Shaughnessy No.: 125851

Date Out of EFGWB: FEB 22 1990

To: J. Miller; E. Wilson
Product Manager #23
Registration Division (H7507C)

From: Emil Regelman, Supervisory Chemist
Chemistry Review Section #2
Environmental Fate and Ground Water Branch

Thru: Hank Jacoby, Chief
Environmental Fate and Ground Water Branch
Environmental Fate and Effects Division (H7507C)

Attached, please find the EFGWB review of . . .

Reg./File #: 1471-RLO

Chemical Name: Isoxaben

Type Product: Herbicide

Common Name: Gallery Herbicide

Company Name: Eli Lilly and Company

Purpose: Addendum to the application for full registration for terrestrial nonfood use.

Date Received: 2 Jan. 1990 Date Completed: 12 Jan. 1990

Action Code: 116

EFGWB #(s): 90604

Total Reviewing Time: 2.2 days

Deferrals to: _____ Ecological Effects Branch, EFED

_____ Science Integration and Policy Staff, EFED

_____ Non-Dietary Exposure Branch, HED

_____ Dietary Exposure Branch, HED

_____ Toxicology Branch

1. CHEMICAL:

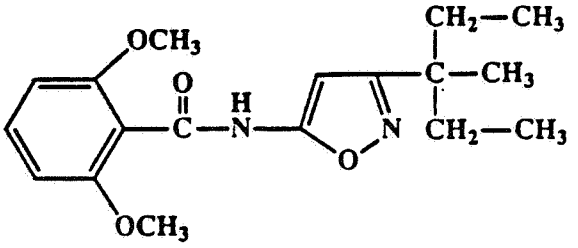
Chemical name: N-[3-(methylpent-3-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide

CAS no.: 82558-50-7

Common name: Isoxaben

Trade name: Gallery Herbicide

Structure:



Molecular formula: $C_{18}H_{12}N_2O_4$

Molecular weight: 332.39

Formulations: 12.5 and 50% WP, 75% FlC

Physical/Chemical properties of active ingredient:

Physical characteristics: White crystalline solid

Melting point: 176-179°C

Vapor pressure: >3.9 X 10^{-7} mm Hg @ 26°C

Octanol/water partition coefficient: Kow = 434 (Log Kow - 2.64)

2. TEST MATERIAL:

Study 1: Dry flowable (75%).
Study 2: Active ingredient (isoxazole ring-labeled [5-^{14}C]isoxaben).
Study 3: Active ingredient (carbonyl-labeled [^{14}C]isoxaben).

3. STUDY/ACTION TYPE:

Addendum to the application for full registration for terrestrial nonfood use sites.

4. STUDY IDENTIFICATION:

Saunders, D.G. and Powers, F.L. PHOTOLYSIS OF ISOXABEN ON SOIL. Sponsored and Submitted by Eli Lilly and Company, Greenfield, IN, under Laboratory Project ID AAC8850; Completed 27 Feb. 1989; Received by EPA 24 May 1989; MRID No. 41106301.

Rainey, D.P. ^{14}C ISOXABEN ANAEROBIC SOIL METABOLISM STUDY. Sponsored and Submitted by Eli Lilly and Company, Greenfield, IN, under Laboratory Project ID ABC-0224; Completed 4 May 1989; Received by EPA 24 May 1989; MRID No. 41106302.

Rainey, D.P. METABOLISM OF ^{14}C EL-107 IN SOIL: CHARACTERIZATION OF VOLATILE RADIOLABELED DEGRADATION PRODUCTS. Sponsored and Submitted by Eli Lilly and Company, Greenfield, IN, under Laboratory Project ID ABC-0224; Completed 1985?; Received by EPA ; MRID No. 00164646.

Rainey, D.P., and L.K. Graper. AEROBIC SOIL METABOLISM OF ^{14}C EL-107. Sponsored and Submitted by Eli Lilly and Company, Greenfield, IN, under Laboratory Project ID ABC-0224; Completed 1985; Received by EPA ; MRID No. 00143786.

Saunders, D.G. and Powers, F.L. SOIL ADSORPTION AND DESORPTION OF ISOXABEN AND SOIL METABOLITE 201469. Sponsored and Submitted by Eli Lilly and Company, Greenfield, IN, under Laboratory Project ID AAC8851; 21 March 1989; MRID No. 41106303.

5. REVIEWED BY:

Gail Maske
Chemist, Review Section #2
OPP/EFED/EFGWB

Signature: _____
Date: 12 Feb 90

6. APPROVED BY:

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

Signature: _____
Date: FEB 22 1990

7. CONCLUSIONS:

a. Photodegradation on Soil

The photodegradation on soil study is not acceptable to meet Subdivision N Data Requirements. A new study will be required to support registration of Isoxaben (1471-RLO) for any terrestrial food use. EFGWB does recommend that a protocol be submitted for review before initiation of the study.

Isoxaben photodegraded with a half-life of 198 days on clay loam soil when irradiated continuously at approximately 25°C with artificial light for 54 days which was equivalent to 33.5 days of sunlight. Approximately 98% of the applied isoxaben was detected in the dark controls at termination of study.

b. Anaerobic Soil Metabolism

The anaerobic soil metabolism study is acceptable to meet Subdivision N Data Requirements. No further anaerobic soil metabolism data is required at this time.

Radiolabelled isoxaben degraded in loam soil with a half-life of >120 days when incubated anaerobic at 23°C for 60 days after aging aerobically for 60 days. The major degradate identified was N-[3-(1-hydroxyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide.

c. Leaching, Adsorption/Desorption Mobility

The leaching, adsorption/desorption study is acceptable and partially fulfills Subdivision N Data Requirements by providing data on mobility (batch equilibrium) of unaged isoxaben and 201469 in sand, loamy sand, sandy loam, loam, and clay loam soils. However, the study can be used to fulfill the data requirement for mobility of aged isoxaben residues since the Toxicology Branch determined that degradates other than 201469 are not of toxicological concern at the concentrations present (as per verbal conversation with Clark Swentzel on 21 February 1990). No further leaching, adsorption/desorption data is required at this time.

