Proposed Registration Decision PRD2014-17

Bacillus thuringiensis subsp. *aizawai* Strain ABTS-1857

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Overview

Proposed Registration Decision for *Bacillus thuringiensis* subsp. *aizawai* Strain ABTS-1857

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 XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide, containing the technical grade active ingredient *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857, to control many lepidopteran larvae that are pests of various fruit, vegetable, oilseed and ornamental crops.

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 *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 and XenTari WG Biological Insecticide.

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.

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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."

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 (for example, 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.

Before making a final registration decision on *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857, 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 *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857, 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 *Bacillus thuringiensis* subsp. *aizawai* Strain ABTS-1857?

Bacillus thuringiensis subsp. *aizawai* strain ABTS-1857 is a bacterium found naturally in soil. Fermentation solids, spores and insecticidal toxins from the culturing of this bacterium are used to formulate XenTari WG Biological Insecticide. The insecticidal toxins produced by *Bacillus thuringiensis* bacteria are proteins that bind to specific receptors on insect gut cells and then disrupt the membranes of the gut cells. This disruption of the gut cells causes the insect to stop feeding and allows germinating spores of the bacterium to invade and cause a fatal infection in the insect. The toxins produced by the subspecies *aizawai* primarily affect larvae of insects in the order Lepidoptera, many of which are pests of food and ornamental crops. Due to the nature of its mode of action, XenTari WG Biological Insecticide must be eaten by the target pests in order to be effective.

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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 *Bacillus thuringiensis* subsp. *aizawai* Strain ABTS-1857 Affect Human Health?

Bacillus thuringiensis subsp. _aizawai_ strain ABTS-1857 is unlikely to affect your health when XenTari WG Biological Insecticide is used according to the label directions.

People could be exposed to *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 when handling and applying XenTari WG Biological Insecticide 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 XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide were tested on laboratory animals, there were no signs that it caused any significant toxicity or disease. Besides the microorganism, soy lecithin present in the end-use product is known to be an allergen and must be labelled as such.

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 established 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 sets science-based MRLs to ensure that the food Canadians eat is safe.

Bacillus thuringiensis subsp. *aizawai* is a ubiquitous bacterium that is commonly found in soil and phylloplane. When XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide, which contain *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 as the active ingredient, were administered orally to rats, no signs of toxicity or disease were observed, and no metabolites of toxicological significance have been shown to be produced by this strain of *Bacillus thuringiensis* subsp. *aizawai*. Also, no adverse effects were reported for this microorganism in the United States where it has been registered since 1992. Therefore, the establishment of an MRL is not required for *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857. As well, the likelihood of residues contaminating drinking water supplies is negligible to non-existent. Consequently, dietary risks are minimal to non-existent.

Risks in Residential and Other Non-Occupational Environments

XenTari WG Biological Insecticide is for use only in agricultural settings. No residential uses were requested. The product application directions on the label include statements to minimize spray drift. Thus, exposure health risks for bystanders in these environments are expected to be negligible.

Occupational Risks From Handling XenTari WG Biological Insecticide

Occupational risks are not of concern when XenTari WG Biological Insecticide is used according to label directions, which include protective measures.

Workers handling XenTari WG Biological Insecticide can come into direct contact with *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 on the skin, in the eyes or by inhalation. For this reason, the product label will specify that workers exposed to XenTari WG Biological Insecticide must wear waterproof gloves, long-sleeved shirts, long pants, a dust/mist filtering respirator/mask (NIOSH approval number prefix TC-21) or NIOSH approved respirators (with any N-95, P-95, R-95 or HE filter), 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 handlers and mixer/loaders and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When XenTari WG Biological Insecticide Is Introduced Into the Environment?

Environmental risks are not of concern.

Bacillus thuringiensis spores are commonly isolated from terrestrial environments and are part of the soil micro-flora. Information available in the published literature on the environmental fate of *Bacillus thuringiensis* spores and crystal proteins suggests some viable spores are expected to survive following application of XenTari WG Biological Insecticide to field crops. These can remain inactive and immobile in soil for several months or years with a gradual decline in spore viability.

XenTari WG Biological Insecticide is not intended for aquatic uses and exposure to aquatic environments is limited to spray drift and runoff (following a rain event) from field applications. The limited survival of *B. thuringiensis* spores in water is influenced by a complex interaction of a number of biological, chemical and physical factors.

Several studies were conducted to determine the effects of XenTari Biological Insecticide Technical Powder on birds, fish, bees, terrestrial and aquatic arthropods and terrestrial non-arthropod invertebrates. These studies showed that XenTari Biological Insecticide Technical Powder was not toxic or pathogenic to birds, fish, or plants. XenTari Biological Insecticide Technical Powder was toxic and/or pathogenic to bees, certain beneficial insects and aquatic arthropods.

Although aquatic non-arthropod invertebrate and terrestrial plants toxicity/pathogenicity testing was not conducted, adequate information was available to determine that no significant adverse effects to these non-target organisms are expected.

Value Considerations

What Is the Value of XenTari WG Biological Insecticide?

Applied as a broadcast foliar spray, XenTari WG Biological Insecticide provides selective control of many Lepidoptera larvae that are pests of various fruit, vegetable, oilseed and ornamental crops.

XenTari WG Biological Insecticide has value for the control of various pest Lepidoptera such as codling moth, leafrollers, cabbage looper, leek moth and grape berry moth on apples, pears, broccoli, cabbage, cauliflower, Chinese cabbage, bok choy, Chinese broccoli, Asian radish, grape, hops, tomato, pepper, eggplant, leek, artichoke and canola and on greenhouse tomato, pepper, eggplant, cucumber, lettuce and beans and greenhouse ornamentals.

XenTari WG Biological Insecticide has value as an alternative for the supported uses, some of which have few or no registered alternatives and a few of which include alternatives that are being phased out. The product may be suitable for organic production and, applied according to the label directions, should have minimal adverse effects on non-target insects, making it well-suited to integrated pest management. Registration in Canada would reduce a technology gap with the United States and would address several high priorities listed in the Canadian Grower Priority Database.

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 XenTari WG Biological Insecticide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Individuals exposed to large quantities of XenTari WG Biological Insecticide, respiratory and dermal sensitivity could possibly develop upon repeated exposure to the product since all microorganisms, including *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857, contain substances that are potential sensitizers. Therefore, anyone handling or applying XenTari WG Biological Insecticide must wear appropriate waterproof gloves, a long-sleeved shirt, long pants, a dust/mist filtering respirator/mask (NIOSH approval number prefix TC-21) or NIOSH approved respirators (with any N-95, P-95, R-95 or HE filter), and shoes plus socks.

Environment

The end-use product label will include environmental precaution statements that prevent the contamination of aquatic systems from the use of XenTari WG Biological Insecticide as well as statements indicating that XenTari WG Biological Insecticide is toxic and/or pathogenic to bees, certain beneficial insects and aquatic organisms.

Next Steps

Before making a final registration decision on *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857, 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 *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 (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

Bacillus thuringiensis subsp. aizawai strain ABTS-1857

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active ingredient	Live endospores of *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857
Function	To suppress various lepidopteran pests on apples, pears, broccoli, cabbage, cauliflower, Chinese cabbage, Bok choy, Chinese broccoli, Asian radish, grape, hops, field/greenhouse fruiting vegetables (tomato, pepper and eggplant), leek, artichoke, greenhouse cucumber, greenhouse leafy vegetables (lettuce), greenhouse legumes (beans), canola and greenhouse ornamentals (carnation, chrysanthemum, geranium, gerbera, hibiscus, kalanchoe and rose)
Binomial name	*Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857
Taxonomic designation[5]	
Kingdom	Bacteria
Phylum	Firmicuties
Class	Bacilli
Order	Bacillales
Family	Bacillaceae
Genus	*Bacillus*
Species Group	*Bacillus cereus* group
Species	*thuringiensis*
Subspecies/Serovar	*aizawai*
Strain	ABTS-1857
Patent Status information	None

[5] http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi

Nominal purity of active	Technical Grade Active Ingredient (TGAI): 89.0% w/v *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857, fermentation solids, spores, and insecticidal toxins. End-Use Product : 48.1% w/v *B. thuringiensis* subsp. *aizawai* strain ABTS-1857, fermentation solids, spores, and insecticidal toxins
Identity of relevant impurities of toxicological, environmental and/or significance.	The technical grade active ingredient does not contain any impurities or micro contaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances. The product must meet microbiological contaminants release standards. In addition, there are no known mammalian toxins or other known toxic metabolites present in the technical grade active ingredient or end-use product. However, it is not known if *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 can produce *Bacillus cereus*-type enterotoxins under some conditions (see Section 3.1.2 for additional details).

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

Technical Product—XenTari Biological Insecticide Technical Powder

Property	Result
Colour	Tan to brown
Physical state	Solid powder
Density/Relative density/Bulk density	0.504 g/mL
Viscosity	Not applicable
Moisture content	Less than 5% moisture
Corrosion characteristics	As a microbial fermentation product, the technical grade active ingredient will not be an oxidizer and will not be capable of reacting exothermically with combustible materials

End-Use Product—XenTari WG Biological Insecticide

Property	Result
Colour	Light brown
Physical state	Fine granule
Odour	Characteristic " *Bacillus thuringiensis* " odour
pH	4.36 at 23°C
Density/Relative density/Bulk density	0.383 g/mL at 23°C
Viscosity	Not applicable
Persistent Foaming	Maximum volume: 5 mL
Wetting of dispersible powders	Wetting time: 5 seconds

Property	Result
Wet sieving after dispersing in water	0.72% retention on a 75 μm sieve
Suspensibility	Low concentration suspensibility: 81% High concentration suspensibility: 85%
Dry sieve analysis	99.98% retention on a 125 μm sieve 98.69% retention on a 250 μm sieve 87.59% retention on a 500 μm sieve No retention on a 1000 μm sieve
Dustiness of granular formulations	Nearly dust free
Flowability of water dispersible granules after heat test under pressure	Passed through 4.75 mm sieve spontaneously
Flammability	Not highly flammable
Explosive properties	Not explosive
Relative self-ignition temperature	Self-ignites at 225°C

1.3 Directions for Use

Bacillus thuringiensis subsp. *aizawai* strain ABTS-1857 fermentation solids, spores and insecticidal toxins are formulated into the commercial class end-use product XenTari WG Biological Insecticide. This product is applied as a broadcast foliar spray by conventional ground application equipment for control of various pest Lepidoptera on apples, pears, broccoli, cabbage, cauliflower, Chinese cabbage, bok choy, Chinese broccoli, Asian radish, grape, hops, tomato, pepper, eggplant, leek, artichoke and canola and on greenhouse tomato, pepper, eggplant, cucumber, lettuce and beans and greenhouse ornamentals (see Table 3 in Appendix I). Application rates are the same for all uses (500-1000 g/ha) except for apples and pears (500-1600 g/ha) and greenhouse ornamentals (750-1000 g/ha). For complete details of the directions for use, please refer to the product label.

1.4 Mode of Action

Active ingredients derived from *Bacillus thuringiensis* bacteria are classified as microbial disruptors of insect midgut membranes (Insecticide Resistance Action Committee mode-of-action group 11). When grown in culture and allowed to exhaust their resources, these bacteria produce dormant spores and crystals of protein. When ingested by an insect, the protein crystals dissolve in the alkaline environment of the insect gut, releasing protein toxins that bind to specific receptors on the insect's midgut cells. Binding of the protein toxins disrupts the midgut cell membranes of susceptible insects, inducing the insect to stop feeding and allowing germinating spores to invade the insect's hemocoel and proliferate, leading to a lethal septicemia.

2.0 Methods of Analysis

2.1 Methods for Identification of the Microorganisms

Bacillus thuringiensis subsp. *aizawai* strain ABTS-1857 can be identified to the species level using a combination of colony morphologies on agar media, cell morphology, production of protein inclusions upon sporulation, and Gram-positive antibiotic sensitivity. *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 can also be identified to the subspecies level by flagellar antigen serotyping and by crystal protein sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) analysis. No methods were provided to distinguish this strain of *B. thuringiensis* subsp. *aizawai* from other naturally occurring strains.

2.2 Methods for Establishment of Purity of Seed Stock

The production strain is maintained as cell banks, master stock cultures and working stock cultures. A cell bank is a permanent collection of lyophilized culture derived from a single colony that can be stored indefinitely. Cell banks were generated in sufficient quantities for hundreds of years. Master Stock cultures are prepared from cell banks in sufficient quantity to last between 10 and 20 years. Working stock cultures are prepared from master stock cultures in sufficient quantity to last two to five years. All stocks are tested for microbial contamination and integrity of the microbial pest control agent (MPCA). Practices for ensuring the purity of the seed stock were adequately described in the method of manufacture and quality assurance program.

