US EPA ARCHIVE DOCUMENT

CASWELL FILE

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

MEMORANDUM: APR 10 1987

SUBJECT: Avermectin (Abamectin); Calculation of Margins of Safety for Use on Citrus for Mixer/Loaders and Sprayers

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

Caswell No. 63AB

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

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

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

Based on the data presented in the EAB review of Jan. 15, 1987 (memo from J.C. Reinert to G. LaRocca, attached), dermal exposure to mixer/loaders wearing long-sleeve shirts, long pants and protective gloves and open pouring abamectin is 0.53 ug/gram a.i. handled. Respiratory exposure is insignificant.

The dermal exposure to airblast sprayers wearing similar clothing is 0.54 ug/gram a.i. handled. Respiratory exposure is insignificant.

If protective gloves are not worn during spraying, the exposure is estimated to be 0.88 ug/gram a.i. handled.

The dermal exposure estimates represent the quantity of abamectin impinging on the skin and were not adjusted by EAB for the percentage dermal absorption of abamectin.

The following example is for mixer/loaders.

Assuming that mixer/loaders prepare abamectin for use for 50 acres/day at 0.025 lbs. a.i./acre, the total amount prepared would result in 1.25 lbs. a.i./day being handled.

$$\frac{1.25 \text{ lb a.i.}}{\text{day}} \times \frac{454 \text{ grams}}{\text{lb.}} = 567 \text{ grams/day}$$

$$\frac{0.53 \text{ ug}}{\text{gm a.i. handled}} \times \frac{567 \text{ grams}}{\text{day}} = \frac{301 \text{ ug}}{\text{day}}$$

Assuming a mixer/loader weighs 70 kg, this is equivlent to:

$$\frac{301 \text{ ug}}{\text{day}} \div 70 \text{ kg} = 0.0043 \text{ mg/kg/day}$$

The upper limit of dermal penetration of abamectin in the monkey (based on review by R. Zendzian, attached) is 1.0%.

Therefore, for 50 acres, the following exposure can be estimated for mixer/loaders.

$$0.0043 \text{ mg/kg/day} \times 0.01 = \underline{4.3 \times 10^{-5} \text{ mg/kg/day}}$$

The margin of safety calculated from this exposure by using the NOEL of 0.05 mg/kg/day for maternotoxicity (lethality) in the CF_1 mouse is as follows:

$$\text{MOS} = \frac{\text{NOEL}}{\text{Exposure}}$$

$$\text{MOS} = \frac{0.05 \text{ mg/kg/day}}{4.3 \times 10^{-5} \text{ mg/kg/day}}$$

$$\text{MOS} = \underline{1163}$$

The margin of safety calculated from this exposure by using the NOEL of 0.2 mg/kg/day for teratogenicity (cleft palate) in the CF_1 mouse is as follows:

$$\text{MOS} = \frac{0.2 \text{ mg/kg/day}}{4.3 \times 10^{-5} \text{ mg/kg/day}}$$

$$\text{MOS} = \underline{4651}$$

Similar calculations were also performed for application to 100 acres/day.

Calculations were also made in a similar manner for other workers using the appropriate EAB exposure.

More detailed calculations are presented below:

Margin of Safety Calculations For Users of Abamectin on Citrus

Maternotoxicity	EAB Exposure Estimates (ug/gm a.i. handled)	Exposure Estimates (mg/kg/day)	Absorption Estimate* (mg/kg/day)	Abamectin NOEL Used (mg/kg/day	NOEL / Exposure	MOS
Mixer/Loaders						
50 Acres	0.53	0.0043	4.3×10^{-5}	0.05	$\frac{0.05}{4.3 \times 10^{-5}} =$	1163
100 Acres	0.53	0.0086	8.6×10^{-5}	0.05	$\frac{0.05}{8.6 \times 10^{-5}} =$	581
Sprayers (with gloves)						
50 Acres	0.54	0.0044	4.4×10^{-5}	0.05	$\frac{0.05}{4.4 \times 10^{-5}} =$	1136
100 Acres	0.54	0.0088	8.8×10^{-5}	0.05	$\frac{0.05}{8.8 \times 10^{-5}} =$	568
Sprayers (no gloves)						
50 Acres	0.88	0.0071	7.1×10^{-5}	0.05	$\frac{0.05}{7.1 \times 10^{-5}} =$	704
100 Acres	0.88	0.0143	1.43×10^{-4}	0.05	$\frac{0.05}{1.43 \times 10^{-4}} =$	350
Teratogenicity Mixer/Loaders						
50 Acres	0.53	0.0043	4.3×10^{-5}	0.2	$\frac{0.2}{4.3 \times 10^{-5}} =$	4651
100 Acres	0.53	0.0086	8.6×10^{-5}	0.2	$\frac{0.2}{8.6 \times 10^{-5}} =$	2326
Sprayers (with gloves)						
50 Acres	0.54	0.0044	4.4×10^{-5}	0.2	$\frac{0.2}{4.4 \times 10^{-5}} =$	4545
100 Acres	0.54	0.0088	8.8×10^{-5}	0.2	$\frac{0.2}{8.8 \times 10^{-5}} =$	2273
Sprayers (no gloves)						
50 Acres	0.88	0.0071	7.1×10^{-5}	0.2	$\frac{0.2}{7.1 \times 10^{-5}} =$	2817
100 Acres	0.88	0.0143	1.43×10^{-4}	0.2	$\frac{0.2}{1.43 \times 10^{-4}} =$	1399

