Shaughnessy No.: 125851

Date Out of EFGWB: MAR 14 1989

To: Susan Lewis
Acting Product Manager #23
Fungicide-Herbicide Branch
Registration Division (H7505C)

From: Emil Regelman, Supervisory Chemist
Environmental Review Section #2
Environmental Fate & Ground Water Branch (H7507C)

Thru: Henry Jacoby, Acting Chief
Environmental Fate & Ground Water Branch
Environmental Fate & Effects Division (H7507C)

Attached, please find the EFGWB review of . . .

Reg./File # : 1471-RLT, 1471-RLD

Chemical Name : Isoxaben

Type Product : Herbicide

Product Name : EL-107, Prolan, Flexidor

Company Name : Eli Lilly and Company

Purpose : Review TLC quantitation data of polar metabolites referred to as Origin Metabolites and explanation of calculated residues data in whole fish in response to deficiencies cited in EFGWB review # 80807/08 for previously submitted fish accumulation study (§165-4).

Date Received: 10/24/88 Action Code: 116 & 116

Date Completed: 3/10/89 EAB # (s): 90076 & 90077

Total Reviewing Time:(decimal days): 2.1 days

Deferrals to:

_____ Ecological Effects Branch, EFED

_____ Science Integration & Policy Staff, EFED

_____ Non-Dietary Exposure Branch, HED

_____ Dietary Exposure Branch, HED

_____ Toxicology Branch, F-H Support/HED

1

1. CHEMICAL: Common name:

Isoxaben

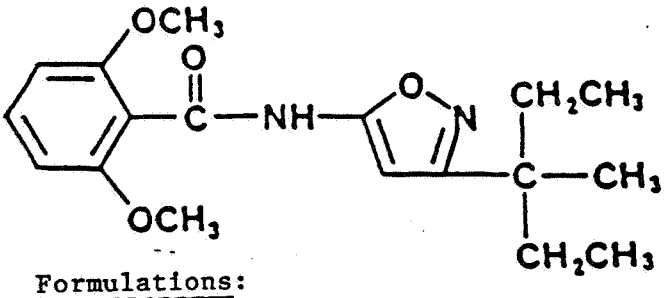
Chemical name:

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

Trade name(s):

EL-107, Prolan, Flexidor

Structure:



Formulations:

12.5 and 50% WP, 75% FlC

Physical/Chemical properties: MW 332.39

Molecular formula:	$C_{18}H_{24}N_2O_4$
Physical state:	White, crystalline solid
Melting point:	176-179°C
Solubility in water:	1.0-2.0 ppm

2. TEST MATERIAL:

N/A.

3. STUDY/ACTION TYPE:

Review adequacy of TLC quantitation data for the group of polar metabolite referred to as Origin Metabolites and explanation of the residue values reported in whole fish.

4. STUDY IDENTIFICATION:

Magnussen, J.D. and D.P. Rainey. 1987. Laboratory studies of ^{14}C EL-107 accumulation in fish. Laboratory project identification ABC-0342, ABC-0354. Prepared and submitted by Eli Lilly and Company, Greenfield, IN. (40059509)

5. REVIEWED BY:

Padma Datta, Ph.D.
Chemist
Environmental Review Section #2
EFGWB/EFED/OPP

Signature: PRDatta

Date: 3/10/89

6. APPROVED BY:

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

Signature: Elog

Date: MAR 14 1989

7. CONCLUSION:

The additional data submitted by Elanco Products Company consisting of: (1) quantitative data for the polar metabolites referred to as Origin Metabolites, and (2) an explanation regarding the use of all parts of the fish including skin and tail, to determine radioactive residue values in edible and non-edible tissue and whole fish to correct the two deficiences cited in the (EFGWB review # 80807 & 80808) are satisfactory. The fish accumulation study (§165-4) is now acceptable to EFGWB and fulfills that data requirement to support continued registration of isoxaben.

