Proposed Registration Decision PRD2010-20

Saponins of *Chenopodium quinoa*

(publié aussi en français)

1 September 2010

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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HC Pub: 100462

ISBN: 978-1-100-16781-7 (978-1-100-16782-4)
Catalogue number: H113-9/2010-20E (H113-9/2010-20E-PDF)

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Overview

Proposed Registration Decision for Saponins of *Chenopodium quinoa*

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Saponins of *Chenopodium quinoa* Technical and Heads Up Plant Protectant, containing the technical grade active ingredient saponins of *Chenopodium quinoa*, against rhizoctonia canker and black scurf on potato seed pieces.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Saponins of *Chenopodium quinoa* Technical and Heads Up Plant Protectant.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on saponins of *Chenopodium quinoa*, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on saponins of *Chenopodium quinoa*, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Saponins of *Chenopodium quinoa*?

Saponins of C*henopodium quinoa* are the main active components in the extract from the bran of C*henopodium quinoa* seeds. Saponins are substances produced naturally by many plant species that have a wide range of bioactive properties, including antimicrobial effects on various fungi and bacteria. It has also been proposed that saponins may induce systemic acquired resistance (SAR) in treated plants.

Health Considerations

Can Approved Uses of Saponins of *Chenopodium quinoa* Affect Human Health?

Saponins of *Chenopodium quinoa* is unlikely to affect your health when used according to label directions.

Potential exposure to saponins of *Chenopodium quinoa* may occur when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

The technical grade active ingredient, Saponins of *Chenopodium quinoa* Technical, is of slight acute toxicity by the inhalation route, low toxicity via the oral and dermal routes, and minimally irritating to the eyes and skin. Based on available information and a long history of human consumption of the food commodity quinoa (which invariably contains residues of saponins of *Chenopodium quinoa* at the time of consumption), exposure to the active ingredient is unlikely to result in any short-term toxicity, prenatal developmental toxicity, genotoxicity, or chronic toxicity.

[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Residues in Water and Food

Dietary risks from food and water are not of concern.

The amount of saponins of *Chenopodium quinoa* present as a residue after application of the end-use product will not be detectable due to the low application rate, use pattern, and rapid biotransformation of the active ingredient. Furthermore, exposure to the active ingredient currently occurs in the Canadian diet from the consumption of quinoa (washed seeds of *Chenopodium quinoa*) as food.

Occupational Risks From Handling Heads Up Plant Protectant

Occupational risks are not of concern when Heads Up Plant Protectant is used according to label directions, which include protective measures

Pesticide applicators handling and applying Heads Up Plant Protectant to seed potatoes can come into direct contact with saponins of *Chenopodium quinoa* on the skin and in the eyes, as well as by accidental ingestion and inhalation. The precautionary label statements adequately mitigate the concern of exposure to applicators.

Only workers are permitted access to the treatment areas, thus the potential for bystander exposure is expected to be negligible and therefore not of concern.

Environmental Considerations

What Happens When Saponins of *Chenopodium quinoa* Is Introduced Into the Environment?

Saponins of *Chenopodium quinoa* are expected to leach from the treated potato seed pieces into the surrounding soil. However, saponins are not persistent in the environment and will not contaminate surface water or drinking water sources.

Value Considerations

What Is the Value of Heads Up Plant Protectant?

Saponins of C*henopodium quinoa,* the active ingredient in Heads Up Plant Protectant, suppresses rhizoctonia canker and black scurf caused by *Rhizoctonia solani* on potato.

Heads Up Plant Protectant is a soluble powder containing 63.02% of saponins of C*henopodium quinoa* that is intended to be used as seed treatment for the suppression of rhizoctonia canker and black scurf (*Rhizoctonia solani*) on potatoes. Heads Up Plant Protectant is a non-conventional fungicide that represents an additional mode of action, and it will provide potato growers an alternative to manage rhizoctonia diseases in potato.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Heads Up Plant Protectant to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Hazard statements and symbols with appropriate precautionary measures are required to address slight inhalation toxicity. Precautionary measures are also required to address minimal irritation to the eyes and skin. Mixers, applicators and handlers must wear long-sleeved shirt and long pants, shoes, socks and waterproof gloves. Mixers must also wear a dust mask and protective eyewear.

Environment

A hazard statement is required to address toxicity of saponins to some aquatic organisms.