Isoxaben is mobile to very mobile in sand, loamy sand, sandy loam, loam, and clay loam soils. There was indications that Isoxaben mobility decreased with increasing soil clay content and CEC. The isoxaben metabolite N-[3-(1-hydroxy-1-methylpropyl)-5-isoxazoyl]-2,6-dimethoxybenzamide (201469) is very mobile in sand, loamy sand, sandy loam, loam, and clay loam soils.

d. Leaching and Ground Water Contamination Characteristics

A comparison of Isoxaben's properties to pesticide properties which have been found characteristic of some pesticides known to leach to ground water are given below:

Property	Pesticides known to leach	Isoxaben
Water solubility	>30 ppm	1 to 2 ppm
K_d	<5.0 usually <1.0 or 2.0	0.81 - 6.6
K_{oc}	<300 - 500	162 - 330

Speciation	Negatively charge	Neutral
Henry's Constant	$<10^{-2}$ atm-m^3/mol	$<10^{-8}$ atm-m^3/mol
Hydrolysis	>25 weeks	stable @ 30 days
Photolysis	>1 week	7 to 15 days
Soil	>2 to 3 weeks	198 days

Pesticides that are generally persistent and mobile are capable of leaching to ground water. The persistence characteristics and some of the mobility characteristics (K_d, K_{oc}, and Henry's Constant) are typical of pesticides found in ground water. There are some physical characteristics that are not found in ground water contaminates (water solubility and speciation). The physical mobility characteristics do not appear to make isoxaben a major concern for leaching and ground water contamination except under extreme circumstances.

8. RECOMMENDATIONS:

The registrant should be informed of the following:

a. The photodegradation on soil study is not acceptable to meet Subdivision N Data Requirement for the following reasons:
   1. The samples were only analyzed for parent isoxaben which gave an incomplete material balance.
   2. There was no comparison of the artificial light source to natural sunlight.
   3. The test material was not technical grade or purer.

   A new study is required to support registration of Isoxaben (1471-RLO) for any terrestrial food use. EFGWB does recommend that a protocol be submitted for review prior to initiation of study.

b. The anaerobic soil metabolism study is acceptable to meet Subdivision N Data Requirement. No further anaerobic soil metabolism data is required at this time.

c. The leaching, adsorption/desorption study is acceptable and partially fulfills Subdivision N Data Requirement by providing data on mobility (batch equilibrium) of unaged isoxaben and 201469 in sand, loamy sand, sandy loam, loam, and clay loam soils. However, the study may be used to fulfill the data requirement for mobility of aged isoxaben residues if the Toxicology Branch determines that degradates other than 201469 are not of toxicological concern. If the Toxicology Branch does determine that isoxaben degradates other than 201469 <u>are</u> of toxicological concern, then a new study of the mobility of aged isoxaben residues or the isoxaben degradates of of concern will be required.

d. The status of Environmental Fate Data Requirements are as follows:

Environmental Fate Data Requirements	State of Data Requirement	MRID No.
Degradation Studies-Lab		
161-1 Hydrolysis	Fulfilled (ER; 09/29/83)	NK
161-2 Photodegradation in Water	Fulfilled (PRD; 04/27/88)	40059507 40097601
161-3 Photodegradation on Soil	This Review	41106301
Metabolism Studies-Lab		
162-1 Aerobic Soil	Fulfilled (PRD; 04/27/88)	00073607 00265370
162-2 Anaerobic Soil	This Review (See MEMORANDUM/ PH; 19 Jan. 1988)	41106302
Mobility Studies		
163-1 Leaching, Adsorption/ Desorption	Partially (PRD; 04/27/88) This Review (See MEMORANDUM/ PH; 19 Jan. 1988)	00265730 41106303
Dissipation Studies- Field		
164-1 Soil	Partially (PRD; 04/27/88)	40059508 40532102 40532103
Accumulation Studies		
165-4 Fish	Fulfilled (PRD; 03/14/89)	40059509

9. BACKGROUND:

General Background:

Gallery is a preemergence herbicide for control of certain broadleaf weeds and annual grasses in established turf, landscape ornamentals, nursery stock, nonbearing fruit and nut crops, nonbearing vineyards, and noncropland areas. Apply Gallery in late summer to early fall or in early spring, prior to germination of target weeds, or immediately after cultivation using a properly calibrated, low-pressure herbicide sprayer.

Environmental Fate Background:

Hydrolysis is not a likely mechanism for the degradation of isoxaben. Virtually all parent compound was recovered unchanged in all samples analyzed (recoveries ranged from 87 to 102%).

Carbonyl- and isoxazole ring-labeled [^{14}C]isoxaben, at 1 ppm, degraded under aerobic conditions with a half-life of 4.3 months in clay loam soil, 5.6 months in loam soil, and 10.6 months in sandy loam soil incubated at 23°C in the dark. The major degradate N-[3-(2-hydroxybut-2-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide (compound 201469) accounted for up to 20.3% of the applied; the degradates N-[3-(1-hydroxyethyl)-isoxazol-5-yl]-2,6-dimethoxybenzamide, N-[3-(2-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2,6-dimethoxybenamide, N-[3-(methylpent-3-yl)isoxazol-5-yl]-2,6-methoxybenzamide (Metabolite A) each accounted for <5.0% of the applied. The molecule did not appear to degrade at the benzamide linkage. After 8-9 months of incubation in the loam soil, unextractable radioactivity accounted for 22.0% of the applied, and volatiles (determined in a separate experiment) totaled 15.5% of the applied.

Isoxazole ring-labeled [^{14}C]isoxaben and aged (30 days) [^{14}C]isoxaben residues were slightly mobile in columns (30-cm length, 1-cm diameter) of sand, sandy loam, loam, and clay loam soils leached with 20 inches of water over a 10-day period. Following leaching, $\leq$0.31% of the applied radioactivity was found in the leachates from the columns treated with unaged [^{14}C]isoxaben, and $\leq$3.61% of the applied was found in leachates from the columns treated with aged [^{14}C]residues. The majority (.84% of the applied) of the [^{14}C]residues remained in the upper 12 cm of the columns. Isoxaben (approximately 81.4%) and N-[3-(2-hydroxybut-2-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide (6.6%; compound 201469) were the major [^{14}C]compounds in the 30-day aged soil prior to leaching.

Isoxaben, applied at 1.0 lb ai/A as a 75% FlC to a turf plot (40 X 40 feet) of clay loam soil in Champaign, Illinois, dissipated with a half-life of 66-106 days from the 0- to 6-inch depth of the soil. The degradate 201469 reached a maximum concentration in the 0- to 6-inch depth of 0.11 lb/A at 66 days posttreatment, and then declined to 0.02 lb/A at 211 days posttreatment. Isoxaben was not detected (detection limit 0.01 lb/A) at the 6- to 12-, 12- to 18-, 18- to 24-, 24- to 30-, and 30- to 36-inch depths. In general, 201469 was not detected in samples taken below the 6-inch depth; however, 201469 was isolated at $\leq$0.02 lb/A in two samples from the 6- to 12-inch depth and in one sample from the 24- to 30-inch depth.

