



BIOPESTICIDES REGISTRATION ACTION DOCUMENT

Saponins of *Chenopodium quinoa*

(PC Code 097094)

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

TABLE OF CONTENTS

I. Executive Summary	5
II. Overview	6
A. ACTIVE INGREDIENT OVERVIEW	6
B. USE PROFILE	6
C. ESTIMATED USAGE	7
D. DATA REQUIREMENTS	7
E. REGULATORY HISTORY	7
F. CLASSIFICATION	8
G. FOOD CLEARANCES/TOLERANCES	8
III. Science Assessment	9
A. PHYSICAL/CHEMICAL PROPERTIES ASSESSMENT	9
1. Product Identity and Mode of Action	9
a. Product Identity.....	9
b. Mode of Action	9
2. Physical And Chemical Properties Assessment.....	9
B. HUMAN HEALTH ASSESSMENT	12
1. Toxicology Assessment	12
a. Acute Toxicity	12
b. Mutagenicity and Developmental Toxicity	13
c. Subchronic Toxicity and Immunotoxicity	14
d. Chronic Exposure and Oncogenicity Assessment	15
e. Effects on the Endocrine System	15
2. Dose Response Assessment.....	16
3. Dietary Exposure and Risk Characterization.....	16
4. Occupational, Residential, School and Day Care Exposure and Risk Characterization	16
a. Occupational Exposure and Risk Characterization	16
b. Residential, School and Day Care Exposure and Risk Characterization.....	16
5. Drinking Water Exposure and Risk Characterization.....	16
6. Acute and Chronic Dietary Risks for Sensitive Subpopulations Particularly Infants and Children	17
7. Aggregate Exposure from Multiple Routes Including Dermal, Oral, and Inhalation.....	17
8. Cumulative Effects.....	17
9. Risk Characterization.....	17

TABLE OF CONTENTS (continued)

C. ENVIRONMENTAL ASSESSMENT	18
1. Ecological Effects Hazard Assessment.....	18
2. Environmental Fate and Ground Water Data.....	21
3. Ecological Exposure and Risk Characterization.....	22
D. EFFICACY DATA	22
IV. Risk Management Decision	23
A. DETERMINATION OF ELIGIBILITY FOR REGISTRATION	23
B. REGULATORY POSITION	23
1. Unconditional Registration	23
2. CODEX Harmonization.....	23
3. Nonfood Registrations	23
4. Risk Mitigation	24
5. Endangered Species Statement	24
C. LABELING RATIONALE.....	24
1. Human Health Hazard.....	24
a. Worker Protection Standard.....	25
b. Non-Worker Protection Standard	25
c. Precautionary Labeling.....	25
d. Spray Drift Advisory	25
2. Environmental Hazards Labeling	26
3. Application Rate	26
D. LABELING	27
V. Actions Required by Registrants	28
A. Reporting of Adverse Effects	29
B. Reporting of Hypersensitivity Incidents	29
VI. Appendix A	30
VII. Appendix B - References	31
VIII. Appendix C - Product Label	34

BIOPESTICIDES REGISTRATION ACTION DOCUMENT TEAM

Office of Pesticide Programs:

Biopesticides and Pollution Prevention Division

Biochemical Pesticides Branch (BPB)

Sheryl K. Reilly, Ph.D.	Biologist, Branch Chief
Linda Hollis	Microbiologist, Team Leader
Russell S. Jones, Ph.D.	Senior Biologist, Health Effects/Non-target Organisms
Todd A. Peterson, Ph.D.	Biologist, Regulatory Action Leader
Denise Greenway	Environmental Protection Specialist, New A.I. Team Captain
Richard King	Biologist, Regulatory Action Leader

I. Executive Summary:

Saponins of *Chenopodium quinoa* are classified as a biochemical pesticide because: 1) they are derived from a seed extract from the plant *Chenopodium quinoa* (Willd) and 2) have a “non-toxic” mode of action. *C. quinoa* (Willd) is a species within the plant family Chenopodiaceae (Goosefoot or Pigweed Family). There are approximately 1300 species of chenopods worldwide, ranging from annual herbs to trees. Spinach, beets, sugar beets, chard and epazote are members of Chenopodiaceae with a high economic value. Seeds from *C. quinoa* are used as a cereal crop, yet because of this plant’s grass-like appearance it is classified botanically as a “pseudocereal.” Seeds of *C. quinoa*, commonly referred to as quinoa, have a long history in South America as a dietary supplement. The plants have been cultivated in the Andean highlands since 3,000 B.C. (Tapia 1982). In the Quechua language of the Incas, quinoa is *chisiya mama* or “mother grain.” In Spanish, it is *quinoa*, *trigo inca*, or *arroz del Peru*. Nutrition from quinoa is based on its amino acid composition, high content of calcium, phosphorus, iron, and low sodium content.

Chemically, saponins include a range of related compounds. The saponins of *Chenopodium quinoa* that are the technical grade active ingredient (TGAI) and the subject of this registration action document, are the major saponin constituents in the extract of *C. quinoa* seeds, which primarily include approximately equimolar amounts of the triterpene bidesmosidic glycosides of oleanolic acid, hederagenin, and phytolaccagenic acid. The pesticide end product (EP), Heads Up[®] Plant Protectant, made with the TGAI is intended for use as a seed treatment on tuber (e.g. potato seed pieces), legume, and cereal seeds or as a pre-plant root dip for roots of transplants, at planting, to prevent fungal growth, bacterial growth, and viral plant diseases. The EP is also intended to be used as a single-application foliar treatment on tomato seedlings prior to transplant.

The Biopesticides and Pollution Prevention Division (BPPD) risk management decision regarding the registration of saponins of *C. quinoa* is based on: 1) the TGAI is naturally occurring, 2) applications of these saponins are “non-food uses” when made to tuber (e.g. potato seed pieces), legume, cereal seeds, and for foliar (one time only) applications to immature, non-flowering, tomato seedlings prior to transplanting, 3) the TGAI as used in the EP does not require a tolerance 4) saponins from *C. quinoa* have a very low mammalian toxicity, 5) no edible commodity is present at the time of pesticide product application; and 6) no detectible product residues will be present at the time of harvest. Residues of saponins from *C. quinoa* rapidly degrade within a few days of application.

BPPD considered saponins of *C. quinoa* in light of the relevant safety factors in the Food Quality Protection Act (FQPA) of 1996 and under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and has not identified any dietary or non-dietary exposure issues that may affect the U.S. population in general, including infants and children. The Agency has thereby determined that there is reasonable certainty that no harm will result from aggregate exposure to saponins of *C. quinoa* residues, including dietary exposures and all other exposures for which there is reliable information.

II. Overview

A. ACTIVE INGREDIENT OVERVIEW

- Common Name:** Saponins of *Quinoa*
- Chemical Names:** Saponins of *Chenopodium quinoa* (approximately equimolar amounts of the triterpene bidesmosidic glycosides of oleanolic acid, hederagenin, and phytolaccagenic acid)
- Trade & Other Names:** Heads Up[®] Plant Protectant
- CAS Registry Number:** 404589-23-7
- OPP Chemical Code:** 097094
- Basic Manufacturer:** Heads Up Plant Protectants
P.O. Box 519, 428 3rd Street
Kamsack, SK SOA 1S0, Canada

B. USE PROFILE

Pesticide uses and application methods include the following:

Type of Pesticide: Biochemical pesticide; Fungicide

Use Sites: Saponins of *Chenopodium quinoa* is intended for use on tuber (e.g. potato seed pieces), legume (e.g. bean, pea), and cereal (e.g. wheat) seeds, and for root dip or foliar application to tomato seedlings prior to transplanting.