*Assuming 1.0% dermal absorption (for all users)

Assume 50 acres & 100 acres/day
at 0.025 lbs a.i./acre =
have 1.25 & 2.5 lbs a.i./day

Shaughnessy #: 122804

Date out of EAB: 15 Jan 87

Signature: C Lamberty

To: C. LaRocca
Product Manager # 19
Registration Division (TS-767)

From: Joseph C. Reinert, Chief
Special Review Section
Exposure Assessment Branch
Hazard Evaluation Division (TS-769)

JCR

Attached please find the EAB review of:

Reg./File No.: 50658-EUP-1

Chemical: Avermectin

Type Product: Insecticide

Product Name: Abermectin MK 936

Company Name: Merck

Submission Purpose: Exposure Study

Date In: 23 October '86

Action Code: 701

Date Completed: 15 January 87

EAB # 70036

Monitoring Requested: X

TAIS (level II) Days

Monitoring Voluntarily Done ____

8

Deferrals To:

____ Ecological Effects Branch

____ Residue Chemistry Branch

____ Toxicology Branch

____ Benefits and Use Division

1.0 Introduction

Merck, Sharp, and Dohme have submitted an airblast applicator exposure study entitled "Field Studies Assessing Exposure of Workers Who Apply Abamectin (MK-936) 0.15 EC with Airblast Sprayers to Citrus Groves" in support of EPA Experimental Use Permit No. 50658-EUP-1. The study was conducted by Orius Associates, Inc. Abamectin is an insecticide/miticide containing avermectin, a macrocyclic lactone derived from Streptomcyes avermectilis. Merck is attempting to register Abamectin for control of pests of citrus and deciduous fruits and nuts at a maximum application rate of 0.025 lb ai/A. The application rate proposed for Abamectin is much lower than rates usually encountered in agricultural practices.

2.0 Methods and Materials

Abamectin 0.15 EC was applied by airblast sprayers at 0.025 lbs ai/A in two citrus groves in California. At each site two workers were monitored for one day. During the morning one individual mixed and loaded three tankfuls of Abamectin while the second individual sprayed the three tankfuls. In the afternoon the two individuals reversed roles for an additional three tankfuls of Abamectin. The total amount of Abamectin handled by each individual during the mixing/loading or spraying of the three tanks of spray was recorded. The method provided four mixer/loader and four applicator replicates.

Dermal exposure was measured by placing dosimeters on ten body locations. Dosimeters were placed on the back, chest, shoulder, forearms, thighs, and ankles. Each site had three sets of dosimeters; however, only one set of dosimeters was analyzed for Abamectin residue. These dosimeters consisted of an outer layer of 65/35 percent polyester/cotton chambray shirt material on the upper body, and 100 percent cotton denim material on the lower body. All dosimeters had an inner layer of chromatography paper. The dosimeters were placed in a waterproof vinyl frame with a 40 cm 2 window. Avermectin residues on the inner layer of the dosimeter represented residues penetrating the clothing to the skin.

Facial exposure was estimated by swabbing 20 cm2 areas on the forehead, cheeks, and throat. Each area was swabbed twice with distilled water and once with 10 percent isopropanol in distilled water. Hand exposure was measured by hand rinses. The first rinse was of the neoprene gloves worn by the workers. The workers wore the gloves during mixing/loading and application. A second rinse of the hands with distilled water and a third rinse with isopropanol were conducted after removal of the neoprene gloves.

Inhalation exposure was measured by placing an air sampler in the worker's breathing zone. An air pump drew 1.0 L/min through the sampler tube which contained 600 mg of charcoal.

