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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: 510 SEC18-OC. Lambda-Cyhalothrin (Karate® Insecticide). Emergency Exemption for Use on Dry Bulb Onions to Control Thrips

Tox. Chem. No. 725C
Related Tox. Chem. No. 271F
Project No. D177571

TO: Andrea Beard (PM Team # 41)
Registration Division (H7505C)

FROM: Pamela M. Hurley, Toxicologist Pamela M. Hurley 5/14/92
Section I, Toxicology Branch I
Health Effects Division (H7509C)

THRU: Roger L. Gardner, Section Head Roger Gardner 5-19-92
Section I, Toxicology Branch I
Health Effects Division (H7509C) KB 5/22/92

Submission No. S416808

Background and Request:

The State of Washington has applied for an emergency exemption for use of Karate™ Insecticide, containing Lambda-cyhalothrin on dry bulb onions to control thrips. The formulation will be sprayed either by ground or air equipment at a rate of 2.56 to 3.84 fluid ounces (0.02 to 0.03 lbs. ai) per acre per application. No more than 3 applications will be conducted per season. A maximum of 585 gallons (585 lbs. a.i.) will be used over 6500 acres. The Toxicology Branch has been asked to determine if the toxicology database can support this use and to advise whether there are worker exposure concerns.

Toxicology Branch Response:

The Toxicology Branch (TB-I) has previously examined the toxicology database in support of a permanent tolerance on dry bulb onions and has found that all the toxicity data base requirements have been satisfied (see memorandum from P. Hurley to A. Heyward, dated 4/16/92). No additional toxicity tests are required at this time. Therefore, TB-I has no objections to granting the experimental use permit for Karate™ Insecticide on dry bulb onions. The following pages contain the toxicology

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profile for lambda cyhalothrin and those requirements that have been satisfied for a permanent registration and tolerance.

Data Requirements (CFR 158.135):

Technical: Lambdacyhalothrin
Action Type: Tolerance
Last Updated: 6/28/91

		Required	Satisfied
81-1	Acute Oral Toxicity	Yes	Yes
82-1(a)	Subchronic Oral (rodent)	Yes	Yes
83-1(a)	Chronic Toxicity (rodent)	Yes	Yes
83-1(b)	Chronic Toxicity (nonrodent)	Yes	Yes
83-2	Oncogenicity (mouse)	Yes	Yes
83-5	Oncogenicity (rat)	Yes	Yes
83-3(a)	Teratology (first species)	Yes	Yes
83-3(b)	Teratology (second species)	Yes	Yes
83-4	Multigeneration Reproduction	Yes	Yes
84-2(a)	Mutagenicity - Gene Mutation	Yes	Yes
84-2(b)	Mutagenicity - Structural Chromosomal Aberrations	Yes	Yes
84-2(c)	Mutagenicity - Other Genotoxic Effects	Yes	Yes
85-1	Metabolism (pure active ingred.)	Yes	Yes

Formulation: Karate® (13.1% a.i.)
Use Pattern: Insecticide, emulsifiable concentrate; used with ground or air equipment
Action Type: For Label Requirements
Last Updated: 4/1/91

		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

Toxicology Profile

Last Updated: 1/16/91

Technical grade lambdacyhalothrin

Guide-line #	Study Identification and Classification	Results
81-1	Acute Oral Toxicity in Rats MRID/Accession 259805 Report # AR-3279, 3377 Date: 1/9/85 Acceptable	LD_{50}: 79 mg/kg (males) LD_{50}: 56 mg/kg (females) TOXICITY CATEGORY: II Decreased activity, splayed gait, dehydration, upward curvature of spine, urinary incontinence, piloerection, salivation, pinched-in sides. No macroscopic signs.
81-2	Acute Dermal Toxicity in Rats MRID/Accession: 259805 Report # CR1690 Date: 1/11/85 Acceptable	LD_{50}: 632 mg/kg (males) LD_{50}: 696 mg/kg (females) TOXICITY CATEGORY: II Decreased activity, tiptoe gait, splayed gait, loss of stability, dehydration, signs of urinary incontinence, upward curvature of spine.
81-4	Primary Eye Irritation in Rabbits MRID/Accession 259805 Report # FB3152 Date: 1/29/85 Acceptable	Maximum Mean Score: 11.3 TOXICITY CATEGORY: II Mild irritant to the rabbit eye.
81-5	Primary Dermal Irritation in Rabbits MRID/Accession 259805 Report # EB2430 Date: 1/11/85 Acceptable	Primary Irritation Score: 0 TOXICITY CATEGORY: IV Not irritating to rabbit skin.

