Proposed Registration Decision PRD2011-06

Lactobacillus casei strain LPT-111

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Overview

Proposed Registration Decision for *Lactobacillus casei* strain LPT-111

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 *Lactobacillus casei* Technical, Lacto-San-D and Lacto-San, containing the microbial pest control agent *Lactobacillus casei* strain LPT-111, to suppress various foliar diseases on field and greenhouse crops including roses, tomatoes, strawberries, cucumbers, grapes, squashes and pumpkins.

Lactobacillus casei Technical (Registration Number 29599) has full registration in Canada. The original detailed review for *Lactobacillus casei* strain LPT-111 can be found in the Proposed Registration Decision PRD2010-09, *Lactobacillus casei* strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strain LL64/CSL, *Lactococcus lactis* ssp. *lactis* strain LL102/CSL and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, as well as in the Registration Decision RD2010-10, *Lactobacillus casei* strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strain LL64/CSL, *Lactococcus lactis* ssp. *lactis* strain LL102/CSL and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL. The current applications represent major new uses for *Lactobacillus casei* strain LPT-111 in Canada.

An evaluation of available scientific information found that, under the approved conditions of use, the products have value and do 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 *Lactobacillus casei* Technical, Lacto-San-D and Lacto-San.

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 PMRA's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on *Lactobacillus casei* strain LPT-111, 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 *Lactobacillus casei* strain LPT-111, 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 *Lactobacillus casei* strain LPT-111?

Lactobacillus casei strain LPT-111 is a microbial pest control agent (MPCA) currently used as a commercial herbicide. Citric acid and lactic acid are organic acids that are fermentation products of the MPCA, and act as the active ingredients in two new end-use products, namely: Lacto-San and Lacto-San-D.

Lacto-San is a commercial product, while Lacto-San-D is a domestic product. Both products are used as bactericides/fungicides against various diseases (i.e. powdery mildew, downy mildew, bacterial cankers, black spot, and angular leaf spot) on a variety of outdoor and greenhouse crops, and ornamental roses. Lacto-San and Lacto-San-D have a low pH (~4.1). The citric and lactic acids produced during fermentation by *Lactobacillus casei* strain LPT-111 penetrate into the pathogen cell and disrupt cell homeostasis.

Health Considerations

Can Approved Uses of *Lactobacillus casei* strain LPT-111 and It's Fermentation Products, Citric Acid and Lactic Acid, Affect Human Health?

***Lactobacillus casei* strain LPT-111, and it's fermentation products citric acid and lactic acid, are unlikely to affect your health when Lacto-San and Lacto-San-D are used according to the label directions.**

People can be exposed to citric acid and lactic acid and the *Lactobacillus casei* strain LPT-111 when handling and applying Lacto-San and Lacto-San-D and when ingesting treated produce. When assessing the health risks associated with microbial active ingredients, several key factors

[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*.

are considered, such as: a microorganism's biological properties (for example, production of toxic byproducts), reports of any adverse incidents, 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.

For biochemical actives, the levels where no health effects occur and the levels to which people may be exposed are also considered. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no adverse effects in animal testing are considered acceptable for registration.

Lactobacillus casei strain LPT-111 used in the manufacture of Lacto-San and Lacto-San-D, and the subsequent fermentation products (i.e. the organic acids), are already occurring in the food chain for human consumption at similar levels to those found in Lacto-San and Lacto-San-D. In addition, there have been relatively few reports of infection or adverse effects despite their ubiquity.

The active ingredients/fermentation products, citric and lactic acid, are of low acute toxicity by the oral route. Lactic acid is also of low acute toxicity via the dermal route; however, both lactic and citric acid are slightly irritating to the skin. Eye irritation studies indicated that, at the concentrations found in Lacto-San and Lacto-San-D, citric and lactic acid are capable of producing moderate to severe injury to the eye, particularly with repeated or prolonged exposure. Appropriate label statements and requirements for basic personal protective equipment will minimize exposure for individuals with repeated or prolonged exposure.