8. RECOMMENDATIONS:

EFGWB recommends RD inform the registrant, Elanco Products Company, that the fish accumulation study (§165-4) now fulfills that data requirement to support the continued registration of pesticide products containing isoxaben as active ingredient.

9. BACKGROUND:

On 10/20/88 Elanco Products Company responded to the two deficiencies cited re the fish accumulation study (§165-4) in our review # 80807/08. Elanco provided: (1) quantitative data for the group of polar metabolites referred to as Origin Metabolites in the previously submitted report; and (2) an explanation re the calculated residue values in whole fish. The registrant requested the Agency review the additional data submitted for the above two deficiencies.

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES:

In the previously submitted data it was shown that the Origin Metabolites present in the origin of the TLC plate for isoxaben residues in fish tissues represented 4.0% (0.11 ppm) and 16.7% (5.17 ppm) of the total residue in edible tissue and non-edible tissue respectively. EFGWB requested that the registrant provide TLC data quantitation of those polar metabolites

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES (CON'TD):

Elanco Products Company (registrant) had chosen for quantitative TLC the analysis of high level Origin Metabolites present in samples of 21 and 28 day non-edible tissue. The methanol extracts of the non-edible tissue samples were extracted with buffer of pH 1.5 (this fraction should contain virtually all the Origin Metabolites). The more polar metabolites were separated from less polar aglycones using silica gel column chromatography.

The column fractions were subjected to quantitative thin-layer autoradiogram analyses using a solvent system (chloroform/methanol/glacial acetic acid 90:10:1) that would allow characterization of non-polar components. The results showed that Origin Metabolites (Zones 1 and 2) represented 77.4% and 75.4% of total radioactivity in the 21 day and 28 day samples, respectively. 20-25% of the total radioactivity consisted of less polar metabolites identified as 30H (zone 8), 20HA (zone 10) or 20HB (zone 9), whose structures were reported in the original study (see attached Appendix). The details are shown in the attached Figure 1 and Table 1.

The same column fractions were also subjected to quantitative thin-layer autoradiogram analyses using a polar solvent (butanol/water/glacial acetic acid 60:25:15) system. The results showed that the nonpolar component ran in the two front running zones (zones 12 and 13) while polar Origin Metabolite chromatographed as 4 distinct bands (zones 7-10). for both the 21 and 28 day samples. The details are shown in the attached Figure 2 and Table 2.

The percent distribution based on the radioactivity recovered from all 13 zones of individual sample lanes are presented in Table 2. In Table 3 the percent distribution based on the radioactivity recovered from zones 1-11 only of the individual sample lanes are presented; the radioactivity associated with non-polar components (zones 12 and 13) were omitted in those calculations.

Four bands (zones 7-10) represented 90-95% of the total radioactivity of the Origin Metabolites. The percent distribution of the recovered radioactivity was 43.7%-54.7% for OM-1 (zone 10) 21.5-26.3% for OM-2 (zone 8), 15% for OM-3 (zone 9), and 5% for OM-4 (zone 7). OM-1 was identified as being sulphate conjugates of isomeric metabolites referred to as 20HA and 20HB in the Appendix. OM-2 postulated to be the sulphate conjugate of the metabolite referred to as 30H. No attempt was made to identify the low level components OM-3 and OM-4 but they appear to be sulphate conjugates from the r_f values on the thin-layer autoradiogram. (refer to Figure 8 of the original report).

No attempt was made to isolate and identify the Origin Metabolites which were present at low levels in edible tissue (4.0% of the total residue or 0.11 ppm). It was postulated that the distribution of Origin Metabolites in edible tissue was the same as that observed for non-edible tissue because the metabolite spectrum was found to be the same for edible and non-edible tissue on TLC analyses.

11. COMPLETION OF ONE-LINER:

See attached one-liner sheet.

