United States
Environmental Protection
Agency

Office of Pesticides
and Toxic Substances
(H7501C)

540/FS-89-047

EPA

Pesticide Fact Sheet

Name of Chemical: Hexythiazox

Reason for Issuance: New Chemical - First Food Use

Date Issued: April 13, 1989

Fact Sheet Number: 200

1. Description of Chemical

Generic Name: Trans-5-(4-chlorophenyl)-4-methyl-2-oxo-3-thiazolidine-carboxamide

Common Name: Hexythiazox

Trade Name: Savey®

Other Proposed Names: N/A

Code Number: DPX-Y5893, NA-73

EPA Shaughnessy Code: 128849

Chemical Abstracts Service (CAS) Number: 78587-05-0

Year of Initial Registration: 1989

Pesticide Type: Acaricide

U.S. and Foreign Producers: E.I. du Pont de Nemours & Company, Inc.

2. Use Patterns and Formulations

Application Sites: Pears (foliar)

Types and Methods of Application: Ground Application: Use sufficient water, 150 to 800 gallons per acre (gal/A) for dilute application, 50 to 150 gal/A for concentrate applications.

Application Rates: Apply the lower rates (4.0 oz/A) formulated product (form) on low mite egg infestation levels and the high rates (6.0 oz form/A) on moderate to high mite egg infestation levels or to larger trees. Apply only one application per growing season.

Type of Formulation: 50% wettable powder.

Limitations:

- o Use only in commercial plantings; do not use in home plantings.
- o Re-entry Statement - Do not treat areas while unprotected humans or domestic animals are present in the treatment areas.

  Do not allow re-entry into treated areas without protective clothing until sprays have dried.
- o Do not graze or feed livestock on cover crops growing in treated areas.
- o Do not apply more than a total of 6 oz. form/A per growing season
- o Do not apply within 28 days of harvest.
- o Do not apply more than once per growing season.
- o Do not apply this product through any type of irrigation system.

3. SCIENCE FINDINGS

Summary Science Statement:

The EPA Peer Review Committee completed its evaluation of hexythiazox with respect to its oncogenic potential and concluded that the data available for hexythiazox provide limited evidence of oncogenicity for the chemical in mice. According to EPA Guidelines for Carcinogen Risk Assessment (Federal Register September 24, 1986) the Committee classified hexythiazox as a Category C oncogen (possible human carcinogen with limited evidence of carcinogenicity in animals).

The decision supporting a Category C classification (rather than a Category B classification) was based primarily on the fact that only one species was affected (mouse), mutagenicity assays did not support upgrading to a B classification and the structure-activity relationship of hexythiazox to other compounds supported a C classification.

In classifying hexythiazox as a Category C oncogen, the Agency concluded that a quantitative estimation of the oncogenic potential for humans should be calculated because of the increased incidence of malignant and combined benign/malignant liver tumors in the female mouse. Thus, a Q_1^* of 3.9×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents has been calculated. Dietary oncogenic risk to the general population based on the highly conservative assumption

that all pears are treated with hexythiazox and would bear residues at the proposed tolerance level is estimated to be 10^{-6}. Non-dietary oncogenic risk to the mixer/loader, applicator based on a dermal absorption factor of 2%, use of protective clothing and one application per year is estimated to be 10^{-6}.

Technical hexythiazox exhibits low mammalian acute toxicity. The results of the technical acute toxicity data show a very mild eye irritant. It is not a sensitizer, nor considered to be mutagenic, nor teratogenic. Hexythiazox is readily absorbed by mammals, and the majority of the residue is largely excreted in the feces and urine by 24 hours. The results of the acute toxicity on the end-use formulation (50% WP) indicates that it is of low toxicity (Toxicity Category III and IV).