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 the food Canadians eat is safe.

Lactobacillus casei strain LPT-111 is a strain of bacterium commonly used in the food industry to produce dairy products such as cheese and yogurt, and citric acid and lactic acid are naturally found in fruit as well as used as additives in beverages such as soft drinks. The levels of the MPCA and these organic acids that would result on food crops from the proposed use of Lacto-San and Lacto-San-D are expected to be much lower than levels already consumed in the Canadian diet from other sources. Therefore, the establishment of a maximum residue limit is not required for *Lactobacillus casei* strain LPT-111. As well, the likelihood of residues contaminating drinking water supplies is negligible to non-existent. Consequently, dietary risks are minimal to non-existent.

Occupational Risks From Handling Lacto-San and Lacto-San-D

Occupational risks are not of concern when Lacto-San and Lacto-San-D are used according to label directions, which include protective measures.

Workers using Lacto-San and Lacto-San-D can come into direct contact with *Lactobacillus casei* strain LPT-111, citric and lactic acid via the skin, in the eyes, or by inhalation. For this reason, the label will specify that commercial users exposed to Lacto-San must wear waterproof gloves, eye goggles, long-sleeved shirts, long pants, and shoes plus socks. Users are also directed to avoid inhaling the product and its mists. To reduce early-entry worker exposure, the commercial label will restrict workers from re-entering treated areas until the spray has dried. Standard precautionary label statements will warn domestic users of the potential for skin and eye irritation, but personal protective equipment is not required based on the infrequency of application of Lacto-San-D compared to commercial applicators.

Environmental Considerations

What Happens When Lacto-San and Lacto-San-D Are Introduced Into the Environment?

Environmental risks are not of concern.

Lactic acid bacteria, including *Lactobacillus casei,* are considered widespread in nature and are part of the commensal microflora of humans and animals as part of the gastrointestinal tract, oral cavity, and vagina. Published literature indicates that although foreign lactic acid bacteria can survive outside of the dairy environment they are unlikely to thrive there. As well, the number of *Lactobacillus casei* strain LPT-111 contained in Lacto-San and Lacto-San-D is very low, and therefore the use of Lacto-San and Lacto-San-D is not likely to result in an increase of the number of *Lactobacillus casei* strain LPT-111 in the environment. Consequently, the risk to terrestrial and aquatic non-target organisms from the MPCA is negligible.

Citric acid and lactic acid readily undergo biotransformation in terrestrial and aquatic environments. Given the ubiquitous nature of citric and lactic acid in animals, plants, edible food commodities and industrial chemicals, the proposed uses of Lacto-San and Lacto-San-D on fruits, vegetables, and ornamental roses is not expected to result in a considerable increase in exposure to non-target terrestrial and aquatic organisms. Furthermore, reports in published literature of cases of adverse effects, as well as published toxicological endpoints, do not suggest that exposure of non-target terrestrial and aquatic organisms to the levels of citric and lactic acid in Lacto-San and Lacto-San-D will pose a concern with respect to toxicity. Based on the available data, citric acid and lactic acid are expected to pose negligible risk to terrestrial and aquatic organisms under conditions of use.

Value Considerations

What Is the Value of Lacto-San and Lacto-San-D

The Lacto-San end-use products and the acids they contains, which are produced by *Lactobacillus casei* strain LPT-111, are broad spectrum preventative fungicides and bactericides effective in the suppression of many important plant diseases.

The Lacto-San end-use products suppress commercially important fungal plant diseases including black spot on roses, downy mildew on cucumbers and powdery mildew on roses, strawberries, cucumbers, squashes and pumpkins. They have also been shown to have suppressive effects on bacterial diseases such as bacterial canker on tomatoes and angular leaf spot on strawberries. Because the Lacto-San products are manufactured in a food plant with only ingredients used for human consumption, the products represent a valuable reduced-risk alternative tool for disease management. In addition, the risk of disease resistance development by the target pathogens is assumed to be very low given the general nature of its putative mode of action, which includes physical exclusion, plasmolysis and membrane disruption of fungal cells.