Next Steps

Before making a final registration decision on saponins of *Chenopodium quinoa*, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on saponins of *Chenopodium quinoa* (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Saponins of *Chenopodium quinoa*

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Saponins of *Chenopodium quinoa*
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	The product is a mixture of complex compounds
2. Chemical Abstracts Service (CAS)	The product is a mixture of complex compounds
CAS number	404589-23-7 (for crude extract)
Molecular formula	Not applicable. The product is a mixture of complex compounds
Molecular weight	Not applicable. The product is a mixture of complex compounds
Structural formula	Not applicable. The product is a mixture of complex compounds
Purity of the active ingredient	63.02%

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product—Saponins of *Chenopodium quinoa* Technical

Property	Result
Colour and physical state	Cream-beige amorphous solid
Odour	Meaty odour
Melting range	155 – 158°C
Boiling point or range	Not applicable. The product is a solid.
Density	0.20 ± 0.02 g/mL

Property	Result
Vapour pressure at 20°C	Not applicable. The product is an amorphous solid.
Ultraviolet (UV)-visible spectrum	Major absorption is in the 190 – 200 nm range. There was no absorption above 400 nm.
Solubility in water	Highly soluble in water
Solubility in organic solvents at 20°C (g/100 mL)	Not provided
n-Octanol-water partition coefficient (K_{ow})	The product forms an emulsion
Dissociation constant (pK_a)	Not applicable. The product is a complex mixture of several plant extracts
Stability (temperature, metal)	The product is stable to elevated temperatures. There was no drop in the total saponins after storage at room temperature and at 54°C. The test for stability to metal and metal ions was not conducted.

End-Use Product—Heads Up Plant Protectant

Property	Result
Colour	Cream-beige
Odour	Meaty odour
Physical state	Amorphous solid (fine particle size powder)
Formulation type	Soluble powder
Guarantee	63.02%
Container material and description	Plastic re-sealable bag in Mylar bag, 1g – 1kg
Density	0.2 g/mL
pH of 1% dispersion in water	7.2
Oxidizing or reducing action	The product does not contain and oxidizing or reducing agents.
Storage stability	The product is stable for 12 months when stored at ambient temperature in plastic bags
Corrosion characteristics	The product is stable and shows no corrosion characteristics after 12 months storage at ambient temperature in plastic bags.
Explodability	The product does not contain any components which are potentially explosive

1.3 Directions for Use

Heads Up Plant Protectant is a soluble powder containing 63.02% of saponins of C*henopodium quinoa.* It is used as a seed treatment for the suppression of rhizoctonia canker and black scurf (*Rhizoctonia solani*) on potatoes.

Heads Up Plant Protectant is applied by mixing 1 gram of product with 1 litre of water, then applying 1 L of solution for every 100-264 kg of seed potato (cut or whole tubers).

1.4 Mode of Action

Heads Up Plant Protectant is a product containing saponins of *Chenopodium quinoa* which is extracted from the bran of *Chenopodium quinoa* seeds. Saponins are a class of chemical compounds that occur naturally in many plant species. The antifungal activity of saponins has been documented. Systemic acquired resistance (SAR) has also been proposed as the possibly mechanisms on the antifungal activity of saponins. However, there is no clear evidence that supports this mode of action. The role of saponins from *Chenopodium quinoa* in suppressing plant disease is not yet fully understood.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Saponins of *Chenopodium quinoa* Technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

A method of analysis to detect saponins of *Chenopodium quinoa* in potato is not required as residue levels are not expected to be detectable given the low application rate and ready biodegradability of these naturally occurring compounds. Furthermore, the product is limited for use only to seed potatoes at the time of planting and not to harvested potatoes intended for direct human consumption or food processing.

3.0 Impact on Human and Animal Health

3.1 Metabolism

Studies specific to the metabolism of saponins of *Chenopodium quinoa* are not available. Due to the widespread occurrence of saponins (as a class of chemicals) in plants, including food crops, humans are regularly exposed to saponins, including the active ingredient, and as such are expected to have physiological pathways to metabolize these chemicals.

3.2 Integrated Toxicology Summary

A detailed review of the toxicological database for saponins of *Chenopodium quinoa* was conducted by the PMRA, however, elements of this review relied, in part, on data summaries in the United States Environmental Protection Agency's Biopesticides Registration Action Document for saponins of *Chenopodium quinoa*.

The database for saponins of *Chenopodium quinoa* is sufficiently complete (see Appendix I, Table 1), consisting of acute laboratory animal toxicity studies (oral, dermal and inhalation), skin and eye irritation studies, and a skin sensitization study. As well, the applicant provided published scientific literature to address the toxicity of saponins in general, including short-term and chronic toxicity. Together, this information was used to assess the toxicological hazards of both the technical grade active ingredient (Saponins of *Chenopodium quinoa* Technical) and its associated end-use product (Heads Up Plant Protectant). Although the PMRA normally requires acute toxicity and irritation studies on both the technical grade active ingredient and the end-use product, given that the end-use product contains no formulants of toxicological concern, test data only on the technical grade active ingredient was accepted by the Agency to support the end-use product registration application. The overall scientific quality of the database is considered sufficient to characterize the toxicity of the technical grade active ingredient and end-use product.

