122804

Shaughnessy No.: ?

Date out EAB: 28 MAR 1984

To: G. LaRocca
Product Manager #15
Registration Division TS-767

From: Samuel M. Creeger, Chief
Environmental Chemistry Review Section 1
Exposure Assessment Branch
Hazard Evaluation Division TS-769c

Attached, please find the EAB review of:

Reg./File No.: 50658 - EUP - R

Chemical: Avermectin

Type Product: I

Product Name: AVID

Company Name: Merck, Sharpe & Dohme

Submission Purpose: EUP on citrus

ZBB Code: ?

Action Code: 700

Date In: 1/19/84

EFB No.: 4170

Date Completed: 3/27/84

TAIS (Level II)	Days
52	5

Deferrals To:

_____ Ecological Effects Branch

_____ Residue Chemistry Branch

_____ Toxicology Branch

1.0 INTRODUCTION

Merck, Sharp and Dohme has submitted an EUP application for the use of avermectin B_1 on citrus. EPA Acc. No. 252113 - 252115.

2.0 Avid 0.15 EC: avermectin B_1: MK-936

See Figure for structure.

3.0 DISCUSSION

According to the proposed label, a maximum of 1 1/3 pt/acre of product are to be used. Three applications per season are permitted. For the EUP program, a total of 990 acres will be treated consuming 507 gal product or 76.05 lb ai. With a single application about 9 g ai/acre will be used; for three applications about 30 g ai/acre will be applied. The proposed program involves four states, FL, CA, AR and TX. The duration of the program is 2 years. Avid will be applied using air blast equipment.

For an EUP, hydrolysis, aerobic soil metabolism, rotational crop, and fish accumulation studies are required. Merck has satisfied the hydrolysis requirement. Avermectin is stable to hydrolysis (review dated 4/18/83). In this submission, aerobic soil metabolism and fish accumulation data are provided. Citrus products resulting from treatment with avermectin B_1 will not be used for food or feed. A rotational crop study is not required because there ~~are none~~ is no crop rotation in citrus groves.

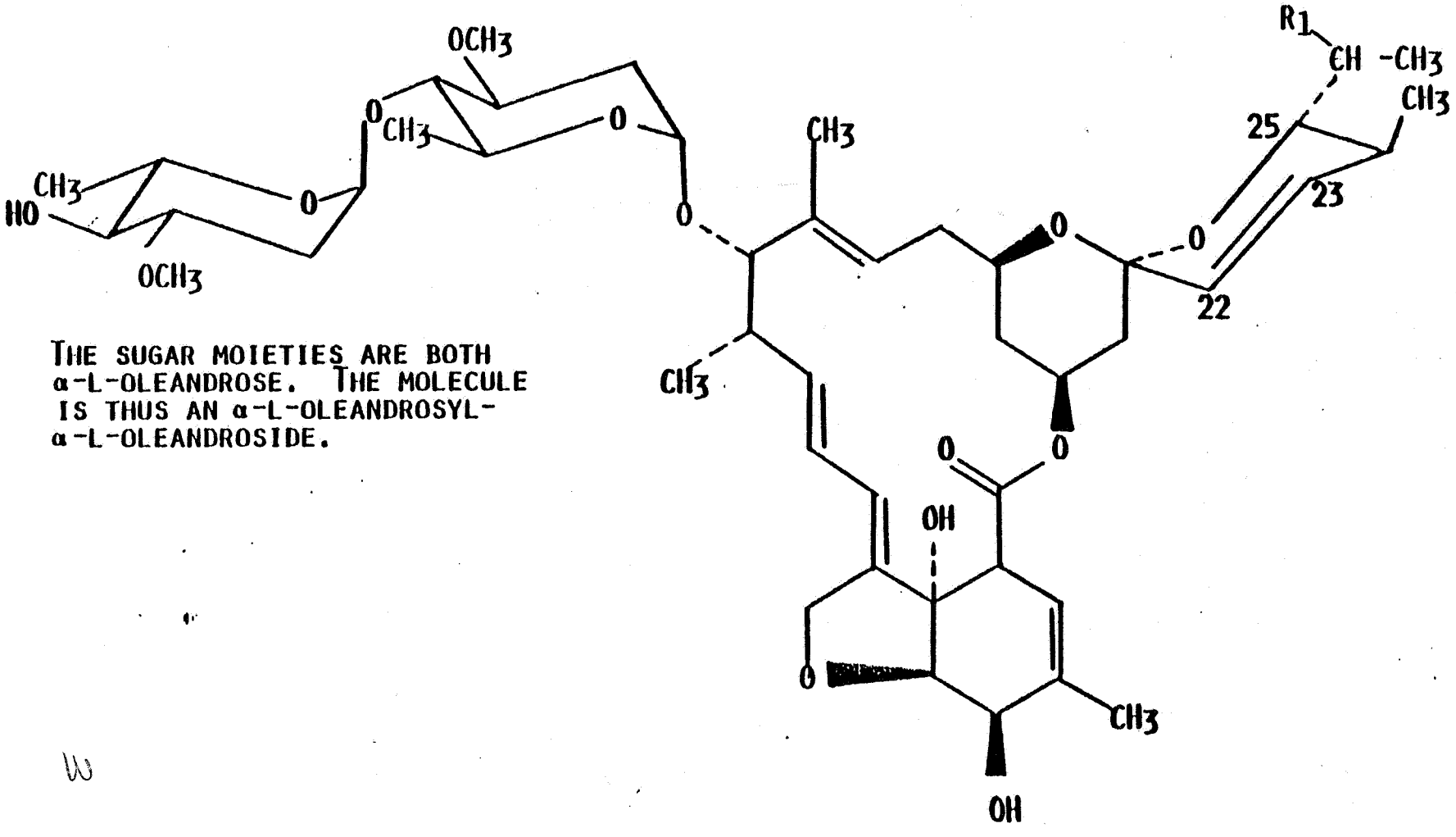
In addition the following studies were submitted:

- aqueous and soil photodegradation
- leaching
- anaerobic soil metabolism

MK-936

AVERMECTIN B_1

L-676,863



THE SUGAR MOIETIES ARE BOTH α-L-OLEANDROSE. THE MOLECULE IS THUS AN α-L-OLEANDROSYL-α-L-OLEANDROSIDE.

W

R_1 = C_2H_5 ≥80% (AVERMECTIN B_{1A}, L-676,895)

3.1 Fate of Avermectin B_{1a} in Soil under Aerobic and Anaerobic Conditions. C.C. Ku and T.A. Jacob, 1983.

For these studies both tritium labeled and ^{14}-C labeled avermectin B_{1a} were prepared. Three soil types, fine sandy loam, Houston clay, and construction grade sand, were used. Table I gives soil properties.

For the aerobic studies, ^{3}H-avermectin B_{1a} was used to produce soil concentrations of 0.1, 1.0, and 50 ppm. Soil samples were kept at 75% moisture content at 0.33 bar. In addition, ^{14}C-avermectin B_{1a} in fine sandy loam was studied at a rate of 1.0 ppm. A bulk sample containing 10 ppm ^{14}C-avermectin was prepared using fine sandy loam soil.

For the anaerobic studies, ^{14}C-avermectin was applied at a rate of 1.0 ppm to fine sandy loam soil. By flushing with nitrogen and by flooding, anaerobic conditions were established without prior aging. In addition, some samples were aged aerobically for one month before anaerobic conditions were established.

To determine $^{14}CO_2$ evolution, four samples of fine sandy loam were mixed with ^{14}C-avermectin B_{1a} to give a concentration of 10 ppm and then placed into glass biometer flasks. The trapping solution (1N NaOH) was sampled weekly and analyzed using LSC procedures.

Soil samples were extracted with acetonitrile. Extracted soil was dried and saved to determine unextracted material. The 50 ppm and bulk (10 ppm) samples were also extracted with a 9:1 acetone:water mixture.

Extracts and rinses from soil samples were radioassayed and then analyzed by TLC. Samples of dried extracted soil were radioassayed by combustion followed by LSC.

Reversed phase HPLC equipped with a uv detector was used to analyze soil extracts treated with ^{3}H-avermectin B_{1a}. Soil metabolites were analyzed using MS, NMR, and fourier transformed IR.

Results

Aerobic soil study

At treatment rates of 0.1 and 1 ppm in fine sandy loam, the t 1/2 of ^{3}H-labeled avermectin B_{1a} was 20 days; for the 50 ppm level, the t 1/2 was 40 days (Tables II, III; Figures 2, 3). By 168 days at least 90% of parent (Compound 11) had degraded. For ^{14}C-labeled avermectin B_{1a} on fine sandy loam, the t 1/2 is about 15 days (Table VI; Figure 4). Half-lives of ^{3}H-avermectin B_{1a} in sand and clay ranged from 47 days in sand to 28 days in clay (Tables IV, V; Figures 5, 6). As many as 13 degradation products were

resolved with Compound 7 being the major degradate in all soils. Compound 12 is the next most predominant metabolite. CO_2 traps indicate low levels of radioactivity were being trapped. Through 21 weeks only 3.2% of applied dose was trapped indicating little structural fragmentation.

