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F&W

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: 3/28/80

SUBJECT: EPA Reg. No. 33955-454
Acme Vegetation Killer
Caswell No. 704C, 315,646

FROM: Sherell A. Sterling 3/28/80 E 3/28/80
FHB/TSS

TO: Willa Garner, Ph.D.
Product Manager (23)

Applicant: Acme Division
PBI/Gordon Corporation
300 South Third Street
P.O. Box 2276
Kansas City, KS 66110

Active Ingredients:

080804 – Prometon..... 3.6%
030001 – 2, 4-Dichlorophenoxyacetic acid..... 1.0%
006601 – Aromatic petroleum distillates.....76.4%
Inert Ingredients.....19.0%

Background: These data were submitted in response to a change in the prometon [redacted] used in formulating this product. Acute Oral, Acute Dermal, Eye and Skin Irritation studies were submitted for B7539 (the pre-amendment Pramitol). Eye and Skin Irritation studies were conducted on B9456 (the amended product). These studies are in Accession No. 241566 and were conducted by Stillmeadow, Inc. of Houston, Texas. A method of support was not indicated for this conditional registration.

Recommendations:

1. The Acute Oral, Acute Dermal, Eye and Skin Irritation studies conducted on B7539 are considered adequate and acceptable for conditional registration purposes.

2. The Eye and Skin Irritation studies conducted on B9456 are considered adequate and acceptable for conditional registration purposes.

3. Acute Oral, Acute Dermal and Acute Inhalation studies were not submitted on the newly formulated product. These data need not be submitted at this time; however, these data may be requested in the future as part of the reregistration process.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED.

4. The Skin Irritation studies suggest that with continued use, dermal sensitization may develop. For this reason, the Dermal Sensitization study must be conducted. Please refer to § 163.81-6 of the Proposed Guidelines for Human Hazard Evaluation. on B9456

5. FHB/TSS has no objection to the continued registration of this product (B9456) provided that Dermal Sensitization studies are submitted and the following labeling revisions are made. Further labeling revisions may be necessary when additional tests are submitted.

Labeling Recommendations:

1. The signal word based on the Skin Irritation studies is DANGER. The signal word must therefore be changed to DANGER on both the front and side panels.

2. The statement "It is a violation of Federal law to use this product in a manner inconsistent with its labeling" must appear under the DIRECTIONS FOR USE heading. Further, the statement "Apply this product as specified on this label" should be deleted from the ENVIRONMENTAL HAZARDS section of the labeling.

Note to the PM: Since there is a change of signal word (from WARNING to DANGER), the request for a "minor formulation change" may not be appropriate.

Review:

1. Rat Acute Oral Toxicity: vegetation killer B7539; Stillmeadow Project No. 1403-79; December 7, 1979.

Procedure: Groups of Sprague-Dawley rats (200-240g) received oral dosages of B7539 by means of oral intubation at dosages of 996.7, 1490, 1958, 2096, 2235, 2555, 2737, 2928, 3352, 4097 and 5015 mg/kg. Animals were observed for 14 days post-treatment. At the termination of the study, all animals were subjected to necropsies

Results: At 996.7 mg/kg, 5M and 5F were tested; no mortalities. At 1490 mg/kg, 5F were tested; no mortalities. At 1958 mg/kg, 5F were tested; no mortalities. At 2096 mg/kg, 5F were tested; no mortalities. At 2096 mg/kg, 5F were tested; 2/5F died. At 2235 mg/kg, 5M and 5F tested; 1/5M and 3/5F died. At 2555 mg/kg, 5F were tested; 5/5F died. At 2737 mg/kg, 5M tested; 4/5M died. At 2928 mg/kg, 5F tested; 4/5F died. At 3352 mg/kg, 5M and 5F tested; 2/5M and 5/5 F died. At 4097 mg/kg, 5M tested; 5/5 M died. At 5015 mg/kg, 5M and 5F tested; 5/5M and 5/5F died. LD50 for males was 2660 mg/kg with a 95% confidence range of 2120-3337

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mg/kg. For females LD50 was 2280 mg/kg with a 95% confidence range of 1921-2706. "In life" symptoms included piloerection, epistaxis, salivation, lacrimation, diarrhea, gasping, melanuria, chromodacryorrhea, polyuria, hematuria, constricted pupils, dilated pupils, ptosis, emaciation, tremors, lethargy, activity decrease, and respiratory gurgle. Necropsies revealed: nose and mouth -- bloody discharge; lungs -- discolored; stomach -- mucinous pseudomembrane, discoloration, mucosa adhered to other tissues of stomach and intestinal contents, ulcers, necrosis, stomach wall fragile; GI tract -- distended with gas to empty; liver -- puffy, discolored, areas of necrosis, abscesses, liver adhered to other tissues; kidneys -- adhered to other tissues, enlarged, necrosis, discoloration of kidneys and adrenal glands, dilated renal pelvis; heart - enlarged; spleen -- adhered to other tissues, necrosis; urinary bladder -- empty to completely full, discoloration of prostate and urinary bladder; testes -- drawn into abdominal cavity, discolored; discoloration of epididymal fat; discoloration of mesenteric lymph nodes; pronounced serosal blood vessels.

