

ISOXABEN ADDENDUM

Final Report

**Task 1: Review and Evaluation of
Individual Studies**

**Task 2: Environmental Fate
Assessment**

Contract No. 68-02-4250

APRIL 27, 1988

Submitted to:
Environmental Protection Agency
Arlington, VA 22202

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ISOXABEN

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INTRODUCTION

Isoxaben is an herbicide developed for preemergent control of various broadleaf weeds on terrestrial food crop (wheat and barley) and 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.

DATA EVALUATION RECORD

ISOXABEN

STUDY 1

CHEM 125851

Isoxaben

BRANCH EAB

FORMULATION--14--FLOWABLE CONCENTRATE (FLC)

FICHE/MASTER ID 40532102

Rutherford, B.S. and O.D. Decker. 1988. Isoxaben turf field dissipation study - Illinois site. Laboratory Project Identification AAC8521. Prepared and submitted by Eli Lilly and Company, Greenfield, IN.

FICHE/MASTER ID 40532103

Rutherford, B.S. et al. 1987. Determination of EL-107 and/or its soil metabolite in soil and soil/turf samples. Laboratory Project ID AM-AA-CA-RO42-AD-755. Prepared and submitted by Eli Lilly and Company, Greenfield, IN.

SUBST. CLASS = S

DIRECT RVW TIME = 8

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CONCLUSIONS:

Field Dissipation - Terrestrial

This study is acceptable and partially fulfills EPA Data Requirements for Registering Pesticides by providing information on the terrestrial field dissipation of the 75% FLC formulation of isoxaben at one test site. A second study (Rutherford and Decker, 40059508) provides information on the terrestrial field dissipation of the FLC formulation of isoxaben at two additional test sites (Texas and Indiana).

SUMMARY OF DATA BY REVIEWER:

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 ≤ 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.

During the test period, air temperatures ranged from 26-100 F, and soil temperatures (4-inch depth) ranged from 46-82 F. Cummulative precipitation plus irrigation totaled 28.16 inches. Isoxaben and its degradate 201469 (N-[3-(2-hydroxybut-2-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide) were not detected in pretreatment samples taken from the 0- to 6-, 6- to 12-, and 12- to 18-inch depths. With a few random exceptions, isoxaben and the degradate 201469 were not detected in samples from the control plot taken from the 0- to 6-, 6- to 12-, 12- to 18-, 18- to 24-, 24- to 30-, and 30- to 36-inch depths; isoxaben and the degradate 201469 were isolated in a few samples at ≤ 0.04 lb/A.

DISCUSSION:

1. Isoxaben and the degradate 201469 were isolated in a few samples taken from the control plot at ≤ 0.04 lb/A; however, since these levels were close to the detection limit (0.01 lb/A), the isolation of isoxaben and 201469 is considered to be due to experimental error and not due to contamination of the control plots.
2. The depth to the water table at the test site was not measured; data were taken from the Champaign County soil survey. The registrant reported that the plot was elevated in comparison to adjoining areas due to use of fill dirt. The actual depth to the water table may have been significantly different from the reported values.
3. Soil storage stability data, including data in this submission, have been previously reviewed in the registration standard (dated 12/11/87) and showed that isoxaben and the degradate 201469 are stable when stored at 4 C.
4. The methods section of the report (MRID 40532102) states that recovery samples of 50 g of soil fortified with isoxaben or 201469 at 0.025 ppm (1.25 ug/50 g soil) were used; this pertains to recovery data provided in the methods section. It is unclear if recovery data contained in the study itself (MRID 40532103) for soil samples (sample size not reported) fortified at 1.25 and 50 ug are also for 50 g soil samples.

MATERIALS AND METHODS

MATERIALS AND METHODS:

Isoxaben (75% FlC) was applied at 1.0 lb ai/A to a turf plot (40 X 40 feet) of clay loam soil in Champaign, Illinois on April 7, 1987. The slope of the plot was 5-10%, and the water table was reported to reach a maximum of 0.5-2 feet. An untreated plot served as a control. The plots were periodically irrigated. Soils were sampled at intervals up to 211 days posttreatment. Soil samples were taken from 0- to 6-, 6- to 12-, 12- to 18- and 18- to 24-inch depths; samples from 24- to 30- and 30- to 36-inch depths were also taken after 150 days posttreatment. Turf from each 0- to 6- inch segment was cut from the soil segment, frozen in liquid nitrogen, ground, and then mixed with the soil from the same sample prior to storage. Samples were stored at 4 C prior to analysis.