Isoxaben (75% FlC), at 1 lb ai/A, degraded with a half-life of 30 to 40 days in spring-treated sand soil in Florida and loam soil in Indiana; it degraded with a half-life of 60-182 days in autumn-treated sand soil in Florida and sandy loam soil in Texas. Isoxaben was <0.02 lb ai/A in samples from the 6- to 12-, 12- to 18-, and 18- to 24-inch depths at all sites. The degradate N-[3-(2-hydroxybut-2-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide (compound 201469) was <0.09 lb ai/A in the 0- to 6-inch depth at all four sites and <0.01 lb ai/A at greater depths.

[^{14}C]Isoxaben residues accumulated in bluegill sunfish with maximum bioconcentration factors of 14X in edible tissues (fillet), 134X in nonedible tissues (head and viscera), and 70X in whole fish during 28 days of exposure. The fish were exposed to isoxazole ring-labeled [^{14}C]isoxaben at 0.25 ppm in a flow-through system. After 21-28 days of exposure, isoxaben comprised 52% of the recovered radioactivity from the edible tissues and 17% from the nonedible tissue. Degradates identified in the edible and nonedible tissues were the diastereamers of N-[3-(2-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide at $\leq$33% of the recovered radioactivity; N-[3-(1-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide at $\leq$23% recovered; N-[3-(methylpent-3-yl)isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide at <4% of the recovered; N-[3-(2-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide at <2%; and N-[3-(1-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide at <2%. Residues accumulated by exposure day 28 were depurated quickly; at day 14 or depuration, [^{14}C]residues were approximately 0.28 ppm in edible, nonedible, and whole fish tissues.

10. DISCUSSION:

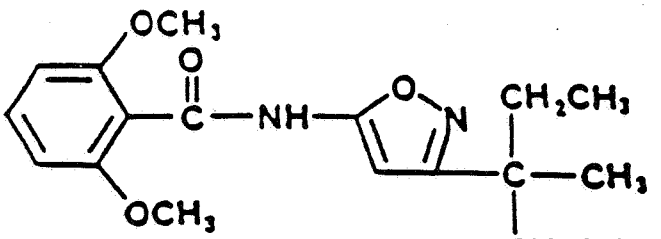
See attached DERs.

11. COMPLETION OF ONE-LINER:

See attached one-liner.

12. CBI APPENDIX:

The information is considered to be CBI by the registrant and should be treated as such.



ENVIROI
PESTICIDE ENVIRONMENTAL FATE ONE LINE SU

Common Name: **ISOXABEN** Date: 01/11/90
Chem. Name . N-[3-(1-ETHYL-1-METHYLPROPYL)-5-ISOXAZOLYL]-2,6-DIMETHOXY-
: BENZAMIDE
Shaugh. # : 125851 CAS Number:
Type Pest. : HERBICIDE
Formulation: 50% SUSP. CONC.(UK); 12.5% SUSP. CONC. (FRANCE)
Uses : CONTROLS NUMEROUS BROADLEAF WEED SPECIES WHEN INCORPORATED
: OR APPLIED TO THE SOIL SURFACE PREEMERGENCE TO WEEDS
:

Empir. Form: $C_{18}H_{24}N_2O_4$
Mol. Weight: 332.39
Solub.(ppm): 2 @ C

VP (Torr):
Log Kow : 2.64
Henry's :

Hydrolysis (161-1)
pH 5:[*] STABLE
pH 7:[*] STABLE
pH 9:[*] STABLE
pH :[ ]
pH :[ ]
pH :[ ]

Photolysis (161-2, -3, -4)
Air :[ ]
Soil :[ ]
Water:[#] 7-15 DAYS IN NATURAL SUN
:[ ]
:[ ]
:[ ]

MOBILITY STUDIES (163-1)

Soil Partition (Kd)

		Sd	Si	Cl	%OM	pH	Kads
1.	[ ]						
2.	[*]	92	5	3	1.0	8.1	8.4
3.	[*]	62	23	15	1.2	7.2	10
4.	[*]	38	41	21	1.9	6.1	16
5.	[*]	30	37	33	3.1	6.4	30
6.	[ ]						

Rf Factors
1.[*] SLIGHTLY MOBILE IN COLUMN
2.[ ] LEACHING OF 20" WATER OVER 10
3.[ ] DAYS. <0.31% OF APPLIED
4.[ ] RADIOACT. WAS FOUND IN LEACH-
5.[ ] ATE FROM COLUMNS TREATED WITH
6.[ ] UNAGED ISOXABEN.

METABOLISM STUDIES (162-1,2,3,4)

Aerobic Soil (162-1)
1.[*] 4.3 MONTHS IN CLAY LOAM
2.[*] 5.6 MONTHS IN LOAM
3.[*] 10.6 MONTHS IN SANDY LOAM
4.[ ]
5.[ ]
6.[ ]
7.[ ]

Anaerobic Soil (162-2)
1.[ ]
2.[ ]
3.[ ]
4.[ ]
5.[ ]
6.[ ]
7.[ ]

Aerobic Aquatic (162-4)
1.[ ]
2.[ ]
3.[ ]
4.[ ]

Anaerobic Aquatic (162-3)
1.[ ]
2.[ ]
3.[ ]
4.[ ]

[*] - Acceptable Study. [#] = Supplemental Study

Common Name: **ISOXABEN** Date: 01/11/90

VOLATILITY STUDIES (163-2,3)

[ ] Laboratory:
[ ] Field:

DISSIPATION STUDIES (164-1,2,3,5)

Terrestrial Field (164-1)
1.[#] T1/2 = 30-40 DAYS IN SPRING-TREATED SAND SOIL IN FLORIDA
2.[ ] SND LOAM SOIL IN INDIANA. PARENT WAS <.02 LB AIA IN SAMPLES
3.[ ] FROM THE 6-12, 12-18, AND 18-24" DEPTHS AT ALL SITES. THE
4.[ ] DEGRADATE 201469 WAS <.09 LB AIA IN THE 0-6" DEPTH AT ALL
5.[ ] FOUR SITES AND <.01 LB AIA AT GREATER DEPTHS.
6.[ ]

Aquatic (164-2)
1.[ ]
2.[ ]
3.[ ]
4.[ ]
5.[ ]
6.[ ]

Forestry (164-3)
1.[ ]
2.[ ]

Other (164-5)
1.[ ]
2.[ ]

ACCUMULATION STUDIES (165-1,2,3,4,5)

Confined Rotational Crops (165-1)
1.[ ]
2.[ ]

Field Rotational Crops (165-2)
1.[ ]
2.[ ]

Irrigated Crops (165-3)
1.[ ]
2.[ ]

Fish (165-4)
1.[*] BLUEGILL SUNFISH BCF: EDIBLE 14 X, NON-EDIBLE 134 X;
2.[ ] WHOLE 70

Non-Target Organisms (165-5)
1.[ ]
2.[ ]

Common Name: **ISOXABEN** Date: 01/11/90

GROUND WATER STUDIES (158.75)

1. [ ]
2. [ ]
3. [ ]

DEGRADATION PRODUCTS

1. DEGRADATE 201469 IS SLIGHTLY MOBILE IN COLUMN STUDIES AND
2. APPEARS TO BE MORE MOBILE THAN THE PARENT.
3.
4.
5.
6.
7.
8.
9.
10.

