



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

APR - 6 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCESMEMORANDUM

SUBJECT: Avermectin B₁ (Also Called Abamectin) - Agrimec
0.15EC - EPA File Symbol 618-OI - PP#7F3500 -
Abamectin in/on Cottonseed - Registration and
Tolerance Request

Caswell No.: 63AB

FROM: William Dykstra, Reviewer
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C) *William Dykstra 4/6/89*

TO: George T. LaRocca, PM 15
Insecticide-Rodenticide Branch
Registration Division (H7505C)

THRU: Edwin R. Budd, Section Head
Review Section I,
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C) *Budd 4/6/89*

Requested Actions

Applicant: Merck Sharp & Dohme

1. Review request to register the formulated product Agrimec 0.15EC, containing 2.0% avermectin B₁ (abamectin), for use on cotton.
2. Review request to establish permanent tolerance for avermectin B₁ and its delta-8,9-isomer in/on cottonseed. It should be noted that permanent tolerances for this chemical have not been previously established.

Conclusions and Recommendations

1. Toxicology Branch I (TB-I) has no objection to registration of Agrimec 0.15EC for use on cotton provided that the label changes discussed below in Item 1 (under Comments) are made.
2. TB-I has no objection to establishment of the requested permanent tolerance in/on cottonseed. The requested tolerance is toxicologically supported. An "8-Point Memorandum" is attached.

Comments

Registration of Agrimec 0.15EC

1. Regarding the proposed label submitted in this package for Agrimec 0.15EC for use on cotton, TB-I understands that the applicant intends to use identical human hazard signal words, precautionary statements, and statements of practical treatment on the labels of all abamectin 0.15EC products intended for use on citrus, cotton, [REDACTED]

[REDACTED] TB-I has no objection to this. A recently submitted eye irritation study, however, has necessitated a change in the human hazard signal word and precautionary statements that should be incorporated into the labels of all three abamectin 0.15EC products. See the TB-I review by William Dykstra dated March 15, 1989. A copy of a representative label with these changes already made is attached to this memorandum. It should also be noted that a further change in the label should be made since it is not necessary to require mixer/loaders to wear a pesticide respirator. The two words "pesticide respirator" should be deleted from the precautionary statements on all three labels (as was done on the attached label). The remainder of the label, with respect to toxicological considerations, is acceptable to TB-I and with the changes indicated above may be used on all three abamectin 0.15EC formulated products.

2. Toxicity data previously submitted for this chemical have established maternotoxic and teratogenic effects in CF-1 mice as being the most sensitive endpoints for toxic effects. Margins of safety (MOS) for these endpoints have previously been calculated for workers involved in the air-blast application of

Agrimec 0.15EC to citrus. These MOS are presented below (quoted from TB review by William Dykstra, dated April 23, 1987, regarding the experimental use permit [EUP] and temporary tolerances for abamectin on citrus).

"Margins of Safety (MOS), based on exposure data from Exposure Assessment Branch for persons wearing long pants, long-sleeved shirts, gloves, and no gloves¹, and utilizing TB conclusions regarding dermal absorption in the monkey, yielded the following values:

<u>Maternotoxicity</u>	<u>Abamectin (CF₁ Mouse)</u> <u>NOEL = 0.05 mg/kg/day</u>	<u>Endpoint is</u> <u>Lethality</u>
<u>Mixer/Loaders (With Gloves)</u>		<u>MOS</u>
50 Acres		1163
100 Acres		581
<u>Sprayers (With Gloves)</u>		<u>MOS</u>
50 Acres		1136
100 Acres		568
<u>Sprayers (No Gloves)¹</u>		<u>MOS</u>
50 Acres		704
100 Acres		350
<u>Teratogenicity</u>	<u>Abamectin (CF₁ Mouse)</u> <u>NOEL = 0.2 mg/kg/day</u>	<u>Endpoint is</u> <u>Cleft Palate</u>
<u>Mixer/Loaders (With Gloves)</u>		<u>MOS</u>
50 Acres		4651
100 Acres		2326
<u>Sprayers (With Gloves)</u>		<u>MOS</u>
50 Acres		4545
100 Acres		2273
<u>Sprayers (No Gloves)¹</u>		<u>MOS</u>
50 Acres		2817
100 Acres		1399"

¹The proposed label requires mixer/loaders and sprayers to wear rubber gloves.

Establishment of Tolerance in/on Cottonseed - In a memorandum dated March 29, 1989 from C. Lunchick to W. Dykstra, the Science Analysis and Coordination Branch concluded that the MOS for maternotoxicity and teratogenicity for cotton crop workers would be greater than 100 (memorandum attached).

