Trichoderma harzianum Rifai Strain T-39 (119200) Technical Document

Issued: 5/00

I. Executive Summary

A. Identity

The fungal active ingredient, *Trichoderma harzianum* Rifai strain T-39, (PC Code 119200) is a naturally occurring strain of *Trichoderma* fungal species. This strain was isolated in Israel from the microflora on the surface of a plant and was selected for its activity against the gray mold, *Botrytis cinerea*, a plant pathogen. T-39 is presumed to suppress penetration of *Botrytis* into plant tissues through competition with the pest for nutrients and space on various plant surfaces. The sole end-use product (EP) TRICHODEX® , which contains 20% of the active ingredient, is manufactured by an integrated process. Makhteshim Agan of North America, the registrant, has submitted sufficient data to demonstrate that it can identify this strain by DNA RAPD screens and control the presence of human pathogens within regulatory levels.

B. Use Sites

The end-use product is a wettable powder which is to be applied by ground and hand spray equipment to terrestrial food crops in greenhouses and in agricultural fields. Certain food crops are excluded from the label pending submission and evaluation of phytopathogenicity data. Applications by air and to aquatic sites are not supported by the current ecological effects database (**Section III**).

C. Risk Assessment

1. Human Health Risk Assessment

Data submitted were evaluated under the provisions of the Food Quality Protection Act of 1996. Acute mammalian toxicology data support the lack of toxicity/pathogenicity of *Trichoderma harzianum* strain T-39. These data are sufficient to support the exemption from tolerance for all food commodities for this microbial pesticide. The Agency has not identified any acute, subchronic, chronic, immune, endocrine, dietary or nondietary exposure issues which may affect children and the general U.S. population. There is a reasonable certainty that no harm will result from dietary, non-dietary, cumulative and aggregate exposure to the active ingredient *Trichoderma harzianum* Rifai strain T-39.

The Technical Grade Active Ingredient (TGAI), *Trichoderma harzianum* strain T-39, demonstrated a low toxicity profile. This microorganism is not known to be an endocrine disrupter. Based on the dose administered during laboratory tests in the rat, the microbial pesticide was placed in Toxicity Category III for acute oral effects. It was considered mildly toxic for acute dermal and primary dermal irritation effects, both of which were classified as Toxicity Category IV. A potential also exists for delayed dermal contact hypersensitivity.

Moderate to severe eye irritation was observed in rabbits treated with concentrated levels of the TGAI. However, administration of diluted test material to satisfy guideline requirements resulted in mild eye irritation, which can be mitigated by goggles. The pesticide was classified Toxicity Category II for acute pulmonary toxicity/pathogenicity effects. EPA believes that the acute pulmonary effect is due to irritation from the inert rather than from the microorganism. Measures to mitigate potential dermal and inhalation worker exposure are discussed under **Human Health Risk Assessment** and in **Section III.B.** of the RED document.

Besides its low dietary toxicity, potential residues of the pesticide can be removed from food commodities by washing, peeling, cooking and processing, to lower dietary exposure and risk. The microorganism is ubiquitous, is not known as an aquatic fungus and is not to be directly applied to water. The microbial pesticide is not expected to percolate through soil and municipal treatment of drinking water is anticipated to reduce any potential risk to adults, children, and infants. Based on its low toxicity potential, an additional FQPA safety factor is not required for residues of *T. harzianum* strain T-39.

2. **Ecological Risk Assessment**

Ecological and environmental effects and potential risks, summarized below, are discussed at length in **Section III.C.** of this RED document. Based on the ubiquitous nature of the microorganism and its low toxicity/pathogenicity profile, there is a reasonable certainty of no adverse effects to the environment if products containing the active ingredient *Trichoderma harzianum* Rifai T-39 strain are used as labeled.

Toxicity/pathogenicity is not expected to avian species, mammals and wildlife from the proposed uses of *T. harzianum* strain T-39. The data for non-target organisms, freshwater fish, aquatic invertebrates (*Daphnia)*,

honeybee, and other non-target insects are sufficient to allow the proposed applications to terrestrial crops. Scientific literature indicates a potential for phytopathogenicity of *Trichoderma* fungal species to 16 crops which are not included on the label. Those reports do not point directly to this T-39 strain (see **Toxicity to Plants: Section III C.1.c.**). The risk posed by ground applications to other agricultural crops is expected to be minimal to non-existent provided the excluded sites are not treated with products containing *T. harzianum* strain T-39.

3. **Environmental Distribution**

T. harzianum and other *Trichoderma* species are common soil habitants and are found worldwide. The natural populations in the soil do not usually exceed 10^2 cfu/g soil. This active ingredient, *T. harzianum* strain T-39, was isolated from plants. It is not prolific in aquatic habitats. Even if there is runoff from treated agricultural sites, the fungal active ingredient is not likely to percolate through the soil to ground water.

D. Data Gaps/Label Restrictions

1. **Data Gaps**

Data requirements and time frames for data submission for a conditional registration are discussed in **Section VI** and **Table 4**. Standard Product Identity data and 5 batch analyses are required when the pesticide is produced. For an unconditional registration of the current label, the registrant must submit records from the *Daphnia* and honeybee studies to upgrade them, and a ladybird beetle study to determine pesticidal effects on non-target insects. Other data requirements apply if the registrant wishes to register certain sites. These data gaps include: (i) a freshwater fish study if aerial and aquatic applications are requested, and (ii) phytopathogenicity data of *T. harzianum* strain T-39 if the registrant wishes to register 16 crops currently excluded from the label.

2. **Labeling**

Environmental Hazard, Precautionary Labeling, and Worker Protection Standards (WPS), and other Agency labeling requirements are discussed in **Section V** of the RED. Personal Protective Equipment (PPE) required for pesticide handlers and early entry workers to comply with the Worker Protection Standards (WPS) for this sole registered EP are: long sleeved shirt, long pants, socks, shoes, goggles, and a dust-mist filtering respirator meeting NIOSH standards with N-95, R-95 or P-95 filter. A Restricted-Entry

Interval (REI) of 12 hours is required for early entry (post-application) workers or other persons entering treated fields. Mitigating label language is also required so that the pesticide is not applied by air or directly to aquatic crops.

E. Public Interest Finding

Section IV indicates few conventional chemical alternatives for treatment of *Botrytis cinerea*. Almost all of the uses are for minor use crops and, therefore, this antifungal agent qualifies for an automatic presumptive finding and its use is presumed to be in the public interest.

II.

III. Overview

A. Product Overview

Biological Name: *Trichoderma harzianum* Rifai strain T-39

Trade and Other Names: TRICHODEX®

OPP Chemical Code: 119200

Basic Manufacturer:

Makhteshim-Agan of North America, Inc. (referred to as MANA)
551 Fifth Ave., Suite 1100
New York, NY 10176.

B. Use Profile

The following is information on the proposed uses with an overview of use sites and application methods.