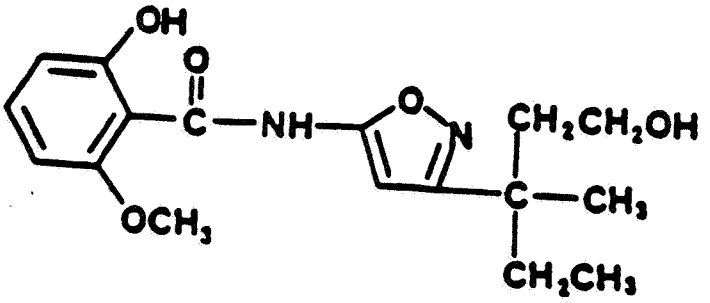
COMMENTS

IN FISH STUDY, THE RESIDUAL ISOXABEN WAS 52% IN EDIBLE TISSUES, 1/% IN NON-EDIBLE TISSUES

ISOXABEN IS PERSISTENT BASED ON HYDROLYSIS, FIELD DISSIPATION, AND AEROBIC SOIL METABOLISM; IT DOES NOT APPEAR TO BE MOBILE BASED ON COLUMN LEACHING, LOW SOLUBILITY, AND LIMITED ADSORPTION/DESORPTION DATA.

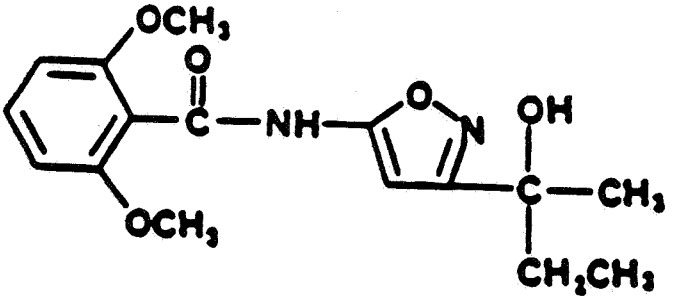
SOXABEN RESIDUES VOLATILIZED AT APPROX. .007 PPM/WK FROM LOAM SOIL TREATED AT 1 PPM; VOLATILES TOTALLED 12-15% OF APPL. RADIOACTIVITY DURINGA 36-WEEK PERIOD.

References: FARM CHEMICALS HANDBOOK; EPA REVIEWS
Writer : J. HANNAN



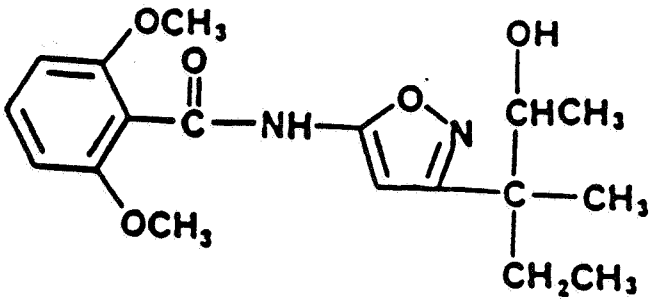
N-[3-(1-Hydroxy-3-methylpent-3-yl) isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide

(Metabolite C)



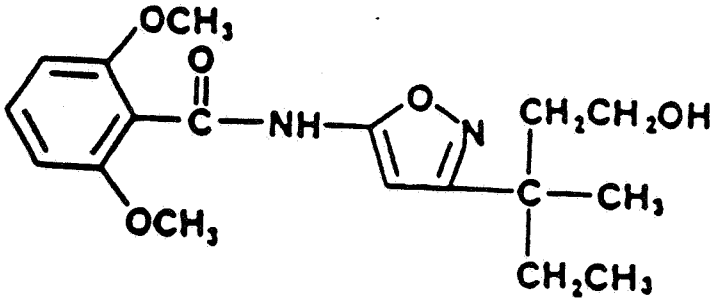
N-[3-(2-Hydroxybut-2-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide

(201469)



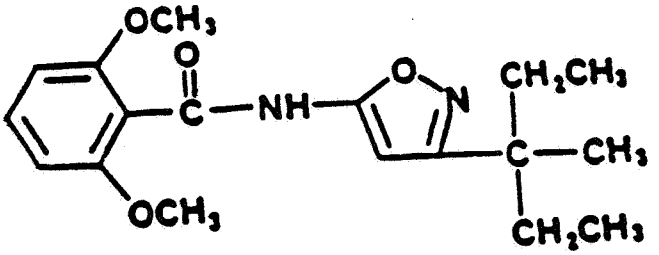
N-[3-(2-Hydroxy-3-methylpent-3-yl)
isoxazol-5-yl]-2,6-dimethoxybenzamide

(20H)



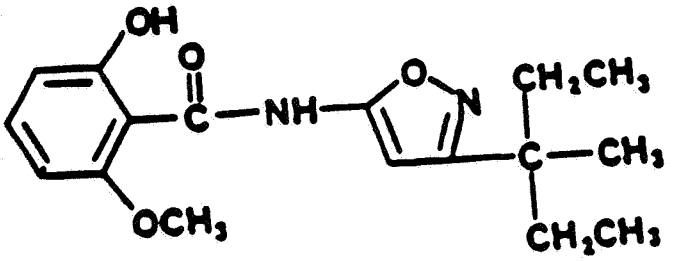
N-[3-(1-Hydroxy-3-methylpent-3-yl)
isoxazol-5-yl]-2,6-dimethoxybenzamide

(30H)



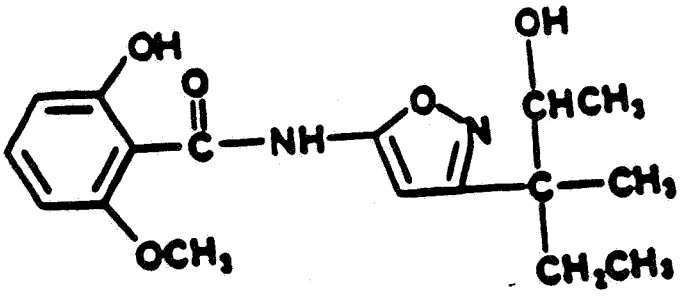
N-[3-(methylpent-3-yl)isoxazol-5-yl]-
2,6-dimethoxybenzamide

