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ENVIRONMENTAL FATE AND GROUND WATER BRANCH

Review Action

To: George LaRocca, PM #13
Registration Division (H7505C)

From: Paul Mastradone, Section Chief
Chemistry Review Section 1
Environmental Fate & Ground Water Branch/EFED (H7507C)

Thru: Henry Jacoby, Chief
Environmental Fate & Ground Water Branch/EFED (H7507C)

Henry Jacoby 6/6/95

Attached, please find the EFGWB review of...

Common Name:	Emamectin Benzoate	**Trade name:**	MK-0244
Company Name:	Merck & Co., Inc.		
ID #:	3G04239, 000618-EUP-RU		
Purpose:	Review environmental fate studies in support of EUP and for registration for MK-0244.		

Type Product:	Action Code:	EFGWB #(s):	Review Time:
Insecticide	701, 241		30.0 days

STATUS OF STUDIES IN THIS PACKAGE:

Guideline #	MRID	Status[1]
161-1	42743642	A
161-2	43404301	A
161-3	43404302	A
162-1	43404303	U
163-1	42851526	A
	42743643	C
164-1	43404304	U
	43404305	A
	43404306	A
165-4	43393005	A

STATUS OF DATA REQUIREMENTS ADDRESSED IN THIS PACKAGE:

Guideline #	Status[2]
161-1	S
161-2	S
161-3	S
162-1	N
163-1	P
164-1	N
165-4	S

[1]Study Status Codes: A=Acceptable U=Upgradeable C=Ancillary I=Invalid.
[2]Data Requirement Status Codes: S=Satisfied P=Partially satisfied N=Not satisfied R=Reserved W=Waived

(1)

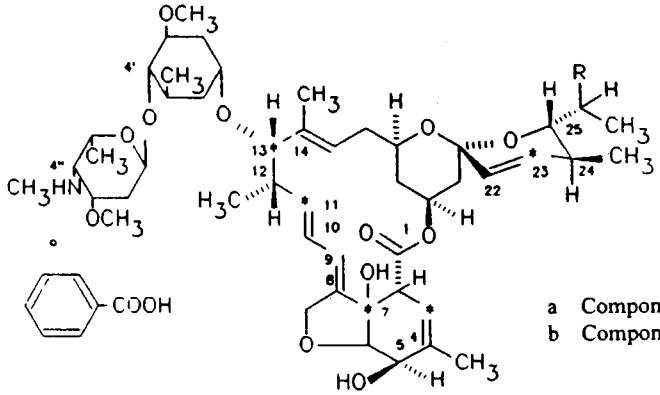
1.0 CHEMICAL:

Common name: Emamectin benzoate

Chemical name:
(4"R)-5-O-demethyl-4"-(methylamino)avermectin A_{1a} benzoate (salt)+(4"R)-5-O-demethyl-25-de(1-methylpropyl)-4"-deoxy-4"-(methylamino)-25-(1-methylethyl)avermectin A_{1a} benzoate (salt) (9:1)

Trade Name: MK-0244

Chemical Structure:



2.0 TEST MATERIAL:

Radiolabeled MK-0244 and active ingredient.

3.0 STUDY/ACTION TYPE: Review MK-0244 studies submitted for EUP.

4.0 STUDY IDENTIFICATION:

Chukwudebe,A.C. 1992. Hydrolysis of 4"-Deoxy-4"-Epimethylamino Avermectin B_{1A} Benzoate as a Function of pH at 25°C (ENC-3). Study performed and submitted by Merck Research Laboratories, Three Bridges, NJ. MRID No. 42743642.

Ballantine, L.G. 1994. Artificial Sunlight Photolysis of [^{14}C]4"-Epimethylamino-4"-Deoxyavermectin B_{1A} Benzoate ([^{14}C]MAB_{1A}) in Aqueous Media. Study performed by Merck Research Laboratories, Hillsborough Road, NJ. and Hazelton Wisconsin, Inc., Madison, Wisconsin. Study submitted by Merck Research Laboratories, Three Bridges, NJ. MRID No. 43404301.

Chukwudebe, A.C. 1994. Photodegradation of [^{14}C]4"-Epimethylamino-4"-Deoxyavermectin B_{1A} Benzoate ([^{14}C]MAB_{1A}) on Soil. Study performed by Agrisearch Incorporated, Frederick, MD. and Merck Research Laboratories, Three Bridges, NJ and submitted by Merck Research Laboratories, Three Bridges, NJ. MRID No. 43404302.

Chukwudebe, A. 1994. Aerobic Soil Metabolism of [^{14}C]4"-Epimethylamino-4"-Deoxyavermectin B_{1a} Benzoate ([^{14}C]MAB_{1a}). Study performed by PTRL East, Inc., Richmond, Kentucky, and Merck Research Laboratories, Three Bridges and Rahway, NJ. MRID No. 43404303.

