



BIOPESTICIDE REGULATORY ACTION DOCUMENT

HARPIN $\alpha\beta$ PROTEIN
(PC Code 006506)

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U.S. Environmental Protection Agency
Office of Pesticide Programs
Biopesticides and Pollution Prevention Division

HARPIN $\alpha\beta$ PROTEIN

(PC Code 006506)

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I. EXECUTIVE SUMMARY

A. IDENTITY/MODE OF ACTION

Harpin $\alpha\beta$ protein is a second generation harpin-based active ingredient that initiates a complex set of metabolic responses in the treated plant, causing natural gene expression and eliciting a plant's natural growth and defense systems. Harpin $\alpha\beta$ protein consists of a combination of four harpin protein fragments derived from three naturally occurring bacteria: (1) harpinN from *Erwinia amylovora*, (2) harpinW from *Erwinia amylovora*, (3) popA from *Ralstonia solanacearum* and (4) harpinZ from *Pseudomonas syringae*. As with all other harpins, harpin $\alpha\beta$ is an acidic protein that is glycine rich, and contains few or no cystine residues; it elicits the hypersensitive response (HR) which is characterized as rapid, localized cell death in plant tissue after infiltration of harpin into the intercellular spaces of plant leaves; and it is heat stable. In terms of chemical structure and biological activity, harpin $\alpha\beta$ is closely related to the harpin protein registered in 2000 (PC Code 006477).

Classified as a biochemical pesticide, harpin $\alpha\beta$ provides growth enhancement, disease suppression (including increased post harvest protection), and/or other crop quality benefits for a wide spectrum of plants. Harpin $\alpha\beta$ is commercially produced in *Escherichia coli* by transfer of a DNA fragment encoding harpin $\alpha\beta$ protein derived from multiple bacterial sources to the cell production strain, *E. coli* K-12. The harpin $\alpha\beta$ producing strain is considered a debilitated strain of *E. coli*, which cannot grow in the human digestive tract, or survive in the environment. *E. coli* K-12 cells are killed and lysed at the end of the fermentation process. Harpin $\alpha\beta$ protein and other cell constituents are then extracted for formulation into an end-use product, code name EBC-351, and hereafter referred to by the brand name: ProAct™.

Harpin $\alpha\beta$ exhibits no direct inhibitory or toxic effect on plant pathogens, and thus cannot exert the selection pressure that would promote the development of resistance in pest populations.

B. USE/APPLICATION

Harpin $\alpha\beta$ protein is proposed for use on all food commodities as well as on turf, trees, and ornamentals. It is formulated as a wettable granule for application with conventional ground or aerial spray equipment, as well as sprinkler, drip or chemigation systems. Use rates are extremely low, generally 0.14 to 3.69 grams of active ingredient per acre.

C. RISK ASSESSMENT

Health Effects

Harpin $\alpha\beta$ protein is classified as a Toxicity Category IV product via the oral and dermal route, and a Toxicity Category IV eye and skin irritant. It is classified as Toxicity Category III via the inhalation route because the limit dose could not be reached. For the previous six years, researchers and workers have worked with harpin $\alpha\beta$ in its production and application, and there has been no indication of any toxicity or hypersensitivity associated with this protein. Because of the lack of demonstrated adverse health effects, low rates of application, and rapid degradation in the field, no residues are expected on treated crops and attendant dietary risks are expected to be minimal to non-existent. Because of the lack of demonstrable toxicity, no

adverse effects are expected to applicators, handlers and other workers. Finally, there is reasonable certainty that no harm to adults, infants or children will result from aggregate exposure to harpin $\alpha\beta$ residues.

Ecological Effects

Harpin $\alpha\beta$ has no demonstrated adverse effects in *Daphnia* and has been shown to be practically nontoxic to honeybees. In addition, the closely related harpin protein registered in 2000 (PC Code 006477) has no effect on bird, fish, algae, and seedling emergence of 10 agronomically important plants. Evidence from these studies suggest that the amounts of harpin $\alpha\beta$ required to elicit acute toxicities in nontarget organism populations would not likely be achieved by exposures to harpin $\alpha\beta$ applied at label rates.

