboxymethylcellulose to pregnant New Zealand White rabbits from Days 7 to 19 of gestation, inclusive. Maternal NOEL: 5 mg/kg/day and LOEL: 15 mg/kg/day, based upon reduced body weight gain during treatment. Developmental NOEL: > 30 mg/kg/day.
84-2(a)	Gene Mutation-Ames MRID#: 427702-23 American Cyanamid # 91-02-001; 03/24/93 Acceptable	Negative for reverse mutation in S. typhimurium strains TA 98, TA 100, TA 1535, TA 1537, TA 1538 and E. coli strain WP2 uvrA- exposed up to cytotoxicity (50 µg/plate, +/- S9)
84-2(a)	Gene Mutation - in mammalian cells (CHO/HGPRT) MRID#: 427702-24 American Cyanamid # 91-05-001; 03/25/93 Not Acceptable	Repeatedly negative at doses up to 250 µg/ml +/- S9, which were not cytotoxic to Guideline levels.
84-2(b)	Structural chromosome aberration - in vivo mouse MRID # 427702-25 American Cyanamid #: 91-18-001; 03/17/93 Non test	Although reportedly negative for micronucleus induction in mice treated orally up to 20 or 30 mg/kg, the highest dose was lethal without causing cytotoxicity to target tissue.
84-4	Repair in vitro (UDS) MRID #: 427702-26 Microbiological#: T9775.380025 02/23/93 Acceptable	Negative for inducing unscheduled DNA synthesis in primary rat hepatocyte cultures exposed up to severely toxic concentrations (≥ 30 µg/ml).

PIRATE® Insecticide-Miticide - EP		
81-1	Acute Oral Toxicity in Rats MRID #:427702-14 Study #:T-0515 1/18/93 Acceptable	LD_{50} (95% C.I.) = 626 (274-1085) mg/kg, combined LD_{50} (95% C.I.) = 283 (101-502) mg/kg, males LD_{50} (95% C.I.) = 999 (431-1821) mg/kg, females Decreased activity, salivation, ataxia, hyperthermia, protruding testes, prostration and mortality were observed at all levels. Grossly, congested and mottled livers and pronounced striations of abdominal muscles were observed. Weight gains of the survivors were not effected. TOX. CATEGORY: II, based on most sensitive sex
81-2	Acute Dermal Toxicity in Rabbits MRID 427702-14 Study #:T-0515 1/18/93 Acceptable	LD_{50} (95% C.I.) = 1782 [1112 - 2856] mg/kg, males LD_{50} (95% C.I.) > 2000 mg/kg, females Nasal discharge (1/5), excessive lacrimation (1/5) and diarrhea (1/5) were observed at the 1000 and 4000 mg/kg. Two of five rabbits in the 4000 mg/kg and 3/5 rabbits in the 2000 mg/kg dose died within 48 hours of treatment. Necropsy of the surviving was unremarkable. TOX. CATEGORY: II, based on most sensitive sex
81-3	Acute Inhalation Toxicity in Rats MRID 427702-15 Cyanamid #:971-92-109 3/8/93 Acceptable	Doses 0, 0.84, 1.9 or 2.6 mg/l in SD rats. LC_{50} (95% C.I.) = 1.3 (0.86 - 2.1) mg/l, males LC_{50} (95% C.I.) = 2.4 (1.6 - 3.5) mg/l, females LC_{50} (95% C.I.) = 2.1 (1.5 - 2.9) mg/l, combined sexes Clinical signs during exposure were labored breathing and excessive salivation at all doses; eye closure at the two high doses; and gasping and decreased activity at the highest dose. Among survivors, in addition to the aforementioned, rales, dried brown material on face and fur, matted coat, wet fur and yellow ano-genital staining were observed. At necropsy, red discoloration in lungs of some deceased animals was noticed. TOX. CATEGORY: III, based on most sensitive sex
81-4	Primary Eye Irritation in Rabbits MRID #: 427702-16 Study #: T-0513 12/4/92 Acceptable	Slight-to-moderate conjunctivitis (6/6) was observed at one and 24 hours; had resolved by 48 hours. TOX. CATEGORY: III
81-5	Primary Dermal Irritation in Rabbits MRID 427702-17 Study #T-0514 1/18/93 Acceptable	Slightly irritating to rabbit skin. A very slight (5/6)-to-moderate (1/6) erythema and slight (1/6) edema at 1 and slight (3/6) erythema at 24 hour post-dosing were observed. At 48 hour examination 1/6 exhibited slight erythema which resolved by 72 hours. TOX. CATEGORY: IV

