Proposed Registration Decision PRD2017-08

Aureobasidium pullulans strain DSM 14940 and Aureobasidium pullulans strain DSM 14941

(publié aussi en français)

5 May 2017

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

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Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2017-8E (print version)
H113-9/2017-8E-PDF (PDF version)

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Overview

Proposed Registration Decision for *Aureobasidium pullulans* strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941

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 *Aureobasidium pullulans* DSM 14940, *Aureobasidium pullulans* DSM 14941 and Botector, containing the technical grade active ingredients *Aureobasidium pullulans* strain DSM 14940 and strain DSM 14941, to suppress anthracnose fruit rot and phomopsis leaf blight on certain berries as well as botrytis grey mould on some berries, fruiting vegetables, leafy vegetables and ornamentals grown in field and in greenhouses or protected environments.

Aureobasidium pullulans DSM 14940 (Registration Number 30554) and *Aureobasidium pullulans* DSM 14941 (Registration Number 30553) are fully registered in Canada for use on terrestrial food crops and outdoor ornamentals. For the detailed review see the Proposed Registration Decision PRD2012-17, *Aureobasidium pullulans* strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941and Registration Decision RD2012-32, *Aureobasidium pullulans* strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941. Botector (Registration Number 31248) is fully registered for use in Canada to suppress botrytis grey mould in grapes.

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 *Aureobasidium pullulans* DSM 14940, *Aureobasidium pullulans* DSM 14941 and Botector.

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.

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

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 (for example, children) as well as organisms in the environment. 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.

Before making a final registration decision on *Aureobasidium pullulans* strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on *Aureobasidium pullulans* strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941, 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 Are *Aureobasidium pullulans* strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941?

Aureobasidium pullulans strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941 are the active ingredients in the end-use product, Botector. These strains of fungi are used as microbial pest control agents (MPCA) against disease pathogens on certain food and non-food crops grown in field and in greenhouses or protected environments. The two *A. pullulans* strains are living yeasts that compete against pathogens for space and nutrients.

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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."

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*.

Health Considerations

Can Approved Uses of *Aureobasidium pullulans* strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941 Affect Human Health?

Aureobasidium pullulans strain DSM 14940 and _Aureobasidium pullulans_ strain DSM 14941 are unlikely to affect your health when Botector is used according to the label directions.

People could be exposed to *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 when handling and applying Botector, and when ingesting treated produce. When assessing health risks, several key factors are considered:

- the microorganism's biological properties (for example, production of toxic byproducts);
- reports of any adverse incidents;
- its potential to cause disease or toxicity as determined in toxicological studies; and
- the level to which people may be exposed relative to exposures already encountered in nature to other isolates of this microorganism.

Toxicological studies in laboratory animals describe potential health effects from large doses in order to identify any potential pathogenicity, infectivity and toxicity concerns. When spores of *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 were tested on laboratory animals, there were no signs that it caused any significant toxicity or disease.

Residues in Water and Food

Dietary risks from food and water are not of concern

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally specified as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada specifies science-based MRLs to ensure that the food Canadians eat is safe.

Residues of *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 on the treated crops, at the time of harvest, are anticipated following foliar applications to agricultural crops. *A. pullulans* is a yeast-like fungus that is commonly found on plants. *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 produced no adverse effects (disease or toxicity) when administered orally to rats and no metabolites of toxicological significance have been shown to be produced by these or other strains of *A. pullulans*. No adverse effects from dietary exposure have been attributed to natural populations of *A. pullulans*. As well, the likelihood of residues of *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 contaminating drinking water supplies resulting from operational applications as a pesticide is considered to be low.

Consequently, dietary risks are considered to be low and not of concern. Therefore, the PMRA has determined that the specification of an MRL under the *Pest Control Products Act* is not required for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941.

Risks in Residential and Other Non-Occupational Environments

Estimated risk for residential and other non-occupational exposure is not of concern.

When Botector is used in commercial greenhouses, it is unlikely that adults, youths and toddlers will be exposed to *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941. Even in the event of exposure, risk to the general population is not a concern since there were no signs of disease or toxicity noted in toxicological studies with these microorganisms.

Occupational Risks from Handling Botector

Occupational risks are not of concern when Botector is used according to label directions, which include protective measures.

Workers handling Botector can come into direct contact with *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 on the skin, in the eyes, or by inhalation. For this reason, the product label will specify that workers exposed to the end-use product must wear waterproof gloves, long-sleeved shirts, long pants, a NIOSH approved respirator for biological products, and shoes plus socks. Eye goggles are not required as the eye irritation studies submitted indicated minimal eye irritation potential.

For the bystander, exposure is expected to be much less than that of workers. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When *Aureobasidium pullulans* strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941 Is Introduced Into the Environment?