Soil samples were analyzed for isoxaben and its degradate, 201469 (N-[3-(2-hydroxybut-2-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide), using Lilly Research Laboratory Analytical Method No. AM-AA-CA-RO42-AC-755 or its revision, AM-AA-CA-RO42-AD-755. Soil samples were blended with methanol:water (80:20), heated, and allowed to cool while the solids settled. An aliquot of the supernatant was removed, treated with 5% sodium chloride solution, and partitioned three times into methylene chloride. The combined extracts were filtered through sodium sulfate and cleaned up on an aluminum column washed with methylene chloride:ethyl acetate (80:20) followed by methylene chloride:methanol (99:1). Isoxaben and 201469 were eluted three times with methylene chloride:methanol (99:1), 98:2, and then 97:3). The fractions were each evaporated to dryness and then redissolved in methanol:water (same proportions as the appropriate mobile phase) prior to quantification by HPLC. The detection limit was 0.02 lb/A (0.01 ppm). Average recoveries (method unspecified) for samples fortified at 1.25 and 50 ug (soil sample size not reported) were 94.1% (35 samples) and 83.9% (38 samples) for isoxaben and the degradate 201469, respectively. For the revised method, average recoveries (2-22 replications) from soil and soil/turf samples fortified with isoxaben at 0.025-1.0 ppm were 98.3-107%; average recoveries (2-25 replications) from samples fortified with the degradate 201469 at 0.025-1.0 ppm were 70.3-92.0%.

ISOXABEN ADDENDUM - ENVIRONMENTAL FATE ASSESSMENT

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Pages 8 through 24 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

ISOXABEN

STUDY 2

CHEM 125851

Isoxaben

BRANCH EAB

FORMULATION--00--ACTIVE INGREDIENT

FICHE/MASTER ID 40097601 and 40059507

Saunders, D.G., J.W. Moran and G.E. Babbit. 1986. Photolysis of isoxaben in aqueous solution. Prepared and submitted by Eli Lilly and Company, Greenfield, IN.

SUBST. CLASS = S

DIRECT RVW TIME = 4

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CONCLUSIONS:

Degradation - Photodegradation in water

In the previous review dated 12/30/87, this study did not fulfill data requirements because degradates comprising >10% of the applied radioactivity were incompletely characterized and the intensity of the sunlight was not reported.

In the original report, the registrant had identified five zones on the TLC plates; further analysis of these zones indicated that they contained one to several compounds. Considerable work was done in an attempt to identify compounds in those zones containing >10% of the applied radioactivity. How-

ever, the registrant failed to provide information on the relative percentage of various compounds within each zone, so that it was unclear if any compound comprised >10% of the applied. In the new submission, additional information on the concentration of each compound within the multiple-compound zones is provided, and the registrant now has clarified that all compounds >10% of the applied have been adequately identified.

Carbonyl- and isoxazole ring-labeled [¹⁴C]isoxaben (radiochemical purities >99.5%), at 0.5 ppm, degraded with half-lives of 7-15 days (calculated 9 days) in sterile buffered (pH 7) solutions irradiated outdoors with natural sunlight at 48-96°F. After 30 days of irradiation, isoxaben comprised 21.6% and 13.8% of the applied radioactivity of the carbonyl- and isoxazole ring-labeled solutions, respectively. Degradates included a benzamide, a pyrazolone, an isoquinolone, and a benzopyrrolidone; no degradate comprised >15.1% of the applied radioactivity. In the dark controls at 30 days posttreatment, isoxaben comprised >94.4% of the applied.

It is not necessary that photolysis data be related to average sunlight intensities, as was done by the registrant; rather, the EPA Data Requirements for Registering Pesticides require only that photolysis be related to the conditions under which the experiment was conducted. The deviation from the data requirements is a minor issue and, by itself, would not prevent this study from being accepted.

