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Registration Division (TS-767)

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Review Section 1
Exposure Assessment Branch
Hazard Evaluation Division (TS-769c)

Attached please find the EFB review of...

Reg./File No.: 1471-EUP-IL

Chemical: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxy-benzamide

Type Product: Herbicide

Product Name: EL-107 50WP

Company Name: Elanco

Submission Purpose: EUP : Use on non-crop areas

ZBB Code: 3(c)(5)

ACTION CODE: 700

Date In: 7/8/83

EFB # 3446

Date Completed: 9/29/83

TAIS (level II)	Days
63	6.0

Deferrals To:

____ Ecological Effects Branch

____ Residue Chemistry Branch

____ Toxicology Branch

1.0 INTRODUCTION

Elanco has submitted data (Accession #250449) to support its request for a 2 year EUP for the terrestrial non-food use of EL-107 (N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxy-benzamide, a broadleaf-weed herbicide (pre- or post emergence).

2.0 STRUCTURE

A data sheet on Chemical and Physical Properties of EL-107 is appended to this review.

3.0 DIRECTIONS FOR USE

A copy of the EUP label is appended to this review. Under the EUP, El-107 is to be applied preemergent by low-pressure sprayer, at a rate of 0.5 to 1.0 lb ai/A in 5 to 40 gallons of water.

4.0 EXPERIMENTAL PROGRAM

A copy of the experimental program is appended to this review.

Briefly, the registrant proposes to apply this 50WP formulation to a total of 12.5 lb a.i. the first year and a total of 25 lbs a.i. the second year to a total of 25 acres in a total of about 17 states. Applications will be to noncrop areas such as railroad yards, tow paths and ballast, tank farms and lumberyards.

The total program will run for two years.

5.0 REVIEW OF SUPPORTING DATA

5.1 Rodewald, J.M. and J.T. Wilson. 1982. n-Octanol-To-Water Partition Coefficient of EL-107. I-AL-82-07. Agricultural Analytical Chemistry, Lilly Research Laboratories, Greenfield, IN. August 1982. 4pp.

Introduction

The octanol-to-water partition coefficient of EL-107 was determined, pursuant to the current Subpart N guidelines.

Experimental

EL-107 was radiolabeled (label site unspecified) and found to have a specific activity of 4.45 uCi/mg and a radiochemical purity of 99.8% (method not specified).

Standard n-octanol solutions of EL-107 were prepared to contain 113 and 225 ug/ml, and were saturated with pH 7.0 phosphate buffer. One ml aliquots of each standard (in duplicate runs) were added to 20 ml solutions containing 10 ml phosphate buffer and 10 ml n-octanol. After moderate shaking (30 min. to 1 hr.), samples were centrifuged, and the two fractions analyzed by LSC (aqueous samples dissolved in dioxane-methyl cellosolve scintillation fluid and n-octanol samples in toluene scintillation fluid). Counting was via Packard Model 3380 Tri-Carb scintillation counter.

Results

K_{ow} was determined to be 434, which was the average of 4 measurements.

Conclusion

This study is conditionally acceptable for the EUP, but some deficiencies exist. The site of the radiolabel and method of determining purity were not specified. Raw data (computer printouts?) were not provided. Data were not provided to support the statement "Between pH 5.0 and 9.0, the solubility of EL-107 was experimentally proven to be independent of pH."

5.2 Mosier, J.W. and D.G. Saunders. 1982. Soil Adsorption and Desorption of EL-107. I-EWD-82-06. Agricultural Analytical Chemistry, Lilly Research Laboratories, Greenfield, IN. May 10, 1982. 12 pages, 5 tables, 1 figure

Introduction

The mobility of EL-107 in a sandy loam soil was determined at four concentrations of the herbicide using the adsorption/desorption technique.

Experimental

Isoxazol ring ^{14}C-labeled EL-107 was sythesized, and found to have a specific activity of 11.21 uCi/mg with a purity of 99% by TLC and radioautography. The soil used in the study had the following characteristics:

Texture	Percentage Sand	Silt	Clay	O.M.	CEC	pH	Bulk Density
Sandy Loam	53.7	32.1	14.2	1.6	13.27	6.0	1.4

The time required for EL-107 to establish equilibrium between soil and water was experimentally determined to be 16 to 24 hours (see report page 6, table II, appended to this review).

The adsorption/desorption phase was initiated using 5 gram aliquots of soil in 50 ml centrifuge tubes. Aqueous solutions of EL-107 were prepared at concentrations of 0.043, 0.113, 0.449 and 1.20 ug/ml. Fifty ml of each solution was added to the respective tube. Fifty ml water (distilled?) was added to another soil-containing tube to serve as a control. A second set of tubes was prepared sans soil to estimated glass-adsorption effects.