2.3 Methods to Define the Content of the Microorganism in the Manufactured Material Used for the Production of Formulated Products

The guarantee of the technical grade active ingredient is expressed as the percent weight of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 spores, fermentation solids, and insecticidal toxins. Representative data on five batches of XenTari Biological Insecticide Technical Powder were submitted.

The guarantee of the end-use product is expressed as the percent weight of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 spores, fermentation solids, and insecticidal toxins. Representative data on five batches of XenTari WG Biological Insecticide were submitted.

Representative data included spore counts, biological activity on cabbage looper (*Trichoplusia ni*), plasmid profiles and sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) protein analysis.

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

As noted in Section 2.1, the MPCA can be identified to the species level using a combination of colony morphologies on agar media, cell morphology, production of protein inclusions upon sporulation, and Gram-positive antibiotic sensitivity. *Bacillus thuringiensis s*subsp. *aizawai* strain ABTS-1857 can also be identified to the subspecies level by flagellar antigen serotyping and by crystal protein SDS-PAGE analysis. These methods can help to identify the MPCA; however, these methods alone may not be sufficient to distinguish this strain of *B. thuringiensis* subsp. *aizawai* from all other naturally occurring strains. No methods are required to quantify viable or non-viable residues of *B. thuringiensis s*subsp. *aizawai* strain ABTS-1857 since residues of *B. thuringiensis* are exempt from the requirement of maximum residue limit (MRL; Section 4(d) of the *Food and Drugs Act*) as defined under Section B.15.002 of the Food and Drug Regulations.

2.5 Methods for Determination of Relevant Impurities in the Manufactured Material

The quality assurance procedures that will be used to limit contaminating microorganisms during manufacture of XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide are acceptable.

During manufacturing, several approaches are used to limit microbial contamination in the technical grade active ingredient and end-use product. These approaches will include purity checks using microscopic techniques, and plating on selective agar media, sterilization of all equipment and media, and sanitization of recovery equipment.

The absence of human pathogens and below-threshold levels of contaminating microorganisms were shown in the microbial screening of production batches using microbe-specific screening methods for detecting and enumerating microbial contaminants of concern. Release standards for microbial contaminants comply with those permitted by the PMRA and are adequate to ensure that the end-us4e product does not contain unacceptable levels of human and animal disease-causing microorganisms.

No known toxic metabolites or hazardous substances are present in XenTari WG Biological Insecticide.

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

Based on the results of a two-year storage stability study, the end-use product is stable when stored at 25ºC for a period of up two years. No storage stability data were provided for XenTari Biological Insecticide Technical Powder. In the absence of any studies of relevant testing periods, the technical grade active ingredient should not be stored at temperatures exceeding 25°C for a period that exceeds six months.

3.0 Impact on Human and Animal Health

3.1 Toxicity and Infectivity Summary

3.1.1 Test Studies

The PMRA conducted a detailed review of the toxicological studies submitted in support of XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide.

The studies submitted to fulfil the requirements for health hazard assessment of the technical grade active ingredient, XenTari Biological Insecticide Technical Powder, included acute oral toxicity/pathogenicity, acute pulmonary toxicity/pathogenicity, acute intraperitoneal infectivity, acute dermal toxicity/irritation, dermal sensitization, and eye irritation studies. These toxicology studies were conducted with ABG-6305, which is equivalent to XenTari Biological Insecticide Technical Powder.

In an acute oral infectivity and toxicity study, groups of fasted, 7-week old, Sprague-Dawley rats (18/sex) were given a single oral dose of XenTari Biological Insecticide Technical Powder at a dose of 7.9×10^{7} CFU/animal and observed over a period of up to 29 days with interim sacrifices performed on Days 1, 4, 8, 15, 22, and 29. There were no unscheduled mortalities and no treatment related clinical signs. Overall, body weights did not appear to be affected by the test microbe. Total microbial clearance was achieved by Day 15. In this study, XenTari Biological Insecticide Technical Powder is of low toxicity, and *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 is not pathogenic or infective to the rat when challenged via the oral route.

In an acute oral toxicity study, young adult Harlan Sprague-Dawley rats (5/sex) were given a single oral dose of XenTari Biological Insecticide Technical Powder at a dose of 5050 mg/kg bw. There were no mortalities, necropsy findings or changes in body weight. Initial clinical signs included piloerection, activity decrease, diarrhea, crust around eyes, nose and mouth, respiratory gurgle, and staining around muzzle, however, animals were asymptomatic by Day 6. Based on this study, XenTari Biological Insecticide Technical Powder is of low toxicity. This oral study did not assess the infectivity potential of the MPCA.

In an acute pulmonary infectivity and toxicity study, groups of 7–10-week old Sprague-Dawley (Crl:CDR) rats (3/sex/groups A-F; 5/sex/group G) were exposed to XenTari Biological Insecticide Technical Powder at a dose of $1.65–1.92\times10^{8}$ CFU/animal by the intratracheal route and observed over a period of up to 50 days with interim sacrifices performed on Days 1, 4, 8 15, 22, 36 and 50. There were no treatment related clinical signs, necropsy findings or changes in body weight. Clearance of the microbe was obtained by Day 7 from all organs except the lungs. Lungs were cleared of microbial counts by Day 35. Based on these results, XenTari Biological Insecticide Technical Powder is of low toxicity, and *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 is not infective to the rat.

In an acute intravenous/subcutaneous infectivity study, groups of 4–7-week old CD rats (21/sex) were injected with XenTari Biological Insecticide Technical Powder at a dose range of 1.03–1.18×10^7 CFU/animal. Animals were then observed for up to 66 days with interim sacrifices performed on Days 1, 4, 8, 8, 15, 22, 36, and 67. There were no treatment related clinical signs, necropsy findings or changes in body weight. By Day 14, 21 and 66, blood, brain and kidney were cleared of microbial counts, respectively. Although microbial numbers were obtained by Day 66, a pattern of clearance was achieved in the mesenteric lymph nodes, lungs, liver and spleen. Based on the results of the study, ***B. thuringiensis*** subsp. ***aizawai*** strain ABTS-1857 is not pathogenic and not infective.

In an acute intraperitoneal infectivity study, groups of CF1 mice (5/sex/group) were injected with XenTari Biological Insecticide Technical Powder at a dose of 0.2 mL into the peritoneal cavity (1×10^6 CFU/animal). Animals were then observed for up to 4 days. There were no mortalities and no signs of toxicity. Infectivity was not assessed in this study. As a result, this intraperitoneal infectivity study is of limited utility in the risk assessment as it did not include data to determine infectivity. A replacement study, however, is not required since an intravenous/subcutaneous infectivity study (as mentioned above) was provided to determine the infectivity potential of ***B. thuringiensis*** subsp. ***aizawai*** strain ABTS-1857 via the injection route of exposure.

In an acute subcutaneous infectivity study, groups of CF1 mice (5/sex/group) were subcutaneously injected with XenTari Biological Insecticide Technical Powder at a dose of 0.25 mL (1.35×10^7 CFU/animal). Animals were then observed for up to seven days. There were no mortalities and no signs of toxicity. Infectivity was not assessed in this study. As a result, this subcutaneous infectivity study is of limited utility in the risk assessment as it did not include data to determine infectivity. A replacement study, however, is not required since an intravenous/subcutaneous infectivity study (as mentioned above) was provided to determine the infectivity potential of ***B. thuringiensis*** subsp. ***aizawai*** strain ABTS-1857 via the injection route of exposure.

In an acute dermal toxicity study, groups of young adult New Zealand White rabbits (5/sex) were dermally exposed to XenTari Biological Insecticide Technical Powder at a dose of 5050 mg/kg/bw for 24 hours to an area of approximately 10% body surface area. There were no treatment related clinical signs, necropsy findings or changes in body weight. In this study, XenTari Biological Insecticide Technical Powder is of low toxicity to male and female rabbits via the dermal route.

In a dermal irritation study, young adult New Zealand White rabbits (3/sex) were dermally exposed to 500 mg of XenTari Biological Insecticide Technical Powder in water for four hours. Irritation was scored by the Draize method. Following application, very slight erythema was present in two females after one hour and in one female after 24 hours. Edema was not observed at any time throughout the study. In this study, XenTari Biological Insecticide Technical Powder is minimally irritating to the skin of rabbits based on a minimum irritation score (MIS) of 0.333/8 (at one hour) and a maximum average score (MAS) of 0.056/8 (at 24, 48 and 72 hours).

In an acute inhalation toxicity study, groups of 2-month old Sprague-Dawley rats (5/sex) were exposed by the inhalation route to XenTari Biological Insecticide Technical Powder for four hours to nose only at concentration(s) of 5.312–5.521 mg/L (7.3×10^{10} CFU/g). Animals then were observed for 14 days. Initially, treated animals showed decrease in activity and piloerection but were asymptomatic by Day 1. There were no treatment related necropsy findings or changes in body weight. In this study, XenTari Biological Insecticide Technical Powder is of low toxicity in male and female rats via the inhalation route of exposure.

In an acute oral toxicity study, young adult Harlan Sprague-Dawley rats (5/sex) were given a single oral dose of XenTari Biological Insecticide Technical Powder in water at doses of 5050 mg/kg bw. Clinical signs included piloerection, decreased activity, diarrhea, crust around eyes, nose and mouth, respiratory gurgle, and staining around muzzle. Animals were asymptomatic by Day 6. Based on the results of this study, XenTari biological Insecticide Technical Powder is of slight toxicity.

In a dermal sensitization study with XenTari Biological Insecticide Technical Powder, young adult Hartley-Albino guinea pigs (10/sex) were tested using the method of Buehler. Only one animal showed very slight erythema 24 hours after the first induction but was asymptomatic by 48 hours. No other animal in either the induction or challenged groups showed signs of erythema. Although XenTari Biological Insecticide is not considered a dermal sensitizer based on the results of this study, all microorganisms are recognized as being able to produce substances that can elicit allergic reactions after repeated exposure to high concentrations.

In a primary eye irritation study, undiluted XenTari Biological Insecticide Technical Powder (50.4 mg) was instilled into the conjunctival sac of the right eye of young adult New Zealand White rabbits (6/sex) and then washed after 24 hours. Additional rabbits (3/sex) had their treated eyes washed 30 seconds after instillation. Irritation was scored by the method of Kay and Calandra. Conjunctival redness, chemosis and discharge was observed in all animals at the one hour time point. After 24 hours, corneal opacity was observed in three of the treated eyes. Signs of ocular irritation subsided in all animals except for one by Day 21. In this study, XenTari Technical Powder is moderately irritating to the eye based on a MIS of 22.5/110 (at 24 hours), a MAS of 19.4/110 (at 24, 48, and 72 hours) and on the observation that irritation was not reversible in one animal by Day 21. The label statement should include “WARNING- EYE IRRITANT”.

In other studies, the genotoxic potential of XenTari Biological Insecticide Technical Powder was studied using the *Salmonella - Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay. In this study, a range of volumes (10–200 µL) of dimethyl sulfoxide extracts of XenTari Biological Insecticide Technical Powder were plated with strains of *S. typhimurium* (TA98, TA100, TA1535, TA1537) and *E. coli* (WP2uvrA). The test substance did not significantly increase the number of revertants above the background rate of spontaneous mutations of any of the tester strains.

The studies submitted to fulfill the requirements for health hazard assessment of XenTari WG Biological Insecticide include acute oral toxicity/pathogenicity, acute dermal toxicity, dermal irritation, acute pulmonary infectivity and toxicity, dermal sensitization and eye irritation studies. These toxicology studies were conducted with ABG-6316 which is equivalent to the XenTari WG Biological Insecticide.

In an oral infectivity and toxicity study, young adult Sprague-Dawley rats (5/sex) were given a single oral dose of XenTari WG Biological Insecticide at doses of 1.3–1.4×10^{11} CFU/animal (5000 mg/kg bw). There were no treatment related clinical signs, necropsy findings or changes in body weight. Although the microbial counts isolated from the feces diminished during the time course and showed a pattern of clearance, there were no interim sacrifices in other parts of the rat that could show that other organs/tissues could clear the microorganism. Based on the results of this study, XenTari WG Biological Insecticide is of low toxicity and did not seem to be pathogenic to the rat. Please note that PMRA has no requirement for acute oral infectivity and toxicity testing for the end-use product.

