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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

SUBJECT: Human Health Risk Assessment for 3rd generation Harpin Peptide PHC-91398

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Pesticide Petition No.	B590
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Decision No.	543353
Submission No.	1022977
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MRID Nos.	50641501-50641507, 50641510, 50668901, 50873701, 50929301-50929306.

Primary Reviewer: Natalya Baranova, Ph.D., Biologist
Emerging Technologies Branch
Biopesticides and Pollution Prevention Division

Secondary Reviewer: John L. Kough, Ph.D., Senior Scientist
Risk Assessment Branch
Biopesticides and Pollution Prevention Division

Approved by: Michael Mendelsohn, Chief
Emerging Technologies Branch
Biopesticides and Pollution Prevention Division

To: Kara Welch, Regulatory Action Leader
Emerging Technologies Branch
Biopesticides and Pollution Prevention Division

I. Action Requested

Plant Health Care submitted an application for registration of the End-Use Product PHC-91398 containing a new active ingredient, Peptide 91398, which is a peptide derived from harpin protein (PDHP). PHC-91398 (EPA Reg. No. 71771-RE) comprises 1% active ingredient peptide 91398 [*CBI removed*]. The end-use product PHC 91398, containing 1% peptide, is equivalent to the TGAI for the purpose of this application and "is acceptable for use in the studies required to support the registration", as has been acknowledged by the Biopesticides and Pollution Prevention Division (BPPD) in the February 2, 2017 pre-submission meeting (US EPA 2017).

The end-use product is intended to be used on a wide variety of vegetable crops, ornamentals, tobacco, small fruit crops, landscape plants, and turf via a pre-plant foliar or root dip, as a

greenhouse or field application using conventional spray and drip ground or aerial equipment, and as a seed pretreatment product.
PHC-91398 stimulates the natural growth and defense systems of crops, enhancing overall plant health. Healthier plants exhibit increased plant stamina and vigor, leading to one or more of the following benefits: increased plant growth, improved stand, suppressed nematode egg production, and increased marketable yield. It has no direct killing effect on pests. Product efficacy is based on its ability to activate the plant's own internal defense and growth mechanisms.

In support of the registration, the applicant has submitted Confidential Statements of Formula (CSFs) (dated 10 June 2019), data matrix (dated 10 September 2019), product chemistry data, mammalian toxicity data, and a tolerance exemption petition (8F8698).

II. Background

Ea Peptide 91398 is a 3rd generation plant response elicitor (PRE) that stimulates innate plant defense, growth, and/or quality mechanisms. The mode of action of Ea Peptide 91398 is non-toxic: the induction of natural defense mechanisms in the plant by way of salicylic acid (SA)- and ethylene/jasmonic acid (JA)-dependent signaling, which in turn activate the "hypersensitive response" (HR) and ultimately elicit systemic acquired resistance (SAR) in the plant. In plants, HR is characterized as rapid, localized cell death in plant tissue after infiltration of the peptide into the intercellular spaces of plant leaves. This reaction initiates a complex set of metabolic responses in the treated plant, causing systemic gene expression and eliciting a plant's natural growth and defense system. The result in the plant is an elevated resistance to bacterial and fungal infection, suppression of nematode egg production as well as increased growth and higher yield.

Ea Peptide 91398 is a [*CBI removed*] peptide derived from the harpin protein HrpW of *Erwinia amylovora*. It is modified compared to HrpW of *Erwinia amylovora.* It contains a single amino acid substitution of Q for E, and it is truncated from 447 aa to 27 aa. This truncation might result in the loss of the secondary structure, in a different secondary structure, in the loss of parts of the protein determining its specificity towards plants, etc. Harpin αβ is even further removed from PHC 91398, being 412 aa in length, and with only 21 aa of PHC 91938 identical to the sequence found in harpin αβ.

[*CBI removed*]

In the February 2, 2017 pre-submission meeting, the Biopesticides and Pollution Prevention Division (BPPD) acknowledged that the "1% material [comprising the EP] is a practical equivalent of the TGAI and is acceptable for use in the studies required to support the registration" (US EPA 2017).

