US EPA ARCHIVE DOCUMENT

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: August 25, 1980

SUBJECT: EPA Reg. No. 100-597
Dual 8E

FROM: Sherell A. Sterling SAS 9-4-80
FHB/TSS E 9/8/80

TO: Richard Mountfort
Product Manager (23)

Applicant: Ciba-Geigy Corporation
Agricultural Division
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Active Ingredient:
Metolachlor.....86.4%
Inert Ingredients.....13.6%

Background: Data were submitted on 4 previously accepted alternate formulations. For each of the 4 formulations, acute oral, acute dermal, eye and skin irritation studies were submitted. The data are under accession numbers 242552-242555. Studies were conducted by Stillmeadow, Inc. of Houston, Texas.

Recommendations:

1. The Acute Oral studies for all 4 formulations are acceptable and adequate for conditional registration purposes.

2. The Acute Dermal studies for all 4 formulations are acceptable and adequate for conditional registration purposes; however, please note the following:

   (a) At least 3 dose levels of the test substance in addition to the controls must be tested.

   (b) If data based on testing with at least 5 animals per sex with abraded skin are submitted showing that the LD_{50} is greater than 2 g/kg with a 24-hour contact period, no further testing at other dose levels is necessary.

3. Acute Inhalation studies were not submitted for any of the formulations. These studies must be submitted if required. You will find an outline of this study as well as a description of when this study is not required under §163.81-3 of the enclosed "Proposed Guidelines for Human Hazard Evaluation." If the study is not required according to §163.81-3, you must submit a statement to that effect.

4. The following Eye Irritation studies are invalid:

   (a) Stillmeadow Report #1252-79
   Formulation FL-790388
   Invalid: Summary states that corneal opacity observed in all eyes; data shows corneal opacity in 1/9 eyes.

   (b) Stillmeadow Report #1165-79
   Formulation FL-790401
   Invalid: Summary says opacity in 4/6 eyes; data shows only 2/6 eyes with corneal opacity. Summary says conjunctival irritation disappeared by day 7; data shows irritation still present at day 14.

   (c) Stillmeadow Report #1166-79
   Formulation FL-790403
   Invalid: Summary states opacity in 4/6 eyes at 24 hours; data showed no opacity.

   These discrepancies between the data and the data summaries must be reconciled by the registrant in writing.

   The remaining Eye Irritation study on formulation FL-790393 is adequate and acceptable for conditional registration purposes.

5. The Skin Irritation studies are adequate and acceptable for conditional registration purposes.

6. We note that for the Acute Oral, Acute Dermal studies each of the 4 formulations is in the same toxicity category. The Skin Irritation studies place formulations FL-790393, FL-790401, FL-790403 in toxicity category III; however, formulation FL-790388 is in toxicity category II for skin irritation. Since the two toxicity categories would include two differing precautionary statements, the four formulations may not be considered together as "alternate formulations."

7. FHB/TSS objects to the acceptance of the four alternate formulations until the concerns raised about the Acute Inhalation, Eye Irritation and Skin Irritation studies are satisfactorily resolved.

Labeling Recommendations

1. The statement "Avoid contamination of food" is a general restriction and must therefore be placed under the Directions for Use as a general restriction.

2. The preferred heading is "Statement of Practical Treatment", not "First Aid."

3. Further labeling revisions may be necessary whenever requested data (above) are submitted.

Enclosures: Proposed Guidelines

Review

1. Acute Oral Study on Dual 8E Formulation FL-790388; Stillmeadow #1355-79; November 26, 1979; Acc. No. 242552.

   Procedure: 35M and 30F Sprague-Dawley rats received oral dosages of FL-790388 at dosage rates of 1494 mg/kg (no M), 1780 mg/kg (no M), 2120 mg/kg (no M), 2516 mg/kg, 2999 mg/kg, 3570 mg/kg (no F), 4251 mg/kg (no F) or 5053 mg/kg. Initial weight of M was 200-300 g; F was 200-220 g. Animals were observed for 14 days. All animals studied were subjected to necropsies.