Target Pests: Pathogenic fungi, bacteria, and viral plant diseases.

Formulation Type: Powder

Method and Rates of Application: For agronomic application, saponins of *Chenopodium quinoa* at 49.65% is mixed as a dip or spray at a rate of 0.035 ounces per 34 ounces of water (1 liter) for application to 375 pounds of legume (e.g., bean, pea) or cereal (e.g., wheat) seed, or 110 to 220 pounds of tuber (e.g., potato seed pieces). Seeds or roots are to be dipped (submerged for sixty seconds) or sprayed with solution until thoroughly covered. Foliar application, sprayed until leaves are completely wet, is made once to immature tomato seedlings, up to 6 inches tall, pre-flowering, up to 4 days before transplanting.

Timing: Applications are made: 1) before tubers or seeds are planted, 2) to roots at transplanting of seedlings, or 3) to foliage up to 4 days before transplanting seedlings.

Use Practice Limitations: For tubers and seeds at seeding and for root dip or foliar application to tomato seedlings at transplant. For foliar treatment of tomato seedlings, apply only one time to immature (up to six inch tall), pre-flowering, seedlings up to 4 days prior to transplanting. Foliar applications are to be made inside a greenhouse or outside within portable spray chambers when pre-transplant applications are conducted in the field. Foliar application to other food or feed crops is prohibited.

C. ESTIMATED USAGE

None used yet since this is the first registered product.

D. DATA REQUIREMENTS

The Biopesticides and Pollution Prevention Division (BPPD) reviewed data requirements for granting this registration under Section 3(c)(5) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). The product analysis and manufacturing process data requirements are adequately satisfied by the data submitted by the registrant for the technical grade active ingredient and the end product (see Table 1). Physical and Chemical Properties for the end use product are adequately satisfied by the data submitted as listed in Table 2. The mammalian toxicology requirements were satisfied by data submitted for acute toxicity and primary irritation (see Table 3). Ecological effects data requirements for saponins of *Chenopodium quinoa* were fulfilled by submission of waiver requests supported by over 150 refereed journal article citations (MRIDs 463536-11 & -12) pertaining to toxicity and non-target organisms. The Agency reviewed all of the data and waiver requests and determined that they adequately satisfy current guideline requirements. The Agency issued a product registration for Heads Up[®] Plant Protectant, EPA Registration Number 81853-1, on September 16, 2005. In granting this product registration, the Agency does not foresee any unreasonable adverse effects to humans and the environment from any of the uses of saponins of *C. quinoa* when used as directed by the product labeling.

E. REGULATORY HISTORY

Heads Up[®] Plant Protectants, Inc. submitted an application for the registration of Heads Up[®] Plant Protectant, EPA Registration Number 81853-1, active ingredient saponins of *Chenopodium quinoa* on August 27, 2004. A notice of receipt of an application for registration of Heads Up[®] Plant Protectant, containing saponins of *Chenopodium quinoa* as an active ingredient, was published in the Federal Register on December 15, 2004 (69 FR 75063) with a 30-day comment period. No comments were received following this publication. Saponins of *C. quinoa* is a new active ingredient for a pesticide formulation. The registered end product (EP) is intended to be

used as a non-food, biochemical seed treatment (tuber, legume, cereal crops), root dip (i.e., tomato seedlings), and single-application foliar treatment for seedlings prior to transplanting (i.e., tomato seedlings). Applications are made to mitigate fungal growth, bacterial growth, and viral plant disease in tuber, legume, cereal seeds and tomato transplants. An unconditional registration for this active ingredient was issued on September 16, 2005.

F. CLASSIFICATION

On September 7, 2000, the Biochemical Classification Committee determined that saponins of *Chenopodium quinoa* can be classified as a biochemical pesticide due to its apparent non-toxic mode of action. However, additional information is needed to further clarify the mode of action. Many saponins are known to be toxic. The mode of action for saponins of *Chenopodium quinoa* remains an open issue because they appear to exhibit characteristics of a fungicidal nature. To amend the uses for saponins of *C. quinoa* to include food use, additional data (e.g., additional toxicological and residue data) will be required.

G. FOOD CLEARANCES/TOLERANCES

This end product registration is for non-food use and no food clearances or tolerances are required due to the non-food status of the current registered uses.

III. Science Assessment

A. PHYSICAL/CHEMICAL PROPERTIES ASSESSMENT

All product chemistry data requirements for registration of saponins of *Chenopodium quinoa*, when formulated into the end-use product Heads Up[®] Plant Protectant, have been satisfied.

1. Product Identity and Mode of Action

a. Product Identity

Saponins of *Chenopodium quinoa* are a cream beige powder with a meaty odor characteristic of finely ground proteinaceous material. The saponins are derived by an extraction from seeds of *C. quinoa*. The major saponin constituents in the extract of *C. quinoa* seeds (containing 49.65% saponins of approximately equimolar amounts of the triterpene bidesmosidic glycosides of oleanolic acid, hederagenin, and phytolaccagenic acid) are together the active ingredient in the end-use product Heads Up[®] Plant Protectant.

The descriptions of the product formulation and production process as well as the formation of impurities were examined by the Agency and found to be acceptable in meeting current guideline standards. A preliminary analysis of saponins of *C. quinoa* was conducted using five batches of end use product by an independent laboratory and determined to be acceptable by the Agency. The analytical results were used to set the nominal concentrations and certified limits of the active ingredient. The analytical method is a high performance liquid chromatography (HPLC) method that involves quantitation of the total saponins in the product.

b. Mode of Action

Heads Up[®] Plant Protectant inhibits fungal growth, bacterial growth, and viral plant diseases.

2. Physical and Chemical Properties Assessment

The physical and chemical characteristics of saponins of *Chenopodium quinoa* were submitted to support the registration. The product chemistry requirements are summarized in Table 1. The physical and chemical properties of saponins of *Chenopodium quinoa* are summarized in Table 2.

Saponins of *Chenopodium quinoa*
 Biopesticides Registration Action Document

TABLE 1. Product Chemistry Data Requirements			
OPPTS GUIDELINE NO.	STUDY	RESULTS	MRID NO.
830.1550 to 830.1670	Product identity; Manufacturing process; Discussion of formation of unintentional ingredients	Submitted data satisfies the data requirements for product identity, manufacturing process, and discussion of formation of impurities	463536-01
830.1700	Analysis of samples	Submitted data satisfy the data requirements for analysis of samples	463536-02
830.1750	Certification of limits	Limits listed in the CSF are adequate / Acceptable	463536-03
830.1800	Analytical Method	Acceptable	463536-02

TABLE 2. Physical and Chemical Properties for saponins of <i>Chenopodium quinoa</i>^a	
OPPTS Guideline Reference No./Property	Description of Result
830.6302 Color	Cream beige
830.6303 Physical State	Amorphous solid, a fine particle sized powder
830.6304 Odor	Mild slightly meaty odor characteristic of finely ground proteinaceous material
830.6313 Stability	50.1 ^b at room temperature for 14 days; 49.8 ^b at 54°C for 14 days
830.6314 Oxidation/Reduction: Chemical incompatibility	Product does not contain oxidizing or reducing agents.
830.6315 Flammability	Not applicable.
830.6316 Explodability	Product is not potentially explosive.
830.6317 Storage Stability	The total of the saponins (% w/w) was 96, 92, and 99% of the initial concentration after storage in plastic bags at room temperature for 11, 36, and 48 months, respectively. The product was similar to its original appearance after storage.
830.6319 Miscibility	Not addressed
830.6320 Corrosion Characteristics	No signs of physical or chemical interaction of the product with the polyethylene bags were noted after three years.
830.6321 Dielectric Breakdown Voltage	Not addressed
830.7000 pH	6.27± 0.07 (1% in distilled, deionized water)

