8-9-79

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

TCX

DATE: August 9, 1979

SUBJECT: EPA File Symbol: 59-RIO DERMATON DUST
Caswell #187

003232

FROM: B. T. Backus
IRB/TSS

TO: Mr. Jay S. Ellenberger
Acting Product Manager 15

Applicant: Burroughs Wellcome Co.
3030 Cornwallis Rd.
Research Triangle Park, NC 27709

Active Ingredients:
Chlorfenvinphos (2-chloro-1-(2,4 dichlorophenyl) vinyl diethyl phosphate.....0.5%
Inert Ingredients:.....99.5%

Recommendations:

1. The submitted Oral LD50, Dermal LD50, Inhalation LC50, Dermal and Eye Irritation studies are acceptable and adequate for registration purposes.

2. The eye irritation study indicates the formulation is in toxicity category II with respect to eye effects; therefore, the appropriate signal word is WARNING, rather than the CAUTION proposed by the applicant.

3. IRB/TSS would have no objection, on the basis of incremental risks to man and domestic animals, to the conditional registration of this proposed product with the labeling revisions indicated below.

Labeling:

1. As indicated above, the signal word should be WARNING.

2. The brackets around "& DOMESTIC ANIMALS" should be removed.

3. The HAZARDS TO HUMANS & DOMESTIC ANIMALS statement should be revised to something like the following:

WARNING: Causes eye irritation. Do not get in eyes. May be harmful if swallowed, inhaled or absorbed through skin. Avoid breathing of dust and contact with skin. DO NOT USE ON CATS. Wash after handling.
STATEMENT OF PRACTICAL TREATMENT (This heading is not necessary, and may be removed if the applicant wishes)
IF SWALLOWED: CALL A PHYSICIAN IMMEDIATELY. Drink a glass of water and induce vomiting by administering syrup of ipecac or by touching back of throat with a finger or blunt object.

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IF IN EYES: Immediately flush eyes with water for at least 15 minutes and get medical attention.

4. The "NOTE TO PHYSICIAN" should be revised to something like: "This product contains an organophosphate. If symptoms of cholinesterase inhibition develop, atropine is antidotal."

5. The "STORAGE AND DISPOSAL" heading should be revised to simply "DISPOSAL."

Review:

All studies were conducted on the product as proposed for registration, and were received 6-15-79, and are in EPA Acc. 238739.

1. Acute Oral Toxicity Study in Rats; study conducted by Hazleton Laboratories America, Inc. 9200 Leesburg Tpk, Vienna, VA 22180; project no. 309-126; dated December 19, 1977.

   Procedure: Varying amounts of the test material were dissolved in 0.5% methyl cellulose to achieve concentrations necessary to dose the test subjects at a rate of 25 ml/kg. Groups of 5M, 5F Sprague-Dawley rats were orally intubated in 1000, 1780, 3160, 5620 and 10000 mg/kg with 14-day observation, sacrifice, and gross pathological examination.

   Results: At 1000 mg/kg, no deaths; at 1780 mg/kg, 2/5M, 2/5F died; at 3160 mg/kg, 4/5M, 5/5F; at 5620 and 10000 mg/kg all died. Oral LD50 in male rats=2112 mg/kg, with 95% confidence limits of 1388.7-3212.2 mg/kg. In female rats oral LD50 = 1877.9 mg/kg, with 95% confidence limits of 1333.9 to 2643.8 mg/kg. Symptomology included red stains around nose, depression, tremors, ataxia. No body weight data reported.

   Study Classification: Core Minimum Data

   Product Classification: Tox. Cat. III

2a. Oral LD50 of Supona 0.5% Dust in Female Rats; study conducted by the Wellcome Research Laboratories, Proj. no. S04, Lab no. TL 38-75, Nov. 27, 1975.

   Procedure: A 50% w/v suspension was prepared by mixing product with sterile water. Groups of 6 Wistar rats were dosed by gavage at levels of (calculated by this reviewer) 500, 1000, 2000 and 4000 mg/kg. Animals were observed 14 days, sacrificed, and then examined for gross pathology.

   Results: No deaths at 500 mg/kg; 1/6 died at 1000 mg/kg; all died at two highest dosages. Oral LD50 (female rat) = 1840 mg/kg (= 9.2 mg/kg of the active ingredient) with 95% confidence limits of 1680 - 1980 mg/kg. Symptomology included transient hypersensitivity with muscle tremors; dying animals had fluid in small intestines, yellow staining on muzzles and perineal areas, and lung congestion. No abnormalities in survivors.

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2b. Oral LD50 of 0.5% Supona Dust in male rats; study conducted by the Wellcome Research Laboratories, Project No. S04, Lab. Ref. No. TL.43-75, dated Nov. 27, 1975.

Procedure: Same as in 2a, above.

