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

6-23-89 007308

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Thiabendazole. Review of Three Acute Studies

EPA No. 060101
Record No. 234290

Project No. 9-0287
Tox. Chem. No. 849A

TO: Geraldine Werdig, PM #50
Registration Division (H7505C)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section 1, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

John Whalan
4-4-89

THRU: Edwin R. Budd, Section Head
Section 1, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

E.R.B. 6/23/89

In response to a Data-Call-In, Merck Sharp & Dohme Research Laboratories has submitted supplemental reports of three acute studies for review:

1. Thiabendazole Veterinary (Lot ERM-211): Primary Eye Irritation Study in Rabbits. Supplement to MRID No. 00100705. Project No. TT #81-2593, April 6, 1981.

2. Thiabendazole Veterinary (Lot ERM-211): Primary Dermal Irritation Study in Rabbits. Supplement to MRID No. 00100705. Project No. TT #81-2592, April 6, 1981.

3. Thiabendazole: Cutaneous Sensitization in the Guinea Pig. Supplement to MRID No. 402717-01. Project No. TT #66-0135, March 31, 1966.

The primary eye and primary dermal irritation studies had been previously reviewed (Deloris F. Graham memorandum; May 24, 1982). The original reports were totally lacking substantiating data tables, which were supplied in the supplemental reports. A number of deficiencies remained. Both studies were rereviewed and classified Core Minimum in light of the minimal irritation observed, and in the interest of avoiding waste of life.

There is no record of the dermal sensitization study having been reviewed. This study was performed by Merck Institute for Therapeutic Research. Dr. George R. Lankas of Merck conceded that the study's design does not meet the specifications of the Pesticide Assessment Guidelines, but thought it might support the conclusions of a more recent study performed at Bio/Dynamics, Inc. (Study 402717-01, August 7, 1986). The latter study, reviewed by the Toxicology Branch and classified Core Minimum (Judith Hauswirth memorandum; EPA No. 7F-3553; January 11, 1988), showed thiabendazole is not a sensitizer (attached). Since this study is acceptable, nothing is gained by reviewing an older study which the Registrant concedes does not meet EPA guidelines.

PROTOCOL: Five male and five female New Zealand White rabbits (2.57-3.50 kg; 18-20 weeks old) were dosed with 0.1 g aliquots of thiabendazole powder in the conjunctival sacs of their left eyes. The eye lids of 6 rabbits were held shut for 1 minute, and were not rinsed. The eye lids of the other 4 rabbits were held shut for 30 seconds, after which their eyes were rinsed with 20 ml of lukewarm tap water. The right eyes were untreated, and served as negative controls.

The eyes were scored for irritation by the method of Draize (Draize, et al., J. Pharm. & Exptl. Therap. 82: 377, December, 1944) 15 minutes, 2 hours, and 24 hours after dosing, and daily thereafter for 14 days. Body weights were measured prior to dosing, and on days 7 and 14. The rabbits were housed in stainless steel cages.

RESULTS: Slight to crimson conjunctival redness and slight to marked discharge were seen at 15 and 120 minutes in the unrinsed eyes. The eyes that were rinsed 30 seconds after dosing had slight to crimson conjunctival redness at 15 and 120 minutes, and moderate discharge at 15 minutes. There was no corneal or iridic irritation, and no conjunctival chemosis in any rabbits. All signs of irritation had reversed 24 hours after dosing. Body weight gain was normal for all rabbits.

Fourteen days after the last induction exposure, the animals were challenged at a second site with either test or control agent, employing the same manner of administration as that described for the induction phase.

At the conclusion of six hours exposure, patches were removed and the test sites wiped free of excess material. In addition to the test and positive control test animals, three non-induced guinea pigs of each sex were similarly challenged with the test and control agents to identify any irritation, apart from sensitization, that the respective materials might cause.

Dermal evaluations were made at 24 and 48 hours after the challenge phase and challenge sites scored for edema, necrosis and eschar.

RESULTS

Mertect 340-F did not elicit y sensitization in the guinea pig. Erythema was noted in all animals tested with 1-chloro-2,4-dinitro benzene, where the magnitude of response would be characterized as slight to moderate.

NOTE: No record of animal weight changes occurring during the course of study were reported although such data are required by Section F Guidelines.

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Reviewed by: John E. Whalan 4-7-89
Section 1, Tox. Branch I (H7509C)
Secondary reviewer: Edwin R. Budd
Section 1, Tox. Branch I (H7509C)

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DATA EVALUATION REPORT

This study was previously reviewed by Deloris F. Graham (EPA No. 618-67, May 24, 1982) Supplemental data have since been submitted and are considered in this review.

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STUDY TYPE: Primary Eye Irritation Study in Rabbits

ACCESSION NUMBER: 247279, 407898-06

TX. CHEM. NO.: 849A

TEST MATERIAL: Thiabendazole Veterinary
Lot No. ERM-211 (purity unknown)
Dry powder

MRID NO.: 00100705

SYNONYMS: 2-(4-'Thiazolyl)-benzimidazole

STUDY NUMBER(S): TT #81-2693

REPORT NUMBER(S): TT #81-2693

SPONSOR: Merck & Co.

