Shaughnessy No.: 122804

Date Out of EAB: 8/10/88

To: George LaRocca
Product Manager 15
Registration Division (TS-767C)

FILE COPY

From: Frank Davido, Chief Frank Davido
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THRU: Paul F. Schuda, Chief
Exposure Assessment Branch/HED (TS-769C) Paul F. Schuda

Attached, please find the EAB review of....

Reg./File # : 618-02

Chemical Name : Avermectin

Type Product : Insecticide/Miticide

Product Name : AVID 0.15 EC, Abamectin

Company Name : Merck, Sharp & Dohme Research Laboratories

Purpose : Review of foliar dislodgeable residue data in support of the use of avermectin (Avid 0.15 EC) on citrus: Addendum to Previous Submission

Action Code: 181 EAB # (s) : 80794

Date Received : 5/26/88 TAIS Code : 50

Date Completed: 8/10/88 Reviewing Time: 15 d

Monitoring Study Requested: NO

Monitoring Study Voluntarily: NO

Deferrals to:

NO Ecological Effects Branch

NO Residue Chemistry Branch

NO Toxicology Branch

285

CHEMICAL:

Common Name: Avermectin

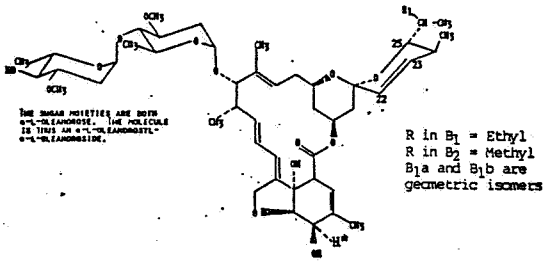
Product Name: AVID 0.15 EC

Other Names: Abamectin (MK 0936)

Company: Merck, Sharp & Dohme Research Laboratories, Inc.

Shaughnessy No.: 122804

Structure:



The active ingredient is composed of at least 80% Avermectin B1a and not more than 20% Avermectin B1b.

TEST MATERIAL:

AVID 0.15 EC

STUDY/ACTION TYPE:

Additional reentry data submitted to support the registration of Avermectin to control mites and ticks on citrus.

STUDY IDENTIFICATION:

Reg. File Nos.: 610-02
Accession Nos.: 404430-11
Record Nos.: 223065 MRID #s: Not Available
Merck, Sharp & Dohme Research Laboratories Report Doc. No. 11 dated July 15, 1986, "Dislodgeable Foliar Residue Data in Support of a Registration/Petition for the use of Abamectin 0.15 EC On Citrus in the USA" by Helene S. Rosenthal, Lab. Project ID/Study No. 001-84-102R

REVIEWED BY:
Linda L. Kutney, Chemist
Monitoring Section 6
EAB/HED/OPP

Linda L Kutney

Date: 8/10/88

APPROVED BY:
James D. Adams, Chemist
Field Studies and Special Projects Section 5
EAB/HED/OPP

James D Adams

Date: 8/10/88

286

CONCLUSIONS:

The submitted data are not acceptable for estimation of human exposure [and, therefore, risk estimates] for work in treated citrus groves. Additional data concerning storage stability of samples is necessary to estimate the exposure scenario resulting from nationwide use of avermectin on citrus. Insufficient data have been submitted for prediction of fieldworker exposure or to support a reentry interval if necessary.

The 2-hour reentry interval proposed by William Dykstra of Tox in his 5/19/88 review is not supported by the data presented in this submission. Under 40 CFR 170.3, no reentry after use of any pesticide is allowed, "..... until the sprays have dried or dusts have settled.....". Two hours may or may not be sufficient time for the spray to dry.

RECOMMENDATIONS:

EAB feels that additional data concerning the storage stability of the samples should be provided befor a reentry interval is proposed.

The 2-hour reentry interval recommended by the Toxicology Branch should not be established. The petitioner has stated in this submission that the spray may not be completely dried on foliage within 3 hours or more.

Additional data concerning the storage stability of the samples must be provided.

