4-22-83

005019

Date: April 22, 1983

Subject: EPA Registration Number: 100-607 (1)
Ridomil 2E Fungicide

EPA Registration Number: 100-619 (2)
Subdue 2E Fungicide

EPA Registration Number: 100-626 (3)
Apron 2E Fungicide

From: Delores F. Graham
FHB/JB — F 4/26/83

To: Henry Jacoby
Product Manager (21)

Applicant: CIBA-GEIGY Corporation
Agricultural Division
P.O. Box 18300
Greensboro, NC 27419

Active Ingredients: (1)(2)(3)
Metalaxyl: N-(2,6-dimethylphenyl)-N-(methoxyacetyl) alanine-methyl ester 25.1%
Inert Ingredients 74.9%

Background: Submitted Acute Oral, Acute Dermal, Acute Inhalation, Eye Irritation, Skin Irritation and Dermal Sensitization studies. Studies conducted by Stillmeadow, Inc. and Toxigenics, Inc. Data under accession number 249614. Method of support ~~not~~ indicated as not applicable.

Recommendations:
(1) FHB/JB finds these data acceptable to support

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conditional registration of this product.

(2) The appropriate signal word is WARNING

Label:

(1) The precautionary statement must be revised to include "Causes eye injury".

(2) The statement of practical treatment must be revised to included, "If swallowed drink 1 and 2 ~~glasses~~ of water and induce vomiting by placing fingers in back of throat and call a physician, hospital or local poison control center." If inhaled remove victim to fresh air. If not breathing give artificial respiration, preferably mouth-to-mouth. Get medical attention.

(3) See enclosed copy for appropriate storage and disposal statements.

Review:

(1) Acute Oral Toxicity Study: Stillmeadow, Inc.; Project # 2834-82; January 27, 1983.

Procedure: 5 groups consisting of five males each ~~received~~ received one of the following doses: 1000, 2240, 2800, 3500 and 5010 mg/kg. 5 groups consisting of five females each received one of the following doses: 1000, 1210, 1480, 1790 and 2800 mg/kg. Observations made at least three times on the day of treatment, ~~and~~ then daily thereafter for 14 days.

Necropsy performed on all animals.

Results: At 1210 mg/kg, 2/5 F died; at 1480 mg/kg, 4/5 F died; at 1790 mg/kg, 5/5 F died; at 2800 mg/kg, 3/5 M and 5/5 F died; at 3500 mg/kg, 4/5 M died; at 5010 mg, 5/5 M died. Toxic signs observed included activity decrease, ataxia, constricted pupils, convulsions, corneal opacity, dilated pupils, lacrimation, lethargy, nasal discharge, polyuria, piloerections, ptosis, rapid breathing and salivation. Necropsy: sensual salivation, polyuria, lacrimation, epistaxis, chromodacryorrhea and nasal discharge; discoloration of the contents of the stomach and the intestines, stomach empty; discoloration of the liver, sensual blood vessels pronounced on gastrointestinal tract, urinary bladder completely full and distended. LD50 for males was 3008 mg/kg with 95% confidence limits of 2630 to 3441 mg/kg. LD50 for females was 1289 mg/kg with 95% confidence limits of 1095 to 1518 mg/kg. LD50 for males and females combined was 1822 mg/kg with 95% confidence limits of 1102 to 3011 mg/kg.

Study Classification: Core Guideline Data.

Toxicity Category: III - CAUTION

2) Acute Dermal Toxicity Study: Stillmeadow, Inc.; Project # 2835-82; January 4, 1983.

Procedure: 5M and 5F New Zealand rabbits received 2010 mg/kg of the test material at abraded skin sites under occlusive wrap for 24 hour exposure. Observations made at ½, 3, and 6 hours after treatment & and atleast once daily thereafter for 14 days. Necropsy performed on all animals.

Results: No mortalities. Toxic signs observed included constricted pupils, activity decrease

ptosis, salivation, decreased defecation, unable to coordinate use to right and left hind limbs. Slight to well defined erythema and well defined to severe edema ~~also~~ and brown discoloration of exposure area hair and shallow lateral fissuring also noted. LD50 greater than 2010 mg/kg.

Study Classification: Core Guideline Data

Toxicity Category: III - CAUTION

(3) Eye Irritation Study: Stillmeadow, Inc.; Project No. 2747-82; January 12, 1983.

Procedure: Twelve New Zealand rabbits received 0.1ml of the test material in one eye each. The treated eyes of three of the rabbits were washed 30 seconds post treatment. Observations made at 1, 24, 48 and 72 hours and at 4, 7, 9, 14, 16, 19 and 21 days after treatment.