Currently two other related harpin-derived products are registered with EPA: harpin and harpin αβ. Harpin is a full length (404 amino acid (AA)) protein first registered with EPA in 2000 (PC code 006477). Harpin αβ is a 412 AA combination of harpin protein fragments derived from various bacterial plant pathogens and was registered in 2004 (PC code 006506). Harpin αβ

contains a sequence that is approximately 71% identical to PHC 91398. These products are referenced in conjunction with this application.

III. Product Identity and Analysis Review

The deficiencies identified in the guideline requirements are as follows:

Physical and Chemical Properties:

-In the 10-day and again in 75-day letters, the company was asked to perform shake flask determination of water solubility as described in OPPTS 830.7840 on pp. 9 and 11, using purified peptide PHC 91398, 100%. This request was not addressed and the deficiency remains.

-Melting point determination is not relevant since peptides do not melt at atmospheric pressure.

-Stability (or a waiver request) to normal/elevated temperatures is required.

Description of the starting materials, production, and formulation process:

-MSDS for materials necessary for [*CBI removed*] of PHC 91398 and [*CBI removed*] are not provided.

Deficiencies are described in more detail in the attached Data Evaluation Records. Both sections were classified SUPPLEMENTAL, BUT UPGRADEABLE.

IV. Summary of Toxicology and Allergenicity Data

A BLAST analysis of PHC 91398 by this reviewer has identified homology with gliadins from wheat by searching allergenonline database. The highest % identity is 41% over the length of harpin peptide. However, E-scores are very high (0.25 or higher). Harpin peptide content of Q and P is quite high; as a consequence, it is somewhat similar to the characteristic allergenic poly Q, P runs found in gliadins. However, harpin peptide does not share well characterized sequence containing the majority of T-cell epitopes with gliadins (see alighnment below, also Shan 2002). It is also on the very end of the length range of peptides that can be allergens (harpin is 27 aa long; the shortest known allergen from bee venom is 26 aa long). In conjunction with its easy digestibility by simulated gastric fluid and lack of dermal sensitization in guinea pigs, this reviewer finds it highly unlikely that harpin peptide is allergenic based on its bioinformatics profile.

Alignment of PHC 91398 peptide and allergen pre-alpha-/beta-gliadin A-III:

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PHC 91398                                QQPIDRQTIEQMAQ---LLAQLLKSLLSPQ
                                         ::::::  .:. :    : :.:.. : :
gliadin          PYPQTQPFPPQQPYPQPQPQYPQPQQPISQQQAQQQQQQQQTLQQILQQQLIPCRDVVLQQHNI
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Table 1 provides the status of the toxicity data requirements as published in 40 CFR § 158.2050 for the proposed PHC 91398 manufacturing-use/end-use pesticide for the human health risk assessment.

Information from the scientific rationales and studies is included in the section below and in the attached Data Evaluation Records.

MRID 50929305 (OCSSP 870.2500 - Primary Dermal Irritation) is classified SUPPLEMENTAL and UPGRADEABLE.

Hypersensitivity incidents, if any, need to be reported to the EPA.

The rest of the submitted studies are classified ACCEPTABLE.

Table 1. Summary of data submitted to comply with toxicology data requirements published in 40 CFR § 158.2140 for support of the registration of proposed product containing PHC 91398.

Data Requirement	OCSPP Guideline No.	Results Summary, Classification and Toxicity Category (As Applicable)	MRID No.
Product-specific EP/MP/TGAI Toxicology Data – PHC 91398			
Acute Oral Toxicity	870.1100	An initial limit dose of 5000 mg/kg was administered to one healthy female rat by oral gavage. Due to the absence of mortality in this animal, two additional females received the same dose level, simultaneously. Since these animals survived, no additional animals were tested. All animals were observed for mortality, signs of gross toxicity, and behavioral changes at least once daily for 14 days after dosing All animals survived test substance administration, gained body weight, and appeared active and healthy during the study. There were no signs of gross toxicity, adverse clinical effects, or abnormal behavior. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period. Under the conditions of this study, the acute oral LD_{50} of the test substance is greater than 5000 mg/kg of body weight in female rats. Based on the results of this study, PHC 91398 meets the requirements for **EPA Toxicity Category IV** for oral toxicity. **Classification: Acceptable** **MRID 50641510** notes a formula change that occurred after toxicity testing and provides rationale why the new formula is not more toxic than the one tested. This rational is ACCEPTABLE.	50929301 50641510

