12-15-80 TOX

TXR 000835 - 363A

DATE: December 15, 1980

SUBJECT: Avenge S Wild Oat Herbicide
EPA File Symbol: 241-EAE

FROM: Sherell A. Sterling SAS 12-22-80 E 12/22/80
FHB/TSS

TO: Richard Mountfort
Product Manager (23)

Applicant: American Cyanamid Company
Agricultural Research Division
P. O. Box 400
Princeton, NJ 08540

Active Ingredient:
Difenzoquat methyl sulfate.....62.5%
Inert Ingredients.....37.5%

Background: An application for conditional registration was submitted under the "combined" method of support. Acute Oral, Acute Dermal, Eye and Skin Irritation studies were submitted for a similar product.

Recommendations:

1. The Acute Oral study is considered adequate and acceptable data for conditional registration purposes.

2. The Acute Dermal study is considered adequate and acceptable data.

3. An Acute Inhalation study was not submitted. Since this product is a dust, an inhalation study is required. Please consult §163.81-3 of the enclosed "Proposed Guidelines for Human Hazard Evaluation" for an outline of an acceptable testing method.

4. The Eye Irritation study is considered adequate and acceptable for conditional registration purposes. However, please note for future studies that the group of 6 animals should not be subjected to an eyewash. Also, a complete description of the test method (including eyewash substance and amount used) must be included in the report.

5. The Skin Irritation study is adequate and acceptable for conditional registration purposes. Please note for future studies that four sites must be tested per animal, 2 intact and 2 abraded. Further, solid substances must be slightly moistened before application.

6. The Skin Irritation study indicates that a Dermal Sensitization study should be conducted on this product.

7. It is the opinion of FHB/TSS that an Acute Inhalation and a Dermal Sensitization study are needed to complete the battery of acute-toxicological testing.

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EPA FORM [illegible]

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Labeling Recommendations:

1. Please delete the parentheses from around the phrase "and Domestic Animals."

2. The "Hazards to Humans and Domestic Animals" statements must be revised in the following or similar manner:

   "Corrosive, causes eye damage and skin irritation. Do not get in eyes, on skin or on clothing. Wear goggles or face shield and rubber gloves when handling. May be fatal if swallowed or absorbed through the skin. Do not breathe dust. Wash thoroughly after handling."

3. Under the Environmental Hazards section, the statement "Keep out of lakes, streams and ponds" may be revised to "Do not apply directly to lakes, streams or ponds."

4. Further labeling may be required when additional data are submitted.

Comments:

1. The "Avenge S" formulation tested (see copy of page 232 from original report under section C) is not identical to the formulation submitted on the Confidential Statement of Formulation. This may be of significance to the Product Manager since the method of support is "combined."

Review:

1. Single Oral Dose; American Cy. Report #A79-133; May 14, 1979; Acc. No. 243670

   Procedure: Groups of 5 albino rats received dosages of "Avenge S" at varying levels. Test substance was administered orally in a 12% aqueous solution. Animals were observed for 14 days. At terminiation of study, survivors were sacrificed. Necropsies were performed on all animals.

   Results: Deaths were reported as follows: 0/5M and 0/5F at 0 gm/kg; 0/5M and 0/5F at 150 mg/kg; 3/5M and 1/5F at 225 mg/kg; 5/5M and 5/5F at 300 mg/kg; 5/5M and 5/5F at 600 mg/kg; 5/5M and 5/5F at 1200 mg/kg. Symptoms included: ataxia, tremors, salivation, bloody nose. Necropsy revealed: liver-congested; kidneys-congested; lungs-congested, hemorrhagic. The M-LD50 was 220 mg/kg; the F-LD50 was 238 mg/kg; the combined M and F-LD50 was 229 mg/kg.

   Study Classification: Core Guideline Data.

