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

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AUG 13 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

**MEMORANDUM**

SUBJECT: N-Phenyl-N'-(1,2,3-thidiazyl) urea (Thidiazuron Technical): Review of 2 studies submitted by the registrant on the primary dermal irritation (81-5) and the primary eye irritation (81-4) of Thidiazuron Technical in rabbits.

Caswell No.: 659A
HED Project No.: 2-0857
MRID Nos: 420996-01, -02

FROM: Walter J. Kozumbo, Ph.D., Toxicologist
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)
Walter J Kozumbo 8-5-92

TO: Christine Rice/Thomas Myers, PM Team 52
Special Review and Reregistration Division (H7508W)

THRU: Stephen C. Dapson, Ph.D., Acting Section Head
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)
Stephen C. Dapson 8/5/92

and

Marcia Van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (H7509C)
MVanGemert 8/5/92

REGISTRANT: NOR-AM Chemical Company

ACTION REQUESTED: For reregistration purposes, evaluate studies on the potential of Thidiazuron Technical to induce primary eye and primary dermal irritation in rabbits, according to FIFRA guidelines 81-4 and 81-5, respectively.

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**CONCLUSIONS:**

1. Primary Eye Irritation in Rabbits (81-4) (MRID # 420996-01): In rabbits, Thidiazuron Technical produced mild irritation of the conjunctiva, consisting of redness and chemosis that resolved within 48 h. The intensity of irritation was sufficiently mild (numerical score of 1) so as not to be considered a positive effect. Only positive responses are considered in characterizing toxicity categories.

This study satisfies guideline requirements and is classified as Guideline. Toxicity Category IV.

2. Primary Dermal Irritation in Rabbits (81-5) (MRID # 420996-02): Neither erythema nor edema was observed in rabbit skin for up to 4 days after a 4-h dermal treatment with Thidiazuron Technical at a dose of 0.5 g/rabbit. This study indicates that Thidiazuron Technical is nonirritating to rabbit skin.

This study satisfies guideline requirements and is classified as Guideline. Toxicity Category IV.

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Reviewed by: Walter J. Kozumbo, Ph.D. Walter J. Kozumbo 8-5-92
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Stephen C. Dapson, Ph.D. Stephen C. Dapson 8/5/92
Section I, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

| | |
|---|---|
| STUDY TYPE: | Primary Eye Irritation/Rabbits (81-4) |
| CHEM. TOX. NO.: | 659A |
| MRID NUMBER: | 420996-01 |
| TEST MATERIAL: | Thidiazuron Technical |
| STUDY NUMBER: | TOX 91116 |
| TESTING FACILITY: | Huntingdon Research Centre, Ltd.<br>P.O. Box 2<br>Huntingdon, Cambridgeshire<br>PE18 6ES, ENGLAND |
| SPONSOR: | NOR-AM Chemical Company<br>3509 Silverside Road<br>P.O. Box 7495<br>Wilmington, DE 19803 |
| TITLE OF REPORT: | Thidiazuron Technical: Rabbit Eye Irritancy Study |
| AUTHORS: | Sheena R. Kynoch, Michael P. Liggett, and Lewis A. McRae |
| REPORT ISSUED: | October 23, 1991 |
| CONCLUSIONS: | In rabbits, Thidiazuron Technical produced mild irritation of the conjunctiva, consisting of redness and chemosis that resolved within 48 h. The intensity of irritation was sufficiently mild (numerical score of 1) so as not to be considered a positive effect. Only positive responses are considered in characterizing toxicity categories. |
| TOXICITY CATEGORY: | IV |
| CLASSIFICATION: | Guideline --- This study satisfies guideline requirements (81-4) for a primary eye irritation study in rabbits. |

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## I. MATERIALS

### A. Test Material:

Thidiazuron technical is a beige powder that was stored under darkened conditions at room temperature. It was 99.3% pure (batch # CR 19111/01/820902).

### B. Test Animals:

The test animals were 3 (2 females and 1 male) adult New Zealand white rabbits obtained from Froxfield Farms (U.K.) LTd., Petersfield, Hampshire, England. At the start of the ocular study, the rabbits were 13 to 14 weeks old and weighed between 2.9 and 3.3 kg. The animals were housed individually in metal cages with perforated floors. They were acclimated for an undescribed period prior to initiation of the study and were provided food (SDS Stanrab P Rabbit Diet) and water ad libitum. Data from quarterly analysis of water were housed in the Archives at the Huntingdon Research Centre. Temperature was maintained at about 19 °C and relative humidity at between 30 and 70%. A light/dark cycle of 12/12 h was artificially imposed upon animals identified by ear tags.

## II. METHODS

The eyes of the rabbits were examined prior to the study (without use of fluorescein dye). The corneas and irises were found to have no pre-existing abnormalities or irritation. Thidiazuron Technical (0.1 ml or 87 mg) was instilled under the lower eyelid into the conjunctival sac of one eye from each animal and gently held shut for 1 second. The other eye of was untreated and served as negative control. No statement was made to indicate that eyes were washed out at any time during the experimental period (7 days). Animals were examined daily for clinical signs of toxicity.

