

US EPA ARCHIVE DOCUMENT

Shaughnessy No: 060101

Date Out of EFGWB: FEB 20 1990

TO: Frank Rubis
Product Manager #50
Registration Division (H7505C)

FROM: Emil Regelman, Supervisory Chemist
Environmental Chemistry Review Section #2
Environmental Fate and Ground Water Branch, EFED (H7507C)

THRU: Henry M. Jacoby, Chief
Environmental Fate and Ground Water Branch, EFED (H7507C)

Henry M. Jacoby
2/26/90

Attached, please find the EFGWB review of:

Reg./File #: 060101-3

Common Name: Thiabendazole

a. 2-(Thiazole-4-yl)benzimidazole

Chemical Name: b. 2-(1,3-Thiazole-4-yl)benzimidazole

Type product: Fungicide

Product Name: MERTEC Fungicide Products

Company Name: Merck and Company, Inc.

Purpose: Screen/review hydrolysis, photodegradation in water, and batch-equilibrium adsorption/desorption studies submitted as part of the Data Call-In on this chemical.

Date Received: a. 7/10/89; b. 10/13/89 EFGWB #: a. 90-0079; b. 90-0080
c. 10/16/89 c. 90-0179

Action Code: 495 Total Reviewing Time (decimal days): 1.5

Deferrals to: _____ Ecological Effects Branch, EFED
_____ Science Integration & Policy Staff, EFED
_____ Non-Dietary Exposure Branch, HED
_____ Dietary Exposure Branch, HED
_____ Toxicology Branch I, HED
_____ Toxicology Branch II, HED

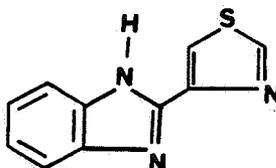
1. CHEMICAL:

Common name: Thiabendazole

Chemical name: 2-(Thiazol-4-yl)benzimidazole;
2-(1,3-Thiazol-4-yl)benzimidazole

Trade name(s): MERTEC Fungicide Products

Chemical Structure:



Formulations: WP (40, 60, 90%); FC

Physical/Chemical Properties:

Molecular formula: C₁₁H₇N₃S

Molecular weight: 201.1

Physical state: Powder

Vapor Pressure 4 x 10⁻⁹ Torr

Solubility:

Water (25C).....ca.10 mcg/L (pH 2)
< 50 mcg/L (pH 5-12)
> 50 mcg/L (pH > 12)

Acetone (25C).....4.2 g/L
Ethanol (25C).....7.9 g/L
Ethyl acetate (25C).....2.1 g/L

Benzene ("Room Temp.").....230 mcg/L
Chloroform (Room Temp.)....80 mcg/L
DMF (Room Temperature).....39 g/L
DMSO (Room Temperature).....80 g/L
Methanol (Room Temp.).....9.3 g/L

DMF= Dimethylformamide; DMSO= Dimethyl sulfoxide

3. STUDY/ACTION TYPE:

Screen/review studies (hydrolysis, photodegradation in water, and batch-equilibrium adsorption/desorption studies) submitted in response to a comprehensive Data Call-In for this chemical.

4. STUDY IDENTIFICATION:

- Dykes, J. 1989. Soil adsorption/desorption with thiabendazole. ABC Final Report #37635. Unpublished study performed by Analytical

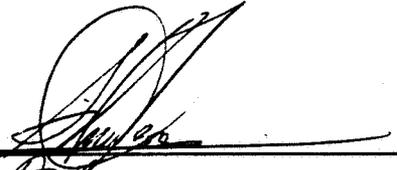
Bio-Chemistry Laboratories, Inc., Columbia, MO. Laboratory Project 37635; Completed June 8, 1989. Submitted by Merck and Company, Inc., Iselin, NJ.
MRID #41170102

- Kabler, K. and Dykes, J. 1989. Determination of the photolysis rate of ¹⁴C-thiabendazole in pH 5 buffered solution at 25°C. ABC Final Report #37637; Completed October 2, 1989. Conducted by Analytical Bio-Chemistry Laboratories, Columbia, MO. Submitted by Merck and Company, Iselin, NJ.
MRID #41265101

- Kabler, K. and Dykes, J. 1989. Hydrolysis as a function of pH at 25°C of ¹⁴C-thiabendazole. ABC Final Report #37636: Completed July 26, 1989. Conducted by Analytical Bio-Chemistry Laboratories, Columbia, MO. Submitted by Merck and Company, Iselin, NJ.
MRID #41265301

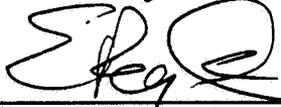
4. REVIEWED BY:

Silvia C. Termes, Chemist
Review Section #2
OPP/EFED/EFGWB

Signature: 
Date: February 15, 1990

5. APPROVED BY:

Emil Regelman
Supervisory Chemist
Review Section #2
OPP/EFED/EFGWB

Signature: 
Date: FEB 20 1990

6. CONCLUSIONS:

The hydrolysis and batch-equilibrium adsorption/desorption studies are unacceptable. The photodegradation in water study may be acceptable if the additional information requested in the RECOMMENDATIONS Section is submitted and found acceptable by the Branch. Thus, new hydrolysis and batch-equilibrium adsorption/desorption studies are required.

One of the major problems found, in general, with all of these studies is the analytical methods used to identify reaction products. The use of TLC alone (particularly when only one solvent system is used) is not a satisfactory identification. Confirmatory methods (such as MS, nmr, or other suitable spectroscopic method) should follow the chromatographic methods used to separate the different reaction products.

Photodegradation in water- Reported results:

Thiabendazole is susceptible to photodegradation in water (pH 5 buffer). The reported half-life of photodegradation is 10 days, as compared to

ca. 180 days observed in nonirradiated samples. Samples were irradiated with a xenon arc lamp. The main reaction products were benzimidazole, benzimidazole-2-carboxylic acid, benzimidazole-2-carboxamide, and 5-hydroxythiabenzodiazole. The study was conducted with ^{14}C -thiabenzodiazole labeled in the phenyl ring.

There is no acceptable data available at the present time that allows an assessment of the environmental fate of thiabenzodiazole. From the data reported in the hydrolysis study, there is suggestion that thiabenzodiazole may be persistent to hydrolysis. However, the photodegradation in water study indicates that photodegradation may be an important degradation pathway for thiabenzodiazole.

7. RECOMMENDATIONS:

The registrant should be informed of the following:

- a. The submitted hydrolysis and adsorption/desorption studies were found to be unacceptable. New studies are required.

The major problem with the hydrolysis study is the determination of the 0-time solution. Keeping in mind that thiabenzodiazole is susceptible to photodegradation, care should be exerted in keeping stock/test solutions in the dark at all times.

The major problem with the adsorption/desorption study is that the soils were treated with sodium azide before use. This treatment affects the physical/chemical properties of the soil.

- b. For the photodegradation in water study, the following additional information is required,
 1. Clarify the discrepancies found between TLC and HPLC data on shared sampling intervals. Provided that the samples have been kept frozen for further analyses and that there is data to support storage stability, all samples should be analyzed by HPLC (including days 1, 3, and 7) and their identity confirmed by MS or other suitable analytical technique.
 2. There is ca. 19% of radioactivity that was not accounted for in the sensitized solution and ca. 17% in the non-sensitized solutions. From the data provided, it was not possible to determine if this total radioactivity correspond to a single component or to multiple components each at <10%. Clarify.
 3. Formation of the degradates benzimidazole-2-carboxamide, benzimidazole-2-carboxylic acid, and benzimidazole require that the thiazolyl group be eliminated. Provide evidence on what type of products are formed from this eliminated thiazolyl group.
 4. It is recommended that, when reporting electronic absorption spectra in solution, the molar absorptivity of each absorption maxima be

included. Although Figure 2 shows the UV-VIS spectrum of thiabendazole in the 10 mg/mL test solution, the molar absorptivity ($\text{Lmol}^{-1}\text{cm}^{-1}$) cannot be estimated because the pathlength of the cell (cuvette) is not known.

- c. If the information requested for the photodegradation in water study is not acceptable, then a new study will be required.
- d. None of the environmental fate data requirements for thiabendazole have been satisfied.

8. BACKGROUND:

a. Introduction

The Agency issued a comprehensive data call-in for thiabendazole on 3/24/88. In a 135-day response letter by the registrant (8/15/88) requested a waiver for the following studies: photodegradation in air volatility (laboratory and field), field dissipation (combination and tank mixes), field rotational crop, and fish accumulation. Of these studies, only the accumulation in fish studies was not waived (EFGWB review of 12/15/88). The registrant was informed of these decisions in a letter dated 5/16/89 (E. Tinsworth), where the registrant was also notified that the droplet size spectrum and drift field evaluation studies were not required because the Agency did not have at that time any toxicity concerns (humans or nontarget organisms). The hydrolysis, photodegradation in water, and adsorption/desorption studies have been submitted in response to the data call-in. Comments on a draft report for a photodegradation on soil study appear in a EFGWB Memorandum dated 1/4/90.

b. Directions for use:

Thiabendazole is a systemic fungicide registered for use on terrestrial food crop and terrestrial nonfood (ornamentals, turf, tobacco) sites. Single active ingredient formulations include wettable powder and flowable. Applications may be made during the growing season to control pathogenic fungi and postharvest to control storage diseases.