Study Classification: Core Guideline Data

Toxicity Category: III - CAUTION. High incidence of ascended testes noted, especially at higher dosages.

2. Rabbit Acute Dermal Toxicity: vegetation killer B 7539; Stillmeadow Project No. 1404-79; December 6, 1979.

Procedure: 5M and 5F New Zealand white rabbits (2.4 - 3.3 kg) with abraded skin received an application of 2010 mg/kg of B7539. Exposure was for 24 hours under occlusive wrap. A sham group was treated similarly, but did not receive an application of the test substance. Animals were observed for 14 days. At termination of study all animals were sacrificed and subjected to necropsies.

Results: In the sham group, 1/5M died; in the treated group, 2/5M died. Symptoms in treated animals included very slight to severe erythema lasting through day 14 and very slight to severe edema lasting through day 14. Lateral fissuring, eschar, deep lateral fissuring with bleeding, sloughing, focal areas of pustules, dislocation of hind legs, small feces, few feces, small amount of urination and a decrease in activity were also noted. Necropsies of the sham group revealed ruptured stomach and GI tract distended with gas in the dead animal; all survivors showed no abnormalities. From the treated group, necropsies showed dead animals with pronounced serosal blood vessels, distention of the intestines with mucoid material, discoloration of stomach and intestinal contents, discoloration of the lungs; all survivors appeared normal. LD50 is greater than 2010 mg/kg.

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Study Classification: Core Guideline Data.

Toxicity Category: III - CAUTION

3. Rabbit Eye Irritation: vegetation killer B 7539; Stillmeadow Project No. 1406-79; November 29, 1979

Procedure: 0.1 ml of B7539 was applied into one eye of each of 9 New Zealand white rabbits. Three rabbits received an eye wash for one minute with room temperature deionized water 30 seconds post-treatment; remaining 6 were unwashed. Scoring at 1, 24, 48, 72 hours; 4, 7, 10, 13, 16, 19, 21 days.

Results: Corneal opacity in nonwash eyes noted in 4/6 rabbits; first observed in 2/6 at 4 days, 1/6 at day 10 and 1/6 at day 13; opacity continued through day 21. Apparent invasion of cornea by blood vessels in 5/6 rabbits. Positive fluorescein staining and stippling observed in 6/6 rabbits. Iris irritation at 24 hours observed in 6/6 eyes (6/6 = 1); 5/6 clear by day 7 and all were clear by day 19. Conjunctival redness observed in 6/6 animals at 24 hours (5/6 = 3, 1/6 = 2); at 7 days, 6/6 showed redness (1/6 = 1, 5/6 = 2). Chemosis at 24 hours in 6/6 eyes (6/6 = 4) and again 6/6 at 7 days (2/6 = 2, 2/6 = 3, 2/6 = 4). At 24 hours, discharge in 6/6 animals (6/6 = 2); at 7 days (2/6 = 1, 3/6 = 2).

In the washed eyes, no corneal opacity was observed but 1/3 exhibited invasion of the cornea by blood vessels at day 4; 1/3 showed positive fluorescein tests; 2/3 showed stippling. Iris irritation in 1/3 from 24 hours through day 4 (1/3 = 1). Conjunctival redness at 24 hours in 3/3 = 2, but all clear by day 7; 1/3 showed slight hair loss around eye on days 13-21. At 24 hours, chemosis in 3/3 (2/3 = 3, 1/3 = 2). Discharge in 3/3 at 24 hours (2/3 = 1, 1/3 = 2) with all clear by day 7.

Study Classification: Core Guideline Data. Tox. Cat.: I - DANGER

4. Rabbit Eye Irritation: veg killer B9456; Stillmeadow Project No. 1463-79; December 7, 1979

Procedure: 0.1 ml of B9456 was applied into one eye of each of 9 New Zealand white rabbits. Three rabbits received an eye wash for one minute with room temperature deionized water 30 seconds post-treatment; remaining 6 were unwashed. Scoring at 1, 24, 48, 72 hours, 4, 7, 10, 13, 16, 19 and 21 days.