In regards to other registrant responses to comments made by the reviewers about this study, the study was faulted only for the issues listed in the Conclusion section of the review. The points raised in the Discussion (excluding the issues also listed in the conclusions) are minor issues that deviate from the standard procedures mentioned under "Subdivision N" guidelines. They do not in any way affect acceptance of the study, and it is not necessary that the registrant respond to these comments. These points are listed so that the registrant may take them into consideration for future experiments, or to "red-flag" them to gain the attention of other reviewers. Also, the photodegradation in pond and river water studies that were submitted with the photodegradation in sterile buffered solution are scientifically sound studies that demonstrate what may occur under natural conditions, but they are not useful in fulfilling this specific data requirement because it was not clear if the solutions were sterilized before use. Therefore, degradation due to photolysis and microbial activity could not be differentiated. The purpose of the Photodegradation in Water study is to isolate the photolysis/hydrolysis reactions from microbial degradation.

The photodegradation in water study (Saunders et al., MRID #40097601 and MRID #40059507) is now considered acceptable and fulfills data requirements.

DATA EVALUATION RECORD

ISOXABEN

STUDY 3

CHEM 125851

Isoxaben

BRANCH EAB

FORMULATION--00--ACTIVE INGREDIENT

FICHE/MASTER ID NONE

Graper, L.K. 1985. Aerobic soil metabolism of ¹⁴C EL-107. Study No. ABC-0224. Submitted by Eli Lilly and Company, Greenfield, IN. Acc. No. 073607.

FICHE/MASTER ID 00265370

Rainey, D.P. The metabolism of [¹⁴C]EL-107 in soil: characterization of volatile radiolabeled degradation products. Experiment ABC-0226. Prepared and submitted by ELI Lilly and Company, Greenfield, IN.

SUBST. CLASS = S

DIRECT RVW TIME = 4

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CONCLUSIONS:

Metabolism - Aerobic Soil

In the previous review dated 12/30/87, the aerobic soil metabolism study using isoxazole ring-labeled [¹⁴C]isoxaben (originally reviewed in December, 1985, for the EUP) was judged to be acceptable but an additional study was required using carbonyl-labeled isoxaben. Because of its complex molecular structure, information is automatically required on the fate of both the isoxazole and carbonyl moieties. However, it was originally overlooked that the degradates

identified in the existing aerobic metabolism study contain both the isoxazole and carbonyl moieties, the molecule did not degrade at the benzamide linkage (this argument was presented by the registrant for the mobility requirement, but not for the aerobic soil metabolism requirement although it is applicable). Therefore, an aerobic soil metabolism study using carbonyl-labeled [¹⁴C]isoxazole would provide no additional information. The data requirement is now considered to be completely fulfilled.

Isoxazole ring-labeled [¹⁴C]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 28° 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-dimethoxybenzamide, and N-[3-(methylpent-3-yl)isoxazol-5-yl]-2-hydroxy-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 (by acid and base hydrolysis) radioactivity accounted for 22.0% of the applied and volatiles (determined in a separate experiment) totaled 15.5% of the applied.

DATA EVALUATION RECORD

ISOXABEN

STUDY 4

CHEM 125851

Isoxaben

BRANCH EAB

FORMULATION--00--ACTIVE INGREDIENT

FICHE/MASTER ID 00265730

Saunders, D.G., S.K. Smith and J.W. Moiser. 1985. Mobility of EL-107 and a soil metabolite in soil. Report No. EWD8442. Prepared and submitted by Eli Lilly and Company, Greenfield, IN.

SUBST. CLASS = S

DIRECT RVW TIME = 4

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CONCLUSIONS:

Mobility - Leaching and Adsorption/Desorption

Since the initial review of this study, the groundwater assessment team has expressed concern that isoxaben and its degradates may have the potential to leach to groundwater. The results of the column leaching study were judged to be inconclusive, and an additional batch equilibrium study using four soils at four concentrations has been required. The request for additional data on the mobility of aged material has been withdrawn; the mobility data requirement will be fulfilled with the submission of an acceptable batch equilibrium study.

Isoxazole ring-labeled [¹⁴C]isoxaben and aged (30-day) [¹⁴C]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, <0.31% of the applied radioactivity was found in the leachates from the columns treated with unaged [¹⁴C]isoxaben and <3.61% of the applied was found in leachates from the columns treated with aged [¹⁴C]-residues. The majority (>84% of the applied) of the [¹⁴C]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 [¹⁴C]compounds in the 30-day aged soil prior to leaching. Based on the column leaching study, K_d values for the four soils ranged from 8.4 to 30.