(Isoxaben, EL-107)



N-[3-(methylpent-3-yl)isoxazol-5-yl]-
2-hydroxy-6-methoxybenzamide

(Metabolite A)



N-[3-(2-Hydroxy-3-methylpent-3-yl)
isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide

(Metabolite B)

DYNAMAC
CORPORATION

ISOXABEN ADDENDUM

TASK 1: REVIEW AND EVALUATION OF INDIVIDUAL STUDIES

TASK 2: ENVIRONMENTAL FATE ASSESSMENT

February 9, 1990

Final Report

Contract No. 68D90058

Submitted to:
Environmental Protection Agency
Arlington, VA 22202

Submitted by:
Dynamac Corporation
The Dynamac Building
11140 Rockville Pike
Rockville, MD 20852

INTRODUCTION

Isoxaben is an herbicide developed for preemergent control of various broadleaf weeds on terrestrial nonfood (noncrop) use sites. Single active ingredient formulations consist of 12.5 and 50% WP, and 75% FlC. According to the submitted label, isoxaben 50% WP should be applied at 0.5-1 lb/A to the soil surface using a low pressure sprayer.

ISOXABEN

Table of Contents

DATA EVALUATION RECORD

STUDY 1

CHEM 125851 Isoxaben §161-3

FORMULATION--XX--DRY FLOWABLE

STUDY ID 41106301
Saunders, D.G. and F.L. Powers. 1989. Photolysis of isoxaben on soil. Laboratory Project ID AAC8850. Unpublished study performed and submitted by Lilly Research Laboratories, Greenfield, IN.

DIRECT REVIEW TIME = 12

REVIEWED BY: L. Binari TITLE: Staff Scientist

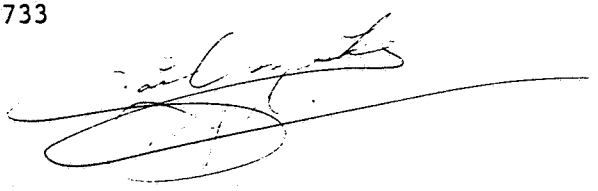
EDITED BY: T. Colvin-Snyder TITLE: Staff Scientist

APPROVED BY: W. Spangler TITLE: Project Manager

ORG: Dynamac Corporation
Rockville, MD
TEL: 468-2500

APPROVED BY: G. Maske
TITLE: Chemist
ORG: EFGWB/EFED/OPP
TEL: 557-9733

SIGNATURE:



CONCLUSIONS:

Degradation - Photodegradation on Soil

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

2. Isoxaben (75% dry flowable) photodegraded with a calculated half-life of 198 days on clay loam soil irradiated continuously with artificial light (fluorescent sunlamps and black lights) for 54 days (equivalent to 33.5 days of sunlight) at approximately 25°C. At 54 days post-treatment, approximately 98% of the applied isoxaben was detected in the dark controls.

3. This study is scientifically sound, but does not meet Subdivision N guidelines for the following reasons:

material balances were incomplete because the samples were only analyzed for parent isoxaben (approximately 10-11% of the applied was unaccounted for);

the artificial light source was not comparable to natural sunlight; and,

the test substance was not technical grade or purer.

4. Since the artificial light source was not comparable to sunlight, this study cannot be corrected with a submission of additional data. This study must be repeated.

METHODOLOGY:

Clay loam soil (31% sand, 37% silt, 32% clay, 2.1% organic matter, pH 6.9, CEC 16.3 meq/100 g) was air-dried overnight, sieved (10-mesh), and added to twelve petri dishes (9-cm diameter) to a depth of 2 mm (14.6 g soil/dish). The samples were treated with a dry flowable formulation of isoxaben (Lilly Research Laboratories) at 47.1 ppm (0.965 lb/A), then air-dried for approximately 5 hours. Following this period, each treated sample was covered with a Pyrex glass lid. Then, three of the samples were wrapped in foil for dark controls, three of the samples were analyzed to determine the amount of isoxaben at time zero, and the remaining six samples were irradiated. Irradiated and dark control samples were incubated (25 ± 5 C) on a rotating turntable in a chamber equipped with four fluorescent sunlamps (FS20T12, Westinghouse) and four florescent black lights (F20T12BC, General Electric) that were mounted vertically inside the chamber and emitted light of 3.6-5.7 x 10^{-4} W/cm^2/nm intensity. The light intensity was monitored periodically using a radiometer with a detector-filter combination intended to generate an irradiation band centered at 320 nm, and was also determined by comparing the photodegradation rates of solutions of paranitroacetophenone (PNAP; 5 ppm in 0.06 M aqueous pyridine) in the chamber and in natural sunlight. Triplicate samples were collected after 50 and 54 days of irradiation, equivalent to 30.5 and 33.5 days of natural sunlight. The dark control samples were collected at 54 days posttreatment.

Soil samples were refluxed in methanol:water (8:2) for 1 hour. Extracts were filtered and analyzed for isoxaben by reverse-phase HPLC with UV detection at 254 nm.

DATA SUMMARY:

Isoxaben (75% dry flowable), at approximately 47 ppm, degraded with a calculated half-life of 198 days on clay loam soil continuously irradiated for 54 days with fluorescent light (sunlamps and black lights) at approximately 25°C. The intensity of the light source was 3.6-5.7 x 10^{-4} W/cm^2/nm, and 54 days of irradiation was determined to

be equivalent to 33.5 days of sunlight. At 54 days posttreatment, isoxaben comprised 88.7 and 97.7% of the applied in the irradiated and dark control samples, respectively.

COMMENTS:

1. Material balance data were incomplete because the samples were only analyzed for parent isoxaben; approximately 10% of the applied was unaccounted for in the samples that were irradiated for 50 days (equivalent to 30.5 days of sunlight). The registrant needs to determine if the unaccounted for material comprised a single degradate (which must be identified), more than one degradate, bound residues, or volatiles.

2. The artificial light source, fluorescent sunlamps and black lights, was not comparable to sunlight. The intensity of the artificial light source was approximately two-thirds the intensity of natural sunlight. The wavelength distribution of the light source was not provided. Currently, a xenon arc lamp is the only artificial light source considered by the EFGWB to be similar to sunlight.

3. The test substance was formulated (75% dry flowable) and, therefore, was not technical grade or purer. In addition, it is preferred that a radiolabeled test substance be used.

