United States Environmental Protection Agency

Office of Pesticides and Toxic Substances (H7501C)

540/FS-89-055

EPA

Pesticide Fact Sheet

Name of Chemical: Avermectin B_1

Reason for Issuance: Update - First Food Use (Cotton)

Date Issued: May 1989

Fact Sheet Number: 89.1

1. Description of Chemical

Generic Name: Avermectin B_1 [A mixture of avermectins containing $\geq$ 80% avermectin B_{1a} (5-O-dimethyl avermectin A_{1a}) and $\leq$ 20% avermectin B_{1b} (5-O-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl) avermectin A_{1a})]

Common Name: None assigned

Trade Names: Affirm®, Agrimec®, Avid®, MK-936, Zephyr®

Other Name: Abamectin

EPA Shaughnessy Code: 0122804

Chemical Abstracts Service (CAS) Numbers: 65195-55-3 and 65195-56-4

Year of Initial Registration: 1986

Pesticide Type: Insecticide/Miticide

Chemical Family: Avermectins (macrocylic lactones isolated from soil organism Streptomyces avermitilis).

U.S. Producers: Merck and Co., Inc.

2. Use Patterns and Formulations

Application Sites: Control of imported fire ants on turf, lawns, and other non-crop areas; control of mites and other insects on shadehouse, greenhouse, and field-grown flowers, foliage plants, and other ornamentals, and on cotton.

Type of Formulations: 0.011% insecticide bait, 2.0% Spray (0.15% EC), 70% technical.

Method of Application: Bait broadcast (ground or air application) and individual mound to mound treatment (fire ants). Foliar spray (ground application) mixed with water for use on field grown flowers, foliage plants and ornamentals. Foliar spray (ground or air application) mixed with water for use on cotton.

Rates of Application: For Fire Ants - Use rate is 50mg active ingredient (ai) per acre (1 pound (lb) product/acre); For Field Grown Flowers ands Ornamentals - Use rate is 0.005 to 0.01 lb ai/acre (4 to 8 oz product/acre); For Cotton - Use rate is 0.01 to 0.02 lb ai/acre (8 to 16 oz product/acre) and 3 applications per season.

Usual Carriers: Pregelled defatted corn grit carrier and water.

3. Science Findings

Summary Science Statement

Technical avermectin exhibits high mammalian acute toxicity. It is not considered to be mutagenic and does not sensitize skin. It is not readily absorbed by mammals and the majority of the residue is excreted in the feces within 2 days. The 24-month rat chronic feeding /oncogenicity study and 94-week mouse chronic toxicity oncogenicity study were negative for oncogenic potential. The results of a series of developmental toxicity studies (rat, rabbit, mouse) have been evaluated and showed that avermectin B_1 produces developmental toxicity (cleft palate) in the CF_1 mouse. Toxicology data were also evaluated for the delta-8,9-isomer of avermectin B_1 which is a plant photodegradate that can range between 5 and 20 percent of the residue on/in cottonseed. This isomer possesses avermectinlike toxicological activity. It was concluded that the delta 8,9-isomer also produces developmental toxicity (cleft palate) in mice, but not in rats.

In addition to avermectin and its delta 8,9-isomer, toxicology data were also evaluated for the "polar degradates" of avermectin, which constitute a large percentage (up to 70%) of the total residue on cottonseed. Review of the toxicology data indicated that these polar degradates do not possess avermectin-like toxicological activity and for this reason need not be included in the tolerance expression for residues in/on cottonseed.

Sufficient data are available to characterize avermectin from an environmental fate and ecological standpoint. Avermectin is extremely toxic to mammals and aquatic invertebrates and highly toxic to fish and bees. Avermectin is relatively non-toxic to birds. Based upon terrestrial residue analysis, aquatic run-off modeling and cluster analysis it appears that certain endangered species may be impacted by the use of avermectin on cotton. EPA and the Fish and Wildlife Service are in the process of updating the

cotton cluster. The results when available will be applicable to the registration of avermectin on cotton.