Type of Pesticide: Antifungal agent, Fungicide

Use Sites: For ground application only to all food commodities, except apple fruit, sugar cane, rice, corn, pechay (bok choy), tomato, mushrooms, lemon, kiwi, cotton, tobacco, wheat, barley, oats, and soybean. Not to be used on aquatic sites nor for aerial applications

Target Pests: *Botrytis cinerea*

Formulation Types: Solid

Method and Rates of Application: Foliar sprays are to be applied with ground equipment at rates of 2 to 4 pounds per acre in a minimum of 50 gallons of water or adequate volume of water to provide coverage.

Use Practice Limitations: Tank mixes with some fungicides are not allowed because of the fungal nature of the active ingredient. The pesticide may be used in rotation with certain chemical pesticides as labeled.

Timing: The product is to be applied by ground and hand spray equipment and works best if all parts of the crop receive uniform spray coverage. The label requires preparation of the spray solution in a clean, empty spray tank and maintaining agitation until spraying is completed. Use clean coarse spray filters and discard unused spray material. Consult local TRICHODEX[7] agricultural specialist for specific information on the best rates, timings and spray volumes for region of intended use.

C. Estimated Usage

Estimates based on existing commercial use cannot be made since this is the first registered product.

D. Regulatory History

Experimental Use and Temporary Tolerance Exemption

On September 22, 1995, Makhteshim Agan of North America, Inc., applied for an Experimental Use Permit (EUP) for use of a microbial antifungal agent containing the active ingredient *Trichoderma harzianum* Rifai strain T-39 for use on table grape, wine grape, and strawberry. A petition for an exemption from the requirement of a temporary tolerance (PP6G4622) was filed concurrently with the proposed EUP registration request. Both the EUP and the exemption from temporary tolerance were granted for 2 years on May 8, 1996. According to the EUP, 8,120 pound of TRICHODEX® were allowed on table grapes, wine grapes, and strawberries, on a total of 360 acres (A) in the following states: Arizona (10 A), California (250 A), Florida (20 A), New York (25 A), Ohio (5 A), Oregon (25 A) and Washington (25 A).

The exemption from the requirement of a temporary tolerance for residues of this microbial pesticide was revised in 1998, and the data submissions found to comply with the Food Quality Protection Act of 1996. Both the temporary tolerance exemption and the Experimental Use Permit were extended until November 30, 2000

(FR Vol. 63, No. 121, pp. 28371-28374 and 40 CFR 180.1201). No adverse effects were reported in connection with this EUP.

Section 3(c) Registration

Subsequent to the EUP, the registrant proposed an exemption from tolerance in Pesticide Petition 7F4812 and a Section 3(c) registration of *T. harzianum* strain T-39 on January 3, 1997. Notices of these applications were published in the Federal Register on August 22, 1997 and April 20, 1999 respectively. No comments were received in response to any of the FR Notices within the comment period. Final Rules for the permanent exemption from tolerance, and the conditional registration of this new active ingredient, will be published in the Federal Register on approval of this RED.

On May 21, 1999, the Agency informed the registrant of the data required for an unconditional registration for the active ingredient *Trichoderma harzianum* strain T-39 (letter from Kathleen Knox, BPPD to Dr. Robert Everich, MANA). The registrant has made a commitment to provide the data and labeling required to proceed to an unconditional registration (letter from MANA dated May 25, 1999). Details of the data requirements and the time frames for submitting them are discussed in **Section VI** and outlined in **Table 4**. Some of the data required have already been submitted and are awaiting Agency review.

E. Food Clearances/Tolerances

The Agency evaluated data under the Food Quality Protection Act (FQPA) of 1996. Safety factors were considered for human health effects, as well as aggregate and cumulative exposures. Dietary exposure and risk from eating food treated with the pesticide, and from the potential secondary transfer of residues to drinking water, is expected to be minimal to non-existent. The data submitted are sufficient to support the

exemption from the requirement of a tolerance in/on all food/feed commodities.

IV.

V. Science Assessment

A. Product Identity and Mode of Action

1. Product Identity and Mode of Action

Product Identity

The Agency has classified *Trichoderma harzianum* Rifai strain T-39 as an active ingredient for use in microbial pesticides. RICHODEX®, the End-use product (EP), contains the active ingredient *Trichoderma harzianum* T-39 including dried fermentation solids and solubles resulting from fermentation and T-39 fungus propagules as either conidia or mycelia. *Trichoderma harzianum* T-39 is a naturally occurring strain that was isolated in Israel from the natural microflora and was selected for its activity against *Botrytis cinerea*, a plant pathogen.

Trichoderma species aggregates are differentiated primarily by conidiophore branching patterns and conidium morphology. Characteristics of the genus include: rapidly growing colonies bearing repeatedly branched conidiophores in tufts with divergent, often irregularly bent, flask-shaped phialides. Conidia can be either smooth walled or roughened and are usually green, but can be hyaline. Photomicrographs of this strain were provided.

The conidia of *Trichoderma harzianum* species are 2.8-3.2 x 2.5-2.8 Fm and are smooth walled with a subglobose to short oval shape. When grown on oatmeal agar at 20^{B}C, colonies may reach over 9 cm in diameter. Optimum temperature for growth is in the range of 15^{B}C - 35^{B}C.

Trichoderma harzianum species T-39 was differentiated from 23 other *T. harzianum* strains by using the PCR-RAPD techniques. Of 23 strains tested, 10 (including the T-39 strain) shared similar RAPD profiles using four PCR primers. Further testing resulted in a subset of primers which can identify T-39 from other isolates.

Mode of Action

Presumably, the primary mechanism through which T-39 suppresses penetration of the gray mold, *Botrytis cinerea*, into plant tissues is by competitive displacement. Nutrients naturally secreted by the plants induce germination of *Botrytis* conidia. T-39 is presumed to prevent germination and penetration of *Botrytis* into the host plant tissue by competing with the pest for nutrients and space on the plant surfaces.

2. **Food Clearances/Tolerances**

An exemption from the requirement of temporary tolerances, which was established for residues of *Trichoderma harzianum* strain T-39 in/on table grape, wine grape and strawberry expires November 30, 2000 (40

CFR'180.1201). Data evaluated for this registration action comply with the Food Quality Protection Act of 1996 and support the exemption from the requirement of a tolerance for residues of strain T-39 on all food commodities. The permanent exemption from tolerance for residues of *Trichoderma harzianum* strain T-39 on all food commodities will be published in the Federal Register on approval of this conditional registration action. Inert ingredients for the End-use Product, TRICHODEX®, are exempt from the requirement of a tolerance under 40 CFR 180.1001. Food/feed commodities not included on the label are excluded on the basis of potential phytopathogenic ecological effects and not health effects data.

Exemption from the requirement of tolerances for other *Trichoderma* strains exist. Another Rifai strain of *Trichoderma harzianum*, strain T-22, has been in use for several years and is exempt from the requirement of tolerances (40 CFR'180.1102). There is no Codex Maximum Residue Level (MRL) for *Trichoderma harzianum* spp.

3. **Physical And Chemical Properties Assessment**

Product identity and manufacturing data support the registration of *Trichoderma harzianum* strain T-39 *(*Table 1.) Starter cultures are screened for potential human pathogens of concern and batches with contamination above regulatory levels are to be destroyed.