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81-6	Dermal Sensitization in Guinea Pig MRID 427702-18 Study #:T-0530 3/5/93 Acceptable	Not a sensitizer

AC 303,630 2SC Insecticide-Miticide		
81-1	Acute Oral Toxicity in Rats MRID #:432682-04 Study #:T-0588 6/9/94 Acceptable	LD_{50} (95% C.I.) = 560 (410-890) mg/kg, males LD_{50} (95% C.I.) = 567 (281-988) mg/kg, females Decreased activity, salivation, writhing and abnormal posture. Necropsy was unremarkable in surviving animals. In dead animals, grossly, dark and molted liver, pronounced striations of abdominal wall, tetany, salivation, pale intestinal tracts, dark lungs and diarrhea were observed. TOX. CATEGORY: III
81-2	Acute Dermal Toxicity in Rabbits MRID 432682-05 Study #:T-0592 6/9/94 Acceptable	LD_{50} (95% C.I.) > 2000 mg/kg, males and females Nasal discharge and lacrimation were observed. There were no deaths. Grossly, red foci in kidneys, pale colored kidneys and pale lungs were observed only in males. TOX. CATEGORY: III
81-3*	Acute Inhalation Toxicity in Rats MRID 427702-15 Cyanamid #:971-92-109 3/8/93 Acceptable	Doses 0, 0.84, 1.9 or 2.6 mg/l in SD rats. LC_{50} (95% C.I.) = 1.3 (0.86 - 2.1) mg/l, males LC_{50} (95% C.I.) = 2.4 (1.6 - 3.5) mg/l, females LC_{50} (95% C.I.) = 2.1 (1.5 - 2.9) mg/l, combined sexes Clinical signs during exposure were labored breathing and excessive salivation at all doses; eye closure at the two high doses; and gasping and decreased activity at the highest dose. Among survivors, in addition to the aforementioned, rales, dried brown material on face and fur, matted coat, wet fur and yellow ano-genital staining were observed. At necropsy, red discoloration in lungs of some deceased animals was noticed. TOX. CATEGORY: III, based on most sensitive sex
81-4	Primary Eye Irritation in Rabbits MRID #: 432682-06 Study #: T-0593 3/12/94 Acceptable	Slight (5/6)-to-moderate (1/6) redness of conjunctivae, and slight ocular discharge were present at 1 hour. All signs of irritation had resolved by 24 hours. The mean conjunctival (redness + chemosis + discharge; range 2 - 20) score for this evaluation was 3.0. The overall eye irritation score was 1 (range 0 - 110) and was considered practically non-irritating. TOX. CATEGORY: IV
81-5	Primary Dermal Irritation in Rabbits MRID 432682-07 Study #T-0594 5/12/94 Acceptable	Slight erythema (3/6) was observed at 1 hour and persisted in 1 rabbit at 24 hours. All signs of irritation had resolved by 48 hours. TOX. CATEGORY: IV

81-6*	Dermal Sensitization in Guinea Pig MRID 427702-18 Study #:T-0530 3/5/93 Acceptable	Not a sensitizer

* These studies conducted with AC 303,630 3SC Formulation (32% ai) were cross-referenced in support of AC 303,630 2SC Formulation (21% ai).

V. **DATA GAPS:**

The toxicity data requirements for an **Experimental Use Permit** appear adequate, except for the chromosomal aberrations using mouse micronucleus assay test. Although this test will not be required for this EUP (see IX.B.), the registrant will be required to submit an chromosomal aberration study (other than the micronucleus) for full registration of this chemical.

VI. **ACTION BEING TAKEN TO OBTAIN ADDITIONAL INFORMATION OR CLARIFICATION:**

The sponsor should be notified of the issues discussed under Section V and will be required to rectify for full registration of this chemical.

VII. **REFERENCE DOSE (RfD):**

The recommended PADI (Preliminary Acceptable Daily Intake) is 0.004 mg/kg/day. This value was calculated by using the 90-Day Dog Study NOEL of 4.23 mg/kg/day and a uncertainty factor of 1000, based on extremely limited data base. This has not been presented to the Health Effects Division or Agency RfD Committees.

VIII. **PENDING REGULATORY ACTIONS:**

The Toxicology Branch is unaware of any pending regulatory actions against this pesticide.