Data Requirement	OCSPP Guideline No.	Results Summary, Classification and Toxicity Category (As Applicable)	MRID No.
Acute Dermal Toxicity	870.1200	Under the conditions of this study, the single dose acute dermal LD_{50} of the test substance is greater than 5000 mg/kg of body weight in male and female rats. Based on the results of this study, PHC 91398 meets the requirements for **EPA Toxicity Category: IV** for dermal toxicity. **Classification: Acceptable** **MRID 50641510** notes a formula change that occurred after toxicity testing and provides rationale why the new formula is not more toxic than the one tested. This rational is ACCEPTABLE.	50929302 50641510

Data Requirement	OCSPP Guideline No.	Results Summary, Classification and Toxicity Category (As Applicable)	MRID No.
Acute Inhalation Toxicity	870.1300	An acute inhalation toxicity test was conducted with rats to determine the potential for PHC 91398 to produce toxicity from a single exposure via the inhalation (nose-only exposure) route. After establishing the desired generation procedures during the pre-test trials, ten healthy rats (5/sex) were exposed to the test atmosphere for 4 hours. Chamber concentration and particle size distributions of the test atmosphere were determined periodically during the exposure period. The animals were observed for mortality, signs of gross toxicity, and behavioral changes at least once daily for 14 days following exposure. Body weights were recorded prior to exposure (initial) and again on Days 1, 3, 7, and 14 (terminal). Necropsies were performed on all animals at terminal sacrifice. Under the conditions of this study, the single exposure acute inhalation LC_{50} of the test substance is greater than 5.23 mg/L in male and female rats. Based on the results of this study, PHC 91398 meets the requirements **for EPA Toxicity Category IV** for inhalation toxicity. **Classification: Acceptable** **MRID 50641510** notes a formula change that occurred after toxicity testing and provides rationale why the new formula is not more toxic than the one tested. This rational is ACCEPTABLE.	50929303 50641510

Data Requirement	OCSPP Guideline No.	Results Summary, Classification and Toxicity Category (As Applicable)	MRID No.
Acute Eye Irritation	870.2400	One-tenth of a milliliter (0.052 grams) of the test substance was instilled into the right eye of three healthy rabbits. The left eye remained untreated and served as a control. Ocular irritation was evaluated by the Draize method of scoring. One hour after test substance instillation, minimal conjunctivitis was noted for all three treated eyes, which cleared by 24 hours. There was no corneal opacity or iritis observed in any treated eye during this study. Under the conditions of this study, the test substance is classified as minimally irritating (**EPA Toxicity Category Class IV**) to the eye of a female rabbit. **Classification: Acceptable** **MRID 50641510** notes a formula change that occurred after toxicity testing and provides rationale why the new formula is not more toxic than the one tested. This rational is ACCEPTABLE.	50929304 50641510

Data Requirement	OCSPP Guideline No.	Results Summary, Classification and Toxicity Category (As Applicable)	MRID No.
Primary Dermal Irritation	870.2500	A primary skin irritation test was conducted with rabbits to determine the potential for PHC 91398 to produce irritation after a single topical application. Five-tenths of a gram of the test substance was moistened with distilled water and applied to the skin of three healthy female rabbits for 4 hours. Following exposure, dermal irritation was evaluated by the Draize method of scoring. Within twenty-four hours of patch removal, two treated sites exhibited very slight erythema. The overall incidence and severity of irritation decreased with time. All animals were free of dermal irritation by 72 hours. Under the conditions of this study, the test substance is classified as **EPA toxicity Category IV** for Primary Skin Irritation. **Classification: Supplemental and Upgradeable** Control (for example, the side of the trunk left untreated) should be described. The origin of mechanical damage around the dose side observed in all three animals, at every observation time, should be explained. **MRID 50641510** notes a formula change that occurred after toxicity testing and provides rationale why the new formula is not more toxic than the one tested. This rational is ACCEPTABLE.	50929305 50641510