Products containing *Aureobasidium pullulans* strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941 are not expected to pose risks of concern to the environment when used according to label directions.

The active ingredients in Botector are individual isolates of the species *A. pullulans*, which is a yeast-like fungus that naturally occurs globally on plants, as well as in soil and water, at varying levels. Although levels may temporarily increase after application to crop plants, the populations of *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 are expected to return to the naturally occurring background levels over the course of the growing season.

No information was submitted on the fate of *A. pullulans* in aquatic environments. As there are no direct aquatic uses, exposure to aquatic environments will be low. Since *A. pullulans* naturally occurs in aquatic environments, it is expected that introduced *A. pullulans* will survive in water. Any *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 that reach aquatic environments from the use of Botector through run-off and/or leaching are expected to return to the naturally occurring background levels over time.

Based on results of laboratory studies with *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 and a critical review of information in the published scientific literature, no significant effects to birds, wild mammals, terrestrial and aquatic arthropods, non-arthropod invertebrates, fish and plants are expected when Botector is applied according to directions on the product label.

Value Considerations

What Is the Value of Botector?

Botector suppresses anthracnose fruit rot and phomopsis leaf blight on certain berries as well as botrytis grey mould on some berries, fruiting vegetables, leafy vegetables and ornamentals grown in the field and in greenhouses or protected environments.

Botector can be used in a conventional spray program to reduce disease pressure. *A. pullulans* offers a new mode of action to the growers to manage *Botrytis cinerea* which is susceptible to resistance development. Because of its mode of action, Botector is not prone to resistance development.

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 Botector to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

All microorganisms, including *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941, contain substances that are potential sensitizers and thus, respiratory and dermal sensitivity may possibly develop in individuals exposed to potentially large quantities of *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941. In turn, anyone handling or applying Botector must wear appropriate waterproof gloves, a long-sleeved shirt, long pants, a NIOSH approved mist filtering mask or respirator, and shoes plus socks. Eye goggles are not required as the eye irritation studies submitted indicated minimal eye irritation.

Environment

The end-use product includes environmental precautionary statements that prevent the contamination of aquatic systems from the use of Botector, as well as standard greenhouse statements to properly manage greenhouse effluent.

Next Steps

Before making a final registration decision on *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941, the PMRA will consider any 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 *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 (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

Aureobasidium pullulans strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active microorganism	*Aureobasidium pullulans* strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941
Function	For management of anthracnose (*Colletotrichum acutatum*) and phomopsis (*Phomopsis obscurans*) on certain berries, management of botrytis grey mould (*Botrytis cinerea*) on some berries, fruiting vegetables, leafy vegetables and ornamentals grown in the field and in greenhouses and/or protected environments.
Binomial name	*Aureobasidium pullulans* strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941
Taxonomic designation[1]	
Kingdom	Fungi
Phylum	Ascomycota
Class	Dothideomycetes
Order	Dothideales
Genus	*Aureobasidium*
Species	*pullulans*
Strains	DSM 14940 and DSM 14941
Patent Status information	No patents are held by the applicant in Canada.
Minimum purity of active	Technical grade active ingredients: 5.0×10^9 colony forming units (CFU)/g End-use product: 5.0×10^9 CFU/g (total of both strains DSM 14940 and DSM 14941)
Identity of relevant impurities of toxicological, environmental and/or significance.	The technical grade active ingredient does not contain any components, impurities or micro contaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances. The product must meet microbiological contaminants release standards. *Aureobasidium pullulans* strain DSM 14940 and *Aureobasidium pullulans* strain DSM 14941 are not known to produce any potentially toxic secondary metabolites (see Section 3.0).

[1] Taxonomy browser at: http://www.ncbi.nlm.nih.gov/pubmed/

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

Technical Grade Active Ingredients–*Aureobasidium pullulans* DSM 14940 and *Aureobasidium pullulans* DSM 14941

Properties	*Aureobasidium pullulans* DSM 14940	*Aureobasidium pullulans* DSM 14941
Physical state	Granule	Granule
Colour	Light brown to pink	Light brown to pink
Odour	Slightly sweet, bread-like	Slightly sweet, bread-like
pH	n/a	n/a
Guarantee	5×10^9 CFU/g	5×10^9 CFU/g
Corrosion Character	None	None
Suspendibility	Suspendible	Suspendible
Viscosity	Not applicable	Not applicable

End-Use Product–Botector

Property	Result
Colour	Off-white to light pink
Physical State	Granular
Odour	similar to bread
Miscibility in water	Dispersible
pH	6.6 at 20°C

1.3 Directions for Use

Botector is applied as a foliar treatment at a rate of 1 kg/ha in 500 to 2000 L of water/ha with a reapplication interval of 7 to 10 days.