DATA EVALUATION RECORD

ISOXABEN

STUDY 5

CHEM 125851

Isoxaben

BRANCH EAB

FORMULATION--14--FLOWABLE CONCENTRATE

FICHE/Master ID 40059508

Rutherford, B.S. and O.D. Decker. 1986. Isoxaben soil/turf field dissipation study. Project No. AAC8521. Prepared and submitted by Eli Lilly and Company, Greenfield, IN.

SUBST. CLASS = S

DIRECT RVW TIME = 4

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CONCLUSIONS:

Field Dissipation - Terrestrial

In the previous review dated 12/30/87, this study was faulted because the frequency of sampling the deeper soil layers was insufficient to adequately assess the leaching potential of isoxaben. This is of special concern with isoxaben, since the laboratory mobility study indicates that isoxaben and its residues may have the potential to leach. Field studies can be used to determine whether the observed potential to leach is a laboratory phenomenon. The preliminary groundwater assessment indicates that at "worst-case" sites in Florida that have a shallow water table within a foot of the soil surface and high irrigation/rainfall amounts, isoxaben residues will reach ground water.

Based on the original terrestrial field dissipation study, a new field dissipation study (Study 1 in this report), and additional information provided by the registrant, it is clear that significant amounts of isoxaben residues are present only in the 0- to 6-inch depth, and residues below the 6-inch depth are generally below the detection limit (0.005 ppm which is normally 0.01 lb ai/A). However, isoxaben residues were detected at 0.02 lb ai/A (approximately 0.01 ppm) in the 6- to 12-inch depth at 129 days posttreatment in the turf plots in Florida treated with isoxaben (75% FIC) at 1 lb ai/A. Since the water table at this site is within 10 inches of the surface during the year, in this case the groundwater could have been contaminated.

Since the newly-submitted field dissipation study (conducted in Illinois) is acceptable, and since it is unlikely that isoxaben residues leached below the 12-inch depth (since residues in the 6- to 12-inch depth were below the detection limit) at the Indiana and Texas sites in the original study, adequate data have now been submitted to fulfill the terrestrial field dissipation data requirement. The registrant is advised that the groundwater assessment team may require a groundwater monitoring study, depending on the results of the batch equilibrium study currently required to fulfill mobility data requirements.

Isoxaben (75% FIC), at 1 lb ai/A, degraded with a half-life of 30-40 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.

DATA EVALUATION RECORD

ISOXABEN

STUDY 6

CHEM 125851

Isoxaben

BRANCH EAB

FORMULATION--00--ACTIVE INGREDIENT

FICHE/MASTER ID 40059509

Magnussen, J.D. and D.P. Rainey. 1987. Laboratory studies of ¹⁴C EL-107 accumulation in fish. Laboratory project identification ABC-0342, ABC-0354. Prepared and submitted by Eli Lilly and Company, Greenfield, IN.

SUBST. CLASS = S

DIRECT RVW TIME = 4

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CONCLUSIONS:

Laboratory Accumulation - Fish

In the previous review dated 12/30/87, this study was faulted because [¹⁴C]residues (specifically degradates D and E and the origin material) were incompletely characterized, and residues in whole fish were not determined experimentally but by calculation.

No additional characterization of the degradates has been provided; the registrant has requested that the original characterization be reevaluated. In the original report, it was stated that degradates D and E (Unknowns 1 and 2), which each accounted for 0.53-0.56 ppm of [¹⁴C]residues in the nonedible

tissue and <0.03 ppm in the edible tissue, underwent partial conversion/degradation to N-[3-(1-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide (3OH) during the TLC cleanup attempts by the study authors; based on their behavior, it was postulated that these compounds were unstable conjugates of 3OH. The study authors stated that insufficient undegraded material remained for structure elucidation. It is unlikely that additional work to achieve a more definite identification of the compounds would provide useful information; the characterization of degradates D and E is accepted.

The study authors stated that TLC analysis of origin material (up to 5.17 ppm of [¹⁴C]residues) using a solvent system developed for use with polar conjugates showed the material to be composed of one major radioactive zone and three minor zones. The major zone was identified (using MS) as various sulphate conjugates of N-[3-(2-hydroxy-3-methylpent-3-yl)-isoxazol-5-yl]-2,6-dimethoxybenzamide (2OH A and 2OH B isomers). Other polar degradates were characterized as being "most likely sulfate conjugates of the other identified fish metabolites". The results of the TLC analysis of the polar conjugates were not reported in detail; the study authors did not provide numerical data defining "major" and "minor". This information should be provided; if the majority of polar degradates have been identified the characterization of origin material will be accepted.