Acute toxicity studies indicated that saponins of *Chenopodium quinoa* are of low oral and dermal toxicity in rats with an oral LD_{50} of greater than 5000 mg/kg bw and a dermal LD_{50} of greater than 5000 mg/kg bw. Saponins of *Chenopodium quinoa* are slightly toxic according to an acute inhalation study whereby the LC_{50} for male rats was 0.824 mg/L (95% confidence limit 0.170 ─ 4.78 mg/L) and for female rats was greater than 2.04 mg/L.

Saponins of *Chenopodium quinoa* are minimally irritating to the eye and to the skin according to primary irritations studies on rabbits with maximum average scores (MAS) of 4.7/110 and 0.34/8, respectively, scored by the method of Draize. In a skin sensitization study on guinea pigs, saponins of *Chenopodium quinoa* were not shown to be sensitizers according to the Buehler method.

No short-term tier I toxicity data or requests to waive specific short-term toxicity data requirements were submitted for review. However, based on the low toxicity from acute oral and dermal studies coupled with a long history of use of saponins of *Chenopodium quinoa* as constituents in food with no reports of adverse effects (incidents), short-term toxicity from

repeated oral and dermal exposures are not expected to be of concern. However, given that the technical grade active ingredient is mildly acutely toxic via the inhalation route, the potential for short-term toxicological effects cannot be ruled out. Consequently, mitigative measures are required to limit exposure to workers handling and applying the product as noted in section 3.3.1.

Tier I test data on the prenatal developmental toxicity of saponins of *Chenopodium quinoa* were not available. Although it has been reported that both negative (abortifacient, antizygotic, and anti-implantation properties) and positive (increased sperm viability and motility) effects on reproduction occur from exposure to certain types of saponins, such effects have never been reported or associated with the triterpenoid saponins of *Chenopodium quinoa*. Information on the genotoxicity of saponins of *Chenopodium quinoa* was also unavailable; however, Ames and sister chromatid exchange tests performed on saponins (similar to the saponins found in the active ingredient) extracted from endod (*Sarcoca dodecandra*) showed negative results.

Submission of higher tier *in vivo* mutagenicity, developmental and immunotoxicity as well as chronic (including carcinogenicity and reproduction) toxicity test data/information is only required by PMRA if the potential for adverse chronic effects are indicated based on: 1) the short-term effect levels established in tier I short-term oral, dermal or inhalation studies; 2) the proposed use pattern of the end-use product; or 3) the expected frequency and level of repeated human exposure resulting from the proposed use of the end-use product. Based on a critical review of acute toxicity data on saponins of *Chenopodium quinoa* and consideration of the published scientific literature on saponins in general, coupled with the long history of consumption of quinoa as food, and dietary exposure to other triterpenoid saponins from other food sources, with no reported adverse effects, there is no conclusive evidence to suggest that saponins of *Chenopodium quinoa* are carcinogenic, mutagenic, immunotoxic, neurotoxic or reproductive toxicants.

3.3 Occupational/Bystander Exposure and Risk Assessment

While Saponins of *Chenopodium quinoa* Technical is considered a new technical grade active ingredient for use in pest control products in Canada, these chemicals have been consumed in the diet of humans for millennia as a part of the pseudo-cereal food crop quinoa. Although most of the saponins found in the seeds of *Chenopodium quinoa* are removed through the removal of the seed coat and washing with water, some residues of saponins invariably remain at the time of consumption. As well, there is a long history of occupational exposure to the saponins of *Chenopodium quinoa* during the processing of the seeds.

3.3.1 Occupational

Heads Up Plant Protectant is a soluble powder that is to be mixed with water and applied to seed potato tubers prior to planting. Possible user contact is limited to the mixing and application of product. Handling of treated seed potato will result in negligible exposure due to the low application rate (6.3 mg a.i./kg seed potato).

The end-use product may be applied to seed potato pieces at a commercial seed treatment facility or on the farm. The application rate is 1 g Heads Up Plant Protectant per litre of water per 100 ─ 264 kg of seed potato. On average, a farm applicator may treat 50,000 kg of seed potato per day subsequently using up to 0.5 kg of end-use product. An applicator at a commercial seed treatment facility may treat a considerably greater quantity of seed potato, however, due to the low application rate the potential occupational exposure to the active ingredient remains relatively low.

Both applicators and mixers of Heads Up Plant Protectant may be exposed to saponins of *Chenopodium quinoa* by the dermal, inhalation, and ocular route. Since saponins of *Chenopodium quinoa* are mildly irritating to the skin, the product label requires applicators and mixers to wear waterproof gloves, long-sleeved shirt and long pants, shoes and socks during the mixing and application. Mixers are also instructed to wear a dust mask and protective eyewear during mixing of Heads Up Plant Protectant in order to mitigate any potential risk relating from such exposures.