1.4 Mode of Action

A. pullulans is a saprophyte, an epiphyte and is an antagonistic micro-organism to several plant pathogens. The mode of action of *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 is one of competitive exclusion as well as a structural effect on the plant through the production of cutinase which stimulates cell division in the plant's epidermis.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

Refer to the Proposed Registration Decision for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 (PRD2012-17).

2.2 Method for Formulation Analysis

Refer to the Proposed Registration Decision for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 (PRD2012-17).

2.3 Methods for Residue Analysis

Refer to the Proposed Registration Decision for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 (PRD2012-17).

2.4 Methods to Determine and Quantify Residues (Viable or Non-viable) of the Active Microorganism and Relevant Metabolites

Refer to the Proposed Registration Decision for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 (PRD2012-17).

2.5 Methods for Determination of Relevant Impurities in the Manufactured Material

Refer to the Proposed Registration Decision for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 (PRD2012-17).

2.6 Methods to Determine Storage Stability, Shelf-life of the Microorganism

Refer to the Proposed Registration Decision for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 (PRD2012-17).

3.0 Impact on Human and Animal Health

3.1 Toxicity and Infectivity Summary

3.1.1 Test Studies

Botector is a wettable granular formulation that is currently registered as a commercial product only for use outdoors on grapes. The use expansion will broaden the use of Botector to various new crops (berries, fruiting vegetables, leafy vegetables) and ornamentals grown both in greenhouses or protected environments and in the field. The use expansion of Botector does not involve a change in the product chemistry of the technical grade active ingredients.

The PMRA conducted a detailed review of the existing toxicological database for the technical grade active ingredients, *A. pullulans* DSM 14940 and *A. pullulans* DSM 14941, under the review of Blossom Protect (Registration Number 31248), a registered end-use product formulation containing both technical grade active ingredients. The database is complete, consisting of laboratory animal (in vivo) toxicity studies (acute oral toxicity, acute pulmonary toxicity/pathogenicity, acute inhalation toxicity, acute intravenous/subcutaneous infectivity, acute dermal toxicity/irritation, dermal sensitization, and eye irritation) that were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. Additional genotoxicity testing was performed on mice. Certain toxicity studies were conducted with an end-use product formulation similar to Botector, BP2042. Testing on BP2042

is adequate to support the toxicological data requirements for Botector. The scientific quality of the data is high and the database is considered sufficient to characterize the toxicity and infectivity of these pest control agents and associated products.

Refer to the Proposed Registration Decision for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 (PRD2012-17) for details.

3.1.2 Additional Information

During the original review of the technical grade active ingredients, a search of the National Center for Biotechnology Information (NCBI) PubMed database was made using the key words "*Aureobasidium pullulans*" with "pathogen", "infection", "toxic" or "human". The search found that, in immunosuppressed individuals, strains of *A. pullulans* can cause various opportunistic infections (for example, subcutaneous mycosis in a renal transplant patient, keratitis following eye operations, infection of lymphatic system in erythema nodosum leprosum patients). In one immunocompetent individual, an unusual skin infection caused by *A. pullulans* arose from a cat scratch. Infections were treatable in all cases with amphotericin B. Sensitization symptoms (such as hypersensitivity pneumonitis) from contaminated ventilation systems and humidifiers have also been reported.

The search also did not find any reports of toxic metabolites produced by *A. pullulans*.

Refer to the Proposed Registration Decision for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 (PRD2012-17) for details.

A new search of the NCBI PubMed database for reports between 2011–2016 uncovered three new cases of *A. pullulans* infections. Two of the cases were similar to those previously reported in that they were subcutaneous mycosis in immunocompromised individuals.

The third case was of secondary subgungual colonization by *A. pullulans* following onycholysis, a painless separation of the nail from the nail bed. The patient had hypothyroidism caused by Hashimoto thyroiditis. Nail symptoms are often related to thyroid disease, and secondary infections are common. Onycholysis resolved with antifungal therapy (oral itraconzaole and local bifonazole).

The recent published literature also uncovered reports discussing the increased pathological significance of *A. pullulans* as a dermatiaceous fungus that can cause opportunistic infections in humans. Other reports state that despite the emergence of *A. pullulans* as an opportunistic human pathogen the fungus is generally regarded as safe for biotechnological and environmental applications, including pesticidal uses. Nevertheless, a molecular assay for early detection of infection caused by *A. pullulans* was recently published. Given the rise in clinical relevance of *A. pullulans* the method has the potential to be a useful diagnostic tool for clinical cases.