Toxicology Profile

Last Updated: 1/16/91

Technical grade lambdacyhalothrin

Guide-line #	Study Identification and Classification	Results
81-6	Dermal Sensitization in Guinea Pigs MRID/Accession 259805 Report # GG2940 Date: 7/17/84 Acceptable	Does not appear to be a sensitizer under the conditions of the study.
82-1 (a)	Subchronic Feeding in Rats (13 weeks) MRID/Accession 073980 Report # PRO584 Date: 2/14/85 Core Grade: Guideline	NOEL: 50 ppm LOEL: 250 ppm Effects: decrease in body weight gain. Levels tested 0, 10, 50, 250 ppm.
82-2	21-day dermal study in Rabbits MRID/Accession 073203 Report # LB 0023 Date: 3/16/82 Core Grade: Minimum	NOEL: > 1000 mg/kg/day LOEL: N/A Effects: Conducted on cyhalothrin. Dose levels tested: 10, 100, 1000 mg/kg/day, 6 hr./day, 5 day/week. Irritation due to occlusive dressing. Animals had coccidiosis. No clinical signs of systemic toxicity at any level.
83-1	Chronic feeding study in dogs MRID 400179-02 Report # PD05-83, CTL/P1316 Date: 1/22/86 Core Grade: Guideline	NOEL: 0.5 mg/kg/day LOEL: 3.5 mg/kg/day Effects: Levels tested: 0, 0.1, 0.5, 3.5 mg/kg/day by capsule. Clinical signs of neurotoxicity including ataxia, muscle tremors, convulsions. Liquid feces at highest dose level.

Toxicology Profile

Last Updated: 1/16/91

Technical grade lambdacyhalothrin

Guide-line #	Study Identification and Classification	Results
83-2 (a)	Oncogenicity study in mice MRID/Accession 073214-073216 Report # PMO 400 Date: 5/31/84 Core Grade: Minimum	Oncogenic NOEL: > 500 ppm Systemic NOEL: 100 ppm Systemic LOEL: 500 ppm Effects: Conducted on cyhalothrin. Levels tested - 0, 20, 100 & 500 ppm. Decreased body weight gain.
83-3	Teratology Study in Rabbits MRID/Accession 073206 Report # RB 0169 Date: 6/81 Core Grade Minimum	Maternal NOEL: 10 mg/kg/day Maternal LOEL: 30 mg/kg/day Effects: Conducted on cyhalothrin. Levels tested - 0, 3, 10, 30 mg/kg/day. Decreased body weight gain. Developmental NOEL: 30 mg/kg/day. Effects: None reported.
83-3	Teratology Study in Rats MRID/Accession 073206 Report # 0170 Date: 6/81 Core Grade Minimum	Maternal NOEL: 10 mg/kg/day Maternal LOEL: 15 mg/kg/day Effects: Levels tested: 0, 5, 10, 15 mg/kg/day. Conducted on cyhalothrin. Reduced body weight and food consumption. Developmental NOEL: > 15 mg/kg/day Effects: A/D ratio 10/15 = 0.7

Toxicology Profile

Last Updated: 1/16/91

Technical grade lambdacyhalothrin

Guide-line #	Study Identification and Classification	Results
83-4	Multigeneration Reproduction Toxicity in Rats MRID/Accession 073207-073209 Report # CTL/P/906 Date: 5/13/84 Core Grade Guideline	Maternal NOEL: 10 ppm Maternal LOEL: 30 ppm Effects: Conducted on cyhalothrin. Levels tested - 0, 10, 30, 100 ppm. Reduced body weight gain during pregnancy. Reproductive NOEL: 10 ppm Reproductive LOEL: N/A Effects: Decrease in body weight gain during weaning.
83-5	Chronic feed/oncogenicity study in rats MRID/Accession 073210-073212 Report # PRO414 Date: 6/27/84 Core Grade: Guideline	NOEL: 50 ppm LOEL: 250 ppm Effects: Conducted on cyhalothrin. Levels tested: 0, 10, 50, 250 ppm. Reduced body weight gain. No oncogenic effects.
84-2 (a)	Gene Mutation Assay (Ames Test) MRID/Accession 073981 Report # YV1309 Date: 7/12/84 Acceptable	Not mutagenic under conditions of assay. Tested from 1.6 - 5000 ug/plate with & without metabolic activation. Compound precipitated at 1000 and 5000 ug/plate indicating limit of solubility.
84-2 (a)	Gene Mutation Assay (Mouse Lymphoma Cells) MRID/Accession 073981 Report # CTL/P/1340 Date: 8/9/85 Acceptable	Tested at dose levels ranging from 125-4000 ug/ml. Chemical precipitated at all dose levels, particularly higher levels. PP321 did not appear to be mutagenic under conditions of study.

