CASWELL FILE

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

APR - 5 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Avermectin B_1 (Also Called Abamectin) - Agrimec 0.15EC - EPA File Symbol 618-OI - PP#8F3592/8H5550 - Abamectin in/on Citrus - Registration and Tolerance Request

Caswell No.: 63AB
Project No.: 8-0396
Record Nos.: 210590, 210591

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THRU: Edwin R. Budd, Section Head
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Applicant: Merck Sharpe & Dohme

Requested Actions

1. Review request to register the formulated product Agrimec 0.15EC, containing 2.0% avermectin B_1 (abamectin), for use on citrus.

2. Review request to establish permanent tolerances for avermectin B_1 and its delta-8,9-isomer in/on citrus and related commodities. It should be noted that permanent tolerances for this chemical have not been previously established.

1

Conclusions and Recommendations

1. Toxicology Branch (TB-I) has no objection to registration of Agrimec 0.15EC for use on citrus 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 tolerances in/on citrus and related commodities. The requested tolerances are 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 citrus, 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] 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 the chemical have established maternotoxic and teratogenic effects in CF-1 mice as being the most sensitive end-points for toxic effects. Margins of Safety (MOS) for these end-points 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 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 gloves[1], and utilizing TB conclusions regarding dermal absorption in the monkey, yielded the following values.

Maternotoxicity	Abamectin (CF_1 Mouse) NOEL = 0.05 mg/kg/day	Endpoint is Lethality
Mixer/Loaders (With Gloves)		MOS
50 Acres		1163
100 Acres		581
Sprayers (With Gloves)		MOS
50 Acres		1136
100 Acres		568
Sprayers (No Gloves)[1]		MOS
50 Acres		704
100 Acres		350

Teratogenicity	Abamectin (CF_1 Mouse) NOEL = 0.2 mg/kg/day	Endpoint is Cleft Palate
Mixer/loaders (With Gloves)		MOS
50 Acres		4651
100 Acres		2326
Sprayers (With Gloves)		MOS
50 Acres		4545
100 Acres		2273

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

3

Sprayers (No Gloves)[1]	MOS
50 Acres	2817
100 Acres	1399

[End of quotation.]

Establishment of Tolerances on Citrus and Related Products

3. The petitioner requests amending 40 CFR Part 180 pursuant to section 408(j) of the Federal Food, Drug, and Cosmetic Act (FFDCA) by proposing the following permanent tolerances of abamectin including its delta-8,9-isomer:

Commodities	Tolerance
Citrus whole fruit (RAC)	0.005 ppm
Cattle - meat, fat, and meat byproducts	0.01 ppm *
- milk	0.001 ppm

The petitioner also requests to amend 21 CFR pursuant to FFDCA section 409 by proposing the following permanent food and/or animal feed additive tolerances for the combined residues of abamectin and its delta-8,9-isomer:

Dried citrus pulp	0.10 ppm *
Citrus oil	0.10 ppm

4. The delta-8,9-isomer of abamectin, which possesses abamectin-like toxicological activity, is a plant photodegradate that can range between 22 and 42 percent of the residue on citrus. Since the delta-8,9-isomer is a plant photodegradate, and does not occur in animal metabolism studies, the toxic potential of the degradate has been evaluated in a separate series of toxicity studies, including those indicated in point 1 of the "8-Point Memorandum" (see attachment). Like abamectin, the most sensitive toxic end points 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

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

* change recommended by DEB.

4

constitute a large percentage (54 to 84%) of the total residue on citrus. 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 citrus and related products. Selected toxicity studies performed on these "polar degradates" are also listed in point 1 of the "8-point memorandum" (see attachment).

6. The MOS for maternotoxicity and for teratogenicity resulting from dietary exposure to citrus residues have previously been calculated. These MOS are presented below (quoted from TB review by William Dykstra, dated April 23, 1987, regarding the EUP and temporary tolerances for abamectin on citrus):

"The TAS menu screen analysis [for the use of abamectin on citrus] determined that the highest predicted dietary exposure of females 13 years of age and older would be 0.00005 mg/kg/day.

The NOEL for maternotoxicity (lethality) used was 0.05 mg/kg/day (based on abamectin data).

The MOS for this end-point is as follows:

$$MOS = \frac{0.05 \text{ mg/kg/day}}{0.00005 \text{ mg/kg/day}}$$

$$MOS = \underline{1000}$$

The NOEL for terata (cleft palate) used was 0.06 mg/kg/day (based on the delta-8,9-isomer data).

The MOS for this end-point is as follows:

$$MOS = \frac{0.06 \text{ mg/kg/day}}{0.00005 \text{ mg/kg/day}}$$

$$MOS = \underline{1200}$$ "

[End of quotation.]

7. 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.

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

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

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

8. The effect of the proposed tolerances on the percent ADI utilized will be provided by a TAS analysis.

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 (mydrasis 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 LD_{50} dose level (10.6 mg/kg)

o In Vivo Bone Marrow Mutagenicity Cytogenetic 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 LD_{50}	> 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 LD_{50}	> 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 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.

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

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

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

7. There are no regulatory actions pending against the pesticide.

8. There are no other relevant considerations in setting the tolerance.

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R:56518:Dykstra:C.Disk:KENCO:03/27/89:de:jh:rw

Avermectin toxicology review

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