003539 ~~000463~~

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

~~003538~~
003539

MEMORANDUM

#96

Date: November 20, 1980

Subject: EPA Registration Number: 100-ARR
CNTRACK WE-2: Caswell # 96

From: Deloris P. Graham DPG 12/1/80
FHB/TSS
E 12/11/80

To: Robert Taylor
Product Manager (25)

Applicant: CIBA-GEIGY Corporation
Agricultural Division
P.O. Box 11422
Greensboro, North Carolina

BEST AVAILABLE COPY

Active Ingredient:

Prometon: 2,4-bis ( ) -
6-methoxy-s-triazine 25%
Inert Ingredients 75%

Background: An Acute Oral, Acute Dermal, Acute Inhalation, Eye Irritation and Skin Irritation Studies were submitted. All studies except the Inhalation Study were conducted by Stillmeadow, Inc., Houston, Texas. The Inhalation Studies were conducted by Food and Drug Research Laboratories, Inc. These data are under accession number 243395. Cite-all method of support is used.

Recommendation:

(1) The Acute Oral, Acute Dermal, Acute Inhalation, Eye Irritation and Skin Irritation Studies are acceptable to support the conditional registration of this product.

(2) FHB/TSS has no objections to the conditional registration of this product provided the labeling changes noted below are made.

Label:

(1) The appropriate signal word is DANGER as proposed by the applicant.

(2) The precautionary statements must appear on front panel or on side panel if referral statement is used, preceding Directions For Use.

(3) The preferred heading for "First Aid" is "Statement of Practical Treatment."

Review:

(1) Acute Oral Toxicity Study: Stillmeadow, Inc.; Project No. 1672-80; June 24, 1980.

Procedure: 5M and 5F per each of six dose levels. The doses for the males were 1660, 2000, 2400, 2880, 3460 and 5010 mg/kg and for the females 1160, 1390, 1660, 2000, 2400 and 5010 mg/kg. Observations were made at least three times on the day of treatment and at least once daily thereafter for 14 days. Body weights were recorded. Necropsy was performed on all animals.

Results: At 1160 mg/kg, 1/5 females died; at 1390 mg/kg, 1/5 females died; at 1660 mg/kg, 0/5 males and 5/5 females died; at 2000 mg/kg, 1/5 males and 3/5 females died; 2400 mg/kg, 3/5 males died; 3460 mg/kg, 4/5 males; at 5010 mg/kg, 5/5 males and 5/5 females died. Other symptoms observed included salivation, piloerection, activity decrease, ataxia, polyuria, diarrhea, epistaxis, melanuria, constricted pupils, lacrimation, lethargy, ptosis, flaccid muscle tone, chromodacryorrhea, discharge from nose and mouth, deep and slow breathing, difficult and labored breathing, respiratory gurgle, and dilated pupils.

Necropsy revealed polyuria and [illegible] stomach distended with gas; small intestines distended with gas; [illegible] material; thymus discolored red; liver pale, red with dark spots; [illegible] jejunum and ileum filled with yellow liquid; cecum filled with [illegible] liquid; red patches on cardiac region of stomach; spleen is [illegible] stomach filled with white milky liquid; urinary bladder empty; [illegible] filled with dark brown paste; colon filled with white mucoid substance [illegible].

Study Classification: Core Guideline Data.

Toxicity Category: III-CAUTION

(2) Acute Dermal Toxicity Study: Stillmeadow, Inc.; Project No. 1673-80; June 18, 1980.

Procedure: 5 groups, four groups consisting of 4M and 4F and one group consisting of 5M and 5F New Zealand rabbits. One sham control group and four test groups at one of the following concentrations: 1490, 1820, 2230, and 5010 mg/kg. Prior to treatment 2M and 2F animals of each group were abraded. The actual undiluted test material was applied to the abraded areas and placed under occlusive wrap for 24 hour exposure period. Observations were made at 1/2, 3 and 6 hours after treatment and at least once daily thereafter for 14 days for pharmacologic and/or toxicologic effect. Body weights were recorded. Necropsy was performed on each animal. Observations for erythema and eschar formation, edema formation and any other dermal effects or irritation were made at end of 24 hour exposure period and daily thereafter for 14 days.

2

Results: At 1490 mg/kg, 0/8 animals died; 1820 mg/kg, 2/8 animals died; 2230 mg/kg, 8/8 died and at 50/10 mg/kg, 10/10 died. On day 1 at a concentration of 1490, 1820, and 2230 mg/kg well defined erythema and slight edema and persisted for 14. Shallow lateral fissuring of the exposure area, eschar formation, sloughing of skin of various thicknesses, focal areas of pustules. Necropsy revealed diarrhea, brown liquid in colon, cecum and ileum, salivation, yellow mucous material in duodenum, lacrimation, lungs dark red, liver light brown and has grainy texture; light green mucoid material in jejunum and ileum; serosal blood vessels pronounced on cecum; urinary bladder empty, small intestines empty; colon distended with gas; liquid in contents of stomach; dark black spots on inner lining of stomach; yellow mucoid material in small intestines; bloody discharge around nose and mouth.

Symptoms observed included diarrhea, few feces, small amount of urine, loose stool consistency, activity decrease, ptosis, lacrimation, salivation, dilated pupil, nasal discharge, labored breathing, and ataxia. LD50 for males was determined to be greater than 1820 mg/kg but less than 2230 mg/kg. LD50 for females was 1820 mg/kg (1590-2070 confidence limits). The combined male and female LD50 was 1960 mg/kg (1740-2200 mg/kg confidence limits).