The eyes were examined at 1 h post instillation and on days 1, 2, 3, 4, and 7 following treatment. Eye irritation was scored numerically using an ocular irritation index (see attached pp. 13 & 14). For each animal, the mean irritation score was calculated for days 1, 2, and 3.

## III. RESULTS

Table 1 (attached p. 15) presents the individual animal data acquired to the end of the study on day 7. There was no indication of either corneal or iridial irritation at any time during the study. In all three rabbits, mild conjunctival redness was observed 1 h and 1 day post treatment, and mild chemosis at the 1 h time point only. Because each of these effects received a numerical score of 1, they are not

considered to be a positive response. By day 2 resolution of these inflammatory indicators was complete.

GLP/QA statements were signed and attached to the submitted study report.

IV. CONCLUSIONS

In rabbits, Thidiazuron Technical produced mild irritation of the conjunctiva, consisting of redness and chemosis that resolved within 48 h. The intensity of irritation was sufficiently mild (numerical score of 1) so as not to be considered a positive effect. Only positive responses are considered in characterizing toxicity categories.

V. TOXICITY CATEGORY IV

VI. CORE CLASSIFICATION Guideline --- This study satisfies guideline requirements (81-4) for a primary eye irritation study in rabbits.

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Pages 6 through 8 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.

Y FIFRA registration data.

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Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Stephen C. Dapson, Ph.D. Stephen C. Dapson 8/5/92
Section I, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

| | |
|---|---|
| STUDY TYPE: | Primary Dermal Irritation/Rabbits (81-5) |
| CHEM. TOX. NO. | 659A |
| MRID NUMBER: | 420996-02 |
| TEST MATERIAL: | Thidiazuron Technical |
| STUDY NUMBER: | TOX 91115 |
| TESTING FACILITY: | Huntingdon Research Centre, Ltd.<br>P.O. Box 2<br>Huntingdon, Cambridgeshire<br>PE18 6ES, England |
| SPONSOR: | NOR-AM Chemical Company<br>3609 Silverside Road<br>P.O. Box 7495<br>Wilmington, DE 19803 |
| TITLE OF REPORT: | Thidiazuron Technical: Rabbit Skin Irritancy Study |
| AUTHORS: | Michael P. Liggett and Lewis A. McRae |
| REPORT ISSUED: | October 23, 1991 |
| CONCLUSIONS: | Neither erythema nor edema was observed in rabbit skin for up to 4 days after a 4-h dermal treatment with Thidiazuron Technical at a dose of 0.5 g/rabbit. This study indicates that Thidiazuron Technical is nonirritating to rabbit skin. |
| TOXICITY CATEGORY: | IV |
| CLASSIFICATION: | Guideline --- This study satisfies guideline requirements (81-5) for a primary dermal irritation study in rabbits. |

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I. MATERIALS

A. Test Material:

Thidiazuron technical is a beige powder that was stored under darkened conditions at room temperature. It was 99.3% pure (batch # CR 19111/01/820902).

B. Test Animals:

The test animals were 3 female adult New Zealand white rabbits obtained from Froxfield Farms (U.K.) LTd., Petersfield, Hampshire, England. At the start of the study, the rabbits were 10 to 12 weeks old and weighed between 2.3 and 2.7 kg. The animals were housed individually in metal cages with perforated floors. They were acclimated for an undescribed period prior to initiation of the study and were provided food (SDS Stanrab P Rabbit Diet) and water ad libitum. Data from quarterly analysis of water were housed in the Archives at the Huntingdon Research Centre. Temperature was maintained at about 19 °C and relative humidity at between 30 and 70%. A light/dark cycle of 12/12 h was artificially imposed upon animals identified by ear tags.

II. METHODS

Thidiazuron Technical (0.5 g) was applied to a 2.5 $cm^2$ wet (0.5 ml water) gauze that was placed on the previously shaven (24 h earlier) back (10 $cm^2$) of each female rabbit. Elastic adhesive bandage ("Elastoplast") was used to occlude each treatment site for 4 hours. After the exposure period, the semi-occlusive dressing was removed and the treated skin was washed with water to remove remaining residue.

The rabbits were observed at 1 (30 min following treatment), 2, 3, and 4 days post treatment for signs of toxicity and of dermal irritation, which included erythema and edema. Skin irritation reactions were rated relative to unexposed skin near the treated area using a numerical scoring system (see p. 13).

III. RESULTS

After a 4-h exposure to Thidiazuron Technical (0.5 g), none of the 3 rabbits displayed any signs of erythema or edema at any of the post-treatment times (1, 2, 3, and 4 days). See Table 1 on attached p. 14. The test article had a total numerical score of 0.0 for erythema and edema, indicating that it was not irritating to the skin of rabbits.

QA/GLP statements were affixed to the study.

IV. CONCLUSIONS

Neither erythema nor edema was observed in rabbit skin for up to 4 days after a 4-h dermal treatment with Thidiazuron Technical at a dose of 0.5 g/rabbit. This study indicates that Thidiazuron Technical is nonirritating to rabbit skin.

V. TOXICITY CATEGORY: IV

VI. CORE CLASSIFICATION: Guideline --- This study satisfies guideline requirements (81-5) for a primary dermal irritation study in rabbits.

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Pages 12 through 13 are not included.

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____ Identity of product inert ingredients.

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