A recent published report has also suggested that genomic sequencing data from the four recognized *A. pullulans* varieties may warrant re-assignment into separate species. Based on classification using the novel genome sequences generated in the study, *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 remained in the species *A. pullulans*. This is of particular significance since the species *A. pullulans* does not contain any potentially opportunistic pathogens, which are placed within *A. melanogenum*.

3.1.3 Incident Reports Related to Human and Animal Health

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Health Canada website.

As of 29 September 2016, no human or domestic incident reports involving the actives *A. pullulans* strain DSM 14940 or *A. pullulans* strain DSM 14941 had been submitted to the PMRA.

3.1.4 Hazard Analysis

The database submitted in support of registering *A. pullulans* strain DSM 14940, *A. pullulans* DSM strain 14941 and Botector was reviewed from the viewpoint of human health and safety and was determined to be sufficiently complete.

A. pullulans strain DSM 14940 and *A. pullulans* strain DSM 14941 were of low toxicity and not infective or pathogenic to rats via the oral, pulmonary and intravenous/subcutaneous routes.

BP2042, a similar end-use product formulation containing *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941, was of low toxicity via the oral, inhalation and dermal exposure routes and was not irritating to skin and eyes of rabbits. These studies were acceptable as surrogate data for Botector. *A. pullulans* strain DSM 14941 was also found not to be genotoxic in a mouse erythrocyte micronucleus test.

Since *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 were identified as sensitizing agents, the signal words “POTENTIAL SENSITIZER” will appear on the labels for the technical grade active ingredients and the end-use product.

Higher tier subchronic and chronic toxicity studies were not required because of the low acute oral and dermal toxicity of the end-use product, and no indications of infectivity, toxicity or pathogenicity in the test animals treated in the Tier I acute oral, pulmonary and intravenous toxicity/infectivity tests.

Within the available scientific literature, there are no reports that suggest *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 have the potential to cause adverse effects on the endocrine system of animals. Based on the weight of evidence of available data, no adverse effects to the endocrine or immune systems are anticipated for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941.

3.2 Occupational, Residential and Bystander Risk Assessment

3.2.1 Occupational Exposure and Risk

When handled according to the label instructions, the potential for dermal, inhalation, and ocular exposure for workers (applicators, mixer/loaders, and handlers) exists, with primary exposure routes being dermal and/or inhalation. Since unbroken skin is a natural barrier to microbial invasion of the human body, dermal absorption could occur only if the skin were cut, if the microbe were a pathogen equipped with mechanisms for entry through or infection of the skin, or if metabolites were produced that could be dermally absorbed. Other strains of *A. pullulans* have been identified as causing localized host immune responses when exposed to broken skin and there has been one report of a skin infection in an immunocompetent individual following a cat scratch and a case of a secondary infection in the nail bed of an individual with onycholysis arising from a thyroid condition. However, there is no indication that the MPCAs could penetrate intact skin of healthy individuals.

Although the risk of toxicity is low from the end-use product use pattern, the PMRA assumes that all microorganisms contain substances that can elicit positive hypersensitivity reactions, regardless of the outcome of sensitization testing. Therefore, anyone handling or applying Botector must wear a long-sleeved shirt, long pants, shoes plus socks, waterproof gloves, as well as a NIOSH approved respirator for biological products. Eye goggles will not be required for workers based on the result of the primary eye irritation study. In addition, all unprotected workers are restricted from entering enclosed areas (including greenhouses) where Botector has been handled or applied for 4 hours.

Label warnings, restrictions and risk mitigation measures are adequate to protect users of Botector, and anticipated occupational risk from the use of this product is low.

3.2.2 Residential and Bystander Exposure and Risk

Overall, the PMRA does not expect that residential and bystander exposures will pose an undue risk on the basis of the low toxicity/pathogenicity profile for *A. pullulans* DSM 14940, *A. pullulans* DSM 14941, and Botector, and the assumption that precautionary label statements will be followed by commercial applicators in the use of Botector.

As well, *A. pullulans* is a species that is ubiquitous in the environment and the use of Botector is not expected to cause sustained increases in exposure to bystanders beyond natural levels. Consequently, the health risk to infants and children is expected to be low.

3.3 Dietary Exposure and Risk Assessment

3.3.1 Food

Although the use pattern may result in dietary exposure with residues possible in or on agricultural commodities, dietary risk is expected to be low and not of concern for the general population, including infants and children, or animals because *A. pullulans* is commonly found on plants, and since *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 produced no adverse effects (disease or toxicity) when administered orally to rats. No metabolites of

toxicological significance have been shown to be produced by these or other strains of *A. pullulans* and no adverse effects from dietary exposure have been attributed to natural populations of *A. pullulans.* Furthermore, higher tier subchronic and chronic dietary exposure studies were not required because of the low toxicity of the MPCAs and no indications of infectivity, toxicity or pathogenicity in the test animals treated in the Tier I acute oral, pulmonary and intravenous toxicity/infectivity studies. Therefore, there are no concerns for chronic risks posed by dietary exposure of the general population and sensitive subpopulations, such as infants and children.