Avermectin undergoes rapid photolysis, is readily degraded by soil microorganisms and, due to its binding properites and low water solubility, is expected to exhibit little or no potential for leaching; however, a complete assessment cannot be made until additional leaching and soil dissipation data are submitted.

Chemical Characteristics (Technical Grade):

Physical State: Crystalline powder
Color: Yellowish-white
Odor: Odorless
Melting Point: 155 - 157 °C
Vapor Pressure: Being tested, expected to be extremely low
Density: 1.16 $\pm$ 0.05 at 21 °C
Solubility: Insoluble in water ($\leq$ 5 ug/mL), readily soluble in organic solvents
pH: NA. The avermectin molecule has neither acidic nor basic functional groups
Octanol/Water Partition Coefficient: 9.9×10^3

Toxicological Characteristics:

Technical Grade Avermectin B_1

- Dermal Sensitization: Negative for skin sensitization
- Acute Oral LD_{50} - Rat: 10.6 mg/kg (males), 11.3 mg/kg (females)
- 14-Week Oral Study - Rat: NOEL $\geq$ 0.4 mg/kg/day (HDT)
- 18-Week Oral Study - Dog: NOEL = 0.25 mg/kg/day
- Teratology Study - Rat: Negative for terata up to 1.0 mg/kg/day.
- Teratology Study - Rabbit: Negative for terata up to 1.0 mg/kg/day.
- Teratology Studies - Mouse: Teratogenic LEL = 0.4 mg/kg/day (cleft palate); Teratogenic NOEL =

- Maternotoxicity Studies - Mouse: LEL = 0.075 mg/kg/day (lethality); NOEL = 0.05 mg/kg/day

- 2-Generation Reproduction Study - Rat: 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)

- 1-Year Oral Study - Dog: NOEL = 0.25 mg/kg/day; LEL = 0.50 mg/kg/ day (mydriasis in males and females)

- 94-Week Chronic Toxicity/Oncogenicity Study - 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)

- 2-Year Chronic Toxicity/Oncogenicity Study - 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)

- Metabolism Study - Rat: The metabolic T 1/2 in rats is 1.2 days

- Ames Mutagenicity Assay: Negative

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

- Rat Hepatocyte Mutagenicity Study: 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 dosed *in vivo* at the LD_{50} dose level (10.6 mg/kg)

- *In Vivo* Bone Marrow Mutagenicity Cytogenic Study: Negative in male mice at doses of 1.2 and 12.0 mg/kg

Toxicity Studies on the Delta-8,9-Isomer of Avermectin

- Acute Oral LD_{50} - Mouse: > 80 mg/kg (HDT) (males and females)
- Teratology Study - Rat: Negative for terata up to 1.0 mg/kg/day (HDT)
- Teratology Studies - Mouse: Teratogenic LEL = 0.10 mg/kg/day (cleft palate); Teratogenic NOEL = 0.06 mg/kg/day
- Maternotoxicity Studies - Mouse: LEL = 0.50 mg/kg/day (lethality); NOEL = 0.10 mg/kg/day
- 1-Generation Reproduction Study - Rat: NOEL = 0.4 mg/kg/day (HDT)
- Ames Mutagenicity Assay: Negative

Toxicity Studies on the "Polar Degradates" of Avermectin

- Acute Oral LD_{50} - Mouse: > 5000 mg/kg (HDT)
- Teratology Study - Mouse: Negative for terata up to 1.0 mg/kg/day (HDT)
- Teratology Study (polar degradates derived from citrus-treated fruit) - Mouse: Negative for terata up to 1.0 mg/kg/day (HDT)
- Ames Mutagenicity Assay: Negative

Ecological Characteristics:

Avian Oral (Bobwhite quail): LD_{50} > 2000 mg/kg; LC_{50} = 3102 ppm
Avian Dietary (Mallard duck): LC_{50} = 383 ppm
Freshwater Fish (Bluegill): LC_{50} = 9.6 ppb
Rainbow trout: LC_{50} = 3.2 ppb
Estuarine Fish (Fathead minnow): LC_{50} = 15 ppb
Oyster Embryo Larvae: LC_{50} = 430 ppb.
Acute Freshwater Invertebrate (Daphnia): LC_{50} = 0.22 ppb
Acute Estuarine Invertebrate (Shrimp, mysid): LC_{50} = 0.02 ppb

Environmental Characteristics:

Avermectin is stable to hydrolysis at ph 5, 7, and 9 and thus is not expected to hydrolyze in the environment. It photodegrades rapidly in water and soil with half-lives of less than 12 hours and 1 day respectively. Soil metabolism studies conducted in darkness indicate degradation does occur with a half-life of 2 weeks to 2 months under aerobic conditions. Anaerobic degradation is slower. It is not expected to accumulate in fish. Avermectin's solubility in water is determined to be 7.8 ppb. The field dissipation study indicates that avermectin, when applied in the bait formulation directly to the soil, dissipates with a half-life of about a week but may persist longer if the bait is shaded. Due to its binding properties and low water solubility, Avermectin is expected to exhibit little or no potential for leaching; however, a determination cannot be made until the results of the analyses of the three remaining soil core replicates are submitted and evaluated. Also an absorption/desorption leaching study must be conducted since avermectin has shown conflicting results in soil thin-layer chromatographic (TLC) (immobile) and soil column studies.

Tolerance Assessment

A Section 408 tolerance under the Federal Food, Drug, and Cosmetic Act has been established for residues of avermectin B_1 and its delta 8,9-isomer in/on the following raw agricultural commodity (RAC) (40 CFR 180.___)

Commodity	ppm
Cottonseed	0.005

The acceptable daily intake (ADI), based on a NOEL of 0.12 mg/kg/day from a 2-generation rat reproduction study and safety factor of 300, is 0.0004 mg/kg/body weight (bwt) day.

Because of developmental effects seen in animal studies the Agency used the rat reproduction study with a 300 fold safety factor to assess chronic dietary exposure and establish an ADI. The 300 fold safety factor was employed to account for (1) inter- and intra-species differences (2) and pup death observed in the reproduction study. (3)

maternal toxicity (lethality) NOEL = 0.05 mg/kg/day, and (4) cleft palate in the mouse teratology study with the isomer, NOEL = 0.06 mg/kg/day. The theoretical maximum residue contribution (TMRC) from the proposed tolerance as well as pending tolerances on celery, pears and tomatoes and temporary tolerances on citrus with secondary residues in meat and milk is 0.000052 mg/kg/day. This is equivalent to about 13 percent of the ADI. This analysis used tolerance level residues and 100 percent of crop treated. The TMRC from cotton only is .000001 representing less than 0.1 of the ADI.

Because of adverse developmental effects seen in animal studies detailed acute dietary exposure analysis for this tolerance and pending tolerances for this chemical was also conducted using a NOEL of 0.06 mg/kg body weight for developmental effects. The food uses evaluated were the same as those evaluated in the chronic exposure analysis. The acute exposure analysis estimated the distribution of single-day exposures for the overall U.S. population and certain population subgroups. The analysis evaluated the individual food consumption, as reported by respondents in the 1977-78 USDA Food Consumption Survey, and accumulated exposure to avermectin for each food consumed for which a tolerance is being evaluated. Each analysis assumed that avermectin residues were present at tolerance level in all foods consumed. The toxicologic endpoint pertained to developmental toxicity. The subgroup of interest in this analysis was women aged 13 and above, which has the subgroup most closely approximating women of child-bearing age. Based upon this analysis the Margin of Safety (MOS) for the average woman of child bearing age was calculated to be 1579. None of the target population is expected to have a MOS less than 250.