Feely, W.F. 1992. Soil Thin Layer Chromatography (TLC) of ^{14}C-MK-0244. Study performed and submitted by Merck Research Laboratories, Three Bridges, NJ. MRID No. 42743643.

Mushtaq, M. and L.R. Syintsakos. 1993. Sorption and Desorption of [^{3}H]4"-Deoxy-4"-epimethylamino Avermectin B_{1A} (MAB_{1A}) Benzoate with Soils. Study performed and submitted by Merck Research Laboratories, Three Bridges, NJ. MRID No. 42851526.

Norton, J.A. 1994. Dissipation and Leaching of MK-244 Following Multiple Applications of MK-244 0.16EC Applied with Non-Ionic Surfactant to Bare Soil with Ground Equipment. Study performed by A.C.D.S. Research, Inc., Phelps, NY; Pan-Agricultural Labs Inc., Madera, CA; Research Designed for AG., Yuma, AZ; Agvise Laboratories, Inc., Northwood, ND; Analytical Development Corporation, Colorado Springs, CO; and Merck Research Laboratories, Three Bridges and at Rahway, NJ. Study submitted by Merck Research Laboratories, Three Bridges, NJ. MRID No. 43404304.

Wehner, T.A. 1994. Validation of HPLC-Fluorescence Method to Determine the Residue of MK-0244 and its 8,9-Z Isomer in/on Soil. Study performed by Merck Research Laboratories, Rahway, NJ, and submitted by Merck & Co., Three Bridges, NJ. MRID No. 43404305.

Kvaternick, V. 1994. Validation of Method 244-93-3 for MK-0244 and its 8,9-Z Isomer in/on Soil. Study performed by Analytical Development Corporation, Colorado Springs, CO and submitted by Merck & Co., Inc., Three Bridges, NJ. MRID No. 43404306.

Drottar, K.R. 1994. MK-244: A Bioconcentration Test with the Bluegill (Lepomis macrochirus). Study performed by Wildlife International, Ltd., Easton, MD and Merck & Co., Inc., Three Bridges, NJ, and submitted by Merck & Co., Three Bridges NJ. MRID No. 43393005.

5.0 REVIEWED BY:

George Tompkins, Ph.D., Entomologist
Review Section 1, EFGWB/EFED

Signature: George Tompkins
Date: 26 JUN 19

6.0 APPROVED BY:

Paul Mastradone, Ph.D.
Section Chief, Review Section 1
EFGWB/EFED

Signature: Paul J. Mastradone
Date: 26 JUN 9

7.0 CONCLUSIONS:

ENVIRONMENTAL FATE ASSESSMENT

Presently the environmental fate data base is not complete and the information from all acceptable and upgradeable environmental fate

studies for MK-0244 is somewhat dichotomous. At present no defined route of dissipation has been provided. MK-0244 appears to be stable to hydrolysis at pH 5.2, 6.2, 7.2, and 8.0 but hydrolyzed slowly at pH 9.0 with a reported half-life of 19.5 weeks. Photodegradation in water is slow with a reported half-life of 31.8 to 64.5 days (in 0.01 M phosphate buffer with 1% acetonitrile as a cosolvent). Photodegradation on soil appears to be rapid with a reported half-life of 5 days compared to a half-life of 8 days (application rate >50X field application rate) for the dark controls. However, the information from an upgradeable aerobic soil metabolism study indicates a slow degradation rate with a half-life of 193.4 days (application was 5 ppm, which was approximately 50X field application rate). MK-0244 appears to be immobile with reported Freundlich adsorption (K_{ad}) values ranging from 219 (sand) to 2037 (sandy loam soil). Information from incomplete but potentially upgradeable field dissipation studies using multiple applications (at a rate of 0.015 lb ai/A/application) reported the half-life from the top six inches of soil to range from 4.1 hr to 7.9 hr after the first application . The half-life after the sixth (final) application ranged from 7.0 to 9.0 hr. MK-0244 does not appear likely to bioaccumulate with reported BCF values in bluegill sunfish of 31X in edible tissues, 98X in nonedible tissues, and 69X for the whole fish. After 14 days depuration approximately 90% of radioactivity had been eliminated from edible, nonedible, and whole fish.