Saponins of *Chenopodium quinoa*
 Biopesticides Registration Action Document

TABLE 2. Physical and Chemical Properties for saponins of <i>Chenopodium quinoa</i>^a	
OPPTS Guideline Reference No./Property	Description of Result
830.7050 UV/Visible	Absorption dropped off rapidly between 200 and 240 nm, thereafter dropping off steadily until about 400 nm after which there was essentially no absorbance
830.7100 Viscosity	Product is not a liquid.
830.7200 Melting Range	156.2 ± 0.8°C
830.7220 Boiling Range	Not applicable
830.7300 Bulk Density	0.20 ± 0.01 g/mL
830.7370 Dissociation Constant in Water	pK = 5.97 ^c
830.7520 Particle Size/Distribution	Not applicable
830.7550 Partition Coefficient	Not possible to determine the octanol/water partition coefficient due to a very stable emulsion of 1-octanol and water using the saponins as the surfactant
830.7840 Water Solubility	Highly water soluble; value is difficult to determine due to the dark brown, opaque nature of concentrated solutions
830.7950 Vapor Pressure	Product does not vaporize at room temperature and does not have a measurable vapor pressure.

^a Data from MRID 46353604.

^b The measurements were done on three batches of saponin powder.

^c Details were presented in MRID 463536-04

B. HUMAN HEALTH ASSESSMENT

The mammalian toxicity studies submitted to support the registration application for saponins of *Chenopodium quinoa* adequately satisfy the requirements to register a new biochemical pesticide intended for non-food use pattern. The Agency has determined that this use pattern (specifically, on seeds, root systems of tomato seedlings at transplanting, or foliage of young, up to 6 inch tall, non-flowering tomato transplant seedlings), in relation to the information in the current database, qualifies as a non-food use.

1. Toxicology Assessment

Adequate mammalian toxicology data are available to support registration of non-food products containing the new active ingredient saponins of *C. quinoa*. No additional toxicological data are needed.

a. Acute Toxicity

Acute toxicity studies are summarized in Table 3 below. This product is in Toxicity Category IV for acute oral, acute dermal toxicity, and primary dermal irritation, Toxicity Category III for acute inhalation toxicity and primary eye, and is not a dermal sensitizer. Based on the review and analysis of the information, guideline studies and submitted literature, discussed in detail in this section of the BRAD, no additional toxicity data are required to support the non-food uses of this biochemical.

Table 3. Acute Toxicity and Primary Irritation Data for Saponins of *Chenopodium quinoa*¹

Study/ OPPTS Guideline No.	Results	Toxicity Category	MRID No.
Acute Oral Toxicity 870.1100	LD ₅₀ >5000 mg a.i./kg	IV	463536-05
Acute Dermal Toxicity 870.1100	LD ₅₀ >5000 mg a.i./kg	IV	463536-06
Acute Inhalation Toxicity 870.1300	LC ₅₀ = 0.824 mg/L (male) LC ₅₀ = > 2.04 mg/L (female)	III ²	463536-07
Primary Eye Irritation 870.2400	Corneal opacity and conjunctivitis effects to 48 hr post-instillation; symptoms cleared by 72 hours; mild irritant	III	463536-08
Primary Dermal Irritation 870.2500	Moderate to mild dermal irritation effects to 24 hrs; symptoms cleared by 48 hours after patch removal; mild irritant	IV	463536-09
Skin Sensitization 870.2600	Test and naive control animals showed no positive signs of reactivity 24 and 48 hours after challenge	Not a sensitizer	463536-10

1 Table presents Agency's determinations for both the TGAI and the EP containing 49.65% saponins (approx. equimolar mixture of triterpene glycosides of oleanolic acid, hederagenin, and phytolaccagenic acid).

2 Based on male LC₅₀.

b. Mutagenicity and Developmental Toxicity

Requested waivers of the mammalian mutagenicity and teratogenicity data requirements were granted by the Agency because the known exposure of *Chenopodium quinoa* seed products in the human diet and the non-food use make it unlikely that the pre-existing dietary exposure of humans saponins to *C. quinoa* would be increased by the use of the EP. Based on the use

patterns as a pre-plant seed treatment, pre-transplant root dip, and pre-transplant single-application foliar treatment of tomato seedlings, non-occupational exposure to humans will be unlikely. Personal protective equipment (PPE) statements requiring the use of gloves and long-sleeved clothing and protective eyewear (when applying the product as a spray), will prevent dermal and eye exposure to applicators and workers. Indirect exposure via spray drift is also mitigated by label directions restricting spray applications to inside greenhouses or outside within portable spray chambers when pre-transplant applications are conducted in the field. There will be no non-occupational exposure. The active ingredient is not a mutagen nor is it related to any known classes of mutagens. Saponins, in general, are known to have anticarcinogenic properties (Li et al., 2002; Rao and Sung, 1995) and to stimulate the immune system (Kenarova et al., 1990; Wu et al., 1990).

A teratogenicity study is not required. The end use product when used as a pre-plant seed treatment, pre-transplant root dip, or pre-transplant foliar treatment of tomato seedlings is not expected to result in significant exposure to female humans. Use of the product does not require a tolerance or an exemption from the requirement of a tolerance, nor does it require the issuance of a food additive regulation. The product is intended for non-food use. Saponins have generally been reported to have both negative (abortifacient, antizygotic, and anti-implantation properties) and positive (increased sperm viability and motility) effects on animal reproduction (Francis et al., 2002). There are no specific teratogenicity data on triterpenoid saponins of *Chenopodium quinoa*. Triterpenoid saponins (such as those present in the active ingredient) are present in many plants used for human food (Oakenfull, 1981) without any reports of adverse effects.

c. Subchronic Toxicity and Immunotoxicity

Waivers requested for the subchronic and immunotoxicity study requirements were granted by the BPPD. Subchronic studies (90-day feeding (OPPTS 870.3100), 90-day dermal (OPPTS 870.3250), and 90-day inhalation (OPPTS 870.3465)) are not required as described below.

The end use product is applied only once, prior to planting seeds or as a pre-transplant root dip or as a single-application foliar treatment for tomato seedlings. Growth dilution by the plants and rapid biodegradation of the product will reduce any potential product residues to non-detectable levels before any consumable commodity is present. The product label states that treated seeds (i.e., potato tuber, legume, cereal) and seedlings may not be used for animal feed. Furthermore, any potential saponin residues resulting from use of the product may be indistinguishable from saponins already present in the treated plants or seeds. Saponins are widely distributed in diverse plant species (Oakenfull, 1981). Triterpenoid saponins (such as those present in the active ingredient) are common in cultivated crops (Oakenfull, 1981) regularly consumed by humans.

