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

MAY 16 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Section 18: ID# 94AL0002.** Emergency Exemption for Use of Pirate on Cotton in Alabama

Tox. Chem. No.:	None
PC No.:	129093
Barcode No.:	D202863
Submission No.:	S464688

TO: Rebecca Cool, Manager, PM Team 41
Susan Stanton, Reviewer, PM Team 41
Emergency Response and Minor Use Section/Registration Support Branch
Registration Division (H7505C)

FROM: William Dykstra, Ph.D. William Dykstra 5/12/94
Review Section I, Toxicology Branch I
Health Effects Division (H7509C)

THRU: Guruva Reddy, D.V.M., Ph.D. 5/12/94
Review Section IV, Toxicology Branch I
Health Effects Division (H7509C)
and
Roger Gardner, Section Head, Toxicologist
Review Section I, Toxicology Branch I
Health Effects Division (H7509C) KB 5/15/94
Roger Gardner 5/12/94

I. CONCLUSIONS

Although the toxicology data requirements are not complete, the minimum toxicology studies needed to support a Section 18 are available (two 90 day feeding studies, two teratology studies, and mutagenicity data) and no additional toxicology data are required for the issuance of a Section 18 emergency exemption to the State of Alabama for the temporary use of Pirate to control beet armyworms in cotton.

There are no toxicology concerns for acute dietary exposure.

The limited toxicology studies available on the effects of pirate include a 90 day dog feeding study with a NOEL of 4.23 mg/kg/day (120 ppm), a 90 day rat feeding study with a NOEL of 15 mg/kg/day (300 ppm), a rat developmental study with a maternal NOEL

of 25 mg/kg/day and a developmental NOEL of 225 mg/kg/day (HDT), and a rabbit developmental study with a maternal NOEL of 5 mg/kg/day and a developmental NOEL of 30 mg/kg/day (HDT). There also are two negative acceptable mutagenicity studies and a full battery of acute studies on the technical and formulated product. The margins of exposure (MOEs) for acute worker exposure are greater than 100 for the use on cotton by ground equipment when worker exposure is compared to the rabbit maternal NOEL of 5.0 mg/kg/day.

The proposed RfD is 0.0014 mg/kg/day, based on the NOEL of 4.23 mg/kg/day in the 90 day dog feeding study and utilizing an uncertainty factor of 3000 (due to the incomplete data base for pirate).

Toxicology Branch I has no objection to the issuance of this Section 18 exemption.

II. ACTION REQUESTED

In a letter dated April 21, 1994, the Alabama Department of Agriculture requested an emergency exemption under Section 18 for the use of pirate insecticide to control beet armyworms Spodoptera exigua on 180,000 acres of cotton. This is the first request made by Alabama for this use. According to the applicant, the cotton insecticides available are only slightly effective in controlling beet armyworm.

Pirate 3SC (American Cyanamid) is the formulation for the active ingredient. The pesticide will be used for a total of two applications using commercial ground equipment per growing season. The maximum estimated acreage to be treated in Alabama is 180,000. The rate of application will be 0.2 lbs ai/A (8.53 fl.oz. of the 3SC formulation per acre). This is equivalent to 52,000 pounds of active ingredient for the Section 18. The preharvest interval was not specified, but is expected to be the same as in 241-EUP-126.

III. TOXICOLOGY BRANCH I COMMENTS

The toxicology data base for pirate is sufficient to support the proposed Section 18 exemption.

IV. RISK/EXPOSURE ASSESSMENT

This action was submitted to OREB (Occupational and Residential Exposure Branch) for determination of exposure estimates (see attached memo from C. Lewis to W. Dykstra, dated May 12, 1994). Therefore, the OREB exposure estimates, unadjusted for dermal penetration and the rabbit maternal NOEL of 5.0 mg/kg/d (see One Liners and Toxicology Profile, attached) were used to determine the Acute MOEs. Calculations were based on a dermal absorption of

100% (since no dermal penetration data are available). Cancer risk is not known, since cancer studies for pirate have not been submitted at this time.

