(UNDATED)

Shaughnessy No.: 060101

Date Out of EFGWB:_____

To:
Product Manager
Registration Division (H-7505C)

From: Akiva Abramovitch, Chief
Environmental Chemistry Review Section #3
Environmental Fate and Ground Water Branch/EFED (H-7507C)

Through: Henry Jacoby, Chief
Environmental Fate and Ground Water Branch/EFED (H-7507C)

Attached, please find the EFGWB review of . . .

Reg./File # : 148-79-8.

Common Name : Thiabendazole.

Type Product : Fungicide.

Product Name : Arbotect, Mertect, TBZ, Apl-Luster, Bioguard, Bovizole, Eprofil, Equizole, Lombristop, Mertect 160, Metasol TK 100, Mintesol, Mycozol, MK 360, Nemapan, Omnizole, Polival, Tebuzate, Tecto, Thibenzole 200, Thiprazole, Top form wormer, and Agrosol.

Company Name : Merck & Company, Inc.

Purpose : Review of an aerobic soil metabolism study.

Date Received: _____ EFGWB # (s): _____

Action Code : _____

Deferrals to:

_____ Ecological Effects Branch, EFED

_____ Science Integration and Policy Staff, EFED

_____ Non-Dietary Exposure Branch, HED

_____ Dietary Exposure Branch, HED

_____ Toxicology Branch I, HED

_____ Toxicology Branch II, HED

1. CHEMICAL: Common name:

Thiabendazole.

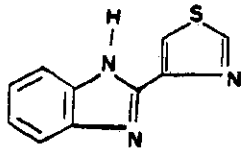
Chemical name:

2-(4'-Thiazolyl)benzimidazole.

Trade name(s):

Arbotect, Mertect, TBZ, Apl-Luster, Bioguard, Bovizole, Eprofil, Equizole, Lombristop, Mertect 160, Metasol TK 100, Mintesol, Mycozol, MK 360, Nemapan, Omnizole, Polival, Tebuzate, Tecto, Thibenzole 200, Thiprazole, Top form wormer, and Agrosol.

Structure:



Formulations:

Wettable powder, flowable concentrate, and dust.

Physical/Chemical properties:

Molecular formula:	$C_{10}H_7N_3S$.
Molecular weight:	201.1.
Physical state:	Colorless powder.
Melting point:	304-305 C.
Solubility (25 C):	c. 10 g/L water (pH 2); <50 mg/L water (pH 5-12); >50 g/L water (pH 12); 4.2 g/L acetone; 7.9 g/L ethanol; 2.1 g/L ethyl acetate. At room temperature: 230 mg/L benzene; 80 mg/L chloroform; 39 g/L dimethylformamide; 80 g/L dimethyl sulfoxide; 9.3 g/L methanol.

2. TEST MATERIAL:

Study 1: Active ingredient.

3. STUDY/ACTION TYPE:

Review of an aerobic soil metabolism study.

4. STUDY IDENTIFICATION:

Daly, D., and M. Williams. 1991. Aerobic soil metabolism of ^{14}C-thiabendazole. ABC Labs No. 37639. Unpublished study performed by Analytical BioChemistry Laboratories, Inc., Columbia, MO, and submitted by Merck & Company, Inc., Three Bridges, NJ. (41791201)

5. REVIEWED BY:

James A. Breithaupt
Agronomist
EFGWB/EFED/OPP
Review Section #3

Signature:_____

Date:_____

6. APPROVED BY:

Akiva D. Abramovitch
Chief
EFGWB/EFED/OPP
Review Section #3

Signature:_____

Date:_____

7. CONCLUSION:

8. RECOMMENDATIONS:

9. BACKGROUND:

A. Introduction

B. Directions for Use

Thiabendazole is a systemic fungicide registered for use on a wide variety of terrestrial food (citrus, bananas, apples, pears, and sweet potatoes) and nonfood (ornamentals, turf, and tobacco) crop sites. Applications may be made during the growing season to control pathogenic fungi and post-harvest to control storage diseases. Single active ingredient formulations include wettable powder, flowable concentrate, and dust. Multiple active ingredient formulations include captan, thiram, quintozene, and prochloraz. Thiabendazole is nontoxic to bees and slightly toxic to fish.

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES:

Refer to attached reviews.

11. COMPLETION OF ONE-LINER:

12. CBI APPENDIX:

All data reviewed here are considered "company confidential" by the registrant and must be treated as such.

DATA EVALUATION RECORD

DRAFT

STUDY 1

CHEM 060101 Thiabendazole §162-1

FORMULATION--00--ACTIVE INGREDIENT

STUDY ID 41791201
Daly, D., and M. Williams. 1991. Aerobic soil metabolism of ^{14}C-thiabendazole. ABC Labs No. 37639. Unpublished study performed by Analytical BioChemistry Laboratories, Inc., Columbia, MO, and submitted by Merck & Company, Inc., Three Bridges, NJ.