The product will not be intentionally applied to human skin. A label PPE statement to require the use of gloves and long-sleeved clothing will prevent any repeated dermal exposure to applicators and workers via application as a pre-plant seed treatment, pre-transplant root dip, or pre-transplant foliar application. There will be no occupational exposure.

d. Chronic Exposure and Oncogenicity Assessment

Repeated dose studies are conditionally required if the potential for adverse chronic effects are indicated based on: 1) the subchronic effect levels established in Tier I subchronic oral, inhalation, or dermal studies, 2) the pesticide use pattern, or 3) the frequency and the level of repeated human exposure that is expected. Oncogenicity studies are required only if the active ingredient or any of its metabolites, degradation products, or impurities produced in Tier I studies any morphologic effects in any organ that potentially could lead to neoplastic changes. None of the results of the submitted studies triggered the need for chronic exposure or oncogenicity testing.

e. Effects on the Endocrine System

The US Environmental Protection Agency (Agency) is required under the Federal Food, Drug, and Cosmetics Act (FFDCA), as amended by Food Quality Protection Act, 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 other such endocrine effects as the Administrator may designate.” Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis for including, as part of the program, the androgen- and thyroid-hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC’s recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, the Agency will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

Based on the weight of the evidence of available data, no endocrine system-related effects have been identified for saponins of *Chenopodium quinoa* and none is expected since it does not share any structural similarity to any known endocrine disruptor.

2. Dose Response Assessment

No toxicological endpoints were identified; therefore, a dose response assessment was not required.

3. Dietary Exposure and Risk Characterization

Current dietary exposure to seeds from *Chenopodium quinoa* includes its use as a cereal crop. Seeds of *C. quinoa*, commonly referred to as quinoa, have a long history in South America as a dietary supplement. The plants have been cultivated in the Andean highlands since 3,000 B.C. (Tapia 1982). Nutrition from quinoa is based on its amino acid composition, high content of calcium, phosphorus, iron, and low sodium content. The end use product will be applied only once, pre-planting to seeds as a seed dip or as a spray, as a pre-transplant seedling root dip, or as a pre-transplant foliar spray to tomato seedlings with specific requirements as to the size and age of the plant. Dietary exposure from its non-food use in Heads Up[®] Plant Protectant is expected to be insignificant.

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

a. Occupational Exposure and Risk Characterization

Occupational exposure to saponins of *C. quinoa* is mitigated as long as the end-use product Heads Up[®] Plant Protectant is used according to label directions. Occupational exposures are not included under the FFDCFA in the assessment of aggregate exposures for the purpose of establishing tolerances and exemptions from tolerance. The signal word on the EP label is “Caution” and precautionary statements include “Causes moderate eye irritation. Harmful if inhaled. Avoid contact with eyes or clothing. Avoid breathing spray mist. Wash thoroughly with soap and water after handling. Remove and wash contaminated clothing before reuse.” for routes of exposure. Indirect occupational exposure via spray drift is unlikely due to label directions restricting spray applications to inside greenhouses or outside within portable spray chambers when pre-plant applications are conducted in the field. The product is registered for agricultural use and a reentry interval of 12 hours is required.

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

Saponins of *Chenopodium quinoa* is intended for agricultural use only. Although accidental non-dietary exposure may occur, the health risk is expected to be minimal due to the low concentration of saponins in the product, lack of oral and dermal toxicity, minimal acute inhalation toxicity, and minimum potential for eye and dermal irritation. Significant human exposure to saponins of *C. quinoa* is highly unlikely in residential, school and day care areas.

5. Drinking Water Exposure and Risk Characterization

No significant exposure is expected from an accumulation of saponins of *Chenopodium quinoa* in the aquatic environment when used according to the product label directions. Low application

rates (≤ 10 g product/A or < 5 g active ingredient/A) and rapid biodegradation (3-5 days; Molgaard et al., 2000) further reduce potential exposure.

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

FFDCA section 408 provides that the Agency shall apply an additional tenfold margin of exposure (safety) for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the database unless the Agency determines that a different margin of exposure (safety) will be safe for infants and children. Margins of exposure (safety) are often referred to as uncertainty (safety) factors. In this instance, based on all the available information, the Agency has concluded that there is reasonable certainty that no harm to infants and children or adults will result from the use of saponins of *Chenopodium quinoa* as registered.

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

There is reasonable certainty that no harm to the US population will result from aggregate exposure to residues of saponins of *Chenopodium quinoa*. This includes all exposures for which there is reliable information. The Agency arrived at this conclusion based on the low level of toxicity and already widespread exposure to saponins of *C. quinoa* without any reported adverse effects on human health. The risks from aggregate exposure via oral, dermal and inhalation exposure are a compilation of three low-risk exposure scenarios and are negligible. Since there are no threshold effects of concern, the provision requiring an additional margin of safety does not apply. Therefore, the Agency has not used a margin of exposure (safety) approach to assess the safety of saponins of *C. quinoa*.

8. Cumulative Effects

When used as proposed, residues of saponins of *Chenopodium quinoa* will not reach levels that are of toxicological concern. Because of its low inherent toxicity and low use rates, no cumulative effect with other toxins is anticipated.

9. Risk Characterization

The Agency considered human exposure to saponins of *Chenopodium quinoa* in light of the relevant safety factors in FQPA and FIFRA. A determination has been made that no unreasonable adverse effects to the U.S. population in general, and to infants and children in particular, will result from the use of saponins of *C. quinoa* when label instructions are followed.

C. ENVIRONMENTAL ASSESSMENT

1. Ecological Effects Hazard Assessment

Non-target organism studies (OPPTS 850.2100 and 850.2200) were not submitted. In lieu of studies, the registrant submitted two summary reports (MRIDs 463536-11 and -12) that contain literature reviews on the health, toxicological, and environmental effects of saponins obtained from a number of plant sources, including *Chenopodium quinoa*.

The report entitled Quinoa Saponin Toxicology (MRID 463536-11) briefly discusses the occurrence, biological activity, toxicity, food use, and ecotoxicity of several classes of saponins, including saponins of *C. quinoa*, based on data found in the public literature. A list of 74 pertinent references is included. The second report (MRID 463536-12) includes results of a literature search on the structure, biological activity, toxicity, and biodegradation of saponins, with some information particular to saponins of *C. quinoa*. A list of 65 pertinent references is included. The Tier I Non-Target Organism Data requirements are discussed below.

Avian toxicity studies (OPPTS 850.2100 and 850.2200) were not submitted, but none are required based on the unlikelihood of exposure of saponins of *C. quinoa* to bird species from the subject pesticide uses. Seeds of treated commodities will be treated prior to planting and covered with soil at planting and will be unavailable for consumption by birds. Since there are no known bird pests of tomato seedlings, pre-transplant (treated) tomato seedlings are unlikely to be consumed by birds. Furthermore, seeds and seedlings treated with the product will have a bitter taste imparted by the saponins of *C. quinoa* and may be unattractive for consumption by birds. The product is not intended for direct applications to birds. Indirect exposure to birds via spray drift is unlikely due to label use directions restricting spray applications to inside greenhouses or outside within portable spray chambers when pre-plant applications are conducted in the field (as indicated on product label). Low application rates (≤ 10 g product/A or <5 g active ingredient/A) and rapid biodegradation (3-5 days; Molgaard et al., 2000) further reduce potential exposure.

