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

004495

3/31/85

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Endosulfan (Thionex) 35 EC Acute Toxicology Studies for the Endosulfan Registration Standard

TO: George La Rocca, PM 15
Registration Division

FROM: Margaret L. Jones
Review Section IV
Toxicology Branch

THROUGH: Robert P. Zendzian, Ph.D., Acting Head
Review Section IV
Toxicology Branch
HED (TS-769)

Theodore M. Farber, Ph.D., Chief
Toxicology Branch

Compound: Endosulfan (Thionex) 35 EC Tox. Chem: 420

Registration No: 11678-25

Registrant: Makhteshim-Agan (America), Inc. for Makhteshim Chemical Works Ltd., Israel

Accession No.: 255157

Action Requested: The Registrant submitted five acute toxicology tests on Endosulfan 35 EC in response to the Endosulfan Registration Standard. The Product Manager asks whether review of these studies will change the signal words for the 35 EC formulation.

Conclusions:

Review of these studies produced the following Conclusions:

1. Acute Oral LD_{50}

Core Classification: Unacceptable

Conclusions: (1) Calculation of the LD_{50} (in mg/kg) was based on the concentration of active ingredient in the formulation. The LD_{50} should be calculated on the basis of mg/kg test material (35 EC) by converting ml/kg to mg/kg. Full calculations of this conversion should be presented in

1/8

the test report. (2) The test substance is not properly identified. Full identification including batch numbers and purity of the test substance should be included in the test report. (3) The LD_{50} should be calculated for males and females separately.

A corrected report must be submitted to the Agency to fulfill the Registration Standard requirements.

2. Acute Dermal LD_{50}
Core Classification: Unacceptable

Conclusion: The conclusions for the Acute Oral toxicity test apply to the Acute Dermal toxicity test.

A corrected report must be submitted to the Agency in order to fulfill the Registration Standard requirements.

3. Acute Inhalation LD_{50}

Core Classification: Unacceptable

Conclusion: The test report apparently combines parts of a report on Acute Inhalation tests on Thionex 35 EC and Thionex 50 WP. Study of the numbers supports this impression. Complete and corrected test reports for both Thionex 35 EC and Thionex 50 WP must be submitted to the Agency in order to fulfill the Registration Standard requirements.

4. Primary Eye Irritation

Toxicity Category: I
Core Classification: Minimum

Appropriate signal wording should appear on the label to reflect the assigned Toxicity Category, as found in 40 CFR 162.10 (i).

5. Primary Skin Irritation

Toxicity Category: III
Core Classification: Minimum

Other changes and recommendations in label signal words should be considered at the completion of review of the corrected reports on the Acute Oral, Acute Dermal, and Acute Inhalation studies.

Compound: Endosulfan (Thionex) 35 EC; EPA Registration No. 11678-25 004495

Citation: Acute Oral Toxicity in Rats; Makhteshim-Agan (America) Inc., Two Park Ave., N.Y., N.Y. 10016 (U.S. Sponsor); Life Science Research, Stock, Essex, CM49PE, England (Laboratory); 13 Sept.-6 Oct. 1978; LSR Report No.: 78/MAK2/432

Reviewed By: Margaret L. Jones
Chemist

Toxicity Category: Undetermined

Core Classification: Supplementary

Conclusions:

1. The LD_{50} determined by this test was 0.07 (0.04-0.14) ml/kg which is equivalent to 25 (13-49) mg/kg by probit analysis, according to the test report. The equivalence in mg/kg was apparently erroneously based on the concentration of active ingredient in the formulation. To calculate the mg/kg equivalent of a ml/kg dose the density of the liquid is necessary. The method of calculating this number should be explicitly indicated in the test report.

2. The LD_{50} was determined by using data from the entire study, including male and female animals in one group. The LD_{50} should be determined separately for males and females, particularly in light of the difference in toxicity between the sexes. (Ref.: Pesticide Assessment Guidelines, 1982, Subdivision F, 81-1 (h)(3)(iv)).

