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

1-11-88

006548

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

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 Kossi
Product Manager No. 21
Registration Division (TS-767C)

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

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 thiabendazole 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.

Reviewed by: Brian Dementi, Ph.D. *Brian Dementi 12/28/87*
Section VI, Toxicology Branch (TS-769C) 006548
Secondary Reviewer: Judith Hauswirth, Ph.D. *Judith W. Hauswirth*
Section VI, Toxicology Branch (TS-769C) *1/4/88*

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

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

Merctect 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.

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 any 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.



Selected Pages only

CASWELL FILE

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

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JUL 14 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Thiabendazole - Request for Specific (Emergency)
Exemption Under FIFRA Section 18, for the Use
of Thiabendazole (as Mertect 340F, 42% ai, 3.8
lb ai per gallon) on Stored Corn Grain for Control
of Aspergillus and Penicillium spp. at 20 ppm

87-1L-02
EPA Reg. No. 618-75

TOX Proj. no. 7-0789
Caswell No. 849A

TO: Don Stubbs/J. Thompkins, PM Team 41
Registration Division (TS-767C)

FROM: Irving Mauer, Ph.D. *Irving Mauer 7-13-87*
Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Judith W. Hauswirth, Ph.D., Head *Judith W. Hauswirth*
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C) *7/13/87*
Mf. 11/13/87

Registrant/Requester

The State of Illinois, Department of Agriculture,
requests a specific exemption under FIFRA section 18 for the
use of Mertect 340F (42% thiabendazole, TBZ, at 3.8 lb/gal)
to suppress and/or control fungal species (Aspergillus,
Penicillium, inter alia) in or on corn grain during storage
and drying, at a level not to exceed 20 ppm.

Background

A previous request for a section 18 exemption for this
use (86-IL-02) expired January 1, 1987.

I. RCB Considerations

Residue data have been previously submitted (with PP#5G3258), and summarized by RCB (see attached memorandum: Metzger to Stubbs, August 18, 1986), with the following conclusions:

- A. The residue of concern in treated plants is the parent alone, TBZ, whereas in animal commodities, the parent as well as 5-hydroxy-TBZ are found.
- B. The following residue levels are the maximal values expected from the proposed use in or on the raw agricultural commodity stored corn grain postharvest:

<u>Commodity</u>	<u>Maximum Likely Residue (ppm)</u>	<u>Established Tolerance (ppm)</u>
Corn grain	20	None
Crude corn oil	50	"
Refined corn oil	50	"
Milled products:		
Bran	125	"
Grits	8	"
Germ	25	"
Fines	40	None
Milk	0.4	0.4
Eggs	0.1	0.1
Meat, fat, and meat byproducts of cattle, goats, hogs, horses, and sheep	0.1	0.1

II. Toxicology Branch Considerations

As previously summarized in response to last year's request (86-IL-02), this request, 87-IL-02, can also be toxicologically supported, and TB has no objection to granting this specific exemption on a limited basis.

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However, it should be noted that none of the pivotal (older) long-term studies have been classified according to TB CORE concepts. Some of these studies are undergoing reevaluation at this Agency, and at least the oncogenicity studies are being further rereviewed by FDA.

Attachments



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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D C. 20460

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~~AUG 24 1986~~OFFICE OF
PESTICIDES AND TOXIC SUBSTANCESMEMORANDUMSUBJECT: Section 18 (86-IL-OZ). Mertect 340 F EPA Reg No.
618 - 75; Toxicology Chemistry No. 49ATO: Housenger/Pemberton-PM Team No. 41
Registration Support & Emergency Response Branch
Registration Division (TS-767)FROM: Carlos A. Rodriguez *CR 8/2/86*
Review Section No. VI
Toxicology Branch/HED (TS-769)THRU: Jane E. Harris, Ph.D., Section Head *JEH 8/22/86*
Review Section No. VI
Toxicology Branch/HED (TS-769) *8/24/86*Petitioner: State of Illinois, Dept. of Agriculture
State Fairgrounds
P.O. Box 4906, Springfield, IL. 62708-4906Action Requested:

The Illinois Department of Agriculture is requesting a Section 18 Specific Exemption for Mertect 340 F (42.3% Thiabendazole) as a postharvest treatment to suppress the growth of Aspergillus spp and Penicillium spp during drying and storage of corn grain at 20 ppm.

Recommendation:

The requested Section 18 can be toxicologically supported. RCB consideration permitting, Toxicology Branch have no objection to the issuance of the requested action.

- A. Inerts cleared under 180.100(c).
- B. No new toxicity data submitted with this request.