Data Requirement	OCSPP Guideline No.	Results Summary, Classification and Toxicity Category (As Applicable)	MRID No.
Dermal sensitization in guinea pigs	870.2600	A dermal sensitization test was conducted with guinea pigs to determine the potential for PHC 91398 to produce sensitization after repeated topical applications. A 75% w/w mixture of the test substance in distilled water was topically applied to twenty healthy test guinea pigs, once each week for a three-week induction period. Twenty-seven days after the first induction dose, a challenge dose of the test substance at its highest non-irritating concentration (HNIC, determined in the preliminary irritation screen to be a 75% w/w mixture in distilled water) was applied to a naive site on each guinea pig. A naive control group (ten animals) was maintained under the same environmental conditions and treated with the test substance at challenge only. Approximately 24 and 48 hours after each induction and challenge dose, the animals were scored for erythema. No positive sensitization reaction was observed. Based on the results of this study, the test substance is **not considered to be a contact sensitizer**. The positive response observed in the historical positive control validation study with alpha-Hexylcinnamaldehyde, $\geq$95% (HCA) validates the test system used in this study. **Classification: Acceptable** **MRID 50641510** notes a formula change that occurred after toxicity testing and provides rationale why the new formula is not more sensitizing than the one tested. This rational is ACCEPTABLE.	50929306 50641510

Data Requirement	OCSPP Guideline No.	Results Summary, Classification and Toxicity Category (As Applicable)	MRID No.
90-day oral toxicity	870.3100	A waiver has been requested based on the following facts and data: 1) the active ingredient is sourced from a bacterial plant pathogen, *Erwinia amylovora*, that has no known pathogenicity to mammals; 2) bioinformatics analysis of Ea Peptide 91398 indicates it is not related to known allergens or toxins; 3) Ea peptide 91398 is not subchronically toxic based on its negligible acute toxicity and evidence of rapid digestibility; 4) mammalian cells do not contain amino acid sequences with significant homology to the PHDP plant receptor protein; 5) previous exposures to naturally occurring harpin-producing bacterial plant pathogens, harpin proteins, and harpin end-use products indicate there are no associated adverse health effects; 6) repeat, long term exposure to Ea Peptide 91398 is not expected. **Classification: Acceptable** Lack of acute toxicity, no indications of allergenicity or similarity to known toxins via bioinformatics, and the finding that the peptide is easily digestible together with the nature of the product (peptide) obviate the need for this guideline requirement.	50668901

Data Requirement	OCSPP Guideline No.	Results Summary, Classification and Toxicity Category (As Applicable)	MRID No.
90-day dermal toxicity	870.3250	A waiver has been requested based on the following facts and data: 1) the active ingredient is sourced from a bacterial plant pathogen, *Erwinia amylovora*, that has no known pathogenicity to mammals; 2) bioinformatics analysis of Ea Peptide 91398 indicates it is not related to known allergens or toxins; 3) Ea peptide 91398 is not subchronically toxic based on its negligible acute toxicity and evidence of rapid digestibility; 4) mammalian cells do not contain amino acid sequences with significant homology to the PHDP plant receptor protein; 5) previous exposures to naturally occurring harpin-producing bacterial plant pathogens, harpin proteins, and harpin end-use products indicate there are no associated adverse health effects; 6) repeat, long term exposure to Ea Peptide 91398 is not expected. **Classification: Acceptable** Lack of acute toxicity, no indications of allergenicity or similarity to known toxins via bioinformatics, and the finding that the peptide is easily digestible together with the nature of the product (peptide) obviate the need for this guideline requirement.	50668901

Data Requirement	OCSPP Guideline No.	Results Summary, Classification and Toxicity Category (As Applicable)	MRID No.
90-day inhalation toxicity	870.3465	A waiver has been requested based on the following facts and data: 1) the active ingredient is sourced from a bacterial plant pathogen, *Erwinia amylovora*, that has no known pathogenicity to mammals; 2) bioinformatics analysis of Ea Peptide 91398 indicates it is not related to known allergens or toxins; 3) Ea peptide 91398 is not subchronically toxic based on its negligible acute toxicity and evidence of rapid digestibility; 4) mammalian cells do not contain amino acid sequences with significant homology to the PHDP plant receptor protein; 5) previous exposures to naturally occurring harpin-producing bacterial plant pathogens, harpin proteins, and harpin end-use products indicate there are no associated adverse health effects; 6) repeat, long term exposure to Ea Peptide 91398 is not expected. **Classification: Acceptable** Lack of acute toxicity, no indications of allergenicity or similarity to known toxins via bioinformatics, and the finding that the peptide is easily digestible together with the nature of the product (peptide) obviate the need for this guideline requirement.	50668901