   Results: Mortalities reported were: 3/5F at 1494 mg.kg (no M); 2/5F at 1780 mg/kg (no M); 4/5F at 2120 (no M); 1/5M and 2/5F at 2516 mg /kg; 1/5M and 4/5F at 2999 mg/kg; 2/10M at 3570 mg/kg; 3/10M at 4251 mg/kg (no F); 4/5M and 5/5F at 5053 mg/kg. Symptoms included: piloerection, epistaxis, salivation, ptosis, lacrimation, diarrhea, polyuria, dilated pupils, activity decrease, exophthalmos, rigid muscle tone, convulsions, hair loss, tremors and ataxia. Necropsy revealed: chromodacryorrhea; urinary bladder empty; discoloration of stomach mucosa; discoloration of stomach and intestinal contents; dilated renal pelvis; duodenum adhered to other tissues; bloody discharge about mouth; discoloration of lungs, discoloration of thymus; gastrointestinal tract distended with gas, testes drawn into abdominal cavity. LD_{50} for M was 4250 mg/kg with a 95% confidence range of 3607-5007 mg/kg. For F, LD_{50} was 2700 mg./kg with a range of 1212-2356 mg/kg.

   Study Classification: Core Guideline Data.

   Toxicity Category: III-CAUTION.

2. Acute Dermal Study on Dual 8E Formulation FL-790388; Stillmeadow #1356-79; October 23, 1979; Acc. No. 242552.

   Procedure: 5M, 5F New Zealand white rabbits were exposed to 5031 mg/kg of FL-790388, 2M and 3F had abraded skin. Exposure was for 24 hours under occlusive wrap. Observations were made for 14 days. All animals were subjected to necropsies.

   Results: Erythema and edema, shallow lateral fissuring, eschar formation, skin sloughing, activity decrease, constricted pupil, no feces, no urination, diarrhea and ptosis were observed. Only death was 1 abraded male. Necropsy revealed: gastrointestinal tract distended with gas and green liquid, discoloration of lungs, intestinal contents. LD_{50} is greater than 5031 mg/kg.

Study Classification: Core Minimum Data. Only 2M, 3F were abraded.

Toxicity Category: III-CAUTION.

3. Eye Irritation Study on Dual 8E Formulation FL-790388; Stillmeadow #1252-79; August 3, 1979; Acc. No. 242552.

Procedure: 0.1 ml of FL-790388 was instilled into one eye of each of 9 New Zealand white rabbits. In 3 eyes 30 seconds post-instillation, eyes were washed with room temperature deionized water for one minute. Eyes were scored at 24, 48, 72 hours; 4, 7, 14 and 21 days.

Results: Nonwashed eyes at 24 hours showed 1/6 with a "+" corneal opacity score, ulceration noted in 1/6, stippling with 3/6; iris irritation in 5/6=1 and 1/6=2; redness described as 5/6=2, 1/6=3; chemosis in 5/6=3, 1/6=4; discharge in 6/6=2. Only true corneal opacity observed was 1/6=5 at 72 hours and 4 days in nonwashed eyes. At 7 days unwashed eyes showed 2/6 with stippling, 5/6=1 for redness; chemosis in 2/6=2 and 1/6=4. By 21 days unwashed eyes showed only redness in 2/6=1 and chemosis in 2/6=1.

Washed eyes showed no corneal opacity, no iris irritation. At 24 hours redness in 2/3=1, 1/3=2; chemosis in 3/3=2 and discharge is 2/3=1 and 1/3=2. All washed eyes were clear by day 7.

Study Classification: Invalid data. Summary states that corneal opacity observed in all eyes; data shows true corneal opacity only in 1/9 eyes. However, according to the data, the correct toxicity category for this formulation would be II.