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Toxicity Data Considered in Setting This Action:

<u>Study</u>	<u>Results</u>	<u>Category of Toxicity</u>	<u>Core - Classification</u>
• Acute oral LD ₅₀ (male rat) (98.5% tech.)	LD ₅₀ = 3.97 g/kg (95% Conf. 2.92 - 2.40 g/kg)	III	Minimum
• (female rat) (95% Conf. = 2.14 - 5.85 g/kg)	LD ₅₀ = 3.54 g/kg	III	Minimum
• Acute oral LD ₅₀ (mouse) (42.28% formulation)	LD ₅₀ = 9 g/kg	IV	Minimum
• Acute dermal LD ₅₀ (rabbit) 98.5% tech.)	LD ₅₀ > 4 g/kg	III	Minimum
• Acute dermal LD ₅₀ (rabbit) (42.28% formulation)	LD ₅₀ > 5 ml/kg	III	Minimum
• Acute inhalation LC ₅₀ (98.5% tech.)	LC ₅₀ > 2.03 mg/L	III	Guideline
• Acute inhalation LC ₅₀ (42.28% formulation)	LC ₅₀ > 20 mg/L	IV	Minimum
• Primary eye irritation (rabbit) (98.5% tech.)	Slight irritation; cleared at 72 hrs.	III	Minimum
• Primary eye irritation (rabbit) (42.28% formulation)	Slight to moderate irritation; slight chemosis. Effects cleared by 72 hrs.	III	Minimum
• Primary dermal irritation (98.5% Tech.)	Slight erythema; cleared 48 hrs.	IV	Minimum
• Primary dermal irritation (42.28% formulation)	Slight erythema; cleared at 11th day	IV	Minimum

2-year rat feeding: Systemic NOEL = 10 mg/kg/day
 Systemic LEL = 40 mg/kg (growth depression). Oncogenic potential negative at 160 mg/kg/day (highest dose tested)
 Dose levels tested: 10, 40 and 160 mg/kg/day.

*2-Year dog feeding: Systemic NOEL = 50 mg/kg/day;
 Systemic LEL = 125 mg/kg/day (decreased body weight).
 Dose levels tested: 20, 50, and 125 mg/kg/day.

*Lifetime oncogenic (mouse feeding) Oncogenic NOEL > 5,330 ppm or 800 mg/kg/day (highest level tested). Systemic NOEL = 600 ppm or 100 mg/kg/day; Systemic LEL = 2000 ppm or 300 mg/kg/day (lower weight gain). Dose levels tested mg/kg/day), 2000 ppm (300 (mg/kg/day), 5,330 ppm (800 (mg/kg/day).

*Rabbit teratology NOEL > 800 mg/kg (HDT)
 Dose level tested: 100, 200 and 800 mg/kg

*Rat teratology: Teratogenic NOEL > 80 mg/kg/day (given by gavage, single dose tested)

*3-Generation reproduction (rat) Reproduction NOEL = 20 mg/kg
 reproduction LOEL = 40 mg/kg -- decreased viability index of Fla.
 Dose levels tested: 20, 40, and 80 mg/kg.

• Mutagenicity Studies:

- | | |
|---|------------|
| 1. Microbial (<u>S. typhimurium</u>) negative for induced revertants. | Acceptable |
| 2. Microbial (<u>E. coli</u>) negative for induced revertants. | Acceptable |
| 3. Host-mediated -, negative | Acceptable |

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4. Primary bone marrow - negative for chromosomal damage.
5. Primary bacterial DNA damage/repair - negative.
6. In vitro cytogenetics - negative - no increase in chromosome breakage in human embryonic fibroblast cultures.

- * Metabolism, absorption, distribution and excretion in man, dog, rat, sheep, goat, cattle and swine.

Rapidly metabolized in man. Radioactive agent in animal species in many respects were similar to those found in man. Tissues from laboratory animals were virtually free of radioactivity.

* Studies not classified under the Grade Core Classification concept.

- D. NO RPAR criteria have been exceeded and no regulatory actions are pending against registration.
- E. The following studies 2-year rat feeding, 2-year dog feeding, lifetime mouse oncogenic, rabbit and rat teratology and 3-generation rat reproduction have been used in support of this action. Since these studies were reviewed prior to the Grade Core Classification was instituted a thorough review of these studies will be done to determine if presently they satisfy a requirement. They will be reevaluated and Grade Core classified for the Registration Standard.
- F. The mouse acute oral LD₅₀ available in this formulation showed a similar toxicity to the rat acute oral LD₅₀ in the technical product, therefore Tox. Branch believes that an additional acute oral LD₅₀ in the rat is not necessary.
- G. Data gaps:

→ 1. Sensitization study

→ 2. Teratology study (2nd species, preferably the rat).

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Evaluation of the ADI

The acceptable daily intake (ADI) based on the 2 - year rat feeding study (NOEL = 10 mg/kg/day) and using a hundred - fold safety factor, is calculated to be 0.1 mg/kg/day. The maximum permitted intake (MPI) for a 60 kg human is 6 mg/day.

The theoretical maximum residue contribution (TMRC) from existing residues published and Toxicology approved for 1.5 kg diet is calculated to be 0.4624 mg/kg/day. The residue requested tolerance under this Section is 0.1 mg/kg/day. Human consumption of thiabendazole since the residue tolerance is 0.1 mg/kg/day is 0.1 mg/kg/day. Computer printout