Data Requirement	OCSPP Guideline No.	Results Summary, Classification and Toxicity Category (As Applicable)	MRID No.
Prenatal developmental toxicity	870.3700	A waiver has been requested based on the following facts and data: 1) the low application rate and high degradation suggest that the intended use will not likely result in significant exposure of female humans to Ea Peptide 91398; 2) the active ingredient is sourced from a bacterial plant pathogen, *Erwinia amylovora*, that has no known pathogenicity to mammals; 3) bioinformatics analysis of Ea Peptide 91398 indicates it is not related to known allergens or toxins; 4) Ea peptide 91398 is not subchronically toxic based on its negligible acute toxicity and evidence of rapid digestibility; 5) mammalian cells do not contain amino acid sequences with significant homology to the PHDP plant receptor protein; 6) despite previous exposures to naturally occurring harpin-producing bacterial plant pathogens, harpin proteins, and harpin end-use, there have been no reports of teratogenicity. **Classification: Acceptable** Lack of acute toxicity, no indications of allergenicity or similarity to known toxins via bioinformatics, and the finding that the peptide is easily digestible together with the nature of the product (peptide) obviate the need for this guideline requirement.	50668901

Data Requirement	OCSPP Guideline No.	Results Summary, Classification and Toxicity Category (As Applicable)	MRID No.
Bacterial reverse mutation test	870.5100	A waiver has been requested based on the following facts and data: 1) Ea Peptide 91398 is not structurally related to a known mutagen; 2) despite previous exposures to naturally occurring harpin-producing bacterial plant pathogens, harpin proteins, and harpin end-use products, there is no evidence of genotoxicity*;* 3) mammalian cells do not contain amino acid sequences with significant homology to the PHDP plant receptor protein; 4) the low application rate and high degradation suggest that the intended use will not result in significant exposure of humans to Ea Peptide 91398; 5) the peptide is incompatible with this assay. **Classification: Acceptable** The nature of the product (peptide) obviates the need for this guideline requirement.	50668901

Data Requirement	OCSPP Guideline No.	Results Summary, Classification and Toxicity Category (As Applicable)	MRID No.
In vivo mammalian chromosomal aberration assay	870.5375	A waiver has been requested based on the following facts and data: 1) Ea Peptide 91398 is not structurally related to a known genotoxin; 2) despite previous exposures to naturally occurring harpin-producing bacterial plant pathogens, harpin proteins, and harpin end-use products, there is no evidence of genotoxicity; 3) mammalian cells do not contain amino acid sequences with significant homology to the PHDP plant receptor protein; 4) the low application rate and high degradation rate suggest that the intended use will not result in significant exposure of humans to Ea Peptide 91398; and 5) the peptide is incompatible with this assay. **Classification: Acceptable** Lack of acute toxicity, no indications of allergenicity or similarity to known toxins via bioinformatics, and the finding that the peptide is easily digestible together with the nature of the product (peptide) obviate the need for this guideline requirement.	50668901

Data Requirement	OCSPP Guideline No.	Results Summary, Classification and Toxicity Category (As Applicable)	MRID No.
Degradation of PDHP by Proteases	Non-guideline	Samples of 91398 PDHP material were used to evaluate the enzymatic degradation of PDHP in the presence of Pepsin and Subtilisin A in order to mimic the processes of natural systems. SDS-PAGE gels under reducing electrophoretic conditions, were used as the detection test system. The 91398 peptide was easily degraded by both enzymes, with digestion taking place within 1 to 20 minutes. The proteins are therefore considered to be readily degraded both in the environment and after oral ingestion. **Classification: Acceptable**	50641508

V. Human Exposure and Risk Characterization Assessment

1. Description of Uses

PHC 91398 containing 1% of Ea peptide 91398 is intended for use as a pre-plant foliar, root dip, or as a foliar application on vegetable and field crops, ornamentals, tobacco, small fruit crops, trees and vines, landscape plants and turf in greenhouse, shade house, nursery, and field production; in ornamental gardens, athletic fields, parks, golf courses and public or private lawns and grounds.