The nature of the residue in cottonseed is adequately defined. The residue of concern is the parent and its delta 8,9-isomer. Based on (1) no accumulation of avermectin in tissues or milk (from a ruminant metabolism study) (2) absence of measurable residues (<2 ppb) in cottonseed treated at exaggerated application rates and (3) feeding restrictions for

cotton foliage the Agency has concluded that there is no reasonable expectation of finite residues in milk, eggs, meat, or poultry and no processing data or food/feed additive tolerances are needed for the use on cotton.

There are no Canadian or Mexican tolerances and no Codex Maximum Residue Limits (MRLS) have been established for avermectin B_1 and its delta 8,9-isomer in/on cotton. Therefore, no compatibility problem exists.

4. Summary of Regulatory Position and Rationale

o The Agency has determined that it should allow the conditional registration of abamectin for agricultural use to control mites on cotton. Adequate data are available to assess the acute and chronic toxicological effects of abamectin to humans. However since long-term fish, aquatic and mammalian data are lacking and additional leaching and soil dissipation data are required, the registration is being conditionally approved with an expiration date of March 31, 1992. Due to the conditional status of the registration the Agency is also establishing the tolerance for this pesticide on cottonseed with an expiration date of March 31, 1993 to cover residues expected to be present during and for one year after the period of conditional registration.

o In view of the high toxicity of technical abamectin to fish, aquatic invertebrates and mammals and the potential hazard associated with exposure from the use on cotton the risk criteria for restricted use classification is exceeded and thus the Agency, is restricting use on cotton to certified applicators.

o Additional data are required to more adequately define the hazards to mammals, fish, and aquatic invertebrates. According to EPA's Ecological Effects Standard Evaluation Procedures presumption of unacceptable risk is triggered when the estimated environmental concentration (EEC) exceeds the bird or mammal LC_{50}, or 1/2 the aquatic LC_{50} or EC_{50}. According to EPA's assessments, these criteria are exceeded for mammals and aquatic invertebrates for the cotton use (mammal 1-day LC_{50} = 2.5 ppm, EEC = 4.8 ppm, aquatic invertebrate (freshwater) EC_{50} = 0.22 ppb, EEC = 0.6 ppb; estuarine invertebrate EC_{50} = 0.02 ppb, EEC = 0.6 ppb).

o Because of adverse developmental effects seen in animal studies non-dietary exposure analysis was also conducted with respect to exposure to mixer/loaders, applicators and harvesters. Based upon surrogate exposure data; persons wearing long pants, long-sleeved shirts, rubber gloves and dermal absorption data in the monkey the calculated MOS for cotton crop applicators and workers were found to exceed 100 in all instances. This MOS is sufficient to adequately protect these workers.

5. Summary of Data Gaps

Name of Study	Reference Number	Due Date
Fish Life Cycle Test	§72-5	October 1991
Mesocosm Aquatic Study	§72-7	October 1991
Simulated Mammal Field Test	§71-5	October 1991
Soil Absorption/Desorption	§163-1	June 1990
Results of the Analysis of the Remaining Soil Core Samples for the Field Dissipation Study	§164-1	July 1989

6. Required Unique Labeling Summary

o All products registered for use on cotton must bear the following restricted use labeling statements:

RESTRICTED USE PESTICIDE

Toxic to Fish, Mammals and Aquatic Organisms

For Retail sale to and use only by Certified Applicators or Persons under their direct supervision and only for those uses covered by the Certified Applicator;s certification

o The following use limitiations must appear on products registered for use on cotton:

Do not apply more than 48 fl oz per acre per year.

Do not apply within 20 days of harvest.

Do not graze or feed cotton foliage.

Do not reenter treated areas until sprays have dried.

Do not apply when weather conditions favor drift from target areas.

Do not apply this product through any type of irrigation system.

o Personal protective equipment and work safety statements must appear on the label of products registered for use on cotton and shade house, greenhouse and field grown flowers, foliage plants and ornamentals.

6. Contact Person at EPA

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