

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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DATE: August 18, 1980

SUBJECT: Treflan MTF
EPA File Symbol: 1471-RRA

FROM: Sherell A. Sterling *SSJ*
FHB/TSS *8-26-80*
E 9/5/80

TO: Richard Mountfort
Product Manager, 23
Applicant: Elanco Products Co.
P.O. Box 1750
Indianapolis, IN 46285

889

Active Ingredient:

Trifluralin..... 41.2%

Inert Ingredients..... 58.8%

Background: The applicant submitted Acute Oral, Acute Dermal, Acute Inhalation, Eye and Skin Irritation studies. The method of support chosen for this conditional registration is "Cite-All." The studies were conducted by the Lilly Research Laboratories in Greenfield, Indiana and are under accession no. 242796.

Recommendations:

1. The Acute Oral study is adequate and acceptable for conditional registration purposes. Please note the following for future studies:
 - a. Individual response data must be reported in tabular form by sex and dose level.
 - b. Animals must be observed for 14 days post-treatment.
 - c. All animals must be subjected to necropsies
 - d. If data based on testing with at least 5 animals per sex are submitted showing that the LD₅₀ is greater than 5g/kg, no further testing at other dose levels is necessary. If such data are not submitted, at least 3 dose levels must be tested.

1
538

-2-

Please refer to §163.81-1 of the "Proposed Guidelines for Human Hazard Evaluation" for further information.

2. The Acute Dermal study is adequate and acceptable for conditional registration purposes. Please note the following for future studies:
 - a. The Acute Dermal and Skin Irritation studies must be conducted separately.
 - b. All animals must be subjected to necropsy.
 - c. Individual responses must be reported in tabular form by sex and dose level.
 - d. If data are submitted with at least 5 animals per sex with abraded skin showing that the LD₅₀ is greater than 2g/kg with a 24 hour contact period, no further testing is necessary. In all other cases, at least 3 other dose levels must be tested.

Please refer to §163.81-2 of the "Proposed Guidelines for Human Hazard Evaluation" (copy enclosed) for further information.

3. The Acute Inhalation study is considered Supplementary Data and is therefore not adequate to support conditional registration. Please note the following comments:
 - a. The atmospheric concentration of the test substance in the test chamber must be determined. Please note that the toxicity categories outlined in 40 CFR 162.10 are based on atmospheric, not nominal concentrations.
 - b. Body weights must be reported.
 - c. Individual response data must be reported in tabular form by sex and dose level (expressed as atmospheric concentration).

Please refer to the "Proposed Guidelines," §163.81-3 for further information concerning an acceptable method of testing.

-3-

4. The Eye Irritation study is adequate and acceptable for conditional registration. However, the following comments are made to improve future tests:
 - a. Scoring must be done by Draize's method which includes scoring for ocular discharge.
 - b. An "eyewash" group (minimum of 3 animals) must be treated and then subjected to ocular irrigation. Please refer to §163.81-4 of the "Proposed Guidelines" for further details.
5. The Skin Irritation study is adequate and acceptable for conditional registration. The following comments are included to improve future testing procedures:
 - a. The Acute Dermal and Skin Irritation studies must be conducted separately.
 - b. The correct dosage for the Skin Irritation test is 0.5 ml liquid or 0.5g solid material.
 - c. Four sites (2 abraded and 2 intact) must be tested on each of six animals.
 - d. Individual response data must be submitted in tabular form.
 - e. The Primary Irritation Index must be calculated and reported.

Please see §163.81-5 of the "Proposed Guidelines" for further details on this study.

6. FHB/TSS has no objection to the conditional registration of this product provided that an acceptable Acute Inhalation study is submitted and the following labeling revisions are made.

-4-

Note to the PM:

Other trifluralin products which would be considered similar (i.e. 1471-112) bear a different signal word, hence, those products are not substantially similar.

Labeling Recommendations:

1. The signal word is WARNING as proposed by the applicant.
2. The preferred placement of the "Keep out of reach of children" statement is above the signal word.
3. The preferred referral statement is "See side panel for additional precautionary statements".
4. On the side panel, the signal word WARNING must be preceded by the heading "Precautionary Statements". This must be followed by the subheading "Hazards to Humans and Domestic Animals", not just "Humans." Likewise, the subheading "Environmental" must be changed to "Environmental Hazards."
5. The "Hazards to Humans and Domestic Animals" section must be revised to the following (or similar) statement:

"Causes eye irritation. Do not get in eyes,
on skin or on clothing. Harmful if swallowed or
absorbed through the skin."
6. The statement "Do not contaminate foodstuffs or feeds" must appear as a general restriction under the "Directions for Use."
7. The heading "First Aid" must be changed to "Statement of Practical Treatment."
8. The statement "Do not use or store near heat or open flame" must appear under the subheading "Physical or Chemical Hazards." This section must directly follow the

-5-

"Environmental Hazards" section. This statement may then be removed from the current "Storage" section.