Since the treated potato seed is typically planted mechanically and the application rate is low, post-application exposure is expected to be negligible.

3.3.2 Bystander Exposure and Risk Assessment

Since Heads Up Plant Protectant is a Commercial class product only to be used on-farm or in a seed treatment facility, it is expected that only workers will have access to areas of treatment. Bystander exposure is expected to be negligible and not of concern.

3.4 Dietary Exposure and Risk Assessment

3.4.1 Food

Heads Up Plant Protectant will be applied once to seed potato tubers prior to planting at a rate of up to 6.3 mg a.i./kg. Due to the rapid biotransformation of the active ingredient and growth dilution by the crop, potential residues in the consumable commodity will be reduced to non-detectable levels by the time of harvest. Also, the product label states that treated seed product is not to be used as animal feed. Furthermore, exposure to the active ingredient currently occurs in the Canadian diet from the consumption of quinoa (washed seeds of *Chenopodium quinoa*) as food and from the consumption of other common food crops that naturally contain triterpenoid saponins. Saponins are widely distributed in diverse plant species, and triterpenoid saponins, such as those derived from *Chenopodium quinoa*, are common in cultivated crops regularly consumed by humans.

3.4.2 Drinking Water

The application of Heads Up Plant Protectant, and the planting of treated seed potato tubers, should not result in exposure to sources of drinking water above levels found naturally in the environment. Therefore, the use of saponins of *Chenopodium quinoa* is not expected to result in a dietary risk from drinking water.

3.4.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

The use of Heads Up Plant Protectant is not expected to result in environmental residues of any kind and currently, there are no other registered pesticidal uses of saponins of *Chenopodium quinoa*. Exposure of the general population and potentially sensitive subpopulations, including infants and children, to saponins of *Chenopodium quinoa* residues above levels found naturally in quinoa and other crop commodities, is not expected to occur as a result of the intended use of Heads Up Plant Protectant.

3.5 Maximum Residue Limits (MRL)

Exposure to the active ingredient currently occurs in the Canadian diet from the consumption of the pseudo-cereal quinoa. The use of Heads Up Plant Protectant as a treatment of seed potato is not expected to increase the dietary exposure of Canadians to saponins of *Chenopodium quinoa*. The rate of application is low and the rate of biotransformation of saponins in the soil environment is rapid such that there are unlikely to be detectable residue levels at the time of harvest. Therefore, the establishment of an MRL will not be required for saponins of *Chenopodium quinoa*.

3.6 Aggregate Exposure

The potential for dietary exposure of the general public to saponins of *Chenopodium quinoa* residues resulting from the proposed use is not expected to be of concern, considering the background levels found naturally in quinoa as well as other crop commodities consumed by humans. Exposure via drinking water is not expected to occur from this use. Non-occupational (i.e. residential) exposure is not expected to occur as a result of this use because there are no residential uses or any other registered use for saponins of *Chenopodium quinoa*.

Given that no appreciable increase in dietary or residential exposure relative to background levels is expected to occur from this use, the PMRA has determined that there is no unacceptable risk of harm expected from aggregate exposure to saponins of *Chenopodium quinoa* residues.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Saponins of *Chenopodium quinoa* will enter the environment when they are used as a seed treatment on potato seed pieces. Once in the soil, saponins of *Chenopodium quinoa* will easily leach from the treated seed due to their high solubility in water. However, given the rapid degradation of saponins (some saponins degrade within 3-5 days), saponins of *Chenopodium quinoa* will not likely leach through the soil profile and reach groundwater or enter surface water through run-off.

4.2 Environmental Risk Characterization

4.2.1 Risks to Terrestrial Organisms

The main area of concern for a seed treatment is related to the potential risk to birds and mammals feeding on treated seeds. A qualitative risk assessment indicates that the risk to birds and mammals from the ingestion of potato seed pieces contaminated with saponins of *Chenopodium quinoa* is minimal for a number of reasons. Saponins are naturally produced by a wide variety of plant species including agricultural crops. The amount of quinoa saponins from the potato seed treatment use is low when compared to amounts already found in the environment, particularly in areas where *C. quinoa* is grown. Studies carried out in the United Kingdom have indicated that quinoa crops harbour birds during the winter season, suggesting that wild birds feed on quinoa seeds without known adverse effects. Adverse effects (mortality and reduction in body weight gain) have been observed in poultry chicks feeding on a diet containing high levels of quinoa saponins. For example, survival was only 13% after 14 days of being fed a diet comprising 95% raw quinoa (raw quinoa contains high levels of saponins; saponins can be removed from the quinoa seeds by washing or dehulling). These effects, however, were attributed to food avoidance given the bitter taste of saponins. Poultry chicks were not affected when fed a diet comprising of 15% raw quinoa. Given the observed avoidance at high levels of dietary saponins, birds are not expected to feed on treated potato seeds in sufficient amounts to cause adverse effects. In addition, potato seed pieces are not a particularly attractive food source for birds. The risk to mammals is considered to be minimal, as saponins of *Chenopodium quinoa* are not toxic to mammals on an acute basis.