Toxicology Profile

Last Updated: 1/16/91

Technical grade lambdacyhalothrin

Guide-line #	Study Identification and Classification	Results
84-2 (b)	Structural Chromosomal Aberration Assay (In vitro cytogenetics in human lymphocytes) MRID/Accession 073981 Report # CTL/P/1333 Date: 7/3/85 Acceptable	Tested at 100, 500 and 1000 ug/ml. Levels based on limit of solubility. Under conditions of bioassay, PP321 was not a clastogen.
84-2 (c)	Other Genotoxicity Assays (Mouse Micronucleus) MRID/Accession 073981 Report # CTL/P/1090 Date: 10/31/84 Acceptable	Test animals given a single i.p. dose of either 35 mg/kg or 22 mg/kg. Number per 500 polychromatic erythrocytes containing micronuclei were scored. No increase in number of micronuclei were found when compared to controls.
85-1	Metabolism - rat MRID/Accession 073217 Report # 1468814 KMR 002/01 Date: 10/08/81 Acceptable in combination with other studies	55% oral absorption. Extensively metabolized when absorbed. After s.c. admin., urinary/fecal excretion ratio 2.5:1.0. Over 50% of dose remained in carcass 7 days after s.c. dose. Metabolism includes cleavage of ester to cyclopropylcarboxylic acid & phenoxybenzyl deriv. Conducted on cyhalothrin.
85-1	Metabolism - rat MRID/Accession Report # 1468814 KMR 002/03 Date: 9/13/84 Acceptable in combination with other studies	Distribution patterns & excretion rates in multiple oral dose studies similar to single oral dose studies. Accumulation of unchanged compound in fat upon chronic admin. Otherwise, rapidly metabolized & excreted. Conducted on cyhalothrin.

Toxicology Profile

Last Updated: 1/16/91

Technical grade lambdacyhalothrin

Guide-line #	Study Identification and Classification	Results
85-1	Metabolism - rat MRID/Accession 073217 Report # MPH 01 Date: 3/23/83 Acceptable in combination with other studies	Cyclopropyl carboxylic acid, 3-phenoxybenzoic acid, glucuronide conjugate 3-4'-hydroxyphenoxy)benzoic acid and sulfate conjugation identified in urine. Conducted on cyhalothrin.
85-1	Metabolism - rat MRID/Accession 073981 Report # URO169 Date: 7/31/84 Acceptable in combination with other studies	Cyhalothrin taken up slowly by fat & released slowly. Rapidly released by blood, kidneys, liver. Rate of metabolism of both enantiomer pairs likely identical (i.e. PP321 & PP563).
85-1	Metabolism - rat MRID/Accession 073981 Report # URO178 Date: 3/19/85 Acceptable in combination with other studies	Absorption, distribution, metabolism & excretion patterns of PP321 & cyhalothrin following single dose of 1 mg/kg in male rat appear to be identical.
85-1	Metabolism - dog MRID/Accession 073217 Report # 146814 KMD 005 Date: 9/17/84 Acceptable	Absorption of C^{14} benzyl label 80% & of C^{14} cyclopropyl label 48%. Metabolite patterns different, indicating extensive cleavage of ester bond. 7 metabolites identified for benzyl (urine) and 12 metabolites identified for isopropyl label. In feces, large proportion radioactivity due to unchanged compound. Excretion in urine & feces rapid (nearly all in 48 hrs.). Cyhalothrin tested.