In an acute dermal toxicity study, young adult New Zealand White rabbits (5/sex) were dermally exposed to XenTari WG Biological Insecticide at a dose of 2000 mg/kg bw for 24 hours to an area of approximately 10%. There were no treatment-related clinical signs of toxicity, necropsy findings or changes in body weight. In this study, XenTari WG Biological Insecticide is of low toxicity in male and female rabbits via the dermal route.

In a dermal irritation study, young adult New Zealand White rabbits (3/sex) were dermally exposed to 0.5 g of XenTari WG Biological Insecticide in water for four hours. Animals then were observed for eight days. Irritation was scored by the Draize method. Very slight to well defined erythema was observed in the rabbits initially, but dissipated such that by Day 7 there were no signs of erythema in any rabbits. No edema or other dermal effects were observed throughout the study. In this study, XenTari WG Biological Insecticide is slightly irritating to the skin based on a MIS of 1.33/8 (at one hour) and a MAS of 0.94/8 (at 24, 48 and 72 hours).

In an acute inhalation toxicity study, groups of young adult Sprague-Dawley albino rats (5/sex/group) were exposed by the inhalation route to XenTari DF for four hours to nose only at concentrations of 5.05–5.28 mg/L (i54% w/w). XenTari DF is equivalent to XenTari WG Biological Insecticide. There were no mortalities. Body weight gain was observed by Day 3 until the end of the 14-day observation period. Irregular respiration was seen initially, but rats were asymptomatic by Day 4 and were active and healthy for the remaining study period. Based on this study, XenTari WG Biological Insecticide is of low toxicity in male and female rats via the inhalation route.

Another acute inhalation toxicity study was submitted where groups of young adult HSD: (SD) rats (5/sex) were exposed by the inhalation route to XenTari WG Biological Insecticide for four hours to whole body at concentrations of 3.05 mg/L (analytical concentrations; equivalent to 5.8×10^{7} CFU/L). There were no mortalities. Clinical signs included decreased activity, lacrimation, nasal discharge, piloerection, polyuria and salivation on day of dosing only. Body weight gains occurred throughout study period. In this study, XenTari WG Biological Insecticide is of low toxicity in rats.

In a dermal sensitization study with XenTari WG Biological Insecticide, young adult Hartley guinea pigs (20 males) were tested using the guinea pig maximization test (GPMT). The test microbe produced no dermal sensitization after the challenge dose. In this study, XenTari WG Biological Insecticide is not considered a dermal sensitizer. The PMRA, however, assumes that all microorganisms contain substances that can elicit positive hypersensitivity reactions regardless of the outcome of sensitization testing.

In a primary eye irritation study, undiluted XenTari WG Biological Insecticide (90 mg) was instilled into the conjunctival sac of the right eye of young adult New Zealand White rabbits (5 males and 4 females). The treated eyes of six rabbits remained unwashed, and the treated eyes of the remaining three rabbits were flushed with water approximately 30 seconds after instillation. Irritation was scored by the Draize method. Conjunctival irritation (redness, chemosis and discharge) was observed by the one-hour interval in rabbits in both groups. Minimal conjunctival redness persisted in two rabbits in the unwashed group through Day 10, and in one rabbit in the washed group through Day 7. Additional observations that were not captured in the irritation scores, included iridal hyperemia at one hour, lackluster of the cornea at 24 hours in one rabbit, conjunctival blistering, conjunctival petechial hemorrhage, purulent discharge and yellow crusting around edges of eyelid, and were noted up to 72 hours. No ocular effects were observed in any of the rabbits by Day 14 of the study. Although the MIS was 12.3/110 (at one hour) in the unwashed group, the additional observations made in the first 72 hours, and the irritation effects that lasted 10 days, indicated XenTari WG Biological Insecticide to be mildly irritating to the eye.

Results of the toxicity and infectivity of XenTari Biological Insecticide Technical Powder and its associated end-use product, XenTari WG Biological Insecticide, are summarised in Appendix I, Table 1.

3.1.2 Additional Information

Valent BioSciences Corporation submitted a request to waive any additional genotoxic studies on *B. thuringiensis* subsp. *aizawai* strain ABTS-1857. Briefly, the applicant discussed that the standard assays are not considered appropriate for testing the mutagenicity and genotoxicity of *B. thuringiensis* subsp. *aizawai* as they were designed for testing chemicals such that studies using the microorganism itself have not been conducted. Although the applicant submitted this rationale to waive genotoxic studies, there is no requirement for genotoxic studies for the technical grade active ingredient nor the associated microbial pest control agent, *B. thuringiensis* subsp. *aizawai* strain ABTS-1857, as it is not known to produce metabolites with genotoxic potential.

A search in the PubMed.gov database using "aizawai" as a keyword found no reports of adverse effects. Although another search in the PubMed database using "thuringiensis infection" as a keyword revealed some reports including periorbital cellulitis, nosocomial bacteremia in patients with underlying diseases, gastroenteritis and corneal ulcer, the number of reports are quite rare despite the extensive use of products containing *B. thuringiensis*.

Bacillus thuringiensis is closely related to *B. cereus*, the only known difference between the species being the production of the delta-endotoxin. Some strains of *B. cereus* cause food poisoning and their pathogenic effects are caused by metabolites and are manifested as one of two types of foodborne poisoning:

1. Vomiting which is caused by the ingestion of a heat stable toxin which consists of a cyclic peptide; and

2. Diarrhoea which is caused by heat labile enterotoxins of which three have been identified. All three components are understood to be necessary for enterotoxic activity to be fully expressed; however, a binary combination of components can have some biological activity.

Although some isolates of *B. thuringiensis* have been shown to produce *B. cereus*-like enterotoxins and there have been occasional reports of putative infections attributed to some *B. thuringiensis* strains, existing commercialized strains of *B. thuringiensis* have been considered relatively innocuous to humans given that their widespread use as microbial biopesticides over several decades has not resulted in reports of illness. Despite the prevalent use of *B. thuringiensis*-based biopesticides, there has only been one report that showed a possible connection between *B. thuringiensis* and actual diarrheal illness. This report did not determine the strain of *B. thuringiensis* or its origin (in other words, a strain from a registered microbial biopesticide product or a non-commercial strain), and Norwalk virus was also found in some of the stool samples.

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 Pesticides and Pest Management portion of Health Canada's website. Incidents were reviewed for the active ingredient *Bacillus thuringiensis* subsp. *aizawai*. As of 24 February 2014, no incident reports involving *Bacillus thuringiensis* subsp. *aizawai* have been reported to the PMRA.

3.1.4 Hazard Analysis

The database submitted in support of registering XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide was reviewed from the viewpoint of human health and safety and was determined to be sufficiently complete to permit a decision on registration.

XenTari Biological Insecticide Technical Powder was of low to slight toxicity to rats via the oral, pulmonary, IV and inhalation routes; to the mouse via the intraperitoneal and subcutaneous routes; and to rabbits via the dermal route. *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 was not infective via the oral, pulmonary and IV routes.

XenTari Biological Insecticide Technical Powder showed minimal dermal irritation and moderate eye irritation in the rabbit. The signal words "WARNING-EYE IRRITANT" and "Causes eye irritation. DO NOT get in eyes" will appear on the technical grade active ingredient label.

Additionally, a study for genotoxic potential and a rationale to waive further testing on genotoxic potential of XenTari Biological Insecticide Technical Powder were deemed acceptable. The technical grade active ingredient is not known to have genotoxic potential. No further testing is required.

The end-use product, XenTari WG Biological Insecticide, was of low toxicity to rats via the oral and inhalation routes, and of low toxicity to rabbits via the dermal route. Slight dermal and mild eye irritation was observed in rabbits treated with XenTari WG Biological Insecticide. The signal words "CAUTION- EYE IRRITANT" and "May irritate eyes. Avoid contact with eyes" should appear on the end-use product label.

Although XenTari Biological Insecticide Technical Powder was not a sensitizer to the guinea pig, the signal words "POTENTIAL SENSITIZER" will appear on the labels for both the technical grade active ingredient and end-use product, XenTari WG Biological Insecticide, as all microorganisms are recognized as being able to produce substances that can elicit allergic reactions after repeated exposure to high concentrations.

Higher tier subchronic and chronic toxicity studies were not required because of the low acute toxicity of the end-use product, and no indications of infectivity, toxicity or pathogenicity of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 in the test animals treated in the Tier I acute oral, pulmonary, intravenous, toxicity/infectivity tests.

Within the available scientific literature, there are no reports that suggest *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 has 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 *B. thuringiensis* subsp. *aizawai* strain ABTS-1857.

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, eye and inhalation exposure for 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. *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 has not been identified as a dermal wound pathogen and does not contain any known toxic secondary metabolites. There is no indication that it could penetrate intact skin of healthy individuals. Furthermore, toxicity testing with XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide showed no significant signs of toxicity via the oral, dermal, or pulmonary routes of exposure. The submitted eye and dermal irritation studies with the XenTari WG Biological Insecticide demonstrated minimal eye and skin irritation.

Although toxicity from dermal or inhalation exposure is considered minimal from the proposed end-use product use, 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 XenTari WG Biological Insecticide must wear waterproof gloves, long-sleeved shirts, long pants, eye goggles, a dust/mist filtering respirator/mask (NIOSH approval number prefix TC-21) or NIOSH approved respirators (with any N-95, P-95, R-95 or HE filter), and shoes plus socks.

Label warnings, restrictions and risk mitigation measures are adequate to protect users of XenTari WG Biological Insecticide, and no significant occupational risks are anticipated for this product.

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 XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide and the assumption that precautionary label statements will be followed by commercial applicators in the use of XenTari WG Biological Insecticide. As well, the active ingredient, *B. thuringiensis* subsp. *aizawai* strain ABTS-1857, belongs to a species that is ubiquitous in the environment and the use of XenTari WG Biological Insecticide is not expected to increase exposure to bystanders beyond natural levels. Furthermore, since the use is agricultural, bystander exposure, including exposure to infants and children in schools, residential and daycare facilities, is likely to be minimal to non-existent. Consequently, the health risk to infants and children is expected to be negligible.

3.3 Dietary Exposure and Risk Assessment

3.3.1 Food

Although the proposed use pattern may result in some dietary exposure with possible residues in or on agricultural commodities, negligible to no risk is expected for the general population, including infants and children, or animals because *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 demonstrated no pathogenicity, infectivity or oral toxicity at the maximum dose tested in the Tier I acute oral toxicity/infectivity study. Furthermore, higher tier subchronic and chronic dietary exposure studies were not required because of the low toxicity of the MPCA and no indications of infectivity, toxicity or pathogenicity in the test animals treated in the Tier I acute oral and pulmonary toxicity/infectivity studies. Although secondary metabolites of toxicological significance have been shown to be produced by other isolates of *B. thuringiensis*, due to the demonstrated low-toxicity of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857, the risks from secondary metabolites to the general population, including infants and children, or animals are negligible. 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

No risks are expected from exposure to this microorganism via drinking water because exposure will be minimal and because there were no harmful effects observed in Tier I acute oral toxicity testing and infectivity testing. The XenTari WG Biological Insecticide label instructs users not to contaminate irrigation or drinking water supplies or aquatic habitats through equipment cleaning or waste disposal. Users are also requested not to allow 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 remove the transfer of residues to drinking water. Therefore, potential exposure to *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 in surface and drinking water is negligible.

3.3.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

Calculations of acute reference doses (ARDs) 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 the *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 is of low toxicity, is not pathogenic or infective to mammals, and that infants and children are likely to be no more sensitive to the MPCA 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 MPCA, including neurological effects from pre- or post-natal exposures, and cumulative

effects on infants and children of the MPCA and other registered micro-organisms that have a common mechanism of toxicity, does not apply to this MPCA. As a result, the PMRA has not used a margin of exposure (safety) approach to assess the risks of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 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, there is reasonable certainty that no harm will result from aggregate exposure of residues of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 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 *B. thuringiensis* encountered in the environment have been reported. Even if there is an increase in exposure to this active ingredient from the use of XenTari WG Biological Insecticide, 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 established 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 sets science-based MRLs to ensure the food Canadians eat is safe.

Bacillus thuringiensis are ubiquitous organisms found in most terrestrial environments. Residues of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 on treated food crops, at the time of harvest, are also anticipated as the active ingredient is comprised of resilient resting structures, which are much more persistent in the environment than vegetative cells. Consequently, the PMRA has applied a hazard-based approach for determining whether an MRL is required for this microorganism. Based on the lack of toxicity and pathogenicity effects observed in the acute toxicity and infectivity studies (particularly the oral study), the risks anticipated for dietary exposure are considered low. Although some strains of *B. thuringiensis* are known to produce secondary metabolites of toxicological significance (beta-exotoxins and enterotoxins), the risks anticipated for dietary exposure are considered low since analytical data were submitted showing that these metabolites were not found in the technical grade active ingredient. In addition, the likelihood of residues contaminating drinking water supplies is negligible to non-existent. Also, residues of *B. thuringiensis* are exempt from the requirement of maximum residue limit (MRL; Section 4(d) of the *Food and Drugs Act*) as defined under Section B.15.002 of the Food and Drug Regulations.