Study Classification: Core Guidel[redacted]

Toxicity Category: II-WARNING

(3) Acute Inhalation Study: Fo[redacted] Research Laboratories, Inc.; [redacted] ID No. 80-0498; July 23, 1980.

Procedure: A fluid metering pump was set to deliver 2.23 g/minute of the test material to the atomizer. Filtered compressed air passed through the atomizer at 15 psi and 20 L/minute developing an aerosal with an average particle size of 4.5m. The exhaust system was operated with a Transvector jet set at a flow rate of 70 L/minute. The atomizer sprayed the test material into the exposure chamber and the resulting aerosal was vented into a hood.

The chamber was constructed of glass and stainless steel and had a volume of 361 liters and operated at a flow rate of 70 L/minute. At the end of the exposure, all animals remained in the chamber for a minimum of 30 minutes. During this time the chamber was operated at the same flow rate using clean air only.

The nominal concentrations were calculated by dividing the net weight of the compound used during the exposure by the total air flow through the chamber (534.6g/16800L = 31.82 mg/L). Actual exposure concentrations were determined gravimetrically. 5M and 5F Sprague-Dawley rats were exposed for 4 hours to an airborne aerosol of the test material. Observations were made during exposure period and daily thereafter for 14 days. Body weights recorded. Necropsies performed on all animals.

Results: By the end of the 4 hour exposure period, eight animals were dead and the last two died within 24 hours. Pharmacotoxic signs included labored respiration, nasal discharge, salivation, decreased activity, decreased coordination.

Necropsy revealed lungs dark with scattered spotting, spleen and kidneys dark, cervical lymph nodes dark red and red spottin on thymus. Most findings showed common post-mortem alterations of anim ls that died before necropsy; none of these finding were considered to be related to test material administration and probably were the result of the pooling of blood in certain organs. Actual concentration was 2.35 mg/L.

Study Classification: Invalid

(4) Acute Inhalation Study: Food and Drug Research Laboratories, Inc.; FDRL ID No. 80-0498; September 3, 1980.

Procedure: A 50cc syringe mounted on a Harvard Apparatus Infusion Pump was set to deliver .29g/minute of the test material to the atomizer. Filtered compressed air passed through the atomizer at 15 psi and 20 L/minute. The exhaust system was operated with a Transvector Jet. The atomizer sprayed the test material into the exposure [redacted] and the resulting aerosal was vented into a hood.

The chamber was constructed o[redacted] stainless steel. The total air flow was constantly monitored durin[redacted]sure period and remained in the chamber for a minimum of 30 m[redacted] exposure period. During this time only clean air passed through the chamber.

Nominal concentrations were calculated by dividing the net weight of compound used during the exposure by the total air flow through chamber. Actual exposure concentrations were determined gravimetrically.

5M and 5F Sprague-Dawley rats were exposed for hours to an airborne aerosal of the test material at an actual concentration of 0.32 mg/L. Observations were made during the exposure period and daily thereafter for 14 days. Body weights recorded. Necropsies performed on all animals.

Results: No mortalities. Pharmacotoxic signs were labored respiration, nasal discharge, decreased activity, dried blood around nose.

Necropsy revealed thymus swollen and red spots; lungs slightly mottled, grayish with dark areas; mesenteric swollen, red, and dark; cervical red, dark and slightly swollen; left auxiliary red; spleen pale, granular around edges; kidneys dark spots, partially hollow, fluid filled; liver dark; pancreas dark; ovaries red and swollen, uterus red, swollen; and fluid filled small cecum red.
the actual concentration was 0.32 mg/L.

4

Study Classification: Core Guideline Data

Toxicity Category: II-WARNING

(5) Eye Irritation Study: Stillmeadow, Inc.; Project No. 1674-80; May 12, 1980.

Procedure: 9 New Zealand rabbits received 0.1 ml dose of the actual undiluted test material at room temperature into the conjunctival sac of the right eye of each animal. Three of the treated eyes were washed with water for one minute beginning 30 seconds after instillation of the test material. Observations were made at 1, 24, 48 and 72 hours and at 4, 7, 10, 13, 16, 19 and 21 days after treatment.

Results: Unwashed group - corneal opacity in 6/6 animals with score of 20 and persisted 21 days. Iris irritation in 6/6 animals with scores ranging from 5-10 and persisted in some for 13 days. Conjunctival redness, chemosis and discharge with scores ranging from 1-4 in 6/6 animals and persisted in some through day 21.

Washed group - 3/3 animals had corneal opacity with score of 20 and persisting in 2/3 animals through day 21. Iris irritation present in 3/3 animals with scores ranging from 5-10 and [illegible] in 1/3 animals through day 21. Conjunctival redness, chemosis [illegible] discharge in 3/3 animals with scores ranging from 1-4 and persist[illegible] day 21.

Study Classification: Core [illegible] Data

Toxicity Category: I-DANGER

(6) Dermal Irritation Study: Stillmeadow, Inc.; Project No. 1675-80; April 25, 1980.

Procedure: 6 New Zealand white rabbits were treated with 0.5 ml actual undiluted test material at two abraded and two intact skin sites per animal under occlusive wrap for 24 hours. Observations at 24 and 72 hours after treatment.

Results: Well defined to moderate erythema and edema at both abraded and intact sites in all animals at 24 hours and persisted through 72 hours. At 72 hours shallow lateral fissuring of some test sites. Primary Irritation Score was 4.44.

Study Classification: Core Guideline Data.

Toxicity Category: III-CAUTION

5

RIN-0334-94 PROMETON REVIEWS (080804)

Page_____ is not included in this copy.

Pages 6 through 11 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

✓ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