The following guideline data requirements were waived because of the nature of the microbial pesticide: melting point, boiling point, solubility, vapor pressure, dissociation constant, octanol/water partition coefficient, stability, oxidizing or reducing potential, flammability/flash point, explodability, viscosity, miscibility, and dielectric breakdown voltage.

Table 1: Physical and Chemical Properties for Trichoderma harzianum strain T-39

Guideline	Study	Result	MRID #
151-20 *885-1100	Product Identity	Acceptable: PCR RAPD identification	43809701 44686801
151-21 *885-1200	Manufacturing Process	Supplemental: must identify and quantify potential contaminants.	43809701
151-22 *885-1300	Discussion of Formation of Unintentional	Supplemental; total contaminant counts well below regulatory levels; upgradable with information of individual	43809701 44686802 44605301

	Ingredients	contaminants.	
151-23 *885-1400	Analysis of Samples	Supplementary: minor data required regarding quality control (media usage to be clarified)	43809702 44686802
	Analytical Method	Media usage and identity of potential contaminants to be clarified.	
151-25 *885-1500	Certification of limits	Supplemental: within limits set on the Confidential Statement of Formula; production data required.	44605301
		Physical/Chemical Properties	
151-26 *885-1600	color	light tan to greenish tan	43809703
	physical state	powder	
	odor	very faint fungi-like	
	density	0.25 - 0.28 g/ml	
	pH of 10% slurry at 22^{B} C	5.6 - 6.0	
	storage stability	Sensitive to heat. For maximum shelf life, store in the vacuum sealed opaque polyethylene-aluminum foil-polyester bag at temperatures at or below 20^{B}C.	

*885-xxxx series = Microbial Pesticide Test guidelines

B. Human Health Assessment

The data submitted comply with the requirements of the Food Quality Protection Act of 1996. There is a reasonable certainty of no harm to human adults, infants and children exposed to *Trichoderma harzianum* strain T-39. This includes all anticipated dietary exposures and all other exposures evaluated with the current database.

1. Toxicology Assessment

Mammalian toxicology data requirements have been submitted and are sufficient to support the registration of the microbial pesticide for the proposed use patterns.

a. Acute Toxicity

Results of the acute toxicity studies are summarized in Table 2.

Acute Oral Infectivity/Pathogenicity

Based on the submitted data, *Trichoderma harzianum* strain T-39 was not infectious, pathogenic or toxic to rats when administered orally at 1.4 to 2.0 x 10^8 CFU/animal. Clearance and infectivity were evaluated in the brain, blood, lymph nodes, kidney, liver, spleen, lungs, caecum and feces. The microbe was detected only in fecal samples, and in those samples a distinct clearance pattern was demonstrated throughout the study. The pesticide was classified Toxicity Category III based on the dose administered during the studies.

Acute Dermal Toxicity

When a single 1150-1570 mg/Kg dose of *Trichoderma harzianum* was applied dermally for a 24 hour exposure period to rabbits, there were no clinical signs of toxicity and no effects on mortality or body weight nor any signs of dermal irritation during the study. The available information indicates that dermal toxicity is not likely to occur at a higher dose. Based on this study, the microbial pesticide is likely to have mild or no dermal effects, and was placed in Toxicity Category IV.

Primary Dermal Irritation Study

A dermal application of 0.5g of *Trichoderma harzianum* strain T-39 at 5 x 10^9 CFU/g produced no dermal response in rabbits after a 4-hour exposure period. The results of this study are classified as Supplementary, but taken in conjunction with the acute dermal toxicity study, the microbial pesticide is likely to be mildly irritating to skin. The pesticide was classified as Toxicity Category IV for primary dermal irritation effects.

Table 2. Acute Mammalian Toxicity: Tier I

Guideline	Study	Toxicity Category	Results	MRID No.
152-30 *885.3050	Acute Oral Toxicity / Pathogenicity	III (based on dose)	Acceptable: not toxic or pathogenic at 1.4 x 10^8 cfu/animal	43809709
81-2 *870.120	Acute Dermal	IV	Supplementary: not toxic or	4380971

0	Toxicity		pathogenic at 1150-1570 mg/kg after 4 hour exposure; observed over 24 hour period	0
152-32 *885.3150	Acute Inhalation Pulmonary toxicity/pathogenicity	II (based on inert)	Supplementary: did not replicate in rat body at 1.4 to $2x10^8$ cfu/animal. No distinct clearance in lungs by day 21, but no adverse effects observed.	43809705
152-33 *885.3200	Intraperitoneal injection toxicity/pathogenicity	Not toxic or pathogenic; not a required study	Acceptable study in rats. LD_{50} was: 644 mg/kg for male; 1087 mg/kg for female; 806 mg/kg for combined male & female.	43809711
81-4 *870.2400	Primary Eye Irritation	TGAI: EP: III	Acceptable: potential severe eye irritation Acceptable: mildly irritating: no corneal involvement after 72 hours; ocular irritation was no longer present after 7 days.	43809706 43809707 43915801
81-5 *870.2500	Primary dermal irritation	IV	Very faint to moderate erythema	43809712
81-6 *870.2600	Dermal sensitization	Dermal sensitizer	guinea pigs: delayed contact hypersensitivity	43809712

*885-xxxx or 870-xxx = Microbial Pesticide Test Guideline Numbers.

Skin Sensitization in Guinea pig

When *Trichoderma harzianum* strain T-39 in physiological saline was applied in occluded dermal patches, it caused delayed contact hypersensitivity in guinea-pigs. This study was designed to meet the requirements of the OECD Guidelines for Testing Chemicals, and was submitted in support of fulfilling EPA data requirements for Hypersensitivity Incidents. While the study is not a substitute for reporting hypersensitivity incidents as discussed below (see **Hypersensitivity Incidents**), it was considered an acceptable study. The Agency requires the registrant to report any hypersensitivity incidents to the Agency under Section 6(a)(2).

Primary Eye Irritation

Three eye irritation studies were submitted. The two acute eye irritation studies conducted with the TGAI, indicate a potential for severe eye irritation, placing the Technical Grade Active Ingredient in acute Toxicity Category I. In one study, a single dose of 0.1g of the active ingredient (approximately 5 x 10^8 cfu) was used to treat 1 rabbit. The results indicated that the microbial pest control agent (MPCA) TGAI, *Trichoderma harzianum* strain T-39, has the potential to cause serious ocular damage. The active ingredient was a severe eye irritant. In another study a single dose of 0.1 g of the active ingredient was administered into the everted lower right eyelid of a sentinel male rabbit. The results of this study indicated that a 3 minute, 180 ml saline rinse, applied 3 minutes post dosing, had no ameliorating effect on the irritancy of the active ingredient. The adhesion of the TGAI to the conjunctivae remained a serious effect of treatment even after rinsing. It is not clear from this study whether the eye effects were due to the active ingredient or the inert, because the product is manufactured by an integrated process.