3.3.2 Drinking Water

Health risks are not expected from exposure to *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 via drinking water because exposure will be low from operational applications and because there were no harmful effects observed in Tier I acute oral toxicity testing and infectivity testing. The end-use product label instructs users not to contaminate irrigation or drinking water supplies or aquatic habitats through equipment cleaning or waste disposal. Users are also to prevent effluent or runoff from greenhouses containing this product to enter lakes, streams, ponds or other waters. Furthermore, municipal treatment of drinking water is expected to reduce the transfer of residues to drinking water.

3.3.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

Calculations of acute reference doses (ARfDs) and acceptable daily intakes (ADIs) are not usually possible for predicting acute and long term effects of microbial agents in the general population or to potentially sensitive subpopulations, particularly infants and children. The single (maximum hazard) dose approach to testing MPCAs is sufficient for conducting a reasonable general assessment of risk if no significant adverse effects (in other words, no acute toxicity, infectivity or pathogenicity endpoints of concern) are noted in acute toxicity and infectivity tests. Based on all the available information and hazard data, the PMRA concludes that *A. pullulans* strains DSM 14940 and DSM 14941 are of low toxicity, are not pathogenic or infective to mammals, and that infants and children are likely to be no more sensitive to the MPCAs than the general population. Thus there are no threshold effects of concern and, as a result, no need to require definitive (multiple dose) testing or apply uncertainty factors to account for intra- and interspecies variability, safety factors or margins of exposure. Further factoring of consumption patterns among infants and children, special susceptibility in these subpopulations to the effects of the MPCAs, including neurological effects from pre- or post-natal exposures, and cumulative effects on infants and children of the MPCAs and other registered micro-organisms that have a common mechanism of toxicity, does not apply to these MPCAs. As a result, the PMRA has not used a margin of exposure (safety) approach to assess the risks of *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 to human health.

3.3.4 Aggregate Exposure and Risk

Based on the toxicity and infectivity test data submitted and other relevant information in the PMRA's files, no harm will result from aggregate exposure of residues of *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 to the general Canadian population, including infants and children, when the end-use product is used as labelled. This includes all anticipated dietary (food and drinking water) exposures and all other non-occupational exposures (dermal

and inhalation) for which there is reliable information. Furthermore, few adverse effects from exposure to other isolates of *A. pullulans* encountered in the environment have been reported. Even if there is an increase in exposure to this active ingredient from the use of Botector, there should not be any increase in potential human health risk.

3.3.5 Maximum Residue Limits

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally specified as an MRL under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada specifies science-based MRLs to ensure the food Canadians eat is safe.

Although *A. pullulans* is ubiquitous in the phyllosphere and that the application of Botector is not expected to significantly increase levels of *A. pullulans* beyond levels that have been observed in nature, residues of *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 on treated crops, at the time of harvest, are anticipated following foliar applications. Consequently, the PMRA has applied a hazard-based approach for determining whether an MRL is required for these microorganisms. There were no signs of toxicity and no signs of pathogenicity observed after the MPCAs were administered orally to rats and no known metabolic by-product of toxicological concern are produced by these microorganisms. In addition, the likelihood of residues contaminating drinking water supplies is low and not of concern. Therefore, the PMRA has determined that the specification of an MRL under the *Pest Control Products Act* is not required for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941.

3.4 Cumulative Effects

The PMRA has considered all the available information on the cumulative effects of residues and other substances that have a common mechanism of toxicity. These considerations included the cumulative effects on infants and children of such residues and other substances with a common mechanism of toxicity.

Besides naturally occurring strains of *A. pullulans* in the environment, the PMRA is not aware of any other microorganisms, or other substances that share a common mechanism of toxicity with this active ingredient. No cumulative effects are anticipated if the residues of *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 interact with related strains of these microbial species.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

A. pullulans is a yeast-like saprophytic fungal organism that is ubiquitously found in terrestrial ecosystems and has also been isolated from aquatic ecosystems. Levels of *A. pullulans* isolated from apples leaves have been observed at levels up to 2.0×10^5 CFU/g.

As *A. pullulans* is ubiquitous in the environment, the level of *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 remaining on treated crop following applications of Botector will be comparable to observed natural background levels of *A. pullulans*. While an increase in overall population density of *A. pullulans* is not expected from the use expansion, an increase in the site-specific distribution of *A. pullulans* is possible. Since the growth of the MPCAs are dependent upon nutrient availability and environmental conditions, the background level of the MPCAs are expected to return to site specific background levels of *A. pullulans* over the growing season.