As a pre-plant foliar or root dip, the recommended rate of application is 1-9 oz per 100 gallons of water. As a foliar application, the recommended rate is 2 oz per 50 gallons of water to landscape plants, and 2 oz per acre of turf. The recommended frequency of foliar application is once per month during the growing season. It is also suggested that PHC 91398 is used as a foliar application in a field for continued vegetable, field, ornamentals, tobacco, trees and vines, and small fruit crop management at a rate of, depending on the crop, between 0.5 and 13 oz per acre, at 14 to 35-day intervals (depending on the crop). PHC-91398 is recommended for foliar application in greenhouses at a rate 1-9 oz per 100 gal of water, at 14-21day intervals. PHC 91398 can be applied up to the day of harvest.

A specified amount of PHC 91398 is mixed with non-chlorinated (or treated with a chlorine-removing product) water. Application is via conventional ground or aerial equipment.
PHC 91398 can also be used as a seed treatment by dissolving in non-chlorinated (or treated with a chlorine-removing product) water, applying to seeds and allowing them to dry before bagging.

Recommended application rates vary between 0.1 and 5 oz per 100 lb seed, depending on the seeds, or between 0.1 to 0.3 oz per 80,000 seeds for corn and 0.15 to 0.45 oz per 140,000 seeds for soybean.

Personal protective equipment for applicators and other handlers includes long-sleeved shirt and long pants, shoes and socks.

2. Aggregate Exposure and Risk Characterization

In examining aggregate exposure, FFDCA section 408 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 sources and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

a. Food Exposure and Risk Characterization

The residue of PHC 91398 can be expected to be found on food items, especially since PHC 91398 has no pre-harvest interval for application. The applicant claims that PHC 91398 is rapidly degraded in the environment. However, the possibility of its use as a seed pre-treatment suggests that this degradation may not be as rapid as suggested. Nevertheless, PHC 91398 was found to be non-toxic via oral application to rats in quantities of 5000 mg per kg of body weight (EPA toxicity category IV). The quantities of PHC 91398 applied to the crops are very small (maximum recommended application rate is 3.69 g of active ingredient per acre), and its presence on treated crops is likely to be further reduced through normal washing and processing. Finally, PHC 91398 is rapidly degraded in simulated gastric fluid. PHC 91398 does not present any risk to human health via food exposure.

b. Drinking Water Exposure and Risk Characterization

There is a possibility that PHC 91398 could contaminate drinking water through run-off from treated fields. However, the quantities of PHC 91398 applied to the crops are very small (maximum recommended application rate is 3.69 g of active ingredient per acre), and it is likely to be significantly further diluted in water. The water treatment process, including the addition of chlorine, is proposed by the applicant to contribute to a significant and rapid degradation of PHC 91398, however, the data confirming this has not been submitted with present application. PHC 91398 was found to be non-toxic via oral and dermal application to rats in quantities of 5000 mg per kg of body weight (EPA toxicity category IV). PHC 91398 is rapidly degraded in simulated gastric fluid.
The assignment of a category for dermal irritation for PHC 91398 is pending addressing several deficiencies, but drinking water contaminated with PHC 91398 is not likely to present any risk due to significant dilution of PHC 91398, as described above.
This reviewer concludes that PHC 91398 does not present any risk to human health via drinking water exposure.

c. Non-occupational, Residential Exposure and Risk Characterization

There is a potential for residential dermal exposure by brushing against treated plants before completely dry when PHC 91398 is applied in residential areas. PHC 91398 was found to be non-toxic via oral and dermal application to rats in quantities of 5000 mg per kg of body weight (EPA toxicity category IV). It was also found to not be a dermal sensitizer. The assignment of a category for dermal irritation for PHC 91398 is pending addressing several deficiencies. However, the quantities of PHC 91398 recommended for application in residential areas are very small (maximum recommended application rate is 3.69 g of active ingredient per acre). It is unlikely that PHC 91398 will pose any risk to human health via residential exposure. Nevertheless, all hypersensitivity incidents should be reported to EPA, in case this conclusion needs to be reconsidered.