4.2.2 Risks to Aquatic Organisms

Because of their detergent-like properties and their ability to disrupt cell membranes, saponins are toxic to some aquatic organisms. However, aquatic organisms are not likely to be exposed to saponins of *Chenopodium quinoa* when used as a potato seed treatment.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

Six field trials were reviewed for the suppression of rhizoctonia canker and black scurf (*Rhizoctonia solani)* on potato using the proposed rate of Heads Up Plant Protectant. The potato seed pieces were treated using the seed treater to ensure adequate coverage. Disease severity on stems was reported in five trials, and Heads Up Plant Protectant improved *Rhizoctonia* control by 32% (ranged from 3% to 69%, n=5). The results were compared with other potato seed piece treatments in four of these trials, including two U.S. products. Maxim (containing fludioxonil) treatments resulted in 66% *Rhizoctonia* control (52-83%, n=3). Disease incidence on potato tubers was reported in three trials as an average of 40% *Rhizoctonia* control in Heads Up Plant Protectant treatments (0-65%, n=3), while Maxim treatments provided 56% control (43-69%, n=2). Disease severity on tubers was recorded in two trials, where Heads Up Plant Protectant

reduced disease severity by 41% in one of two trials. Heads Up Plant Protectant seed treatment did not significantly affect the potato yields in the trials, though the yields were numerically improved in three out of the six trials (2-20%).

Heads Up Plant Protectant was compared with Maxim MZ (containing fludioxonil and mancozeb) in two trials with artificial inoculation of *Rhizoctonia solani*. Black scurf on potato tubers was reduced by 61.2% as a result of treatment with Heads Up Plant Protectant, compared to 71.6% reduction in the Maxim treatment. Heads Up Plant Protectant also significantly increased potato tuber yield by 26.2% in these trials compared to 19.7% yield increase in Maxim treatment. Therefore, a claim of suppression of rhizoctonia canker and black scurf on potato can be supported as outlined in Appendix I, Table 3.

5.2 Phytotoxicity (adverse effects on crop)

No phytotoxicity was observed in all reviewed trials.

5.3 Economics

No market analysis was provided for this application. *Rhizoctonia solani* causes girdling of the stems of the plant and the daughter tubers in potatoes, and "black scurf" on the skin of the harvested potatoes. This disease causes a reduction in yield, visually poor table stock potatoes and complications with skin removal when processing potatoes for other products.

5.4 Sustainability

5.4.1 Survey of Alternatives

The alternative ingredients registered for control/suppression of rhizoctonia canker and black scurf (*Rhizoctonia solani*) on potatoes are presented in Appendix I, Table 2.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

There was no sufficient information to demonstrate the compatibility of Heads Up Plant Protectant with current IPM practices applied on potato production.

5.4.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

No information is available on the development of resistance to saponins of C*henopodium quinoa* present in Heads Up Plant Protectant. Saponins are a class of chemical compounds that occur naturally in many plant species. Although the mechanism of disease reduction is not yet completely understood, the development of resistance to this product is not a concern at this time due to the nature of the active ingredient and the supported use pattern.

5.4.4 Contribution to Risk Reduction and Sustainability

Heads Up Plant Protectant is a non-conventional fungicidal product that represents an additional mode of action against rhizoctonia diseases in seed potatoes.

Saponins occur naturally and are widely distributed in diverse plant species including agricultural crops. The overall contribution of saponins of *Chenopodium quinoa* to the environment when used as a seed treatment on potato seed pieces is low in comparison to natural levels found where *Chenopodium quinoa* is grown. In addition, saponins are known to rapidly degrade in the environment thereby further reducing exposure to non-target organisms.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e., persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, saponins of *Chenopodium quinoa* and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Saponins of *Chenopodium quinoa* does not meet the Track 1 criteria and is not expected to form any transformation products which meet the Track 1 criteria. Saponins of *Chenopodium quinoa* is a naturally occurring substance and is not expected to be persistent or bioaccumulative in the environment.