In addition to the worker residue samples, field blank and avermectin fortified field samples were collected during each monitoring period. Recovery percentages for each of the sampling media were determined. The percentage of recovery ranged from 55 percent of expected value in the distilled water handwash to 75 percent on the chromatography paper. All residue values were adjusted for the percent recovery. The limit of sensitivity for the avermectin B_{1a} homolog of avermectin B was 1.0 ng/cm2 for the facial swabs and dosimeters, 0.5 ng/ml for the hand and glove rinses, and 0.5 ng/L for the personal air monitors.

3.0 EAB Calculation of Worker Exposure

For the purposes of calculating worker exposure, EAB assumed that the workers wore long pants and long-sleeve shirts. Hand exposure was calculated assuming the use of protective gloves during mixing/loading and with and without protective gloves during application.

The residues on the inside dosimeter were used to calculate exposure to the covered areas of the body. The residues per cm2 reported by Orius were multiplied by the surface area of the representative body part. The surface areas presented in Subdivision U of the Pesticide Assessment Guidelines were used. Upper arm exposure was calculated from the average residue per cm2 of the shoulder and forearm patches. The majority of the dosimeters had residues of avermectin that were below the level of sensitivity. For these samples 50 percent of the level of sensitivity was used to estimate exposure.

Exposure to the front of the neck was calculated from the laryngeal swabs. The forehead and cheek swabs were averaged to estimate facial exposure. Since three swabbings were taken for each area, EAB summed the residues of each swabbing until the swabbings contained residues below the level of sensitivity. For example, if the first swabbing contained detectable residues and the second and third swabbings did not, EAB totaled the residues from the first and second swabbings.

Exposure to hands protected by protective gloves was calculated from the residues of both hand rinses. Exposure to unprotected hands was calculated from the residues of both hand rinses and the residue from the glove rinses. Total dermal exposure was expressed as ug avermectin per gram of avermectin handled. Respiratory exposure was not calculated and was assumed to be insignificant because no air samples contained detectable residues of avermectin.

4.0 Results

Dermal exposure during the mixing and loading of avermectin is presented in Table 1. The exposures ranged from 0.29 ug/g ai handled to 1.0 ug/g ai handled. The 1.0 ug/g ai exposure received by mixer/loader #1 was twice the exposure received by mixer/loader #4 who received the next highest level of exposure (0.47 ug/g ai). This was due to increased exposure to the face as compared to the other three replicates. A review of the field notes did not indicate that anything unusual occurred to mixer/loader #1. The average exposure to the four mixer/loader replicates was 0.53 ug/g ai handled.

Dermal exposure during air blast application of avermectin is presented in Table 2. When the exposure was calculated assuming that the individuals would wear protective gloves, the exposure ranged from 0.38 to 0.97 ug/g ai sprayed with an average exposure of 0.54 ug/g ai/sprayed. The dermal exposure, calculated with the assumption that protective gloves are not worn, ranged from 0.43 to 2.0 ug/g ai sprayed with an average exposure of 0.88 ug/g ai sprayed.

5.0 Discussion

The dermal exposure to mixer/loaders and airblast applicators estimated from the data presented in the Merck report is a rough estimate and may be an overestimation of the dermal exposure received. This results from the level of avermectin residues on the inner portion of the dosimeters being less than the level of sensitivity. Of the four mixer/loader and four applicator replicates, only three areas of the body on Applicator #2 received residues above the level of detection. The value used for all other dosimeters was 50 percent of the level of sensitivity (1 ug/cm^2).

The level of avermectin residues on the dosimeters was generally below the level of sensitivity. Therefore, the slight variation in the calculated exposure to residues of avermectin found on the chest, back, forearms, upper arms, thighs, and calves of both the mixer/loaders and applicators resulted from differences in the surface area of the dosimeters analyzed for residues and not from variation in the quantity of avermectin residues. Because of this, EAB believes the standard deviations presented in the Merck report are not indications of variations in exposure expected to occur.

6.0 Conclusions

Based on the data presented in the Merck report, exposure to mixer/loaders wearing long-sleeve shirts, long pants, and protective gloves and open pouring Abamectin is 0.53 ug/g ai.

0.053 ug/g a.i. x 2.5 lbs a.i./lb x 454 g/lb ÷ 70 kg

4 1

The exposure to airblast applicators wearing similar clothing is 0.54 ug/g ai. If protective gloves are not worn during application the exposure is estimated to be 0.88 ug/g ai. The exposure estimates represent the quantity of avermectin impinging on the skin and have not been adjusted for the dermal absorption of avermectin.