4.2 Effects on Non-Target Species

The PMRA has a four-level tiered approach to environmental testing of microbial pesticides. Tier I studies consist of acute studies on up to seven broad taxonomic groups of non-target organisms exposed to a maximum hazard or Maximum Challenge Concentration (MCC) of the MPCA. The MCC is generally derived from the amount of the MPCA or its toxin expected to be available following application at the maximum recommended label rate multiplied by a safety factor. Tier II studies consist of environmental fate (persistence and dispersal) studies as well as additional acute toxicity testing of MPCAs. Tier III studies consist of chronic toxicity studies, (that is, life cycle studies) as well as definitive toxicity testing (for exmaple, LC_{50}, LD_{50}). Tier IV studies consist of experimental field studies on toxicity and fate, and are required to determine whether adverse effects are realized under actual use conditions.

The type of environmental risk assessment conducted on MPCAs varies depending on the tier level that was triggered during testing. For many MPCAs, Tier I studies are sufficient to conduct environmental risk assessments. Tier I studies are designed to represent “worst-case” scenarios where the exposure conditions greatly exceed the expected environmental concentrations. The absence of adverse effects in Tier I studies are interpreted as minimal risk to the group of non-target organisms. However, higher tiered studies will be triggered if significant adverse effects on non-target organisms are identified in Tier I studies. These studies provide additional information that allows PMRA to refine the environmental risk assessments. In the absence of adequate environmental fate and/or field studies, a screening level risk assessment can be performed to determine if the MPCA is likely to pose a risk to a group of non-target organisms. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC).

If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (environmental fate and/or field testing results). Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Effects on Terrestrial and Aquatic Non-Target Species

The studies submitted to address the hazards of the MPCAs to terrestrial and aquatic non-target organisms were originally submitted for the review of Blossom Protect, a registered end-use product formulation containing *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 at the same levels as in Botector. These studies were acceptable as surrogate data for Botector.

For terrestrial non-target organisms, the studies included an acute oral pathogenicity and toxicity study of *A. pullulans* strain DSM 14941 to Japanese quail (*Coturnix japonica*), a dietary toxicity/pathogenicity study and a contact toxicity/pathogenicity study in honeybees (*Apis mellifera*), a contact toxicity/pathogenicity study in predatory mites (*Typhlodromus pyri*), as well as a summary paper of a study on bees. There were no signs toxicity or infectivity in any of these studies.

For aquatic non-target organisms, these studies included an acute toxicity study in rainbow trout (*Oncorhyncus mykiss*), a 21-day toxicity and pathogenicity study in aquatic arthropods (*Daphnia magna*) and a 7-day toxicity study in freshwater aquatic vascular plants (*Lemna gibba*). There were no signs toxicity or pathogenicity in any of these studies.

For details on the studies submitted to address the hazards of the MPCAs to terrestrial and aquatic non-target organisms, refer to the Proposed Registration Decision for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 (PRD2012-17).

Based on all the available data and information in the existing environmental toxicology database for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941, there is reasonable certainty that no harm will be caused to non-target terrestrial organisms (including birds, wild mammals, terrestrial arthropods, terrestrial non-arthropod invertebrates, terrestrial plants, and microorganisms) or aquatic organisms (including fish, aquatic arthropods, aquatic non-arthropod invertebrates or aquatic plants) from the use expansion of Botector.

4.3 Incident Reports related to the Environment

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Health Canada website.

As of 29 September 2016, no environment incident reports involving the actives *A. pullulans* strain DSM 14940 or *A. pullulans* strain DSM 14941 had been submitted to the PMRA. The United States Environmental Protection Agency's Ecological Incident Information System (EIIS) was also queried for environment incidents. None were available in the EIIS database

5.0 Value

5.1 Consideration of Benefits

The addition of these new crops to the Botector label will provide growers with a new mode of action to manage botrytis grey mould which is considered a high risk pathogen for resistance development. Because of its mode of action, Botector has little to no risk of resistance development due to frequent applications. When applied under low disease pressure or in a conventional spray program, Botector may reduce the number of conventional fungicide applications required. Currently, there are several products registered in Canada including conventional and biological fungicides to manage botrytis grey mould on the labelled crops. Botector will offer another microbiological active ingredient option to growers.

5.2 Effectiveness Against Pests

Value information was submitted primarily in the form of efficacy trials and extrapolation rationales. It was demonstrated that Botector provided suppression of anthracnose fruit rot on strawberry (field and greenhouse) and blueberry; partial suppression of phomopsis leaf blight on strawberry (field and greenhouse); suppression of botrytis grey mould on certain berries (greenhouse strawberry), fruiting vegetables (field and greenhouse), leafy vegetables (field and greenhouse), and ornamentals (field, greenhouse and protected environments). The efficacy data indicated that Botector suppressed the above listed diseases under low to moderate disease pressure; however, the level of control decreased to partial suppression when disease pressure increased. As a biological product, Botector will most likely be used under low to moderate disease pressure.