DIRECT REVIEW TIME = 24

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CONCLUSIONS:

Metabolism - Aerobic Soil

1. This study cannot be used to fulfill data requirements.

2. These data are of uncertain value and should not be used to predict the behavior of thiabendazole and its degradates in aerobic soil.

3. This study is unacceptable for the following reason:

   the study results were confounded by degradation that occurred during the ≤6 months of frozen storage prior to analysis.

4. Because the problems with this study cannot be resolved with the submission of additional data, a new study must be submitted.

METHODOLOGY:

Sieved (2 mm) sandy loam soil (58% sand, 30% silt, 12% clay, 0.9% organic matter, pH 7.8, CEC 9.2 meq/100 g) was weighed (10 g) into 50-mL silanized Pyrex culture tubes and incubated at approximately 25 ± 1 C; the soil moisture content during incubation was 35% of field capacity. After 3 days, the soil was treated at 1.05 ppm with phenyl ring-labeled [^{14}C]thiabendazole [2-(4'-thiazolyl)-benzimidazole; uniformly labeled; radiochemical purity 98.6%, specific activity 24.77 uCi/mg, Merck] in methanol, using a syringe. The surface of the soil was flushed with air to evaporate the methanol, then the treated soils were moistened to 75% of field capacity and vortexed. The tubes of soil were placed inside two 3000-mL metabolism chambers. The metabolism chambers were then placed in a darkened incubator set at 25 ± 1 C and connected to a continuous air-flow system (Figure 1). Humidified air was forced (50 mL/minute) through individual metabolism chambers, then through ethylene glycol, 1 N H_2SO_4, and 1 N KOH (two tubes) trapping solutions. The soil moisture content was monitored regularly, and water was added as necessary. Five tubes of treated soil were collected immediately posttreatment, and three tubes of treated soil (two from metabolism chamber I and one from metabolism chamber II) were collected after 1, 3, 7, and 14 days, and 1, 2, 3, 4, 6, 9, and 12 months posttreatment. Trapping solutions were collected on each sampling day for the first month, and at monthly intervals thereafter.

The two soil samples collected at each interval from metabolism chamber I were extracted immediately; samples from metabolism chamber II were stored frozen at -22 C as reserve samples, and some were removed after 14-17 months of storage for extraction. The soil samples were shaken with a 1 N methanolic KOH solution for 1-2 hours on a mechanical shaker, then centrifuged, and the supernatant was decanted. The extracted soil was rinsed twice with additional KOH, and the rinses were combined with the extract. The extracted soil was further extracted by shaking on a mechanical shaker with 6 N HCl:dimethylformamide (1:1, v:v) for 2-4 hours. The samples were centrifuged, and the supernatant decanted. The extracted soil was rinsed twice with additional HCL:dimethylformamide, and the rinses were combined with the extract. Aliquots of the KOH and HCl:dimethylformamide extracts were analyzed for total radioactivity using LSC. The remaining HCl:dimethylformamide extracts were adjusted to pH 12 and partitioned twice with ethyl acetate. The aqueous and organic fractions were separated, and aliquots of each were analyzed by LSC. The soil extracts and the extracted soil were then stored at -22 C for up to 6 months prior to analysis.

For analysis, the methanolic KOH extracts were concentrated with a stream of nitrogen gas, then neutralized with concentrated HCl, which

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resulted in the precipitation of KCl. The solutions were centrifuged, and the supernatant removed. The HCl:dimethylformamide extract was dried under nitrogen gas, and the resulting residues were dissolved in methanol. The concentrated extracts were analyzed by reverse phase HPLC using a Waters Novapak C-18 column eluted with a mobile phase of 0.10 M NaH_2PO_4:0.01 M $NaClO_4$ and methanol, and with UV (279 nm) detection. HPLC fractions were collected and analyzed using LSC. The HPLC samples were cochromatographed with reference standards of unlabeled thiabendazole, benzimidazole, 5-hydroxythiabendazole, benzimidazole-2-carboxamide, and benzimidazole-2-carboxylic acid. In addition, extracts from the immediate posttreatment and 3-, 6-, and 12-month samples were analyzed using two-dimensional TLC on silica gel plates developed with dioxane:toluene:ammonium hydroxide (8:1:1: v:v:v) and butanol:water:acetic acid (13:5:2 v:v:v). The samples were cochromatographed with the reference standards previously listed. Radioactive areas on the plates were located by autoradiography, and the standards were visualized under UV light. [^{14}C]Compounds isolated by TLC were scraped from the glass plate surface, desorbed from the silica with methanol, and quantified using LSC. The extracted soil was analyzed using LSC following combustion.