D. REGISTRATION APPROVAL/LABELING RESTRICTIONS

All data requirements for registration under Section 3(c)(5) have been satisfied and found to be acceptable. The first product registered with Harpin $\alpha\beta$ as the active ingredient was ProAct™, on February 9, 2005.

II. OVERVIEW

A. ACTIVE INGREDIENT OVERVIEW

A.I. Name: Harpin $\alpha\beta$ Protein

Product Name: ProAct™ (originally designated code name: EBC-351)

P.C. Code: 006506

Basic Manufacturer: Eden Bioscience Corporation
3830 Monte Villa Parkway, Suite 100
Bothell, Washington 98021-7266

B. USE PROFILE

Type of Pesticide: Biochemical derived from killed genetically engineered *E.coli* K12

Use Sites: All food commodities; turf, trees, and ornamentals.

Activity: Increases plant health and vigor, assists in the management of certain diseases, enhances crop quality and production and extends shelf life through pre-harvest applications.

Formulation Types: ProAct is an end-use product formulation containing 1% Harpin $\alpha\beta$ protein, formulated as a wettable granule.

Method and Rates of Application: Conventional ground or aerial foliar or pre-plant dip; seed treatment; application via conventional sprinkler, drip, or chemigation systems, and greenhouse drench and transplant applications. Use rates are generally 0.14-3.69 grams of active ingredient per acre at approximately 14-day intervals.

Type of Treatment: Foliar spray; seed treatment; irrigation/chemigation; pre-plant dip; greenhouse soil drench.

Equipment: Conventional ground or aerial spray equipment; sprinkler, drip irrigation, chemigation systems; traveling boom.

Timing: Greenhouse applications after seedling emergence; repeat every 14-21 days. Apply 5-7 days before transplant and/or apply as a drench or pre-plant dip at transplant. Field foliar applications are recommended at planting and at approximately 14-day intervals through harvest. For newly-seeded crop, sprays begin at the appearance of the first true leaf.

C. DATA REQUIREMENTS

The Agency has reviewed the data required for the proposed uses of this pesticide under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) as amended by the Food Quality Protection Act (1996). All data requirements have been satisfied for registration of this biochemical pesticide under Section 3(c)(5). For Harpin $\alpha\beta$ protein, the product identity and product analysis information, as well as data submitted to assess acute mammalian toxicology and ecological effects are sufficient to support the proposed use patterns. Based on submitted information, the Agency foresees no unreasonable adverse effects to human health and the environment from the use of this biochemical pesticide as labeled.

D. REGULATORY HISTORY

Experimental Use Permit and Tolerance Exemption

A 2-year Experimental Use Permit (69834-EUP-2) was issued in April 2004 and the existing exemption from the requirement of a tolerance for harpin protein (40 CFR 180.1204) was amended to cover all harpin proteins that meet the criteria set forth in the amended exemption. As such, both the harpin protein registered in 2000 (PC Code 006477) and harpin $\alpha\beta$ are exempt from the requirement of a tolerance. The approved experimental program encompassed a broad range of use sites, including corn, rice, cotton, soybean, peanut, sugarcane, wheat, ornamentals, and citrus. The maximum quantity of active ingredient approved was 709 pounds, on a total of 4942 acres in 30 states.

Prior to the EUP, the registrant filed Pesticide Petition 3F6765 to amend the existing tolerance exemption for harpin protein on all food commodities (40 CFR 180.1204). A Notice of Filing was published in the Federal Register on January 28, 2004 (69 FR 4151) and the amended exemption from tolerance was published in the Federal Register on May 5, 2004 (69 FR 24992). In addition, a Notice of Receipt of an application for a new active ingredient was

published on August 11, 2004 (69 FR 48867). No comments were received in response to any of these notices.