3.4 Cumulative Effects

The PMRA has considered 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 *B. thuringiensis* in the environment, the PMRA is not aware of any other microorganisms, or other substances that share a common mechanism of toxicity with *B. thuringiensis* subsp. *aizawai* strain ABTS-1857. No cumulative effects are anticipated if the residues of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 interact with related strains of this microbial species.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Bacillus thuringiensis occurs naturally and ubiquitously in the environment. It is a common component of the soil micro-flora and has been isolated from most terrestrial habitats. Although *B. thuringienis* bacteria constitute an indigenous part of the soil micro-flora community, they do not compete aggressively with other soil-microorganisms and are not adapted to survive as an active member of the soil microbial community. Following commercial field applications of formulations containing *B. thuringiensis* subsp. *azawai* spores and crystal proteins, some viable spores are expected to survive. These can remain inactive and immobile in soil for several months or years, during which time a natural breakdown occurs, resulting in gradual spore mortality. Directed field applications of *B. thuringiensis* subsp. *aizawai* to foliage will reduce potential soil exposure, resulting in lower soil concentrations.

Bacillus thuringiensis may survive to a limited extent in water. However, its survival and viability in the natural aquatic environment are influenced by the complex interaction of a number of biological, chemical and physical factors. Predation by protozoans and lower animal forms undoubtedly plays a significant role in controlling the population of *B. thuringiensis* in the aquatic environment. The effects of solar radiation may destroy *B. thuringiensis* endospores, crystal proteins and vegetative cells in the upper layers of an aquatic system and extremes of water temperature may have a detrimental effect on survival and insecticidal activity. The adsorption of bacterial cells to the sediment layer in the natural aquatic environment is also expected to occur. Spores are unlikely to be capable of germinating and multiplying in sediment and the crystalline proteins become inaccessible to insect larvae.

Although there may be some potential for surface water exposure resulting from spray drift from field applications, spray drift from application to developed foliage is unlikely to be significant. Concentrations of *B. thuringiensis* subsp. *azawai* strain ABTS-1857, which are deposited in surface water bodies via drift and/or run off events, are expected at, or below, naturally occurring background levels.

The level of *B. thuringiensis* subsp. azawai strain ABTS-1857 spores and crystal proteins in the terrestrial and aquatic environment will not significantly increase as a result of the use of XenTari WG Biological Insecticide on greenhouse and agricultural field crops.

4.2 Effects on Non-Target Species

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 of the MPCA. The maximum challenge concentration 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 some 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 example, lethal concentration 50% (LC_{50}) and lethal does 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 is calculated by dividing the exposure estimate by an appropriate toxicity value (risk quotient = exposure/toxicity), and the risk quotient is then compared to the level of concern.

If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, 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 Organisms

Several studies were submitted to address the hazards of the technical grade active ingredient to terrestrial non-target organisms. These studies included non-target avian species, arthropods and non-arthropod invertebrates.

Two separate acute oral toxicity and pathogenicity studies were performed on 21-day old mallard ducks (*Anas platyrhynchos*) and 21-day old bobwhite quail (*Colinus virginianus*) over 30 days. In each study, XenTari Biological Insecticide Technical Powder was administered to the birds (six groups of five birds) by oral gavage at 1714 mg/kg bw. There were no signs of toxicity, behavioural abnormalities or pathogenicity observed in the treated birds in either study. There were no treatment related effects on bodyweight gain or feed consumption in either study. The 30-day acute oral LD_{50} was greater than 1714 mg/kg bw in both studies.

In a dietary toxicity/pathogenicity study, one-week old adult honeybees (*Apis mellifera*) were fed XenTari Biological Insecticide Technical Powder daily at concentrations of 1000, 100, 10, and 1 ppm in a 1:1 v/v honey and water solution in three separate trials (9, 11, and 12 days). Food consumption was measured. The mean consumption values for honeybees fed 1000, 100, 10 and 1 ppm XenTari Biological Insecticide Technical Powder were 54, 48, 49, and 51 mg/bee/day, respectively. Increased mortality was observed in the treatment groups that followed a dose-response relationship. Percent mortality in the 1000, 100, 10, and 1 ppm and negative control groups was 94, 61, 32, 15 and 27 in the 9-day trial; 100, 85, 47, 34, and 21 in the 11-day trial; and 98, 21, 33, 28 and 20 in the 12-day trial, respectively. XenTari Biological Insecticide Technical Powder is toxic and/or pathogenic to the adult honeybee via the dietary route.

In a four-week toxicity/pathogenicity study, colonies of honeybees (*A. mellifera*) were exposed to XenTari WG Biological Insecticide once per week for four weeks by opening the hives, removing all frames and spraying all surfaces with a total of 0.2084 g of test substance in deionized water per hive. Colonies were observed for changes in population and hive weight over four weeks. No statistically significant differences in population or hive weight between the treated and negative control hives were observed. However, no definitive conclusions could be made due to the lack of statistical power of the study. There was no contact toxicity observed.

Due to the potential for toxicity and/or pathogenicity to the honeybee, precautionary measures are required on the XenTari WG Biological Insecticide label alerting users to the hazards to bees from the use of this product as well as instructions to limit exposure to bees.

In a contact toxicity/pathogenicity study, green lacewing (*Chrysoperla carnea*) were exposed to XenTari Biological Insecticide Technical Powder by spraying the test material directly onto the green lacewing larvae, all surfaces of the test container, and food (lepidopteran eggs) at three test rates; 0.239 g/L, 2.39 g/L, and 23.9 g/L. The subjects were then observed for larval mortality, pupation, survival to adulthood and egg production until the life-cycle reached the next generation of larvae. Adverse effects were observed (larval mortality, pupation and survival to adulthood) at the 23.9 g/L test concentration; therefore, *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 is toxic and/or pathogenic to green lacewing larvae.

In three separate contact toxicity tests, predatory mites (*Metaseiulus occidentalis*) and twospotted spider mites (*Tetranychus urticae*) were exposed to XenTari Biological Insecticide Technical Powder at rates of 0.239, 2.39 and 23.9 g/L using an airbrush sprayer. In the first test, adult gravid female predatory mites were sprayed with the test substance. In the second test, eggs laid by the predatory mite were sprayed with the test substance. In the third test, adult gravid female, protonymph and eggs of the twospotted spider mite were sprayed with the test substance. An

increase in mortality was observed for adult female gravid predatory mite, and adult gravid female and protonymph two spotted spider mite. XenTari Biological Insecticide Technical Powder is toxic and/or pathogenic to the predatory mite, *M. occidentalis*, and its prey, the twospotted spider mite, *T. urticae*.

Due to the potential for toxicity and/or pathogenicity to these beneficial insects, precautionary measures are required on the XenTari WG Biological Insecticide label alerting users to the hazards to certain beneficial insects from the use of this product as well as instructions to limit exposure to these insects.

In a 27-day dietary toxicity study, ladybird beetles (*Hippodamia convergens*) were exposed to XenTari Biological Insecticide Technical Powder through dietary exposure at concentrations of 1500, 3000, and 6000 ppm test substance in honey. There were no significant increases in mortality, immobility or lethargy in the test groups when compared to the control group.

In a 30-day contact toxicity study, earthworms (*Eisenia fetida*) were exposed to XenTari Biological Insecticide Technical Powder at 1000 mg a.i. (active ingredient)/kg dry soil. There were no mortalities or abnormal behavioural observations made.

No toxicity/pathogenicity data were considered to address the potential for harm to terrestrial plants and wild mammals. Effects on non-target plants were addressed via a scientific waiver rationale and effects to wild mammals were addressed via human health studies submitted with this application.

In a scientific rationale submitted to waive testing on terrestrial plants, no reports of negative effects on plants were found despite decades of use of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 in agriculture. Also, efficacy studies of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 that were presented on numerous plants contained a section on phytotoxicity that showed there were no effects on vegetation.

From the data submitted under Section 3.1.1, it was determined that XenTari Biological Insecticide Technical Powder was not toxic or pathogenic to mammals via the oral, pulmonary, dermal, intravenous or intraperitoneal routes. No further data are required to assess the risk of harm to wild mammals.

Based on all the available data and information on the effects of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 to non-target terrestrial organisms, and the precautionary measures required on the XenTari WG Biological Insecticide label, there is reasonable certainty that no harm will be caused to birds, wild mammals, arthropods (including honeybees), non-arthropod invertebrates, and plants from the proposed use of XenTari WG Biological Insecticide.

4.2.2 Effects on Aquatic Organisms

Several studies were submitted to address the hazards of the technical grade active ingredient to aquatic non-target organisms. These studies included non-target fish species, and arthropods. In addition a study conducted with the end-use product on algae was submitted to address hazards to aquatic plants.

Three studies were submitted to address hazards to freshwater fish. In the first study, no mortalities were observed in a 96-hour aquatic toxicity study on juvenile rainbow trout at 100 mg XenTari Biological Insecticide Technical Powder /L or 6.3×10^6 viable spores per mL.

In the second study, juvenile fish were exposed to a limit concentration of 5.4×10^7 viable spores/ mL over 20 days. By study termination, 77% mortality was observed among treated fish and there was a significant increase in water turbidity in the treated group versus the control. There was no evidence of infectivity or pathogenicity from tissues examined histopathologically. The increase in the incidence and severity of gill changes (fusion of gill lamellae and hyperplasia of gill epithelium) reported for the treated group vs the control, was considered to be nonspecific and not associated with infectivity.

In the third study, fish were exposed to concentrations of 13, 61, 110, 240, 320, 370 and 440 mg of XenTari Biological Insecticide Technical Powder /L over 30 days. The study reported high mortality (60–70%) among fish exposed to 370 and 440 mg/L. Observed mortalities were likely due to high turbidity of the test solution rather than to toxicity of the test substance. No signs of infection were seen in tissues examined histopathologically. The 30-day LC_{50} was 310 mg/L or ~3.2×10^7 CFU/mL.

In a 10-day toxicity study, daphnids *(Daphnia magna)* were aquatically exposed to XenTari Biological Insecticide Technical Powder at 1.1, 2.0, 3.4, 5.9, 10, 20 and 34 mg/L. On Day 9, 100% mortality was observed among organisms at the highest treatment level (34 mg/L). At test termination (Day 10), 30% and 95% mortality was observed among daphnids exposed to the 10 and 20 mg/L treatment levels, respectively. The 10-day LC_{50} for XenTari Biological Insecticide Technical Powder was calculated to be 12 mg/L.

In a 21-day toxicity study, daphnids *(D. magna)* were aquatically exposed to XenTari Biological Insecticide Technical Powder at 0.5, 5.0, and 74 mg/L. The 21-day no observed effect concentration (NOEC) and lowest observed effect concentration (LOEC) based on number of young produced and dry weight of first generation were 0.5 ppm and 5.0 mg/L respectively. The risk quotient calculated for these effects exceeded the PMRA's level of concern for these non-target aquatic organisms. XenTari Biological Insecticide Technical Powder is toxic to aquatic arthropods. Precautionary measures are required on the XenTari WG Biological Insecticide label alerting users to the hazards to aquatic organisms.

The effect of XenTari WG Biological Insecticide on the freshwater green alga, *Selenastrum capricornutum*, was studied at nominal concentrations of 0, 10, 20, 40 80 160 and 320 mg/L over 72 hours under static conditions. The 72-hour EC_{50} for algal growth rate and biomass was 2.35 mg/L and 119 mg/L, respectively.

No toxicity/pathogenicity data were considered to address the potential for harm to aquatic non-arthropod invertebrates. In a scientific rationale submitted to waive data requirements for testing on aquatic non-arthropod invertebrates, no reports of negative effects were found on these non-target aquatic organisms despite decades of use of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 in agriculture and, based on the terrestrial use pattern, no significant exposure to aquatic systems is expected.

Based on all the available data and information on the effects of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 to non-target aquatic organisms and the precautionary measures required on the XenTari WG Biological Insecticide label, there is reasonable certainty that no harm will be caused to fish, aquatic arthropods and non-arthropod invertebrates, and aquatic plants from the proposed use of XenTari WG Biological Insecticide.