4. The intensity of light in the chamber was variable. The study authors reported that the lamps were replaced at day 40. The light intensities were 3.6-3.8 x 10^{-4} W/cm^2/nm from days 0-40 and 4.8-5.7 x 10^{-4} W/cm^2/nm from days 41-54.

5. The statistical estimation of the photodegradation half-life of isoxaben reported in this study is of limited value because the calculations involve extrapolation considerably beyond the experimental time limits of the study. Data are often incapable of accurately predicting trends outside of their range because small differences are magnified and reactions which appear to linear may, in fact, be curvilinear. The statistical estimation provided for the dark control (983 days) was not reported in this rev w because it is not considered meaningful due to the extremeness of the extrapolation; 97.7% of the applied remained as isoxaben at the end of the experiment.

6. The refrigeration unit for the constant temperature room failed on day 4 of the study, and the temperature rose to 30°C on that day, the maximum value during the study. The temperature subsequently declined to a low of 22°C on day 6 when the unit was repaired, then remained at 24-25°C for the rest of the study.

7. The registrant determined the light intensity in the photochamber by using the paranitroacetophenone (PNAP) chemical actinometer method with only periodic monitoring with a radiometer. It is preferred to

determine the light intensity by continuous monitoring with a radiometer. The data provided in Tables II and III were not summarized by the reviewer since these data are irrelevant to the data requirements for photodegradation of isoxaben in soil. These data reflect PNAP photodegradation in sunlight and the irradiation chamber used in this study.

8. Sample extracts were stored at 4°C for an unspecified interval prior to HPLC analysis. However, three control samples were fortified with parent isoxaben and extracted at the beginning of the study, then stored with the sample extracts. Recoveries ranged from 106 to 111.2% of the applied.

DATA EVALUATION RECORD

STUDY 2

CHEM 125851 Isoxaben §162-2

FORMULATION--00--ACTIVE INGREDIENT

STUDY ID 41106302
Rainey, D.P. 1989. ^{14}C Isoxaben anaerobic soil metabolism study. Laboratory Project ID ABC-0224. Unpublished study performed and submitted by Lilly Research Laboratories, Greenfield, IN.

STUDY ID 00143786
Rainey, D.P., and L.K. Graper. 1985. Aerobic soil metabolism of ^{14}C EL-107. ABC-0224. Unpublished study performed and submitted by Lilly Research Laboratories, Greenfield, IN.

STUDY ID 00164646
Rainey, D.P. 1985?. The metabolism of ^{14}C EL-107 in soil: Characterization of volatile radiolabeled degradation products. Experiment ABC-0224. Unpublished study performed and submitted by Lilly Research Laboratories, Greenfield, IN.

DIRECT REVIEW TIME = 20

REVIEWED BY: L. Binari, S. Syslo TITLE: Staff Scientist

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SIGNATURE:

CONCLUSIONS:

Metabolism - Anaerobic Soil

1. This study can be used to fulfill data requirements.

2. Isoxazole ring-labeled [5-^{14}C]isoxaben degraded with a half-life of >120 days in loam soil incubated anaerobically (flooding) at 23°C in the dark for 60 days following 60 days of aerobic incubation. The major degradate identified was N-[3-(1-hydroxyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide; other degradates identified were: N-[3-(1-acetyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide, N-[3-(1-hydroxy-1-ethyl)-5-isoxazolyl]-2,6-dimethoxybenzamide, and N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2-hydroxy-6-methoxyl-benzamide.

3. This study is acceptable and fulfills EPA Data Requirements for Registering Pesticides by providing information on the metabolism of isoxazole ring-labeled [5-^{14}C]isoxaben in anaerobic (flooded) loam soil.

4. No additional information on the metabolism of isoxaben in anaerobic soil is required at this time.

METHODOLOGY:

Loam soil (37.6% sand, 41.2% silt, 21.2% clay, 1.9% organic matter, pH 6.1, CEC "9.1") was collected and stored field-moist at room temperature for an unspecified length of time, then sieved (2-mm) and the moisture content was determined. A portion of the soil (2000 g, dry weight) was treated at 1.0 ppm with isoxazole ring-labeled [5-^{14}C]isoxaben (radiochemical purity >99%, specific activity 4.0 uCi/mg, Lilly Research Laboratories) in methanol. The soil was mixed on a roller mill for 30 minutes, then moistened to 75% of 0.33 bar moisture capacity (12.9% moisture). The treated soil was incubated aerobically in a "loosely covered" plastic container in the dark at 23°C. Water was added to the soil as needed to maintain moisture levels. After 60 days of aerobic incubation, four 25-g portions of the treated soil were transferred to flasks and flooded with distilled water. The flasks were stoppered and incubated at 23°C in darkness for up to 2 months. Soil samples were collected after 0, 0.5, 1, and 2 months of aerobic incubation; duplicate flasks of soil plus water samples were collected after 30 and 60 days of anaerobic incubation (90 and 120 days posttreatment).

Total [^{14}C]residues in the aerobic soil samples were quantified by LSC following combustion. Duplicate portions of the undried soil samples were refluxed with methanol:water (80:20) for 1 hour. The extracts were filtered; aliquots were analyzed for radioactivity by LSC and the remainder was evaporated to dryness. The residues were dissolved in methanol. A portion of the residues was analyzed by LSC; additional aliquots were analyzed by one-dimensional TLC on silica gel plates developed twice in chloroform:acetone (90:10). Radioactive areas were detected by autoradiography or spark chamber radiograms and quantified by scraping and counting the silica gel using LSC. Unlabeled reference isoxaben, cochromatographed with the

samples, was visualized under UV light. Unextractable radioactivity in the soil was determined by LSC following combustion.

Duplicate soil:water samples from the anaerobic incubation were refluxed with methanol for 1 hour, and the samples were filtered. The resulting extracts and extracted soil were analyzed as previously described.

DATA SUMMARY:

Isoxazole ring-labeled [5-^{14}C]isoxaben (radiochemical purity >99%) degraded with a half-life of >120 days in loam soil that was incubated anaerobically (flooding) in the dark at 23°C for 60 days following 60 days of aerobic incubation. [^{14}C]Isoxaben was 1.0 ppm at the start of the study and decreased to 0.60 ppm (65.2% of the applied) after 60 days of aerobic incubation and 0.49 ppm (54.1%) after 60 days of anaerobic incubation (Appendix I, Table 3). The major degradate detected in the anaerobic soil was

N-[3-(1-hydroxyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide (Metabolite II),

which increased from 0.11 ppm to a maximum of 0.15 ppm (12.1 to 16.3% of the applied) during the 60 days of anaerobic incubation (Table 3). Three minor degradates were detected:

N-[3-(1-acetyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide (Metabolite III; maximum of 0.04 ppm or 4.4% of the applied after 1 month anaerobic incubation);

N-[3-(1-hydroxy-1-ethyl)-5-isoxazolyl]-2,6-dimethoxybenzamide (Metabolite I; 0.02 ppm or 1.9% of the applied after 2 months anaerobic incubation); and

N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2-hydroxy-6-methoxylbenzamide (Metabolite V; 0.02 ppm or 2.2% of the applied after 2 months anaerobic incubation).