E. FOOD CLEARANCES/TOLERANCES

The Agency evaluated data under Section 408 of the Federal Food, Drug and Cosmetic Act (FFDCA) as amended by 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 from the potential of secondary transfer of residues to drinking water during applications of the pesticide was also considered. The data submitted are sufficient to support the exemption from the requirement of a tolerance in or on all food/feed commodities.

III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

Product Identity and Mode of Action

The Agency has classified ProAct™, containing the active ingredient harpinαβ, as a biochemical pesticide because it is derived from naturally occurring microorganisms, does not contain any persistent microbes, has a non-toxic mode of action, and does not alter the DNA of treated plants. Harpinαβ is produced in *Escherichia coli* K-12 by transfer of a DNA fragment encoding portions of the harpin protein from *Erwinia amylovora*, *Ralstonia solanacearum* and *Pseudomonas syringae* to the cell production strain. The harpinαβ producing strain is considered a debilitated strain of *E. coli* which has no mammalian gut colonization potential and is reliant upon laboratory conditions for survival. Cells are killed and lysed to release harpinαβ protein and other cell constituents for formulation into an end-use product. Product chemistry data used in support of the registration of ProAct™ are summarized in Table 1.

Table 1. Physical and Chemical Properties for ProAct™

Guideline Number	Study	Result	MRID Number
OPPTS 830.1550	Product Identity and Composition	Acceptable. The sole active ingredient consists of 1% by weight of harpinαβ protein which is agglomerated onto an inert carrier to produce the wettable granular end-use product.	46047001
OPPTS 830.1600	Description of Beginning Materials	Acceptable. ProAct is produced by an integrated process starting with fermentation of a cell line in which the active ingredient is an intracellular constituent.	46047001

Guideline Number	Study	Result	MRID Number
OPPTS 830.1620	Description of Production Process	Acceptable. Following fermentation, several steps are undertaken to disrupt cells and remove cell debris and fermentation media. The final production step involves agglomeration of a liquid product containing harpin $\alpha\beta$ with an inert carrier.	46047001
OPPTS 830.1670	Discussion of Formation of Impurities	Acceptable. Harpin $\alpha\beta$ decomposition products would be amino acids and peptides that are metabolized by cellular organisms. Other unintentional ingredients should fall below 0.1% w/w in the final product. Quality control procedures carefully screen each preparation for biological activity and contamination by microorganisms and dictate the rejection of any contaminated preparation.	46047001
OPPTS 830.1700	Preliminary Analysis	Acceptable. Preliminary analysis was performed on five different lots of ProAct. Harpin $\alpha\beta$ was quantified by an acceptable liquid chromatography method. Moisture content in the final product was determined by a gravimetric method. Product quality evaluation of ProAct also included screening for a range of biological activity and potential contaminants. No microbial contaminants were detected.	46047001 46047002 46047003 46047004 46432001
OPPTS 830.1750	Certified Limits	Acceptable. The upper and lower certified limits have a wider than recommended range; however, the limits are acceptable and are typical of the variability introduced by fermentation, the first step in this integrated manufacturing process.	46047001
OPPTS 830.1800	Enforcement Analytical Method	Acceptable. A detailed enforcement analytical method for the active ingredient was submitted.	46047005
OPPTS 830.6302 830.6303 830.6304 830.7000	Color, Physical State, Odor, pH, Specific Gravity and Bulk Density	Acceptable. ProAct is a light tan to pale yellow granular solid with no odor, and has a pH of 6.125 (1 % w/v in distilled water) a specific gravity of 1.35 g/mL and bulk density of 0.47 g/mL at 24°C.	46047006 46047007

B. HUMAN HEALTH RISK ASSESSMENT

The acute oral, dermal and inhalation toxicity studies were conducted according to Agency guidelines and demonstrated no significant adverse effects from dosing with harpin $\alpha\beta$ protein. Following from this, there is a reasonable certainty of no harm from exposure to harpin $\alpha\beta$ or ProActTM. All anticipated dietary and other exposures for which there is reliable information are included in this assessment.