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 Pesticides and Pest Management portion of Health Canada's website http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/incident/indexeng.php. Only incidents in which the pesticide is determined to be linked to the effects (Canadian causality of highly probable, probable and possible; U.S. causality of highly probable, probable and possible) are considered in the reviews.

As of 24 February 2014, there were no environmental incidents reported in the PMRA Incident reporting database for products containing *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 for use as pesticides.

5.0 Value

5.1 Effectiveness Against Pests

Counting assessments of different pests within a trial as separate trials, efficacy data from a total of 107 trials were evaluated, most of which were conducted in Europe.

5.1.1 Pests of Apple and Pear (cankerworms, codling moth, fruittree leafroller, obliquebanded leafroller, omnivorous leafroller, oriental fruit moth, redbanded leafroller, tufted apple bud moth, variegated leafroller, winter moth)

Efficacy data from total of 14 trials were evaluated for pests of apples and pears, three for codling moth, two for summer fruit tortrix moth and nine for winter moth. One trial for winter moth was conducted on pear in Belgium and the remaining 13 trials were all conducted on apple in Germany. These efficacy data support label claims for codling moth, oriental fruit moth (by extrapolation from codling moth), leafrollers and tufted apple bud moth (by extrapolation from summer fruit tortrix moth), winter moth, and cankerworms (by extrapolation from winter moth). Application rates in the range of 500-1600 g/ha were shown to be effective and this broad range allows for adequate coverage on trees of different sizes.

5.1.2 Pests of Broccoli, Cabbage, Cauliflower, Chinese Cabbage, Bok Choy, Chinese Broccoli and Asian Radish (cabbage looper, cross-striped cabbageworm, diamondback moth, imported cabbageworm)

Efficacy data from total of 24 trials were evaluated for pests of these vegetables, two for cabbage looper, four for cabbage moth, ten for diamondback moth and eight for imported cabbageworm. The trials were conducted on Brussels sprouts, cabbage, cauliflower and collards in Belgium, Germany, Poland, the Netherlands and the United States. These efficacy data support label claims for cabbage looper, diamondback moth and imported cabbageworm at application rates of 500-1000 g/ha, with a lower rate (250 g/ha) showing inferior results in several trials. Considering similarities in life cycles and damage, support for the foregoing pests can be extrapolated to cross-striped cabbageworm.

5.1.3 Pests of Grape (grape berry moth, grape leaffolder, grape leafroller, grapeleaf skeletonizer, obliquebanded leafroller, omnivorous leafroller)

Efficacy data from a total of 14 trials were evaluated for pests of grape, six for European grape berry moth, three for European grapevine moth and five that included both pests without distinguishing between them. All six trials for European grape berry moth were conducted in France and the remaining trials were conducted in Austria, Germany and the Czech Republic. Considering the similarity of the pests, these efficacy data from European pests of grape support the label claim for grape berry moth in Canada. The trials demonstrated the need for an application rate of 1000 g/ha in some cases and the adequacy of 500 g/ha in other cases. Lower rates (250 and 400 g/ha) often failed and when rates above 1000 g/ha (1200 and 1600 g/ha) were tested there was no significant improvement. Label claims for grapeleaf skeletonizer and for the leafrollers and leaffolder can be supported by extrapolation from pests with similar behaviour and feeding habits (winter moth and summer fruit tortrix, respectively) on apples and pears.

5.1.4 Pests of Hops (hop looper)

Efficacy data from a single trial conducted in Washington State were evaluated for hop looper on hops and support the label claim for hop looper with application rates of 500-1000 g/ha.

5.1.5 Pests of Tomato, Pepper and Eggplant (beet armyworm, cabbage looper, tobacco budworm, tomato fruitworm)

Efficacy data from total of 19 trials were evaluated for pests of fruiting vegetables, two for tomato fruitworm, eleven for cotton bollworm, two for unidentified species of *Helicoverpa*, three for beet armyworm and one for cotton leafworm. The trials were conducted on tomato, pepper and eggplant in France, Italy, Spain and the United States. These efficacy data support label claims for beet armyworm, tobacco budworm and tomato fruitworm based on the demonstrated efficacy against these and/or similar pests (cotton leafworm and cotton bollworm). A claim for cabbage looper can be extrapolated from the efficacy data for this pest on other vegetables. The trials also justify the application rates of 500-1000 g/ha, with various trials showing inferior results at a lower rate (250 g/ha), optimum results at 1000 g/ha and no improvement at a higher rate (1500 g/ha).

5.1.6 Pests of Leek (beet armyworm, leek moth)

Efficacy data from two trials conducted in France were evaluated for leek moth on leek and support the label claim for leek moth. Beet armyworm can be supported by extrapolation from other crops. Although the trials were too limited to demonstrate support for the application rates of 500-1000 g/ha, these rates are consistent with those for various pests on various other field crops.

5.1.7 Pests of Artichoke (beet armyworm, corn earworm)

Efficacy data from a total of three trials conducted in France and Spain were evaluated for pests of artichoke, one for cotton bollworm, one for silver Y moth and one for a mixture of those two species with a third species of Noctuidae. These efficacy data, combined with the data for the same and similar pests on various other crops, support the label claims for beet armyworm and corn earworm at the same application rates as on the other crops (900-1000 g/ha).

5.1.8 Pests of Canola (bertha armyworm, diamondback moth)

Efficacy data from two trials conducted in British Columbia were evaluated for diamondback moth on canola. Although the levels of control were not as high as on vegetable crops, the higher treatment threshold on canola allows the submitted efficacy data to support the label claim for diamondback moth on canola. The claim for bertha armyworm can be supported by extrapolation from cabbage moth, considering the similarity in feeding habits of these closely related species.

5.1.9 Pests of Greenhouse Tomato, Pepper and Eggplant (beet armyworm, cabbage looper, tobacco budworm, tomato fruitworm, tomato leafminer, tomato looper)

Efficacy data from total of ten trials were evaluated for pests of greenhouse fruiting vegetables, one for tomato leafminer, one for beet armyworm, five for tomato looper, one for cotton bollworm, one for cotton leafworm and one for unidentified species of Noctuidae. The trials were conducted on tomato, pepper, and eggplant in Belgium, France, Italy, Spain and The Netherlands. These efficacy data support label claims for beet armyworm, tobacco budworm and

tomato fruitworm, based on the demonstrated efficacy against these and/or similar pests (cotton leafworm and cotton bollworm) on greenhouse fruiting vegetables as well as various other crops, and for tomato leafminer and tomato looper. A claim for cabbage looper can be extrapolated from the efficacy data for this pest on other vegetables. Some of the trials also provide support for the application rates of 500-1000 g/ha, with inferior results at the lower rate tested (250 g/ha).

5.1.10 Pests of Greenhouse Cucumber (beet armyworm, cabbage looper, corn earworm, tomato looper)

Efficacy data from a single trial conducted in Spain were evaluated for beet armyworm on greenhouse cucumber. These efficacy data, combined with the data for these and similar pests on various other crops, support the label claims for beet armyworm, corn earworm and tomato looper. A claim for cabbage looper can be extrapolated from the efficacy data for this pest on other vegetables. The application rates of 500-1000 g/ha also are consistent with uses on other crops.

5.1.11 Pests of Greenhouse Lettuce (beet armyworm, cabbage looper, corn earworm, tomato looper)

Efficacy data from two trials conducted in Italy were evaluated for cotton leafworm on greenhouse lettuce. These efficacy data, combined with the data for these and similar pests on various other crops, support the label claims for beet armyworm, corn earworm and tomato looper. A claim for cabbage looper can be extrapolated from the efficacy data for this pest on other vegetables. The application rates of 500-1000 g/ha also are consistent with uses on other crops.

5.1.12 Pests of Greenhouse Beans (beet armyworm, cabbage looper, corn earworm, tomato looper)

Efficacy data from two trials conducted in Spain were evaluated for cotton bollworm on greenhouse beans. These efficacy data, combined with the data for these and similar pests on various other crops, support the label claims for beet armyworm, corn earworm and tomato looper. A claim for cabbage looper can be extrapolated from the efficacy data for this pest on other vegetables. The application rates of 500-1000 g/ha also are consistent with uses on other crops.

5.1.13 Pests of Greenhouse Ornamentals (beet armyworm, corn earworm, tomato looper)

Efficacy data from total of 13 trials were evaluated for pests of greenhouse ornamentals, three for beet armyworm, six for tomato looper and four for cotton bollworm. The trials were conducted on carnation, chrysanthemum, geranium, gerbera, hibiscus and rose in Spain and the Netherlands. These efficacy data, combined with the data for these and similar pests on other various crops, support the label claims for beet armyworm, corn earworm and tomato looper. In some of the trials on ornamentals, application rates as high as 500 g/ha provided inferior results, justifying the application rates of 750-1000 g/ha for this use.

5.2 Non-Safety Adverse Effects

The majority of the efficacy trials included assessments of non-safety adverse effects; no non-safety adverse effects were reported.

5.3 Consideration of Benefits

5.3.1 Social and Economic Impact

The label of XenTari Biological Insecticide Water Dispersible Granule registered in the United States indicates that the product is suitable for organic production, so it may provide an additional pest management tool for organic growers in Canada. Given that the product is registered in the United States, registration in Canada would reduce a technology gap for Canadian growers. XenTari has been identified in the Canadian Grower Priority Database as a high priority for 17 uses on greenhouse tomato, pepper, eggplant, cucumber, and lettuce, and the use pattern currently supported for registration in Canada includes six of those uses.

5.3.2 Survey of Alternatives

Availability of alternative insecticides varies depending on the pest and the crop, with several different alternative active ingredients available for most uses, particularly for major pests. Alternatives include active ingredients in Insecticide Resistance Action Committee mode-of-action groups 1A (carbaryl), 1B (organophosphates), 2A (endosulfan), 3A (pyrethroids), 4A (neonicotinoids), 5 (spinosyns), 11 (*Bacillus thuringiensis* subsp. *kurstaki*), 13 (chlorfenapyr), 15 (novaluron), 18 (diacylhydrazines) and 28 (anthranilic diamides) as well as unclassified active ingredients kaolin and sex pheromones. Diazinon and endosulfan, which are the only registered alternatives for cross-striped cabbageworm, are being phased out and some others are currently under re-evaluation (pyrethroids and neonicotinoids).

No registered alternatives are available for:

- Cankerworms and winter moth on pear.
- Grape leafroller, grapeleaf skeletonizer and omnivorous leafroller on grape.
- Tobacco budworm on fruiting vegetables.
- Beet armyworm on leek.
- Beet armyworm and corn earworm on artichoke.
- Beet armyworm, tomato fruitworm / corn earworm and tomato looper on greenhouse vegetables (except for one alternative for beet armyworm on greenhouse lettuce only and one for tomato looper on greenhouse cucumber only).
- Tomato looper on greenhouse ornamentals.

5.3.3 Compatibility with Current Management Practices Including Integrated Pest Management

XenTari WG Biological Insecticide is compatible with current management practices, being formulated for application by conventional ground equipment. It should be particularly well suited to integrated pest management because the active ingredient primarily affects larvae of Lepidoptera. Applied according to the label directions, it has relatively little effect on most non-target organisms, including some beneficial arthropods that may play a role in integrated pest management.

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

XenTari WG Biological Insecticide contains a new active ingredient that may be used in rotation with registered alternative active ingredients for resistance management. Because *Bacillus thuringiensis* produces a number of different protein toxins, it is less susceptible to resistance than conventional chemicals, although resistance to *B. thuringiensis*, including subspecies *aizawai*, has been reported. Although all subspecies and strains of *B. thuringiensis* are placed within the same mode-of-action group, they contain different combinations of protein toxins, which confer specificity to different insect groups and also limit the potential for cross-resistance. Even though *B. t. aizawai* and *B. t. kurstaki* are both specific to Lepidoptera, they do not contain the same combination of protein toxins.

Bacillus thuringiensis subsp. *aizawai* represents a completely new mode of action (that is, Insecticide Resistance Action Committee mode-of-action group 11) for:

- Cankerworms, codling moth, oriental fruit moth, tufted apple bud moth and winter moth on apple and pear.
- Cross-striped cabbageworm on Brassica vegetables.
- Grape leaffolder, grape leafroller, grape skeletonizer and omnivorous leafroller on grape.
- Beet armyworm and tabacco budworm on tomato.
- Beet armyworm, tobacco budworm and tomato fruitworm on pepper.
- Beet armyworm, cabbage looper, tobacco budworm and tomato fruitworm on eggplant.
- Beet armyworm and leek moth on leek.
- Beet armyworm and corn earworm on artichoke.
- Bertha armyworm and diamondback moth on canola.
- Beet armyworm, tobacco budworm, tomato fruitworm / corn earworm and tomato looper on greenhouse vegetables and ornamentals (except for tomato looper on greenhouse cucumber).