5.3 Non-Safety Adverse Effects

Botector only contains *A. pullulans* which occurs naturally and is widespread in plants. Botector is not expected to have an adverse effect on crop plants due to the nature of the product and its mode of action.

5.4 Supported Uses

The reviewed value information was sufficient to support the claims on the Botector label. Details of the supported uses are provided in Appendix I, Table 1.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substance 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: 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*].

A. pullulans DSM 14940, *A. pullulans* DSM 14941 and Botector were assessed in accordance with the PMRA Regulatory Directive DIR99-03.[5]

- The technical grade active ingredients, *A. pullulans* DSM 14940 and *A. pullulans* DSM 14941, do not meet the Track 1 criteria because the active ingredients are biological organisms and hence are not subject to the criteria used to define persistence, bioaccumulation and toxicity properties of chemical control products.
- There are also no formulants, contaminants or impurities present in the end-use product that would meet the TSMP Track 1 criteria.

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:

- The technical grade active ingredients, *A. pullulans* DSM 14940 and *A. pullulans* DSM 14941 do not contain formulants of health or environmental concern as identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.
- The end-use product, Botector, does not contain formulants of health or environmental concern as identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641-2643: *List of Pest Control Product Formulants of Health or Environmental Concern*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and DIR2006–02.

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5 Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy.*

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/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 I 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 Notice of Intent NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

8 Regulatory Directive DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

7.0 Summary

7.1 Methods for Analysis of the Micro-organism as Manufactured

The PMRA previously concluded that the product characterization data for the technical grade active ingredients were adequate. Storage stability data were sufficient to support a shelf life of 2 years when stored at 8°C and 10 months when stored at 25°C. For additional details, refer to the Proposed Registration Decision for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 (PRD2012-17).

7.2 Human Health and Safety

The acute toxicity and infectivity studies and other relevant information previously submitted in support of *A. pullulans* DSM 14940 and *A. pullulans* DSM 14941, and Blossom Protect were determined to be sufficiently complete to permit a decision on the expansion of use of Botector. Spores of *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 were not pathogenic or infective in the rat via subcutaneous injection exposure routes. Spores of *A. pullulans* strain DSM 14941 were not pathogenic or infective in the rat via the pulmonary route. BP2042, a formulation similar to Botector containing the two MPCAs, was of low toxicity to the rat via the oral, inhalation and dermal exposure routes, and was not irritating to the skin and eyes of rabbits. Since the MPCAs are considered dermal sensitizers, the signal words "POTENTIAL SENSITIZER" are required on the principal display panel of the technical grade active ingredients and the end-use product. *A. pullulans* strain DSM 14941 was not found to be genotoxic in a mouse erythrocyte micronucleus test.

When handled according to the label instructions, the potential for dermal, inhalation, and ocular exposure for workers exists, with primary exposure routes being dermal and/or inhalation. In individuals exposed to large quantities of Botector, respiratory and dermal sensitivity could possibly develop upon repeated exposure to the product since the MPCAs have been identified as sensitizers. Therefore, anyone handling or applying Botector must wear long-sleeved shirt, long pants, shoes plus socks, waterproof gloves, as well as a NIOSH approved mist filtering mask or respirator. In addition, all unprotected workers are restricted from entering enclosed areas (including greenhouses) where Botector has been handled or applied for 4 hours.

The health risk to the general population, including infants and children, as a result of bystander exposure and/or chronic dietary exposure is low and not of concern due the low toxicity/pathogenicity profile for *A. pullulans* DSM 14940, *A. pullulans* DSM 14941 and Botector. The specification of an MRL under the *Pest Control Products Act* is not required for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941.

7.3 Environmental Risk

The environmental toxicology studies and scientific rationales for *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 and supporting published scientific literature available on the environmental fate of *A. pullulans* were determined to be sufficiently complete to permit a decision on registration. The use expansion of Botector containing *A. pullulans* strain DSM 14940 and *A. pullulans* strain DSM 14941 is not expected to pose a risk to birds, mammals, arthropods, fish, and plants when the directions for use on the label are followed.

The Botector label currently instructs users to not contaminate aquatic systems, irrigation, or drinking water supplies from the use of Botector. Standard greenhouse label statements will also be added to instruct users on the proper management of greenhouse effluent.

7.4 Value

Botector suppresses anthracnose fruit rot and phomopsis leaf blight on certain berries as well as botrytis grey mould on some berries, fruiting vegetables, leafy vegetables and ornamentals grown in the field and in greenhouses or protected environments.