12. CBI APPENDIX:

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

/ /

EXPOSURE ASSESSMENT BRANCH
PESTICIDE ENVIRONMENTAL FATE ONE-LINER

File No.: 125851 0 CAS No.: CHEM ABSTR:
Type Pesticide Herbicide
Chemical Name: N-[3-(methylpent-3-yl) isoxazol-5-yl]-2,6-dimethoxybenzamide.
Common Name: Isoxaben
Empirical Form.: $C_{18}H_{12}N_2O_4$
Uses: Terrestrial Nonfood and Terrestrial food crop
Form. Type: 12.5 and 50% WP, 75% FLC

Mole Wt.	Sol. @20°C (ppm)	Vap.Pres.(torr)	Log Kow	Henry
332.39	~~0.00~~ 1.0-2.0	—	~~0.00~~ 5.7	

Hydrolysis
pH 5: } No Hydrolysis
pH 7: } Parent recovered
pH 9: } unchanged (87%-102%

Photolysis
Air:
Soil:
Water:

Soil Partition (Kd)
1
2
3
4
5

Rf Factors

Soil Metabolism Studies - Terrestrial

Aerobic	Anaerobic
1	
2	
3	
4	
5	
6	
7	

Soil Metabolism Studies - Aquatic

Aerobic	Anaerobic
1	
2	
3	
4	

Field Dissipation Studies

Terrestrial	Aquatic
1	
2	
3	
4	
5	
6	

Field Dissipation Studies

Forest	Other
1	
2	

Ground Water Findings
1
2
3

Rotational Crop Restrictions
1
2

Fish Accumulation Studies
1 Bluegill sunfish exposed BCF - 14X in edible tissues; 134X in non-edible tissues; 70X in whole fish during 28 day exposure in flow-through system
2 Residue Isoxaben 52% in edible tissues, 19% in non-edible tissues
Residue 30.28 ppm in edible, non-edible and whole fish tissues after 28 days exposure + ~~day~~ 14 day depuration

Degradation Products

	edible	non-edible	
1	20H	20H3	For structure
2	30	30	see Appendix I Isoxben Scientific Chapter. April 27, 1988
3	Meta A	Meta A	
4	Meta B	Meta B	
5	Meta C	Meta C	

Notes

References

Writer

Date Received 10/25/88

ATTACHMENT 1

OFFICE OF PESTICIDE PROGRAMS DATA REVIEW RECORD 46609EFED

Confidential Business Information-Does Not Contain National Security Information(E.O. 12065)
This form is to be used for individual studies and for submission of pesticide applications

1. PRODUCT NAME	Gallery 75 Dry Flowable	CHEMICAL NAME	Isoxaben	
2. IDENTIFYING NUMBER	3. RECORD NUMBER	4. ACTION CODE	5. MRID/ACCESSION NUMBER	6. STUDY GUIDELINE OR NARRATIVE
1491-RLI	233672	116	—	165-4
1491-RLO	233673	116	—	
7. REFERENCE NUMBER	8. DATE RECEIVED (EPA)	9. PRODUCT/REVIEW MANAGER/DCI	10. PM/RM TEAM NUMBER	11. DATE SENT TO (HED/EFED/RD/BEAD)
1/1	10/21/88	Mountfort	23	10/24/88
12. PROJECTED RETURN DATE	13. DATE RETURNED TO (RD/SRRD)	INSTRUCTIONS:		
12/24/88		Company's response to Dr. P. Datta's review of Sept. 14, 1988 of the fish accumulation study.		