5.3.5 Contribution to Risk Reduction

For many of the supported uses, XenTari WG Biological Insecticide would provide an additional non-conventional alternative to conventional chemical insecticides, including active ingredients that are being phased out (diazinon and endosulfan).

5.4 Supported Uses

Supported uses include control of various pest Lepidoptera on apples, pears, broccoli, cabbage, cauliflower, Chinese cabbage, bok choy, Chinese broccoli, Asian radish, grape, hops, tomato, pepper, eggplant, leek, artichoke and canola and on greenhouse tomato, pepper, eggplant, cucumber, lettuce and beans and greenhouse ornamentals (see Table 3 in Appendix I). Application rates are the same for all uses (500-1000 g/ha) except for apples and pears (500-1600 g/ha) and greenhouse ornamentals (750-1000 g/ha).

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: in other words, 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*.

XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide were assessed in accordance with the PMRA Regulatory Directive DIR99-03[6] and evaluated against the Track I criteria. The PMRA has reached the following conclusions:

- XenTari Biological Insecticide Technical Powder does not meet the Track 1 criteria because the active ingredient is a biological organism and hence is 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] Regulatory Directive 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*[7]. The list is used as described in the PMRA Notice of Intent NOI2005-01[8] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[9] 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 ingredient, XenTari Biological Insecticide Technical Powder, 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 end-use product, XenTari WG Biological Insecticide, contains soy lecithin which is 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* as an allergen known to cause anaphylactic-type reactions. The label for XenTari WG Biological Insecticide will include the precautionary statement "WARNING - CONTAINS THE ALLERGEN SOY".

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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7 *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.*

8 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*.

9 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 product characterization data for XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide were judged to be adequate to assess their potential human health and environmental risks. The technical grade active ingredient was characterized and the specifications of the end-use product were supported by the analyses of a sufficient number of batches. Storage stability data were sufficient to support a shelf life of up to two years for the end-use product when stored at temperatures up to 25°C. No storage stability data were provided for the technical grade active ingredient. In the absence of storage stability data, the technical grade active ingredient can be stored at temperatures up to 25°C for a period of up to six months.

7.2 Human Health and Safety

The acute toxicity and infectivity studies and other relevant information submitted in support of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 were determined to be sufficiently complete to permit a decision on registration. Submitted information suggests XenTari Biological Insecticide Technical Powder to be of low toxicity and not pathogenic by the oral, pulmonary, intraperitoneal, intravenous, subcutaneous and dermal routes; and *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 was not infective via the oral, pulmonary and intravenous injection route of exposure in animals. Also, XenTari WG Biological Insecticide was low in toxicity via the oral, dermal and inhalation routes of exposure in animals. XenTari Biological Insecticide Technical Powder has the potential to irritate eyes. The signal words "WARNING-EYE IRRITANT" and "Causes eye irritation. DO NOT get in eyes" will appear on the technical grade active ingredient label. Both XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide are considered potential sensitizers such that "POTENTIAL SENSITIZER" is required on the principal display panel of both products.

XenTari WG Biological Insecticide contains soy lecithin which is an allergen known to cause anaphylactic type reactions. Therefore, the label for the end-use product will include the precautionary statements "WARNING: CONTAINS THE ALLERGEN SOY" on the principal display panel.

When handled according to prescribed label instructions, the potential for dermal, eye and inhalation exposure for mixer/loaders, applicators, and handlers exists, with the primary source of exposure to workers being dermal and to a lesser extent inhalation.

In individuals exposed to large quantities of XenTari WG Biological Insecticide, respiratory and dermal sensitivity could possibly develop upon repeated exposure to the product since all microorganisms, including *B. thuringiensis* subsp. *aizawai* strain ABTS-1857, contain substances that are potential sensitizers. Therefore, anyone handling or applying XenTari WG Biological Insecticide must wear waterproof gloves, long-sleeved shirts, long pants, a dust/mist filtering respirator/mask (NIOSH approval number prefix TC-21) or NIOSH approved respirators (with any N-95, P-95, R-95 or HE filter), and shoes plus socks.

The health risk to the general population, including infants and children, as a result of bystander exposure and/or chronic dietary exposure is expected to be minimal since XenTari WG biological Insecticide will only applied to commercial terrestrial food and feed crops, and greenhouse food and non-good crops. The product is not to be applied to residential or recreational areas. The establishment of an MRL is not required for *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 since residues of *B. thuringiensis* are exempt from the requirement of maximum residue limit (MRL; Section 4(d) of the *Food and Drugs Act*) as defined under Section B.15.002 of the Food and Drug Regulations.

7.3 Environmental Risk

The non-target organism tests, scientific rationales and supporting published scientific literature submitted in support of XenTari Technical Powder and XenTari WG Biological Insecticide were determined to be sufficiently complete to permit a decision on registration. The use of XenTari WG Biological Insecticide containing *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 is not expected to pose a risk to non-target organisms when the directions for use on the label are followed.

As a general precaution, the label will also prohibit the direct application of XenTari WG Biological Insecticide to aquatic habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs, and wetlands), estuaries or marine habitats, and direct handlers to not contaminate surface water by disposal of equipment wash waters. The product label also advises users that XenTari WG Biological Insecticide is toxic and/or pathogenic to bees, aquatic organisms and some beneficial insects that may be used in greenhouse integrated pest management programs. The statements will also instruct users to avoid direct contact to beneficial insects and to avoid applications when bees are actively foraging.

No other environmental fate studies or non-target organism studies are required to consider a decision on the registration of XenTari WG Biological Insecticide for use on greenhouse and field grown crops.

7.4 Value

XenTari WG Biological Insecticide has value for the control of various pests Lepidoptera on apples, pears, broccoli, cabbage, cauliflower, Chinese cabbage, bok choy, Chinese broccoli, Asian radish, grape, hops, tomato, pepper, eggplant, leek, artichoke and canola and on greenhouse tomato, pepper, eggplant, cucumber, lettuce and beans and greenhouse ornamentals. It provides an additional alternative active ingredient for many of those uses, including some for which older chemistries are being phased out, and a new pest management tool for some uses for which there are few or no other products currently registered. Specificity to larvae of Lepidoptera should make the product particularly well suited to integrated pest management and it may also be suitable for organic production. Registration of XenTari WG Biological Insecticide in Canada would help to bridge the technology gap with the United States and would address at least six high priorities listed in the Canadian Grower Priority Database.

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 XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide, containing the technical grade active ingredient *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857, to control many Lepidoptera larvae that are pests of various fruit, vegetable, oilseed and ornamental crops.

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

♀	female
♂	male
°C	degree(s) Celsius
µg	microgram(s)
µL	microliter(s)
µm	micrometre(s)
a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
Bt	*Bacillus thuringiensis*
bw	body weight
CFU	colony forming units
EC_{50}	effective concentration on 50% of the population
g	gram(s)
ha	hectare(s)
IV	intravenous
kg	kilogram
L	litre(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOEC	lowest observed effect concentration
LOEL	lowest observed effect level
MAS	maximum average score
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
mm	millimetre(s)
MPCA	microbial pest control agent
MRL	maximum residue limit
NIOSH	National Institute for Occupational Safety and Health
NOEC	no observed effect concentration
NOEL	no observed effect level
PMRA	Pest Management Regulatory Agency
ppm	parts per million
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
subsp.	subspecies
TSMP	Toxic Substances Management Policy
v/v	volume per volume dilution
WG	Water-dispersible Granules
w/v	weight per volume
w/w	weight per weight

Appendix I Tables

Table 1 Toxicity and Infectivity of XenTari Biological Insecticide Technical Powder and its associated End-Use Product, XenTari WG Biological Insecticide

Study Type	Species, Strain, and Doses	Results	Comments	Reference(s)
Acute Toxicity/Infectivity of XenTari Biological Insecticide Technical Powder				
Acute Oral Infectivity and Toxicity (29-Day study)	Rat - Sprague-Dawley 18/sex, single oral dose, 7.9×10^7 CFU/animal, interim sacrifices on Days 1, 3,7,14, 21 and 29 Body weight measured on Days 1 (prior to dosing), 4, 8, 15, 22 and 29	$LD_{50} > 7.9\times10^7$ CFU/animal	There were no mortalities and no treatment related clinical signs throughout the study period. Total clearance achieved by Day 15. **LOW TOXICITY, NOT INFECTIVE** **ACCEPTABLE**	2259562
Acute Pulmonary Infectivity and Toxicity (50-Day study)	Rat - Crl:CD^R 23/sex, 1.2 mL suspension in sterile purified water/ kg bw ($1.65–1.92\times10^8$ CFU/animal), interim sacrifices on Days 1,4, 8, 15, 22, 36, and 50 7/sex, untreated, interim sacrifices Days 1, 4, 15, 22, 36, 50. 2/sex, untreated control, housed in same room as treated. 2/sex, untreated control, separate room from treated. Body weight measured on Days 1, 4, 8, 15, 22, 36 and 50.	$LD_{50} > 1.65\times10^8$ CFU/animal	There were no mortalities. There were no treatment related clinical signs, necropsy findings or changes in body weight. Clearance achieved by Day 7 for all organs, except lungs where clearance achieved by Day 35. **LOW TOXICITY, NOT INFECTIVE** **ACCEPTABLE**	2259564

Study Type	Species, Strain, and Doses	Results	Comments	Reference(s)
Acute Intravenous Infectivity (66-Day study)	Rat - CD 21/sex, intravenous injection, 1.03–1.18×10^7 CFU/animal); interim sacrifices on Days 1, 4, 8, 15, 22, 36, and 67. Untreated control: (6 ♀; 6 ♂) Untreated control (housed in separate room from treated: (2 ♀; 2 ♂) Body weights measured on Days 0, 7, 14 and 21	$LD_{50} > 1.18\times10^7$ CFU/animal	No mortalities or effect on bodyweight gain, and no clinical signs of treatment-related toxicity, infectivity or pathogenicity. No necropsy findings. Pattern of clearance achieved. **LOW TOXICITY, NOT INFECTIVE** **ACCEPTABLE**	2259567
Intraperitoneal Infectivity (4-Day study)	Mouse – CF1 5/sex/group, single dose of 0.2 mL in peritoneal cavity: 1×10^6, 1×10^7 or 1×10^8 CFU/animal	$LD_{50} > 1\times10^8$ CFU/animal	No mortalities, no signs of toxicity. Infectivity was not assessed. **LOW TOXICITY** **ACCEPTABLE but of LIMITED UTILITY**	2259566
Subcutaneous Infectivity (7-Day study)	Mouse – CF1 5/sex/group, single dose of 0.25 mL in peritoneal cavity: 1.35×10^7 CFU/animal	$LD_{50} > 1.35\times10^7$ CFU/animal	No mortalities, no signs of toxicity. Infectivity was not assessed. **LOW TOXICITY** **ACCEPTABLE but of LIMITED UTILITY**	2259566

Study Type	Species, Strain, and Doses	Results	Comments	Reference(s)
Acute Dermal Toxicity (14-Day study)	Rabbit- New Zealand 5/sex, 24 hour dermal exposure, 5050 mg/kg bw (3.1×10^{11} CFU/kg bw) Dermal irritation observed on Day 0, 4, 7, 10 and 14. Body weight measured on Days 0, 7 and 14	LD_{50}> 5050 mg/kg bw	There were no mortalities, treatment related clinical signs, necropsy findings or changes in body weight **LOW TOXICITY** **ACCEPTABLE**	2259568
Acute Inhalation Toxicity (14-Day study)	Rat - Sprague-Dawley 5/sex, 4 hour nose-only exposure, 5.312–5.521 mg/L (7.3×10^{10} CFU/g of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857) Body weight measured on Days 0, 7 and 14	LC_{50} > 5.33 mg/L	Treated animals showed decrease in activity and piloerection, but were asymptomatic by Day 1. There were no treatment related necropsy findings or changes in body weight. **LOW TOXICITY** **ACCEPTABLE**	2259565
Acute Oral Toxicity (14-Day study)	Rat – Harlan Sprague-Dawley 5/sex, single oral dose, 5050 mg/kg bw, sacrifices and necropsies on final day Body weight measured Days 0, 7, and 14	LD_{50} > 5050 mg/kg bw	There were no mortalities. Clinical signs included piloerection, decreased activity, diarrhea, crust around eyes, nose and mouth, respiratory gurgle, and staining around muzzle. Animals were asymptomatic by Day 6. **SLIGHT TOXICITY** **ACCEPTABLE for Toxicity only**	2259563
Genotoxic Potential	*Salmonella - Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay 10–200 µL dimethyl sulfoxide extract of	No significant increase in the number of revertants above the background rate of spontaneous mutations of	**ACCEPTABLE**	2259572