3. The test substance is not properly identified. The test substance is not identified in the report other than described as "100 ml. of Endosulphan Thionex 35 EC...received on 26 July 1978". No statement from the sponsor to indicate either the purity of the test sample or its identifying numbers is included in the test report.

4. The lower limit of the range of weights of the male rats at the outset of the test (p. 4 of the Study Report) is illegible in the copy of the report submitted to Toxicology Branch. This can be determined from the tables, however a completely legible copy should be provided for Agency records.

A corrected report must be submitted to the Agency to fulfill the Registration Standard requirements.

Compound: Endosulfan (Thionex) 35 EC; EPA Registration No. 11678-25 11425

Citation: Acute Dermal Toxicity in Rats; Makhteshim-Agan (America) Inc., Two Park Ave., N.Y., N.Y. 10016 (U.S. Sponsor); Life Science Research, Stock, Essex, CM49PE, England (Laboratory); 13 September-2 October 1978; LSR Report No.: 78/MAK3/437

Reviewed By: Margaret L. Jones
Chemist 5/25/85

Toxicity Category: Undetermined

Core Classification: Supplementary

Conclusions:

1. The LD_{50} with 95% confidence intervals determined by this test was 0.73(0.51-1.03) ml/kg or 256(181-362) mg/kg from probit analysis, according to the test report. The equivalence in mg/kg was apparently erroneously based on the concentration of active ingredient in the formulation. To calculate the mg/kg equivalence of a ml/kg dose the density of the liquid is necessary. The method of calculating this number should be explicitly indicated in the test report.

2. The LD_{50} was determined using data from the entire study, including male and female animals in one group. The LD_{50} should be determined for males and females separately, particularly in view of the difference in toxicity between the sexes. (Ref.: Pesticide Assessment Guidelines, 1982, Subdivision F, 81-2 (h)(3)(iv)).

3. The test substance is not properly identified. The test substance is not identified in the report other that described as "500 ml. of Endosulphan Thionex 35 EC...received on 26 July 1978". No statement from the sponsor to indicate either the purity of the sample or its identifying numbers is included in the test report.

A corrected report must be submitted to the Agency to fulfill the Registration Standard requirements.

4

004495

Compound: Endosulfan (Thionex) 35 EC; EPA Registration No. 11678-25

Citation: Acute Inhalation Toxicity in Rats; Makhteshim-Agan (America), Inc.; Two Park Ave.; N.Y., N.Y. 10016 (U.S. Sponsor); Life Seience Research, Stock, Essex, CM4 9PE, England; 23 November- 17 December; LSR Report No. 83/MAK 049/036

Reviewed By: Margaret L. Jones
Chemist

Toxicity Category: Undetermined

Core Guidelines: ~~Supplementary~~

Conclusions:

1. The test report is apparently the combination of two test results, one from Acute Inhalation on the 35 EC and one from Acute Inhalation of the 50 WP. The Quality Assurance Report affirms the results of the Thionex 35 EC study and the Summary pages discuss results of the study with Thionex 35 EC. The Results and Conclusions from the body of the test report, however, discuss details of a test using Thionex 50 WP. Further comparisons of information from the test report confirm the suspicion that two test reports are confused.

2. Appendix 7B is entitled "Individual absolute (g) and relative organ weights...of male rats..." but the groups listed on page 2 are female (1F, 2F, etc.)

The above discrepancies must be resolved and the Regisrant should submit full reports on Acute Inhalation studies of both Thionex 35 EC and Thionex 50 WP, including identification of the test substance and Quality Assurance statements for each study.

5

00415

Compound: Endosulfan (Thionex) 35 EC; EPA Registration No. 11678-25

Citation: Primary Eye Irritation in Rabbits; Makhteshim-Agan (America) Inc., Two Park Ave., N.Y., N.Y. 10016 (U.S. Sponsor); Life Science Research Israel Ltd., P.O. Box 139, Ness Ziona 70 451, Israel (Laboratory); 21 September-4 October 1982; LSRI Report No. MAK/030/TNX 35 EC

Reviewed By: Margaret L. Jones
Chemist

Toxicity Category: I

Core Classification: Minimum

Conclusions: The test compound produces some residual corneal opacity in 4 of 9 animals. Washing eyes after administration of the test substance did not significantly affect the results.

