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

OCT 25 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Subject: EPA ID#: 5G04507 - Alert®/AC 303,630 2SC Insecticide-Miticide: Application for Experimental Use Permit and a Temporary Tolerance for Use on Citrus

P.C.#: 129093
Submission #: S486243
Project No. D215014

From: Guruva B. Reddy, D.V.M., Ph. D.
Section 4
Toxicology Branch I
Health Effects Division (7509C)
9/15/95

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

Thru: John Doherty, Ph.D., D.A.B.T.
Acting Section Head
Section 4, Toxicology Branch I
Health Effects Division (7509C)
9/20/95
10/24/95

I. **CONCLUSIONS:**

The data base supports the requested EUP for use of Alert®/AC 303,630 2SC on citrus with a temporary tolerance.

Attachment I addresses the toxicity data base for this product and pesticide.

cc: CCB, OREB (Dorsey)

I **ACTION REQUESTED:**

American Cyanamid Company, has submitted an application for an Experimental Use Permit for AC 303,630 2SC Insecticide-Miticide on citrus. No new data were submitted with this application.

The experimental use program proposes to evaluate product efficacy against target pests on citrus; and further evaluate compatibility of this insecticide with Integrated Pest Management (IPM) and Insecticide Resistance Management (IRM) program. The petitioner is requesting an authorization for the use of 3,321 lbs of active ingredient on 4,490 acres in the states of Arizona, California, Florida and Texas during the next two years. The rate of application does not exceed 1.05 lbs. a.i. per acre per year.

The proposed residue tolerance for citrus is 0.5 ppm.

III. **COMMENTS:**

1. The toxicity data base for Alert®/AC 303,630 2SC Insecticide-Miticide used to support this EUP program and temporary tolerance is described in Attachment I.

2. Under Section IV of the attachment, the 90-day rat subchronic and rat teratology studies were inadvertently omitted. The studies are acceptable and will be made part of updated Toxicology Profile.

3. We are reevaluating the chromosomal aberration assay study in the light of additional information submitted by the registrant. The review findings will be conveyed under a separate memo.

IV. **DATA REQUIREMENTS:**

Technical: Data requirements have been satisfied (see HED Doc. 010651)

Formulation: Alert™ Insecticide-Miticide/AC 303,630 2SC Formulation

Data requirements on AC 303,630 2SC formulation have been satisfied (see HED Doc. 011245; Attachment I).

Attachment

3

ATTACHMENT I

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

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SEP 3 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
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9/21/94

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

Marion Copley 9/21/94

KB 9/23/94

I. **CONCLUSIONS:**

The data base supports the requested EUP for use on greenhouse and shadehouse ornamentals. 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)

3

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

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: 8/18/94

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 (195 - 832) mg/kg, males LD_{50} (95% C.I.) = 1152 mg/kg, females LD_{50} (95% C.I.) = 626 (274 - 1065) 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)

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82-1(b)	Subchronic Feeding in Dogs (90-Day) MRID 427702-20 Study (American Cyanamid)#:971-92-118 4/8/1993 Minimum	Doses is 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#: T9776.380025 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 (1.8 - 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

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).