It was not clear in the original study that the entire fish was analyzed. The study authors defined edible tissue as the fillet and nonedible tissue as the head and viscera; no mention was made of the skin (scales) and tail. However, since the registrant now clearly states that no portions of the fish were discarded, the reviewer believes that skin and tail portions of the fish were considered nonedible tissue and accepts the calculation of total residues in whole fish.

In regards to other registrant responses to comments made by the reviewers about this study, the study was faulted only for the issues listed in the Conclusion section of the review. The points raised in the Discussion (excluding the issues also listed in the conclusions) are minor issues that deviate from the standard procedures mentioned under "Subdivision N" guidelines. They do not in any way affect acceptance of the study, and it is not necessary that the registrant respond to these comments. These points are listed so that the registrant may take them into consideration for future experiments, or to "red-flag" them to gain the attention of other reviewers.

In summary, the accumulation in laboratory fish study (Magnussen and Rainey, 40059509), is not yet acceptable; however, if the additional information on the origin material is provided and found to be acceptable, the study will be used to fulfill data requirements for the accumulation of isoxaben residues in fish.

[¹⁴C]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 [¹⁴C]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 diastereomers of N-[3-(2-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide (2OH A and 2OH B) at $\leq 33\%$ of the recovered radioactivity; N-[3-(1-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide (3OH) at $\leq 23\%$ of the recovered; N-[3-(methylpent-3-yl)isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide (Metabolite A) at $< 4\%$ of the recovered; N-[3-(2-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide (Metabolite B) at $< 2\%$; and N-[3-(1-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide (Metabolite C) at $< 2\%$. Residues accumulated by exposure day 28 were depurated quickly; at day 14 of depuration, [^{14}C]residues were approximately 0.28 ppm in edible, nonedible, and whole fish tissues.

EXECUTIVE SUMMARY

The following findings are derived from those reviewed studies which have met the requirements of 40 CFR 158.130 and the Subdivision N Guidelines, and were also deemed acceptable.

Hydrolysis

Isoxaben (purity 99.8%) did not degrade during 32 days of incubation in the dark in sterile buffered pH 5, 7, and 9 solutions at 25 ± 1 C (from a review dated 9/29/83).

Photodegradation in Water

Carbonyl- and isoxazole ring-labeled [¹⁴C]isoxaben (radiochemical purities >99.5%), at 0.5 ppm, degraded with half-lives of 7-15 days (calculated 9 days) in sterile buffered (pH 7) solutions irradiated outdoors with natural sunlight at 48-96 F. After 30 days of irradiation, isoxaben comprised 21.6% and 13.8% of the applied radioactivity of the carbonyl- and isoxazole ring-labeled solutions, respectively. Degradates included a pyrazolone, an isoquinolone, and a benzopyrrolidone; no degradate comprised >15.1% of the applied radioactivity. In the dark controls at 30 days posttreatment, isoxaben comprised >94.4% of the applied.

Aerobic Soil Metabolism

Isoxazole ring-labeled [¹⁴C]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-dimethoxybenzamide, and N-[3-(methylpent-3-yl)isoxazol-5-yl]-2-hydroxy-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.

Mobility (Column Leaching)

Isoxazole ring-labeled [¹⁴C]isoxaben and aged (30-day) [¹⁴C]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, <0.31% of the applied radioactivity was found in the leachates from the columns treated with unaged [¹⁴C]isoxaben and <3.61% of the applied was found in leachates from the columns treated with aged [¹⁴C]-residues. The majority (>84% of the applied) of the [¹⁴C]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 [¹⁴C]compounds in the 30-day aged soil prior to leaching.

Based on the column leaching study, K_d valued for the four soils ranged from 8.4 to 30.

Terrestrial Field Dissipation (Illinois site)

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 ≤ 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.

During the test period, air temperatures ranged from 26-100 F, and soil temperatures (4-inch depth) ranged from 46-82 F. Cumulative precipitation plus irrigation totaled 28.16 inches. Isoxaben and its degradate 201469 (N-[3-(2-hydroxybut-2-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide) were not detected in pretreatment samples taken from the 0- to 6-, 6- to 12-, and 12- to 18-inch depths. With a few random exceptions, isoxaben and the degradate 201469 were not detected in samples from the control plot taken from the 0- to 6-, 6- to 12-, 12- to 18-, 18- to 24-, 24- to 30-, and 30- to 36-inch depths; isoxaben and the degradate 201469 were isolated in a few samples at ≤ 0.04 lb/A.

