US EPA ARCHIVE DOCUMENT

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

002218

10/8/82

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Franklin D. R. Gee, Product Manager #17
Registration Division (TS-767)

SUBJECT: EPA Reg. No. 10182-EUP-GE, FAP 2H5362. Request for EUP and for Establishing a Food Additive Tolerance of 0.05 ppm in/on (All) Foods, Resulting From Application of Cypermethrin in Accordance with the Provisions of an EUP.

TOX Chem. No. 271DD

The ICI Americas Inc. is requesting an EUP and a food additive tolerance to use as much as 800 lbs. of a.i. (Cypermethrin) at the rate of up to 2 lbs. a.i. per site trial in tests to control 24 insect pests in and around various outdoor and indoor sites including stores, schools, restaurants, food manufacturing places, nursing homes and other places where humans frequent and/or food is handled. See attached label. The tests will be conducted in 38 states of the United States. The product will be applied as a crack and crevice, spot, general contact and residual spray at an application concentration of 0.125% to 0.25% a.i. The EUP request is for 2 years.

Recommendations and Conclusions:

1. Toxicology data referenced in support of this action includes a mouse oncogenesis study submitted by the ICI Americas, Inc. (EPA Acc. No. 071072) which shows that there were 13/60 females (21.7%) with alveologenic tumors in the high dose group versus only 8/121 females (6.6%) in the control groups. The low and mid dose female groups had 6/61 (9.8%) and 7/60 (11.7%) incidences of this tumor type. Toxicology Branch has not yet completed its review of this study (or other studies submitted September 1, 1982 and related to PP 2F2623). However, since TB has established that the structurally related synthetic pyrethroid permethrin, caused increased incidences of alveologenic tumors in female mice, TB is seriously concerned about the potential of cypermethrin to produce similar tumors. No further indoor uses or tolerances with cypermethrin will be approved by Toxicology Branch pending review of these studies and establishment of a policy for regulating permethrin.

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2. The inerts in this product (DEMON™ 40 WP Insecticide) are cleared for the proposed use (see inert clearance sheet attached).

3. Four new acute studies and a sensitization study with guinea pigs were submitted and reviewed. The label has a WARNING signal word consistent with eye irritation data.

The acute oral LD50 study was determined to be incomplete pending submission of the complete necropsy report and tables showing the individual animal behavioral signs with dose and time. The report as presented indicates possible lung and other tissue damage in the survivors. The registrant must clarify the sequelae of the acute toxicity of this product.

4. The label should be changed to include a statement which says that some individuals may develop an allergic reaction.

Summary of Studies Reviewed (DEMON WP)

Study	Result	Core Classification
1. Acute Oral LD50, rats	1.817 (0.87-3.80) gm/kg for both sexes Tox Cat III	Reserved
2. Acute Dermal LD50, rabbits	> 2000 mg/kg for both sexes Tox Cat III	Minimum
3. Primary Eye Irritation, rabbits	Corneal involvement reversed after 4 days Tox Cat II	Guidelines
4. Primary Skin Irritation, rabbits	PII = 1.06 Tox Cat IV	Guidelines
5. Delayed Contact Sensitization, guinea pig	Potential sensitizer	Minimum

STUDIES REVIEWED

The following studies were conducted by the Wil Research Laboratories, Cincinnati, Ohio with Cypermethrin 40 WP (DEMON™ 40 WP). These can be found in EPA Accession No. 247845.

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Acute Oral Toxicity Study in Albino Rats with Cypermethrin 40 WP (# WIL-81328, March 11, 1982).

Five groups of 10 Sprague-Dawley rats, (5 males and 5 females) were dosed with 0.25, 1.0, 2.0, 3.125 and 5.0 gm/kg of Cypermethrin product (40 WP, a powder) and observed for 14 days. The test material was dispersed in distilled water and administered by gavage.

Results:

LD50's of

1.904 (1.071-3.386) gm/kg for males
0.808 (0.591-1.105) gm/kg for females
1.817 (0.87-3.796) gm/kg for both sexes were determined.