All tubes were shaken for 24 hours, then centrifuged to clear the supernatant. Twenty-five ml aliquots of the supernatant were measured radiochemically in dioxane-methyl cellosolve scintillation fluid, counting for 5 minutes. An additional 25 ml water was then added to each tube, which was subject to an additional 24 hours shaking/analysis.

Results and Discussion

The results are summarized on report pages 7 and 8, tables III and IV, appended to this review. In the glass-adsorption testing, significant adsorption was found at the highest concentrations, disqualifying the parallel results from the soil portion of the experiment.

The amount of EL-107 on each day was estimated by subtracting the total amount found in the water on the preceding day(s). This data was used in the following equation to compute the Freundlich isotherm (plot of C_{ad} vs. C_{aq})...

$K_a = C_{ad}/C_{aq}^{1/N}$, where... K_a = adsorption/desorption coefficient
C_{ad} = conc. of pesticide on soil (ug/g)
C_{aq} = conc. of pesticide in H_2O (ug/ml)
N = constant

The linear form of the equation is...

$$\text{Log } C_{ad} = \text{Log } K_a + 1/N \text{ Log } C_{aq}$$

The adsorption coefficient was computed to be 5.7, indicating that EL-107 is readily adsorbed to sandy loam soil. The desorption coefficients (data summarized in report page 9, table V, appended to this review) suggest low tendency for bound EL-107 to desorb.

Conclusions

This study is unacceptable.

Samples were not run in duplicate (a minimal number). In addition, only one soil type was used; at least 4 different types are required.

The study should be repeated.

5.3 Graper, L.K. and D.P. Rainey. 1982. Behavior of ^{14}C EL-107 in Field Soil (Interim Report). ABC-0097 and ABC-0146. Agricultural Analytical Chemistry, Lilly Research Laboratories, Greenfield, IN. December, 1982. 17 pages, 6 tables, 2 figures

Discussion

This study is not required for the EUP.

Conclusions

Since this is only an interim report, the entire study should be submitted as a unit when completed.

5.4 Smith, S.K., J.W. Mosier and D.G. Saunders. 1982. An Aged Soil Leaching Study with EL-107. I-EWD-81-16. Agricultural Analytical Chemistry, Lilly Research Laboratories, Greenfield, IN. May 10, 1982. 9 pages, 3 tables

Experimental

Isoxazol ring ^{14}C-labeled EL-107 was synthesized and found to have a specific activity of 11.21 uCi/mg and a radiopurity of >99%.

Soil used in the study was aged for 6 months (dry), then rehydrated, seived (8 mesh) and analyzed. Characteristics were as follows:

Texture:	Sandy Loam
Composition:	Sand:53.7%, Silt:32.1%, Clay:14.2%, O.M.:1.6%
C.E.C.:	13.27 mcg/100g
pH:	6.0
Bulk Density:	1.4 g/cc.

Two 300-gram portions of the soil were prepared. One was spiked with 0.40 mg EL-107 (in acetone), equivalent to an application rate of 1.2 lb ai/A, the other untreated (control). Both were hydrated with 40 ml water (reason for this amount unspecified). Jars were wrapped in foil and incubated in a greenhouse for 30 days; additional water was added twice weekly to maintain field moisture capacity (method of determining this unspecified). After 30 days, soils were air dried, uniformly mixed and sampled for analysis.

Leaching columns consisted of five 5-cm and one 7.5 cm section of 6.35 cm i.d. aluminum electrical conduit. The bottom section of the "stack" consisted of a 5 cm section of conduit welded to an aluminum plate, breached to allow collection of eluate. Two column "stacks" were assembled by waterproof gluing. Each was filled with untreated soil, to a depth of 27.5 cm. Both were "wetted" with 500 ml water each, and allowed to drain. Additional soil was added as needed, to maintain the 27.5 cm depth. Approximately 100 g of each experimental soil was then added to each column, respectively. For 5 days/week over a 45 day period, 40 ml portion of water were added to each column (total volume = 1020 est.), with the leachate collected and stored until analysis at the end of the experiment (storage conditions unspecified).

At the conclusion of the leaching phase, the "stack" was disassembled and the soil air dried, pulverized and uniformly mixed preparatory to analysis.

Analysis was by LSC. Leachate was mixed with dioxane-methane cellosolve scintillation fluid and counted on a Tracor Mark III 6882 LSC counter. Soil was combusted, and the trapped $^{14}CO_2$ quantified on a Packard 3380 Tri-Carb LSC counter.