- 9. DISCUSSION OF INDIVIDUAL STUDIES: See individual data evaluation records.
- 10. COMPLETION OF ONE-LINER: No one-liner has been completed.
- 11. CBI APPENDIX: No claim of confidentiality is made for any information contained in the reviewed studies.

DISCUSSION OF INDIVIDUAL STUDIES

THIABENDAZOLE

Table of Contents

	<u>Page</u>
Introduction	
Scientific Studies	
1. Hydrolysis. (Kabler and Dykes, 41265301)	1.1
2. Photodegradation in water. (Kabler and Dykes, 41265101)	2.1
3. Mobility (batch equilibrium). (Dykes, 41265102)	3.1
Appendix	4.1

INTRODUCTION

Thiabendazole is a systemic fungicide registered for use on terrestrial food crop and terrestrial non-food crop (ornamentals, turf, and tobacco) sites. Single active ingredient formulations include wettable powder and flowable. Applications may be made during the growing season to control pathogenic fungi and post-harvest to control storage diseases. Thiabendazole is slightly toxic to fish.

DATA EVALUATION RECORD

STUDY 1

CHEM 060101

Thiabendazole

§161-1

FORMULATION--00--ACTIVE INGREDIENT

STUDY ID 41265301

Kabler, K., and J. Dykes. 1989b. Hydrolysis as a function of pH at 25 C of ¹⁴C-thiabendazole. ABC Final Report #37636. Unpublished study performed by Analytical Bio-Chemistry Laboratories, Inc., Columbia, MO, and submitted by Merck and Company, Inc., Three Bridges, NJ.

DIRECT REVIEW TIME - 8

REVIEWED BY: E. Hirsh

TITLE: Staff Scientist

EDITED BY: K. Patten

TITLE: Task Leader

APPROVED BY: W. Spangler

TITLE: Project Manager

ORG: Dynamac Corporation
Rockville, MD

TEL: 468-2500

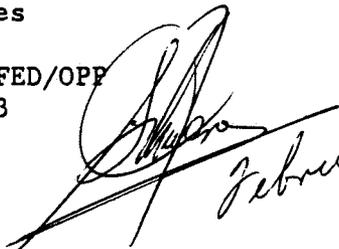
APPROVED BY: S. Termes

TITLE: Chemist

ORG: EFGWB/EFED/OPP

TEL: 557-2243

SIGNATURE:



February 15, 1990

CONCLUSIONS:

Degradation - Hydrolysis

1. This study cannot be used to fulfill data requirements.
2. These data are considered to be of uncertain value and should not be used to predict the environmental behavior of thiabendazole and its degradates.
3. This study is unacceptable for the following reason:

there was an unresolved problem with the original time 0 samples, which may have affected the validity of later samples. Following determination that the initial time 0 buffered test solutions were significantly different (not further described) from the intended nominal concentration, the study authors

prepared a new time 0 solution and all data concerning the hydrolytic half-lives were calculations using these values.

4. Since there were problems with the original sample solutions which were not identified and which may have affected the validity of the data, the problems with this study cannot be resolved with the submission of additional data. A new study must be conducted.

METHODOLOGY:

Phenyl-labeled [¹⁴C]thiabendazole (uniformly labeled, radiochemical purity 98.1%, specific activity 24.77 uCi/mg, Merck and Company) dissolved in methanol was added to four Erlenmeyer flasks. The solvent was evaporated with a stream of nitrogen, and sterile buffer solutions (prepared in filtered and autoclaved deionized water) were added to each flask to produce a final nominal concentration of 10 ppm. The buffered solutions were: pH 5 - 0.1 M acetate; pH 7(A) - 0.1 M TRIS; pH 7(B) - 0.01 M HEPES; and pH 9 - 0.1 M borate. The solutions were sonicated for 20 minutes, then fourteen 10-mL aliquots of each of the four test solutions were transferred to borosilicate culture tubes and sealed with teflon-lined tops. Two tubes of each solution were reserved for time 0 analysis; the remainder were incubated in the dark in an environmental chamber maintained at 25 ± 1 C. Duplicate samples were collected at 0, 1, 3, 7, 14, 21, and 30 days posttreatment. The pH of the buffer solutions was measured at the initiation and termination of the study.

