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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PESTICIDE PROGRA

MAY 18 2000

MEMORANDUM

SUBJECT: Review of Information to Support a Food Tolerance Determination for *Trichoderma hamatum* isolate 382 (ATCC# 20765), the Active Ingredient in Floraguard Related to Tolerance Petition (7E7188)

FROM: John L. Kough, Ph.D., Biologist
Microbial Pesticides Branch, Biopesticides and
Pollution Prevention Division (7511P)

TO: Ann Sibold
Regulatory Action Leader
Microbial Pesticides Branch, Biopesticides and
Pollution Prevention Division (7511P)

ACTION REQUESTED: To review the toxicology data submitted to support the petition for a food tolerance for *Trichoderma hamatum* isolate 382.

CONCLUSION: The submitted data and information can support establishing an exemption from the requirement for a food tolerance for *Trichoderma hamatum* isolate 382 (ATCC 20765).

DATA REVIEW RECORD

Active Ingredient:	*Trichoderma hamatum* isolate 382 (ATCC 20765)
Product Name:	Floraguard
Company Name:	Sellew and Associates
ID No:	74205-G
Chemical Number:	119205

Submission Number: 855319, 855500
DP Barcode: 368020, 368019

BACKGROUND: Sellew and Associates has submitted a petition for a food tolerance determination (7E7188) for *Trichoderma hamatum* isolate 382. The company has provided a data package of product identity, manufacturing process and toxicology studies that have been reviewed (memorandum from I. Barsoum to A. Sibold, Dec. 14, 2009 & Apr. 27, 2010). There are no existing tolerances or tolerance exemptions for *T. hamatum* species but there are tolerance exemptions for two strains of closely related *T. harzianum* (40 CFR 180.1102 & 180.1201)

DISCUSSION: The company has provided acceptable toxicology studies and waivers rationales for other toxicity endpoints. For the current uses described on the label as potting mixes, soil incorporation and soil drench, the Agency can make a finding of a reasonable certainty of no harm from the aggregate exposure to residues of the microbial pesticide.

RECOMMENDATION: An exemption from the requirement for a food tolerance is justified by the data and waiver rationales provided. This determination should be revisited prior to granting any label amendments, if the label uses are expanded beyond the current soil incorporation to include foliar sprays or post-harvest applications.

RISK ASSESSMENT FOR DIETARY EXPOSURE

The classifications that are found for each data submission are assigned by EPA science reviewers and are an indication of the usefulness of the information contained in the documents for risk assessment. A rating of "ACCEPTABLE" indicates the study is scientifically sound and is useful for risk assessment. A "SUPPLEMENTAL" rating indicates the data provide some information that can be useful for risk assessment. The studies may have certain aspects determined not to be scientifically acceptable ("SUPPLEMENTAL: UPGRADABLE"). If a study is rated as "SUPPLEMENTAL: UPGRADABLE," the Environmental Protection Agency always provides an indication of what is lacking or what can be provided to change the rating to "ACCEPTABLE." If there is simply a "SUPPLEMENTAL" rating, the reviewer will often state that the study is not required by the current 40 CFR Part 158. Both "ACCEPTABLE" and "SUPPLEMENTAL" studies may be used in the risk assessment process as appropriate. An "UNACCEPTABLE" rating indicates that new data must be submitted.

For product-specific acute toxicity data requirements, toxicity categories are assigned based on the hazard(s) identified from studies and/or information submitted to the Agency. The product is classified into Toxicity Category I, II, III, or IV, where Toxicity Category I indicates the highest toxicity and Toxicity Category IV indicates the lowest toxicity.

Product Analysis Assessment

All product analysis data requirements (40 CFR § 158.2120) for Section 3(c)(5) registration of Floraguard containing *Trichoderma hamatumi* isolate 382 as an active ingredient, have been satisfied by either acceptable guideline studies or waiver rationales. A full review of these data and information are available in the memoranda from I. Barsoum to A. Sibold (Dec. 14, 2009 & Apr. 27, 2010).

1. Product Chemistry and Composition

Trichoderma hamatum isolate 382 is an MPCA soil fungicide found as the active ingredient in Floraguard. The product is to be used a soil incorporated mix in potting media. The product contains 0.9% w/w *Trichoderma hamatum* isolate 382 as active ingredient with the concentration of not less than 1×10^7 cfu/g dry weight. The label indicates that the product also contains 95% other ingredients. The strain has been deposited in the American Type Culture Collection as #20765. No relationships are known between the *Trichoderma* genus and any pathogen of man, animals, or plants.

Submitted data satisfied the requirements for manufacturing process, and discussion of formation of unintentional ingredients.