Study Type	Species, Strain, and Doses	Results	Comments	Reference(s)
	XenTari Biological Insecticide Technical Powder	any of the tester strains.		
Genotoxic Potential	The registrant submitted a scientific rationale for genotoxic studies based on the appropriateness of the standard assays for testing micro-organisms. The guidelines currently in place for genotoxicity testing have been developed to test chemicals. The physicochemical properties of a substance can sometimes make standard test conditions inappropriate, especially when microbial organisms are to be tested. The reviewer found the rationale acceptable, but notes that genotoxic studies were not required as *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 is not known to produce metabolites with genotoxic potential.			2259574
Acute Irritation/Sensitization of XenTari Biological Insecticide Technical Powder				
Dermal Irritation	Rabbit-New Zealand white 3/sex, 4-hour dermal exposure, 500 mg/animal (containing 6.15×10^{10} CFU/g of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857) Observed for 3 days	Maximum irritation score (MIS)=0.33/8 at 1 hour	Very slight erythema was present in two females at 1 hour and one female at 24 hours. No edema. **MINIMALLY IRRITATING** **ACCEPTABLE**	2259569
Eye Irritation	Rabbit-New Zealand white 6 ♂; 6 ♀, 24-hour ocular exposure, 50.4 mg/animal (containing 6.15×10^{10} CFU/g) 3 ♂; 3 ♀, 30 second ocular exposure, 50.4 mg/animal (containing 6.15×10^{10} CFU/g) Observed for 21 days	Maximum average score (MAS)= 19.4/110 at 24, 48 and 72 hours MIS= 22.5/110 at 24 hours Irritation was not reversible in one animal until Day 21	Conjunctival redness, chemosis and discharge was observed in all animals (1 hour). At 24 hours, corneal opacity was observed in three of the treated animals. Signs of ocular irritation subsided by Day 17 in all animals except for one by Day 21. **MODERATELY IRRITATING** **ACCEPTABLE** **"WARNING- EYE IRRITANT"** and "Causes eye irritation. Do not get in eyes" required on principal and secondary display panels, respectively.	2259570

Study Type	Species, Strain, and Doses	Results	Comments	Reference(s)
Dermal Sensitization (29-Day study)	Guinea Pig – Hartley-Albino 5/sex induced and challenged Induction: Days 1, 8, 15 Topical applications of 400 mg in water Challenge: Topical application of 400 mg in water on Day 29 Dermal reactions were made approximately 24 hours after each treatment and also 48 hours after the first induction treatment and 48 hours after the challenge treatment.	Negative	There were no signs of erythema in any of the treated test animals after any of the challenge treatments. **NOT A SENSITIZER** **ACCEPTABLE** Note: PMRA assumes that all microorganisms contain substances that can elicit positive hypersensitivity reactions regardless of the outcome of sensitization testing. Therefore the label statement, "POTENTIAL SENSITIZER" should appear on the primary display panel.	2259571
Acute Irritation/Sensitization of XenTari WG Biological Insecticide				
Dermal Irritation	Rabbit-New Zealand white 3/sex, 4-hour dermal exposure, 0.5 g/animal in 0.5 mL deionized water (containing 2×10^{10} spores/g *B. thuringiensis* subsp. *aizawai* strain ABTS-1857) Observed for 8 days	MIS=1.33/8 At 1 hour	Very slight to well defined erythema initially observed, dissipated by Day 7. No signs of erythema in any rabbits. No edema or other dermal effects were observed throughout the study. **SLIGHTLY IRRITATING** **ACCEPTABLE**	2259702

Study Type	Species, Strain, and Doses	Results	Comments	Reference(s)
Eye Irritation	Rabbit-New Zealand white 3/sex, instilled in right eye, 0.09 g/animal in 0.5 mL deionized water (containing 2×10^{10} spores/g *B. thuringiensis* subsp. *aizawai* strain ABTS-1857), unwashed 2 ♂;1 ♀ same as above except treated eye was washed 30 seconds after instillation Observed for 14 days	MIS= 12.3/110 at 1 hour	All rabbits showed conjunctival irritation by the one-hour interval. Minimal conjunctival redness persisted in two rabbits in the unwashed group through Day 10, and in one rabbit in the washed group through Day 7. Iridal hyperemia at one hour, lackluster of the cornea at 24 hours in one rabbit, conjunctival blistering, conjunctival petechial hemorrhage, purulent discharge and yellow crusting around edges of eyelid, and were noted up to 72 hours. No ocular effects were observed in any of the rabbits on Day 14 of the study. **MILDLY IRRITATING** **ACCEPTABLE** **"CAUTION- EYE IRRITANT"** and "May irritate eyes. Avoid contact with eyes" required on principal and secondary display panels, respectively.	2259703
Skin Sensitization	Guinea Pig-Hartley 20/male, 2 induction treatments (1 week intervals, 0.1 mL intradermal injections, 0.5 g topical application) followed by challenge treatment (2 weeks after last induction), 0.25 g/animal. 20/male, control, challenge only. Irritation was assessed 24, 45 and 72 hours	No evidence of skin sensitization	There was no dermal irritation noted after challenge treatments. **NEGATIVE FOR SKIN SENSITIZATION** **ACCEPTABLE**	2259704

Study Type	Species, Strain, and Doses	Results	Comments	Reference(s)
	after challenge treatments.			
Acute Toxicity of XenTari WG Biological Insecticide				
Acute Oral Infectivity and Toxicity (14-Day study)	Rat- Sprague-Dawley 5/sex, single oral dose 5000 mg/kg bw (1.3–1.4×10^{11} CFU/animal); no interim sacrifices performed; microbial enumeration on feces only throughout study Body weight measured on Days 0, 7, 14, 21 and 26.	LD_{50}> 5000 mg/kg bw (1.3–1.4×10^{11} CFU/animal)	No treatment related clinical signs, necropsy findings or changes in body weight. **LOW TOXICITY,** **ACCEPTABLE for toxicity only**	2259698
Acute Dermal Toxicity (14-Day study)	Rabbit- New Zealand White 5/sex, 24-hour dermal exposure (area of 10%), 2000 mg/kg bw (containing 2×10^{10} spores/g) Body weight measured on Days 0, 7 and 14	LD_{50}> 2000 mg/kg bw	There were no mortalities. There were no treatment-related clinical signs of toxicity, necropsy findings or changes in body weight. **LOW TOXICITY** **ACCEPTABLE**	2259701
Acute Inhalation Toxicity (14-Day study)	Rat- Sprague-Dawley 5/sex, 4-hour nose-only exposure, 5.05–5.28 mg/L (54% w/w) Body weight measured on Days 0, 7 and 14	LC_{50} > 5.10 mg/L	There were no mortalities. Body weight gain, was observed by Day 3 until the end of the 14-day observation period. Irregular respiration was seen initially, but rats were asymptomatic by Day 4 and were active and healthy for the remaining study period. **LOW TOXICITY** **ACCEPTABLE**	2259700

Study Type	Species, Strain, and Doses	Results	Comments	Reference(s)
Acute Inhalation Toxicity (14-Day study)	Rat- HSD:SD 5/sex, 4-hour nose-only exposure, 3.05 mg/L (5.1×10^{10} CFU/g) Body weight measured on Days 0, 7 and 14	LC_{50} > 3.05 mg/L	There were no mortalities. Rats showed in-life signs including decrease activity, lacrimation, nasal discharge, piloerection, polyuria and salivation only on day of dosing. Body weight gains occurred throughout study period. **LOW TOXICITY** **ACCEPTABLE**	2259699

Table 2 Toxicity to Non-Target Species

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
Terrestrial Organisms				
		Vertebrates		
Birds	Oral – *Anas platyrhynchos*, 21-day old	Six replicates of birds (5/replicate) were gavaged with XenTari Biological Insecticide Technical Powder at a dose of 1714 mg/kg bw (3.4×10^{11} CFU/kg bw) for 5 consecutive days. Two replicates of birds (5/replicate) were gavaged with distilled water at a dose of 10 mL/kg bw (negative control). Birds were observed for 30 days.	There were no treatment-related mortalities or effects on body weight and behaviour. At necropsy, there were no treatment-related findings. 30-day acute oral LD_{50} was > 1714 mL (3.4×10^{11} CFU)/kg bw per day for five days. 30-day NOEL (no observed effect level) was > 1714 mL (3.4×10^{11} CFU)/kg bw per day for five days.	2259587
	Oral – *Anas platyrhynchos*, 21-day old	Six replicates of birds (5/replicate) were gavaged with XenTari Biological Insecticide Technical Powder at a dose of 1714 mg/kg bw (3.4×10^{11} CFU/kg bw) for 5 consecutive days.	There were no treatment-related mortalities or effects on body weight and behaviour. At necropsy, there were no treatment-related findings. 30-day acute oral LD_{50} was >	2259586

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		Two replicates of birds (5/replicate) were gavaged with distilled water at a dose of 10 mL/kg bw (negative control). Birds were observed for 30 days.	1714 mL (3.4×10^{11} CFU)/kg bw per day for five days. 30-day NOEL was > 1714 mL (3.4×10^{11} CFU)/kg bw per day for five days.	
	Pulmonary	Although a request to waive the requirement for test data was not submitted. No adverse effects were observed in the avian acute oral toxicity/pathogenicity study and no reports of adverse effects were found in published scientific literature. The requirement for avian pulmonary testing has been waived.		
Wild Mammals	From the data submitted under the Part M4 Human Health and Safety Testing, it was determined that XenTari Biological Insecticide Technical Powder was not toxic or pathogenic to mammals via the oral, pulmonary, dermal, intravenous or intraperitoneal routes. No further data are required to assess the risk of harm to non-target wild mammals.			
Invertebrates				
Arthropods				
Terrestrial Arthropods	Dietary – *Apis mellifera*, one-week old adult	Three trials, each with three replicates (28 – 62 bees/replicate), were fed XenTari Biological Insecticide Technical Powder (2.0×10^{11} CFU/g) in a 1:1 v/v honey and water solution at 1000, 100, 10, and 1 ppm. Three trials each with three replicates (28 – 69 bees/replicate) were fed 1:1 honey and water solution (negative control). Diets were renewed and consumption measured every 24 hours. Trial 1, 2, and 3 were observed for 12, 11 and 9 days respectively.	There were no differences in feed consumption between treatment groups and negative control. Percent mortality in the 1000, 100, 10, and 1 ppm and negative control groups was 94, 61, 32, 15 and 27 in the 9-day trial; 100, 85, 47, 34, and 21 in the 11-day trial; and 98, 21, 33, 28 and 20 in the 12-day trial, respectively. The NOEL was 0.051 µg/bee/day. The LOEL (lowest observed effect level) was 0.49 µg/bee/day. **TOXIC AND/OR PATHOGENIC**	2259602
	Field – *Apis mellifera*, colony	5 hives (10 frames/hive) were	Mean percent change in population was -70.4 in the	2259710

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		opened, frames removed and all surfaces spayed with 0.2084 g of XenTari WG Biological Insecticide (3.55×10^{10} CFU/g) in deionized water once per week for 4 weeks. 5 hives (10 frames/hive) were opened, frames removed and all surfaces spayed with deionized water once per week for 4 weeks (negative control). Population and hive weight were measured at the beginning and after 4 weeks.	treated hives and -68.1 in the negative control. Mean percent change in hive weight was 16.6 in the treated hives and 21.2 in the negative control. No statistically significant differences in population or hive weight between the treated and negative control hives were observed in the test hives. However, adverse effects could not be evaluated due to the lack of statistical power of the study.	
	Dietary – *Chrysoperla rufilabris*, larvae	A group of larvae (100) was sprayed (including test chambers) with XenTari Biological Insecticide Technical Powder (2.0×10^{11} CFU/g) at rates of 0.239 g/L, 2.39 g/L, and 23.9 g/L. Another group of larvae (100) was sprayed with water only (including test chambers) (Negative Control). Larvae were observed for mortality for 7 days; percent (including mean number of days) to reach pupation; percent to survive to adulthood; and mean number of eggs laid and percent egg hatch.	Percent larval mortality in the negative control, 0.239, 2.39 and 23.9 g/L groups was 5, 5, 17 and 61 respectively on Day 7. Percent to reach pupation in the negative control, 0.239, 2.39 and 23.9 g/L groups was 84, 80, 69 and 18 respectively. Percent to reach adulthood in the negative control, 0.239, 2.39 and 23.9 g/L groups was 61, 59, 52, and 14 respectively. No other treatment related effects were observed. **TOXIC AND/OR PATHOGENIC**	2259611