[5] DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade Saponins of *Chenopodium quinoa* and the end-use product Heads Up Plant Protectant do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

7.0 Summary

7.1 Human Health and Safety

The available toxicological information on saponins of *Chenopodium quinoa* is adequate to identify the majority of toxic effects that could result from exposure to the active ingredient. Saponins of *Chenopodium quinoa* is minimally irritating to the eyes and to the skin. It is of slight acute inhalation toxicity. It is of low toxicity via the oral and dermal route. Short-term toxicity data were not provided, however, it is of low toxicological concern due to the low oral, dermal and inhalation exposure. No chronic toxicity studies were submitted or found in the published scientific literature, but given the long history of use of quinoa as food, which contains the active ingredient, coupled with the long history of occupational exposure to the active ingredient from the processing of quinoa, there is no evidence to suggest that saponins of *Chenopodium quinoa* is carcinogenic, genotoxic, neurotoxic, or a developmental/reproductive toxicant.

Workers are not expected to be exposed to concentrations of saponins of *Chenopodium quinoa* of any consequence if the product label precautionary statements are observed. Bystander exposure is expected to be negligible.

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6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

8 DIR2006-02, PMRA Formulants Policy.

The establishment of an MRL was not required for saponins of *Chenopodium quinoa*, since the use of Heads Up Plant Protectant as a seed treatment on potato is not expected to significantly increase the dietary exposure to saponins of *Chenopodium quinoa* from the levels that already occur in the Canadian diet from the consumption of quinoa. Dietary exposure is not of concern.

7.2 Environmental Risk

Saponins of *Chenopodium quinoa* are naturally occurring in many plant species and its use as a seed treatment on potato seed pieces presents a negligible risk to the environment.

7.3 Value

There is adequate evidence to support the claim for using Heads Up Plant Protectant for suppression of rhizoctonia canker and black scurf on potato at the proposed rate for seed piece treatment.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Saponins of *Chenopodium quinoa* Technical and Heads Up Plant Protectant, containing the technical grade active ingredient saponins of *Chenopodium quinoa*, against rhizoctonia canker and black scurf on potato seed pieces.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

°C	degrees Celsius
a.i.	active ingredient
bw	body weight
CAS	Chemical Abstracts Service
C.L.	confidence limits
g	gram(s)
h	hour(s)
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
mg	milligram(s)
mL	millilitre(s)
MAS	maximum average score
MRL	maximum residue limit
nm	nanometre(s)
pKa	dissociation constant
PMRA	Pest Management Regulatory Agency
SAR	systemic acquired resistance
TSMP	Toxic Substances Management Policy
U.S.	United States
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Acute Toxicity of Saponins of *Chenopodium quinoa* Technical

Study Type	Species	Result	Comment	Reference
Oral	Rat	LD_{50} (♂♀) > 5000 mg/kg bw	Low toxicity	1745268, 1745254
Dermal	Rat	LD_{50} (♂♀) > 5000 mg/kg bw	Low toxicity	1745269, 1745254
Inhalation	Rat	♂ LC_{50} 0.824 mg/L (95% C.L. 0.170 ─ 4.78 mg/L) ♀ LC_{50} > 2.04 mg/L	Slight toxicity	1745270, 1745254
Skin Irritation	Rabbit	MAS[1] = 0.34/8 (24, 48 & 72 h~~rs~~)	Minimally irritating	1745273, 1745254
Eye Irritation	Rabbit	MAS[1] = 4.7/110 (24, 48 & 72 h~~rs~~)	Minimally irritating	1745271, 1745254
Skin Sensitization[2]	Guinea Pig	Negative results	Negative skin sensitizer	1745274, 1745254

[1] Maximum average score according to the method of Draize
[2] Buehler method

Table 2 Alternative active ingredients registered for control/suppression of claimed disease on the Heads Up Plant Protectant accepted label

Active ingredient	End-Use Product	Fungicide Classification	
		Group	Mode of Action
Azoxystrobin	Quadris Flowable Fungicide	11	Respiration
Captan	Co-op Potato Seed-piece Treatment	M	Multisite
Metiram	Polyram 16 Dust Fungicide	M	Multisite
Mancozeb	Penncozeb 80WP Fungicide	M	Multisite
Fludioxonil	Maxim PSP Fungicide	12	Signal transduction
Formaldehyde	Formalin Fungicide	U	Unknown
Mancozeb & fludioxonil	Maxim MZ PSP Fungicide	M, 12	Multisite, signal transduction
Thiophanate-methyl	Senator PSPT1 Potato Seed Piece Treatment	1	Mitosis and cell division
Thiophanate-methyl & mancozeb	Genesis XT Potato Seed Piece Treatment	1, M	Mitosis and cell division, multisite