TESTING FACILITY: Merck Sharp & Dohme Research Laboratories

TITLE OF REPORT: 1. Thiabendazole Veterinary (Lot ERM-211): Acute Ocular and Dermal Irritation Studies in Rabbits and Acute Oral Toxicity Study in Rats
2. Thiabendazole Veterinary (Lot ERM-211): Primary Eye Irritation Study in Rabbits

AUTHOR(S): 1. W.W. Stolz
2. George R. Lankas

REPORT ISSUED: 1. April 13, 1981
2. August 8, 1988

CONCLUSIONS: The test article caused conjunctival redness and clear discharge 15 and 120 minutes after dosing in unrinsed eyes. Eyes which were rinsed had somewhat less irritation. All irritation reversed by 24 hours. There was no corneal or iridic irritation, and no conjunctival chemosis in any rabbits.

STUDY CLASSIFICATION: Core Minimum - Toxicity Category IV. The first report (1981) was poorly documented and lacked substantiating data. The text of the results sections in the first and second reports was identical, and did not reflect the eye irritation data tables in the supplemental report. The purity of the test article was not given. The supplemental report did not receive Quality Assurance review to assure the validity of the data. In light of the minimal irritation observed, this study is being accepted rather than wasting additional life repeating this study.

Special Review Criteria (40 CFR 154.7): N/A

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Reviewed by: John E. Whalan Jw 4-7 89
Section 1, Tox. Branch I (H7509C)
Secondary reviewer: Edwin R. Budd
Section 1, Tox. Branch I (H7509C)

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DATA EVALUATION REPORT

This study was previously reviewed by Deloris F. Graham (EPA No. 618-67, May 24, 1982) Supplemental data have since been submitted and are considered in this review.

STUDY TYPE: Primary Dermal Irritation Study in Rabbits

ACCESSION NUMBER: 247279, 407898-07

TOX. CHEM. NO.: 849A

TEST MATERIAL: Thiabendazole Veterinary
Lot No. ERM-211 (purity unknown)
Dry powder

MRID NO.: 00100705

SYNONYMS: 2-(4-'Thiazolyl)-benzimidazole

STUDY NUMBER(S): TT #81-2692

REPORT NUMBER(S): TT #81-2692

SPONSOR: Merck & Co.

TESTING FACILITY: Merck Sharp & Dohme Research Laboratories

TITLE OF REPORT: 1. Thiabendazole Veterinary (Lot ERM-211): Acute Ocular and Dermal Irritation Studies in Rabbits and Acute Oral Toxicity Study in Rats
2. Thiabendazole Veterinary (Lot ERM-211): Primary Dermal Irritation Study in Rabbits

AUTHOR(S): 1. W.W. Stolz
2. George R. Lankas

REPORT ISSUED: 1. April 13, 1981
2. August 8, 1988

CONCLUSIONS: The test article did not irritate intact skin, and caused only very slight erythema in the abraded skin of one rabbit.

STUDY CLASSIFICATION: Core Minimum - Toxicity Category IV. The first report (1981) was poorly documented and lacked substantiating data. The second report (1988) was also deficient. Its summary contained more information than the report. The purity of the test article was not given, there was no discussion of clinical signs, and an irritation grading scale was not provided. The trauma of abrading the skin should elicit at least mild erythema, yet erythema was found in only one rabbit. The supplemental report did not receive Quality Assurance review to assure the validity of the data. In light of the minimal irritation observed, this study is being accepted rather than wasting additional life repeating this study.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: Three male and three female New Zealand White rabbits (2.77-3.60 kg; 18-20 weeks old) were dosed with 0.5 g aliquots of thiabendazole. Two dosing sites (2.5 cm square) were prepared on the backs of each rabbit by clipping the hair. One dosing site was intact, and the other was abraded through the superficial layers of skin. Each dose was moistened with about 0.5 ml of saline, covered with a gauze patch, and occluded with an occlusive plastic dressing. The rabbits were individually housed in stainless steel cages.

After 24 hours, the dressings were removed. The dosing sites were examined for dermal irritation by the method of Draize (J. Pharmacol. and Exp. Therap. 82: 377, 1944) immediately after dose removal, and daily thereafter. The rabbits were observed for clinical signs throughout the day of dosing, and daily thereafter for 14 days. Body weights were measured prior to treatment and on days 7 and 14.

RESULTS: The abraded skin of one male had very slight erythema 24 hours after dosing. No other indications of irritation were observed, even in the abraded sites. Body weight gain was normal for all but one male (the one with erythema), which lost 1.5% of its body weight. There was no discussion of clinical signs.