Little data are available regarding the toxicity of triterpenoid quinoa saponins to birds. Weight gain and survival of broiler chicks administered a diet consisting solely of raw quinoa seed was significantly reduced after 28 days, relative to birds fed wheat, sorghum or maize (Improta and Kellems, 2001). However, the authors attribute low survival rates and low weight gain to significantly reduced food consumption caused by food aversion to the saponins in the diet. Conversely, Miah et al. (2004) reported improved growth and meat quality of male broiler chickens fed up to 75 mg of an unidentified saponin in a diet of maize/soybean meal. A mixture of six unidentified saponins extracted from the highly poisonous plant Alfombrilla (*Drymaria arenarioides*) resulted in 100% mortality 4-hrs after being fed to 1-week old chicks at 2% of their body weight (Williams, 1978), although these saponins are unlikely to be the triterpenoid

saponins typically found in edible crop plants. An ECOTOX search did not report any saponin toxicity data for birds.

Saponins are widely distributed in diverse plant species (Francis et al., 2002). Triterpenoid saponins (such as those present in the active ingredient) are common in cultivated crops (Oakenfull, 1981). Therefore, bird exposure to naturally-occurring saponins in plants is likely to be widespread.

Freshwater fish and aquatic invertebrate studies (OPPTS 850.1075, 850.1300 and 850.1035) were not submitted, but none are required based on the unlikelihood of exposure of saponins of *C. quinoa* to these taxa. Some saponins are known to be toxic [24-hr LD₅₀s ranging from 4.4 (moderately toxic) to 12.5 mg/L (slightly toxic)] to fish and aquatic invertebrates, including mosquito larvae (D' Souza et al., 2002; Lambert et al., 1991; Lemma et al., 1991; Molgaard et al., 2000; Neuwinger 2004; Weisman and Chapagian, 2003) primarily due to effects on respiratory membranes (Francis et al., 2002), whereas other saponins only stun fish temporarily (Cannon et al., 2004). A brine shrimp lethality assay is used as a crude bioassay for the presence of saponin activity (D' Souza et al., 2002). A mixture of saponins derived from Endod berry (*Phytolacca dodecandra*), a relative of pokeweed, are a potent molluscicide (Lambert et al., 1991). Endod saponins were comprised primarily of monodesmosides of oleanolic acid (Lambert et al., 1991). There are no specific data available regarding the toxicity of bidesmoside triterpenoid quinoa saponins to fish and aquatic invertebrates, although bidesmosides have been shown to be less toxic than monodesmosides (Duncan, 1985; Hostettman et al., 1982).

Regardless of the toxicity of some saponins to fish and aquatic invertebrates, the end use product is not intended for direct application to aquatic environments. Spray drift will be mitigated by label use directions restricting spray applications to inside greenhouses or within portable spray chambers when applications are conducted to seeds or pre-transplant seedlings in the field. Although the product is highly water soluble, runoff of product active ingredient into aquatic environments from treated seeds or washing off of treated tomato transplants is highly unlikely due to: 1) low application rates (≤ 10 g product/A or < 5 g active ingredient/A); and 2) rapid biodegradation in water (3-5 days; Molgaard et al., 2000).

An ECOTOX literature search provided the following saponin mortality data for shrimp, prawn, and daphnids (no specific toxicity data were available for triterpenoid quinoa saponins) as shown in Table 4.

Saponins of *Chenopodium quinoa*
 Biopesticides Registration Action Document

Table 4. Information from ECOTOX Literature Search			
Species (Common name; Habitat)	LC50/EC ₅₀ (ppm); exposure	Toxicity Category	Reference
Shrimp			
<i>Metapenaeus ensis</i> (Greasyback shrimp; saltwater)	130-230; 24-hr	practically non-toxic	Liao et al., 1989
<i>Penaeus japonicus</i> (Kuruma shrimp; saltwater)	41-59; 24-hr	slightly toxic	
<i>Penaeus semisulcatus</i> (shrimp; saltwater)	118-180; 24-hr	practically non-toxic	
Prawn			
<i>Macrobrachium rosenbergii</i> (Giant river prawn; saltwater)	141-199; 24-hr	practically non-toxic	Cruz-Lacierdo, 1993; Liao et al., 1989
<i>Penaeus monodon</i> (Jumbo tiger prawn; saltwater)	107-170; 24-hr 100; 96-hr	practically non-toxic	
<i>Penaeus penicillatus</i> (Redtail prawn; saltwater)	107-170; 24-hr	practically non-toxic	
Daphnids			
<i>Daphnia magna</i> (Water flea; freshwater)	10; 24-hr 10; 30-days	moderately toxic	Apostol, 1987
Fish			
<i>Oncorhynchus kisutch</i> (Coho salmon; freshwater)	10; 24-hr	moderately toxic	MacPhee and Ruelle, 1969
<i>Oncorhynchus tshawytscha</i> (Coho salmon; freshwater)	10; 24-hr	moderately toxic	
<i>Ptychocheilus oregonensis</i> (Northern squawfish; freshwater)	10; 24-hr	moderately toxic	

Non-target plant studies (OPPTS 850.4100) were not required. No plant toxicity was observed in any product efficacy trials conducted by the registrant (see MRID 463536-13: Compilation of Quinoa Saponins Efficacy Studies, dated 8/9/2004). Furthermore, saponins are widespread in

plants and triterpenoid saponins (such as those present in the active ingredient) are common in many cultivated crops (Fenwick et al. 1991). The product is not intended for use on forests or grasslands. Spray drift will be mitigated by label directions restricting spray applications to inside greenhouses or outside within portable spray chambers when applications are made to seeds or pre-transplant seedlings in the field.

Non-target insect studies (OPPTS 850.3030 and 850.3040) were not required. The *C. quinoa* plant is susceptible to attack by many insect pests from seed germination through harvest (Hellin and Higman, 2005; Oelke et al., 1992; Rasmussen et al., 2001 & 2003; Yabar et al., 2002) demonstrating that insects are already widely exposed to triterpenoid quinoa saponins and are not adversely affected by the saponin content of the plants. Available information suggests that saponins are toxic to larval forms of aquatic insects, but not adults (Francis et al., 2002), due to effects on respiratory membranes. An ECOTOX search reported the following saponin mortality data for larval mosquitoes: *Culex fatigans* 24-hr LC₅₀ = 58 ppm. The product is not intended for direct application to insects or aquatic environments where certain insect species may breed. The product is applied as a pre-plant seed and root dip or as a pre-transplant foliar spray (restricted to inside greenhouses or other enclosures) treatment for tomato seedlings. Therefore, there will be no inadvertent direct application to insects and no indirect application to insects via spray drift.

2. Environmental Fate and Ground Water Data

There are no specific data regarding the degradation of saponins of *Chenopodium quinoa* in the environment. In a study conducted by Molgaard et al. (2000), biodegradability of endod (*Phytolacca dodecandra*) berry saponins, a potent molluscicide, was evaluated. The freshwater snail *Biomphalaria glabrata* and red blood cells were used as bioassays to measure saponin potency, in conjunction with an HPLC method to quantitatively assess saponin levels in "clean" water or river water (from the Gurove River in Zimbabwe). Using the hemolysis (red blood cell) bioassay, saponins extracted with water from endod berries (at initial concentrations of 15, 30, 75 and 150 mg/L) were observed to be stable for two days, then degraded rapidly between Days 3 and 4 in both clean and river water. In the same aquaria, snail survival in clean water was 0% on Day 0, approximately 40% on Day 4, and 100% on Days 9 to 30; in river water, survival was 0% on Day 0, approximately 60% on Day 4, approximately 80% on Day 9, and 100% on Days 23 to 30. Snail mortality ranged from LC₅₀ = 6.8 to 9.6 mg/L. In a second study, HPLC analysis of clean water demonstrated similar decreases in saponin concentrations over time, regardless of initial concentration (15, 35, or 75 mg/L) and the decreases were in agreement with decreases in saponin potency as measured with the hemolysis assay. In this study, initial saponin concentrations of 15 mg/L and 75 mg/L declined to non-detectable levels in 5 and 11 days, respectively. A third study using Organization for Economic Co-operation and Development (OECD) 301 F protocols, demonstrated that endod saponins had a half-life of 15.8 hours in activated sludge.