Hypersensitivity reactions to harpin products have not been seen to date in any environment including those where production worker exposure levels are much higher than would be expected in field application situations. The lack of hypersensitivity incidents noted among those working closely with harpin-based products is expected in that these proteins do not have known characteristics similar to environmental allergens and are generally applied in small quantities in a liquid form. Given the strong similarity of harpin $\alpha\beta$ to the harpin protein registered and used commercially since 2000, one would not expect harpin $\alpha\beta$ to exhibit inherent allergenic potential. However, the registrant must report any adverse reactions through the mandated FIFRA 6(a)2 reporting guidelines.

Based upon the lack of demonstrable toxicity and the non-pathogenic nature of K-12 derivatives, it is not anticipated that any human health consequence will result from application of ProActTM. Additionally, mixers are directed to wear personal protective equipment including a dust mask (N-95, P-95, R-95) to preclude inhalation of aerosolized carrier, protein, or residual fermentation biomass.

1. Human Toxicology Assessment

a. Acute Toxicity

All the required mammalian toxicology data requirements have been submitted and adequately satisfy data requirements to support registration. An acute oral toxicity study was conducted at the limit value of 5,050 mg/kg body weight, placing this product in Toxicity Category IV. No mortalities or clinical signs of toxicity were observed in the inhalation toxicity study, but a Toxicity Category III was assigned because the limit dose was unachievable in the study. The dermal toxicity study also resulted in a Toxicity Category IV assessment. A skin irritation study indicated that ProActTM is slightly irritating and an eye irritation study indicated the product is minimally irritating, resulting in a classification of Toxicity Category IV for both routes of exposure. Toxicology data used in support of the registration of ProActTM are summarized in Table 2.

Table 2. Toxicity Data Requirements

Guideline Number	Study	Result	MRID Number
OPPTS 870.1100	Acute Oral Toxicity Study in Rats	Acceptable. ProAct LD ₅₀ is > 5050 mg/kg body weight. All animals gained weight and no clinical manifestations were noted during the study. Toxicity category IV.	46047008
OPPTS 870.1200	Acute Dermal Toxicity Study in Rabbits	Acceptable. The acute dermal LD ₅₀ for ProAct in albino rabbits is > 5050 mg/kg. Toxicity category IV.	46204001
OPPTS 870.1300	Acute Nose-Only Inhalation Toxicity Study in Rats	Acceptable. The LC ₅₀ of ProAct is > 0.832 mg/L, the maximum concentration attainable. No mortalities, no clinical signs of toxicity. Two animals displayed gross lesions at necropsy. Findings of multifoci of the lung, pale liver, and pale kidneys in one animal were considered as being treatment related. Toxicity category III.	46204002
OPPTS 870.2400	Acute Eye Irritation Study in Rabbits	Acceptable. No positive effects in any eyes at 24 hours after treatment. ProAct is rated minimally irritating. Toxicity category IV.	46282701
OPPTS 870.2500	Acute Dermal Irritation Study in Rabbits	Acceptable. ProAct is rated slightly irritating. Toxicity category IV.	46204004
None	Hypersensitivity Incidents	Acceptable. The current observations suggest that harpins are not likely to be allergenic.	46047009
None	Homology Search of Harpin $\alpha\beta$ Protein Active Ingredient with Potentially Hazardous Proteins	No homology was found with any known toxic or allergenic proteins or polypeptides from humans or mammals.	46047010
OPPTS 870.2600	Skin Sensitization	Waived because of worker exposure history.	
OPPTS 870.5100 to 870.5500	Genotoxicity Testing	Waived	