This exposure study is interesting because of the unusually low application rate. EAB has developed a linear regression equation to predict airblast applicator exposure. The equation, $y = 4.8x + 16$, where y is exposure in mg/hr and x is the application rate in lbs a.i./acre, is derived from several thousand data points, the majority of which were based on application rates between 1 and 7 lbs a.i./acre. Based on the study application rate of 0.025 lbs a.i./acre, the equation would predict an exposure of 16.1 mg/hr. The study report calculated an exposure of 0.343 ug/min or 21 ug/hr. The predicted exposure is approximately three orders or magnitude greater than the measured exposure. This result is not suprising and suggests that the exposure equation is not linear throughout the entire range. We note however that it is an inherent property of linear regressions that the confidence limits expand toward infinity at the extremes of the range of the independent variable. This is true regardless of which region of the range most data points were collected.

Curt Lunchick

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

12 January 87

Table 1. Dermal Exposure to Mixer/Loaders

Body Area	Surface Area (cm^2)	Dermal Exposure (ug) #1	#2	#3	#4
Chest	3550	2.1	2.0	2.1	2.1
Back	3550	2.1	2.0	2.0	2.0
Forearms	1210	0.78	0.64	0.68	0.68
Upper arms	2910	1.9	1.6	1.7	1.6
Thighs	3820	2.3	2.3	2.1	2.5
Calves	2380	1.5	1.5	1.4	1.6
Hands	820	2.7	1.2	1.2	1.2
Face	650	22	0.52	1.6	3.8
Front of neck	150	0.12	0.12	0.47	0.44
Total Exposure (ug)		35.5	11.9	13.3	15.9
Grams ai Handled		34	34	45	34
Exposure (ug/g ai)		1.0	0.35	0.29	0.47

Table 2 . Dermal Exposure to Airblast Applicators

Body Area	Surface Area (cm^2)	Dermal Exposure (ug) #1	#2	#3	#4
Chest	3550	2.1	2.2	2.0	2.0
Back	3550	2.1	2.0	2.0	1.9
Forearms	1210	0.76	2.5	0.68	0.66
Upper arms	2910	1.9	10.3	1.7	1.6
Thighs	3820	2.6	5.5	2.6	2.6
Calves	2380	1.5	1.4	1.5	1.5
Hands (No gloves)	820	8.4	35	2.9	2.8
Hands (Gloves)	820	1.2	1.2	1.2	1.2
Face	650	0.83	7.7	3.7	1.3
Front of neck	150	0.12	0.12	0.44	0.12
A. Exposure Without Protective Gloves					
Total (ug)		20	67	18	14
Grams ai Sprayed		34	34	36	34
Exposure (ug/g ai)		0.60	2.0	0.49	0.43
B. Exposure With Protective Gloves					
Total (ug)		13	33	16	13
Grams ai Sprayed		34	34	36	34
Exposure (ug/g ai)		0.38	0.97	0.44	0.38

REVIEW OF STUDIES

HED REVIEWER CHECK SHEET

EPA ID NUMBER: 50658-EUP-1
(noted on bean sheet)

REGISTRATION STANDARD REVIEW SUBMISSION CRITERIA (Policy Note #31):
(the correct category is noted on the bean sheet)

___ 1. data which meet 6(a)(2) or meet 3(c)2(B) flagging criteria

___ 2. data of particular concern

___ 3. data necessary to determine tiered testing requirements

RESULTS OF HED REVIEW (Check the most appropriate box)

___ 1. Special Review trigger hit

X 2. Study acceptable/review complete/no Special Review trigger

___ 3. Next tiered study required to complete review

___ 4. Additional data required to complete review

___ 5. Inadequate Study

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM March 27, 1987

SUBJECT: Avermectin B_1, Dermal Absorption

TO: Edwin Budd, Head
Review Section II
Toxicology Branch

FROM: Robert P. Zendzian PhD
Pharmacologist
Mission Support Staff
Toxicology Branch
HED (TS-769)

Based on the data submitted by the Registrant, Merk, one may reasonably conclude that the maximum dermal absorption of Avermection B_1 is one percent of the applied dose.

A meeting was held in Dr. Farber's office on March 27, 1987 at 9:00 A.M. with representatives of Mecck Sharp & Dohme concerning the dermal absorption of Avermectin B_1. The Registrant presented information on the dermal absorption, physical properties, metabolism and relative acute oral/dermal toxicity of Avermection B_1 (copy attached). The Registrant concluded that this information justified accepting a value of one percent as the maximum of Avermectin B_1. I agree with this conclusion.

Avermectin toxicology review

Page _____ is not included in this copy.

Pages 13 (2) through 35 (24) are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

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