Relative amounts of these degradates did not change appreciably during anaerobic incubation. Polar residues (those remaining at the origin) increased from 0.01 to 0.04 ppm (1.5 to 4.2% of the applied; Table 3) during the study. Unextractable [^{14}C]residues were 0.11 ppm in the soil (12.0% of the applied; Table 2) after 60 days of anaerobic incubation. The material balance decreased from 96.9 to 94.8% of the applied during the 60 days of anaerobic incubation (Appendix I, Table 2).

COMMENTS:

1. The data were expressed as "percent of the radioactivity present when anaerobic conditions were established". The values in the Data Summary were recalculated by the reviewer and are reported as "percent of the applied" using the values presented in Appendix I.

2. Additional information is not required for the phenyl ring-labeled moiety; all degradates formed during the course of the study contained both the isoxazole and phenyl rings.

3. It is recommended that development of TLC plates be conducted in three solvent systems of different polarities for maximum confidence in separation of [^{14}C]compounds. In this study, the samples were analyzed using one-dimensional TLC with a single solvent system (chloroform:acetone). However, the separation system used appears to have been adequate, since in a companion study using clay loam soil (MRID 00143786), metabolite identification involved column chromatography on silica gel, followed by purification of radioactive fractions using one-dimensional preparative TLC; radioactive areas on the TLC plates were further purified using HPLC with UV detection, and metabolites were identified using MS and NMR.

4. Units for the CEC of the soil were not provided (Table 1).

5. Volatiles were not trapped during the study; the material balance after 120 days of incubation had decreased to 94.8% of the applied. In a companion study (MRID 00164646), 12-15% of the applied radioactivity was evolved during 36 weeks of aerobic incubation in loam soil at 1.0 ppm. The evolved [^{14}C]residues were identified as $^{14}CO_2$; no radioactivity was found in either the ethylene glycol or sulfuric acid trapping solutions.

6. The study author stated that the aerobic incubation period was extended to 2 months in order to produce higher concentrations of isoxaben degradates, so the patterns of formation and decline of degradates under anaerobic conditions could be more easily determined.

DATA EVALUATION RECORD

STUDY 3

CHEM 125851 Isoxaben §163-1

FORMULATION--00--ACTIVE INGREDIENT

STUDY ID 41106303
Saunders, D.G. and F.L. Powers. 1989. Soil adsorption and desorption of isoxaben and soil metabolite 201469. Laboratory Project ID AAC8851. Unpublished study performed and submitted by Lilly Research Laboratories, Greenfield, IN.

DIRECT REVIEW TIME = 24

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SIGNATURE:

CONCLUSIONS:

Mobility - Leaching and Adsorption/Desorption

1. This study can be used to fulfill data requirements.

2. Carbonyl-labeled [^{14}C]isoxaben is mobile to very mobile in sand, loamy sand, sandy loam, loam, and clay loam soils. Isoxaben mobility decreased with increasing soil clay content and CEC. The isoxaben metabolite, N-[3-(1-hydroxy-1-methylpropyl)-5-isoxazoyl]-2,6-dimethoxybenzamide (201469), is very mobile in sand, loamy sand, sandy loam, loam, and clay loam soils.

3. This study is acceptable and partially fulfills EPA Data Requirements for Registering Pesticides by providing information on the mobility (batch equilibrium) of unaged isoxaben and 201469 in sand, loamy sand, sandy loam, loam, and clay loam soils.

4. This study fulfills the data requirements for mobility of unaged isoxaben in soil. In addition, this study may be used to fulfill the data requirement for mobility of aged isoxaben residues if the toxicology branch determines that degradates other than 201469 are not of toxicological concern. If the toxicology branch does determine that isoxaben degradates other than 201469 are of toxicological concern, then a new study of the mobility of aged isoxaben residues or the isoxaben degradates of concern will be required.

METHODOLOGY:

Sand, loamy sand, sandy loam, loam, and clay loam soils (Table II) were air-dried, crushed, sieved (10- or 20-mesh), and stored at 4 C until use. Based on data from a previously submitted adsorption/-desorption study (Mosier and Saunders, Acc. No. 250449), an equilibration time of 22 hours was selected.

For the adsorption studies, solutions of carbonyl-labeled [^{14}C]isoxaben (radiochemical purity 99%, specific activity 9.47 μCi/mg, Lilly Research Laboratories) were prepared with sterile 0.01 M calcium chloride solution at 0.02, 0.05, 0.2, and 0.5 ug/mL, then added to triplicate samples of each soil type contained in 50-mL glass centrifuge tubes. For each soil type, an additional tube containing only calcium chloride solution and soil was prepared as a control. The soil solution slurries (40 mL of isoxaben solution:5 to 20 grams of soil depending on the soil type) were equilibrated for 22 hours at 25 ± 1 C by rotation on a revolving wheel (16 rpm) which inverted each tube every 2 seconds. The soil weights were 20, 10, 10, 5, and 5 g for the sand, loamy sand, sandy loam, loam, and clay loam soils, respectively. Following equilibration, the tubes were centrifuged, and an aliquot (2 mL) of the supernatant was analyzed for total radioactivity by LSC.

Desorption of isoxaben was investigated in the soil samples described above by removing an additional 20 mL of supernatant, adding 22 mL of pesticide-free 0.01 M calcium chloride solution, and then equilibrating for 22 hours on the revolving wheel. After equilibration, the slurries were centrifuged and the supernatant was analyzed by LSC. This procedure was repeated to obtain a second set of desorption values.

To determine material balances and verify that isoxaben did not degrade during the adsorption/desorption procedures, an additional adsorption/desorption experiment was conducted as described above using [^{14}C]isoxaben in 0.01 M calcium chloride at 0.5 ug/mL combined with sandy loam (40 mL:10 g) or clay loam (40 mL:5 g) soil. Aliquots

of the supernatants obtained following the adsorption and first desorption were analyzed by LSC, then combined. Following the second desorption, the soil:solution slurry was refluxed for one hour with methanol. The extract was filtered, analyzed by LSC, then combined with the previous supernatants. An aliquot (50 mL) of the combined extract was diluted with 5% aqueous sodium chloride, then partitioned twice with methylene chloride. Organic phases were combined, concentrated, and analyzed by TLC on silica gel plates developed in chloroform:methanol:acetic acid (88:10:2). Reference labeled and unlabeled isoxaben were cochromatographed with the samples. Radioactive areas were detected by autoradiography.