Guideline Number	Study	Result	MRID Number
OPPTS 870.3550	Immunotoxicity	Waived	
OPPTS 870.3100	90-Day Subchronic Feeding Study	Waived	
OPPTS 870.3700	Teratogenicity Study	Waived	

b. Subchronic Toxicity and Chronic Toxicity

Skin sensitization testing was waived and replaced with the requirement for reporting hypersensitivity incidents in workers, handlers, and other individuals repeatedly exposed to harpin $\alpha\beta$ protein during research, testing, and field use of the product. Production workers at Eden Bioscience have been exposed to harpin $\alpha\beta$ at levels several hundred times greater than those which would occur during actual field use under label conditions and to date, no evidence of hypersensitivity has been observed. In addition, over a period of six years, many people have been involved in the research, development and field testing of harpin $\alpha\beta$ protein internationally, and no hypersensitive effects have been noted.

Immunotoxicity, teratogenicity, genotoxicity and subchronic feeding studies have been waived for the following reasons: 1) The proteinaceous nature of harpin $\alpha\beta$, in combination with its lack of demonstrable toxicity in acute studies, contributes a level of safety since proteins which are known to be chronically toxic can be demonstrated to be acutely toxic at high dose levels (Sjoblad, Roy D., et al. "Toxicological Considerations for Protein Components of Biological Pesticide Products," *Regulatory Toxicology and Pharmacology*, 15, 3-9). Therefore, because no significant adverse effects were observed in acute studies, even at the limit doses, harpin $\alpha\beta$ is not considered to be an acutely toxic protein. 2) Repeated (subchronic or chronic) dietary exposure is highly unlikely because residues are undetectable even immediately after application due to the extremely low application rates (approximately 0.14-3.69 grams of protein per acre) and because harpin $\alpha\beta$ protein is rapidly degraded by microbial and oxidative agents (e.g., chlorinated water) as well as by sunlight, as has been shown by environmental fate and residue data on harpin $\alpha\beta$ and/or the harpin protein registered in 2000. 3) Because harpin proteins are inactivated by chlorine, if any residues were present, they would be rapidly degraded by washing in municipally treated water, which typically contains chlorine. 4) In addition to the above arguments, genotoxicity studies were not required since these studies are typically done with bacterial or mammalian cell cultures. The harpin product would directly interfere with the growth of these cultures either by providing nutrients to supplement the growth of the bacterial mutants or enhancing proliferation of the mammalian cell cultures.

For all the above reasons, the Agency believes that no further subchronic or chronic testing is necessary to characterize the toxicological properties of harpin $\alpha\beta$ protein or its end-use product ProActTM.

c. Effects on the Immune and Endocrine Systems

The Agency has no data to indicate that the active ingredient harpin $\alpha\beta$ or the end-use product ProAct™ have any effect on the immune or endocrine systems. Due to the low or lack of toxicity observed in studies following oral, pulmonary, dermal and ocular exposure, it is unlikely that harpin $\alpha\beta$ has any endocrine effects on man or other animals. Hence, the Agency is not requiring any studies on the endocrine system at this time.

2. Dose Response Assessment

No toxicological endpoints are identified.

3. Dietary Exposure and Risk Characterization

The use of ProAct™ is not expected to result in any appreciable new dietary exposure to this protein. Harpin proteins are common constituents of plant pathogenic bacteria that are often found on fruits and vegetables. The quantities of ProAct™ applied to crops is very small and residues are virtually undetectable soon after treatment due to the instability of harpin $\alpha\beta$ protein in the environment. Hence, the increase of harpin-like proteins expected from the use of ProAct™ is minuscule relative to the natural occurrence of these proteins.