Aliquots of the sample solutions were analyzed for total radioactivity without extraction using LSC, and for specific compounds using TLC on reverse-phase plates developed in acetonitrile:water:phosphoric acid (27:75:0.3, v:v:v). The samples were cochromatographed with a radiolabeled thiabendazole stock solution. Radioactive areas on the plates were detected using a radioscaner (RTLIC).

DATA SUMMARY:

Phenyl ring-labeled [¹⁴C]thiabendazole (radiochemical purity 98.1%), at a nominal concentration of 10 ppm, degraded with registrant-calculated half-lives of ≥203 days in sterile aqueous buffered solutions adjusted to pH 5, 7, or 9 that were incubated in the dark at 25 C for 30 days (Tables III-VI). [¹⁴C]Thiabendazole was the only compound detected (using TLC with one solvent system) in the buffer solutions at all sampling intervals, and comprised 97.9-98.9% of the radioactivity recovered at 30 days posttreatment. Between 1 and 30 days posttreatment, the material balance of the pH 5 solution ranged from 80.9 to 83.6% of the applied, of the pH 7-HEPES solution from 90.3 to 102.4%, of the pH 7-TRIS solution from 88.9 to 99.5%, and of the pH 9 solution from 86.7 to 95.6% (Table VII).

COMMENTS:

1. The study authors stated that "The concentrations of the initial time zero buffered test solutions were determined to be significantly different from the nominal concentration of 10 ug/ml. A great degree of variability was also seen in the original time zero samples. The concentration of subsequent sample points were determined to be more consistent . . ." with the nominal concentration. ". . . Therefore, new time zero solutions were prepared for each buffer, as per the original nominal concentrations. . . . These new 'time zero' values were used in all calculations and tables."

The study authors did not explain the meaning of "significantly different", they did not report the original time 0 data, and they did not report that any attempts were made to determine the reason for the original time zero samples being "significantly different". There was no indication of equipment malfunction. Since all samples were aliquots of the stock buffer solutions, it is probable that the problems that existed with the time 0 samples also existed at the later sampling intervals, although perhaps to a lesser degree (for example, if the test material adsorbed to the glassware, an equilibration period would be required for the test solution to reach a steady concentration). Therefore, the validity of the later sampling intervals is in doubt.

Also, it is not acceptable scientific practice to create the time 0 samples after the fact; the time 0 sample is supposed to reflect the concentration of parent present at the start of the study. The inappropriateness of creating a new time 0 is especially true when the original time 0 was an aliquot of a stock buffer solution used for all other samples.

2. The material balances are variable; in the pH 5 and pH 7 (TRIS) solutions, more radioactivity was present at 30 days than at 1 day. Disregarding day 0 (refer to Comment 1), the material balance of the pH 5 solution ranged from 80.9 to 83.6% of the applied, of the pH 7-HEPES solution from 90.3 to 102.4%, of the pH 7-TRIS solution from 88.9 to 99.5%, and of the pH 9 solution from 86.7 to 95.6% (Table VII).
3. Volatilization was neither measured nor controlled.
4. The statistical estimates of the hydrolysis half-lives of thiabendazole computed by the study authors are of limited value because the calculations involve extrapolation considerably beyond the experimental time limits of the study.
5. A storage stability test was conducted for 14 days at 4 C. Following 14 days of storage, approximately 100% of the applied radioactivity was present in the solution as [¹⁴C]thiabendazole (Table II).

6. EFGWB prefers that [¹⁴C]residues in samples be separated by chromatographic methods (such as TLC, HPLC, or GC) with at least three solvent systems of different polarity, and that specific compounds isolated by chromatography be identified using a confirmatory method such as MS in addition to comparison to the R_f of reference standards.

In this study, the sample extracts were analyzed using one-dimensional TLC with a single solvent system. The single radioactive area detected on the TLC plates was identified only by comparison to the location of a known reference standard chromatographed on the same plates.

7. Contrary to the claims of the study author, data from a preliminary study using 10 ppm of [¹⁴C]thiabendazole in a pH 5 buffer solution demonstrated that some adsorption of the [¹⁴C]thiabendazole to the glassware may have occurred (Table I). In the silanized glassware, the material balance was 97.4-97.8% of the applied during the first 7 days of the study, then decreased to 93.9% at day 14. In the non-silanized glassware, the material balances were variable and ranged from 90.7 to 94.3%. The study authors' conclusions that adsorption did not occur were based solely on the material balances from day 14.
8. Recovery efficiencies and method detection limits were not reported.