Anaerobic soil study

When anaerobic conditions were established without aging the treated soil, no degradation of avermectin occured. In the aged study, the degradation of active ingredient occurred but at a slower rate than aerobic metabolism (Table VII and Figure VII).

Soil metabolites

Compound 7 was identified by MS and NMR analysis as an equilibrium mixture of 8-α-hydroxy derivative and the ring opened aldehyde derivative of the parent in a 1:25 ratio (Figure 8). Compound 12 was not identified.

The "lost" residues indicated in the various tables represent amounts of volatile radioactive material that was inefficiently trapped in containers where condensed volatiles were measured. Columns headed "Volatile" represent material condensed in water and is thought to be tritiated water resulting from the release of tritium from the C-5 position of avermectin B_{1a} by metabolic oxidation.

Conclusion

The t 1/2 of avermectin B_{1a} under aerobic conditions appears to be 2 wks to 2 months depending on soil type. Anaerobic degradation is slower or non-existent depending on when anaerobic conditions are established.

Table 1. Properties of Test Soils*

	Lufkin Fine Sandy Loam	Houston Clay	Construction Grade Sand
pH	6.8	6.8	8.0
Organic matter, %	1.1	1.3	0.6
C.E.C. mequiv./100 g	9.31	33.12	0.39
Bulk density g/cm^3	1.19	1.08	1.54
H_2O retention % at $^1/_3$ atm	14.4	38.6	0.8
Mechanical analysis, %			
Sand	60.7	12.6	98.4
Loam	28.3	38.6	0.8
Clay	11.0	48.8	0.8

*Data from Bull and Ivie, J. Agric. Food Chem., 30, (1) 150 (1982).

Avermectin science review

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___ A draft product label

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3.2 Uptake, Depuration and Bioconcentration of ^{3}H-Avermectin B_{1a} by Bluegill Sunfish. Analytical Bio-Chemistry Laboratories. Report No. 30261, 1983.

Bluegill sunfish were exposed to a nominal concentration of 0.1 ppb for 28 days. Test aquaria (including control) were maintained at 22°C. Table 10 gives the sampling schedule for water and fish. Following the 28 day uptake phase, the fish were exposed to flowing uncontaminated well water for 14 days.

Radioanalysis of water was performed by LSC. Fish were dissected except for whole fish analysis, combusted, and quantified by LSC. Samples of water and fish were also set aside for metabolite characterization.

Results

Results indicate that avermectin B_{1a} ceased accumulating after 10 days. Bioconcentration factors of 69 for whole fish, 30 for fillet and 110 for viscera were determined. After 14 days depuration in clean water, up to 95% is eliminated (Tables 6, 7 and Figure 1).

Conclusion

Avermectin does accumulate in edible portions at a moderately low rate. Depuration is rapid with almost total elimination in two weeks.

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3.3 Photodegradation of Avermectin B_{1a} in Water and Soil Environment. C.C. Ku and T.A. Jacob, 1983.

A sterile aqueous suspension of 7 ppm ^{14}C-avermectin B_{1a} using 1% acetonitrile was irradiated in sterile glassware for 29 hours. A dark control was used and duplicate tests were run. Samples were taken at 0 (before irradiation), 1, 2, 4, 8, 12, 15, 20, and 29 hours. Sunlight intensity, time, and temperatures were recorded. The location of the study was Three Bridges, NJ during Aug 9-15, 1983.

A similar experiment using both tritium and carbon labels was carried out under a sunlamp. This time 20 ppm avermectin suspension consisting of 2% acetone, 48% acetonitrile, and 50% water was irradiated. The acetone served as a photosensitzer.

Soil thin layer plates were prepared using Houston clay loam soil. ^{3}H-avermectin B_{1a} was applied to the plates and placed under sunlight and sampled at 0, 1, 2, 4, 8, 16 and 31 hours exposure time. A dark control was used.

Photodegradation products were prepared for structure identification work taking a 240 ppm equimolar mixture of $^{1}H/^{2}H$-labeled material with a trace of ^{3}H-avermectin B_{1a} in an acetone/acetonitrile/water solvent mixture (2/58/40, v/v/v).