BACKGROUND:

This submission contains data intended to satisfy the requirements of 40 CFR 158.390 (Reentry Protection) for the use of Avermectin on citrus. Merck has previously submitted foliar dislodgeable residue data for lemons in Oxnard, Ventura County, California (See Review dated April 21, 1988, by Linda Kutney, EAB #70045).

The previous EAB review requested additional foliar dislodgeable residue data, for avermectin, including the Delta 8, 9 metabolite, for a worst-case scenario following the proposed use of Avermectin on citrus. Storage stability data was also cited as a deficiency. That review also stated that only a geographically-restricted use should be recommended.

In his 5/19/88 review, William Dykstra of Tox recommended that a reentry interval of 2 hours or more be set for humans exposed to avermectin on citrus, throughout the United States. This was based on the NOEL for maternolethality in the CF-1 mouse of 0.05 mg/kg/day for avermectin. The terata NOEL (cleft palate) in the CF-1 mouse of 0.06 mg/kg/day for the delta-8,9-isomer of

avermectin was also considered. Tox Branch calculated that the exposure for a 70-kg person at a 1 % dermal absorption rate would be 0.00000169 mg/kg/day. Using this information, Tox concluded that the 2 hour margin of safety would be adequate as a reentry interval.

This 2-hour reentry interval is inadequate because data included in this submission indicates that additional time may be needed (3 hours or more) before Avermectin is dry on the foliage. No reentry is permitted under 40 CFR 170.3(b) until a pesticide spray is dried or the dust has settled. For that reason, a 2-hour reentry interval should not be established.

This submission contains foliar dislodgeable residue data for avermectin after its application to orange trees in the San Joaquin Valley, Fresno, California. The study was initiated in August, 1984.

Applications were made using ground equipment and both concentrated (100 gal/acre) and more dilute (500 gal/acre) sprays at the 0.025 lb ai/acre (the maximum 1x rate) and the 0.050 lb ai/acre (2x the maximum proposed rate). Three applications were made on approximately 60 days apart. One to 1.25 gal/NR-400 crop oil was added to the formulation in accordance with the label (the label requires that at least one gal of oil/gal be added).

There is a seasonal maximum of three applications to be used, but there is no label restriction concerning the minimal interval between applications. According to information provided by Merck on 4/13/88, farmers would wait approximately six weeks between Avermectin applications, due mainly to cost considerations.

The data do not include an adequate study of storage stability of the samples. The samples were reported to have been stored frozen, except for an undetermined time for log-in(s). However, the chain of custody and integrity of the samples is confusing. The submission states that the samples (collected in California on 12/84) were shipped frozen from California to Three Bridges Farm, in NJ on 12/84. From NJ, they were then shipped on 4/85 to ABC Labs in MO, for analysis. For some reason, however, the samples were not analysed in MO, but were shipped back again to Three Bridges Farm, in NJ, where they were received on April 1, 1986, almost 1 1/2 years after the time they were sampled. From Three Bridges Farm, the samples were sent to the Merck facility in Rahway, NJ, where they were kept frozen until analysis, which was performed from 2/87 to 4/87, almost 2 1/2 years after sampling.

Avermectin from the samples was not extracted until 4/87, and final analysis not completed until almost 2 weeks after extraction. Given the amount of travel time that these samples were subjected to, and the fact that they may not have been frozen

throughout their itinerary, we are concerned with the possible loss or degradation of avermectin.

For further consideration, the petitioner may consider submitting a storage stability study for avermectin B1a, B1b, and its Delta 8, 9 metabolite. This study should show recoveries which could be expected after a 2 1/2 year period of storage similar to that of the samples.

DISCUSSION OF INDIVIDUAL TESTS AND STUDIES:

A: MATERIALS AND METHODS

Pesticide Application:

AVID 0.15 EC was applied at 0.025 lb a.i./acre (the 1x rate) and at 0.050 lb a.i./acre (the 2x rate) in 1984. Field trials used to obtain foliar dislodgeable residue data were conducted on California oranges in the San Joaquin Valley, Fresno County.