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Pages 13 through 23 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.
 - FIFRA registration data.
 - The document is a duplicate of page(s) _____.
 - The document is not responsive to the request.
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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

DATA EVALUATION RECORD

STUDY 2

CHEM 060101 Thiabendazole §161-2

FORMULATION--00--ACTIVE INGREDIENT

STUDY ID 41265101

Kabler, K., and J. Dykes. 1989a. Determination of the photolysis rate of ¹⁴C-thiabendazole in pH 5 buffered solution at 25 C. ABC Final Report #37637. Unpublished study performed by Analytical Bio-Chemistry Laboratories, Inc., Columbia, MO, and submitted by Merck and Company, Inc., Three Bridges, NJ.

DIRECT REVIEW TIME = 10

REVIEWED BY: E. Hirsh TITLE: Staff Scientist

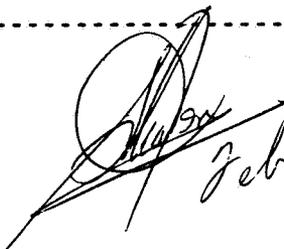
EDITED BY: K. Patten TITLE: Task Leader

APPROVED BY: W. Spangler TITLE: Project Manager

ORG: Dynamac Corporation
Rockville, MD

TEL: 468-2500

APPROVED BY: S. Termes
TITLE: Chemist
ORG: EFGWB/EFED/OPP
TEL: 557-2243


February 15, 1990

SIGNATURE:

CONCLUSIONS:

Degradation - Photodegradation in Water

1. This study cannot be used to fulfill data requirements at this time.
2. These data are considered to be of uncertain value and should not be used to predict the environmental behavior of thiabendazole and its degradates.
3. This study is unacceptable at this time for the following reasons:

The TLC and HPLC data were not similar on shared sampling intervals. The study authors suggested that the TLC analysis had not fully resolved the parent compound; if so, the TLC

method was inadequate. The HPLC analyses were not done frequently enough to provide adequate sampling.

The material balance of the sensitized irradiated solution was incomplete; up to 19.3% of the applied radioactivity was not accounted for.

In addition, this study does not fulfill Subdivision N guidelines for the following reason:

Up to approximately 17% of the applied radioactivity that was detected using LSC was not identified by HPLC. From the data provided, it could not be determined if the unidentified radioactivity consisted of one or many compounds, or included any compounds that comprised >10% of the applied.

4. In order for this study to fulfill the photodegradation in water data requirement (and assuming that the original samples have been kept in frozen storage), the registrant should analyze all samples (including days 1, 3, and 7) by HPLC and identify all [¹⁴C]compounds isolated by a confirmatory method such as MS; stability data will be needed to demonstrate that the samples did not degrade during storage. Also, the registrant should account for all radioactive residues in the solutions, and any compounds that comprise >10% of the applied should be identified.

METHODOLOGY:

Preliminary study: Phenyl-labeled [¹⁴C]thiabendazole (uniformly labeled, radiochemical purity 98.1%, specific activity 24.77 uCi/mg, Merck and Company) dissolved in methanol was added to an Erlenmeyer flask. The solvent was evaporated with a stream of nitrogen, and a sterile pH 5, 0.1 M acetate buffer solution (prepared in filtered and autoclaved deionized water) was added to the flask to produce a final nominal concentration of 10 ppm. The test solution was sonicated for 25 minutes, then fourteen 10-mL aliquots were transferred to borosilicate culture tubes and sealed with teflon-lined tops. Two tubes of solution were reserved for time 0 analysis; six were placed in the photolysis apparatus; and six were wrapped in foil and placed in a closed box, and the box was placed in the photolysis apparatus (Figure 3). The photolysis apparatus was continuously irradiated using a 6000-watt xenon arc lamp having an intensity that was approximately half the intensity of sunlight (Tables I and II, Figure 10). The photolysis chamber was maintained at 25 ± 1 C. Samples of the irradiated and dark control solutions were collected at 0, 0.10, 0.25, 1, 2, 3, and 6 days posttreatment.

Aliquots of the sample solutions were analyzed for total radioactivity without extraction using LSC, and for specific compounds using TLC on reverse-phase plates developed in acetonitrile:water:phosphoric acid (27:75:0.3, v:v:v). The samples were cochromatographed

with a radiolabeled thiabendazole stock solution. Radioactive areas on the plates were detected using a radioscanner (RTLC).