Sufficient data are available to characterize hexythiazox for pear use from an environmental and ecological effects standpoint. The results of acute testing indicates that hexythiazox is practically non-toxic to birds on both an acute oral and dietary basis. Hexythiazox is moderately to highly toxic to aquatic invertebrates. Hexythiazox is highly toxic to fish. Although technical hexythiazox is toxic to aquatic biota, the application rates and physical/chemical properties of the end-use product minimize potential adverse effects for the pear use. Hexythiazox is relatively non-toxic to non-target insects such as honeybees.

No effects to endangered/threatened species are expected, as the trigger for endangered species concern has not been exceeded (the estimated environmental concentration (EEC) is less than 1/20 the LC_{50}).

Adequate data are sufficient to define the fate of hexythiazox in the environment. Hexythiazox is very stable to hydrolysis, with an estimated T 1/2 exceeding 50 days at environmentally expected temperatures and pH values. Hexythiazox undergoes slow photolytic degradation under sunlight, with T 1/2 of 16.6 days in water and 116 days in soil. Hexythiazox degrades in soil under laboratory conditions. The T 1/2 in aerobic soils ranged from 17 to 35 days. Hexythiazox and its soil aged residues do not leach significantly in soil due to its low solubility in water, high soil adsorption characteristics, and slight vertical movement in soils tested. Hexythiazox is not likely to persist in the field, with T 1/2 ranging from 5 to 15 weeks. No crop rotation study is required for this orchard crop use. Both accumulation and depuration of hexythiazox will occur in bluegill sunfish. Bioconcentration factors of approximately 1300X were calculated in the bluegill sunfish flowthrough study. During 28 days of depuration, 97% of the radiolabeled material was eliminated.

Chemical/Physical Characteristics of the Technical Grade Product

Physical State: Crystalline solid
Color: Pale yellow
Odor: Odorless
Melting Point: 105 to 107.5 °C
108 to 108.5 °C for analytical grade
Vapor Pressure: 2.54×10^{-8} mmHg (20 °C)
Molecular Weight: 352.5
Solubility:

Chloroform	137.9 (g/100 mL)
Acetone	16.0
n-Hexane	0.39
Methanol	2.06
Xylene	36.2
Acetonitrile	2.86
Water	0.5 ppm

Specific Gravity: d_4^{20} 1.289
Bulk Density: 0.50 to 0.70 g/mL
Octanol/Water Partition Coefficient: 340
pH: Stability to Hydrolysis
(t 1/2 of 0.25 ppm at 22 °C)

pH 5	> 7×10^4 (hours)
7	> 7×10^4
9	1.21×10^4

Stability to Temperature: Stable after 3 months at 50 °C
Storage Stability: 100% active ingredient stable at room temperature and at 50 °C for 180 days

Toxicology Characteristics of the Technical Grade:

- Acute Oral Toxicity - Rat: LD_{50} > 5000 mg/kg
  Toxicity Category IV
- Acute Dermal Toxicity - Rat: LD_{50} > 5000 mg/kg
  Toxicity Category III
- Acute Inhalation LC_{50} > 2.0 mg/L
  Toxicity Category III
- Primary Dermal Irritation - Rabbit: Not a primary skin irritant. Toxicity Category IV
- Primary Eye Irritation: Very mild eye irritant.
  Toxicity Category III

- o Dermal Sensitization: Non-sensitizer
- o 1-Year Feeding - Dog: NOEL = 100 ppm (2.5 mg/kg/day)
- o 2-Year Feeding/Oncogenicity - Rat: NOEL (Systemic) = 430 (21.5 mg/kg/day); oncogenicity-negative at 3000 ppm (HDT)
- o 2-Year Feeding/Oncogenicity - Mouse: NOEL (Systemic) = 250 ppm (37.5 mg/kg/day); Oncogenic in female mouse liver at 1500 ppm (225 mg/kg/day) HDT
- o Reproduction (2 generation) - Rat: Reproductive NOEL > 2400 ppm (120 mg/kg/day); Maternal NOEL = 400 ppm (20 mg/kg/day)
- o Teratology - Rabbit: NOEL > 1080 mg/kg/day for developmental toxicity (HDT). Maternal toxicity NOEL > 1080 mg/kg/day (HDT)
- o Teratology - Rat: Maternal NOEL = 240 mg/kg/day; Fetotoxic NOEL = 240 mg/kg/day; Teratogenic NOEL > 2160 mg/kg/day (HDT)
- o Mutagenicity: Negative in a battery of mutagenicity studies.