A variety of clinical signs resulted which included severe convulsions, tremors, lethargy, ataxia, inactivity and salivation. Deaths occurred between 2 hours and 1 day. Some of the symptoms persisted for several days. Necropsy revealed several findings which were related to the test chemical. These included hemorrahages and congestion in the survivors (14 days after treatment) in the brain, stomach, and lungs. The report as presented implies that the test material causes long lasting (greater than 14 days) injury to the internal organs.

Core Classification of this study is reserved. The registrant must provide the complete necropsy reports and tables showing the individual animal behavior responses versus time.

Acute Dermal Toxicity Study in Albino Rabbits with Cypermethrin 40 WP (#WIL-81329, Feb. 9, 1982)

Ten rabbits (New Zealand White) (5 males and 5 females) were prepared by clipping and abrading and Cypermethrin 40 WP was applied at a dose level of 2 gm/kg and kept in place for 24 hours. The rabbits were observed for 14 days.

No signs of systemic toxicity or changes in behavior were reported as resulting. Necropsy after 14 days was unremarkable. There were definite signs of local irritation to the product.

This study is Core Minimum. Toxicity Category III. The LD50 is > 2000 mg/kg for both sexes.

Acute Eye Irritation Study in Albino Rabbits with Cypermethrin 40 WP (#WIL-81330, Feb. 9, 1982)

Nine rabbits (4 males and 5 females) were dosed with 100 mg of test material (Cypermethrin 40 WP) directly into their eyes. After application the treated eyes of 3 of these rabbits were rinsed with lukewarm distilled water. The rabbits were observed for 14 days for eye irritation and other toxic signs.

Signs of corneal opacity were noted in all six of the unrinsed eyes and only 1 in 3 of the rinsed eyes. All rabbits were reported as having an irregular corneal surface not including opacity. The cornea was reported as being free of effects after day 4. Other signs of irritation persisted to day 10 (mild signs of conjunctivae irritation).

This study is Core Guidelines. Toxicity Category II. A Warning signal label based on eye irritation will be required.

Primary Skin Irritation Study in Albino Rabbits with Cypermethrin 40 WP (#WIL-81331, Feb. 9, 1982)

Six rabbits, 3 males and 3 females (New Zealand White) were prepared by clipping and abrading and dosed with 0.5 gm of test material (Cypermethrin 40 WP) and kept in place for 24 hours.

A PII was determined to be 1.06.

This study is Core Guidelines. Toxicity Category IV. It should be noted that the dermal LD50 test resulted in indications of a higher degree of dermal irritation when a higher level of test material was applied.

Delayed Contact Hypersensitivity in Guinea Pigs with Cypermethrin 40 WP (#WIL-81332, Feb. 9, 1982)

Thirty guinea pigs (Hartley albino, 15 males and 15 females) were grouped as 10 controls and 20 test animals. They were prepared by clipping and dosed with 25%, 10%, 5.00%, 2.5%, 1.25% and 0.75% w/v solution of Cypermethrin 40 WP. A preliminary experiment indicated that a 25% preparation was the highest concentration which could be applied without primary irritation. The doses were applied as 0.5 ml of test solution to 4 pigs at each dose level. Contact was allowed for 6 hours with the material being kept in place with rubber dental daming. Inductions were made three times each week for a total of 10 applications. The challenge application was made two weeks after the last induction application. The challenge was made by applying a 25% solution of Cypermethrin 40 WP.

Results:

The challenge application resulted in a low grade positive response as indicated by slightly higher irritation scores in both incidences and severity when compared to the controls. The testing laboratory determined that Cypermethrin 40 WP is a potential sensitizer.

Conclusion:

Cypermethrin 40 WP must be considered as a potential sensitizer. Note that other studies with cypermethrin formulations have also indicated a potential for sensitization. This study is Core Minimum. No positive control was used.

John Doherty, Ph.D. October 8, 1982
Toxicology Branch
Hazard Evaluation Division TS-769
OEF 10/8/82 10/8/82

OPP:HED:TOX:J.DOHERTY:sb 9/7/82re:9/22/82 X73711 Rm. 814 #ml5

CYPERMETHRIN TOXICOLOGY REVIEWS

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___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

x A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

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