Table 3 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Proposed label claim	Supported use claim
Suppression of *Rhizoctonia solani* on potato: **Application Rate:** 1 gram of Heads Up Plant Protectant per 1 litre of water. **Use Directions:** Mix Heads Up Plant Protectant with water. Apply 1 L of solution for every 100-264 kg of potato seed.	Accepted as proposed.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number: 1745256
Reference: 2009, DACO 2.1, 2.2, 2.12.1 and 2.14.14 for Saponins Of *Chenopodium quinoa* Technical (the active ingredient of Heads Up Plant Protectant), Data Numbering Code: 2.1, 2.2, 2.12.1, 2.14.14 Confidential Business Information

PMRA Document Number: 1745257
Reference: 2003, Product chemistry, product identity and composition, production process, and impurities, Data Numbering Code: 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, 2.11.1, 2.11.2, 2.11.3, 2.11.4, 2.12.1 ,2.13.2, 2.13.4, 2.14.1 Confidential Business Information

PMRA Document Number: 1745260
Reference: 2003, Preliminary analysis, certified limits and enforcement method, Data Numbering Code: 2.12.1, 2.13, 2.13.1, 2.13.3 Confidential Business Information

PMRA Document Number: 1745262
Reference: 2003, Physical and chemical characteristics, Data Numbering Code: 2.14.1, 2.14.10, 2.14.11, 2.14.12, 2.14.13, 2.14.14, 2.14.2, 2.14.3, 2.14.4, 2.14.6, 2.14.7, 2.14.9, 2.16

PMRA Document Number: 1747683
Reference: 2009, DACO 3.1.1, 3.1.2, 3.3.1 and 3.5.10 for Heads Up Plant Protectant, Data Numbering Code: 3.1.1, 3.1.2, 3.3.1, 3.5.10 Confidential Business Information

2.0 Human and Animal Health

PMRA Document Number: 1745238
Reference: Oakenfull D, 1981, Saponins in food – a review, Food Chemistry 6: 19-40, Data Numbering Code: 4.8, 5.14, 6.4

PMRA Document Number: 1745239
Reference: United States Environmental Protection Agency, 2007, Biopesticides registration action document: Saponins of *Chenopodium quinoa* (PC Code 097094), Data Numbering Code: 12.5.2, 12.5.3, 12.5.4, 12.5.5, 12.5.6, 12.5.7, 12.5.8, 12.5.9

PMRA Document Number: 1745241
Reference: Francis G, Kerem Z, Makkar HPS, Becker K, 2002, The biological action of saponins in animal systems: a review, British Journal of Nutrition 88: 587-605, Data Numbering Code: 4.8, 5.14, 6.4

PMRA Document Number: 1745259
Reference: 2002, Quinoa saponins research: Results of a literature search on the structure, biological activity, toxicity and biodegradation of saponins, with particular reference to quinoa saponins, Data Numbering Code: 2.11.1, 2.16, 2.7, 3.7, 4.2.9, 4.4.1, 4.5.4, 8.2

PMRA Document Number: 1745267
Reference: 2001, Quinoa saponin toxicology report, Data Numbering Code: 4.1, 4.3.1, 4.7.1, 9.1, 9.4, 9.5.1

PMRA Document Number: 1745268
Reference: 2003, Acute oral toxicity study in rats - limit test, Data Numbering Code: 4.2.1

PMRA Document Number: 1745269
Reference: 2003, Acute dermal toxicity study in rats - limit test, Data Numbering Code: 4.2.2

PMRA Document Number: 1745270
Reference: 2003, Acute inhalation toxicity study in rats - defined LC_{50}, Data Numbering Code: 4.2.3

PMRA Document Number: 1745271
Reference: 2003, Primary eye irritation study in rabbits, Data Numbering Code: 4.2.4

PMRA Document Number: 1745273
Reference: 2003, Primary skin irritation study in rabbits, Data Numbering Code: 4.2.5

PMRA Document Number: 1745274
Reference: 2003, Dermal sensitization study in guinea pigs (Buehler method), Data Numbering Code: 4.2.6

PMRA Document Number: 1745275
Reference: Agriculture and Agri-Food Canada, 2000, Feeding strategies for minimizing nutrient excretion and odours in swine manure, Data Numbering Code: 4.3.8

PMRA Document Number: 1745277
Reference: 2004, Correspondence Document: Explainations And Waiver Requests, Data Numbering Code: 4.5, 4.5.4, 4.5.8, 9.1, 9.3.1, 9.3.2, 9.4.1, 9.4.2, 9.5.2.3, 9.6.2.3, 9.6.2.6

PMRA Document Number: 1745279
Reference: 2008, Environmental chemistry and fate of Heads Up Plant Protectant and Saponins of *Chenopodium quinoa* Technical fungicide, Data Numbering Code: 8.1

PMRA Document Number: 1745280
Reference: 2008, Metabolism and bioaccumulation of Heads Up Plant Protectant and Saponins of *Chenopodium quinoa* Technical fungicide, Data Numbering Code: 6.1, 9.5.6