Human Health Assessment

1. Toxicology

Acceptable Tier I mammalian toxicology data and data waivers information support the registration of *Trichoderma hamatum* strain 382 found in Floraguard. A short summary of the active ingredient specific data follows.

a. Acute Toxicity/Pathogenicity – Tier I (40 CFR § 158.2140)

ACUTE ORAL TOXICITY/PATHOGENICITY (MRID# 455836-03)
Fasted, 9 week old Sprague-Dawley HSD:SD rats were given a single oral dose of *Trichoderma hamatum* isolate 382, Lot No. 6022C (concentration of 1×10^8 cfu/g) at a dose of 3.6×10^8 cfu to one male, 3.8×10^8 cfu to another male, and 3.9×10^8 cfu to 13 males and 15 females. There were no treatment related clinical signs, necropsy findings, or changes in body weight. No test organism was recovered from blood, brain, kidney, liver, cervical lymph nodes, or spleen of any animal. *Trichoderma hamatum* isolate 382 does not appear to be toxic, infective, and/or pathogenic in rats, when dosed at 3.9×10^8 cfu/animal.
CLASSIFICATION: ACCEPTABLE

ACUTE PULMONARY TOXICITY/PATHOGENICITY (MRID# 46999701/46010602)
Eighteen male and eighteen female 9 week old Sprague-Dawley rats were exposed by the intratracheal route to *Trichoderma hamatum* isolate 382 in sterile buffer at a dose of 1.3×10^7 cfu/animal. There were no test substance related clinical signs or necropsy findings. One treated male lost weight during the second week of the study. All other animals gained weight prior to scheduled sacrifice. The test organisms were recovered from the lungs of treated males and females sacrificed one hour post dosing with clearance by day 7. The test organism was not detected in the lungs or any of the other tissues in the treated animals at day 7 or 14. The control animals had no test organism in any of the tissues, blood, and cecum contents. *Trichoderma hamatum* isolate 382 does not appear to be toxic, infective, and/or pathogenic in rat, when dosed at 1.3×10^7 cfu/animal.
CLASSIFICATION: ACCEPTABLE

ACUTE INJECTION TOXICITY/PATHOGENICITY (MRID # 47598908)
Groups of young adult CD® outbred Sprague-Dawley rats were injected with *Trichoderma hamatum* isolate 382 in 0.1% Tween 80 solution at a dose of 4.0×10^7 cfu/animal. The animals were observed for up to 28 days. There were no adverse clinical signs, necropsy findings, or changes in body weight of the test material treated animals. The relative kidney weights and relative brain weights were significantly decreased on days 14 and/or 28 in females in the treated animal group compared with day 0, but no statistically significant differences were seen when compared with the naïve control group at day 28. Test organism was detected in the lungs, spleen, liver, kidneys, mesenteric lymph nodes, and cecum fluid on days 0, 3, 7, and/or 14 in the test material treated animals, with clearance by day 28. No test organism was detected in the tissues/ organs of the animals treated with the autoclaved test material or the naïve control group. *Trichoderma hamatum* isolate 382 does not appear to be toxic, infective, and/or pathogenic in rats, when dosed at 4.0×10^7 cfu/animal.
CLASSIFICATION: ACCEPTABLE

b. Acute Toxicology and Subchronic Toxicity/Pathogenicity – Tier II; Reproductive Fertility Effects, Carcinogenicity, Immunotoxicity, and Infectivity/Pathogenicity Analysis – Tier III (40 CFR § 158.2140)

Tier II and Tier III studies were not required for *Trichoderma hamatum* isolate 382 strain based on the lack of acute toxicity/pathogenicity in the Tier I studies.

c. Effects on the Endocrine System

Section 408(p) of the Federal Food, Drug, and Cosmetic Act (FFDCA) requires EPA to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of its program,

androgen and thyroid hormone systems, in addition to the estrogen hormone system. The Environmental Protection Agency also adopted EDSTAC's recommendation that the Program include evaluations of potential effects on wildlife.

The Agency has no information to suggest that *Trichoderma hamatum* isolate 382 has an effect on the endocrine system. The submitted acute pulmonary toxicity/pathogenicity study in rodents indicated that following pulmonary exposure, the immune system is still intact and able to process and clear the active ingredient. *Trichoderma hamatum* isolate 382 is a ubiquitous organism in the environment and there have been no reports of the organism affecting endocrine systems. Therefore, it is unlikely that this organism would have estrogenic or endocrine effects and it is practically non-toxic to mammals. Additional data on possible endocrine effects of this microbial pesticide, are not required at this time.

2. Dietary Exposure and Risk Characterization

Dietary exposure to the microbial pesticide is likely to occur, but the lack of acute oral toxicity, infectivity, and pathogenicity support the establishment of an exemption from the requirement of a tolerance for *Trichoderma hamatum* isolate 382.

Dietary exposure to the microbial active ingredient is expected to be minimal. The product is typically mixed into potting soil or applied to soil and will not likely result in residues on the crops. The Agency expects residues on food to be minimal because of the typical method used to apply the microbial fungicide to soils. Moreover, *Trichoderma* lives in soils and is unlikely to live on the plants because any spores that do end up on the plant due to application would decrease over time due to weathering, desiccation and ultraviolet radiation, which can kill even quiescent forms of the fungus. In the remote likelihood that the applied fungus grew on the edible portions of a treated crop, the results of the oral toxicity testing demonstrated that no toxicity or pathogenicity in treated animals occurred, even when dosed with the fungus at high levels by the oral route of exposure.