However, another eye irritation study was conducted in which the test material, administered at guideline levels, was mildly irritating to the eyes or in acute Toxicity Category III. Six male rabbits were treated with a single dose of 0.1 ml (0.04 g) of test material into the everted lower right eyelid. The maximum average irritation score was determined to be 15.3 at 24 hours post dosing. There was no corneal involvement after 72 hours and ocular irritation was no longer present after 7 days, equivalent to a mildly irritating rating.

This study was considered acceptable and can be used for labeling of the EP. Workers, who are most likely to be exposed to the pesticide during mixing/loading, application and post application activities, are required to wear goggles to mitigate against potential eye irritation.

Acute Intraperitoneal Toxicity/Pathogenicity

When TRICHODEX®, containing *Trichoderma harzianum* Rifai strain T-39, was administered via intraperitoneal injection, the LD_{50} for the EP was 644 mg/Kg in male rats, 1087 mg/Kg in female rats and 806 mg/Kg for combined results from male and female rats. The lowest dose administered, 1.5×10^7 cfu/animal, showed no indications of significant adverse effects. This study was considered acceptable and is a substitute for the intravenous study with fungi as active pesticidal ingredients.

Acute Pulmonary Toxicity/Pathogenicity

Small 2 mm pale raised areas were found in the lungs of some animals of both genders treated with the EP containing the active fungi. There were no significant macroscopic lesions found in any test animals in the other experimental groups. The active ingredient was not found in samples of liver, brain, spleen, kidneys, lymph nodes or blood. Microbial clearance through the caecum was evident. Although there was no evidence of MPCA reproduction in the tissues, colony forming units persisted in the lungs of animals treated with the active fungus. However, minimal clinical signs and no deaths were observed. Also, no adverse effects were seen even in the absence of lung clearance by day 21. This study suggested that the active ingredient may not be producing adverse effects. Rather, the lung effects may be due to the predominant inert, which is a known inhalation irritant, even though cleared for food use in 40 CFR 180.1001. The EP was classified as an acute Toxicity Category II pesticide for pulmonary effects. Workers, who are most likely to be exposed during mixing/loading, application and post application activities, are required to wear the recommended dust/mist filtering respirators with NIOSH prefixes, N-95, P-95 or R-95, to mitigate exposure.

Other toxicology studies

In addition to the studies above, the registrant conducted tests to determine chromosomal damage, mutagenicity and dermal sensitization. Single doses each of TRICHODEX7 at 200, 1000, or 5000 mg/kg. TRICHODEX7, were administered orally to mice and erythrocytes observed at 24, 48, or 72 hours post dosing. Under conditions of this study (MRID 43809713), there was no evidence of chromosomal damage leading to micronucleus formation in polychromatic erythrocytes of treated mice. This study was considered supplemental. Another study was the mutagenicity test or Ames Assay which was considered supplementary. However, these studies are not required by EPA for a risk assessment under Subdivision M of the Pesticide Testing Guidelines for microbial pesticides. No further data are required to upgrade these studies.

b. **Hypersensitivity incidents**

A skin sensitization study (MRID 43809712), conducted using the guinea pig as test organism was submitted in lieu of a hypersensitivity incidents report (See *Skin Sensitization in Guinea Pig* above). This study was classified as acceptable, but is not a substitute for timely reports of hypersensitivity incidents and other incident data as required under Section 6(a)(2). Another report was submitted claiming no adverse effects observed in workers manufacturing the product. The study was found acceptable and indicates a lack of hypersensitivity or other health concerns in workers associated with the manufacture of this biofungicide. The company must report any subsequent findings of hypersensitivity or other health incidents to workers, applicators, or anyone exposed to the biopesticide under FIFRA reporting requirements Section 6(a)(2). Appropriate PPE is required to mitigate potential dermal sensitization and risk for occupationally exposed handlers (see **Labeling, Section V**).

c. **Subchronic, Chronic Toxicity and Oncogenicity**

Survival, replication, infectivity, toxicity, or persistence of the microbial agent was not observed in the test animals treated in the Tier I acute oral infectivity test. Consequently, Tier II tests (Guidelines 152-40 through 152-49) involving acute oral, acute inhalation, subchronic oral, acute intraperitoneal, intracerebral, primary dermal irritation, primary eye irritation, immune response, teratogenicity, virulence enhancement, and mammalian mutagenicity

(40 CFR 158.740(C)(2)(vi through xv) were not required. In addition, Tier III tests (Guidelines 152-50 through 53) involving chronic testing, oncogenicity testing, mutagenicity, and teratogenicity were not required (40 CFR 158.740(C)(2)(xvi through xix) based on the lack of concerns following analysis of Tier I test results.

2. **Dietary Exposure and Risk Characterization**

The proposed food use pattern is likely to result in dietary exposure or residues on food and feed. However, residues of the microbial pesticide are likely to be removed from treated food by washing, peeling, cooking and processing. Based on the low toxicity potential for acute oral effects, dietary exposure is not likely to result in any undue hazard.

3. **Occupational and Residential Exposure and Risk Characterization**

a. **Occupational and Residential Exposure and Risk**

The Agency does not expect that occupational and residential exposures will pose an undue risk on the basis of the low toxicity profile (Table 2) and the assumption that appropriate label language is followed. The potential for dermal, eye and inhalation exposure for pesticide handlers exists, with the major source of exposure to workers being generally dermal. The pesticide has demonstrated mild dermal effects on guinea pigs (Toxicity Category IV), and may cause dermal sensitization and delayed contact hypersensitivity. While studies indicate a potential for a moderate pulmonary risk, inhalation exposure is not of concern if the required respirator is used. To mitigate dermal, inhalation and eye exposure and risk to workers, the Agency requires use of appropriate Personal Protective Equipment (PPE) as described under **Labeling** in **Section V.**

b. **Residential, School and Day Care Exposure and Risk Characterization**

The label does not allow applications to turf, residential or recreational areas. Because the use sites are primarily agricultural, exposure to infants and children in school, residential and daycare facilities is likely to be minimal to non-existent. Consequently, the

health risk to infants and children is expected to be negligible to nonexistent based on evaluations of the submitted studies.

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

The microorganism *Trichoderma harzianum* is ubiquitous. It is not known as an aquatic microorganism, and therefore is not expected to proliferate in aquatic habitats. Moreover, *Trichoderma harzianum* is not considered to be a risk to drinking water. Accordingly, drinking water is not being screened for *T. harzianum* T-39 as a potential indicator of microbial contamination or as a direct pathogenic contaminant. Both percolation through soil and municipal treatment of drinking water would reduce the possibility of significant transfer of residues to drinking water. Therefore, the potential of exposure and risk via drinking water is likely to be minimal to nonexistent.

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

This microbial pesticide is intended for use on food crops. The Agency did not require subchronic and chronic dietary exposure studies, since the Tier I acute oral studies demonstrated a low toxicity and no pathogenicity potential. The microbial pesticide can be removed from food/feed commodities by washing, peeling, cooking and processing. Thus potential acute dietary exposure and risk are expected to be minimal to non-existent. Based on the low toxicity profile and low exposure potential of the microbial pesticide, there is no concern for chronic risks posed by dietary exposure of sensitive subpopulations, such as infants and children.