PMRA Document Number: 1747708
Reference: 2009, Occupational exposure for Heads Up Plant Protection, Data Numbering Code: 5.2

PMRA Document Number: 1747709
Reference: Agriculture and Agri-Food Canada, 2005, Crop profile for potato in Canada, Data Numbering Code: 5.2, 10.2.2

3.0 Environment

PMRA Document Number: 1745239
Reference: United States Environmental Protection Agency, 2007, Biopesticides registration action document: Saponins of *Chenopodium quinoa* (PC Code 097094), Data Numbering Code: 12.5.2, 12.5.3, 12.5.4, 12.5.5, 12.5.6, 12.5.7, 12.5.8, 12.5.9

PMRA Document Number: 1745242
Reference: 2004, The use of winter bird crops by farmland birds in lowland England. Biological Conservation 118: 21-32, Data Numbering Code: 9.6.1

PMRA Document Number: 1745244
Reference: 2008, Winter bird use of seed-rich habitats in agri-environment schemes. Agriculture, Ecosystems and Environment 126: 189–194, Data Numbering Code: 9.6.1

PMRA Document Number: 1745259
Reference: 2002, Quinoa saponins research: Results of a literature search on the structure, biological activity, toxicity and biodegradation of saponins, with particular reference to quinoa saponins, Data Numbering Code: 2.11.1, 2.16, 2.7, 3.7, 4.2.9, 4.4.1, 4.5.4, 8.2

PMRA Document Number: 1745267
Reference: 2001, Quinoa saponin toxicology report, Data Numbering Code: 4.1, 4.3.1, 4.7.1, 9.1, 9.4, 9.5.1

PMRA Document Number: 1745278
Reference: 2008, Environmental toxicology of Heads Up Plant Protectant and Saponins of *Chenopodium quinoa* Technical fungicide, Data Numbering Code: 9.1, 9.2, 9.3.2, 9.5.2.1, 9.5.2.2, 9.5.2.3, 9.6.2.1, 9.6.2.2, 9.6.2.3, 9.6.2.4, 9.6.2.5, 9.6.2.6, 9.8

PMRA Document Number: 1745279
Reference: 2008, Environmental chemistry and fate of Heads Up Plant Protectant and Saponins of *Chenopodium quinoa* Technical fungicide, Data Numbering Code: 8.1

4.0 Value

PMRA Document Number: 1747677
Reference: 2009, Efficacy and crop tolerance of Heads Up Plant Protectant used as a potato seed piece treatment, Data Numbering Code: 10.1, 10.2.1, 10.2.2, 10.2.3, 10.3

PMRA Document Number: 1747679
Reference: 2008, Systemic acquired resistance and induced systemic resistance in plants: Literature review, Data Numbering Code: 10.2.1

PMRA Document Number: 1747709
Reference: Agriculture and Agri-Food Canada, 2005, Crop profile for potato in Canada, Data Numbering Code: 5.2, 10.2.2

PMRA Document Number: 1747710
Reference: Ducheshen JM, 2005, Method for protecting plants from fungal and bacterial diseases, United States Patent Application Publication 2005/0261129 A1, Data Numbering Code: 10.2.1, 10.2.2, 10.2.3

PMRA Document Number: 1747712
Reference: 2006, Efficacy of Heads Up for managing soil-borne potato diseases, Data Numbering Code: 10.2.3

PMRA Document Number: 1747713
Reference: 2003, Potato late blight control trials, Data Numbering Code: 10.2.3

PMRA Document Number: 1747714
Reference: 2005, Rhizoctonia control with in-furrow and seed treatments with low disease pressure, Data Numbering Code: 10.2.3

PMRA Document Number: 1747715
Reference: 2005, Control of early blight, Rhizoctonia, white mold and pink rot in Russet Burbank potatoes, Data Numbering Code: 10.2.3

PMRA Document Number: 1747716
Reference: 2006, Seed treatments and seed plus foliar treatments for control of seed- and soil-borne Rhizoctonia, Data Numbering Code: 10.2.3

PMRA Document Number: 1747717
Reference: 2004, Seed treatments, in-furrow and seed plus foliar treatments for control of potato stem canker and black scurf, Data Numbering Code: 10.2.3

PMRA Document Number: 1769620
Reference: 2009, Effect of saponins of *Chenopodium quinoa* applied as seed treatment and foliarly on dry rot, common scab and black scurf diseases of potato, Data Numbering Code: M10.2.2

B. Additional Information Considered

1.0 Environment

PMRA Document Number: 1903561
Reference: Kuljanabhagavad T, Wink M, 2009, Biological activities and chemistry of saponins from *Chenopodium quinoa* Willd., Phytochem Rev 8: 473-490, Data Numbering Code: 8.1