4. Occupational, Residential, School and Day Care Exposure and Risk Characterization

a. Occupational Exposure and Risk Characterization

During the preparation and application of ProAct™ the primary routes of exposure to the mixers and applicators would be through dermal and pulmonary routes. Harpin $\alpha\beta$ is not considered to be a dermal irritant and the natural barrier of the skin would preclude significant absorption of this protein. Pulmonary toxicity tests, place this product in Toxicity Category III because the limit dose was not achieved. Test results indicate that exposure to high levels of the end-use product may result in treatment-related lung lesions. Therefore, use of a dust mask is indicated for mixers of this product. Use of such personal protective equipment will preclude exposure from the inhalation route. Based upon the results of acute toxicity tests and the small quantities of product applied, risks from dermal or pulmonary exposures are considered to be minimal.

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

The approved use of ProAct™ for greenhouses, field crops, and commercial application to turf, trees and ornamentals should not result in significant increased exposure to residences, schools or day care institutions. Due to the intended sites of application, the methods of application and the small quantities applied, risks to humans, including children, are considered to be negligible. Based upon the results of acute toxicity tests and the small quantities of product applied, risks from oral, dermal or pulmonary exposures are considered to be minimal.

5. Drinking Water Exposure and Risk Characterization

Harpin $\alpha\beta$ protein or closely related molecules are normal constituents of many bacteria present in the environment and can be expected to be found in water and other places in the environment. In addition, harpin $\alpha\beta$ protein is susceptible to degradation by chlorine as well as microbial enzymes, and as such would not be found in typical municipal drinking water. The inert ingredients included in the end-use product are also non-toxic and may be found in some food products.

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

No reports of allergic reactions have been reported for harpin proteins and reports of production workers and researchers exposed to these entities indicate no reports of hypersensitivity. Moreover, harpin $\alpha\beta$ protein was not homologous with any known toxic or allergenic proteins or polypeptides from humans or mammals.

Based upon the toxicity information discussed above, EPA concludes that there is a reasonable certainty that no harm will result from aggregate exposure of the United States population, including infants and children, to residues of harpin $\alpha\beta$ protein and of its end-use product, ProAct™. This includes dietary and all other exposures for which there is reliable information. The Agency has reached this conclusion based on the results of the toxicity studies and available literature which indicate that harpin $\alpha\beta$ is practically non-toxic to mammals and under reasonably foreseeable circumstances it does not pose a risk.

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

The application of ProAct™ to field and greenhouse crops occurs at extremely low rates and the residues on crops soon after treatment are minuscule to non-detectable. The active ingredient, harpin $\alpha\beta$, is unstable in sunlight, and when subjected to chlorination, other oxidizing agents, or microbial enzymes and therefore is not expected to persist in the environment. Due to this lability, the lack of significant toxicological concerns, as demonstrated by the Agency's evaluation of mammalian toxicological studies, and the low use rates, the potential risks to humans are considered negligible.

8. Cumulative Effects

ProAct™ and its active ingredient, harpin $\alpha\beta$, are practically non-toxic to mammals. No mechanism of toxicity for this protein has been identified in mammals, thus no cumulative effect is anticipated.

C. ENVIRONMENTAL RISK ASSESSMENT

1. Ecological Toxicity

a. Toxicity to Nontarget Organisms

Data were cited on avian oral, avian dietary, rainbow trout, and algal toxicity, and seedling emergence of 10 agronomically important plants for the active ingredient, harpin protein registered in 2000 (PC Code 006477). Evidence from these studies suggests that the amounts of harpin required to elicit acute toxicities in nontarget organism populations would not likely be achieved by intended exposures to labeled applications. Because of the close structural, chemical and biological similarity of harpin $\alpha\beta$ protein to the harpin protein evaluated in these studies, the safety findings are deemed to be applicable to harpin $\alpha\beta$. Moreover, to further substantiate the environmental safety of harpin $\alpha\beta$, data on two highly sensitive “indicator” species - honeybee and *Daphnia* – were submitted. Results of these studies indicate that harpin $\alpha\beta$ was practically non-toxic. Non-target organism toxicity data used in support of the registration of ProAct™ are summarized in Table 3.