7.1 Status of Data Requirements :

Data requirements	MRID	Terrestrial Food
Hydrolysis (161-1)	42743642	Satisfied
Aqueous Photolysis (161-2)	43404301	Satisfied
Soil Photolysis (161-3)	43404302	Satisfied
Aerobic Soil Metab (162-1)	43404303	Not Satisfied[1]
Anaerobic Soil Metabolism (162-2)	--	Not Satisfied
Leaching/Adsorp/Desorp (163-1)	42851526 42743643	Not Satisfied[2]
Terrestrial Field Dissipation (164-1)	43404304 43404305, 43404306	Not Satisfied[3]
Accumulation in Fish (165-4)	43393005	Satisfied

[1]The aerobic soil metabolism study is upgradeable and considered acceptable for an EUP at this time.

[2]The unaged portion of the leaching/adsorption/desorption data requirement is fulfilled; however, the aged portion is unfulfilled.

[3]The terrestrial field dissipation study is presently an interim report.

It is to be noted that at present all of the requirements for an

EUP have not been fulfilled. The aerobic soil metabolism study is potentially upgradeable and the aged portion of the Leaching/Adsorption/Desorption study is lacking.

7.2 EFGWB concludes that the following studies for the EUP and registration of MK-0244 for Terrestrial Food Crop Use are acceptable and satisfy the data requirements:

a). Hydrolysis (161-1), MRID No. 42743642. MAB_1 was stable to hydrolysis at pH 5.2, 6.2, 7.2, and 8.0. At pH 9.0 the reported half-life was 19.5 weeks. Two products, A and B, were observed to form during the hydrolysis of MAB_{1a} in the pH 9.0 buffer at levels of 6.3% and 6.9% of the total radioactivity, respectively. No further identification was made since neither A nor B represented 10% or more of the total radioactivity after 30 days.

b). Photodegradation in Water (161-2), MRID No. 43404301. MAB_{1a} photodegraded slowly with a reported half-life ranging from 31.8 to 64.5 days (in 0.01 M phosphate buffer with 1% acetonitrile as a cosolvent). The acetonitrile cosolvent samples photodegraded into 2 components; the 8,9-Z isomer of MAB_{1a} and polar residues. Indirect photolysis through either a photosensitizer (acetone-$t^{1/2}$ =13.5 to 22.5 hrs) or a radical hydrogen donor (ethanol-$t^{1/2}$=150-203 hrs) was rapid. In the presence of acetone ^{14}C-MAB_{1a} photodegraded into at least 10 individual components (ranging from 0.36 to 6.57% of recovered radioactivity) and to polar residues (5 distinguishable components ranging from 0.14 to 2.44% of recovered radioactivity).

c). Photodegradation on Soil (161-3), MRID No. 43404302. MAB_{1a} photodegraded on microbially active soil with a reported half-life of 5 days (rate constant of 1.32×10^{-1} day^{-1}) compared to dark controls which had a half-life of 8 days (rate constant of 8.68×10^{-2} day^{-1}). At least 8 residues were identified, which were in approximately increasing polarity: 8,9,Z-MAB_{1a}, parent MAB_{1a}, AB_{1a}, 8a oxo-MAB_{1a}, MFB_{1a}, FAB_{1a}, and MSB_{1a}. None of these identified residues individually constituted 5% or more of the initially applied radiocarbon. Additionally, a polar fraction was observed which was resolved into at least 12 different components, none of which individually constituted 2% or more of the initially applied radiocarbon.

d). Unaged portion of the Leaching/Adsorption/Desorption (163-1), MRID No. 428515-26 and 42743643. In batch equilibrium studies unaged tritium labeled MAB_{1a} was shown to be immobile in four soils with Freundlich adsorption (K_{ad}) values ranging from 219 (Florida sand) to 2037 (Texas sandy loam soil). The K_{oc} values ranged from 25,382 to 730,000. Although soil thin layer chromatography studies (MRID No. 42743643) are not currently accepted to demonstrate mobility of a compound in

the soil, this additional study provided supplemental information indicating that MAB_{1a} was not mobile in comparison to other reference pesticides in the 6 soils tested.

e). Accumulation in Fish (165-4), MRID No. 43393005. After 28 days exposure to a nominal concentration of 1.6 ug ai/L of MAB_{1a} the reported BCF values were 31X in edible tissues, 98X in nonedible tissues, and 69X for the whole fish. After 14 days depuration there was an elimination of 91.72% of the radioactivity in the edible tissues, 89.07% in the nonedible tissues, and 90% in the whole fish. The major residues found in edible and nonedible tissues were parent MAB_{1a} and its demethylated metabolite, AB_{1a}. Additional low level radioactive residues, totaling about 39% in the edible and 38% in the nonedible tissues, were distributed throughout the radiochromatograms. None of these residues individually exceeded 5% of the total radioactive residues.