End-Use Formulation

The stated results for the following acute studies are for the 50 percent wettable powder formulation: Oral (rat), dermal (rat), inhalation (rat), primary dermal irritation (rabbit), and primary eye irritation (rabbit) and dermal sensitization (guinea pig).

- o Acute Oral - Rat: LD_{50} > 5000 mg/kg (male (M) and female (F) Toxicity Category III
- o Acute Dermal Toxicity - Rat: LD_{50} > 5000 mg/kg (M&F) Toxicity Category III
- o Acute Inhalation - Rat: LC_{50} > 2.8 mg/L (M&F) Toxicity Category III
- o Primary Dermal Irritation - Rabbit: Negative (N) Toxicity Category IV
- o Primary Eye Irritation - Rabbit: Reddened conjunctivae, maximum score of 2, maximum duration 6 days. Chemosis ended by day 3 (M); Toxicity Category III
- o Dermal Sensitization - Guinea Pig: Not a sensitizer

Physiological and Biochemical Characteristics:

Foliar Absorption: N/A

Translocation: Not translocated.

Mechanism of Pesticide Action: Neurotoxicity Characteristic - Controls mites through ovicidal/chemosterilant activity when spray mist comes in contact with mite eggs or female mites.

Environmental Characteristics:

The environmental fate data indicate that hexythiazox and its soil-aged residues did not have significant vertical mobility and thus are not likely to leach and contaminate ground water. Field data also indicate that hexythiazox dissipates with half-life of 5 to 26 weeks. Hexythiazox underwent slower photolytic degradation on soil than in aqueous solution with a half-life of 116 days. Hexythiazox did not undergo any noticeable hydrolysis under acidic to neutral conditions at 22 °C. At pH 9 at 22 °C, hexythiazox hydrolyzed very slowly with an estimated half-life of 416 days.

^{14}C-DPX-Y5893 (labeled at C-5 of thiazole moiety) was bioaccumulated in bluegill sunfish under flow-through conditions with a biological concentration factor (BCF) range of 1000 to 1600 at peak on the basis of whole fish. The highest accumulation occurred in viscera with a BCF range of 1.3 to 1.7 x 10^4. After 14 days of depuration, about 97 percent of the accumulated radioactivity was removed. Residue analysis of the 28-day fish samples showed that about 52 to 88 percent of the ^{14}C-residue was present as polar material(s), 5 to 23 percent as parent DPXY5893, 2 to 15 percent as cyclohexane-hydroxylated metabolites of parent, 4 to 7 percent as conjugated material, and 2 to 4 percent as tissue bound residues.

Ecological Characteristics:

Technical Formulation

- Avian Oral Toxicity: > 2510 mg/kg (mallard duck LD_{50}).
- Avian Dietary Toxicity (8 days): > 5620 ppm (bobwhite quail LC_{50}) and > 5620 ppm (mallard duck LC_{50}).
- Freshwater Fish Acute Toxicity: (96-hr LC_{50}: 0.53 mg/L (bluegill) and > 1 mg/L (rainbow trout).
- Freshwater Invertebrate Acute Toxicity (48-hr LC_{50} - Grade: 1.22 mg/L (Daphnia crinata); (48-hr EC_{50}): 0.74 mg/L.

- o Invertebrate Life Cycle: NOEL 0.5 mg/L (Daphnia magna).