IX. **TOXICOLOGY ISSUES PERTINENT TO THIS REQUEST:**

A. The data indicate no toxicity concerns at this time. There is no difference in toxicity between males and females; oral administration resulted in increased absorption over dermal route of administration. It is not a developmental toxicant in rabbits up to 30 mg/kg/day. The 13-week dog study did not result in any organ pathology identifiable with doses up to 240 ppm. Proposed **EUP** labeling contains common precautionary statements for this type of use and that the **re-entry statement "Do not enter or allow worker entry into treated areas during the restricted entry interval (REI)**

of 12 hours without protective clothing" is adequate based on toxicity of the technical.

B. **Mutagenicity** - The current mutagenicity guidelines require 3 studies: Ames and mammalian gene mutation assays as well as an acceptable chromosomal aberration assay. The chromosomal aberration assay submitted earlier is a **non-test** due to lack of target organ cytotoxicity at lethal levels. However, there is an acceptable UDS test. Therefore, new studies are not being required for this EUP but will be required for full registration of this chemical.

C. **Risk Concerns:**

Dietary

There are no dietary exposure concerns because the request is for nonfood use.

Worker Exposure

There is no endpoint of concern for acute exposure. If worker exposure for non acute exposure is less than 0.042 mg/kg/day, the Margin of Exposure would be at least 100. This is based on NOELs from both the Developmental rabbit study (Maternal NOEL = 5 mg/kg/day) and 90 day dog study (NOEL = 4.2 mg/kg/day).

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 8/22/94
Section IV, Tox. Branch I (7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (7509C) 9/19/94

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity/Rat

TOX. CHEM. NO.: N.A.

P. C. NO.: 129093

MRID NO.: 432682-04

GUIDELINE #: 81-1

TEST MATERIAL: AC 303,630 2SC Formulation

SYNONYMS: Pyrrole -3-carbonitrile, 4-bromo-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluromethyl) 3 SC Formulation

STUDY NUMBERS: T-0588

SPONSOR: American Cyanamid Company
Princeton, NJ 08543-0400

TESTING FACILITY: American Cyanmid Company
Princeton, NJ 08543-0400

TITLE OF REPORT: Oral LD_{50} Study in Albino Rats with AC 303,630 2SC Formulation

AUTHORS: D.M. Bradley
J.E. Fischer

REPORT ISSUED: June 9, 1994

EXECUTIVE SUMMARY:

In an acute toxicity study, Crl:CD(SD)BR albino rats (5/sex) were administered orally with AC303,630 2SC Formulation (21.24% a.i.) at doses of 312.5 (M&F), 460 (M), 540 (M), 625 (M&F), 1250 (M&F) or 2500 mg/kg (M&F) and then observed for a period of 14 days.

Overt signs of toxicity included, decreased activity, salivation, writhing and abnormal posture. Weight gains were not affected. Necropsy was unremarkable in the surviving animals. In animals, which died, the most noticeable findings were dark and mottled liver, pronounced striations of abdominal muscle wall, tetany, salivation, pale intestinal tracts, dark lungs and diarrhea. **The oral LD_{50} (95% C.I.) in rales was 560 (410-890)**

mg/kg and LD_{50} (95% C.I.) in females was 567 (281-988) mg/kg.

The study is classified as Core - Acceptable with TOXICITY CATEGORY III and satisfies the requirement, § 81-1 for a oral toxicity (LD_{50}) study in rats.

MATERIALS:

1. **Test Compound:** AC 303,630 2SC Formulation, (beige liquid), Lot # AC 8053-139, Purity 21.24%, Sp. Gravity 1.1083 g/ml, was used in this study.

   The test material was administered as received, once orally, by gavage, to the overnight fasted rats. No untreated control were used in this study.

2. **Test Animals:** Species: albino rats, Strain: Crl CD(SD)BR, Age: 6 - 8 weeks, Weight: males - 165-248 and females - 170-223 g, Source: Charles River Labs., Inc.. The animals were housed individually and maintained under atmospheric conditions to a 12-hour dark/light cycles. The rats were acclimated for 7 days to the laboratory environment.

METHODS:

LD_{50} Study: Dosages were selected based on earlier studies. Excessive mortality in males and females necessitated the addition of 625 and 312.5 mg/kg groups. Limited mortality in males required the addition of 540 and 460 mg/kg. The experimental design and mortality for this study is provided in Table 1.