Analysis of avermectin B_{1a} and its photoproducts was by HPLC with a uv detector. Radioactivity in samples was measured by standard LSC techniques. Soil samples were combusted before LSC measurements. Some photoproducts were analyzed by MS and NMR procedures.

Results

The aqueous photodegradation studies indicate that avermectin B_{1a} will degrade when exposed to sunlight with a halflife ranging from 3.5 - 12 hours. Some degradation occured in the control indicating thermal and/or microbial degradation is taking place. Results are shown in Table I.

The results of the soil thin layer study are given in Table II. Halflife is determined to be about 21 hours.

The results of the $^{3}H/^{14}C$ labeled aqueous photodegradation study (Table III) indicate that the ratio of tritium to ^{14}C product remains about the same in all fractions collected: polar, moderate polar, avermectin B_{1a}, and non polar.

MS and NMR data indicates no functional group differences between avermectin B_{1a} and nonpolar photoproduct. This photoproduct is thought to be isomeric with avermectin B_{1a} and its structure (proposed) is given in Figure 9.

The structure of the moderate polar product could not be specified using MS and NMR data. The analysis of the polar fraction indicated multiple components with the macrocycle destroyed but with the sugar moiety intact.

Conclusion

The photolysis of avermectin B_{1a} appears to be rapid with half-lives of <12 hours for aqueous photolysis and <1 day for soil photolysis using natural sunlight.

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3.4 Mobility of Avermectin B_{1a} in Soils. C.C. Ku and T.A. Jacob, 1983.

^{3}H and ^{14}C-labeled avermectin B_{1a} mobility was studied using both soil thin layer plates and soil columns. Six soils were used on the thin layer plates. Soil characteristics are given in Table I. Four ^{14}C-pesticides (2,4,-D, Temik, Mirex and parathion) standards were applied side by side with avermectin B_{1a}.

Only few soils (Lakeland fine sand, Lufkin sandy loam, Houston clay loam and Three Bridges silt loam) were used for the soil columns. Each soil type was packed into six columns. Ten ppm ^{3}H-avermectin B_{1a} was applied to four soil columns; the other two were controls. All six were wrapped in foil to keep out the light. For each soil type, two treated columns and 1 control were set aside for 29 days for the aged leaching study.

Each column both aged and fresh received 760-800 ml H_2O. The leachate was collected and the soil was sectioned in six segments each six cm.

The amount of radioactivity in the leachate was determined by LSC techniques. Soil samples were first combusted and then analyzed by LSC. After extraction with acetonitrile and methanol/water, soil samples were analyzed by HPLC with a uv detector.

Results

The results of the soil TLC plates are shown in Table II. On the Helling scale, the mobility of avermectin is placed in Class I (immobile).

Tables III, IV and V give the results of both fresh and aged leaching studies. Leaching seems to occur beyond 6 cm only in the Three Bridges silt loam. Some radioactivity was detected in leachate in all soil types from 2.5-7.8% in unaged to 1.4-6.4% in aged study. Analysis of soil residues and leachates indicates presence of polar metabolites in both components. Parent is found in soil residues but not in leachate.

Conclusion

Avermectin and its metabolites seem to have a low propensity to leach.

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4.0 SUMMARY

- Avermectin B_{1a} degrades aerobically in soil with a t 1/2 range of about 2 weeks to 2 months depending on soil. Under anaerobic soil conditions, degradation processes in soil are slowed.

- Avermectin B_{1a} accumulates to a low extent (BCF = 30 for fillet, 69 for whole fish and 110 for viscera) in fish and is almost totally eliminated within 14 days when placed in uncontaminated water.

- Photodegradation of avermectin B_{1a} is rapid in solution and and on soil with half life ~~decontamination~~ of <12 hours in water and <1 day on soil.

- Avermectin has a very low propensity to leach. Its metabolites were detected in leachate of all column studies but at low levels.

Avermectin B_{1a} is not expected to hydrolyze in the environment. It will undergo rapid photodegradation whether in water or in soil. Under aerobic conditions, it will degrade but a halflife up to 2 months could be expected. Leaching of parent is not expected.

5.0 CONCLUSION and RECOMMENDATION

The data requirements for an EUP have been satisfied. In addition, photodegradation and leaching studies have been submitted and found acceptable. EAB concurs with the granting of this EUP.

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