3. The petitioner requests amending 40 CFR Part 180 pursuant to section 408 of the Federal Food, Drug, and Cosmetic Act by proposing a permanent tolerance of 0.005 ppm (limit of reliable quantitative measurement) for avermectin B₁ and its delta-8,9-isomer in or on the raw agricultural commodity cottonseed.
4. The delta-8,9-isomer of abamectin, which possesses abamectin-like toxicological activity, is a plant photodegradate that can range between 5 and 10 percent of the residue on cotton. Since the delta-8,9-isomer is a plant photodegradate, and does not occur in animal metabolism studies, the toxic potential of this degradate has been evaluated in a separate series of toxicity studies, including those indicated in point 1 of the "8-Point Memorandum" (see below). Like abamectin, the most sensitive toxic endpoints for the delta-8,9-isomer are also maternotoxicity (NOEL = 0.10 mg/kg/day) and teratogenicity (NOEL = 0.06 mg/kg/day) in CF-1 mice.
5. In addition to abamectin and its delta-8,9-isomer, the so-called "polar degradates" of abamectin constitute a large percentage (up to 70%) of the total residue on cotton. It has been determined, however, that these "polar degradates" do not possess abamectin-like toxicological activity, and for this reason need not be included in the tolerance expression for residues in/on cotton. Selected toxicity studies performed on these "polar degradates" are also listed in point 1 of the "8-Point Memorandum" (see below).
6. Calculation of the Acceptable Daily Intake (ADI)

The ADI is based on the NOEL of 0.12 mg/kg/day in the 2-generation rat reproduction study. A 300-fold safety factor was used to calculate the ADI. At the LEL of 0.40 mg/kg/day in the study, effects included increased retinal folds in the weanlings, increased dead pups at birth, decreased viability indices, decreased lactation indices, and decreased pup body weight.

$$ADI = \frac{NOEL}{SF}$$

$$ADI = \frac{0.12 \text{ mg/kg/day}}{300}$$

$$ADI = 0.0004 \text{ mg/kg/day.}$$

The ADI was verified by the HED RfD/ADI Committee on March 30, 1989.

7. The effect of the proposed tolerance on the percent ADI utilized will be provided by a TAS analysis. Additionally, MOS resulting from dietary exposure to cottonseed residues for maternotoxicity, based on the NOEL of 0.05 mg/kg/day for abamectin, and for teratogenicity, based on the NOEL of 0.06 mg/kg/day for the delta-8,9-isomer, will be calculated by an acute menu screen analysis and submitted in a separate document (from the Science Analysis and Coordination Branch) to the Registration Division.

Attachments

"8-Point Memorandum"

1. The data considered in setting the tolerances included the following:

a. Toxicity Studies on Technical Grade Abamectin

- | | |
|---|---|
| o Rat Acute Oral LD ₅₀ | 10.6 mg/kg (males);
11.3 mg/kg (females) |
| o 14-Week Oral Rat Study | NOEL $\geq$ 0.4 mg/kg/day
(HDT) |
| o 18-Week Oral Dog Study | NOEL = 0.25 mg/kg/day |
| o Rat Teratology Study | Negative for terata up
to 1.6 mg/kg/day (HDT) |
| o Rabbit Teratology
Study | Negative for terata up
to 2.0 mg/kg/day (HDT) |
| o Mouse Teratology Studies | Teratogenic LEL = 0.4
mg/kg/day (cleft palate);
Teratogenic NOEL = 0.2
mg/kg/day |
| o Mouse Maternotoxicity
Studies | LEL = 0.075 mg/kg/day
(lethality); NOEL =
0.05 mg/kg/day |
| o 2-Generation Rat
Reproduction Study | NOEL = 0.12 mg/kg/day;
LEL = 0.40 mg/kg/day
(increased retinal folds
in weanlings, increased
dead pups at birth,
decreased viability
indices, decreased
lactation indices,
decreased pup body
weights) |
| o 1-Year Oral Dog Study | NOEL = 0.25 mg/kg/day;
LEL = 0.50 mg/kg/day
(mydriasis in males and
females) |
| o 94-Week Chronic
Toxicity/Oncogenicity
Study in Mice | Oncogenic potential:
Negative up to 8 mg/kg/day
(HDT); Systemic NOEL =
4 mg/kg/day; Systemic
LEL = 8 mg/kg/day |