6. **Aggregate Exposure from Multiple Routes Including Oral, Dermal, and Inhalation**

Oral

Oral exposure would occur primarily from eating treated foods and from drinking water. Residues of the microbial pesticide can be easily removed from treated commodities by washing, cooking, peeling and processing. Transfer of residues to drinking water is not likely as discussed previously. Thus dietary exposure and risk are likely to be minimal to non-existent.

Dermal

Dermal exposure via the skin would be the primary route of exposure for mixer/loader applicators. Since unbroken skin is a natural barrier to microbial

invasion of the human body, dermal absorption could occur only if the skin were cut, if the microbe were a pathogen equipped with mechanisms for entry through or infection of the skin, or if metabolites were produced that could be dermally absorbed. *Trichoderma harzianum* strain T-39 is not known to be a human pathogen nor is it known to produce metabolites that are dermally absorbed. Based on the demonstrated lack of adverse effects in the intravenous study, it is the Agency's opinion that even cut skin should not pose a risk to health via entry of absorbed *Trichoderma harzianum* strain T-39 into the body.

However, some of the studies indicate the potential for dermal irritation and delayed contact hypersensitivity due to dermal exposure to the microbial pesticide at 10 to 30 percent concentrations. Accordingly, the Agency has imposed label restrictions and risk mitigation measures to protect populations who are likely to be primarily exposed to the pesticide. Such exposure to pesticide handlers can be ameliorated if they wear long sleeved shirts, long pants, shoes, socks and goggles.

Inhalation

Inhalation would be another route of exposure for mixer/loader applicators and possibly early-entry workers. Based on the Toxicity Category II classification of the pulmonary study, the Agency has decided that pesticide handlers must wear a dust/mist filtering respirator with the NIOSH prefix N-95, P-95 or R-95.

In summary, the potential aggregate exposure and risk derived from the multiple routes discussed above should be adequately mitigated if the pesticide is used as labeled.

7. **Cumulative Effects**

There are registered products containing other species and strains of the fungus *Trichoderma*. The Agency is not aware of a common mechanism of toxicity among these microbes. Given the low toxicity and pathogenicity profile of *Trichoderma harzianum* strain T-39 and the other registered strains of *T. harzianum*, no adverse cumulative effects are expected.

8. **Effects on the Immune and Endocrine Systems**

The active ingredient, *Trichoderma harzianum* strain T-39, is not known to be a human pathogen nor an endocrine disrupter. The submitted

toxicity/pathogenicity studies in the rodent indicate that, following several routes of exposure, the immune system is still intact and able to process and clear the active ingredient. Therefore, no adverse effects to the endocrine or immune systems are known or expected.

C. Environmental Assessment

1. Ecological Exposure and Risk Assessment

Below is a summary of the ecological effects database evaluated in support of this action. The database for studies (Table 3) and information of acute toxicity of *Trichoderma harzianum* strain T-39 to nontarget organisms are sufficient to allow conditional registration as a microbial pesticide for use on all food commodities, except those discussed under **Toxicity to Plants (Section III.C.1.c.**)

2. Ecological Toxicity

a. Toxicity to Terrestrial Animals

i. Avian Species: Acute Toxicity/Pathogenicity

There are two studies on file for the mallard duck and the bobwhite quail (MRIDs 43809714 and 43809715 respectively). These were rated as Supplemental (scientifically sound but not meeting Guideline requirements) because the testing was done with nominal concentrations of the test substance. The studies were conducted according to section 8.1 Part B of the European Communities Council Directive 91/414/EEC and Guideline 71-1 of the EPA Subdivision E, 1982 Pesticide Assessment Guidelines and deviated significantly from the 1989 EPA Subdivision M Guideline. Nevertheless, these avian oral LD_{50} tests performed with the mallard duck and bobwhite quail showed no treatment-related effects after dosing the birds at 2000 mg/kg.

A non-guideline temperature growth study (MRID 44214301) was submitted to supplement the claim of no adverse effects on avian species. It was reported as not meeting the requirements of 40 CFR Part 160 for Good Laboratory Practices (GLP). This study did not conclusively demonstrate that the active ingredient cannot replicate at the basal body

temperatures of birds. It is not a required study and does not need to be duplicated.

The Agency considered all these studies in support of the guideline requirement. Given the natural and widespread occurrence of *T. harzianum* and the lack of reported avian pathogenicity in the open literature, the Agency does not anticipate any avian toxicity or pathogenicity from the proposed uses of TRICHODEX®. This data requirement is satisfied.

ii. **Wild Mammals and Other Terrestrial Animals: Acute Toxicity/Pathogenicity**

The pesticide is to be applied to agricultural sites only. Data submitted demonstrate low mammalian toxicity/pathogenicity. This microbial pesticide is not likely to pose a hazard to wild mammals if it is used as labeled. No further data are required for this guideline at this time.

b. **Toxicity to Aquatic Animals**

i. **Freshwater Fish**

The study on file for freshwater fish deviated substantially from recommended guidelines under Subdivision M. However, given the natural occurrence of *T. harzianum*, and the lack of pathogenicity for fish reported in the literature, only toxicity testing was required. The study was graded as Supplemental and an approximate LC_{50} of 85 mg/L is estimated using the binomial method. This rough estimate is inadequate for quantitative risk assessment, but can be used as a marker for the Agency's decision to impose use limitation to **terrestrial ground application only**. This data requirement is satisfied for the current use patterns.

Aquatic uses, or aerial applications are likely to result in greater exposure to aquatic organisms. For registration of aquatic crops and application by air, the Agency requires 96-hr LC_{50} static renewal studies to demonstrate more precise LD_{50} values for rainbow trout and the bluegill sunfish.

Table 3: Eco-Toxicology Summary

Guideline No.	Study	Status, Classification Comments	MRID #
154-16 *885-4050	Avian oral toxicity/pathogenicity	No treatment-related effects after dosing the mallard duck and bobwhite quail at 2000 mg/kg. No further data required.	43809714 43809715 44214301
154-19 *885-4200	Fresh water fish toxicity/ pathogenicity	Supplementary; approximate LC_{50} of 85 mg/L. Freshwater fish data required for aquatic sites and/or aerial application.	43809704
154-20 *885-4240	Fresh water aquatic invertebrate toxicity/pathogenicity	Upgradable to Supplemental; not toxic to *D. magna* at $1.2x10^3$ cfu/ml over 10 days. Require entire enumeration data for the 10 day range finding study to upgrade study.	44192501
154-22 *885-4300	Nontarget plant toxicity/pathogenicity	Certain sites excluded (see text). Terrestrial ground applications only. Require data to demonstrate that T-39 is not pathogenic to excluded sites.	No MRID
154-23 *885-4340	Nontarget insect toxicity/pathogenicity	Require lady bird beetle study.	No MRID
154-24	Honeybee	Supplemental,	4380971

*885-4380	toxicological/pathogenicity	upgradable to core. Require details of honeybee study.	74380971844439301

*885 series = Microbial Pesticide Test Guideline Numbers.