(THIS SECTION APPLIES TO REVIEW OF STUDIES ONLY)

14. CHECK APPLICABLE BOX:

15. NUMBER OF INDIVIDUAL STUDIES SUBMITTED ____

☐ ADVERSE 6(a)(2) DATA (405) ☐ GENERIC DATA (660) ☐ PRODUCT SPECIFIC DATA (655)
☐ SPECIAL REVIEW DATA (870) (REREGISTRATION) (REREGISTRATION)

16. HAVE ANY OF THE ABOVE STUDIES (in whole or in part) BEEN PREVIOUSLY SUBMITTED FOR REVIEW? (circle: yes or no) IF YES, PLEASE IDENTIFY THE STUDY(IES):

17. RELATED ACTIONS:

18.	TO	TYPE OF REVIEW	19. REVIEWS ALSO SENT TO	
HED		SCIENCE ANALYSIS & COORD.	SAC	PC
		TOXICOLOGY/HFA	TOX/HFA	PL
		TOXICOLOGY/IR	TOX/IR	
		DIETARY EXPOSURE	DEB	EA
		NON-DIETARY EXPOSURE	NDE	AC
EF ED		ECOLOGICAL EFFECTS		BA
	X	ENVIRONMENTAL FATE & GROUND H2O	EEB	
SRRD		SPECIAL REVIEW	EFGWB	
		REREGISTRATION		
		GENERIC CHEMICAL SUPPORT	SR	
RD		INSECTICIDE-RODENTICIDE	RER	
		FUNGICIDE-HERBICIDE	GSC	
		ANTIMICROBIAL		
		PRODUCT CHEMISTRY	IR	
		PRECAUTIONARY LABELING	FH	
BEAD		ECONOMIC ANALYSIS	AM	
		ANALYTICAL CHEMISTRY		
		BIOLOGICAL ANALYSIS		

20. DATA REVIEW CRITERIA

A. Policy Note #31
☐ 1 = data which meet 6(a)(2) or meet 3(c)(2)(B) flagging criteria
☐ 2 = data of particular concern from registration standard
☐ 3 = data necessary to determine tiered testing requirements

B. Section 18
☐ 1 = data in support of section 3 in lieu of section 18

C. Inert Ingredients
☐ 1 = data in support of continued use of List 1 inert

☐ CONFIDENTIAL STATEMENT OF FORMULA (TRADE SECRETS) ☐ LABEL ATTACHED

White - Data Coordinator Pink - PM/RM/DCI
Yellow - Data Review Section Green - Return with completed review
Include original + two (2) copies with each submission

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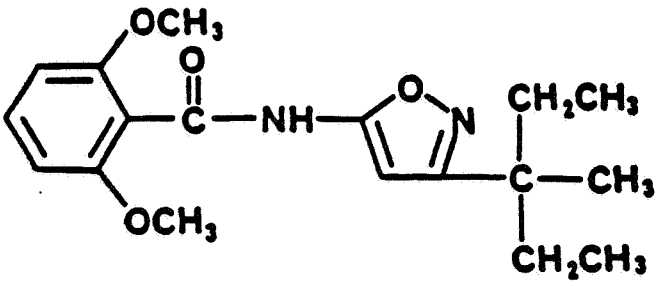
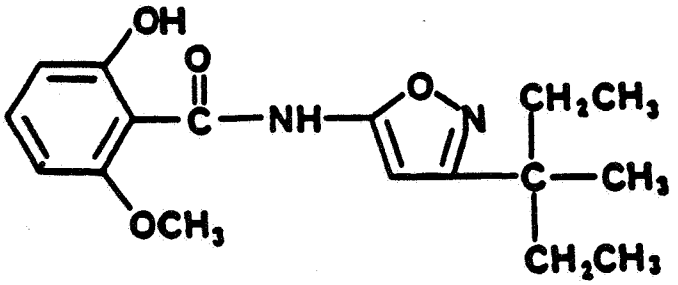
APPENDIX

ISOXABEN AND ITS DEGRADATES



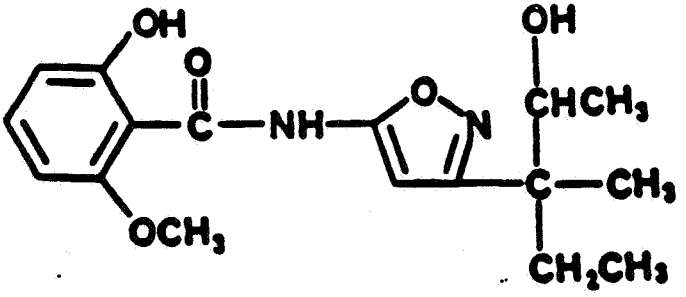
N-[3-(methylpent-3-yl)isoxazol-5-yl]-
2,6-dimethoxybenzamide

