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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Avermectin - 88-FL-05 - Section 18 Request to Use
Avermectin on Tomatoes for "Fresh Market Only"

Caswell No.: 63AB
Project No.: 8-0468
Record No.: 214108

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

William Dykstra
3/17/88

TO: Don Stubbs, PM Team 41
Registration Support and
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Registration Division (TS-767C)

THRU: Edwin Budd, Section Head
Review Section II, Toxicology Branch
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Budd
3/18/88
L. Grosso
3/18/88

The Florida Department of Agriculture and Consumer Services requests a section 18 specific exemption for the use of avermectin to control leafminers on tomatoes grown for the fresh market only. It is anticipated that 53,550 acres of tomatoes in Florida could be treated. Under the proposed labeling a total of 10 applications would be made during a growing season. This would result in a total of 10,710 pounds of active ingredient (avermectin) needed under this exemption if the maximum number of applications were necessary.

The formulation to be used is Agrimec 0.15 EC. Inerts are cleared under §180.10001. In a telephone conversation on March 7, 1988 with L. Grosso of Merck, Dr. Grosso stated that

No permanent tolerances have been established for avermectin. Temporary tolerances and experimental use permit (EUP) programs are currently in effect for citrus and cotton.

COMMERCIAL/FINANCIAL INFORMATION IS NOT INCLUDED

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The label for the section 18 for tomatoes and the label for the EUP programs are essentially identical with respect to signal word, precautionary labeling, and statement of practical treatment. The EUP citrus label has been reviewed in the memorandum of April 23, 1987 from W. Dykstra to G. LaRocca (attached). The precautionary labeling for the use of a pesticide respirator and goggles can be deleted from the section 18 label for tomatoes.

In the memorandum of April 23, 1987, the margins of safety (MOS) for mixer/loaders and sprayers (both with and without gloves) range from 350 to 1163 when maternolethality is the endpoint and from 1399 to 4651 when cleft-palate (a developmental effect) is the endpoint. Based on a verbal communication on March 3, 1988 with D. Jaquith of the Exposure Assessment Branch (EAB), exposure to mixer/loaders and sprayers (applicators) from the section 18 tomato use is expected to be less than for citrus. Therefore, the MOS for mixer/loaders and applicators for the section 18 tomato use will be greater than for citrus.

In a telephone conversation on March 7, 1988 with Dr. J. Adams of EAB, Dr. Adams considered that exposure to pickers from tomato harvest would be less than exposure to pickers from citrus harvest.

Pivotal toxicity data which were available in support of the temporary tolerances and EUP programs are listed below:

- o Rat Acute Oral LD₅₀: 10.6 mg/kg (males); 11.3 mg/kg (females).
- o Dermal Sensitization in Guinea Pig (Abamectin): negative for skin sensitization.
- 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 1-Year Dog Study: NOEL = 0.25 mg/kg/day.
- o Rat Teratology Study (Abamectin): negative for terata up to 1.6 mg/kg/day (HDT).
- o Rabbit Teratology Study (Abamectin): negative for terata up to 2.0 mg/kg/day (HDT).
- o Mouse Teratology Study (Abamectin): teratogenic LEL = 0.4 mg/kg/day (cleft-palate); teratogenic NOEL = 0.2 mg/kg/day.

- o Mouse Teratology Study (delta-8,9-isomer):
teratogenic LEL = 0.10 mg/kg/day (cleft-palate);
teratogenic NOEL = 0.06 mg/kg/day.
- o Mouse Maternotoxicity Study (Abamectin): LEL =
0.075 mg/kg/day (lethality); NOEL = 0.05 mg/kg/day.
- o Two-Generation Rat Reproduction Study: NOEL = 0.12
mg/kg/day.
- o Rat Metabolism Study.
- o Ames Mutagenicity Assay (Abamectin): negative.
- o Mutagenicity Assay for Chromosomal Aberrations In Vitro
in Chinese Hamster Ovary Cells: negative.
- o Mammalian Cell Mutagenic Assay (Abamectin): negative
for V-79 cells.
- o Rat Hepatocyte Mutagenicity Study (Abamectin): under
conditions of the study, abamectin (0.3 and 0.6 mM)
caused an induction of single strand DNA breaks in
rat hepatocytes in vitro; no effect was observed when
the assay was carried out on hepatocytes from rats
doses in vivo at the LD₅₀ 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.

An oncogenic mouse study and a 2-year feeding/oncogenic rat study are currently under review. Additionally, toxicology studies with the delta-8,9-isomer and polar degradates of avermectin are required before permanent tolerances can be established (see memorandum of April 23, 1987, W. Dykstra).

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

$$\text{PADI} = \frac{\text{NOEL}}{\text{SF}}$$

$$\text{PADI} = \frac{0.12 \text{ mg/kg/day}}{1000}$$

$$\text{PADI} = 0.00012 \text{ mg/kg/day}$$

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The previous temporary tolerances on citrus utilized 32 percent of the PADI for the U.S. population average based on TAS analysis (see attached memorandum from Dr. Stephen Saunders to G. LaRocca, dated March 10, 1987).

Additionally a TAS Menu Screen Analysis determined that a MOS of 1200 was present for the developmental toxicity (cleft-palate) endpoint for females 13 years of age and older (S. Saunders, memorandum of March 10, 1987).

A new TAS analysis for dietary exposure and TAS Menu Screen Analysis for the section 18 for tomatoes will be provided by the Residue Chemistry Branch (RCB) (verbal communication on March 7, 1988 with S. Stanton of RCB).

The registrant of avermectin, Merck, has also provided a risk assessment for the section 18 use for tomatoes.

It should be noted that the registrant's risk assessment states that 0.85 percent of the ADI would be utilized by the U.S. general population. However, the registrant's ADI is based on the NOEL of 0.25 mg/kg/day in the 1-year dog study and utilizes a hundredfold safety factor. The Toxicology Branch PADI is based on the NOEL of 0.12 mg/kg/day in the two-generation rat reproduction study and utilizes a thousandfold safety factor. Therefore, the percent PADI utilized by RCB's TAS analysis should be greater than the registrant's percent ADI utilized.

The registrant has also provided MOS's for females of 13 years of age or older using the TAS Menu Screen Analysis and the appropriate NOELs. MOS's of 909 for teratogenicity and 758 for maternolethality were calculated by the registrant.

These MOS calculations will also be provided by RCB.

Conclusions and Recommendations

The MOS's for mixer/loaders, sprayers, and pickers in the section 18 for tomatoes are expected to be greater than the MOS for citrus workers.

Additionally, if RCB can conclude that the MOS for cleft-palate (developmental effect) and maternolethality exceed 100, and the percent PADI utilized is less than 100, the section 18 can be toxicologically supported.

Attachments

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Avermectin toxicology review

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Pages 5 through 8 are not included in this copy.

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- Identity of product inert ingredients
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