7.3 EFGWB concludes that the following studies submitted for the EUP and registration of MK-0244 are upgradeable:

a). Aerobic Soil Metabolism (162-1), MRID No. 43404303. MAB_{1a} applied at a rate of 5 ppm (approximately 50 times the recommended field application rate) degraded with a reported half-life of 193.4 days. After 366 days aerobic incubation 27.1% of the applied radioactivity remained as parent MAB_{1a}. The major characterized degradates were 8 aOH-MAB_{1a} (maximum of 8.3% of initially applied radiocarbon at 1 month) and a complex polar fraction containing at least 18 different components (maximum of 18.6% at 7 days). With the exception of the putative 8 a oxo-MAB_{1a} (maximum of 7.2% at month 12), none of the uncharacterized residues individually constituted 5% or more of the initially applied radiocarbon. The cumulative $^{14}CO_2$ evolved by day 366 was 16.5% of applied radiocarbon.

b). Terrestrial Field Dissipation (164-1), MRID No. 43404304, 43404305, 43404306. Six applications of MK-0244 were applied by a tractor mounted sprayer at a rate of 0.015 lb ai/A on each application at spray intervals of 6-8 days at three agricultural sites (California, New York, and Arizona). The interim report half-lives reported from the top six inches of soil was 4.1 hours for CA, 4.9 hr from AZ, and 7.9 hr from NY after the first application. The half-lives reported after the sixth (final) application were 7.0 hr from CA, 9.0 hr from AZ, and 7.9 hr from NY. The Mk-0244 residues were reported to be stable on soil stored frozen for at least three months. In the validation of the HPLC-Fluorescence method to determine residues of MK-0244 and its 8-9-Z isomer, the detection limit was determined to be below 0.2 ng/g and the quantitation limit was determined to be $\geq$0.2 but $\leq$.4 ng/g. The validation data demonstrated reasonable recovery of MK-0244 residues at different fortification levels (0.4 to 120 ng/g) in different soils. The range of recoveries ranged from 70-141% for different recoveries of spiked soil samples.

8.0 RECOMMENDATIONS:

8.1 At present no clearly defined route of dissipation has been provided. The submitted aerobic soil metabolism data indicates that MK-0244 has a relatively long half-life (193.4 days with an application rate of approximately 50X field application rate). However, in an acceptable soil photolysis study the half-life in the dark controls was reported as 8 days (application rate 50X field application rate). The reported half-life in the field dissipation interim report indicated a rapid half-life (4.1 to 7.9 hours from the top six inches of soil) with no clearly defined route of dissipation indicated. For any submission and support for full registration the route of dissipation has to be clearly defined and the above discrepancies need to be addressed.

8.2 Presently the hydrolysis, unaged portion of the leaching/adsorption/desorption study, and the accumulation in fish data requirements have been fulfilled for this EUP. The aerobic soil metabolism study is upgradeable and the field dissipation study is considered an interim report that may be upgradeable when the completed results are submitted. The photolysis studies are acceptable and fulfill the data requirements for registration. An anaerobic soil metabolism study was not received.

9.0 BACKGROUND:

Avermectins are naturally occurring disaccharide derivatives of a pentacyclic 16-membered lactone ring produced by the soil microorganism, Streptomyces avermitilis. MK-0244 is chemically synthesized abamectin by modification of the terminal disaccharide; substituting an aminomethyl ($-NHCH_3$) group for a hydroxyl (-OH) group at the 4"-position (see Figure 1). MK-0244 is composed of a mixture of two homologous compounds; a major constituent ($\geq$90%), 4"-deoxy-4"-epimethylaminoavermectin B_{1a} (MAB_{1a}) benzoate and a minor constituent ($\leq$10%), 4"-deoxy-4"-epimethylaminoavermectin B_{1b} (MAB_{1b}) benzoate. MAB_{1a} and MAB_{1b} differ only by a methylene ($-CH_2-$) group at the C-27 position. MK-0244 has high activity against a broad range of lepidopterous larvae and reduces feeding damage on vegetables and sweet corn.

10.0 DISCUSSION OF INDIVIDUAL STUDIES:

It was noted that there was a significantly longer half-life reported for MK-0244 in the aerobic soil metabolism study (193.4 days, MRID No. 43404303) than there was for the dark controls in the soil photolysis study (8 days, MRID No. 43404302). The application rate in both of these studies was similar with a rate of 5.0 ppm ai/A for the aerobic soil metabolism study and 5.8 ppm for the soil photolysis study. It

is recommended that an explanation be provided for these noted differences in degradation rates.

11.0 COMPLETION OF ONE-LINER: updated

12.0 CBI APPENDIX: N.A.

AVERMECTIN / EMAMECTIN BENZOATE

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Pages _____ through _____ are not included in this copy.

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_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

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_____ A draft product label.

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