Toxicology Profile

Last Updated: 4/1/91

13.1 % Formulation - Karate® Insecticide

Guide-line #	Study Identification and Classification	Results
81-1	Acute Oral Toxicity in Rats MRID/Accession 259805 Report # AR 3617 Date: 4/25/85 Acceptable	LD_{50}: 64 mg/kg (males) LD_{50}: 101 mg/kg (females) TOXICITY CATEGORY: II Ataxia, reduced stability, chromodacryorrhea, lacrimation, piloerection, salivation, urinary incontinence/signs of incontinence and upward curvature of spine. No macroscopic abnormalities.
81-2	Acute Dermal Toxicity in Rats MRID/Accession 259805 Report # CR1933 Date: 4/24/85 Acceptable	LD_{50}: > 2 ml/kg (both sexes) TOXICITY CATEGORY: III One female was killed <u>in extremis</u> on day 4. Signs of moderate skin irritation (erythema, desquamation, edema, thickening, wrinkling, necrosis and scabbing). Ataxia, reduced stability, chromodacryorrhea, lacrimation, piloerection, salivation, urinary incontinence/signs of incontinence and upward curvature of spine. No macroscopic abnormalities.
81-3	Acute Inhalation Toxicity in Rats MRID/Accession 259805 Report # HRO563 Date: 8/9/85 Acceptable	LC_{50}: 0.315 mg/l (males) LC_{50}: 0.175 mg/l (females) (Four hour exposure) TOXICITY CATEGORY: II At top dose level animals showed respiratory abnormalities (gasping), central nervous system activity (reduced reflexed) and convulsions. Other effects noted included respiratory irritation, piloerection and hunched posture.

Toxicology Profile

Last Updated: 4/1/91

13.1 % Formulation - Karate® Insecticide

Guide-line #	Study Identification and Classification	Results
81-4	Primary Eye Irritation in Rabbits MRID/Accession 259805 Report # NY/83-33B Date: 12/18/84 Acceptable	Maximum Mean Score: 20.7 TOXICITY CATEGORY: II Moderately irritating to unwashed eyes & mildly irritating to washed eyes.
81-5	Primary Dermal Irritation in Rabbits MRID/Accession 259805 Report # EB2657 Date: 6/4/85 Acceptable	Primary Irritation Score: 6.7 TOXICITY CATEGORY: 1 Extremely irritating to rabbit skin.
81-6	Dermal Sensitization in Guinea Pigs MRID/Accession 259805 Report # GG3112 Date: 4/18/85 Acceptable	Mild sensitizer under conditions of study.
82-4	21-Day Inhalation Study in Rats MRID 413877-02 Report # CTL/P/2772 Date: 1/16/90 Guideline	81.5% pure material tested at dose levels of 0.3, 3.3 & 16.7 ug/l. NOEL: 0.3 ug/l. LOEL: 3.3 ug/l (decreased bodyweight gains; clinical signs of toxicity; punctate foci on cornea; raised prothrombin time; changes in clinical chem., hematology and urinalysis; and a slight increase in incidence of alveolitis in females).

Data Gaps: The long term studies conducted on cyhalothrin have been used in partial fulfillment of the toxicity data requirements for lambdacyhalothrin. Lambdacyhalothrin consists of 2 of the 4 enantiomers of cyhalothrin. On the basis of structural considerations and metabolism and subchronic data on both lambdacyhalothrin and cyhalothrin, TB has previously accepted the long term data on cyhalothrin in partial fulfillment of the toxicity study requirements for lambdacyhalothrin (see original tolerance request for cotton, memorandum from P. Hurley to G. LaRocca, dated 7/20/86). Extensive metabolism studies have been conducted on the purified form of cyhalothrin. A comparative study between cyhalothrin and lambdacyhalothrin has indicated that their absorption, distribution, metabolism and excretion patterns are identical following a single 1 mg/kg dose in the male rat. Therefore, TB has also previously accepted the metabolism studies conducted on cyhalothrin along with the comparison study mentioned above in fulfillment of the metabc studies required for lambdacyhalothrin (see memorandum from P. Hu to G. LaRocca, dated 7/20/86).

Actions Being Taken to Obtain Additional Information or Clarification: None.

Reference Dose (RfD):

The recommended RfD (to the RfD Workgroup) is 0.005 mg/kg/day. This value was calculated by using the 3-generation rat reproduction study NOEL of 0.5 mg/kg/day and a safety factor of 100. This RfD has been verified or approved by the Health Effects Division and the Agency RfD Committee.

Pending Regulatory Actions: None.

Toxicologic Issues Pertinent to This Request: None.

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