Counting efficiency was determined on using ^{14}C toluene as an internal standard.

Results and Discussion

The reported leachate and soil column data are summarized in report tables II and III, appended to this review. An apparently consistent amount of radiolabeled material was found to be eluting on every day after day 9 (mean = 2440 dpm), despite no watering on the weekends.

About 11% of the total applied radioactivity was found in the 10 to 15 cm section of the column. No attempt was made to identify or quantify metabolites or degradates.

Conclusion

This study is unacceptable.

Significant deficiencies include inadequate water volume (1020 ml vs the recommended 1609 ml), no analysis for metabolites or degradates, only one test column run, no control data reported, no details of storage stability or conditions for samples, low material balance (83% recovered), only one soil type used (at least four different types are required).

In addition, no reference was provided supporting the use of aluminum conduit in experiments such as this.

No attempt was made to classify the mobility of EL-107, either based on estimated K_d or estimated R_f values. The authors concluded that the experiment suggested EL-107 was only slightly susceptible to leaching, a conclusion unsupported by the limited data submitted.

5.5 Mosier, J.W. and D.G. Saunders. 1982. Hydrolysis of EL-107 in Buffer Solution. I-EWD-82-05. Agricultural Analytical Chemistry, Lilly Research Laboratories, Greenfield, IN. May 7, 1982. 8 pages, 2 tables, 1 figure.

Experimental

Standard (unlabeled) EL-107 was synthesized and found to be 99.8% pure (method unspecified). Suitable buffers of pH 5,7 and 9 were prepared, and sterilized prior to use. Aliquots of EL-107 were added to dodecuplicated test vials at each pH, then maintain at 25+/-1°C in the dark. Samples taken at days 0,4,8,16,24 and 32 were analyzed by solvent extraction/HPLC.

Results and Discussion

Virtually all parent compound was recovered unchanged in all samples analyzed (recoveries ranged from 87% to 102%).

Conclusions

This study is acceptable. Hydrolysis is not a likely mechanism for the degradation of EL-107.

5.6 Mosier, J.W. and D.G. Saunders. 1982. An Aqueous Photolysis Rate Study with EL-107. I-EWD-82-04. Agricultural Analytical Chemistry, Lilly Research Laboratories, Greenfield, IN. May 10, 1982. 7 pages, 1 table, 2 figure, 2 references.

Experimental

Standard (unlabeled) EL-107 was synthesized and found to be 99.8% pure (method unspecified). Water was redistilled and oxygenated prior to use. Artificial sunlight was provided by sunlamps and blacklight (referenced to Hirt, et.al. 1960). Vials were certified to not pass light with wavelength below about 280 nm. A total of 14 ampoules were prepared, each containing 1.0 ug of EL-107. Temperature during irradiation was maintained at about 27°C.

Analysis and quantification was by solvent extraction and HPLC against external standardization.

Results and Discussion

Parent EL-107 was found to degrade to unspecified products with a half-life of 38 hours (our computation; reported = 34 hours). Since photoexposure was continuous, the 38 hour figure should be multiplied by 3, assuming an average 8 hour day. Thus a more realistic estimate of the aqueous photolytic half life would be about 114 "environmental" hours, or about 5 days.

Conclusions

This study is unacceptable. No analysis was done for degradates and no material balance was provided. Sample chromatogram did not reproduce, and should be resubmitted if the study is not repeated.

6.0 EXECUTIVE SUMMARY

The following EF studies have been submitted and found to be acceptable or conditionally acceptable:Hydrolysis, Octanol/Water.

The following EF studies have been submitted and found to be unacceptable or severely deficient:Batch Equilibrium, Aged Leaching, Aqueous Photolysis.

The following EF studies, required for this EUP have not been submitted: Accumulation in Fish, Aerobic Soil Metabolism.

Hirt, R.C., Schmitt. R.G , Searle, N.D. and Sullivan, A.P.. J. Opt. Soc. Amer., 50, 706 (1960)

7.0 CONCLUSIONS AND RECOMMENDATIONS

The experimental program itself appears to be satisfactory, and is acceptable to EAB.

The accumulation in fish study must be submitted based on the moderate soil mobility and low hydrolytic rate (even under direct photolysis). However, this data requirement will be waived for the EUP, due to the apparently low (434) octanol/ water partition coefficient.

We cannot concur with this EUP until an acceptable aerobic soil metabolism study has been submitted and reviewed by EAB.

The various deficiencies noted in this review should be addressed by the registrant, or the studies redone.

The interim small-plot study should be resubmitted when completed.

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September 29, 1983