8-2-88

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: EPA Registration No. 100-542
Technical Prometryn

FROM: Mary L. Waller
Technical Support Section
Fungicide-Herbicide Branch
Registration Division (TS-767C)

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (TS-767C)

APPLICANT: Ciba-Geigy Corporation
Agricultural Division
P.O. Box 18300
Greensboro, NC 27419

ACTIVE INGREDIENT:
Prometryn: 2,4-bis(isopropylamino)-6-(methylthio)-s-triazine 97%
INERT INGREDIENTS: 3%

BACKGROUND:

The registrant has submitted two primary eye irritation studies, an acute oral, acute dermal, primary skin irritation, acute inhalation and dermal sensitization study. One primary eye irritation study was conducted by Pharmaceuticals Division of Ciba-Geigy Corporation. All other studies were conducted by Stillmeadow, Inc. The MRID numbers are 404575-08 through -14. The method of support was not indicated.

RECOMMENDATION:

FHB/TSS finds the data acceptable and the signal word is "CAUTION."

The registrant should be informed that the acute dermal toxicity study was classified as Core Minimum Data. The study contains a contradiction; however, it does not affect the outcome of the study. On page 11, in the second paragraph, it is stated that gross necropsy findings indicate that the abnormalities observed in the two mortalities were treatment related. In the next paragraph, it is stated that the deaths were thought not to be treatment related. This contradiction should be corrected.

LABELING:

Revise Statement of Practical Treatment for dermal exposure as follows: "Wash with plenty of water. Get medical treatment."

REVIEW:

(1) Acute Oral Toxicity Study: Stillmeadow, Inc.; Study no. 5009-87; MRID no. 404575-08; 11-16-87.

PROCEDURE:

Three groups of 5 male and 5 female albino rats were administered by oral intubation either 3500, 4500 or 5050 mg/kg of test material administered as a 25.0% w/v concentration in 0.5% w/v aqueous carboxymethyl cellulose. Animals were observed three times on day of dosing and at least once daily thereafter for 14 days. Body weights were recorded prior to dosing and on days 7 and 14. Animals were necropsied upon discovery of death.

RESULTS:

At 3500 mg/kg, no deaths occurred. At 4500 mg/kg, 2/5 males and 3/5 females died. At 5050 mg/kg, 3/5 females and 5/5 males died. The LD_{50} for males was reported to be 4786 (4227-5419) mg/kg. The LD_{50} for females was reported to be 4455 (4243-4673) mg/kg.

Toxic symptoms observed were activity decrease, body tremors, constricted pupils, diarrhea, emaciation, lacrimation, piloerection, polyuria, ptosis, salivation, and sensitivity to touch. Gross necropsy revealed discoloration of the contents of the gastrointestinal tract, discoloration of the kidneys, and testes withdrawn into abdominal tract.

STUDY CLASSIFICATION: Core Guideline Data

TOXICITY CATEGORY: Category III - CAUTION

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(2) Acute Dermal Toxicity Study: Stillmeadow, Inc.; Study no. 5010-87; MRID no. 404575-09; 11-16-87.

PROCEDURE:

Five male and five female albino rabbits were administered a topical application of 2020 mg/kg of test material moistened with 1.60 ml/kg of saline. The moistened test material was applied to the previously shaven dorsal surface of each animal's trunk and covered with occlusive wrap for 6 hours of exposure. An additional group of 5 males was dosed with 2020 mg/kg. Animals were observed at 1/2, 3 and 6 hours after treatment and once daily thereafter for 14 days. Body weights were recorded prior to treatment and on days 7 and 14. Animals were necropsied.

RESULTS:

At 2020 mg/kg, 2/5 males died. No deaths occurred in the second group of males dosed at 2020 mg/kg. The LD_{50} was reported to be > 2020 mg/kg. Toxic symptoms observed were activity decrease, decreased or no defecation, decreased urination and small feces. Gross necropsy revealed no abnormalities in study survivors. Gross necropsy of the study mortalities revealed discoloration of the contents of the small intestine, gas in the small intestine and green slurry in the intestines.

STUDY CLASSIFICATION:

Core Minimum Data - See comments under Recommendation.

TOXICITY CATEGORY: Category III - CAUTION

(3) Acute Inhalation Toxicity Study: Stillmeadow, Inc.; Study no. 5014-87; MRID no. 404575-10; 11-5-87.

PROCEDURE:

Five male and five female albino rats were exposed for 4 hours in a 200 L stainless steel dynamic flow inhalation chambers to an aerosol generated from the test material having a mean gravimetrically measured concentration of 5.17 mg/L. Animals were observed during exposure and at least once daily thereafter for 14 days. Body weights were recorded prior to exposure and at 7 and 14 days. Animals were necropsied at study conclusion.