Based on the above studies, it is highly unlikely that non-target organisms, especially aquatic organisms, will be exposed to potentially toxic levels of saponins via runoff and/or movement through the soil, based on: 1) rapid biodegradation in soil and water (3-5 days), and 2) low application rates (< 5 mg a.i./A), which are below the LC₅₀s for most organisms reported in the literature.

3. Ecological Exposure and Risk Characterization

The potential for exposure to non-target wildlife is minimal. Based on the results of the studies cited above, it is highly unlikely that non-target organisms will be exposed to potentially toxic levels of saponins due to: (i) rapid biodegradation in soil and water (3-5 days); and (ii) low application rates (< 5 mg a.i./A) which will likely result in environmental concentrations that are well below the LC₅₀s for all organisms reported in the literature.

D. EFFICACY DATA

Efficacy data (MRID 463536-13) were submitted in support of label claims and product performance. Submission of product performance data (Efficacy Trials, OPPTS 810.300) is listed as a requirement for all pesticide products. However, customarily the Agency only requires this data to be submitted for review in connection with the registration of products directly pertaining to the mitigation of disease bearing human health organisms and certain designated Quarantine Pests, i.e., ticks, mosquitoes, fleas, Mediterranean fruit flies, Gypsy Moths, Japanese Beetles and etc. In this case, the registrant submitted summaries of eight field studies (MRID 463536-13) conducted to evaluate the efficacy of some saponins of *Chenopodium quinoa* formulations (a.i., saponins of *C. quinoa*, 49.65%) against various diseases of legumes, cereals, potatoes, and tomatoes. Depending on the study, saponins of *C. quinoa* was applied as a seed treatment, a foliar treatment, a root dip, or some combination thereof. Studies were conducted in Canada and Michigan. Generally, saponins of *C. quinoa* decreased the incidence of some diseases, accompanied by an increase in yield, on some crops.

There were no reports of phytotoxicity in any of the treated crops. Also, the Agency determined during this review process that these efficacy trials are inconclusive because of various deficiencies: certain formulations of the end use product, saponins of *C. quinoa* were not adequately described; some trial summaries did not include specific application rates and timing of applications; and certain application methods used in efficacy trials were not conducted according to the use directions proposed on the product label, i.e. in-furrow spray treatments and multiple post-emergence foliar treatments to potato vines.

IV. Risk Management Decision

A. DETERMINATION OF ELIGIBILITY FOR REGISTRATION

Section 3(c)(5) of FIFRA provides for the 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, saponins of *Chenopodium quinoa* products are not expected to cause unreasonable adverse effects when used according to label instructions. Criteria “B” is satisfied by the current label and the data presented in this document. It is believed that this pesticidal active ingredient will not cause any unreasonable adverse effects, is a fungicide, and does provide protection as claimed satisfying Criteria “C.” Criteria “D” was satisfied by the data presented in the initial registration of this biochemical. Therefore, saponins of *C. quinoa* are eligible for registration.

B. REGULATORY POSITION

1. Unconditional Registration

All of the data requirements are fulfilled and BPPD granted an unconditional registration for the active ingredient, saponins of *Chenopodium quinoa*.

Tolerance Establishment

The uses of saponins of *C. quinoa* have been determined to be “non-food” uses and therefore do not require the establishment of a food tolerance or an exemption from the requirements of a tolerance.

2. CODEX Harmonization

Not applicable because all of the uses have been determined to be non-food.

3. Nonfood Registrations

There are no issues at this time.

4. Risk Mitigation

There are no significant risk issues identified for dietary risk, residential risk, or ground and surface water contamination. Mitigation measures for occupational routes of exposure are required in that mixers and applicators are required to wear additional PPE (protective eyewear) for spray applications. Indirect exposure via spray drift is also mitigated by label directions restricting spray applications to inside greenhouses or outside within portable spray chambers when pre-transplant applications are made in the field. Risk to nontarget organisms will be mitigated by appropriate label precautions.

5. Endangered Species Statement

Based on the information discussed above, the Agency has determined that registered use of saponins of *Chenopodium quinoa* (comprised of roughly equimolar amounts of the triterpene glycosides of oleanolic acid, hederagenin, and phytolaccagenic acid) as its active ingredient, will have **No Adverse Effects (NAE)** on threatened and/or endangered species. When the product is used according to label use directions, there are no concerns for any non-target organisms.

C. LABELING RATIONALE

The Agency's position is that the labeling for the product containing saponins of *C. quinoa* as the active ingredient, complies with current pesticide labeling requirements imposed under FIFRA and 40 CFR §156.10.

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 Pesticide Registration (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). 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.

Uses of the end-use product containing saponins of *Chenopodium quinoa* are subject to the requirements of WPS, and as such it has the appropriate language as required by the standard.

For uses of this product that are covered by the Worker Protection Standard (WPS), worker entry into treated areas is not allowed during the restricted entry interval of 12 hours. The PPE requirement for early entry to treated areas that is permitted under the WPS and that involves contact with anything that has been treated, such as plants, soil, or water, is coveralls, protective eyewear, waterproof gloves, and shoes plus socks.

b. Non-Worker Protection Standard

There are no non-worker (non-mixer/loader/applicator) human health hazard issues.

c. Precautionary Labeling

The Agency has examined the toxicological data base for saponins of *Chenopodium quinoa* and has concluded that the precautionary labeling (i.e., Signal Word, First Aid statement, and other label statements) listed on the label (See Appendix A - Product Label) adequately mitigates the risks associated with the currently registered uses.

The following Personal Protective Equipment Language (PPE) and the User Safety Recommendations Box immediately below the Precautionary Statement reads as follows:

“Personal Protective Equipment (PPE): Applicators and handlers must wear long-sleeved shirt and long pants, shoes, socks, and waterproof gloves. For spray applications, applicators must protective eyewear. Follow the manufacturer’s instructions for cleaning/maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.”

d. Spray Drift Advisory

No spray drift advisory statement is necessary for this proposed use.

<p>User Safety Recommendations</p> <p>Users should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet.</p> <p>Users should remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.</p> <p>Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.</p>
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or any requirements specific to your State or Tribe, consult the State/Tribal agency responsible for pesticide regulation.

2. Environmental Hazards Labeling

The following language is to appear in this section of the label:

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 equipment washwater or rinsate. This pesticide is toxic to fish and aquatic invertebrates. Do not use seed or seedlings treated with this product for animal feed. Do not use treated seed for food, feed, or oil purposes. Treat only those seeds needed for immediate use and planting. Do not store excess treated seed beyond planting time. Dispose of excess treated seed by burial away from streams and bodies of water.

3. Application Rate

For agronomic application, saponins of *Chenopodium quinoa* at 49.65% is mixed as a dip or spray at a rate of 0.035 ounces per 34 ounces of water (1 liter) for application to 375 pounds of legume (e.g., bean, pea) or cereal (e.g., wheat) seed, or 110 to 220 pounds of tuber (e.g., potato seed pieces). Seeds or roots are to be dipped (submerged for sixty seconds) or sprayed with solution until thoroughly covered. Foliar application, sprayed until leaves are completely wet, is made once to immature tomato seedlings, up to 6 inches tall, pre-flowering, up to 4 days before transplanting.