Table 3. Non-Target Toxicity Tier I Guideline Requirements for Harpin $\alpha\beta$

OPPTS Guideline No.	STUDY	RESULTS	MRID Nos.
850.2100	Avian Acute Oral Toxicity	(1) LD ₅₀ >4,000 mg Messenger/kg body weight; NOEC =4,000 mg messenger/kg body weight ; (2) LD ₅₀ > 2,250 mg/kg harpin/kg body weight	(1) 448702-18; (2) 445424-09
850.2200	Avian Dietary Toxicity	(1) LC ₅₀ >100,000 mg Messenger/kg body weight; (2) LC ₅₀ > 5,620 mg harpin/kg body weight	(1) 448702-19; (2) 445424-10
850.1075	Cold Water Fish Acute Toxicity	LC ₅₀ >3,270 mg Messenger/L; NOEC = 378 mg Messenger/L	448702-20
850.1010	Aquatic Invertebrate Acute Toxicity	EC ₅₀ = 1473 mg ProAct/L; NOEC = 626 mg ProAct/L	46204005
850.3020	Acute Contact Toxicity with the Honeybee	48-hour LD ₅₀ > 13 ug harpin $\alpha\beta$ /bee. Classified as relatively non-toxic	46204006

850.4100; 850.4225	14-day Seedling Emergence	NOEC = ~1430 L/ha (~143 g Harpin/ha)	448702-22
850.4025	Non-Target Plant Studies	Waived	
850.2600	Non-Target Insect Studies	Waived	
850.5400	Freshwater Algal Acute Toxicity	EC ₅₀ = 182 mg Messenger/L; NOEC = 120 mg Messenger/L	448702-23

2. Environmental Fate and Ground Water Data.

Harpin $\alpha\beta$ was rapidly degraded by the enzymes pepsin and subtilisin A under the conditions examined. It is likely that the natural proteolysis taking place in soil and on plant surfaces will ensure that harpin-derived proteins do not persist. Similarly, mammalian ingestion of harpin $\alpha\beta$ protein residues on plant surfaces would likely result in their degradation in a typical mammalian monogastric stomach should they survive in an intact form until harvest. Environmental fate data used in support of the registration of ProAct™ is summarized in Table 3a.

Table 3a. Environmental Fate Data Requirements

Title of Study	Results	MRID No.
Enzyme Degradation of Harpin Proteins	Harpin $\alpha\beta$ was rapidly degraded by pepsin and subtilisin A under the conditions examined.	46047013

3. Ecological Exposure and Risk Characterization

A potential for exposure exists for ProAct™ to all terrestrial nontarget organisms because of the foliar use patterns. However, the nontarget data base for products containing 3 percent of a harpin protein that is closely related to harpin $\alpha\beta$ (Table 3), indicates that ProAct™ is practically nontoxic to avian, freshwater fish and aquatic invertebrates, plant seedlings, and freshwater algae. Based on the results of the honeybee study, harpin $\alpha\beta$ protein would be classified as practically non-toxic to honeybees, relative to the positive control dimethoate. Depending on the agricultural use site and IPM practices, estimated environmental concentrations (EEC values) would range from a low of 0.6 ppm harpin $\alpha\beta$ /A (= 2 oz. ProAct™ in a 25-gallon application) to a maximum of 4 ppm harpin $\alpha\beta$ /A (= 13 oz ProAct™ in a 25 gallon application). BPPD believes that intended exposures of harpin $\alpha\beta$ to honeybee populations will not approach the maximum EEC in the majority of cases.

IV. RISK MANAGEMENT AND REGISTRATION DECISION

A. DETERMINATION OF ELIGIBILITY FOR REGISTRATION

Section 3(c)(5) of FIFRA provides for the registration of a new active ingredient if it is determined that (1) it will not generally cause unreasonable adverse effects on human health or the environment when used in accordance with widespread and commonly recognized practices and (2) its labeling and other materials required to be submitted comply with the requirements of FIFRA.