RESULTS:

No deaths occurred. The LD_{50} was reported to be > 5.17 mg/L. Toxic symptoms observed were activity decrease, nasal discharge, piloerection and ptosis. No abnormalities were noted at necropsy.

STUDY CLASSIFICATION: Core Guideline Data
TOXICITY CATEGORY: Category IV - CAUTION

(4) Primary Eye Irritation Study: Stillmeadow, Inc.; Study no. 5011-87; MRID no. 404575-11; 9-17-87.

PROCEDURE:

Nine albino rabbits were each administered 100 mg of test material which was placed in the conjunctival sac of the right eye of each animal. The treated eyes of 3/9 animals were rinsed for 30 seconds after test material instillation. Eye irritation was scored at 1, 24, 48 and 72 hours.

RESULTS:

In the unwashed group, at 24 hours 5/6 animals exhibited conjunctivae redness (5/6 = 1) and at 72 hours, all irritation had cleared. In the washed group, 3/3 animals exhibited conjunctivae redness (3/3 = 1) and 3/3 animals exhibited discharge (1/3 = 2, 2/3 = 1). At 24 hours, all irritation has subsided.

STUDY CLASSIFICATION: Core Guideline Data

TOXICITY CATEGORY: Category III - CAUTION

(5) Primary Eye Irritation Study: Pharmaceuticals Division, Ciba-Geigy Corporation; Study no. 218-84; MRID no. 404575-12; 10-19-84.

PROCEDURE:

Nine New Zealand White rabbits were each administered 100 mg of test material which was placed in the conjunctival sac of the right eye of each animal. The treated eyes of 3/9 animals were rinsed 30 seconds after dosing. Eye irritation was scored at 1, 24, 48 and 72 hours.

RESULTS:

Eye irritation in the washed group was scored as follows: at one hour, conjunctivae redness (3/3 = 1) and chemosis (2/3 = 1); and at 24 hours, all irritation had cleared.

Eye irritation in the unwashed group was scored as follows: at one hour, conjunctivae redness (1/6 = 2, 5/6 = 1), and chemosis (2/6 = 1); at 24 hours, conjunctivae redness (4/6 = 1); and at 48 hours, all irritation had subsided.

STUDY CLASSIFICATION: Core Guideline Data

TOXICITY CATEGORY: Category III - CAUTION

(6) Dermal Sensitization Study: Stillmeadow, Inc.; Study no. 5013-87; MRID no. 404575-14; 10-28-87.

PROCEDURE:

Two groups of 10 Hartley-albino guinea pigs were administered induction treatments to the previously shaven dorsal trunk on days, 1, 3, 6, 8, 10, 13, 15, 17, 20, and 22. Induction treatments consisted of the following: the test group received 500 mg of test material moistened with 0.5 ml of deionized water and the positive control group received 0.05% w/v solution of 2,4-dinitrochlorobenzene in ethanol. Each treatment was covered with occlusive wrap for 6 hours and animals were restrained during exposure. On day 36, each group was challenged at the previously treated test site and at a virgin test site. Skin irritation was scored at 24 hours after each treatment and at 48 hours after the first induction treatment and challenge treatment.

RESULTS:

The positive control group exhibited very slight erythema after the 3rd induction treatment. Severity of irritation and number of animals involved increased with subsequent treatments. At the last induction treatment, the positive control group exhibited moderate to severe erythema and slight to moderate edema. One animal in the positive control group died prior to challenge treatment. At challenge, 9/9 positive control animals exhibited very slight to well-defined erythema and very slight to well-defined edema.

The test group did not exhibit any irritation during the induction or challenge phase.

STUDY CLASSIFICATION: Core Guideline Data

TOXICITY CATEGORY: Nonsensitizer

(7) Primary Skin Irritation Study: Stillmeadow, Inc.; Study no. 5012-87; MRID no. 404575-13; 10-8-87.

PROCEDURE:

Six New Zealand White rabbits were each administered 500 mg of test material moistened with 0.5 ml of saline topically to a previously shaven test site located on the dorsal area of the trunk of each animal. Each test site was covered with occlusive wrap for 4 hours. After exposure, the wrap and residual test material were removed. Skin irritation was scored at 1, 24, 48 and 72 hours.

RESULTS: No irritation was observed.

STUDY CLASSIFICATION: Core Guideline Data

TOXICITY CATEGORY: Category IV - CAUTION