Definitive study: Phenyl-labeled [¹⁴C]thiabendazole dissolved in methanol was added to an Erlenmeyer flask. The solvent was evaporated with a stream of nitrogen, and a sterile pH 5, 0.1 M acetate buffer solution was added to the flask to produce a final nominal concentration of 10 ppm. Acetonitrile (<1% by volume) was added to the solution as a cosolvent. The solution was sonicated for 25 minutes, then divided into two equal portions. Acetone (<1% by volume) was added to one of the two flasks as a photosensitizer, and the solution was sonicated again for 25 minutes. Aliquots of the nonphotosensitized and photosensitized solutions were transferred to 10-mL borosilicate glass culture tubes and sealed with teflon-lined screw caps. The tubes were filled to capacity to minimize head space and reduce interactions with air. Two tubes of each solution were reserved for time 0 analysis; half of the remaining tubes were placed in the photolysis apparatus; and the remainder were wrapped in foil and placed in a closed box, and the box was placed in the photolysis apparatus. The samples were continuously irradiated using the xenon arc lamp; the chamber was maintained at 25 ± 1 C. Duplicate vials of the irradiated and dark control, nonsensitized and sensitized solutions were sampled at 1, 3, 7, 14, 21, and 30 days posttreatment. The pH of the samples was determined at each sampling interval.

Duplicate aliquots of each sample were analyzed without extraction for total radioactivity by direct LSC, and for specific compounds using TLC as previously described. Additional aliquots of the 0-, 14-, 21-, and 30-day sensitized and nonsensitized irradiated solutions were analyzed for specific compounds using HPLC, with a linear gradient of sodium phosphate:sodium perchlorate buffer to methanol and UV detection at 279 nm. [¹⁴C]Compounds were identified by comparison to the movement of reference standards and quantified using LSC.

DATA SUMMARY:

Phenyl ring-labeled [¹⁴C]thiabendazole (radiochemical purity 98.1%), at 9.5 ppm, degraded with a half-life of <14 days in both nonsensitized and sensitized (1% acetone) sterile aqueous buffered pH 5 solutions that were irradiated with a xenon arc lamp at 25 ± 1 C (HPLC data, Tables VIII and X). The measured intensity of the xenon lamp was 0.0042-1.508 watts/m² at wavelengths of 300-750 nm, approximately half that of sunlight (Table I and II). After 14 days of irradiation, [¹⁴C]thiabendazole was 39.2% of the applied in the nonsensitized solution and 30.2% in the sensitized solution. [¹⁴C]-Thiabendazole did not degrade in the dark controls during 30 days of incubation at 25 C (Tables IX and XI).

Four degradates were isolated from the nonsensitized and sensitized irradiated solutions (Tables XIV and XV). In the nonsensitized irradiated solution:

benzimidazole was a maximum 30.8% of the applied at day 30;

benzimidazole-2-carboxamide was a maximum 14.1% at 21 days;

benzimidazole-2-carboxylic acid was a maximum 57.1% at 21 days;
and

5-hydroxythiabendazole was 6.2% at 30 days.

Degradates were present in approximately similar amounts in the sensitized solution.

During the study, the material balances of the irradiated nonsensitized samples decreased from 100 to 91.7% of the applied and of the irradiated sensitized samples from 100 to 81.5% (Tables XII and XIII). The material balances of the nonsensitized and sensitized dark controls ranged from 94.5 to 107.6% of the applied.

COMMENTS:

1. The irradiated solutions were analyzed by TLC on days 0, 1, 3, 7, 14, 21, and 30, and by HPLC on days 0, 14, 21, and 30. The TLC and HPLC data are not similar; for example, in the nonsensitized irradiated solutions at day 14, TLC and HPLC identified 70.2 and 39.2% of the applied as parent, respectively. The study authors stated that "... HPLC revealed that the parent had degraded to a greater extent than was resolvable by RTLC." It must therefore be concluded that the TLC method was inadequate to accurately assess the degradation of thia-bendazole. Unfortunately, the samples analyzed by HPLC were too infrequent and at poorly spaced intervals, so that 60-70% of the applied degraded between the first and second analysis (days 0 and 14) and the degradation rate could not be accurately determined.
2. The half-life calculations made by the study authors were done using a combination of the TLC (1, 3, and 7 day) and HPLC (0, 14, 21, and 30 day) data. Since the TLC and HPLC data for day 14 were not similar, these data should not have been combined.
3. Up to 17% of the radioactive residues detected in the solutions by LSC were not identified by HPLC. The study authors only reported the concentration of radioactive residues that cochromatographed with the chosen reference standards; it could not be determined if the unidentified radioactivity consisted of one or many compounds, or included any compounds that comprised >10% of the applied. Subdivision N guidelines specify that all residues present at >10% of the applied must be identified.