Results: In nonwash eyes at 24 hours, only 1/6 showed corneal opacity; by 72 hours opacity noted in 4/6 eyes (2/6 = +/4, 1/6 = 10, 1/6 = 5). All animals were positive for the

fluorescein test, but clear by day 7. Stippling observed in 5/6 animals, clear by day 7. Iris irritation at 24 hours in 5/6 eyes (4/6 = 1, 1/6 = 2); all clear by day 7. At 24 hours, conjunctival redness in 6/6 eyes (6/6 = 2) and 6/6 at 7 days (6/6 = 1); all clear by day 21. Chemosis noted in 6/6 (3/6 = 3, 3/6 = 4) at 24 hours in 6/6 (6/6 = 2) and only 1/6 at day 7 (1/6 = 1). Vocalization in 1/6 animals upon instillation.

In washed eyes, no corneal opacity noted at 24 hours; 1/3 showed opacity (1/3 = 20) from 48 hours through day 4; 1/3 exhibited opacity on day 4; 1/3 exhibited opacity on day 4 (1/3 = 10). Positive fluorescein readings in all animals through 72 hours. Stippling noted through day 7. Iris irritation at 24 hours in all animals (3/3 = 1); by day 7, all were clear. Conjunctival redness at 24 hours in 3/3 (3/3 = 2); on day 7 only 2/3 showed redness (2/3 = 1). Chemosis in 3/3 at 24 hours (3/3 = 3) and also at day 7 (3/3 = 1). At 24 hours discharge noted in all animals (2/3 = 2, 1/3 = 1); all clear by day 7.

Study Classification: Core Guideline Data.

Toxicity Category: II - WARNING

5. Rabbit Skin Irritation: vegetation killer B7539; Stillmeadow Project No. 1405-79; December 3, 1979

Procedure: 0.5 ml of B7539 was applied to each of 4 sites (2 intact, 2 abraded) on each of 6 New Zealand white rabbits. Exposure was for 24 hours under occlusive wrap. Scoring at 24, 72 hours, 4 through 21 days; however, one animal was mistakenly sacrificed on day 15.

Results: At 24 hours, intact sites all showed erythema (12/12 = 2) and edema (2/12 = 1, 6/12 = 2, 4/12 = 3); abraded sites all showed erythema (12/12 = 2) and edema (2/12 = 1, 7/12 = 2, 3/12 = 3) and edema (1/12 = 3, 11/12 = 4); abraded sites also showed erythema (2/12 = 2, 6/12 = 3, 4/12 = 4). Symptoms included eschar, lateral fissuring on test site, deep lateral fissuring with bleeding, sloughing, focal area of pustules. Primary irritation index was 5.56.

At 72 hrs., all intact sites showed erythema (2/12=2, 6/12=3, 4/12=4)

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Study Classification: Core Guideline Data.

Toxicity Category: I - DANGER. Symptoms included deep lateral fissuring with bleeding.

6. Rabbit Skin Irritation: veg killer B9456; Stillmeadow Project No. 1464-79; November 30, 1979

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Procedure: 0.5 ml of B9456 was applied to each of 4 sites (2 intact, 2 abraded) on each of 6 New Zealand white rabbits. Exposure was for 24 hours under occlusive wrap. Scoring at 24 and 72 hours, 4 through 14 days.

Results: At 24 hours, intact sites all showed erythema (6/12 = 2, 6/12 = 3) and edema (2/12 = 2, 10/12 = 3); abraded sites all exhibited erythema (6/12 = 2, 6/12 = 3) and edema (2/12 = 2, 10/12 = 3). [redacted] At 72 hours, intact sites all showed erythema (3/12 = 2, 9/12 = 3) and edema (1/12 = 3, 11/12 = 4); abraded sites all showed erythema (3/12 = 2, 9/12 = 3) and edema (12/12 = 4). By day 14, the intact sites showed 9/12 with erythema (9/12 = 1) and 10/12 with edema (5/12 = 1, 4/12 = 2, 1/12 = 3); abraded sites exhibited erythema at 9/12 sites (9/12 = 1) and edema at 9/12 sites (5/12 = 1, 3/12 = 2, 1/12 = 4). Symptoms observed from 72 hours through day 14 included eschar, lateral fissuring of test sites, focal areas of bleeding, lateral fissuring and bleeding, lateral fissuring and bleeding, sloughing. The Primary Irritation Index was 6.02.

Study Classification: Core Guideline Data.

Toxicity Category: I - DANGER. Deep lateral fissuring with bleeding observed.

RIN-0334-94 PROMETON REVIEWS (080804)

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Pages _____ through _____ are not included.

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____ Identity of product inert ingredients.

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