The maximum proposed application rate on citrus, which is to be permitted only three times per season, is 0.25 lb a.i./A. Both dilute (500 gallons/acre) and concentrated (100 gallons/acre) applications were made with at least 1 gallon/acre of oil (the proposed rate). Applications were made using ground sprayer equipment. In this study, three applications were made at approximately 60 day intervals.

Foliar Dislodgeable Residues (FDRs)

Foliar dislodgeable residue samples (FDR's) were taken at -1 days, 3 hours, 6.5 hours, 24 hours, 3 days, 7 days, and 14 days after the last application.

The details concerning techniques for taking leaf punches were not given with this submission, but methods reviewed previously (See 4/21/88 Kutney review of avermectin on citrus) were satisfactory. Collection techniques appear to be satisfactory.

Results for field-fortified control punches were not reported, for avermectin B1a or B1b, or the Delta 8,9 isomer. If this information is available, it should be submitted as documentation of storage stability of the samples during their travels.

Analytical Methods:

Briefly, the FDR's were determined using Merck Method 4007, "HPLC-Fluorescence Determination of Foliar Dislodgeable Residues of Avermectin B1 and its Delta 8,9 Isomer." Avermectin B1 and the Delta 8, 9 metabolite were extracted with aqueous Triton X-100; 30% NaCl in methanol was added; and the resultant solution was further extracted with (1/4) iso-octane/0.01% t-butanol in methylene chloride. Two more extractions were then made using the 0.01% t-butanol/methylene chloride, and the

combined extracts were concentrated using evaporation and cleaned using an acidic alumina column.

The sample was then evaporated to dryness and a fluorescent derivative formed with N,N dimethylformamide/trifluoroacetic anhydride/1-methylimidazole reagent (Reagent A) followed by reaction with methanolic ammonium hydroxide (Reagent B). This derivatization step was not present in Merck Method 4005. The mixture was then dissolved in chloroform and separated using column chromatography with the metabolic derivative passing through in the eluant. The eluant was then taken to dryness and re-dissolved in methanol.

The derivatized residue is detected using reverse-phase liquid chromatography with fluorescence detection. The avermectin B1a delta 8,9 isomer results in a peak with the same deteaction time as the parent avermectin B1a, as do the respective B1b isomers.

Finally, reversed-phase liquid chromatography with fluorescence detection was used to quantify avermectin and the Delta 8,9 metabolite in the same peak. A ratio of avermectin B1a or B1b to the corresponding Delta 8,9 metabolites in the standard solution is used to quantitate the amount of the metabolite present in the sample.

B: REPORTED RESULTS

Dislodgeable Residues:

The selection of the site in Fresno, California eliminates one of the previous discrepancies sited in L. Kutney's 4/21/88 review, that only a west-coast site was selected for testing.

However, lack of storage stability data was also sited as a discrepancy in the aformentioned 5/21/88 review, and is still necessary for validation of the data submitted here.

A summary of the FDR's reported by Merck along with whole body dose rates estimated from FDRs using the EAB exposure data base are included in the tables below. Tables 1 and 2 contain the data from the application at the maximum (1X) proposed rate, for the concentrated and dilute sprays. Table 3 and 4 contain the data from the 2.0 X rate, for the concentrated and the dilute sprays.

Data was submitted for the predominant Avermectin isomer, B1a, the Delta 8,9 metabolite, and Avermectin B1b isomer (reported to be approximately 10% of the B1a/Delta 8,9 amount).

TABLE 1C

FOLIAR DISLODGEABLE RESIDUE/HUMAN REENTRY EXPOSURES

Application Rate = 0.025 lb ai/A (1.0 X)
CONCENTRATED SPRAYS (IN 100 GAL)

Hours After Avermectin Application		Reported FDRs B1a/Delta-8,9 (ng/cm^2)	Avg Whole Body Dose (ug/day)	Reported FDRs B1b Isomer (ng/cm^2)	Avg Whole Body Dose (ug/day)
-24.0	(-1d)	0.25	8.7	0.02	0.5
3.0		15.50	830.6	1.32	54.6
6.5		24.80	1396.2	2.12	92.2
24.0		13.10	689.7	1.09	44.2
72.0	(+3d)	8.02	401.1	0.70	27.1
168.0	(+7d)	3.60	165.5	0.33	11.8
336.0	(+14d)	1.26	51.9	0.11	3.5

