Caswell

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 19 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Avermectin (Also Called Abamectin) - EPA
Experimental Use Permit No. 50658-EUP-1 - EAB
Deferral Regarding Reentry in Citrus Crops

Caswell No.: 63AB
Project No.: 8-0699

FROM: William Dykstra, Reviewer
Toxicology Branch
Hazard Evaluation Division (TS-769C)

William Dykstra 5/13/88

TO: George T. LaRocca, PM 15
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

and

Exposure Assessment Branch
Hazard Evaluation Division (TS-769C)

THRU: Edwin Budd, Section Head
Review Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Budd 5/18/88
5/19/88

Requested Action

Review EAB deferral and determine a safe reentry interval into avermectin-treated citrus crops.

Conclusions and Recommendations

TB concludes that the safe (margin of safety [MOS] > 100) reentry interval is 2 hours or more for humans exposed to avermectin in treated citrus crops.

Review

In the April 28, 1988 memorandum of L. Kutney of EAB (attached), EAB defers to TB for the calculation of a safe reentry interval for avermectin on citrus crops.

To calculate human exposure to avermectin or the delta-8,9-isomer, TB assumes that the body weight of the exposed person is 70 kg and that dermal absorption is 1 percent (see attached).

The maximum exposure that can be expected is based on data in EAB Table 3. An application rate of 0.05 lb ai (2.0X) concentrated sprays (in 100 gallons) results in an average whole body dose ranging between 653 ug/day at 2 hours to 11.8 ug/day at 14 days.

As an example, for the 2-hour reentry period at the 2.0X application rate, the following maximum exposure can be expected.

Avg. Whole Body Dose (ug/day)	For 70 kg Person and 1% Dermal Absorption (mg/kg/day)
653	0.0000933

For this maximum amount of exposure, the MOS can be calculated by comparison to the appropriate toxic end points. The NOEL for maternolethality in the CF-1 mouse is 0.05 mg/kg/day for avermectin. The NOEL for terata (cleft palate) in the CF-1 mouse is 0.06 mg/kg/day for the delta-8,9-isomer of avermectin.

Therefore, the MOS for the 0.0000933 mg/kg/day level of maximum exposure is as follows:

Maternolethality	Terata
535	643

At the 14-day reentry interval for an application rate of 0.050 lb ai (2.0X), as shown in Table 3, the level of whole body exposure is 11.8 ug/day. The calculated human exposure for a 70 kg person at a 1 percent dermal absorption rate is 0.00000169 mg/kg/day.

Therefore, the MOS for the 0.00000169 mg/kg/day level of maximum exposure at 14 days is as follows:

Maternolethality	Terata
29,986	35,503

Consequently, the MOSs for reentry for the maximum exposure (based on Table 3) range between 535 to 29,986 for maternolethality and from 643 to 35,503 for developmental toxicity.

It can be noted from the average whole body exposure (ug/day) values for Tables 1, 2, and 4 of the EAB memorandum, that the MOS would exceed those MOSs calculated for maximum exposure (Table 3).

Based on these data, TB concludes that the safe (MOS > 100) reentry interval is 2 hours or more for humans exposed to avermectin or the delta-8,9-isomer in treated citrus crops.

Shaughnessy No.: 122804

Date Out of EAB: APR 21 1988

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

From: Frank Davido, Chief
Field Studies and Special Projects Section #5
Exposure Assessment Branch
Hazard Evaluation Division (TS-769C)

THRU: ~~Paul F. Schuda, Chief~~ Deputy Chief
Exposure Assessment Branch/HED (TS-769C)

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

Reg./File # : 50658-EUP-1

Chemical Name : Avermectin

Type Product : Insecticide/Miticide

Product Name : AVID 0.15 EC, Abamectin

Company Name : Merck, Sharp & Dohme Research Laboratories

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

Action Code: 714 EAB # (s) : 70045

Date Received : 10/28/86 TAIS Code : 36

Date Completed: 4/20/88 Reviewing Time: _____

Monitoring Study Requested: _____

Monitoring Study Voluntarily: _____

Deferrals to:

__ Ecological Effects Branch

__ Residue Chemistry Branch

X Toxicology Branch

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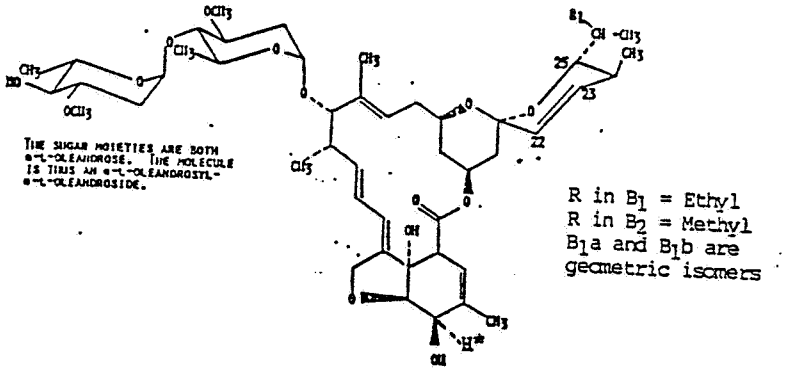
1. CHEMICAL:

Common/Chemical 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.

2. TEST MATERIAL:

AVID 0.15 EC

3. STUDY/ACTION TYPE:

Reentry data submitted as additional support for registration of Avermectin to be used as an acaricide to control mites and ticks on citrus.

4. STUDY IDENTIFICATION:

Reg. File Nos.: 50678/EUP/1
Accession Nos.: 265590, -1, -2, -3, -4, -5, -6, and -7.
Record Nos.: 184282 MRID #s: Not Available
Merck, Sharp & Dohme Research Laboratories Report ANR-001-86-2, dated July 15, 1986, "Foliar Dislodgeable Residue Data in Support of the Use of AVERMECTIN B1 0.15 EC On Citrus in the USA" by J. Jenkins.

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

linda L Kutney
Date: 4/20/88

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

James D. Adams
Date: 4/20/88

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7. CONCLUSIONS:

The submitted data are acceptable for estimation of human exposure [and, therefore, risk estimates] during work in treated citrus groves in the coastal counties of California. The data are also acceptable for other states where pesticide dissipation rates are higher due to higher rainfall and presence of morning dew. These states include Florida and Texas.

These data are not acceptable for the estimation of human reentry exposure to Avermectin on citrus crops in areas more arrid than Ventura County, California, such as San Joaquin or Imperial Valley, California. Foliar dislodgeable residue (FDR) data from Ventura, California do not represent the the worst-case exposure scenario for the proposed use of Avermectin on citrus. Title 40, Code of Federal Regulations, Part 158.140 requires that, at least, the worstcase exposure be submitted to the Agency for review.

Ventura county is located on the coast of California, and it typically receives more precipitation and dew than the arrid, inland citrus groves of the San Joaquin or Imperial Valleys. In addition, no data was submitted for the weather conditions present during the Ventura study. It is therefore impossible to evaluate the impact of precipitation, including dew deposition, in the submitted Ventura study.

Human exposure rates estimated from the reported FDRs range from 546 ug/day at 2 hours after application to 2.8 ug/day at 14 days after application. These low rates of exposure are a reflection of the low usage rate of Avermectin. As stated above, however, the submitted data are inadequate for calculation of the exposure scenario resulting from nationwide use of Avermectin on citrus.

R. Douglas of Merck, and other company representatives, stated in a 4/14/88 meeting that additional FDR data is available from studies conducted in California and Florida. This data has not been submitted for review to EAB. Merck may wish to submit this data for further consideration. They may wish to include data for the Delta 8,9 metabolite at that time, also.

8. RECOMMENDATIONS:

Additional data, reflecting the maximum worst-case scenario, will be required to calculate the human exposure following the proposed use of Avermectin on citrus. This data should include foliar dislodgeable residue data for the Delta 8,9 metabolite as well as the parent Avermectin. We recommend that Toxicology Branch choose a reentry interval for Avermectin on citrus crops from the exposure rates listed in Table 1, but that reentry interval should not apply to citrus grown in inland counties of California. The pesticide should not be registered for those counties until appropriate data are submitted.

9. BACKGROUND:

This submission contains data intended to satisfy the data requirements of 40 CFR 158.140 for reentry after application of Avermectin to citrus. The data include foliar dislodgeable residues of Avermectin after its application to lemon trees in Ventura County, California.

Applications were made using ground equipment and both concentrated (100 gal/acre) and dilute (1000 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). Applications were made on 6/11/84, 8/9/84 and 10/8/84, approximately 60 days apart. Crop oil was added to the formulation in accordance with the label.

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.