Table 1. Summary of dosages and mortality

Dose (mg/kg)	No. Animals		Mortality	
	♂	♀	♂	♀
312.5	5	5	1/5	1/5
460	5	not tested	1/5	not tested
540	5	not tested	1/5	not tested
625	5	5	4/5	2/5
250	5	5	5/5	5/5
2500	5	5	5/5	5/5

The animals were observed for signs of toxicity several times on the day of dosing and daily for the remainder of the study. Individual body weights were determined on Days 0, 7, and 14 or at death. Necropsies were performed on all dead and survivors at the end of the study. The liver, kidney, spleen, stomach, intestinal tract, lung, urinary bladder and external surfaces were grossly examined. LD_{50} values and 95% confidence

intervals were calculated by Probit Analysis as described by D.J. Finney Probit Analysis, Ed. 2, Cambridge University press, Cambridge, 1993.

QUALITY ASSURANCE:

A statement signed by Kenneth A. Sund, Quality Assurance Consultant, attested that the study was audited four times and a single report provided.

RESULTS/DISCUSSION:

Mortality is presented in Table 1. Males and females exhibited clinical signs of toxicity within 24 hours following administration of compound. Deaths occurred in all dosage groups. Overt signs of toxicity included, decreased activity, salivation, writhing and abnormal posture. No toxic signs were seen in the 312.5 mg/kg group. Weight gains were not affected due to compound administration. Necropsy was unremarkable in the surviving animals. In animals, which died, the most noticeable findings were dark and mottled liver, pronounced striations of abdominal muscle wall, tetany, salivation, pale intestinal tracts, dark lungs and diarrhea.

The data reporting was thorough and the summary means were supported by individual animal data. The above information supports the following:

LD_{50} (95% C.I.) = 560 (410-890) mg/kg, males
LD_{50} (95% C.I.) = 567 (281-988) mg/kg, females

The study is Core-Acceptable
Toxicity Category III

As presented the study satisfies the requirements set forth in Subdivision F, Guideline 81-1 for Acute Oral Toxicity in Rats.

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Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 8/25/94
Section IV, Tox. Branch I (7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (7509C) 9/19/94

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity/Rabbit

TOX. CHEM. NO.: N.A.

P. C. NO.: 129093

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MRID NO.: 432682-05

GUIDELINE #: 81-2

TEST MATERIAL: AC 303,630 2SC Formulation

SYNONYMS: Pyrrole -3-carbonitrile, 4-bromo-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluromethyl) 3SC Formulation

STUDY NUMBERS: T-0592

SPONSOR: American Cyanamid Company
Princeton, NJ 08543-0400

TESTING FACILITY: American Cyanmid Company
Princeton, NJ 08543-0400

TITLE OF REPORT: Dermal LD_{50} Study in Albino Rabbits with Ac 303,630 2SC Formulation

AUTHORS: D.M. Bradley
J.E. Fischer

REPORT ISSUED: June 9, 1994

EXECUTIVE SUMMARY:

In an acute toxicity, New Zealand White Rabbits (5 males and 5 females) were dermally exposed to 2000 mg/kg (**Limit Dose**) AC 303,630 2SC Formulation (21.24% a.i.) for 24 hours (to clipped dorsal area of trunk, approximately 10% of body surface), wiped with cloth and then observed for a period of 14 days.

The only signs of overt toxicity were limited nasal discharge and lacrimation. There were no deaths. Grossly, red foci in kidneys, pale colored kidneys and pale lungs were observed only in males. **The dermal LD_{50} in rabbits for AC 303,630 2SC Formulation is greater than 2,000 mg/kg.**

The study is classified as **Core - Acceptable)** with a

TOXICITY CATEGORY III and **satisfies** the requirement, § 81-2 for a dermal toxicity (LD_{50}) study in rabbits.

MATERIALS:

1. **Test Compound:** AC 303,630 2SC Formulation (beige liquid), Lot # AC 8053-139, Purity 21.24%, Sp. Gr. 1.1083 g/ml, was used in this study.

   The test material, as received was administered once to the shaved backs of the test animals.

2. **Test Animals:** Species: rabbits, Strain: New Zealand White, Age: Young adults, Weight: Males - 2029 to 2922, Females - 2327 to 2752 g, Source: Skippack Farms, Skippack, PA.. The animals were housed individually and maintained under atmospheric conditions to a 12-hour dark/light cycles. The rabbits were acclimated for 3 days to the laboratory environment. Purina Laboratory Rabbit Chow and water were provided ad libitum.