To satisfy criterion (1) above, it is believed that this biochemical pesticide will not cause any unreasonable adverse effects on human health or the environment given its lack of toxicity, extremely low use rates, and instability in the environment. In addition, all data and labeling requirements have been fulfilled and found acceptable, thereby satisfying criterion (2).

Therefore, harpin $\alpha\beta$ protein is eligible for registration under FIFRA Section 3(c)(5). The registered uses are contained in Table 4, Appendix A.

B. REGULATORY POSITION

1. Registration

Data submitted are sufficient for the registration under Section 3(c)(5) of FIFRA of Harpin $\alpha\beta$ (ProAct™) for the use patterns presented in Table 4, Appendix A.

2. Tolerance Exemption

The Agency has published a final rule exempting residues of harpin proteins from the requirement of a tolerance.

3. CODEX Harmonization

There is currently no CODEX Maximum Residue Limit set for food use of this active ingredient.

4. Non-Food Registration

The registered uses for Harpin $\alpha\beta$ protein include turf, trees and ornamentals, in addition to food uses.

5. Risk Mitigation

Because Harpin $\alpha\beta$ protein is classified in Toxicity Category III due to the inability to reach the limit dose in the inhalation toxicity study, minimal personal protective equipment (PPE) is required to be worn by pesticide applicators and handlers i.e., long-sleeved shirt and long pants; shoes and socks; and dust mask when mixing. In

addition, a Restricted Entry Interval (REI) of 4 hours is required to mitigate potential occupational exposure.

6. Endangered Species Statement

There are no expected toxic effects on non-target species based on toxicity data and lack of expected residues. Therefore, the Agency has determined that this action will have no effect on listed species.

C. LABELING RATIONALE

1. Human Health Hazard

a. 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.

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, such as, and including the WPS labeling.

Workers and handlers (including mixer/loaders, and applicators) applying this product must wear long sleeved shirt, long pants, shoes and socks, and a particulate dust mask when mixing. Post application agricultural workers and early-entry workers must wear coveralls, shoes and socks, and waterproof gloves during the restricted entry interval (REI) of 4 hours.

b. Non-Worker Protection Standard

For non-agricultural users, workers must not enter the treated area without protective clothing until sprays have dried.

c. Precautionary Labeling

Since the End-Use Product is in Toxicity Category III for inhalation toxicity, the following precautionary and first-aid statements are required:

Precautionary Statement - Hazards to Humans and Domestic Animals

“Harmful if inhaled. Avoid breathing spray mist. Remove and wash contaminated clothing before reuse.”

First-Aid Statement

- “If inhaled: - Move person to fresh air
- If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably mouth-to-mouth if possible.
- Call poison control center or doctor for further treatment advice

d. Spray Drift Advisory

Since Harpinαβ may be applied with conventional aerial equipment, the following language will be required:

SPRAY DRIFT FOR AERIAL APPLICATION

Avoiding spray drift at the application site is the responsibility of the applicator. The interaction of many equipment-and-weather-related factors determine the potential for spray drift. The applicator and the grower are responsible for considering all these factors when making decisions.

2. Environmental Hazards Labeling

a. End-Use Product Environmental Hazards

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 cleaning equipment or disposing of equipment washwaters.

b. Manufacturing-Use Product Environmental Hazards

There is currently no manufacturing-use product registered for Harpinαβ.

D. LABELING

1. End-Use Product Name: ProAct

Active Ingredient:

Harpinαβ Protein	1.0%
Other Ingredients	99.0%
Total.....	100.0%

V. APPENDICES

A. USE SITES

Table 4. Registered Use Sites

<u>Food Use Sites</u>	<u>Official Date Registered</u>
<i>All food commodities</i>	February 9, 2005
<u>Non-Food Use Sites</u>	
<i>Trees, turf and ornamentals</i>	

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