From Microfiche

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

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

Subject: Thiabendazole - Dermal Sensitization Study in Guinea Pigs and Tolerance Petition for the Establishment and Revocation of Certain Tolerances, submitted by Merck and Co., Inc. July 15, 1987.
EPA ID No.: 7F3553; Accession Nos.: 40271701 and 40271707.
Tox. Br. Project No.: 7-1109 Tox. Chem. No.: 849A

To: Lois Rossi
Product Manager No. 21
Registration Division (TS-767C)

From: Judith W. Hauswirth, Ph.D. Judith W. Hauswirth 1/11/88
Section Head, Section VI
Toxicology Branch/HED (TS-769C)

Thru: Theodore M. Farber, Ph.D., Chief
Toxicology Branch/HED (TS-769C)

Action Requested: Review submitted dermal sensitization study in guinea pigs and consider requested tolerances and tolerance revocations.

Recommendation/Conclusion:

1. The dermal sensitization study is acceptable. Thiabendazole is not a skin sensitizer in the guinea pig (DER is attached).

Core Classification: Minimum

2. TB has no objection to the revocation of tolerances of thiabendazole residues in or on the raw agricultural commodity grapes and in the processed feed grape pomace (dry or wet).

3. TB recommends against the establishment of tolerances of thiabendazole residues of 20 ppm in or on the raw agricultural commodity corn grain and on processed feeds from corn grain: bran, 125 ppm; fines, 40 ppm; germ, 30 ppm; and soapstock, 25 ppm.

4. TB recommends that thiabendazole be scheduled for a registration standard before any further tolerance requests are approved.

Discussion: (This discussion concerns point number 3 above only.)

Many of the major toxicology studies on thiabendazole are old and were reviewed prior to establishment of the core concept and therefore, are not core graded. For example, two chronic feeding studies have been

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conducted in the rat. One of these studies was conducted in the 1960's and the other apparently in the early 1970's. After a quick review of the Tox. Br. files neither would be adequate by today's standards. In addition, FDA is presently considering the possible oncogenicity of thiabendazole based upon the results of an oncogenicity study in the mouse. This study has also been reviewed by EPA and found to be negative for oncogenicity. However, FDA has new information on this study which raises into question the oncogenicity of thiabendazole in the mouse. FDA has agreed to keep us informed on the progress of their review.

In light of the above discussion, TB cannot recommend for the establishment of tolerances for thiabendzole on corn grain and recommends that thiabendazole be scheduled for registration standard in order that the data base for registration be reviewed and updated. At that time further tolerance requests can be considered.

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Reviewed by: Brian Dementi, Ph.D. Brian Dementi 12/28/87
Section VI, Toxicology Branch (TS-769C)
Secondary Reviewer: Judith Hauswirth, Ph.D. Judith W. Hauswirth 1/4/88
Section VI, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization, Guinea Pig

TOX. CHEM. NO.: 849A

ACCESSION NUMBER: 7F3553; 7H5541

MRID NO.: 402717-01

TEST MATERIAL: MERTECT 340-F

SYNONYMS: Active Ingredient: Thiabendazole; 2-(4-Thiazolyl) benzimidazole

STUDY NUMBER(S): 402717-01

SPONSOR: Merck and Co., Inc., Three Bridges, NJ

TESTING FACILITY: Bio/Dynamics, Inc., East Millstone, NJ

TITLE OF REPORT: A Closed-Patch Repeated Insult Dermal Sensitization Study in Guinea Pigs (Modified Buehler Method)

AUTHOR(S): Donna L. Blaszcak

REPORT ISSUED: August 7, 1986

CONCLUSIONS: Test agent was non-sensitizing

CLASSIFICATION: Core Minimum

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A. EXPERIMENTAL DESIGN

The test material, MERTECT 340-F, was assayed for dermal sensitization potential by the method of Buehler, an EPA approved test procedure. Essentially, ten guinea pigs (5m, 5f) were first exposed to the test material by dermal application and then, following an appropriate time interval, were challenged in like manner with the same material and scored to determine if and to what degree sensitization may have occurred. 1-Chloro-2,4-dinitro benzene was employed as a positive control in the study.

B. MATERIALS

Mertect 340-F, the agent being evaluated in this study, was provided by Merck and Co., Inc. However, such information as purity of the test material or statement of formulation was not provided in the body of this particular study. The positive control, 1-chloro-2,4-dinitro benzene, was identified as a product of Eastman Kodak Co., Rochester, NY, but no information as to the purity of the sample used was provided.

Test animals were Hartley albino guinea pigs of weight range 302-383 grams, supplied by Hazelton-Dutchland Laboratory Animals, Denver, PA. Animals were fed and watered Ad libitum.

METHODS

Hair was clipped short at the application site of each animal on the day prior to the induction and challenge phases of the study.

At the time of the induction phase, the test material and the positive control agent were applied to appropriate animals in a volume of 0.3 ml directly to the skin test site. The material was covered by a patch (Hilltop Chamber®). The patch in turn was covered by impermeable plastic, followed by an elastic adhesive bandage (Elastoplast®). The patch was left in place for six hours, then removed and the site wiped free of any excess material. The induction phase procedure was pursued with each animal on a weekly basis for a total of three exposures.

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