Results: At 24 hours, 8/9 animals of the unwashed group and 1/3 animals of the washed group had corneal opacity (6/9 = 5, 7/9 = 10) (1/3 = 20); 3/9 + 1/3 iris irritation (3/9 = 5) (1/3 = 5); 8/9 + 3/3 redness (6/9 = 1, 2/9 = 2) (2/3 = 1, 1/3 = 2); 8/9 + 3/3 chemosis (1/9 = 1, 4/9 = 2, 2/9 = 3, 2/9 = 4) (1/3 = 1, 1/3 = 2, 1/3 = 4) and 9/9 + 2/3 discharge (3/9 = 1, 4/9 = 2, 2/9 = 3) (1/3 = 1, 1/3 = 2).

At day 7, no corneal opacity in ~~same~~ unwashed group; 1/3 of the washed group had corneal opacity (1/3 = 10); 1/3 had iris irritation (1/3 = 5); 1/9 + 1/3 redness (1/9 = 1) (1/3 = 1 2/9 + 1/3 chemosis (2/9 = 2) (1/3 = 2); 1/9 + 1/3 discharge (1/9 = 1) (1/3 = 1). After day 7 observation one animal was sacrificed due to corneal vascularization.

At day 14,
At day 14, 1/3 had corneal opacity (1/3 = 5); 1/9 had chemosis ~~to~~ (1/9 = 2) and discharge (1/9 = 1).

at day 21, corneal opacity present in 1/3 ($Y_3=10$, 1/9 chemosis ($Y_9=1$).

Faint vascularization to vascularization obvious without magnification noted in most animals.

Study Classification: Core Guideline Data.

Toxicity Category: II - WARNING

(4) Skin Irritation Study: Stillmeadow, Inc; Project No. 2678-82; July 12, 1982.

Procedure: Six New Zealand rabbits received 0.5 ml of the test material at two abraded and two intact skin sites proximal under occlusive wrap for 24 hour exposure period. Observations made at 24 and 72 hours after treatment and daily thereafter through 19 days.

Results: At 24 hours, 6/6 had well defined to moderate erythema (Scores of 2+3) and slight to moderate edema (Scores of 1 to 3). At 72 hours, 6/6 had well defined to moderate erythema (Scores of 2+3) and slight to moderate edema (Scores of 1 to 3). Primary Irritation Score was 3.92. Erythema through day 10, decreasing in severity. Edema persisted in one animal through day 18.

Study Classification: Core Guideline Data

Toxicity Category: III - CAUTION

(5) Acute Inhalation Toxicity Study: Toxikinetics, Inc.; Study # 420-1157; February 4, 1983.

Procedure: 5M and 5F rats were exposed for four hours to a 4.53 mg/l aerosol analytical.

concentration. The mass median diameter and geometric standard deviation were 2.01 micrometers and 1.88, respectively. The temperature was 70-76°F and humidity was 32-62%. Observations were made daily for 14 days. Necropsy performed on all animals.

Results: 1/5F animals died during the study. Toxic signs observed included irregular breathing, crusty nose, squinting, crusty eye, damp fur, red stained fur, ataxia, matted eye, prostration, no life signs visible, crusty mucous, poor coat quality, injury, hyperactivity, exophthalmus, swollen face, and crusty substance around ear tag. At necropsy 6/10 rats showed nasal appearance and 4/10 lung and skin abnormalities were noted. LC50 greater than 4.53 mg/l.

Study Classification: Core Guideline Data

Toxicity Category: III - CAUTION

(6) Dermal Sensitization Study: Stillmeadow, Inc.; Project No. 283-82; February 4, 1983.

Procedure: Two groups consisting of 10 male guinea pigs each received one of the following treatments. Group I animals were treated with a 0.05% w/v solution of 2,4-dinitrochlorobenzene in ethanol as a positive control group. Group II animals were treated with a 1.0% v/v solution of the test material in deionized water as a test group. The animals were treated on days 0, 2, 5, 7, 9, 12, 14, 16, 19, 21, 35 and 43. The animals were treated on each of the first 10 treatment days by introducing 0.5 ml of the appropriate test material on a gauze patch secured by a piece of adhesive and then wrapped in clear polyethylene film to secure

patches in place. Each animal was then placed in a restrainer for approximately six hours. At end of exposure period animals were removed from the restrainers, the wrapping removed and the animals were returned to their cages. Observations made at 24 hours after each treatment.

Results: The average skin reaction scores for Group I (Positive Control Group) were 0.0 for initial treatment (day 1) 1.7 for the first virgin challenge site and 3.2 for the original test site after the eleventh treatment (Day 35) and 3.0 for the second virgin challenge site and 3.6 for the original test site after the final treatment (day 43). The final irritation score was significantly greater than the initial treatment. Therefore a sensitizing reaction was produced.

The average skin reaction scores for Group II (test group) were 0.0 for the initial treatment, 0.4 for the first virgin challenge site and 0.3 for the original test site after the eleventh treatment, and 0.4 for the second virgin site and 0.2 for the original test site after the final treatment. The final irritation score was significantly greater than the initial treatment. Therefore a sensitizing reaction was produced.

Study Classification: Core Guideline Data

Toxicity Category: Sensitizing

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