Terrestrial Field Dissipation (Texas, Indiana, and Florida sites)

Isoxaben (75% FLC), at 1 lb ai/A, degraded with a half-life of 30-40 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.

The following findings are derived from those reviewed studies which have not met the requirements of 40 CFR 158.130 and the Subdivision N Guidelines, but which have been deemed good studies following generally sound scientific practice. They thereby provide supplemental information on the fate of isoxaben.

Accumulation in Laboratory Fish

[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 diastereomers of N-[3-(2-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide (2OH A and 2OH B) at <33% of the recovered radioactivity; N-[3-(1-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2,6-dimethoxybenzamide (3OH) at <23% of the recovered; N-[3-(methylpent-3-yl)isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide (Metabolite A) at <4% of the recovered; N-[3-(2-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide (Metabolite B) at <2%; and N-[3-(1-hydroxy-3-methylpent-3-yl)isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide (Metabolite C) at <2%. Residues accumulated by exposure day 28 were depurated quickly; at day 14 or depuration, [¹⁴C]residues were approximately 0.28 ppm in edible, nonedible, and whole fish tissues.

RECOMMENDATIONS:

Available data are insufficient to fully assess the environmental fate of isoxaben. The submission of data required for full registration for terrestrial nonfood (noncrop) use sites is summarized below:

The following data are required:

Laboratory studies of pesticide accumulation in fish: One study (Magnussen and Rainey, 40059509) was previously reviewed, has been amended, and is scientifically sound. This study may be judged acceptable to fulfill data requirements for accumulation in fish when the detailed results of the TLC separation of origin material are submitted for review.

The following data requirements are partially fulfilled:

Leaching and adsorption/desorption studies: One study (Saunders et al., 00265730) was previously reviewed and accepted. Because of concerns that isoxaben and its degradates may be mobile enough to contaminate groundwater, an additional study using batch equilibrium techniques with four soils at four concentrations is required.

Terrestrial field dissipation studies: One study (Rutherford and Decker, 40532102, and Rutherford et al., 40532103) was reviewed and is acceptable; a second study (Rutherford and Decker, 1986; 40059508) was previously reviewed and amended, and is now acceptable. Together these studies partially fulfill data requirements by providing information on the terrestrial field dissipation of the 75% FlC formulation of isoxaben at several test sites. Additional studies using the WP formulation at two test sites are required.

The following data requirements are fulfilled:

Hydrolysis studies: No data were reviewed. Based on previously reviewed data (I-EWD-82-05), (9/29/83), no additional data are required.

Photodegradation studies in water: One study (Saunders et al., 40097601 and 40059507) was previously reviewed and has been amended. This study is now considered acceptable and fulfills data requirements by providing information on the photodegradation of carbonyl- and isoxazole ring-labeled [¹⁴C]isoxaben in sterile buffered (pH 7) solutions irradiated outdoors with natural sunlight at 48-96°C.

Aerobic soil metabolism studies: One study (Graper, 00073607 and Rainey, 00265370) was previously reviewed and has been amended. This study is acceptable and fulfills data requirements by providing information on the metabolism of isoxazole ring-labeled [¹⁴C]isoxaben in aerobic soil. No data are required for carbonyl-labeled [¹⁴C]isoxaben because during a 12-month study the molecule did not degrade at the benzamide linkage, creating separate isoxazole ring and carbonyl moieties.

The following data requirements are deferred or are not required for presently registered uses:

Photodegradation studies on soil: No data were reviewed, but no data are required for terrestrial nonfood uses.

Photodegradation studies in air: No data were reviewed. The data requirement is deferred pending receipt of an acceptable laboratory volatility study.

Anaerobic soil metabolism studies: No data were reviewed, but no data are required for terrestrial nonfood uses.

Anaerobic aquatic metabolism studies: No data were reviewed; however, no data are required because isoxaben has no aquatic or aquatic impact uses.

Aerobic aquatic metabolism studies: No data were reviewed; however, no data are required because isoxaben has no aquatic or aquatic impact uses.

Laboratory volatility studies: No data were reviewed, but no data are required for terrestrial nonfood uses.