4. The absorbance spectra of [¹⁴C]thiabendazole over the range of 290-750 nm is presented in Figure 2. Maximum absorbance was at 305 nm.
5. A storage stability test was conducted for 14 days at 4 C. Approximately 100% of the initial, as parent, was present following 14 days of storage (Table IV).
6. EFGWB prefers that [¹⁴C]residues in samples be separated by chromatographic methods (such as TLC, HPLC, or GC) with at least three solvent systems of different polarity, and that specific compounds isolated by chromatography be identified using a confirmatory method such as MS in addition to comparison to the R_f of reference standards.

In this study, the sample extracts were analyzed using one-dimensional TLC with a single solvent system and by HPLC with a different solvent system. The radioactive areas detected on the TLC plates and by HPLC were identified only by comparison to the location of a known reference standard chromatographed in the same system.

7. Contrary to the claims of the study author, data from a preliminary study using 10 ppm of [¹⁴C]thiabendazole in a pH 5 buffer solution demonstrated that some adsorption of the [¹⁴C]thiabendazole to the glassware may occurred. In the silanized glassware, the material balance was 97.4-97.9% of the applied during the first 7 days of the study, then decreased to 93.9% at day 14 (Table III). In the non-silanized glassware, the material balances were variable and ranged from 90.6 to 94.3%. The study authors' conclusions that adsorption did not occur were based solely on the material balances from day 14.
8. The study authors stated that the TLC plates containing the time 0 sample were autoradiographed after development. A copy of the autoradiograph was not provided.
9. Recovery efficiencies and method detection limits were not reported.
10. The study authors stated that the 7-, 21-, and 30-day nonsensitized dark control samples were also analyzed using HPLC; however, only TLC data were provided for these samples.

Page _____ is not included in this copy.

Pages 29 through 49 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.

FIFRA registration data.

___ The document is a duplicate of page(s) _____.

___ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

DATA EVALUATION RECORD

STUDY 3

CHEM 060101

Thiabendazole

§163-1

FORMULATION--00--ACTIVE INGREDIENT

STUDY ID 41170102

Dykes, J. 1989. Soil adsorption/desorption with thiabendazole. ABC Final Report #37635. Unpublished study performed by Analytical Bio-Chemistry Laboratories, Inc., Columbia, MO, and submitted by Merck and Company, Inc., Three Bridges, NJ.

DIRECT REVIEW TIME - 10

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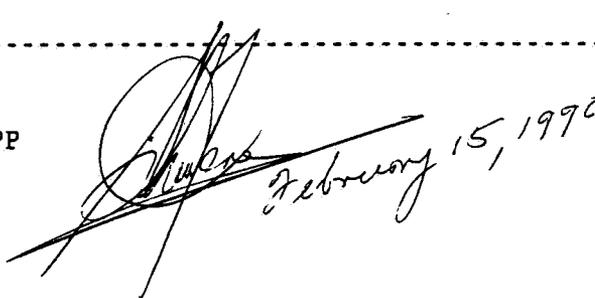
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February 15, 1990

CONCLUSIONS:

Mobility - Leaching and Adsorption/Desorption

1. This study cannot be used to fulfill data requirements.
2. These data are considered to be of uncertain value and should not be used to predict the environmental behavior of thiabendazole.
3. This study is unacceptable for the following reason:

the soils were sterilized with sodium azide before use. Sodium azide has been shown to alter the physical properties of soil; therefore, the behavior of a pesticide in sodium azide-treated soil may not be similar to the behavior of the pesticide in untreated soil.

4. Since the physical properties of the soils may have been altered in unknown ways prior to use, the problems with this study cannot be resolved with the submission of additional data. A new study must be conducted.

METHODOLOGY:

Sand, sandy loam, clay, and silt loam soils (Table 1) were air-dried, ground, sieved through a 2-mm mesh screen, and sterilized by the homogeneous addition of 1% sodium azide (w:w). Based on preliminary experiments to define test parameters, an equilibration time of 24 hours and soil:water ratios of 1:5 for the sand, sandy loam, and silt loam soils and 1:10 for the clay soil were selected for the definitive experiment.

For the adsorption portion of the study, 1-g samples of soil and 10 mL of 0.01 M calcium chloride solutions containing 0, 0.45, 0.90, 1.76, or 4.62 ug/mL of phenyl ring-labeled [¹⁴C]thiabendazole (uniformly labeled, radiochemical purity 98.1%, specific activity 24.77 uCi/mg, Merck and Company) were combined in culture tubes. The tubes were sealed with teflon-lined caps, and the slurries were shaken in the dark at 25 ± 1 C for 24 hours. Following shaking, the slurries were centrifuged, and the supernatants were removed using a pipette. Triplicate aliquots of the supernatants were analyzed for total radioactivity using LSC.