The adsorption/desorption of a major soil metabolite of isoxaben, N-[3-(1-hydroxy-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide (201469), was studied by methods similar to those described for isoxaben. A preliminary test conducted using 201469 at 5.0 ug/mL combined with sandy loam or clay loam (40 mL:20 g) confirmed that an equilibration time of 22 hours was adequate. An additional test determined that calcium chloride solutions of 201469 at 5.0 ug/mL were stable for up to 68 days at 4°C. For the adsorption studies, solutions of 201469 (purity 98.8%, Lilly Research Laboratories) were prepared in 0.01 M calcium chloride at 0.4, 1, 5, and 25 ug/mL, then equilibrated with the five soil types as described above. After centrifugation, 20 mL of the supernatant were removed from each tube and stored at 4 C for up to 67 days until analysis. Following storage, an aliquot of each supernatant was combined with acetonitrile, then the sample was evaporated to dryness. The residue was dissolved in methanol:water (60:40) and analyzed for 201469 by reverse-phase HPLC with UV detection at 254 nm. The detection limit was 0.8 ug of 201469.

Desorption of 201469 was investigated by adding 20 mL of pesticide-free calcium chloride solution to the samples and equilibrating for 22 hours. After equilibration, the slurries were centrifuged, and the supernatant was analyzed by HPLC. This procedure was repeated.

To determine material balances and to verify that 201469 did not degrade during the adsorption/desorption procedures, an additional adsorption/desorption experiment was conducted as described above using 201469 in 0.01 M calcium chloride solution at 25 ug/mL combined with sandy loam or clay loam soil (40 mL:20 g). After one adsorption and two desorption steps, the soil:solution slurry was refluxed in methanol for one hour, then filtered. The extract was combined with aliquots from both the adsorption and first desorption phase, diluted to volume, then analyzed for 201469 as previously described.

DATA SUMMARY:

Based on batch equilibrium studies, carbonyl-labeled [^{14}C]isoxaben (radiochemical purity 99%), at 0.02, 0.05, 0.2, and 0.5 ug/mL, was determined to be mobile to very mobile in sand, loamy sand, sandy

loam, loam, and clay loam soil:calcium chloride solution slurries (5-20:40) equilibrated for 22 hours at 25 ± 1 C. Freundlich K_{ads} values were 0.81 for the sand soil, 2.18 for the loamy sand soil, 2.48 for the sandy loam soil, 4.41 for the loam soil, and 6.63 for the clay loam soil (Table VI); respective K_{oc} values were 280, 190, 310, 420, and 570 (Table X). Adsorption increased with increasing soil clay content and CEC. Following desorption, K_d values (soil concentration:aqueous concentration) were 0.95-1.70 for the sand soil, 3.05-5.58 for the loamy sand soil, 3.17-5.64 for the sandy loam soil, 5.64-10.2 for the loam soil, and 9.25-15.77 for the clay loam soil (Appendix E). TLC and autoradiography analysis of combined solutions from the adsorption and desorption phases found only one major radioactive zone, identified as isoxaben.

N-[3-(1-hydroxy-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide (201469), at 0.4, 1, 5, and 25 ug/mL, was determined to be very mobile in the same five soils equilibrated for 22 hours at 4 C. Freundlich K_{ads} values were 0.06 in the sand soil, 0.30 in the loamy sand soil, 0.22 in the sandy loam soil, 0.37 in the loam soil, and 0.84 in the clay loam soil (Table VII); respective K_{oc} values were 21, 26, 27, 42, and 73. Following desorption, the K_d values were 0.03-0.60 for the sand soil, 0.35-0.92 for the loamy sand soil, 0.24-0.86 for the sandy loam soil, 0.06-1.15 for the loam soil, and 0.81-1.59 for the clay loam soil (Appendix E). HPLC analysis of combined solutions from the adsorption and desorption phases yielded quantitative recovery of the applied 201469.

COMMENTS:

1. The registrant failed to analyze the soil and, therefore, assumed that whatever radioactivity or test substance was not in solution was adsorbed to the soil and not adsorbed to the glass tubes. The registrant did conduct a test in which solutions of 201469 at 1 and 5 ug/mL were equilibrated in glass tubes for 22 hours, then analyzed by HPLC; no adsorption to the glass occurred. The registrant also referenced a previously submitted study (Mosier and Saunders, Acc. No. 250449) in which solutions of isoxaben at 0.0427, 0.1130, 0.486, and 1.15 ug/mL were equilibrated for 24 hours. The registrant reported that no adsorption occurred at 0.0427 and 0.1130 ug/mL, slight adsorption occurred at 0.486 ug/mL, and significant adsorption occurred at 1.15 ug/mL. In this study, aqueous concentrations of [^{14}C]isoxaben did not exceed 0.35 ug/mL.

2. The sand and loamy sand soils were sieved with a 20-mesh screen. Sieving soil with a 20-mesh screen would tend to decrease the mobility of the test substance by removing all of the very coarse and part of the coarse sand fractions. However, since isoxaben and the degradate 201469 were very mobile in these soils, the study does not need to be repeated.

3. The experiment studying the mobility of the degradate 201469 was conducted at 4°C.

4. The "desorption isotherm slopes" reported in Tables VIII and IX are not true Kdes values, but instead are the slopes of the decline of Kd values following two desorptions for each final adsorption concentration. Kd values (Appendix E) were reported in this review because they are more meaningful.

5. The registrant provided sample chromatograms of 201469 (Figure 1); however, no interpretation of these data could be made since the figure was illegible.

6. In the aerobic soil metabolism study (Accession No. 073607 and MRID 00265370, EAB review dated April 27, 1988), the major isoxaben degradate was 201469, and three additional degradates each comprised <5% of the applied radioactivity. This study may be used to fulfill the data requirement for mobility of aged isoxaben residues if the toxicology branch determines that degradates other than 201469 are not of toxicological concern. However, if the toxicology branch does determine that isoxaben degradates other than 201469 are of toxicological concern, then a new study of the mobility of aged isoxaben residues or the isoxaben degradates of concern will be required. Additional information may also be required for the phenyl and the isoxazole ring-labeled moieties, if degradates of concern do not contain both the isoxazole and phenyl rings.