10. 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 conducted in Florida and California (two in each state) were used to obtain foliar dislodgeable residue data. The maximum proposed application rate on citrus, which is permitted only up to three times per season, is 0.25 lb. a.i./acre. Both dilute and concentrated (less than 250 gallons/acre) applications were made and at least 1 gallon/acre of oil (the proposed rate) was added to the tank mix. Applications were made using ground sprayer equipment.

Of the four field trials conducted, only results of the lemon study in Oxnard, California in Ventura county was submitted to EAB (field trial 001/84/103R).

In this study, three applications were made at 60 day intervals. As per the 4/12-3/88 conversation between the Product Managers, George LaRocca and Adam Heyward, Merck representatives, and Linda Kutney, additional data may be submitted at a later date. As of this time, no further foliar dislodgeable residue data on citrus have been submitted to EAB.

Foliar Dislodgeable Residues (FDRs)

Foliar dislodgeable residue samples (FDR's) were taken at 2, 4, 8 and 24 hours and at 3, 7, and 14 days after the last of three

applications. Three replicates were taken at each sampling interval. Each sample consisted of 40 leaf punches with a diameter of 2.54 cm (one inch), giving a single-sided leaf surface area of 202.7 cm2.

Collection and extraction techniques described by Gunther, et. al., in 1977 and 1973 were used. Leaf punches were placed into plastic-impregnated cloth bags and stored frozen until analyzed. In addition, samples from untreated control plots were also collected.

Control punches were fortified, in the field, with Avermectin B1, but not the Delta 8,9 isomer.

Analytical Methods:

Briefly, the FDR's were determined using Merck Method 4005, "HPLC-Fluorescence Determination of Avermectin B1 Foliar Dislodgeable Residues." Avermectin B1 (but not the Delta 8, 9 metabolite) was extracted with aqueous Triton X-100; 10% 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 roto-evaporation and cleaned using an acidic alumina column. The sample was then evaporated to dryness and a fluorescent derivative formed with N,N dimethylformamide/ acetic anhydride/1-methylimidazole reagent for 1 hour at 95°C. 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.

Finally, reversed-phase liquid chromatography with fluorescence detection was used to quantify Avermectin but not the Delta 8,9 metabolite. The petitioner may wish to submit additional data concerning residue levels of the Delta 8, 9 metabolite in any future submission.

B: REPORTED RESULTS

Dislodgeable Residues:

Apart from shortcomings with selection of the westcoast site and lack of storage stability data, the foliar dislodgeable residue data appear to be of good quality. 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 proposed rate, for the concentrated and dilute sprays. Table 3 and 4 contain the data from the 2.0 times that rate, for the concentrated and the dilute sprays. Analysis was submitted only for the Avermectin B1a compound, no data were submitted for the Delta 8,9 metabolite.

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TABLE 1:

FOLIAR DISLODGEABLE RESIDUE AND HUMAN REENTRY EXPOSURE LEVELS

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

Hours After Application	Reported FDRs of Avermectin B1, (ng/cm2)	Average FDRs, (ng/cm2)	Avg Whole Body Dose, ug/day
2 (0.08d)	7.96		
2	11.85		
2	12.01	10.61	546
4 (0.17d)	2.98		
4	5.88		
4	4.74	4.53	213
24 (1 day)	6.58		
24	1.81	4.20	196
72 (3 days)	0.45		
72	0.37		
72	0.55	0.45	16.6
168 (7 days)	0.43		
168	0.28		
168	0.15	0.29	10.2
336 (14 days)	0.11		
336	N.D.		
336	0.06	0.09	2.8

NOTE: The whole body dose rates in this table should be used for risk estimates and reentry interval calculations. Based on other published data, at least 99% of this exposure is expected to be via the dermal route.

TABLE 2:

FOLIAR DISLODGEABLE RESIDUE AND HUMAN REENTRY EXPOSURE LEVELS

Application Rate = 0.025 lb ai/A (1.0 X)
DILUTE SPRAYS (IN 1000 GAL)

Hours After Application	Reported FDRs of Avermectin B1, (ng/cm2)	Average FDRs, (ng/cm2)	Avg Whole Body Dose, ug/day
2 (0.08d)	6.23		
2	4.93		
2	4.11	5.09	243
4 (0.17d)	2.91		
4	3.23		
4	2.13	2.81	126
8 (0.34d)	2.21		
8	2.19		
8	1.92	2.10	91.2
24 (1 day)	0.11		
24	1.67		
24	0.79	0.85	33.6
72 (3 days)	0.24		
72	0.46		
72	0.20	0.30	10.6
168 (7 days)	0.16		
168	0.19		
168	0.12	0.16	5.3
336 (14 days)	0.05		
336	0.05		
336	N.D.	0.05	1.5

NOTE: There is no need to use the data in this table for risk estimates or reentry interval calculations. The data in Table 1 will give more conservative estimates and are, therefore, more appropriate for risk estimation.