- o Honeybee LC_{50}: >1000 ppm

Tolerance Assessment

A Section 408 tolerance under the Federal Food Drug and Cosmetic Act has been established for residues of hexythiazox in/on the following raw agricultural commodity (40 CFR 180.448)

Commodity	Part Per Million
Pears	0.3

The acceptable daily intake (ADI), based on a NOEL of 2.5 mg/kg/day from a 1-year dog feeding study and a safety factor of 100 is 0.025 mg/kg/body weight/day. The TMRC from the proposed tolerance is 0.000037 mg/kg body weight/day. This is equivalent to about 7.4 percent of the ADI

The nature of the residue in pears (pome fruit) is adequately defined. The residue of concern is the parent and its hydroxylated cyclohexane ring metabolites.

There are no animal feed items with pear orchard use therefore the nature of the residue in animals is not relevant. Since there are no feed items involved with pears and the label includes the restriction "Do not graze or feed livestock or cover crops growing in treated areas", no secondary residues (meat, milk) are anticipated from this proposed use.

No processing data have been submitted however none are required since residue levels in pear juice and nectar will not exceed the tolerance level on the raw agricultural commodity pears.

There are no Canadian or Mexican tolerances and no Codex Maximum Residue Limits (MRLS) have been established for hexythiazox and its metabolites in/on pears. Therefore, no compatibility problem exists.

Reported Pesticide Incidents: None

4. Summary of Regulatory Position and Rationale

A full review of the data indicates that although hexythiazox is an oncogen in mice the dietary and nondietary risks would be extremely small from the proposed use on pears. Estimated dietary oncogenic risk to the general population based on the highly conservative assumption that all pears are treated with Savey and would bear residues at the proposed tolerance level is estimated to be 10^{-6}.

The Agency believes that actual exposure and risk would be lower. The basis for this is that the risk of 10^{-6} reflects a worst-case dietary exposure because it assumes that 100 percent of the United States pear crop is treated with Savey and that all quantities of the food consumed will bear residue levels as high as the proposed tolerance. In reality, the Agency knows that all pears would not be treated with this pesticide. Based upon an analysis of the market penetration of currently registered acaricides, the Agency expects the percent of crop treated with Savey in a typical year would be about 30 percent. Likewise, the Agency believes that residue levels in pear juice and nectar will not exceed the established tolerance of 0.30 ppm in or on the RAC pears, since the maximum residue level in pear juice is less than 50 percent of the residue level in whole fruit. In addition, since there are no animal feed items involved with pears and the petitioner has included the label restriction "Do not graze or feed livestock or cover crops growing in treated areas," no secondary residues in meat or milk are expected.

Estimated non-dietary oncogenic risk to the mixer/loader applicator based on a dermal absorption factor of 2%, the use of protective clothing and 1 application of per year is 10^{-6}. The Agency believes that this estimate is an overestimation of the lifetime cancer risk and that actual exposure and risk would be much lower since the surrogate data base for calculating exposure reflected application rates of 1 to 7 ai/A whereas the proposed use on pears is for 0.2 lb ai/A. An estimated risk of less than 1×10^{-5} is considered to be an acceptable risk relative to mixer, loaders and applicators.

Thus, based on the above risk assessment the Agency has characterized the risk posed to the general public and to pesticide applicators from the proposed use of Savey as extremely small.

The Agency has determined, based on the available data and use pattern, that endangered/threatened species would not be adversely affected.

Hexythiazox is not likely to leach and contaminate ground water.

The Agency has reviewed all relevant data and has determined that no additional data are necessary to make the determination required by FIFRA sec 3(c)(5). Thus, the Agency is approving this registration under FIFRA sec 3(c)(5).

The Agency has determined that the product will perform its intended function without unreasonable adverse effects on the environment, and that when used in accordance with the label directions, the product will not generally cause unreasonable adverse effects on the environment.

The Agency has determined that all necessary tolerances have been issued under FIFRA sec. 408.

5. Summary of Data Gaps

None

6. Contact Person at EPA

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