4. Skin Irritation Study on Dual 8E Formulation FL-790388; Stillmeadow #1357-79; October 5, 1979; Acc. No. 242552.

Procedure: 6 New Zealand white rabbits were exposed to 0.5 ml of FL-790388. Each animal was exposed at 4 sites, 2 abraded and 2 intact. Exposure was for 24 hours under occlusive wrap. Scoring was done at 24 and 72 hours.

Results: Intact sites at 24 hours showed erythema at 12/12=3; edema observed was 1/12=1, 3/12=2, 5/12=3, 3/12=4. By 72 hours intact sites showed erythema at 11/12=2, 1/12=3; edema was 1/12=1, 8/12=2, 3/12=3. Abraded sites at 24 hours showed erythema at 12/12=3 and edema was 2/12=2, 7/12=3, 3/12=4. At 72 hours, abraded sites showed erythema at 9/12=2, 3/12=3; edema exhibited was 7/12=2, 5/12=3 with 1/12 sites showing shallow lateral fissuring. The Primary Irritation Index is 5.21.

Study Classification: Core Guideline Data.

Toxicity Category: II-WARNING.

5. Acute Oral Study on Dual 8E Formulation FL-790393; Stillmeadow #1352-79; Nov. 29, 1979; Acc. No. 242553.

Procedure: 30M (200-290g) and 45F (200-225g) received a dosage of FL-790393 by oral intubation. Animals were observed for 14 days. All animals were subjected to necropsies.

Results: Mortalities reported were: 1/5F at 1577 mg/kg (no M); 4/5F at 1755 mg/kg (no M); 4/5F at 1955 mg/kg (no M); 4/5F at 2177 mg/kg (no M); 4/5F at 2422 mg/kg (no M); 2/5F at 2699 mg/kg (no M), 0/5M and 4/5F at 2999 mg/kg; 5/5F at 3333 mg/kg (no M); 4/5M at 4544 mg/kg (no F); 2/5M and 5/5F at 5055 mg/kg; 5/5M at 5632 mg/kg (no F); 4/5M at 6265 mg/kg (no F); 4/5M at 6976 mg/kg (no F). Symptoms included: epistaxis; salivation; lacrimation; bright yellow urine; emaciation; chromodacryorrhea; diarrhea; polyuria; hematuria; rigid muscle tone; hypersensitivity to touch; pupils constricted, dilated; ptosis; exophthalmos; convulsions; tremors; activity decrease; ataxia; respiratory gurgle. Necropsy revealed: discoloration of stomach, intestinal mucosa and contents, liver, lungs, mesenteric lymph nodes, thymus, adrenal glands; bloody discharge from mouth; pronounced serosal blood vessels; gastrointestinal tract distended with gas; testes drawn into abdominal cavity. The LD_{50} for M was 4550 mg/kg with a 95% confidence range of 3622-5716 mg/kg; LD_{50} for F was 1680 mg/kg with a range of 1305-2163 mg/kg.

Study Classification: Core Guideline Data.

Toxicity Category: III-CAUTION.

6. Acute Dermal Study for Dual 8E Formulation FL-790393; Stillmeadow #1353-79; Oct. 23, 1979; Acc. No. 242553.

Procedure: 5M, 5F New Zealand white rabbits were exposed to a 5010 mg/kg dosage of FL-790393. Abrasions were made on 2M, 3F. Exposure was for 24 hours under occlusive wrap. Animals were observed for 14 days. All animals were subjected to necropsies.

Results: No deaths. Symptoms included: shallow lateral fissuring of exposure area, eschar formation, sloughing, deep lateral fissuring accompanied by bleeding, erythema and edema.

Study Classification: Core Minimum Data. Only 2M, 3F were abraded.

Toxicity Category: III-CAUTION.

7. Eye Irritation Study on Dual 8E Formulation FL-790393; Stillmeadow #1253-79; Aug. 7, 1979; Acc. No. 242553.

Procedure: 0.1 ml of FL-790393 was instilled into one eye of each of

9 New Zealand white rabbits. Three of the rabbits had the treated eye rinsed 30 seconds post-treatment with room temperature deionized water for 1 minute. Animals were scored at 24, 48, 72 hours; 4, 7, 14 and 21 days.

