Dihydroazadirachtin (121702) Technical Fact Sheet

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1. Description of the Chemical

Generic Name of the Active Ingredient: Dihydroazadirachtin (DAZA)

OPP Chemical Codes: 121702

Year of Initial Registration: 1997

Trade Names: DAZA

Pesticide Type: Biochemical

U.S. and Foreign Producers:

Thermo Trilogy Inc.1500 Grace Drive
Columbia, MD 21044-4098

2. Use Sites, Application Timing & Target Pests

- **Target Pests:** Numerous pests including insects, centipedes, millipedes, mites, nematodes and sowbugs.

- **Registered Uses**: DAZA is registered as a technical powder and an end-use product for indoor and outdoor use. The end-use involves aerial and/or ground applications to horticultural and ornamental plants, trees, shrubs, and agricultural crops. Formulated product will be used on plants that are potted, grown in soil or soilless mixtures grown hydroponically, including bedding plants, flowers, potted plants and foliage plants, ornamentals, trees and shrubs, turfgrass, fiber crops, forage and fodder crops, and other agricultural crops.

- **Application Timing:** As needed. Application to agricultural crops is limited to a maximum application rate of 20 grams per acre, and up to seven applications per crop season.

3. Food Clearances / Tolerances

The Final Rule establishing an exemption from the requirement of a tolerance for residues of DAZA in or on all raw agricultural commodities was published in the Federal Register on July 19, 1996 (40 CFR 180.1169). The exemption applies when DAZA is applied as an insect growth regulator and/or antifeedant at 20 gms or less of the active ingredient per acre with a maximum of seven applications per growing season.

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4. Science Findings

A. Biochemical Description

The active ingredient, dihydroazadirachtin (DAZA), is a reduced (hydrogenated) form of the naturally occurring azadirachtin (AZA) obtained from the seed kernels of the neem tree, *Azadirachta indica* A. Juss. DAZA is structurally similar to AZA, and the two compounds are functionally identical in their anti-pupation properties. DAZA has both antifeedant and insect growth regulator properties.

B. Biochemical Classification

For regulatory purposes, DAZA is considered a biochemical based on its natural occurrence and non-toxic mode of action towards target pests.

C. Toxicology

The following toxicity studies were submitted and reviews were found acceptable using a technical grade manufacturing product:

1. **Guideline No. 152-10 Acute Oral Toxicity in Rats.**

   The acute oral toxicity of DAZA in rats has an LD_{50} >5 g/kg, Toxicology Category IV.

2. **Guideline No. 152-11 Acute Dermal Toxicity in Rabbits.**

   The acute dermal toxicity of DAZA in rabbits has an LD_{50} >2 g/kg, Toxicology Category III.

3. **Guideline No. 152-12 Acute Inhalation Toxicity in Rats.**

   The acute inhalation toxicity of DAZA in rats has an LC_{50} > 2.9 mg/L, Toxicology Category IV.

4. **Guideline No. 152-13 Primary Eye Irritation in Rabbits.**

   The primary eye irritation of DAZA in rabbits shows slight conjunctival irritation which clears in 24 hours (Non-irritating), Toxicology Category IV.

5. **Guideline No. 152-14 Primary Dermal Irritation in Rabbits.**

   he acute dermal irritation of DAZA in rabbits shows barely perceptible erythema in all test sites at 24 hours, and no irritation at 72 hours (Non-irritating), Toxicology Category IV.

6. **Guideline No. 152-15 Hypersensitivity in Guinea Pigs.**

   Not a dermal sensitizer.

7. **Guideline No. 152-16 Hypersensitivity Incidents.**

   No reported incidents.

8. **Guideline No. 152-17 Genotoxicity Studies in *Salmonella* / Mammalian Microsomal Reverse Mutation Assay.**

   No detectable mutations were observed in the *Salmonella* / Mammalian Microsomal Reverse Mutation Assay with 5 tester strains (TA98, TA100, TA1535, TA1537, and TA1538 with additional mutations) at levels of 6.6 to 5000 Âµg/plate of DAZA with ethanol vehicle controls, positive mammalian controls, or no microsome controls. (This study not required for non-food/non-feed use).