9. Please refer to the enclosed "Storage and Disposal" sheets. These sheets list the statements which are required for this product.
10. If the product bulletin contains information with regards to the precautionary labeling, the product bulletin must be revised as outlined above.
11. Further labeling revisions may be necessary when the requested data are submitted.

Review:

1. Acute Toxicity of Orally Administered Treflan 4EC in Rats ;
Lilly Research Labs #R-0-23 1-75 and R-0-232-75; April 1979

Procedure: Groups of 10 M (114 ± 1.9 g) and 10 F (119 ± 1.5 g) Wistar rats received an oral dosage of 2 ml/kg (2.33g/kg) of Treflan 4EC, lot # X-27572. Animals were observed for 7 days post-dosing.

Results: No mortalities, Hypoactivity, leg weakness noted at 2 hours post-treatment; diuresis with yellow urine at 24 hours. All animals appear normal at 48 hours.

Study Classification: Core Minimum Data. Individual response data must be reported in tabular form. Animals should be observed for 14 days. All animals must be subjected to necropsies at death or termination of the study. One dosage level only was tested.

Toxicity Category: III - CAUTION

2. Acute Dermal Toxicity and Irritation Testing of Treflan 4EC in Rabbits (Acute Dermal); Lilly labs No. B - D - 94-75; April 1979

-6-

rabb^{its} *sd*

Procedure: 3M, 3F New Zealand white ~~rats~~ (2.11 ± 0.12kg) received an application of 2 ml/kg (2.33 g/kg) of Treflan 4 EC, lot #X-27572. Three animals had the application site abraded. Exposure was for 24 hours under occlusive wrap.

Results: No mortalities. One animal had diarrhea 3 days after treatment, cleared within 24 hours which reoccured after 14 days; this animal experienced weight loss. At 24 hours, 4/6 rabbits had slight erythema which cleared by 72 hours. Increased weight seen in 5/6 rabbits.

Study Classification: Core Minimum Data for Acute Dermal study. No necropsies. Only 6 animals; only 3 abraded animals. No individual responses reported.

Toxicity Category: III-CAUTION for Acute Dermal study.

3. Acute Inhalation Toxicity Testing of Treflan 4EC in Rats;
Lilly Labs #R-H-43-75; April 1979

Procedure: 5M, 5F Wistar rats were exposed to a nominal concentration of 38.5 µl Trifluralin 4EC/L air. Exposure was head only for 1 hour. The chamber was a 61 liter spherical chamber with an air flow of 338 L/hr. Aerosol was generated by DeVilbiss model 841 nebulizer. Animals were observed for 2 weeks.

Results: No mortalities. Ataxia was observed in animals, but returned to normal within 24 hours. Exposed pelage stained yellow.

Study Classification: Core Supplementary Data. Atmospheric concentration must be 5mg/l for 4 hours or documented as the maximum obtainable concentration. Body weights not taken. Individual response data not reported. Only nominal concentration determined.

4. Acute Ocular Irritation Testing of Treflan 4EC in Rabbits;
Lilly Labs #B-E-76-75; April 1979

-7-

Procedure: 0.1 ml of Treflan 4EC was instilled into one eye of 6 New Zealand white rabbits without irrigation. Animal eyes were scored at 1, 24, 48, 72 hours and 7 days; sodium fluorescein testing at 24, 72 hour observation.

Results: At 24 hours, corneal irritation in 5/6=1; iris irritation in 2/6=1; hyperemia in 6/6=1; chemosis observed in 4/6=1, 1/6=2. All eyes appeared normal at 7 days. Fluorescein stain was positive for 5/6 at 24 hours, negative for 6/6 at 72 hours.

Study Classification: Core Minimum Data. Discharge scores not reported. An eyewash group was not tested.

Toxicity Category: II - WARNING

5. Acute Dermal Toxicity and Irritation Testing of Treflan 4EC in Rabbits (Skin Irritation); Lilly Labs # B-D-94-75; April 1979

Procedure: See #2 above.

Results: See #2 above.

Study Classification: Core Minimum Data. This study should be run with 6 animals at 4 sites per animal (2 abraded, 2 intact) at a level of 0.5 ml test substance.

Toxicity Category: IV - CAUTION.