- (Dermatitis in males, extramedullary hematopoiesis in the spleen in males, increased mortality in males, tremors and body weight loss in females)
- o 2-Year Chronic Toxicity/Oncogenicity Study in Rats

Oncogenic potential: Negative up to 2.0 mg/kg/day (HDT); Systemic NOEL = 1.5 mg/kg/day; Systemic LEL = 2.0 mg/kg/day (tremors in both sexes)
 - o Rat Metabolism Study
 - o Ames Mutagenicity Assay

Negative
 - o Mutagenicity Assay for Chromosomal Aberrations in vitro in Chinese Hamster Ovary Cells

Negative
 - o Mammalian Cell Mutagenic Assay

Negative for V-79 cells
 - o Rat Hepatocyte Mutagenicity Study

Under conditions of the study, abamectin (0.3 and 0.6 mM) caused an introduction of single strand DNA breaks in rat hepatocytes in vitro; no effect was observed when the assay was carried out on hepatocytes from rats dosed in vivo at the LD₅₀ dose level (10.6 mg/kg)
 - o In Vivo Bone Marrow Mutagenicity Cytogenic Study

Negative in male mice at doses of 1.2 and 12.0 mg/kg
- b. Toxicity Studies on the Delta-8,9-Isomer of Abamectin
- o Mouse Acute Oral LD₅₀

> 80 mg/kg (HDT) (males and females)
 - o Rat Teratology Study

Negative for terata up to 1.0 mg/kg/day (HDT)

- o Mouse Teratology Studies Teratogenic LEL = 0.10 mg/kg/day (cleft palate);
Teratogenic NOEL = 0.06 mg/kg/day
 - o Mouse Maternotoxicity Studies LEL = 0.50 mg/kg/day (lethality); NOEL = 0.10 mg/kg/day
 - o 1-Generation Rat Reproduction Study NOEL = 0.4 mg/kg/day (HDT)
 - o Ames Mutagenicity Assay Negative
- c. Toxicity Studies on the "Polar Degradates" of Abamectin
- o Mouse Acute Oral LD₅₀ > 5000 mg/kg (HDT)
 - o Mouse Teratology Study Negative for terata up to 1.0 mg/kg/day (HDT)
 - o Mouse Teratology Study (polar degradates derived from citrus-treated fruit) Negative for terata up to 1.0 mg/kg/day (HDT)
 - o Ames Mutagenicity Assay Negative

2. Data considered desirable but currently lacking: None
3. N/A
4. No permanent tolerances have been previously established for abamectin.
5. The percent ADI utilized and TMRC will be provided by a TAS analysis.
6. The ADI is based on the NOEL of 0.12 mg/kg/day in the 2-generation rat reproduction study. A 300-fold safety factor was used to calculate the ADI. At the LEL of 0.40 mg/kg/day in the study, effects included increased retinal folds in the weanlings, increased dead pups at birth, decreased viability indices, decreased lactation indices, and decreased pup body weight.

$$ADI = \frac{NOEL}{SF}$$

$$ADI = \frac{0.12 \text{ mg/kg/day}}{300}$$

$$ADI = 0.0004 \text{ mg/kg/day}$$

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7. There are no regulatory actions pending against the pesticide.
8. There are no other relevant considerations in setting the tolerance.

Avermectin toxicology review

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Pages 10 through 13 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
 - ☐ FIFRA registration data
 - ☐ The document is a duplicate of page(s) _____
 - ☐ The document is not responsive to the request
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

MAR 29 1989

SUBJECT: Exposure Assessment for Workers Exposed to Avermectin B1
Applied to Cotton, Celery, and Tomatoes

TO: William Dykstra
Review Section 1
Toxicology Branch 1 (IRS)
Health Effects Division (H7509C)

FROM: Curt Lunchick *Curt Lunchick*
Registration Standards and Special Review Section
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

The exposure to workers exposed to Avermectin B1 applied to cotton, celery, and tomatoes is expected to be less than that of citrus workers. Exposure during mixing/loading would be roughly twice as high for these crops than for citrus based on acreage differences. However this increase would be more than offset by the reduced exposure during application since airblast application produces significantly higher exposures than ground boom application, as would occur with these crops. In addition, the citrus exposures were predominately based on 50% of the detection limit since the residues of Avermectin B1 were mostly nondetectable. Daily harvester exposure on a given crop is less than the daily mixer/loader/applicator exposure. Since citrus gave MOS's of 350 and 4650 for maternal lethality and teratogenicity respectively, use of Avermectin B1 would yield MOS's in excess of 100.