Field volatility studies: No data were reviewed, but no data are required for terrestrial nonfood uses.

Aquatic field dissipation studies: No data were reviewed; however, no data are required because isoxaben has no aquatic or aquatic impact uses.

Forestry dissipation studies: No data were reviewed; however, no data are required because isoxaben has no forestry uses.

Dissipation studies for combination products and tank mix uses: No data were reviewed; however, no data are required because data requirements for combination products and tank mix uses are currently not being imposed.

Long-term field dissipation studies: No data were reviewed. No data are required because results from the aerobic soil metabolism and field dissipation

tion studies indicate that >50% of the applied isoxaben will dissipate prior to the subsequent application of isoxaben.

Confined accumulation studies on rotational crops: No data were reviewed, but no data are required for terrestrial nonfood uses.

Field accumulation studies on rotational crops: No data were reviewed, but no data are required for terrestrial nonfood uses.

Accumulation studies on irrigated crops: No data were reviewed; however, no data are required because isoxaben has no aquatic food crop or aquatic nonfood uses.

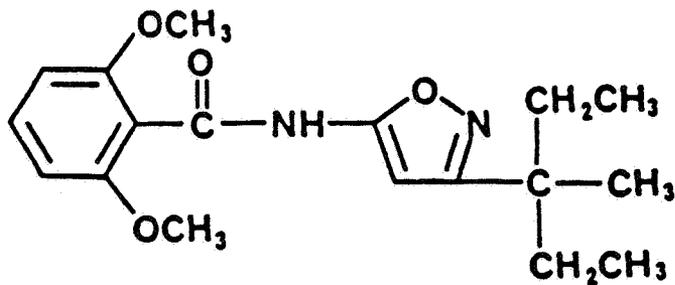
Field accumulation studies on aquatic nontarget organisms: No data were reviewed. The data requirement is deferred pending receipt of acceptable data on the accumulation of isoxaben in laboratory fish.

Reentry studies: No data were reviewed. The toxicological category of isoxaben has not been established.

REFERENCES:

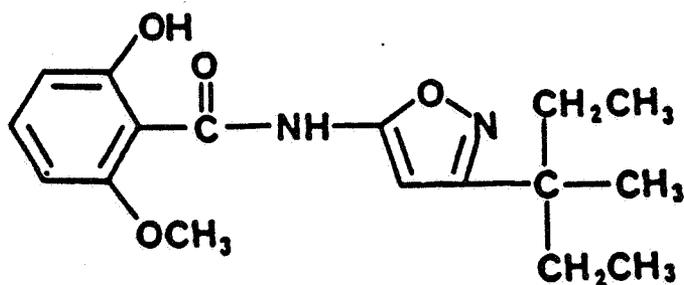
- Magnussen, J.D. and D.P. Rainey. 1987. Laboratory studies of ¹⁴C EL-107 accumulation in fish. Laboratory project identification ABC-0342, ABC-0354. Prepared and submitted by Eli Lilly and Company, Greenfield, IN. (40059509)
- Rainey, D.P. The metabolism of [¹⁴C]EL-107 in soil: Characterization of volatile radiolabeled degradation products. Experiment ABC-0226. Prepared and submitted by Eli Lilly Company, Greenfield, IN. (00265370)
- Rutherford, B.S. and O.D. Decker. 1986. Isoxaben soil/turf field dissipation study. Project ID No. AAC8521. Prepared and submitted by Eli Lilly and Company, Greenfield, IN. (40059508)
- Rutherford, B.S. and O.D. Decker. 1988. Isoxaben turf field dissipation study - Illinois site. Laboratory Project Identification AAC8521. Prepared and submitted by Eli Lilly and Company, Greenfield, IN. (40532102)
- Rutherford, B.S. et al. 1987. Determination of EL-107 and/or its soil metabolite in soil and soil/turf samples. Laboratory Project ID AM-AA-CA-RO42-AD-755. Prepared and submitted by Eli Lilly and Company, Greenfield, IN. (40532103)
- Saunders, D.G., J.W. Moran, and G.E. Babitt. 1986. Photolysis of isoxaben in aqueous solution. Prepared and submitted by Eli Lilly and Company, Greenfield, IN. (40097601 and 40059507)
- Saunders, D.G., S.K. Smith, and J.W. Mosier. 1985. Mobility of EL-107 and a soil metabolite in soil. Report No. EWD8442. Prepared and submitted by Eli Lilly and Company, Greenfield, IN. (00265730)