D. LABELING

Product name: **Heads Up[®] Plant Protectant**

Active Ingredient:

Saponins of *Chenopodium quinoa* (approximately
Equimolar amounts of the triterpene bidesmosidic
glycosides of oleanolic acid, hederagenin, and
phytolaccagenic acid).....49.65%

Other Ingredients.....50.35%

Total 100.00%

Signal word is "CAUTION".

The product shall contain the following information:

- Product Name
- Ingredient Statement
- Registration Number
- Signal Word (CAUTION)

Label Language Requirements

The following labeling language as listed below is required for Federal registration.

PRECAUTIONARY STATEMENTS

Hazard to Humans and Domestic Animals. Caution. Causes moderate eye irritation. Harmful if inhaled. Avoid contact with skin, eyes or clothing. Avoid breathing spray mist. Wash thoroughly with soap and water after handling. Remove and wash contaminated clothing before reuse.

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 disposing of equipment washwater or rinsate. This pesticide is toxic to fish and aquatic invertebrates. Do not use seed or seedlings treated with this product for animal feed. Do not use treated seed for food, feed, or oil purposes. Treat only those seeds needed for immediate use and planting. Do not store excess treated seed beyond planting time. Dispose of excess treated seed by burial away from streams and bodies of water.

FIRST AID:

If in eyes:

Hold eye open and rinse slowly and gently with water for 15-20 minutes.
Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
Call a poison control center or doctor for treatment advice.

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 a poison control center or doctor for further treatment advice.

The following statement must accompany the First Aid text block: “Have the product container or label with you when calling a poison control center or doctor, or going for treatment.” The Agency guidance also suggests including a contact telephone number for additional emergency medical treatment information.

Use Directions:

The Directions for Use pertaining to the pre-transplant foliar treatment of tomato seedlings must be explicit to insure that applications are not made when flowers or fruit are present on the plant. The following language appears in the use directions for pre-plant foliar application to tomato transplants.

“Apply only one foliar application of this product to tomato seedlings, up to 6 inches in height, at transplant or up to 4 days prior to transplanting. Do not apply this product to tomato seedlings when blooms or fruits are present on the plant.”

V. Actions Required by Registrants

There are no data requirements, label changes or other responses necessary for the reregistration of the end-use product since the product is being registered after November 1984 and is, therefore, not subject to reregistration. There are also no existing stocks provisions at this time.

The Agency evaluated all of the data submitted in connection the initial registration of saponins of *Chenopodium quinoa* and determined that these data are sufficient to satisfy current registration guideline requirements. Therefore, the active ingredient saponins of *Chenopodium quinoa* is eligible for registration. No additional data are required to be submitted to the Agency at this time.

Notwithstanding the information stated in the previous paragraph, it should be clearly understood that certain, specific, data are required to be reported to the Agency as a requirement for maintaining the Federal registration for a pesticide product. A brief summary of these types of data are listed below.

A. REPORTING OF ADVERSE EFFECTS

Reports of all incidents of adverse effects to the environment must be submitted to the Agency under the provisions stated in FIFRA, Section 6(a)(2).

B. REPORTING OF HYPERSENSITIVITY INCIDENTS

Additionally, all incidents of hypersensitivity (including both suspected and confirmed incidents) must be reported to the Agency under the provisions of 40 CFR Part 158.690(c), guideline reference number 152-16.

VI. Appendix A

Table 5 lists the use sites for the product. The label for the product is also attached (see **Appendix B**).

Table 5. Use Sites	
Heads Up Plant Protectant Seeds: Potato (tuber, seed pieces), bean, pea, wheat. Roots (as a root dip): Tomato seedling Transplant Seedlings (foliar spray): Tomato	Official date registered:

VII. Appendix B

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Saponins of *Chenopodium quinoa*
Biopesticides Registration Action Document

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VIII. Appendix C

Product Label

HEADS UP® PLANT PROTECTANT

**Preplant seed and pretransplant seedling treatment
 for the prevention of fungal, bacterial and viral diseases of plants**

ACTIVE INGREDIENT

Extract of <i>Chenopodium quinoa</i> saponins (containing approximately equimolar amounts of triterpene bidesmosidic glycosides of oleanolic acid, hederagenin, and phytolaccagenic acid)	49.65%
OTHER INGREDIENTS	50.35%
TOTAL	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

FIRST AID	
If in eyes	<ul style="list-style-type: none"> - Hold eye open and rinse slowly and gently with water for 15-20 minutes. - Remove contact lenses, if present, after the first five minutes, then continue rinsing eye. - Call a poison control center or doctor for treatment advice.
If inhaled	<ul style="list-style-type: none"> - 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 a poison control center or doctor for further treatment advice.
<p>HOT LINE NUMBER For 24-hour Medical Emergency Treatment Information 1-306-655-1010</p>	
<p>Have the product container or label with you when calling a poison control center or doctor, or going for treatment.</p>	

NET WEIGHT 0.11 lbs. (50 grams)

EPA Registration Number 81853-

EPA Establishment Number 81853-CAN-1

Heads Up Plant Protectants, Inc.
 Box 519, 428 3rd Street
 Kamsack, Saskatchewan S0A 1S0
 Canada
 Telephone: 1-866-368-9306

PRECAUTIONARY STATEMENTS

Saponins of *Chenopodium quinoa*
Biopesticides Registration Action Document

Hazards to Humans and Domestic Animals. Caution. Causes moderate eye irritation. Harmful if inhaled. Avoid contact with eyes or clothing. Avoid breathing spray mist. Wash thoroughly with soap and water after handling. Remove and wash contaminated clothing before reuse.

Personal Protective Equipment (PPE) Requirements: Applicators and handlers must wear: long-sleeved shirt and long pants, shoes, socks and waterproof gloves. For spray applications, wear protective eyewear. Follow manufacturer's instructions for maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

User Safety Recommendations

- Users should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet.
- Users should remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.
- Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.

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 disposing of equipment washwater or rinsate. This pesticide is toxic to fish and aquatic invertebrates. Do not use seed or seedlings treated with this product for animal feed. Do not use treated seed for food, feed or oil purposes. Treat only those seeds needed for immediate use and planting. Do not store excess treated seed beyond planting time. Dispose of excess treated seed by burial away from streams and bodies of water.

DIRECTIONS FOR USE

It is a violation of federal law to use this product in a manner inconsistent with its labeling.

Do not apply this product through any type of irrigation system.

Use this product only in accordance with the directions for use on the label.

Use this product thoroughly dissolved and only when mixed with water. Read entire directions for use and conditions of sale and warranty before using, and if said terms are not acceptable, return the product unused in its unopened container immediately.

Seed treatment on agricultural establishments in hopper-box, or other seed treatment application at or immediately before planting is within the scope of WPS.

Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application. For any requirement specific to your State and Tribe, consult the State/Tribal agency responsible for pesticide regulation.

AGRICULTURAL USE REQUIREMENTS

Saponins of *Chenopodium quinoa*
Biopesticides Registration Action Document

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR part 170. This standard contains requirements for the protection of agricultural workers on farms, forests, nurseries, and greenhouses, and handlers of agricultural pesticides. It contains requirements for training, decontamination, notification, and emergency assistance. It also contains specific instructions and exceptions pertaining to the statements on this label about the Personal Protective Equipment (PPE), notification to workers, and restricted-entry interval. The requirements of this box only apply to uses of this product that are covered by the Worker Protection Standard.

Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours.

Exception: If the product is soil injected or soil incorporated, the Worker Protection Standard, under certain circumstances, allows workers to enter the treated area if there will be no contact with anything that has been treated.

PPE required for early entry to treated areas (that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water) is: coveralls, socks and shoes and waterproof gloves.

NON-AGRICULTURAL USE REQUIREMENTS

The requirements in this box apply to uses of this product that are NOT within the scope of the Worker Protection Standard for agricultural pesticide (40 CFR Part 170). The WPS applies when this product is used to produce agricultural plants on farms, forests, nurseries, or greenhouses.

GENERAL INFORMATION

Heads Up® Plant Protectant is a preplant seed and pretransplant seedling treatment for the prevention of fungal, bacterial and viral diseases of plants.

Heads Up® Plant Protectant is made from plant sources. Apply this product as directed to seeds, roots of transplants, or sprayed on tomato seedlings in trays, as part of a general disease management program.

TREAT ONLY HEALTHY VIGOROUS SEED OR SEEDLINGS: Application of **Heads Up® Plant Protectant** to damaged or diseased seed or seed of low quality or vigor will not improve seed performance. Always apply to healthy seed or seedlings that are vigorous and actively growing under stress-free conditions.

MIXING DIRECTIONS

Apply dissolved into solution with water, and thoroughly coat the surface of the seed, roots or leaves. Do not apply in packaged powder form. Ensure that the product is thoroughly dissolved in solution and the solution agitated before application. Return any unused powder to original container.

Clean application equipment. Prepare only the amount of solution needed to be applied to treat the seeds. Once in solution the product will be subject to bacterial degradation. Mix only enough product that is required for use. Use the solution IMMEDIATELY AFTER COMPLETE MIXING and no longer than 4 to 6 hours after mixing. Unused solution should be disposed according to the Storage and Disposal section of this label.

PREPLANT SEED TREATMENT

Saponins of *Chenopodium quinoa*
Biopesticides Registration Action Document

SITES

Potatoes, wheat, peas and beans

APPLICATION RATES

Wheat, Pea and Bean Seeds

Mix at a ratio of 0.035 oz. (1 gram) of **Heads Up® Plant Protectant** per 34 ounces (1 liter) of water.
34 ounces (one liter) of this solution will treat 375 lbs. (170 kgs.) of legume or cereal seed

Potato Seeds

Mix at a ratio of 0.035 oz. (1 gram) of **Heads Up® Plant Protectant** per 34 ounces (1 liter) of water.
34 ounces (one liter) of this solution will treat 110 - 220 lbs. (50kgs. – 100 kgs.) of potato seeds.

APPLICATION

Seeds must be prepared and ready for seeding. The object is to achieve a wet shiny appearance to the seed. This will dry off or be absorbed by the seed; however, the treatment will remain in effect. Treat the seeds by dipping, spraying or dribbling the solution into a rotating auger conveyor or some other approved seed treatment device. Spray applications to seeds within an enclosed spray booth or other enclosed spray device are also acceptable providing thorough coverage is achieved.

For potato seeds, whether fresh cut or suberized, the **Heads Up®** solution **must be applied to germinating seed potatoes**, as indicated by obvious sprouting activity coming from the potato eyes. This sprouting activity can be from peeking to full spout length, but before green leaves appear.

Proper calibration and operation of application equipment is essential. Treat only the seed that you intend to plant and insure all treated seed is used for planting purposes.

PRETRANSPLANT SEEDLING ROOT TREATMENT

SITES

Tomato seedlings

APPLICATION RATES

Carefully read and understand this label for use information and restrictions.
Mix at a ratio of 0.035 oz. (1 gram) of **Heads Up® Plant Protectant** per 34 ounces (1 liter) of water.
Root dip or spray bare roots of transplants until solution is exhausted.

APPLICATION

FOR ROOT AREAS ONLY.

Plants should be actively growing and free of stress conditions.

Seedlings must be prepared and ready for transplanting. Treat roots by dipping the exposed root mass completely and holding submersed for sixty (60) seconds in the **Heads Up®** solution. It is not necessary to completely remove all adhering soil from the root mass; however gently shaking to remove excess adhering soil is generally recommended. When seedlings are started in flats, dip and hold the root area of the whole plant in the flat for 60 seconds in a shallow tray of **Heads Up®** solution. The tray must be deep enough to immerse the plant's roots. Individual seedlings may be treated by removing them from the starter soil and shaking off excess soil, placing them in a container holding the **root mass area only** submersed in **Heads Up®** solution for 60 seconds, and then transplanted. Treat individual seedlings by spraying the exposed root mass until they are completely wet with the **Heads Up®** solution. After treatment, plant the seedlings immediately. Treat only the seedlings that you intend to plant and insure all treated

Saponins of *Chenopodium quinoa*
Biopesticides Registration Action Document

seedlings are used for planting purposes.

For tomato seedlings also to receive foliar treatment, see directions below.

PRETRANSPLANT SEEDLING FOLIAR TREATMENT

SITES

Apply only one foliar application of this product to tomato seedlings, up to 6 inches in height, at transplant or up to 4 days prior to transplanting. Do not apply this product to tomato seedlings when blooms or fruits are present on the plant. No other foliage treatments of Heads Up® solution are permitted.

APPLICATION RATES

Mix at a ratio of 0.035 oz. (1 gram) of **Heads Up® Plant Protectant** per 34 ounces (1 liter) of water. Apply 0.17 – 0.51 ounces (5 – 15 milliliters) of solution per square foot of started tomato seedlings in trays or until foliage is completely wet.

APPLICATION

Seedlings must be prepared and ready for planting. Spray one application only to immature seedlings up to 4 days before transplanting. Spray seedlings until foliage is completely wet. Apply indoors in greenhouses or other enclosed structures or outdoors in enclosed spray booths or other enclosed spray devices.

For tomato seedlings also to receive root dip treatment, see directions above.

STORAGE AND DISPOSAL

Do not contaminate food, feed or water by storage or disposal.

Pesticide Storage: Store in original container, tightly sealed, in a dry location.

Pesticide Disposal: Wastes resulting from the use of this product must be disposed of on site or at an approved waste disposal facility.

Container Disposal: When product is completely used, dispose of empty bag in a sanitary landfill or by incineration, or, if allowed by State and local authorities, by burning. If burned, stay out of smoke.

CONDITIONS OF SALE AND WARRANTY

Seller's guarantee shall be limited to the contents and merchantability of the product and the terms of the label, and subject thereto. To the fullest extent permitted by law, the buyer assumes all risks to persons or property arising out of use or handling and accepts the product on these conditions. Because the time, place, rate of application and other conditions of use are beyond the Seller's control, Seller's liability from storage, handling and use of this product is limited to replacement of the product or a refund of the purchase price. **Heads Up® Plant Protectant** is applicable as a disease preventive only. The directions for use of this product are based on test plots, greenhouse trials and the opinions of experts. They are believed to be reliable and correct; however, it is not possible to eliminate all possible detrimental effects associated with use, whether they are crop injury, ineffectiveness or other unintended consequences which may occur as a result of weather or other materials, or the manner of use or application, beyond the control of the manufacturer or the seller. To the fullest extent permitted by law, the buyer shall assume all risks.

Heads Up® is a trademark of Heads Up Plant Protectants, Inc., Patent Numbers 6,743,752 and 6,482,770