Formula used in calculations:

Acute MOE = NOEL (5.0 mg/kg BW/d) ÷ Exposure (mg/kg BW/d)

OPERATION*	EXPOSURE* (mg/kg/d)	ACUTE MOE
Mixer/Loaders, ground boom	0.0092	543
Applicator, ground boom	0.0055	909

Minimum clothing requirements for Applicators are long pants, long-sleeved shirt, and gloves; Mixer/Loader exposure is based on wearing long pants, long sleeves, and gloves (Worker Protection Standard for Agricultural Pesticides).

V. SPECIAL TOXICOLOGY ISSUES AND PROBLEMS

1. Labelling. The labelling precautionary statements for Pirate 3SC are governed by toxicity studies on the formulated product. The label signal word is Warning due to acute oral and dermal toxicity studies. Acute inhalation and Primary eye are Toxicity Category III and Primary skin is Toxicity Category IV. Pirate 3SC is not a dermal sensitizer.

2. Carcinogenicity. There is no information regarding cancer risk associated with exposure to this chemical, because the cancer studies have not been submitted.

3. RfD. The RfD/Quality Assurance Peer Review Committee has not met to assess the reference dose for this chemical. A Committee member (Dr. Ghali) recommended that an RfD of 0.0014 mg/kg/day should be established, based upon a NOEL of 4.23 mg/kg/d in a 90-day feeding study in dogs. In the 90 day dog study, the LEL was 6.1 mg/kg/day (HDT) and the effects were decreased body weight gain, decreased feed efficiency, and emaciation. An uncertainty factor of 3000 was used to account for the incomplete data base for pirate.

4. Other Biological Effects. There is limited data on pirate. In a rabbit teratology study, pregnant NZW rabbits were gavaged from days 7-19 of gestation at doses of 0, 5, 15 or 30 mg/kg/day. The maternal NOEL was 5.0 mg/kg/day and the LEL was 15 mg/kg/day with the effects being decreased body weight gain during treatment. The developmental NOEL was 30 mg/kg/day (HDT).

   Personal Communication with M. Copley on 5/5/94 indicates that a 90 day rat study and a rat teratology study have been recently reviewed and are acceptable. In the 90 day rat

feeding study, the NOEL is 300 ppm (15 mg/kg/day) and the LEL is 600 ppm with the effects being decreased body weight gain and increased relative liver weights in males and decreased HGB and increased absolute/relative liver weight in females.

In a rat teratology study, the doses are 0, 25, 75, or 225 mg/kg/day during gestation days 6-15 by gavage in Sprague-Dawley rats. The maternal NOEL is 25 and the LEL was 75 mg/kg/day with the effects being reduced weight gain, reduced relative food and water intake. The developmental NOEL is 225 mg/kg/day (HDT).

5. Mutagenicity/genetic toxicity comments. In studies conducted for the Agency, pirate at concentrations up to 50 ug/plate (cytotoxic level) was not mutagenic in Salmonella typhimurium strains TA100, TA1535, TA1537, and TA98, with and without metabolic activation. Pirate was also negative for inducing unscheduled DNA synthesis up to 30 ug/ml (severely cytotoxic) in primary rat hepatocyte cultures.

6. Dermal Penetration. There are no available dermal penetration data for pirate.

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

MAY 12 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Exposure Assessment for Section 18 Use of Pirate 3SC on Cotton in Alabama.

FROM: Charles Lewis
Special Review and Registration Section II

TO: W. Dykstra
Toxicology Branch I (7509C)

THRU: Mark I. Dow, Ph.D., Section Head
Special Review and Registration Section II

Larry C. Dorsey, Chief
Occupational and Residential Exposure Branch
Health Effects Division (7509C)

The Occupational and Residential Exposure Branch (OREB) has been requested by Toxicology Branch I (TB I) to provide an exposure assessment for the proposed Section 18 use of Pirate 3SC on cotton in Alabama. The assessment is attached.

DP Barcode: D202862

Pesticide Chemical Code: 129093

EPA Reg. No.: 94AL0002

PHED: Yes; ground-boom equipment, Run # 25.

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I. INTRODUCTION:

A. Background:

Pirate® 3SC (EPA Reg. No. 241-EUP-126) is the product name for 4-bromo-2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluromethyl)-1H-pyrrole-3-carbonitrile. American Cyanamid Company is the manufacturer. The purpose of the emergency exemption is to control beet armyworm (Spodoptera exigua) in cotton. Applications are to be made with ground equipment. A maximum of 180,000 acres may be treated in Alabama at a rate of 0.2 lb ai/A. Two applications per season may be required on 80,000 acres.