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
	Dietary – *Hippodamia convergens*, adults	Two replicates (25/replicate) were fed XenTari Biological Insecticide Technical Powder (6.2×10^{10} CFU/g) in a honey diet at 1500, 3000, or 6000 ppm Two replicates (25/replicate) were fed honey diet (negative control). Diets were renewed weekly. Beetles were observed mortality, immobility and lethargy over a period of 27 days.	There were no significant differences in mortality, immobility or lethargy observed.	2259610
	Contact – *Metaseiulus occidentalis*, and *Tetranychus urticae*	Test i) Twelve replicates (6/replicate) of gravid *M. occidentalis* adult females were sprayed with XenTari Biological Insecticide Technical Powder (2.0×10^{11} CFU/g) at rates of 0.239 g/L, 2.39 g/L, and 23.9 g/L. Twelve replicates (6/replicate) of gravid *M. occidentalis* adult females were sprayed with water (negative control). Mortality was observed for 7 days and number of eggs laid for 5 days.	Test i) Gravid female *M. occidentalis* percent mortality was 25.7, 32.9, 43.9, an 11.8 for the 0.239 g/L, 2.39 g/L, 23.9 g/L, and negative control, respectively. There were no treatment related differences in the number of eggs laid.	2259605
		Test ii) Twelve replicates (3/replicate) of *M. occidentalis* eggs were placed on bean leaves with *T. urticae* prey and sprayed with XenTari Biological	Test ii) There were no treatment related differences in egg hatch, survival to adulthood, and male:female ratio.	2259605

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		Insecticide Technical Powder (2.0×10^{11} CFU/g) at rates of 0.239 g/L, 2.39 g/L, and 23.9 g/L. Twelve replicates (6/replicate) of gravid *M. occidentalis* eggs placed on bean leaves with *T. urticae* prey and sprayed with XenTari Biological Insecticide Technical Powder (2.0×10^{11} CFU/g) (negative control). Observations for egg hatch, survival to adulthood, and male:female ratio were made.		
		Test iii) Twelve replicates (3/replicate) each of gravid female, protonymph *T. urticae*; and 12 replicates (# eggs laid by 4 – 5 gravid females/ replicate) of *T. urticae* were sprayed with XenTari Biological Insecticide Technical Powder (2.0×10^{11} CFU/g) at rates of 0.239 g/L, 2.39 g/L, and 23.9 g/L. Twelve replicates (3/replicate) each of gravid female, protonymph *T. urticae*; and 12 replicates (# eggs laid by 4 – 5 gravid females/ replicate) of *T. urticae* were sprayed with water (negative Control).	Test iii) Gravid female *T. urticae* percent mortality was 20.1, 6.9, 69.5, and 11.7 for the 0.239 g/L, 2.39 g/L, 23.9 g/L, and negative control, respectively. Protonymph *T. urticae* percent mortality was 25.0, 26.9, 82.7, and 5.5 for the 0.239 g/L, 2.39 g/L, 23.9 g/L, and negative control, respectively. There were no treatment related differences in egg hatch. **TOXIC AND/OR PATHOGENIC**	2259605

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		Gravid female and protonymph were observed for mortality and eggs were observed for successful hatching for 8 days.		
Non-arthropods				
Terrestrial Non-Arthropod Invertebrates	Contact – *Esisenia fetida*	Four replicates (10/per replicate) of *E. fetida* were exposed to XenTari Biological Insecticide Technical Powder in soil at 1000 mg a.i./g dry soil for 30 days. Four replicates (10/per replicate) of *E. fetida* were exposed to untreated soil for 30 days. Worms were observed for mortality, behaviour and body weight.	There were no mortalities or signs of abnormal behaviour. There were no treatment related differences in body weight.	2259619
Plants				
Plants	A request to waive the requirement for test data was submitted. There is a lack of reports of negative effects on plants from decades of use in agriculture. Also, the efficacy studies presented on numerous plants contains a section on phytotoxicity showing no effects on vegetation. No further data are required to address the hazard of *B. thuringiensis* subspecies *aizawai* strain ABTS-1857 to terrestrial plants.			2328460
Microorganisms				
Micro-organisms	A request to waive the requirement for test data was not submitted. No further data are required to assess the risk of harm to microorganisms.			

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
Aquatic Organisms				
		Vertebrates		
Fish	Aqueous– *Oncorhynchus mykiss*, juveniles, static renewal	Thirty fish (10 per replicate) were exposed to XenTari Biological Insecticide Technical Powder in dilution water at 100 mg/L. A group of 30 fish remained untreated (Negative Control). Test suspensions were renewed daily. Fish were observed daily for 96 hours.	There were no mortalities or signs of toxicity noted throughout the study period. No observable findings at necropsy. Pathogenicity and infectivity were not assessed. 96-hour LC_{50} > 100 mg/L (6.3×10^6 viable spores per mL).	2259588
	Aqueous and Dietary – *Oncorhynchus mykiss*, juveniles, static renewal	Thirty fish (10 per replicate) were exposed to XenTari Biological Insecticide Technical Powder in dilution water and the feed at 5.54×10^7 CFU/mL and 1.47×10^{10} CFU/g of food respectively. Another group of 30 fish remained untreated (Negative Control). Test suspensions were renewed every 3 days. Treated feed was prepared on Day 0 then refrigerated for entire study period. Fish were observed daily until Day 20.	Mortality of 77% was observed among treated fish. An increase in turbidity of approximately 160X was noted in the treated group versus the control. There was an increase in incidence and severity of gill changes (fusion of gill lamellae and hyperplasia of gill epithelium) reported for the treated group vs the controls. There was no evidence of infectivity or pathogenicity from tissues examined histopathologically. 20-day LC_{50} was 5.4×10^7 viable spores/mL	2259589
	Aqueous and Dietary – *Oncorhynchus mykiss*, juveniles, static renewal	Thirty Fish (10 per replicate) were exposed to XenTari Biological Insecticide Technical Powder in dilution water and the feed at mean adjusted nominal concentrations of 13, 61, 110, 240, 320, 370	Turbidity was observed in aquaria of all treated groups and was directly proportional to the concentration of test substance. Mortality (60–70%) among fish exposed to 370 and 440 mg/L was reported.	2259590

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		and 440 mg/L and 1.47×10^8 CFU/g of food, respectively. In addition a group (10) were was exposed to irradiated test substance at 460 mg/L Another group of 30 fish remained untreated (Negative Control). Test suspensions were renewed every 3 days. Treated feed was prepared on Day 0 then refrigerated for entire study period. Fish were observed daily until Day 20.	Mortality of 90% was reported for fish exposed to the attenuated control. Observed mortalities were likely due to high turbidity of the test solution rather than to toxicity of the test substance. 30-day LC_{50} was 310 mg/L or 3.2×10^7 CFU/mL	
Invertebrates				
Aquatic Arthropods	Aqueous – *Daphnia magna*, <24 hours old, static renewal	Four groups (5/group) were exposed to XenTari Biological Insecticide Technical Powder in dilution water at 0.5, 5 and 74 mg/L. Seven groups of daphnids were also exposed individually to the same concentrations. Similarly a group of daphnids (27) remained untreated (Negative Control). Test suspensions were renewed on Days 2, 4, 7, 9, 12, 14, 16, and 18 Daphnia were observed daily for 21 days.	There was 100% mortality for the 74 mg/L group by Day 6 when housed individually and by Day 7 when housed in a group. For individuals housed in groups, mortality was 5, 0 and 20 % in control and 0.5 and 5 mg/L groups respectively. Pathogenicity and infectivity were not assessed. The 21-day NOEC (no observed effect concentration) and LOEC (lowest observed effect concentration), based on number of young produced and dry weight of first generation were 0.5 mg/L (4×10^8 CFU/L) and 5.0 mg/L (4×10^9 CFU/L) respectively **TOXIC**	2259594

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
	Aqueous – *Daphnia magna*, <24 hours old, static renewal	Seven groups (20/group) of daphnids were exposed to XenTari Biological Insecticide Technical Powder in dilution water at 1.1, 2.0, 3.4, 5.9, 10, 20 and 34 mg/L. Negative control with 20 daphnids in untreated test culture. Test suspensions were renewed every 48 hours. Observed daily for mortality for 10 days.	Mortality in the 10, 20 and 34 mg/L was 30, 95 and 100%, respectively. Pathogenicity and infectivity were not assessed. 10-day LC_{50} 12 mg/L	2259591
Aquatic Non-Arthropod Invertebrates	A request to waive the requirement for test data was submitted. The rationale was based on the lack of adverse effects in the published literature. A search in the PubMed database using the keywords "Bacillus" or "thuringiensis" found no reports of adverse effects to any aquatic non-arthropod invertebrates. No further data are required to address the hazard of ***B. thuringiensis*** subsp. *aizawai* strain ABTS-1857 to aquatic non-arthropod invertebrates.			2328454
Plants				
Aquatic Plants	Aqueous – *Selenastrum capricornutum* static	Three replicates (300 mL culture flasks with 10^4 cells/mL) were exposed to XenTari WG Biological Insecticide at 10, 20, 40 80 160 and 320 mg/L. Untreated flasks served as the negative control. Plates were incubated for 72 hours at 23±2°C, 24 hour light/0 hour dark (8000 lux ±20% light intensity).	Pathogenicity and infectivity were not assessed. The study reported algal cells were partly deformed or swollen after 48 hours for the 40, 80 and 160 mg/L in treated groups. The highest treatment group (320 mg/L) reported swollen cells after 24 hours. EC_{50} (Growth): 275mg/L EC_{50} (Biomass): 119mg/L	2259713

Table 3 List of Supported Uses

Crop	Pest	Rate (g/ha)
Apples Pears	Cankerworms Codling moth Fruittree leafroller Obliquebanded leafroller Oriental fruit moth Redbanded leafroller Tufted apple bud moth Variegated leafroller Winter moth	500–1600
Broccoli Cabbage Cauliflower Chinese cabbage Bok choy Chinese broccoli Asian radish	Cabbage looper Cross-striped cabbageworm Diamondback moth Imported cabbageworm	500–1000
Grape	Grape berry moth Grape leaffolder Grape leafroller Grapeleaf skeletonizer Obliquebanded leafroller Omnivorous leafroller	500–1000
Hops	Hop looper	500–1000
Fruiting Vegetables Tomato Pepper Eggplant	Beet armyworm Cabbage looper Tobacco budworm Tomato fruitworm	500–1000
Leek	Beet armyworm Leek moth	500–1000
Artichoke	Beet armyworm Corn earworm	500–1000
Canola	Bertha armyworm Diamondback moth	500–1000
Greenhouse Uses		
Fruiting Vegetables Tomato Pepper Eggplant	Beet armyworm Cabbage looper Tobacco budworm Tomato fruitworm Tomato leafminer Tomato looper	500–1000

Crop	Pest	Rate (g/ha)
Cucumber Lettuce Beans	Beet armyworm Cabbage looper Corn earworm Tomato looper	500–1000
Ornamentals Carnation Chrysanthemum Geranium Gerbera Hibiscus Kalanchoe Rose	Corn earworm Beet armyworm Tomato looper	750–1000

References

A. List of Studies/Information Submitted by Registrant

1.0 The Active Substance, its Properties and Uses

PMRA Document Number	Reference
2259536	2005, *Bacillus thuringiensis* subsp. *aizawai*, Strain ABTS-1857 - OECD Document J, DACO: M2.0, M2.2 CBI
2259537	1990, Microbial characterization of ABG-6305 production strain, DACO: M2.7 CBI
2259538	1996, Rationale for considering XenTari strain an *aizawai* subspecies of *Bacillus thuringiensis*, DACO: M2.7 CBI
2259540	2005, Method of production and quality control for XenTari products (*Bacillus thuringiensis* subsp. *aizawai*), DACO: M2.7, M2.8, M2.9, M2.9.3 CBI
2259541	2005, Genetic comparison of *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 to other *Bacillus* strains using AFLP, DACO: M2.7 CBI
2259543	2005, *Bacillus thuringiensis* subsp. *aizawai*, Strain ABTS-2857: Lack of metabolites of concern. Expert review for EU Dossier, DACO: M2.7.2 CBI
2259544	1990, Quantitation of active ingredient ABG-6305 technical powder by SDS-PAGE, DACO: M2.10.1 CBI
2259545	1990, ABG-6305 technical powder: Product chemistry of ABG-6305 technical powder, DACO: M2.7, M2.8, M2.9, M2.9.3 CBI
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