Results: At 24 hours nonwashed eyes exhibited no corneal opacity, 4/6 with stippling, 1/6 with ulceration; iris irritation in 3/6=1, 2/6=2; redness in 3/6=2, 3/6=3; chemosis in 3/6=3, 3/6=4; discharge in 1/6=1, 4/6=2, 1/6=3. At 7 days only 1/6 with stippling; redness in 3/6=1; chemosis in 4/6=1 and 1/6=2 for nonwashed eyes. All eyes were clear at day 21. Only corneal opacity observed in nonwashed eyes was 1/6=15 at 72 hours which decreased to 1/6=10 at 4 days, then clear.

Washed eyes at 24 hours showed no corneal opacity, no iris irritation; redness in 2/3=1, 1/3=2; chemosis in 2/3=1, 1/3=2; discharge in 2/3=1. By day 7, chemosis in 1/3=1. All clear by day 14.

Study Classification: Core Guideline Data.

Toxicity Category: II-WARNING.

8. Skin Irritation Study for Dual 8E Formulation FL-790393; Stillmeadow #1354-79; Oct. 5, 1979; Acc. No. 242553.

Procedure: 6 New Zealand white rabbits were exposed to 0.5 ml of FL-790393 at each of 4 sites (2 abraded, 2 intact) per animal. Animals were scored at 24, 72 hours.

Results: Intact sites at 24 hours showed erythema at 2/12=2, 10/12=3 and edema at 6/12=2, 6/12=3. At 72 hours, intact sites showed erythema at 5/12=1, 7/12=2 and edema at 4/12=1 and 8/12=2 with 2 having shallow lateral fissuring. Abraded sites at 24 hours exhibited erythema at 3/12=2, 9/12=3 and edema at 5/12=2 and 7/12=3. By 72 hours, abraded sites showed erythema at 5/12=1, 7/12=2 and edema at 4/12=1, 8/12=2 with 2 sites having shallow lateral fissuring. The Primary Irritation Index was 4.30.

Study Classification: Core Guideline Data.

Toxicity Category: III-CAUTION.

9. Acute Oral Study of Dual 8E Formulation FL-790401; Stillmeadow #1349-79; Nov. 21, 1979; Acc. No. 242554.

Procedure: 40M (200-300g) and 35F (200-230g) Sprague-Dawley rats were dosed with FL-790401 by oral intubation. After receiving dosage, animals were observed for 14 days. All animals were subjected to necropsies.

Results: Mortalities reported are: 1/5F at 666 mg/kg (no M); 4/5F at 812.4 mg/kg (no M); 0/5M and 3/5F at 995.5 mg/kg; 0/5M and 1/5F at 1233 mg/kg; 0/5M and 5/5F at 1513 mg/kg; 1/5M and 4/5F at 1860 mg/kg; 1/5M at 2297 mg/kg (no F); 5/5M at 2835 (no F); 4/5M at 3485 mg/kg (no F); 5/5M and 5/5F at 5042 mg/kg. Symptoms included: piloerection; salivation; lacrimation; bloody discharge about mouth; chromodacryorrhea; diarrhea; polyuria; pupils constricted, dilated; ptosis; exophthalmos; rigid muscle tone; convulsions; hypersensitivity to touch; tremors; activity decrease; ataxia; respiratory gurgle. Necropsy revealed: discoloration of thymus, stomach, intestinal contents, lungs, adrenals, spleen; enlarged ovaries; red liquid in ovaries; pronounced serosal blood vessels; gastrointestinal tract distended with gas; testes drawn into abdominal cavity. The LD_{50} for M was 2690 mg/kg with 95% confidence range of 2157-3355 mg/kg. For F, the LD_{50} was 820 mg/kg with a 95% confidence range of 512-1314 mg/kg.

Study Classification: Core Guideline Data.

Toxicity Category: III-CAUTION.