Materials:

Test Substance: 1144 g of Thionex 35 EC (gross) Batch No. 870021, a brown liquid received on 21 July 1982. The purity of the test substance was not specified.

Test Animals: New Zealand White rabbits from A. Loebenstein Laboratory Animals, Yoqneam, Israel.

Methods:

Nine rabbits were selected from a group which was allowed to acclimate an average of 6 days. Sodium fluorescein dye was used to detect any corneal damage or abnormality prior to testing. Animals were replaced if they showed any such lesions.

Six animals were administered 0.1 ml of the test material in one eye which remained unwashed. The remaining three animals were treated similarly but after 30 seconds exposure the eye was irrigated.

Observations were made at (unspecified) regular intervals during the first day and then at 24, 48, and 72 hours and 4, 7, 9, 12, and 13 days.

6

00445

Lesions were scored according to the method of Draize (1959) and the method described in the 1978 EPA Proposed Guidelines. Damage to the cornea was evaluated using fluorescein dye.

Results:

Unwashed Eyes: The cornea of all animals in the unwashed group showed opacity which was scattered (grade 1) or showed an iris slightly obscured (grade 2). The lesions lessened in severity by day 9 in 5 of 6 animals and three remained slightly opaque on day 13. The iris in most eyes was little affected (grade 1 in 3 animals) and cleared by day 7 in all animals. Conjunctivae were affected in all individuals with redness, chemosis, and some discharge which cleared by day 7. Total scores on day 13 did not exceed 5 for any individual and the cornea was the affected part.

Washed Eyes: The three animals in this group showed similar effects to those with washed eyes. The majority of effects cleared by day 7. Slight residual corneal opacity remained in one animal at day 13.

7

004495

Compound: Endosulfan (Thionex) 35 EC; EPA Registration No. 11678-25

Citation: Primary Skin Irritation in Rabbits; Makhteshim-Agan (America) Inc., Two Park Ave., N.Y., N.Y. 10016 (U.S. Sponsor); Life Science Research Israel, Ltd., P.O. Box 139, Ness Ziona, 70 451, Israel (Laboratory); 4-13 October 1982; LSRI Report No. MAK/029/TNX 35 EC

Reviewed By: Margaret L. Jones
Chemist

Toxicity Category: III

Core Guideline: Minimum

Conclusions: Thionex 35 EC is a moderate irritant at 72 hours after removal of the test patch.

Materials:

Test Substance: Thionex 35 EC, Batch No. 870021 received on 21 July 1982, stored at room temperature. Purity of the sample was unspecified.

Test Animals: Four New Zealand White Albino rabbits from A. Loebenstein Laboratory Animals, Yoqneam

Methods:

Four rabbits were allowed to acclimate to laboratory conditions for at least five days. The test area was prepared on the day before dosing by clipping the hair from the back of each between limb girdles. Any animals with abnormal skin were replaced with acclimated rabbits.

One dose of 0.5 ml of the test substance undiluted was applied to the skin on a gauze patch which was anchored by adhesive dressing. The test patch was removed after 4 hours and excess test material was removed.

Observations were made at 1, 24, and 72 hours and at 4,5,6,7,8, and 9 days after patch removal. The system of Draize (1959) was used for scoring the reactions.

Results:

Very slight erythema appeared in all animals at one hour. The reaction proceeded to slight erythema in all by 24 hours. At 72 hours erythema was moderate to severe in three animals and well-defined in one animal. The moderate to severe erythema continued to 4 days in one animal. By day 9 erythema had disappeared in all animals.

The test compound produced either very slight or slight edema in one half of the test group. All symptoms of edema cleared by day 8.