   Toxicity Category: II-WARNING

2. Single Dermal Dose (Intact); American Cy. Report #A79-133; May 14, 1979, Acc. no. 243670

Procedure: Groups of 5 New Zealand white rabbits were exposed to "Avenge S" for 24 hours. Test substance was moistened and administered under occlusive wrap, all at intact sites. Animals were observed for 14 days post-exposure. At termination of study, survivors were sacrificed. All animals were subjected to necropsies.

Results: Deaths were reported as follows: 0/5M and 0/5F at 0 mg/kg; 0/5F at 313 mg/kg; 0/5M and 1/5F at 625 mg/kg; 0/5M and 4/5F at 1250 mg/kg; 3/5M and 5/5F at 2500 mg/kg; 5/5M at 5000 mg/kg. Symptoms observed included: tremors, diarrhea, diuresis. The M-LD50 was 2396 mg/kg; the F-LD50 was 884 mg/kg with a 95% confidence range of 509-1536 mg/kg; the combined M and F-LD50 was 1439 mg/kg with a 95% confidence range between 1014-2092 mg/kg. Necropsies showed: liver-discolored, congested; kidney-congested, pale; adrenals-congested; lungs-congested; skin-severe erythema and edema.

Study Classification: Core Minimum data. No abraded sites tested.

Toxicity Category: II-WARNING

3. Rabbit Eye Irritation; American Cy. Report #A79-133; May 14, 1979; Acc. No. 243670

Procedure: Nine New Zealand white rabbits each received 0.1 g of "Avenge S" in one eye. Three of the eyes were washed 20 seconds post-treatment; the remaining six eyes were washed 24 hours post-treatment. Scoring at 24, 48, 72 hours; 4, 7, 10 and 14 days.

Results: After 24 hours, the "24 hour wash group" showed corneal opacity in 1/6=20, 5/6=40; iris irritation in 6/6=5; conjunctival irritation in 2/6=16; 4/6=18. At 7 days, the "24 hour wash group" showed corneal opacity in 6/6=80; all with vascularization; iris irritation in all animals was unscoreable due to corneal irritation; conjunctival irritation on 6/6=16. By day 14, corneal opacity in 1/6=40; 1/6=60; 4/6=80, all with vascularization; iris irritation in 4/6 was unscoreable; conjunctival irritation in 2/6=2, 1/6=6, 1/6=12; 2/6=16.

After 24 hours, the "twenty second wash" group exhibited corneal opacity in 1/3=15, 2/3=20; iris irritation in 2/3=5; conjunctival irritation in 1/3=12, 1/3=14, 1/3=18. At 7 days, corneal opacity in 1/3=40, 1/3=60, 1/3=80 with vascularization in 2/3; iris irritation in 1/3 is unscoreable; conjunctival irritation in 2/3=10, 1/3=12. By day 14, corneal opacity in 1/3=10 with 2/3 vascularized; no other irritation observed.

Comments included destruction/irreversible change in tissue at 24 hours.

Study Classification: Core Minimum Data. Group of 6 animals should not have received eye wash. Eye wash not described.

Toxicity Category: I-DANGER. Irreversible change noted.

4. Rabbit Skin Irritation; American Cy. Report #A79-133; May 14, 1979; Acc. No. 243670.

Procedure: Six New Zealand white rabbits received 0.5g of "Avenge S" at each of 2 sites, 1 abraded and 1 intact. Exposure was under occlusive wrap for 24 hours. Scoring at 24 and 72 hours.

Results: At 24 hours in intact sites, edema and erythema were slight in all animals; abraded sites exhibited moderate to severe erythema and edema. By 72 hours, intact sites exhibited slight erythema in 4/6 and slight edema in 1/6 sites; abraded sites with severe erythema and eschar formation at all sites and moderate edema in 4/6 sites. The Primary Irritation Index was 3.98.

Study Classification: Core Minimum Data. Four sites per animal must be tested. Substance must be moistened.

Toxicity Category: II-WARNING. Severe irritation noted at 72 hours; eschar formation.