Botector can be used in a conventional spray program to reduce disease pressure. *A. pullulans* offers a new mode of action to the growers to manage *Botrytis cinerea* which is susceptible to resistance development. Because of its mode of action, Botector is not prone to resistance development.

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 *A. pullulans* DSM 14940, *A. pullulans* DSM 14941 and Botector, containing the technical grade active ingredients *A. pullulans* strain DSM 14940 and strain DSM 14941, to suppress anthracnose fruit rot and phomopsis leaf blight on certain berries as well as botrytis grey mould on some berries, fruiting vegetables, leafy vegetables and ornamentals grown in field and in greenhouses or protected environments.

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

ADI	acceptable daily intake
ARfD	acute reference dose
°C	degree(s) Celsius
CFU	colony forming unit
DACO	data code
DSM	German Collection of Microorganisms and Cell Cultures (aka DSMZ)
EIIS	Ecological Incident Information System
EP	End-use Product
g	gram
ha	hectare(s)
kg	kilogram
L	litre
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOC	level of concern
MCC	Maximum Challenge Concentration
MPCA	microbial pest control agent
MRL	maximum residue limit
n/a	not applicable
NCBI	National Center for Biotechnology Information
NIOSH	National Institute for Occupational Safety and Health
PMRA	Pest Management Regulatory Agency
PRD	Proposed Registration Decision
RQ	risk quotient
TGAI	technical grade of the active ingredient
TSMP	Toxic Substances Management Policy

Appendix I Tables and Figures

Table 1 List of Supported Uses

Supported Use Claims
Suppression of anthracnose fruit rot caused by *Colletotrichum acutatum* on field strawberries and blueberries (highbush and lowbush) as well as greenhouse strawberries at a rate of 1 kg/ha in 500-2000 L of water/ha with a maximum of 6 applications. Repeat as needed on a 7-10 day interval up to harvest.
Partial suppression of phomopsis leaf blight caused by *Phomopsis obscurans* on field and greenhouse strawberries at a rate of 1 kg/ha in 500-2000 L of water/ha with a maximum of 6 applications. Repeat as needed on a 7-10 day interval up to harvest.
Suppression of botrytis grey mould caused by *Botrytis cinerea* on blackberry; blueberry, highbush; blueberry, lowbush; cranberry; currant, black; currant, red; elderberry; gooseberry; huckleberry; jostaberry; raspberry, black; raspberry, red; strawberry; and greenhouse strawberries at a rate of 1 kg/ha in 500-2000 L of water/ha with a maximum of 6 applications. Repeat as needed on a 7-10 day interval up to harvest.
Suppression of botrytis grey mould caused by *Botrytis cinerea* on tomato, eggplant, pepper, bell pepper, nonbell; and greenhouse (same crop list) at a rate of 1 kg/ha in 500-2000 L of water/ha with a maximum of 5 applications. Repeat as needed on a 7 day interval up to harvest.
Suppression of botrytis grey mould caused by *Botrytis cinerea* on lettuce, head and leaf endive; radicchio (red chicory); greenhouse (same crop list) at a rate of 1 kg/ha in 500-2000 L of water/ha. Repeat as needed on a 7-10 day interval up to harvest.
Suppression of botrytis grey mould caused by *Botrytis cinerea* on African violet; asters; begonia; chrysanthemum; cyclamen; cymbidium; dahlia; fuchsia; gerbera; geranium; gladiolus; hydrangea; marigolds; orchids; pansy; pelargonium; petunia; poinsettia; primrose; primula; ranunculus; rose; snapdragon; zinnia; greenhouse or protected environment (same crop list) at a rate of 1 kg/ha in 500-2000 L of water/ha. Repeat as needed on a 7-day interval up to harvest.

References

A. List of Studies/Information Submitted by Registrant

PMRA Document Number | References

1.0 Value

2579021 2015, Value Assessment, DACO: 10.1
2636371 2014, Summary report creating of bio crop protection technology against *Botrytis cinerea* in blackberry, DACO: 10.1

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

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2704707 Rodrigues de Oliviera, L. et al., 2013, *Aureobasidium pullulans* infection in a patient with chronic lymphocytic leukemia. Revista da Sociedade Brasileira de Medicina Tropical 46(5):660-662, DACO: M2.14, M4.9, M9.9
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2704713 Wan-Ting Chen . Mei-Eng Tu . Pei-Lun Sun., 2016, Superficial Phaeohyphomycosis Caused by *Aureobasidium melanogenum* Mimicking Tinea Nigra in an Immunocompetent Patient and Review of Published Reports. Mycopathologia 181:555-560, DACO: M2.14, M4.9, M9.9
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