METHODS:

Groups of five animals/sex were dosed at a rate of 2000 mg/kg of body weight. The test dosages were based on studies done with similar formulations. The backs were clipped (≈ 10%), wrapped with plastic wrap and measured amount of test material was injected under the plastic wrap. The plastic wrap was then covered with cloth bandage. After 24 hours the test site was cleaned and rabbits observed for 14 days.

QUALITY ASSURANCE:

A statement signed by Kenneth A. Sund, Quality Assurance Consultant, attested that the study was audited five times and a single report provided.

RESULTS:

There were no deaths. Clinical signs were limited to lacrimation and nasal discharge during the study. Necropsy findings were unrelated to treatment. Grossly, red foci in kidneys, pale colored kidneys and pale lungs were observed only in males.

DISCUSSION:

The data reporting was thorough and the summary means were supported by individual animal data. **Limit Dose** was reached in males and females. Based on the data presented

the acute dermal LD_{50} is > 2000 mg/kg

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The study is **Core-Acceptable**
Toxicity Category III

As presented the study satisfies the requirements set forth in Subdivision F Guideline, 81-2 for Acute Dermal Toxicity in Rabbits.

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Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 5/25/94
Section IV, Tox. Branch I (7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (7509C) Marion Copley 9/19/94

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation/Rabbit

TOX. CHEM. NO.: N.A

P. C. NO.: 129093

MRID NO.: 432682-06

GUIDELINE #: 81-4

TEST MATERIAL: AC 303,630 2SC Formulation

SYNONYMS: Pyrrole -3-carbonitrile, 4-bromo-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluromethyl) 3SC Formulation

STUDY NUMBERS: T-0593

SPONSOR: American Cyanamid Company
Princeton, NJ 08543-0400

TESTING FACILITY: American Cyanamid Company
Princeton, NJ 08543-0400

TITLE OF REPORT: Eye Irritation Study in Albino Rabbits with AC 303,630 2SC Formulation

AUTHORS: L.M. Boczon

REPORT ISSUED: March 12, 1994

EXECUTIVE SUMMARY:

In a primary eye irritation study, six male New Zealand White rabbits were dosed with 0.1 ml of AC 303,630 2SC Formulation (21.24% a.i.) in to the left conjunctival sac for 1 hour, rinsed with tap water and was evaluated for irritation at 1, 24, 48 and 72 hours.

Slight (5/6)-to-moderate (1/6) redness of conjunctivae, and slight (4/6) ocular discharge were present at one hour. All signs or irritation had resolved by 24 hours. The mean conjunctival (redness + chemosis + discharge; range 2 - 20) score for this evaluation was 3.0. The overall eye irritation score was 1 (range 0 - 110) and was considered practically non-irritating.

The study is classified as **Core - Acceptable** with a **TOXICITY CATEGORY IV** and **satisfies** the requirement, § 81-4 for a primary eye irritation study in rabbits.

MATERIALS:

1. **Test Compound:** AC 303,630 2SC Formulation, Lot # AC 8053-139, Purity 21.24%, Sp. Gr. 1.1083 g/l and described as beige liquid, was use in this study.

2. **Test Animals:** Species: rabbits, Strain: New Zealand White, Age: Young adult males (10 - 13 weeks), Weight: Not given, Source: Skippack Farms, Skippack, PA.. The animals were housed individually and maintained under controlled atmospheric conditions to a 12-hour dark/light cycles. The rabbits were acclimated for 3 days to the laboratory environment. Purina Laboratory Rabbit Chow and tap water were provided ad libitum.

METHODS:

A single group of six males rabbits were instilled with a dosed of 0.1 ml of test material into conjunctival sac of their left eye. Following dosing, the upper and lower eye lids were held together for 1 second. The contralateral eye of each rabbit acted as the control. At the end of the 24 hours exposure period, the treated eyes were rinsed with tap water and examined for irritation under ultraviolet light and fluorescein stain. The eyes were examined for irritation at pre-treatment (-4 hours) 1, 24, 48 and 72 hours, after dosing. Eyes were scored using the Draize scale.

QUALITY ASSURANCE:

A statement signed by Kenneth A. Sund, Quality Assurance Consultant, attested that the study was audited thrice and a single report provided.

RESULTS:

Corneal opacity was not observed.

1 Hour Evaluation

Slight (5/6)-to-moderate (1/6) redness of conjunctivae, and slight (4/6) ocular discharge were present at 1 hour. The mean conjunctival (redness + chemosis + discharge; range 2 - 20) score for this evaluation was 3.0. The overall eye irritation score was 1 (range 0 - 110) and was considered practically non-irritating.