3. Drinking Water Exposure and Risk Characterization

Drinking water exposure is expected to be negligible because the microbial fungicide will not be applied to water. Further, *Trichoderma hamatum* is a soil microorganism, and would not proliferate in aquatic environments. Moreover, the Agency believes that *Trichoderma* within the soil will not likely percolate into water due to the large size of the fungal spores and the fact that they adhere to soil particles. Even in the unlikely event that dietary exposure occurs through drinking water, the Agency concludes that there is a reasonable certainty that no harm will result because of the lack of acute oral toxicity/pathogenicity to mammals as previously described.

4. Acute and Chronic Dietary Exposure and Risks for Sensitive Subpopulations, Particularly Infants and Children

Section 408(b)(2)(C) of the FFDCA provides that EPA shall assess the available information about consumption patterns among infants and children, the special susceptibility of infants and children

to pesticide chemical residues, and the cumulative effects on infants and children from the residues and other substances with a common mechanism of toxicity. In addition, FFDCA section 408(b)(2)(C) also provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database unless EPA determines that a different margin of safety will be safe for infants and children. Margins of exposure (safety), often referred to as uncertainty factors, are incorporated into EPA risk assessment either directly or through the use of a margin of exposure analysis, or by using uncertainty (safety) factors in calculating a dose level that poses no appreciable risk.

Based on the acute toxicity and pathogenicity data, the Environmental Protection Agency concludes that there is a reasonable certainty that no harm to sensitive subpopulations, including infants, children, and adults, will result from the use of *Trichoderma hamatum* isolate 382. This includes all anticipated dietary exposures and all other exposures for which there is reliable information. The Agency has arrived at this conclusion because the data available on *Trichoderma hamatum* isolate 382 do not demonstrate toxic, pathogenic, or infective potential to mammals. Thus, there are no threshold effects of concern and, as a result, the provision requiring an additional margin of safety does not apply. Further, the considerations of consumption patterns, special susceptibility, and cumulative effects do not apply to pesticides without a demonstrated significant adverse effect.

5. Occupational, Residential, School, and Daycare Exposure and Risk Characterization

a. Occupational Exposure and Risk Characterization

In light of the Tier I acute toxicity/pathogenicity studies, which did not show any toxicity or pathogenicity *via* the oral, pulmonary, or intraperitoneal injection routes of exposure, handler exposure to *Trichoderma hamatum* isolate 382 is not expected to pose any undue risk. Regardless, requirements for the use of appropriate personal protective equipment, and precautionary statements are required on the product label to mitigate any potential risks to pesticide handlers due to prolonged exposure. Handlers working with *Trichoderma hamatum* isolate 382 must wear a long-sleeved shirt, long pants, socks, shoes, waterproof gloves, and a dust/mist filtering respirator meeting NIOSH standards of at least N-95, R-95, or P-95 when mixing, loading, or applying the product.

b. Residential, School, and Daycare Exposure and Risk Characterization

Trichoderma hamatum isolate 382 is a naturally occurring microorganism and is ubiquitous in the environment. *Trichoderma hamatum* isolate 382 will be applied to substrate mixes, ornamental plants, and various plants grown in greenhouses. Although some applications to ornamental plants may be in residential areas, non-dietary exposure would be expected to be below the Agency's level of concern because of its low toxicity classification, and because the lab results indicate *Trichoderma hamatum* isolate 382 is not pathogenic to mammals.

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

Inhalation

In examining aggregate exposure, Section 408 of the FFDCA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

Trichoderma hamatum isolate 382 will be applied to substrate mixes, ornamental plants, and various plants grown in greenhouses. Although some applications to ornamental plants may be in residential areas, non-dietary exposure would be expected to be below the Agency's level of concern because of its low toxicity/pathogenicity to mammals.

7. Cumulative Effects

Section 408(b)(2)(D)(v) of the FFDCA requires the Agency to consider the cumulative effect of exposure to *Trichoderma hamatum* isolate 382 and to other substances that have a common mechanism of toxicity. These considerations include the possible cumulative effects of such residues on infants and children. Based on tests in mammalian systems, *Trichoderma hamatum* isolate 382 does not appear to be toxic to humans via dietary and pulmonary exposure. Therefore, the requirement to consider cumulative effects does not apply.

8. Risk Characterization

The Agency considered human exposure to *Trichoderma hamatum* isolate 382 in light of the standard for registration and safety factors in FIFRA and FFDCA, as amended by the FQPA. A determination has been made that no unreasonable adverse effects to the United States population in general, and to infants and children in particular, will result from the use of *Trichoderma hamatum* isolate 382 when used in accordance with EPA-approved labeling.

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