10. Acute Dermal Study of Dual 8E Formulation FL-790401; Stillmeadow #1350-79; Oct. 25, 1979; Acc. No. 242554.

Procedure: 5M, 5F New Zealand rabbits were exposed to 5009 mg/kg of FL-790401. Of these 10 animals, 2M and 3F were abraded. Exposure was for 24 hours under occlusive wrap. Animals were observed for 14 days. All animals were subjected to necropsies.

Results: Mortalties were 1M and 1F with abraded skin. Symptoms included: small, few feces; constricted pupils; labored breathing; activity decrease; respiratory gurgle. Necropsies revealed: gastrointestinal tract distended with gas; red liquid in abdominal, pleural cavity; discoloration of liver, lungs. LD_{50} is greater than 5009 mg/kg. Also observed during study were erythema and edema without necrosis or ulceration.

Study Classification: Core Minimum Data. Only 2M and 3F were abraded.

Toxicity Category: III-CAUTION.

11. Eye Irritation Study for Dual 8E Formulation FL-790401; Stillmeadow #1165-79; June 4, 1979; Acc. No. 242554.

Procedure: One eye of each of 9 New Zealand white rabbits received 0.1 ml of FL-790401. Three of the treated eyes were rinsed 30 seconds post-instillation with room temperature deionized water for 1 minute. Animals were observed at 24, 48, 72 hours; 4, 7, 14 and 21 days.

Results: The nonwashed eyes at 24 hours showed no corneal opacity, 2/6 with stippling and 1/6 with ulceration; iris irritation in 4/6=1; redness in 4/6=2 and 2/6=3; chemosis in 1/6=2, 2/6=3 and 3/6=4; discharge in 1/6=1, 5/6=2. By 7 days, unwashed eyes exhibited no corneal opacity, no iris irritation; redness in 3/6=1; chemosis in 1/6=1 and 1/6=2. Only corneal opacity observed was in 1/6=5 at 4 days. All nonwashed eyes were clear at 21 days. Washed eyes at 24 hours exhibited no corneal opacity; no iris irritation; redness in 2/3=1; chemosis in 2/3=2; discharge in 1/3=1. At day 7, redness in 1/3=1. All washed eyes were clear at 14 days.

Study Classification: Invalid Data. Summary says opacity in 4/6 eyes; data shows only 2/6. Summary says conjunctival irritation disappeared by day 7; data shows irritation still present at day 14. If data were correct, correct toxicity category would be II.

12. Skin Irritation Study for Dual 8E Formulation FL-790401; Stillmeadow #1351-79; Oct. 8, 1979; Acc. No. 242554.

Procedure: 6 New Zealand white rabbits were exposed to 0.5 ml of FL-790401 at each of 2 abraded and 2 intact sites per animal. Exposure was for 24 hours under occlusive wrap.

Results: At 24 hours, intact sites showed erythema at 1/12=1, 3/12=2, 8/12=3 and edema at 1/12=1, 3/12=2, 7/12=3 and 1/12=4. Intact sites at 72 hours exhibited erythema in 2/12=1, 9/12=2, 1/12=3 and edema in 1/12=1, 8/12=2, 3/12=3. At 24 hours, abraded sites exhibited erythema in 4/12=2, 8/12=3 and edema in 1/12=1, 3/12=2, 6/12=3 and 2/12=4. By 72 hours, erythema in 2/12=1, 9/12=2, 1/12=3 and edema at 1/12=1, 7/12=2 and 4/12=3 for abraded sites. The Primary Irritation Index was 4.73.

Study Classification: Core Guideline Data.

Toxicity Category: III-CAUTION.

13. Acute Oral Study for Dual 8F Formulation FL-790403; Stillmeadow #1346-79; Nov. 26, 1979; Acc. No. 242555.

Procedure: 40M (200-290g) and 30F (200-230g) Sprague-Dawley rats received a dosage of FL-790403 by oral intubation. Animals were observed for 14 days. All animals were subjected to necropsies.