24 - 72 Hour Evaluation

All signs of irritation had resolved by 24 hours.

Based on the above irritation scores, the chemical is considered practically non-irritating to the rabbit eye.

DISCUSSION:

The data reporting was thorough and the summary means were supported by individual animal data.

The study is **Core-Acceptable**
Toxicity Category IV.

As presented the study satisfies the requirements set forth in Subdivision F Guideline, 81-4 for Primary Eye Irritation Study in Rabbits.

011245

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 8/25/94
Section IV, Tox. Branch I (7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (7509C) 9/29/94

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation/Rabbit

TOX. CHEM. NO.: N.A

011245

P. C. NO.: 129093

MRID NO.: 432682-07

GUIDELINE #: 81-5

TEST MATERIAL: AC 303,630 2SC Formulation

SYNONYMS: Pyrrole -3-carbonitrile, 4-bromo-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluromethyl) SC Formulation and Pirate®

STUDY NUMBERS: 1-0594

SPONSOR: American Cyanamid Company
Princeton, NJ 08543-0400

TESTING FACILITY: American Cyanamid Company
Princeton, NJ 08543-0400

TITLE OF REPORT: Skin Irritation Study in Albino Rabbits with AC 303,630 2SC Formulation

AUTHORS: L.M. Boczon

REPORT ISSUED: May 12, 1994

EXECUTIVE SUMMARY:

In a primary dermal irritation study, six male New Zealand White rabbits were dermally exposed to 0.5 ml of AC303,630 2SC Formulation (21.24% a.i.) for 4 hours and evaluated for irritation at 1, 24, 48 and 72 hours after removal of patch.

Slight erythema (3/6) was observed at 1 hour and persisted in 1 rabbit at 24 hours. All signs of irritation had resolved by 48 hours.

The study is classified as **Core - Acceptable** with the **TOXICITY CATEGORY IV** and **satisfies** the requirement, § 81-5 for primary dermal irritation study in rabbits.

MATERIALS:

1. **Test Compound:** AC 303,630 2SC Formulation, Lot # AC 8053-139, Purity 21.24%, Sp. Gr. 1.1083 g/ml and describe. as beige liquid, was used in this study.

2. **Test Animals:** Species: rabbits, Strain: New Zealand White, Age: Young adults (10 - 13 weeks), Weight: Not given, Source: Skippack Farms, Skippack, PA.. The animals were housed individually and maintained under controlled atmospheric conditions to a 12-hour dark/light cycles. The rabbits were acclimated for 3 days to the laboratory environment. Purina Laboratory Rabbit Chow (#5321) and tap water were provided ad libitum.

METHODS:

On day prior to dosing, six male rabbits were prepared by clipping the trunk free of hair. Two test sites, one control site and one treated site, were selected on opposite sides of the dorsal midline. A 0.5 ml of the test material was applied to 1" square gauze patches moistened with water and applied to the test site. The patches were held in place with adhesive tape, plastic sheet and filter cloth. The bandages were removed after 4 hours and the site wiped to remove excess material. Observations for dermal irritation were made 1, 24, 48 and 72 hours after patch removal. Draize method was employed for evaluating skin irritation potential of AC 303,603 2SC Formulation. Erythema was scored on a scale of 0 to 4, 0 = normal and 4 = severe erythema. Edema formation was scored on a scale of 0 to 4, 0 = no edema and 4 = severe edema.

QUALITY ASSURANCE:

A statement signed by Kenneth A. Sund, Quality Assurance Consultant, attested that the data was audited thrice and a single report provided.

RESULTS:

No overt signs of toxicity were observed during the course of the study.

Slight erythema (3/6) was observed at 1 hour and persisted in 1 rabbit at 24 hours. All signs of irritation had resolved by 48 hours. The mean erythema 1 hour score was 0.5 and the 24 hour score was 0.2. The primary irritation score, calculated by adding the 24 and 48 hour mean erythema and edema scores and divided by 4, was 0.05.

DISCUSSION:

The data reporting was thorough and the summary means were supported by individual animal data. Based on the primary irritation index the chemical is slightly irritating to rabbit skin.

The study is **Core-Acceptable Toxicity Category IV.**

As presented the study satisfies the requirements set forth in Subdivision F Guideline, 81-5 for Primary Dermal Irritation Study in Rabbits.