Tox. Endpoints [1]

Maternal NOEL (rabbit) = 5.0 mg/kg.

OREB has not previously prepared an exposure assessment for this chemical.

B. Purpose:

OREB has been requested by TB I to provide an exposure assessment for the proposed Section 18 use of Pirate® 3SC on cotton in Alabama.

[1] Tox. endpoints provided by W. Dykstra, Toxicology Branch I.

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II. DETAILED CONSIDERATIONS:

OREB used assumptions provided by Dr. Yuen-shaung Ng, Biological and Economic Analysis Division (BEAD) and the Pesticide Handlers Exposure Database, Version 1.01 (PHED) to develop the exposure assessment.

Ground-boom Equipment

application rate 0.2 lb ai/A (from Alabama submission);
88 acres treated per day;
17.6 lb ai applied per day.

Mixer-loaders

Minimum work clothing required by the Worker Protection Standard (WPS) and personal protective equipment (PPE) for this pesticide (see TABLE 1) includes: coveralls worn over short-sleeved shirt, short pants, shoes plus socks, chemical resistant gloves, chemical resistant headgear for overhead exposure, and chemical resistant apron when cleaning equipment, mixing, or loading. The information provided by Alabama did not specify the clothing to be worn or PPE required. A label was not provided with the submission.

TABLE 1. Clothing and PPE requirements for Pirate® 3SC based on tox oneliners.

Study Type	Tox Category of End-Use Product	Clothing/PPE Requirement
Signal word - Warning	II	Coveralls worn over short-sleeved shirt, short pants, headgear, apron, shoes plus socks, and gloves.
Acute Oral	II	Same as above.
Acute Dermal	II	Same as above.
Acute Inhalation	III	None.
Primary Eye Irritation	III	None.
Primary Dermal Irritation	IV	None.

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OREB's estimates of exposure are based on the assumption that long pants, long-sleeved shirt, shoes, socks, and chemical resistant gloves will be worn. OREB does not currently have data that would permit quantification of the degree of protection provided by additional PPE.

According to PHED, estimated total exposure for mixer/loaders of ground-boom equipment is 9.2 μg ai/kg bw/day.

Applicators

With the same work clothing and PPE as for mixer/loaders, applicator estimated total exposure for ground-boom equipment is 5.5 μg ai/kg bw/day.

III. CONCLUSIONS:

OREB has estimated the total exposure for mixer/loaders and applicators using Pirate® 3SC on cotton (TABLE 2). The calculated values are based on a single application of 0.2 lb ai/A. Two applications per season are permitted under this emergency use.

TABLE 2. Estimated total exposure (μg ai/kg bw/day) for mixer/loaders and applicators using Pirate® 3SC on cotton.

Equipment type	Mixer/loaders (μg ai/kg bw/day)	Applicators (μg ai/kg bw/day)
Ground-boom	9.2	5.5

CALCULATIONS

Mixer/loaders

Ground-boom Equipment

31.3 µg/lb ai handled (PHED unit of exposure value, run # 25, for mixer/loader, open loading, long-sleeved shirt, long pants, wearing gloves) X 17.6 lb ai/day = 550.88 µg ai/day ÷ 60 kg bw = 9.18 µg ai/kg bw/day.

Applicators

Ground-boom Equipment

18.86 µg/lb ai applied (PHED unit of exposure value, run # 25, for ground-boom applicator, open cab, long-sleeved shirt, long pants, wearing gloves) X 17.6 lb ai/A = 331.94 µg ai/day ÷ 60 kg bw = 5.53 µg ai/kg bw/day.

cc: C. Lewis, OREB
Correspondence File
Chemical File (129093)
Circulation

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U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TB-1
TOX ONELINERS

CASWELL#: 962
CAS-REG#:

P.C. CODE 129093- Pirate FILE LAST PRINTED: 05/04/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
83-3(b) Developmental Toxicity Study Species: rabbit Argus Research Labs 101-016; 03/02/93	AC 303,630 Tech. 94.5%; Lot# AC 7504-59A	427702-22	Doses: 0, 5, 15 or 30 mg/kg/day, admin. by gavage in 0.5% carboxymethylcellulose to pregnant NZW rabbits from days 7 through 19 of gestation, inclusive. Maternal NOEL = 5 mg/kg/day. Mat. LOEL = 15 mg/kg/d, based upon, reduced body weight gain during treatment. Developmental NOEL > 30 mg/kg/day.		Minimum 010648
82-1(b) Feeding-3 month Species: dog Pharmaco LSR Inc. 04/08/93	AC 303,630 tech., 94.5%; Lot# 7504-59A	427702-20	Doses tested in beagles: 0, 60, 120 or 247 ppm (0, 2.16, 4.23 or 6.1 mg/kg/day) in feed. The 247 pm value 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.		Minimum 010651
84-2(a) Mutagenic-Ames Species: salmonella American Cyanamid Co. 91-02-001; 03/24/93	Pirate tech. (94.5%)	427702-23	Negative for reverse mutation in Ames strains of S. typhimurium exposed up to cytotoxicity (50 ug/plate +/- S9).		Acceptable 010651
84-2(b) Mutagenic-micronucleus assay Species: mice American Cyanamid Co. 91-18-001; 03/17/93	Pirate tech. (94.5%)	427702-25	Although reportedly negative for micronucleus induction in mice treated orally up to 20 or 30 mg/kg, highest doses were neither clearly cytotoxic nor was it cytotoxic to target tissue.		Not Acceptable 010651
84-4 Mutagenic-(HGPRT) Species: CHO cells American Cyanamid Co. 91-05-001; 03/25/93	Pirate tech. (94.5%)	427702-24	Reportedly negative at doses up to 250 ug/mL +/- S9, which were not cytotoxic to guideline levels.		Not Acceptable 010651
84-4 Mutagenic-unscheduled DNA synt Species: rat hepatocytes Microbiological Associates T9775.380025; 02/23/93	Pirate tech. (94.5%)	427702-26	Negative for inducing unscheduled DNA synthesis in primary rat hepatocyte cultures exposed up to severely toxic concentrations (=> 30 ug/mL).		Acceptable 010651

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TB-1
TOX ONELINERS

CASWELL#: 962
CAS-REG#:

P.C. CODE 129093- Pirate FILE LAST PRINTED: 05/04/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-1 Acute oral LD50 Species: rat American Cyanamid Co. T-0417; 07/20/92	AC 303,630 tech., lot# AC 7504 -59A, purity 94.5%	427702-07 428842-01	LD50 (95% CL) = 626 (274-1085) mg/kg combined. LD50 (M) = 441 (195-832) mg/kg. LD50 (F) = 1152 mg/kg.	2	Acceptable 010651
81-1 Acute oral LD50 Species: rat American Cyanamid Co. T-0516; 03/19/93	AC 303,630 3SC formulation 33.3% a.i.; Lot# AC8053-87B	427702-13	LD50 (M&F) = 626 (274-1085) mg/kg. LD50 (M) = 283 (101-502) mg/kg. LD50 (F) = 999 (431-1821) mg/kg.	2	Acceptable 010651
81-2 Acute Dermal LD50 Species: rabbit American Cyanamid Co. T-0406; 07/20/92	AC 303, 630 tech. 94.5%; lot# AC 7509-59A	427702-08	LD50 > 2000 mg/kg (limit dose).	3	Acceptable 010651
81-2 Acute Dermal LD50 Species: rabbit American Cyanamid Co. T-0515; 01/18/93	AC 303,630 3SC formulation 33.3% a.i.; Lot# AC8053-87B	427702-14	LD50 (M) = 1782 (1112-2856 mg/kg). LD50 (F) > 2000 mg/kg.	2	Acceptable 010651
81-3 Acute inhalation LC50 Species: rat Bio/dynamics Inc. 91-8351; 03/25/93	AC 303,630 tech. 94.5%; Lot# 7509-59A	427702-09	Doses: 0, 0.34, 0.71, 1.8 or 2.7 mg/L in SD rats. LC50 (M) = 0.83 (0.48-1.4) mg/L. LC50 (F) > 2.7 mg/L. LC50 (M&F) = 1.9 (1.1-3.3) mg/L.	3	Acceptable 010651
81-3 Acute inhalation LC50 Species: rat Bio/dynamics Inc. 92-8396; 03/08/93	AC 303,630 3SC formulation 33.3% a.i.; Lot# AC8053-87B	427702-15	Doses: 0, 0.84, 1.9 or 2.6 mg/L in SD rats. LC50 (M) = 1.3 (0.86-2.1) mg/L. LC50 (F) = 2.4 (1.6-3.5) mg/L. LC50 (combined) = 2.1 (1.5-2.9) mg/L.	3	Acceptable 010651
81-4 Primary eye irritation Species: rabbit American Cyanamid Co. T-0404; 07/20/92	AC 303,630 tech 94.5%, Lot# 7504-59A	427702-10	Corneal opacity (4/6), iritis (2/6) and conjunctivitis (6/6) were observed at 48 hrs. Iritis was resolved in 72 hrs, however, corneal opacity (1/6) and conjunctivitis (6/6) were present. Normal by day 7.	3	Acceptable 010651