TABLE 1D:

FOLIAR DISLODGEABLE RESIDUE/HUMAN REENTRY EXPOSURES

Application Rate = 0.025 lb ai/A (1.0 X)
DILUTED SPRAYS (IN 500 GAL)

Hours After Avermectin Application		Reported FDRs B1a/Delta-8,9 (ng/cm^2)	Avg Whole Body Dose (ug/day)	Reported FDRs B1b Isomer (ng/cm^2)	Avg Whole Body Dose (ug/day)
-24.0	(-1d)	0.05	1.5	0.02	0.5
3.0		37.30	2191.9	3.06	138.3
6.5		9.20	466.7	0.79	31.0
24.0		2.66	118.5	0.23	7.9
72.0	(+3 d)	0.93	37.1	0.13	4.2
168.0	(+7 d)	0.21	7.2	0.02	0.5
336.0	(+14 d)	0.05	1.5	0.02	0.5

NOTE: The whole body dose rates in Tables 1C and 1D should be used for risk estimates and reentry interval calculations only if adequate storage stability studies are submitted. At least 99% of this exposure is expected to be via the dermal route.

TABLE 2C
FOLIAR DISLODGEABLE RESIDUE/HUMAN REENTRY EXPOSURES

Application Rate = 0.05 lb ai/A (2.0 X)
CONCENTRATED SPRAYS (IN 100 GAL)

Hours After Avermectin Application	Reported FDRs B1a/Delta-8,9 (ng/cm^2)	Avg Whole Body Dose (ug/day)	Reported FDRs B1b Isomer (ng/cm^2)	Avg Whole Body Dose (ug/day)
-24.0 (-1d)	0.21	7.2	0.02	0.5
3.0	27.40	1558.9	2.31	101.4
6.5	61.90	3836.3	5.32	254.8
24.0	31.30	1805.8	2.88	129.3
72.0 (+3d)	15.70	842.5	1.33	55.1
168.0 (+7d)	3.66	168.6	0.34	12.2
336.0 (+14d)	1.86	79.8	0.16	5.3

TABLE 2D
FOLIAR DISLODGEABLE RESIDUE/HUMAN REENTRY EXPOSURES

Application Rate = 0.05 lb ai/A (2.0 X)
DILUTED SPRAYS (IN 500 GAL)

Hours After Avermectin Application	Reported FDRs B1a/Delta-8,9 (ng/cm^2)	Avg Whole Body Dose (ug/day)	Reported FDRs B1b Isomer (ng/cm^2)	Avg Whole Body Dose (ug/day)
-24.0 (-1d)	0.05	1.5	0.02	0.5
3.0	91.30	5894.0	7.86	392.2
6.5	20.20	1113.0	1.68	71.3
24.0	9.30	472.3	0.68	26.2
72.0 (+3d)	2.01	86.9	0.18	6.0
168.0 (+7 d)	0.35	12.6	0.05	1.5
336.0(+14 d)	0.13	4.2	0.02	0.5

NOTE: There is no need to use the data in this table for exposure estimates or reentry interval calculations at this time. The data in Tables 1C and 1D are appropriate for exposure estimation at the proposed usage rate of 0.025 lb ai/A - provided that adequate storage stability studies are submitted.

C: STUDY AUTHORS QUALITY ASSURANCE MEASURES

No data was submitted indicating that avermectin, Bla, Blb or the Delta 8,9 metabolite was fortified in the field. In addition, no data was submitted concerning storage stability. This information will be necessary for the evaluation of the validity of the data.

The quality control is not acceptable.

D: REVIEWER'S DISCUSSION AND INTERPRETATION OF STUDY RESULTS

EAB expects that nearly 100% of the human reentry exposure to the proposed use of avermectin in citrus crops will be via the dermal route. The submitted data is not adequate for estimation of FDR.

COMPLETION OF ONE-LINER:

Not Applicable

CBI APPENDIX:

Not Applicable