ii. **Freshwater Aquatic Invertebrate**

TRICHODEX ®, containing *Trichoderma harzianum* strain T-39, was not toxic to *D. magna* at $1.2x10^3$ cfu/ml over 10 days. While the lack of pathogenicity by *Trichoderma harzianum* T-39 to *Daphnia magna* is evident from the submitted data, the study does not, however, fulfill the guideline requirement of a 21 day pathogenicity study. Daphnid death due to a fungus infection would be well apparent within the 10 day time period but is more likely to be detected during the 21 days if the study was continued to comply with guideline requirements. The study was, therefore, rated as supplemental, or scientifically sound but not meeting guideline requirements. However, it is sufficient to make an assessment that the fungus poses a minimal risk to invertebrates for the proposed label use patterns. This conclusion is further supported by the natural occurrence of *Trichoderma harzianum* without any known detrimental effects on aquatic invertebrate populations. Data required to verify the integrity of the study and to upgrade it to supplemental are outlined in **Data Gaps, Section VI.**

c. **Toxicity to Plants**

The registrant submitted lists of crops on which the active ingredient has been used in other parts of the world for many years without adverse effects. The Agency reviewed published literature and found reports that some *Trichoderma* species may be pathogenic to certain crops at different stages of their development. Some of the crops in these reports include **sugarcane, pechay (bok choy), rice, tomatoes, mushrooms, kiwi, tobacco, wheat, barley, oats, soybean, cotton, corn, lemon, apples and chickpea**. The potential adverse effects were extremely variable but were not directly attributable to this strain T-39 of *Trichoderma harzianum*.

Even though the published reports of the adverse effects were not specific for *T. harzianum* strain T-39, the Agency is not allowing its use on the 16 crops listed above until the registrant provides data to support these sites. Risk to other nontarget plants would be negligible provided the pesticide is applied by ground applications only and not applied to aquatic sites.

d. **Toxicity/Pathogenicity to Honeybees and Nontarget Insects**

Honeybee

Two studies were submitted to demonstrate the effects of *T. harzianum* T-39 on honeybees. The first honeybee dietary toxicity/pathogenicity study (MRID 43809717) did not quantify the dose rates of *T. harzianum* T-39, or verify the test medium. Although this study showed no toxicity to adult honeybees, it was considered supplemental/unrepairable. The results of the reported study do not aid in risk characterization or assessment of infectivity or pathogenicity to nontarget organisms, since duration of the study was only 96 hours.

The second submission (MRID 44439301) indicated no infectivity or significant differences in honeybee hive health as measured by (i) field bee longevity, (ii) brood size and pattern, and (ii) hive weight and overall vigor. The submitted results summarized toxicity/pathogenicity to honeybee and compared untreated hives with those exposed to *T. harzianum* T-39 over a 30 day period. It is not possible to make an independent assessment of the exposure and risk to honeybees based on this summary. To upgrade the submission, the Agency requires recorded details of the study to support the claim that the product is not hazardous to honeybee as specified under **DATA GAPS (Section VI: Actions Required by Registrants).**

In the meanwhile, the Agency requirement to demonstrate a lack of pathogenicity to honeybees has been met by the recorded observations that no evidence of *Trichoderma harzianum* strain T-39 growth or infection was seen during the hive experiment. No fungus infected bees were found in the hives throughout the study. Until the recorded data are provided to verify the integrity of the data, labeling must include appropriate Environmental Hazard statements

to protect honeybees (see **End-use Product Environmental Hazards Labeling** in **Section V**).

Other Nontarget Insects

Certain *Trichoderma* species demonstrated larvicidal activity against the plant pests, bark beetles, *Scolytus scolytus,* and *Scolytus multistriatus*. Published literature imply that *Trichoderma* spp. may be useful biological control agents for these plant pests, the bark beetles. However, during field application, the main problem is getting the fungi to the larvae which are under the bark. The results of these studies indicate that it seems unlikely that the antagonistic fungi will establish the type of infection that would spread throughout natural populations of bark beetles. The fungus appears to be symbiotic with the striped bark beetle, and is associated with forest bark engraving beetle, *Ips calligraphus,* but not found pathogenic in laboratory bioassay in the Philippines. *Trichoderma harzianum* strain T-39 has not been directly implicated in these published findings. To clarify these reports for potential infectivity of strain T-39 towards other non-target beetles, the Agency is requiring further data, using the lady bug, a beneficial insect, as an indicator organism (see **Section VI: Actions Required by Registrants**)

3. **Environmental Fate**

a. **Environmental Fate, Transport and Risk Characterization**

T. harzianum and other *Trichoderma* species are common soil inhabitants and are found in soils worldwide, though the natural populations in the soil do not usually exceed 10^2 cfu/gram soil. However, this strain was not isolated from soil, but from the microflora of a plant.

D. Efficacy Data

No efficacy data were required to be submitted for Agency review since no public health uses are involved.

VI.

VII. Public Intrest Findings

The Agency believes the use of *Trichoderma harzianum* strain T-39 under this conditional registration would be in the public interest. The criteria for Agency evaluation of public interest findings is outlined in 51CFR No. 43, Wednesday March 5, 1986. Under part IV.A., the proposed product may qualify for an automatic presumptive finding if it is for minor use, is a unique replacement for pesticides of concern, or is for use against a public health pest.

Trichoderma harzianum strain T-39 is intended for formulation into end-use products for control of *Botrytis*. Almost all of the uses are for minor use crops and, therefore, the product qualifies for an automatic presumptive finding and its use is presumed to be in the public interest. However, because not all end-uses are for minor crops, the Agency has determined that the registration of *Trichoderma harzianum* strain T-39 is in the public interest because there are few other registered alternatives available for the proposed antifungal uses. The Agency has determined that products containing a naturally occurring microbe, such as *Trichoderma harzianum* strain T-39, may provide an alternative which can reduce the hazards posed by conventional chemical pesticides. Therefore, it is in the public interest to grant a conditional registration for *Trichoderma harzianum* strain T-39.

VIII. Risk Management and Registration Decision

A. Determination of Eligibility

Section 3(c)(7)(C) of FIFRA provides for the conditional registration of new active ingredients if it is determined that (A) its composition is such as to warrant the proposed claims for it; (B) its labeling and other materials required to be submitted comply with the requirements of FIFRA; (C) it will perform its intended function without unreasonable adverse effects on the environment; and (D) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment.

To satisfy criteria "A" above, *Trichoderma harzianum* strain T-39 is not expected to cause unreasonable adverse effects when used according to label instructions. Criteria "B" is satisfied by the current label and by the data presented in this document. It is believed that this new pesticidal active ingredient will not cause any unreasonable adverse effects, and is likely to provide protection as claimed, satisfying Criteria "C". Criteria "D" is satisfied in that the toxicological properties of this product are less toxic than other conventional pesticide products currently in use for this target pest.

Therefore, *Trichoderma harzianum* strain T-39 is eligible for conditional registration. The proposed registration sites are for agricultural food/feed commodities. These uses are listed in Table 5, Appendix A.

B. Regulatory Position

1. Conditional/Unconditional Registration

Data submitted are sufficient for a conditional Section 3(c)(7)(C) registration of Trichoderma harzianum strain T-3 9 for the use patterns discussed in this RED.