APPENDIX
ISOXABEN AND ITS DEGRADATES



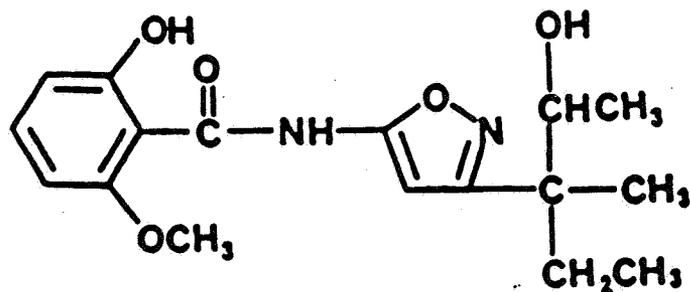
N-[3-(methylpent-3-yl)isoxazol-5-yl]-
2,6-dimethoxybenzamide

(Isoxaben, EL-107)



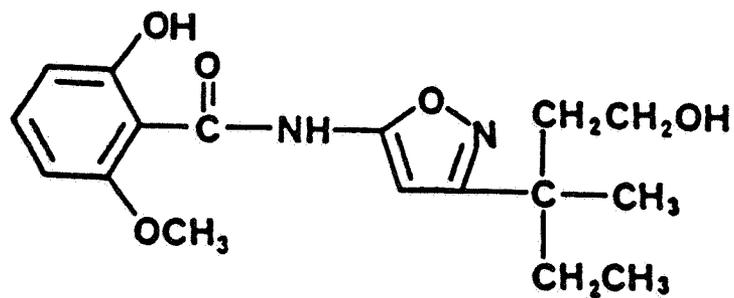
N-[3-(methylpent-3-yl)isoxazol-5-yl]-
2-hydroxy-6-methoxybenzamide

(Metabolite A)



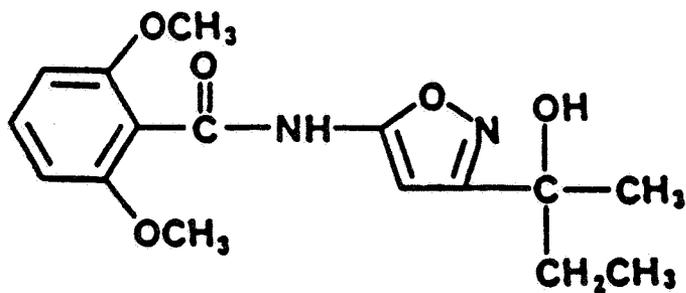
N-[3-(2-Hydroxy-3-methylpent-3-yl)
isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide

(Metabolite B)



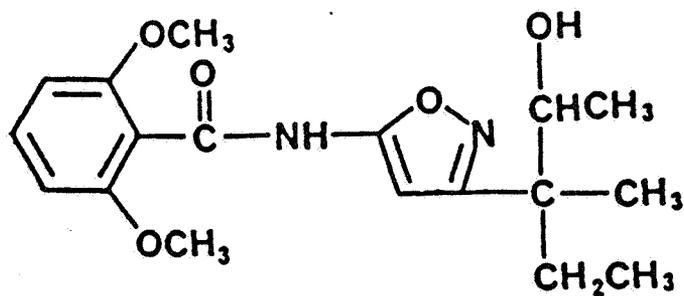
N-[3-(1-Hydroxy-3-methylpent-3-yl)
isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide

(Metabolite C)



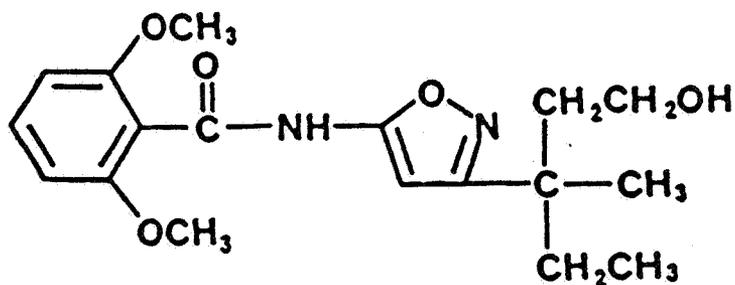
N-[3-(2-Hydroxybut-2-yl)isoxazol-5-yl]-
2,6-dimethoxybenzamide

(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)