Results: Mortalities reported were: 0/5F at 808.4 mg/kg (no M); 0/5M and 2/5F at 994.8 mg/kg; 1/5M and 3/5F at 1224 mg/kg; 0/5M and 2/5F at 1505 mg/kg; 2/5M and 5/5F at 1853 mg/kg; 1/5M at 2279 mg/kg (no F); 3/5M at 2807 mg/kg (no F); 4/5M at 3447 mg/kg (no F); 5/5M and 5/5F at 5053 mg/kg. Symptoms included: piloerection; salivation;

lacrimation; polyuria; diarrhea; rigid muscle tone; chromodacryorrhea; pupils dilated, constricted; Straub tail; activity decrease; tremors; ptosis; ataxia. Necropsy showed: stomach, small intestines filled with milky liquid; brown spots on cardiac region of stomach; testes withdrawn into abdomen. The LD_{50} for M was 2500 mg/kg with a 95% confidence range of 1977-3161 mg/kg; the LD_{50} for F was 1250 mg/kg with a 95% confidence range of 979-1595 mg/kg.

Study Classification: Core Guideline Data.

Toxicity Category: III-CAUTION.

14. Acute Dermal Study for Dual 8E Formulation FL-790403; Stillmeadow #1347-79; Oct. 23, 1979; Acc. No. 242555.

Procedure: 5M, 5F New Zealand white rabbits (1.8 - 2.9kg) were exposed to 5008 mg/kg of FL-790403. In this study, 2M and 3F had abraded skin. Exposure was for 24 hours under occlusive wrap. Animals were observed for 14 days. All animals were subjected to necropsies.

Results: No mortalities. Observations included very slight to severe erythema, very slight to severe edema, shallow lateral fissuring, eschar formation, sloughing of various thicknesses of skin, focal areas of bleeding. Necropsies revealed only 1/10 lungs white with red spots.

Study Classification: Core Minimum Data. Only 2M, 3F abraded.

Toxicity Category: III-CAUTION.

15. Eye Irritation Study for Dual 8E Formulation FL-790403; Stillmeadow #1166-79; June 4, 1979; Acc. No. 242555.

Procedure: 0.1 ml of FL-790403 was instilled into one eye of each of 9 New Zealand rabbits. After thirty seconds the treated eyes of 3 rabbits were washed for one minute with room temperature deionized water. Eyes were scored at 24, 48, 72 hours; 4, 7, 21 days.

Results: Nonwashed eyes at 24 hours showed no corneal opacity, 2/6 with stippling, 2/6 with ulcerations; iris irritation in 2/6=1; redness in 2/6=1, 4/6=2; chemosis in 1/6=1, 3/6=2 and 2/6=3; discharge in 2/6=1; 2/6=2. At 7 days, redness in 2/6=1; chemosis in 4/6=1. All nonwashed eyes clear by day 21.

Washed eyes at 24 hours showed no corneal opacity; no iris irritation; redness in 2/6=1; chemosis in 2/6=1, 1/6=2. All washed eyes were clear by 72 hours.

Study Classification: Invalid Data. Summary states opacity in 4/6 eyes at 24 hours; data showed no opacity. If data are correct, toxicity category would be II.

16. Skin Irritation Study for Dual 8E Formulation FL-790403; Stillmeadow #1348-79; October 5, 1979; Acc. No. 242555.

Procedure: 6 New Zealand white rabbits were exposed to 0.5ml of FL-790403 at each of 4 sites, 2 abraded and 2 intact. Exposure was for 24 hours under occlusive wrap. Scoring at 24, 72 hours.

Results: At 24 hours intact sites showed well-defined to severe erythema and slight to severe edema. By 72 hours intact sites exhibited very slight to severe erythema and very slight to moderate edema. With abraded sites at 24 hours, well-defined to severe erythema and slight to severe edema observed. At 72 hours the abraded sites exhibited very slight to moderate edema. The Primary Irritation Index was 4.65.

Study Classification: Core Guideline Data.

Toxicity Category: III-CAUTION.