2. Tolerance Reassessment

During the processing of the extension of the Experimental Use Permit, the exemption from temporary tolerance was reassessed as required by the Food Quality Protection Act (FQPA) of 1996. The petition for the permanent exemption from tolerance for the Section 3 conditional registration of *Trichoderma harzianum* strain T-39 was also considered in the light under FQPA requirements. The Agency decided that in both cases the health effects data support the exemption from tolerance and comply with FQPA for the labeled uses.

3. Ineligible Uses

The label **must not include sugarcane, pechay (bok choy), rice, tomatoes, mushrooms, kiwi, tobacco, wheat, barley, oats, soybean, cotton, corn, lemon, apples and chickpea** until the reports regarding phytotoxicity and/or pathogenicity to these plants by *T. harzianum* strain T-39 are satisfactorily addressed. Aquatic sites and aerial applications are not supported by the current database and must not be included in the label.

4. CODEX Harmonization

There are no Codex harmonization considerations since there is no Codex Maximum Residue Limits set for food use of this active ingredient.

5. Non-food Re/Registrations

This is a new active ingredient and, therefore, not the subject of reregistration at this time. Currently, there are no nonfood uses associated with this active ingredient.

6. Risk Mitigation

There is minimal or negligible potential risk to wildlife, or ground and surface water contamination for products containing this active ingredient. Dietary risk will be adequately mitigated by washing, peeling, cooking and processing of treated foods. Appropriate PPE (long sleeved shirt, long pants, shoes, socks, goggles and respiratory equipment) and a Restricted-Entry Interval (REI) of 12 hours are required to mitigate potential occupational exposure and risk to pesticide handlers. Certain sites are to be excluded from the label as discussed under **Ineligible Uses** to mitigate risks to nontarget organisms. The pesticide is to be applied by ground equipment only until data are provided to allow aerial or aquatic applications. The product label will bear Environmental Hazards text to mitigate any potential risk to beneficial insects.

7. **Endangered Species Statement**

Currently, the Agency is developing a program (The Endangered Species Protection Program) to identify all pesticides whose use may cause potential adverse impacts on endangered and threatened species and their habitats. To aid in the identification of threatened and endangered species and their habitats, several companies have formed an Endangered Species Task Force (EST) under the direction of the American Crop Protection Association (ACPA). Moreover, the EST will assist in providing species location information at the subcounty level, and particularly if an endangered species occurs in areas where pesticides would be used. This information will be useful once the Endangered Species Protection Program has been implemented.

The Agency has no evidence to believe that any endangered of threatened species will be adversely affected if products containing *T. harzianum* strain T-39 are used as labeled. In this regard, specific labeling is not imposed at this time for such products.

C. Labeling Rationale

It is the Agency's position that the labeling for products containing *Trichoderma harzianum* Rifai Strain T-39 must comply with the current pesticide labeling requirements. TRICHODEX® is manufactured by the integrated process such that the manufacturing use product (MP) is also the End-use Product.

1. **Manufacturing Use Product Labeling**

Precautionary Statements must include the requirement for workers to wear a dust-mist filtering respirator with NIOSH/MSHA approval number prefix N-95, R-95 or P-95 and goggles when handling this product.

Directions for Use statements must include the following:

"For formulation into End-use Products only," if the MP is to be used for manufacturing purposes only;

"Apply via ground applications only" if the MP is the same as the End-use Product as is the case with TRICHODEX®, which is intended for use on crops.

Environmental Hazard Statement:

"Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA."

2. **End-use Product Labeling**

a. **Human Health Hazard**

i. **Worker Protection Standard**

Any product whose labeling reasonably permits use in the production of an agricultural plant on any farm, forest, nursery, or greenhouse must comply with the labeling requirements of PR Notice 93-7, "Labeling Revisions required by the Worker Protection Standard (WPS)", and PR Notice 93-11, "Supplemental Guidance for PR Notice 93-7", which reflect the requirements of EPA's labeling regulations for worker protection statements (40 CFR part 156, subpart K). These labeling revisions are necessary to implement the Worker Protection Standard for Agricultural Pesticides (40 CFR part 170) and must be completed in accordance with, and within the deadlines specified in, PR Notices 93-7 and 93-11. Unless otherwise specifically directed, all statements

required by PR Notices 93-7 and 93-11 are to be on the product label exactly as instructed in those Notices.

After April 21, 1994, except as provided in PR Notices 93-7 and 93-11, all products within the scope of those notices must bear WPS PR Notice complying labeling when they are distributed or sold by the primary registrant or any supplemental registered distributor.

After October 23, 1995, except as provided in PR Notices 93-7 and 93-11, all products within the scope of those notices must bear WPS PR Notice complying labeling when they are distributed or sold by any person.

The labels and labeling of all products must comply with EPA's current regulations and requirements as specified in 40 CFR 156.10 and other applicable notices. Labeling must also conform to Worker Protection Safety standards where re-entry into sprayed fields must not take place until sprays have dried unless protective clothing is employed.

Workers and handlers (includes mixer/loader, applicators, and early-entry workers) applying this product must wear long sleeved shirt, long pants, shoes, socks and goggles as well as a dust/mist filtering respirator with NIOSH approval number prefix N-95, R-95 or P-95. Agricultural workers wearing appropriate PPE can enter treated areas during the restricted entry interval (REI) of 12 hours.

ii. **Non-Worker Protection Standard**

There are no non-WPS human health hazard issues.

iii. **End-Use Product Precautionary Labeling**

The Agency has examined the toxicological data base for *Trichoderma harzianum* Rifai Strain T-39 and concluded that the precautionary labeling required during this conditional registration process (i.e. Signal Word, Statement of Practical Treatment and other label statements) adequately mitigates the risks associated with the proposed uses.

For the End-use Product, TRICHODEX®, which contains *Trichoderma harzianum* Rifai Strain T-39:

"**WARNING - AVISO**" and the Spanish and English statement "Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detaile. (If you do not understand the label, find someone to explain it to you in detail.)"

and

"Do not breathe spray mist. Causes moderate eye irritation. Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals. Avoid contact with skin, eyes or clothing. Harmful if absorbed through skin. Harmful if swallowed. If on skin, wash with plenty of soap and water. Get medical attention if irritation persists."

b. **End-use Product Environmental Hazards Labeling**

Provided the following statements are placed in the Environmental Hazards statement, the risk of exposure to *Trichoderma harzianum* Rifai Strain T-39 is minimal to nonexistent to nontarget organisms including endangered species:

i. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of rinsate or equipment washwaters."

ii. "Do not apply this product while bees are actively visiting the treatment area."

3. **Application Rate**

It is the Agency's position, that the labeling for the pesticide products containing *Trichoderma harzianum* Rifai Strain T-39 must comply with the current pesticide labeling requirements. The Agency has not required a maximum number of applications for the active ingredient.

D. Other Labeling Requirements

1. **Manufacturing Use Product name**

   There is no separate manufacturing use product (MP) at this time because the sole registered product containing this active ingredient is manufactured by an integrated process. In the event that the formulation should be used for manufacture into other products, the label must clearly state so.