Desorption of thiabendazole was determined by replacing the supernatant that had been removed from the soil after adsorption with pesticide-free calcium chloride solution. The soil slurries were shaken in the dark at 25 ± 1 C for 24 hours, then centrifuged. The supernatants were analyzed by LSC, and [¹⁴C]residues remaining adsorbed to the soil were determined by LSC following combustion. Also following desorption, subsamples of the clay soil were extracted three times with 1 N methanolic KOH. The extracts were combined and analyzed for total radioactivity by LSC.

DATA SUMMARY:

Based on batch equilibrium studies, [¹⁴C]thiabendazole (radiochemical purity 98.1%), at 0.45, 0.90, 1.76, and 4.62 ug/mL, was determined to be very mobile in sand, mobile in sandy loam and silt loam, and slightly mobile in clay:calcium chloride solution slurries (1:10) that were equilibrated for 24 hours at 25 ± 1 C. K_{ads} values were 2.76 in sand, 15.97 in sandy loam, 21.75 in silt loam, and 269.6 in clay soils; respective K_{oc} values were 1104, 3992.5, 1812.5, and 22467 (Table XVI). Average adsorption of thiabendazole ranged from 12.7% in sand to 98.67% in clay (Tables III-VI). Adsorption increased with increasing CEC and clay content.

Following desorption in pesticide-free calcium chloride solutions (1:10 soil solution ratio) for 24 hours, approximately 1-2% of the radioactivity adsorbed to the clay soil, 16-28% to the silt loam soil, 28-32% to the sandy loam soil, and 41-60% to the sand soil was desorbed (Tables III-VI). The material balances for samples ranged from 90-107% (Tables XVII-XX).

COMMENTS:

1. The soils were sterilized with sodium azide before use, although the use of sterile soils is not required by Subdivision N guidelines for mobility studies. Sodium azide has been shown to alter the physical and chemical properties of soil; therefore, the behavior of a pesticide in treated soil may differ significantly from the behavior of that pesticide in untreated soil.
2. In a preliminary study to determine if the test material adsorbed to glassware, aliquots of pH 5 acetate buffer solution containing 10 ppm of [¹⁴C]thiabendazole were placed in silanized and nonsilanized culture tubes; the solutions were analyzed by LSC at 1, 3, 7, and 14 days posttreatment. The study author stated that no adsorption occurred, but no data were presented to support this conclusion.

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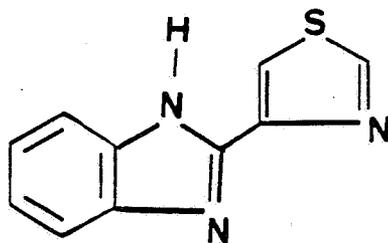
Pages 54 through 66 are not included.

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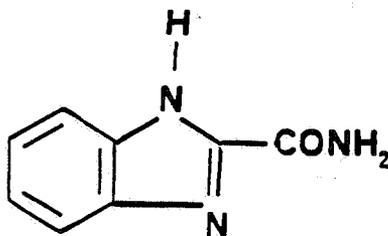
- Identity of product inert ingredients.
 - Identity of product impurities.
 - Description of the product manufacturing process.
 - Description of quality control procedures.
 - Identity of the source of product ingredients.
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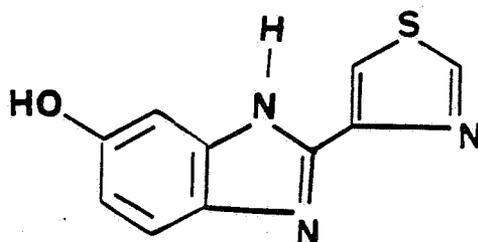
APPENDIX
THIABENDAZOLE AND ITS DEGRADATES



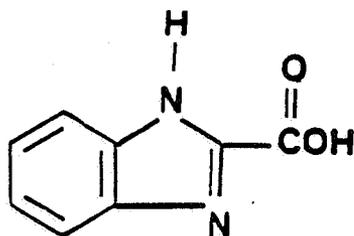
Thiabendazole



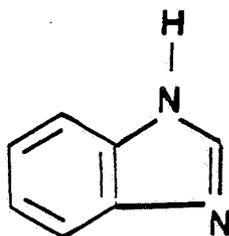
Benzimidazole-2-carboxamide



5-Hydroxythiabendazole



Benzimidazole-2-carboxylic acid



Benzimidazole