TABLE 3:

FOLIAR DISLODGEABLE RESIDUE AND HUMAN REENTRY EXPOSURE LEVELS

Application Rate = 0.050 lb ai/A (2.0 X)
CONCENTRATED SPRAYS (IN 100 GAL)

Hours After Application	Reported FDRs of Avermectin B1, (ng/cm2)	Average FDRs, (ng/cm2)	Avg Whole Body Dose, ug/day
2 (0.08d)	6.50		
2	14.48		
2	16.44	12.47	653
4 (0.17d)	9.80		
4	7.80		
4	11.06	9.55	486
24 (1 day)	5.72		
24	3.46		
24	4.88	4.69	222
72 (3 days)	0.25		
72	2.17		
72	4.94	2.45	108
168 (7 days)	1.11		
168	1.30		
168	0.70	1.04	42.0
336 (14 days)	0.22		
336	0.40		
336	0.38	0.33	11.8

NOTE: There is no need to use the data in this table for risk estimates or reentry interval calculations at the present time. This data may be useful later if the Registrant asks for registration at this higher use rate.

TABLE 4:

FOLIAR DISLODGEABLE RESIDUE AND HUMAN REENTRY EXPOSURE LEVELS

Application Rate = 0.050 lb ai/A (2.0 X)
DILUTE SPRAYS (IN 1000 GAL)

Hours After Application	Reported FDRs of Avermectin B1, (ng/cm2)	Average FDRs, (ng/cm2)	Avg Whole Body Dose, ug/day
2 (0.08d)	12.54		
2	14.42		
2	12.98	13.31	87.7
4 (0.17d)	3.73		
4	4.11		
4	5.99	4.61	27.2
8 (0.34d)	N.A.		
8	N.A.		
8	N.A.	N.A.	N.A.
24 (1 day)	2.70		
24	2.16		
24	2.27	2.38	13.1
72 (3 days)	0.62		
72	0.91		
72	1.68	1.68	8.91
168 (7 days)	0.29		
168	0.47		
168	0.31	0.36	1.62
336 (14 days)	0.13		
336	0.11		
336	0.06	0.10	0.39

NOTE: There is no need to use the data in this table for risk estimates or reentry interval calculations at the present time. This data may be useful later if the Registrant asks for registration at this higher use rate.

C: STUDY AUTHORS CONCLUSIONS/QUALITY ASSURANCE MEASURES

The parent Avermectin, B1, was fortified in the field at the 0.05, 0.25, 0.50, 2.50, and 5.00 ng/cm2 levels. The cover summary of results stated that no correction of residue data was made for recoveries below 100%, but that correction was made for sample recoveries above 100%. Recoveries were acceptable. This data is given in Table 1 of Appendix C of the submission and are summarized below.

Fortification Level (ng/cm2)	% Recovery	Average % Recovery (Standard Deviation =S.D.)
0.05	220	
0.05	262	
0.05	320	
0.05	169	
0.05	94	213 (S.D.= 8.8)
0.25	84	
0.25	94	89 (S.D.= 2.2)
0.50	86	
2.50	92	
5.00	45	

No field-fortifications or sample results of the Delta 8,9 metabolite were submitted.

A separate study of eight laboratory-fortified Avermectin samples showed higher recoveries, 80-109% (avg. 94%). This indicates some loss of residue may have occurred during the handling, shipping, or storage of the sample at 5.00 ng/cm^2.

The quality control generally is 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 (although not worse case) suggests that at the 1.0 X rate of application (0.025 lb. a.i./acre), about 10.6 ng/cm2 FDR could initally be expected. After 4 hours, this amount dropped to 4.5 ng/cm2; after 3 days, less than 0.5 ng/cm2 was available as FDR.

11. COMPLETION OF ONE-LINER:

Not Applicable

12. CBI APPENDIX:

Not Applicable