Results: 1/6 died at 500 mg/kg; 2/6 died at 1000 mg/kg; 4/6 at 2000 mg/kg; and 5/6 at 4000 mg/kg. Oral LD50 (male rats) = 1420 mg/kg (= 7.1 mg/kg of the active) with 95% confidence limits = 920-2760 mg/kg. Symptomology included hypersensitivity and muscular tremors. Several survivors had fatty livers. No final body weight data.

Study Classification: (both 2a and 2b):Core Minimum Data

Product Classification: Tox. Cat. III

3. Acute Dermal Toxicity Study in Rabbits; study conducted by Hazleton Laboratories; Project No. 309-127; dated Jan. 20, 1978.

Procedure: Groups of 4 New Zealand rabbits, 2.3-3.1 kg, 2 with intact and 2 with abraded skin sites, were dermally exposed to dosage levels of 4640, 6000, 7750 and 10000 mg/kg. Sites had been premoistened with physiological saline, and were occluded for 24 hrs. Subjects were observed 14 days, sacrificed, and examined for gross pathology.

Results: 1 animal died at 7750, 1 died at 10000 mg/kg levels. "These deaths were considered to be incidental and not related to treatment..." Animals which died had shown depression, anorexia and/or bloated appearance. Among survivors, one animal at the 6000 mg/kg level had shown anorexia. Body weight gains in survivors. Dermal LD50 reported as greater than 10000 mg/kg.

Study Classification: Core Minimum Data

Product Classification: Tox. Cat. III (FR43, #163, August 22, 1978, pp. 37356-37357).

4. Primary Skin Irritation Study in Rabbits with Dermaton Dust; conducted by Hazleton Laboratories, Inc. Project No. 309-128; dated Dec. 19, 1977.

Procedure: 0.5 gms of test material was applied to an intact and abraded site on each of 6 rabbits following premoistening (whether of the sites or formulation is not clear) with sterile water. Sites were occluded, and rabbits were immobilized for 24 hrs, with Draize scoring at 24 and 72 hrs postapplication.

Results: All animals scored "1" for erythema at 24 hrs at intact and abraded sites; all scores for edema "0" at 24 hrs; all scores 0 at 72 hrs. Primary Irritation Score = 0.5 .

Study Classification: Core Guideline Data

Product Classification: Tox. Cat. IV

5. Acute Eye Irritation Potential Study in Rabbits; Hazleton Laboratories, Inc. Project No. 309-129; dated Dec. 20, 1977.

Procedure: 91 mg of test material was instilled in left eye of each of 9 rabbits; 6 eyes remained washed, 3 were washed 20-40 seconds post-installation with lukewarm tap water. Eyes were examined and scored at 24, 48, 72 hrs and 7 days.

Results: Corneal opacity in 6/6 unwashed, 1/3 washed eyes at 24 hrs. Redness in 6/6 unwashed eyes at 72 hrs; 3/3 washed at 48 hrs. All scores zero at 7 days.

Study Classification: Core Guideline Data

Product Classification: Tox. Cat. II:WARNING

6. Acute Inhalation Toxicity Study in Rats; Hazleton Laboratories, Inc., Project No. 309-142, dated May 31, 1978.

Procedure: 10 male Sprague-Dawley rats, 200-300 gms, were exposed to a atmospheric concentration of 28.1 mg/liter for 1 hour, with a 14-day observation period, sacrifice, and gross pathological examination.

Results: No mortalities. Some animals showed signs of eye and nasal irritation during exposure. Also, during exposure, animals were inactive. 7/10 subjects had pale kidneys on gross pathological examination. LC50 above 28 mg/liter.

Study Classification: Core Minimum Data (only males used, no body weight data).

Product Classification: Tox. Cat IV

7. Safety Test on Dogs Using 0.5% Supona Dusting Powder; conducted by Environmental Consultants, Inc; dated Oct. 23, 1975.

Procedure: 12 dogs, of mixed breeds, sex and ages were divided into 3 groups of 4 animals. One group was control; one group was dusted once daily for 5 days, and last group was dusted daily for 10 days.

Results: No symptomology indicative of organophosphate poisoning noted; one animal in second group had an abcess and was sacrificed and autopsied; lesions were found on the lung and kidney. Noted that the smaller animals were receiving as much as 2.5 times on a per-weight basis as what the larger animals were.

Study Classification: Core Supplementary Data

8. Multiple Application Dusting Trial on Unweaned Puppies for Safety

Procedure: Eight litters containing 41 puppies were used. 23 puppies were dusted at 14 and 21 days; eighteen other pups were dusted with a placebo.

Results: High mortality found in certain litters for both exposed animals and controls; no mortality in others. Fourteen pups died; this included 5/18 controls (27.8%) and 9/23 (39.1%) of exposed. No symptomology indicative of organophosphate poisoning was noted.

Study Classification: Core Supplementary Data (Question arises, was the mortality percentage in treated pups higher because of the stress of exposure to this formulation?).

Byron T Backus 08-09-79

Byron T. Backus
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