(Isoxaben, EL-107)



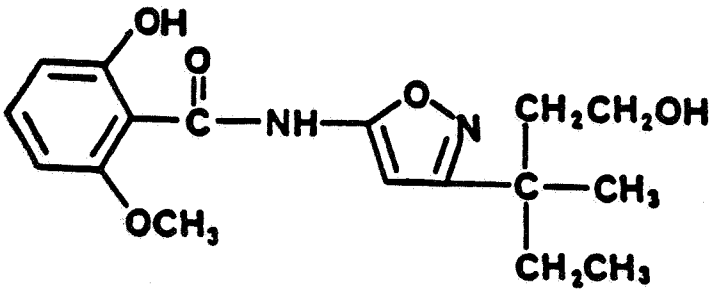
N-[3-(methylpent-3-yl)isoxazol-5-yl]-
2-hydroxy-6-methoxybenzamide

(Metabolite A)



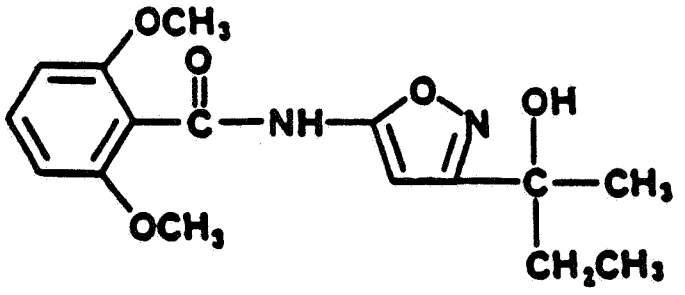
N-[3-(2-Hydroxy-3-methylpent-3-yl)
isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide

(Metabolite B)



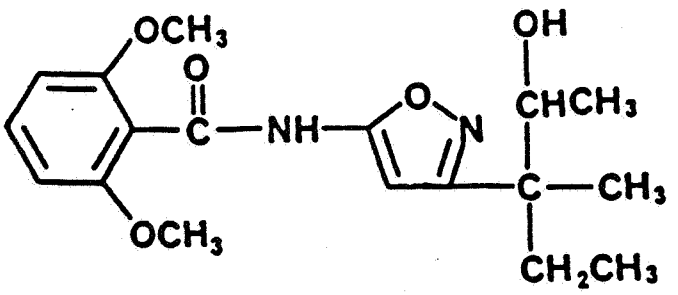
N-[3-(1-Hydroxy-3-methylpent-3-yl)
isoxazol-5-yl]-2-hydroxy-6-methoxybenzamide

(Metabolite C)



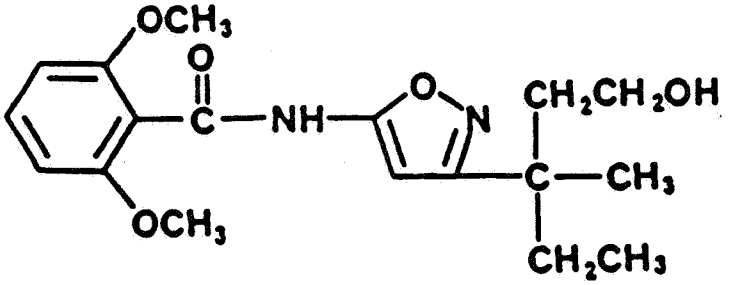
N-[3-(2-Hydroxybut-2-yl)isoxazol-5-yl]-
2,6-dimethoxybenzamide

(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)

ISOXABEN EFGWB REVIEW

Page_____ is not included in this copy.

Pages 13 through 18 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.