9. **Guideline No.s 152-17, 152-18, 152-20, 152-21, 152-22, 152-23**

These toxicology studies were satisfied either by data waivers based on low mammalian toxicity of the compound, or data were bridged from the structurally similar compound AZA.

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D. Food Quality Protection Act Requirements

No unreasonable adverse effects to human health are expected from the use of DAZA. An exemption from the requirement of a tolerance was established under Section 408(c)(2)(A)(i) of the Federal Food, Drug, and Cosmetics Act. The Agency has assessed the toxicology data base for DAZA and the biologically similar parent compound AZA in light of the safety factors listed in the Food Quality Protection Act and has concluded with reasonable certainty that the proposed uses of DAZA do not pose aggregate and/or cumulative risks to the general population, including infants and children.

E. Human Health Effects

1. **Acute and Chronic Dietary Risks for Sensitive Subpopulations, Particularly Infants and Children**

Dihydroazadirachtin and AZA have low mammalian toxicity as demonstrated in an acute oral (Toxicity Category IV), a dermal (Toxicity Category III), an inhalation (Toxicity Category IV), a primary eye irritation (Toxicity Category IV), and a primary dermal (non-irritating)] study. Both active ingredients, DAZA and AZA, test negatively for dermal sensitization and genotoxicity *(Salmonella typhimurium* reverse mutation, unscheduled DNA synthesis in rat hepatocytes, and chromosome aberration in Chinese hamster ovary cells). Based on low mammalian toxicity as indicated by acute and subchronic toxicity test results, low application rate (20 grams or less per acre with a maximum number of seven applications per growing season), and rapid dissipation in the environment, the Agency concludes that there is a reasonable certainty of no harm from dietary exposure.

2. **Common Mode of Action**

The Agency considered the potential for cumulative effects of DAZA or AZA with other substances that have a common mechanism of toxicity. EPA concluded that consideration of a common mechanism of toxicity is not appropriate at this time. A common mode of action (mechanism of toxicity) with other pesticides is not easily identified for DAZA, an anti-feedant/anti-

molting pesticide for chitin-producing invertebrates. Investigations on the mode of action of AZA-based compounds are underway, especially with the use of molecules with fewer functional groups. Evidence is available showing that AZA interferes with the molting process via antagonism with ecdysone; a naturally occurring insect hormone. This hormone system is unknown among vertebrates.

3. **Risks Posed by Potential Residential, School or Daycare Exposure**

No school or daycare uses are on the current label. Terrestrial food and nonfood crop including outdoor residential uses are permitted. However, available toxicity information and history of safe use of the parent compound AZA indicate that the active ingredient will pose a minimal to nonexistent nondietary risk to children who may be present when used according to label directions.

4. **Drinking Water Exposure and Risk Characterization**

No significant exposure is expected to result from an accumulation of DAZA in the aquatic environment because it is likely to be biodegraded in the terrestrial and aquatic environments.

5. **Aggregate Exposure**

The Agency has considered the various routes of exposure (dietary, drinking water, and exposure from non-occupational sources) and potential risks of the subject compound and determined that the proposed use of the active ingredient does not pose significant risk over a lifetime to populations including infants and children. This is demonstrated by low acute and subchronic mammalian toxicity, biodegradable nature of the compound, and a history of safe use of the parent compound AZA.

F. Occupational and Residential Expsoure and Risk Charterization:

Using conservative calculations for exposure to an end-use product containing DAZA, used at a 1:128 dilution, with minimal personal protective equipment, a person would be exposed to <0.01% of the lipid content of the normal daily diet after spraying 5 gallons of the diluted product from a 5 gallon application with a backpack.