2. **End-use Product Name:** TRICHODEX®

Active Ingredient: *Trichoderma harzianum* Rifai Strain T-39	20.00%
Inert Ingredients	80.00%
Total	100.00 %

3. Signal word is "**WARNING - AVISO**" based on the evaluation of the acute pulmonary toxicity/pathogenicity study submitted in support of the conditional registration of the product, TRICHODEX, containing *Trichoderma harzianum* Rifai Strain T-39.

4. **All End-use products**

5. All product labels shall comply with Agency labeling requirements and must contain the following information:

6. Product Name

7. Ingredient Statement

8. Registration Number

9. "Keep Out of Reach of Children"

10. Signal Word (depending on the formulation)

IX.

X. Actions Required by Registrants

Reports of incidents of adverse effects to humans or domestic animals are required under FIFRA, Section 6(a)2 and incidents of hypersensitivity under 40 CFR Part 158.690(c), guideline reference number 152-16. Before releasing these products for shipment, the

registrant is required to provide appropriate labels and other Agency requirements as discussed in this RED and Agency communications.

A. Data Gaps

The data required to fulfill these data gaps are discussed below and the time frames for submission summarized in Table 4.

1. **Guidelines 885-1100 through 885-1600 (151-20 through 151-26): Product Identity, Manufacturing Process and Quality Control**

   a. Analyses of 5 batches are required at production and must include data relevant to detection, identification, enumeration and rejection limits of potential human pathogens (bacterial and fungal) using the selective media proposed in the analysis of production batches. All batches containing human pathogens above regulatory levels must be destroyed. The production data will be a condition of registration and must be submitted within one year of the date of this conditional registration.

   b. A data set demonstrating the efficacy of the PCR-RAPD protocol for strain identity is required within 90 days of receipt of this RED document and the conditional registration notice.

2. **Guideline 885-4200 (154-19): Freshwater Fish toxicity/pathogenicity**

   For registration of aquatic sites or by aerial equipment, the Agency requires 96-hr LC50 static renewal studies to demonstrate more precise LD50 values for rainbow trout and the bluegill sunfish.

3. **Guideline 885-4240 (154-20): Freshwater aquatic invertebrate toxicity/pathogenicity**

   The following additional information is required as a condition of registration to verify the integrity of the data submitted in support of this guideline:

   The relationship between the 120 hour stability and 10 day range finding study must be explained to support the integrity of the data. The fact that the recovery percentages are identical at times 0 and 24 hours for 3 treatment levels is inconsistent with expected biological variability. The entire enumeration data for the 10 day range finding study must also be reported. Provided the requested information supports the integrity of the data, the submitted study may satisfy the stated objective of determining the acute toxicity of the microbial pesticide to *Daphnia magna*. Should this information not be sufficient to verify the integrity of the data, the registrant has agreed to submit a new 21 day *Daphnia* study.

4. **Guideline 885-4300 (154-22): Non-target Plant**

Data to demonstrate no pathogenicity to plants listed below must be submitted to the Agency for this guideline if the registrant wishes to register the crops listed below. The label **must not include sugarcane, pechay (bok choy), rice, tomatoes, mushrooms, kiwi, tobacco, wheat, barley, oats, soybean, cotton, corn, lemon, apples and chickpea** until the reports regarding phytotoxicity and/or pathogenicity to these plants by *T. harzianum* strain T-39 are satisfactorily addressed.

5. **Guideline 885-4340 (154-23): Non-target insect**

As a condition of registration, the Agency requires a non-target insect pathogenicity study **on the lady bird beetle** to elucidate the effects of the active ingredient on the beetle family. The study must be submitted within 1 year of the conditional registration to satisfy this data requirement. A protocol had been submitted and is under Agency review.

6. **Guideline 885-4380 (154-24): Honeybee toxicity/pathogenicity**

The honeybee studies are considered supplemental and upgradable to core or scientifically sound if the registrant submits, as a condition of registration:

i. all recorded data, including individual brood size and hive weights by hive number;

ii. *Trichoderma harzianum* strain T-39 weight in application trays and individual spore counts;

iii. the hive numbers and day of swarming for those hives that swarmed. Also, please explain why five of the 15 hives were not used in the experiment.

Table 4: Summary of data gaps and time frames for submission

Standard data required from production batches (Guidelines 151-10 through 15).

Guideline	Title of Study	Data required	Date due
151-20 *885-1100	Product Identity	PCR RAPD identification	within 90 days of conditional registration
151-22 *885-	Discussion of Formation of Unintentional	Human pathogen identification and	1 year after conditional registration

1300	Ingredients	quantification	date
151- 23 *885-1400	Analysis of Samples	5 batch analysis	1 year after conditional registration date
151-25 *885-1500	Certification of limits	Standard data requirement for production batches	1 year after conditional registration date

Ecological Effects data required as conditions of registration

At a minimum data listed below for guidelines 154-20, 154-23, and 154-24 are required for unconditional registration, provided aerial, aquatic and excluded sites are not added to the label.

Guideline	Title of Study	Data required	Date due
154-20 *885-4240	Freshwater aquatic invertebrate toxicity/pathogenicity	Recorded data to upgrade study	6 months after conditional registration date
154-23 *885-4340	Non-target insect	Lady bird beetle study	1 year after conditional registration date
154-24 *885-4380	Honeybee toxicity/pathogenicity	Recorded data	6 months after conditional registration date

Data for guidelines 154-19 and 154-22 are only required if excluded sites, aquatic and aerial applications are requested.

% 154-19 *885-4200	Freshwater Fish toxicity/ pathogenicity	If registering aquatic sites	As required
% % 154-22 *885-4300	Non-target Plant	If registering sites with potential phytopathogenicity (sugarcane, pechay, rice, tomatoes, mushrooms, kiwi, tobacco, wheat, barley, oats,	Must satisfactorily demonstrate no pathogenicity to restricted plants.

soybean, cotton, corn, lemon, apples and chickpea).

iv. *885-xxxx = Microbial Pesticide Test Guideline Numbers.

v. % required for aerial and aquatic applications

vi. %% required if registering excluded crops

XI. APPENDIX A Use Site Registration/Reregistration

This is a new active ingredient and not subject to reregistration. Table 5 lists the use sites which can be treated with products containing the active ingredient, *Trichoderma harzianum* strain T-39. The registrant must comply with the appropriate labeling requirements before releasing these products for shipment.

Table 5. Use Sites

All food/feed commodities except **sugarcane, pechay (bok choy), rice, tomatoes, mushrooms, kiwi, tobacco, wheat, barley, oats, soybean, cotton, corn, lemon, apples and chickpea** in greenhouses and agricultural fields by ground applications only.	**Official date registered:**

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XIII. APPENDIX C - Registration Eligibility Decision Team

Office of Pesticide Programs
Biopesticides and Pollution Prevention Division
Microbials and Plant Pesticides Branch

Phil Hutton Entomologist, Branch Chief

John Kough Biologist, Senior Scientist

Chris Wozniak Biologist, Health Effects

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Mike Mendelsohn Microbiologist, Ecological Effects

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