P.C. CODE 129093- Pirate FILE LAST PRINTED: 05/04/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-4 Primary eye irritation Species: rabbit American Cyanamid Co. T-0513; 12/04/92	AC 303,630 3SC formulation 33.3% a.i.; Lot# AC8053-87B	427702-16	Slight to moderate conjunctivitis (6/6) was observed at one and 24 hrs; had resolved by 48 hrs.	3	Acceptable 010651
81-5 Primary dermal irritation Species: rabbit American Cyanamid Co. T-0405; 07/20/92	AC 303,630 tech 94.5%, Lot# 7504-59A	427702-11	Non irritating to rabbit skin.	4	Acceptable 010651
81-5 Primary dermal irritation Species: rabbit American Cyanamid Co. T-0514; 01/18/93	AC 303,630 3SC formulation 33.3% a.i.; Lot# AC8053-87B	427702-17	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 hr. post dosing were observed. At 48 hr. examination, 1/6 exhibited slight erythema which resolved by 72 hrs.	4	Acceptable 010651
81-6 Dermal sensitization Species: guinea pig American Cyanamid Co. T-0439; 03/26/93	AC 303,630 tech 94.5%, Lot# 7504-59A	427702-12	Not a skin sensitizer.		Acceptable 010651
81-6 Dermal sensitization Species: guinea pig American Cyanamid Co. T-0530; 03/05/93	AC 303,630 3SC formulation 33.3% a.i.; Lot# AC8053-87B	427702-18	Not a skin sensitizer.		Acceptable 010651

IV. Toxicology Profile Updated: 10/20/93

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 - 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 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#: 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

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

V. Data Gaps:

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

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V. **Data Gaps:**

The toxicity data requirements for an **Experimental Use Permit** appear adequate, except for the Gene mutation - mammalian system and chromosomal aberrations using mouse micronucleus assay test. Although these tests will not be required for this EUP (see IX.B.), the registrant will be required to submit an acceptable mammalian Gene mutation and a 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 it prior to the second year renewal.

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. It appears that males are more sensitive than females; oral administration resulted in increased absorption over dermal route of administration. Acute toxicity of the technical and the formulation are similar (even though the formulation is only 36% a.i.) which is possibly a result of increased absorption of a.i. due to surfactants and solvents in the formulation. 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.

B. **Mutagenicity** - The current mutagenicity guidelines require 3 studies: Ames and a mammalian Gene mutation assays as well as an acceptable chromosomal aberration assay. The current mammalian test is unacceptable and the chromosomal aberration assay is a non-test due to no

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

The sponsor explained that based on the low NOEL, for 90-Day dog of 4.23 mg/kg/day, and rabbit developmental study, of 5 mg/kg/day, supports a preliminary acceptable daily intake (PADI) of 4.2 µg/kg b.w./day or 0.25 mg for a 60 kg person. Also, the maximum daily exposure or theoretical maximum residue contribution (TMRC) of AC 303,630 in cotton seed is 0.001 mg/day (assuming daily diet intake of 1.5 kg and a cotton seed factor of 0.15%) at the proposed temporary tolerance of 0.5 ppm. This would utilize only 0.4% of PADI.

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).

Note to RD: The remainder of the data submitted with this package has not been reviewed. It has been attached to a new subordinate data package for S442669 with a DP barcode of D196061. These data are currently considered low priority by HED and have been assigned a due date of May 30, 1994.

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