G. Environmental Assessment

The ecological database for DAZA is adequate and will support registration. All guideline requirements for DAZA technical have been satisfied. Because of the similar biological functionality (between DAZA and AZA) to the target organisms, in mammalian toxicity testing, ecological effects testing and QSAR, several data submissions for AZA are used to support the DAZA registration.

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H. Ecological Effects

The following ecological effects studies were submitted and reviews were found acceptable using the technical grade active ingredient:

1. **Guideline No. 154-6 Avian Acute Oral LD_{50}, Bobwhite Quail, *Colinus virginianus***

   The avian acute oral LD_{50} for DAZA administered by way of gelatin capsule to the bobwhite quail, *Colinus virginianus,* is >816 mg/kg (slightly toxic).

2. **Guideline No. 154-7 Avian Dietary LD50, Bobwhite Quail, Colinus virginianus**

   DAZA is slightly toxic to bobwhite quail, *Colinus virginianus,* with an LD_{50} >1875 mg/kg.

3. **Guideline No. 154-8 Freshwater Fish, LC_{50}, Rainbow Trout, *Oncorhynchus mykiss***

   DAZA is slightly toxic to freshwater fish, with an LD_{50} = 17.65 mg/kg.

4. **Guideline No. 154-8 Freshwater Fish, LC_{50}, Bluegill Sunfish, *Lepomis macrochirus***

   DAZA is moderately toxic to freshwater fish, with the 96-hour LD_{50} = 9 mg/kg.

5. **Guideline No. 154-9 Freshwater Invertebrate, LC_{50}, *Daphnia magna***

   DAZA is slightly toxic to freshwater invertebrates, with an LD_{50} = 11.625 mg/L.

6. **Guideline 154-10 Nontarget Plant**

   This data requirement is waived on the basis of relatively nontoxic nature of the biologically similar AZA and mitigating label language.

7. **Guideline 154-11 Nontarget Insect**

DAZA was classified as relatively nontoxic to honeybees, as demonstrated by a 96-hour acute dust exposure of honey bees to DAZA. Being broad spectrum insecticides, both AZA and DAZA are believed to be slightly toxic to beneficial insects (green lacewing, immature and mature mites, whitefly parasitoids, and ladybird beetles).

I. Environmental Fate and Transport

Based on the chemical structure (i.e., its high oxygen content and numerous functional groups), the properties of DAZA are consistent with the likelihood that ubiquitous microbial populations (soil and aquatic) will readily degrade it and, thereby, preclude its accumulation in the environment. The environmental fate data requirements were not triggered because no human health or ecological effects issues were manifested in the acute toxicity (Tier I) studies.

J. Ecological Risk Assessment

Risk to the environment is not expected because, under current use conditions, DAZA is not persistent, is relatively non-toxic, high in oxygen content, consists of several functional groups, is relatively short-lived in the environment (in the order of days), and is likely to be metabolized by ubiquitous microorganisms in the soil and aquatic environments. Moreover, DAZA is relatively nontoxic to most ubiquitous non-chitinous organisms that do not undergo metamorphosis.

1. **Required Environmental Hazards Statement on the End-Use Product Label**

"This pesticide is toxic to fish and aquatic invertebrates. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Drift and runoff may be hazardous to aquatic organisms in neighboring areas. Do not contaminate water when disposing of equipment wash water or rinsate."

2. **Required Environmental Hazards Statement of the Technical Product Label**

"Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or public waters unless this product is specifically addressed in an NPDES permit. Do not discharge effluent containing this product to sewer systems without previously notifying the sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA."

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5. Summary of Required Data

All hypersensivity incidents must be reported to the Agency when/if they occur.

6. Regulatory Actions

Unacceptable adverse effects from the use of dihydrazadirachtin are not expected. Unconditional registrations of the manufacturing use product DAZA Technical and end-use product DAZA 4.5WDG were issued.

7. Additional Contact Information

Ombudsman, Biopesticides and Pollution Prevention Division (7511P)
Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460