3. Cumulative Effects

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, EPA consider "available information concerning the cumulative effects of PHC 91398 . . . residues and other substances that have a common mechanism of toxicity." No risk of cumulative toxicity/effects from PHC 91398 has been identified as no toxicity has been shown for PHC 91398 in the submitted studies, therefore, no common mechanism of toxicity exists for PHC 91398 with other compounds.

4. Determination of Safety for U.S. Population, Infants and Children

a. U.S. Population

PHC 91398 does not present any risks for US population.

b. Infants and Children

FFDCA section 408(b)(2)(C) provides that EPA shall apply an additional tenfold (10X) 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 on toxicity and exposure, unless EPA determines based on reliable data that a different margin of safety will be safe for infants and children. This additional margin of safety is commonly referred to as the Food Quality Protection Act Safety Factor. In applying this provision, EPA either retains the default value of 10X or uses a different additional safety factor when reliable data available to EPA support the choice of a different factor. Since EPA has concluded that there is no risk from the PHC 39318 use according to the guidelines suggested on the product label to the general population, there is also no risk for infants and children.

5. Occupational Exposure and Risk Characterization

There is a potential for occupational dermal, eye and inhalation exposure from manufacturing PHC 91398, from mixing the powder with solvent for application, and from surface spraying. The potential for dermal and inhalation exposure is somewhat mitigated by personal protective equipment required for applicators and other handlers, which includes long-sleeved shirts and long pants and shoes with socks. In addition, PHC 91398 was found to be non-toxic via oral and dermal application to rats in quantities of 5000 mg per kg of body weight, and via inhalation at a rate of 5.23 mg/L (EPA toxicity categories IV). It was also found to not be a dermal sensitizer.

The assignment of a category for dermal irritation for PHC 91398 is pending addressing several deficiencies. If these are adequately addressed, the information will be sufficient to conclude that there are no occupational risks associated with manufacture of PHC 91398, or its application according to the guidelines suggested on the product label. Nevertheless, all hypersensitivity incidents should be reported to EPA, in case this conclusion needs to be reconsidered.

VI. Human Health Risk Conclusions

The assignment of a category for dermal irritation for PHC 91398 is pending addressing several deficiencies. Additionally, several more deficiencies were identified in the product characterization data submitted. If these are adequately addressed, the information will be sufficient to conclude that there are no risks associated with manufacture of PHC 91398, or its application according to the guidelines suggested on the product label. Nevertheless, all hypersensitivity incidents should be reported to EPA, in case this conclusion needs to be reconsidered

References

Shan L, Molberg Ø, Parrot I, Hausch F, Filiz F, Gray GM, Sollid LM, Khosla C. Structural basis for gluten intolerance in celiac sprue. Science. 2002 Sep 27;297(5590):2275-9.

VII. Registration of the [*CBI removed*] harpin peptide.

In addition to the application for the Ea peptide 91398, the company subsequently inquired about an alternate manufacturing process and the associated requirements for registration of a harpin peptide [*CBI removed*] and is only different from the Ea peptide 91398 by one amino acid. We have determined that the following data must be submitted to support human health and product characterization requirements for registration of such a peptide.

The following data is required because of the different production process:

OCSPP 880.1100	Product identity and composition
OCSPP 880.1200	Description of starting materials, production and formulation process
OCSPP 880.1400	Discussion of formation of impurities
OCSPP 830.1700	Preliminary analysis

New data on the Physical and Chemical Characteristics must be submitted since analysis of the proposed EP containing peptide [*CBI removed*] may yield different results.

New data on the toxicity of the proposed product, or well-supported waivers, need to be submitted because of the difference in sequence between the current Ea peptide 91398 and the proposed product.

New data on the stability of the proposed product in the environment, or a well-supported waiver, is needed since the sequence of the [*CBI removed*] peptide is changed to improve its stability under certain conditions.