The trapping solutions were analyzed by LSC. [^{14}C]Residues trapped in the KOH solutions were confirmed as CO_2 by barium carbonate precipitation.

DATA SUMMARY:

Uniformly phenyl ring-labeled [^{14}C]thiabendazole (2-(4'-thiazolyl)-benzimidazole; radiochemical purity 98.6%), at 1.05 ppm, degraded with a half-life of >1 year in sandy loam soil that was incubated in the dark at 25 ± 1 C and 75% of moisture capacity for 12 months. In soil extracts that were stored for up to 6 months prior to analysis, [^{14}C]thiabendazole comprised 89.1% of the applied immediately posttreatment, 73.2% at 1 month, and 56.8% at 1 year (Table IV). Two degradates were identified.

Benzimidazole

was not detected in the immediate posttreatment samples, was a maximum of 2.20% of the applied at 1 day, and decreased to 0.97% at 1 month and 0.17% at 12 months;

5-hydroxythiabendazole

was a maximum of 0.33% of the applied at 9 months. Unknown 1 was 0.95% of the applied in the immediate posttreatment samples, 7.57% at 1 day, 12.29% (maximum) at 7 days, 7.50% at 14 days, 0.53-5.25% between 1 and 6 months with no discernable pattern, and 0.86% at 12 months. Unknown 2 was detected twice, at 0.32% of the applied at 1 day posttreatment and at 0.56% at 6 months. At 12 months

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posttreatment, 5.59 and 0.24% of the applied had been evolved as $^{14}CO_2$ and other [^{14}C]volatiles, respectively. Unextracted [^{14}C]residues were 1.24-6.3% of the applied at ≤1 month posttreatment and 13.9-20.2% at 2 through 12 months. Throughout the study, material balances were 91.5-101.7% of the applied with no discernable pattern of decline.

COMMENTS:

1. The study results were confounded by degradation that occurred during the frozen storage of the soil extracts prior to analysis. The study authors suggested that Unknown 1, present at up to 12.29% of the applied, was an artifact that formed during the approximately 6-month frozen storage of the soil extracts. To support their theory, the study authors cited data from the analyses of the reserve soil samples (those from metabolism chamber II) and from a second metabolism study that was conducted for only 14 days. The study authors stated that the reserve soil samples were stored frozen for up to 17 months prior to extraction, and that the extracts were analyzed immediately after extraction. Only samples collected through 2 months posttreatment were analyzed. The concentrations of thiabendazole in the fresh extracts were similar to those in the stored extracts; Unknown 1, however, was ≤0.95% of the applied at all sampling intervals (Table V). Benzimidazole and 5-hydroxy-thiabendazole were not detected. In the 14-day experiment, which was initiated expressly to obtain fresh samples, the soil samples were treated at 1 or 10 ppm, then incubated under conditions similar to those described for the definitive experiment. The soil was extracted immediately upon sampling, and the soil extracts were stored frozen at -22 C for up to 16 days prior to analysis. In these samples, thiabendazole appeared to approximate the degradation pattern in the definitive experiment, benzimidazole was a maximum of 0.12% of the applied, and 5-hydroxythiabendazole was a maximum of 0.07% (Table VI). Unknown 1 was detected at every sampling interval at 0.10-0.40% of the applied.

   Although Unknown 1 was present at much higher concentrations in the soil extracts stored frozen for 6 months prior to analysis, Unknown 1 was also detected in the fresh extracts from the frozen reserve soil samples and in the frozen (≤16 days) extracts from the fresh soil samples. Therefore, it cannot be concluded that Unknown 1 was solely an artifact of the frozen storage. However, a comparison of the three sets of data does demonstrate that the results of the 12-month study may have been compromised by the frozen storage and are of uncertain accuracy.

   Insufficient data were provided by the frozen soil analyses (data provided for only 2 months posttreatment) and the 14-day experiment to accurately establish the pattern of decline of thiabendazole and the patterns of formation and decline of its degradates. Neither

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study can be used to fulfill the aerobic soil metabolism data requirement.

2. The registrants calculated three half-lives for thiabendazole, all of which are of limited value because the calculations involve extrapolation considerably beyond the duration of the experiments. Using data obtained from the frozen extracts of the 12-month soil study, a half-life of 730 days was determined. Using data from the frozen soil plus data from the 3- through 12-month frozen extracts, a half-life of 630 days was determined. Using data from the 14-day experiment plus 1- through 12-month frozen extracts, a half-life of 503 days was determined.

3. Up to 13.8% of the radioactivity in the soil extracts was not accounted for by the study authors following HPLC (Table IV). No explanation for the missing [^{14}C]residues was provided.

4. The microflora of the soil from both the 12-month and 14-day experiments were assayed at regular intervals. The numbers of bacteria and fungi remained stable over the course of both experiments.

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Pages 9 through 20 are not included in this copy.

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