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 labels of Lacto-San and Lacto-San-D to address the potential risks identified in this assessment are as follows:

Key Risk-Reduction Measures

Human Health

To minimize exposure to *Lactobacillus casei* strain LPT-111, citric and lactic acid, all commercial applicators, mixer-loaders and handlers must wear waterproof gloves, long-sleeved shirts, long pants, shoes and socks and eye goggles. A label statement directing users to avoid inhaling the product and its mists is also included. Furthermore, to reduce early-entry worker exposure, the commercial label will restrict workers from re-entering treated areas until the spray has dried. Standard precautionary label statements will alert domestic users of the potential for skin and eye irritation.

Environment

As a general precaution from adverse effects on plants from high concentrations of acids, a precautionary statement will be imposed on the commercial and domestic end-use product labels warning users to follow mixing instructions carefully to ensure the product is properly diluted prior to application.

Furthermore, standard environmental precaution label statements to reduce runoff and to prevent handlers from contaminating aquatic habitats and systems will be added to the end-use product labels. Standard greenhouse label statements will also be added to advise users not to allow effluent or runoff from greenhouses to reach aquatic habitats.

Next Steps

Before making a final registration decision on *Lactobacillus casei* strain LPT-111, 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 *Lactobacillus casei* strain LPT-111 (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

Lactobacillus casei strain LPT-111

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Refer to the Proposed Registration Decision PRD2010-09, *Lactobacillus casei* strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strain LL64/CSL, *Lactococcus lactis* ssp. *lactis* strain LL102/CSL and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL for information on the identity of the active ingredient *Lactobacillus casei* strain LPT-111.

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

Technical Product—*Lactobacillus casei* Technical

Refer to PRD2010-09 for the physical and chemical properties of *Lactobacillus casei* Technical.

End-Use Product—Lacto-San

Physical state	Aqueous suspension
Guarantee	Lactic acid ……21.37 g/L nominal (limits 17.10–21.37 g/L) Citric acid ……10.73 g/L nominal (limits 8.57–10.73 g/L) (present as fermentation products of *Lactobacillus casei* strain LPT-111)
Colour	Opaque yellow
Viscosity	6.70 ± 1.31mPa(s)
pH	4.1
Density	1.13 ± 0.01 g/mL @ 20ºC

End-Use Product—Lacto-San-D

Physical state	Aqueous suspension
Guarantee	Lactic acid ……21.37 g/L nominal (limits 17.10–21.37 g/L) Citric acid ……10.73 g/L nominal (limits 8.57–10.73 g/L) (present as fermentation products of *Lactobacillus casei* strain LPT-111)

Physical state	Aqueous suspension
Colour	Opaque yellow
Viscosity	6.70 ± 1.31mPa(s)
pH	4.1
Density	1.13 ± 0.01 g/mL @ 20ºC

1.3 Directions for Use

Lacto-San and Lacto-San-D are used for the suppression of various fungal and bacterial plant foliar diseases including bacterial canker on field and greenhouse tomatoes, powdery mildew and downy mildew on greenhouse cucumbers, angular leaf spot and powdery mildew on strawberries, powdery mildew on squashes and pumpkins, black spot and powdery mildew on roses, as well as downy mildew on grapes. The recommended concentrations for applications of both products range between 1.5% and 12% in a water solution.

1.4 Mode of Action

Some details of the Lacto-San end-use product's mode of action remain to be fully elucidated; however, the product has been shown to influence the early stages of disease development through inhibition of conidial germination, suppression of germ tube formation and elongation, disruption of appressoria formation, and reduction of hyphal branching. The mode of action behind the Lacto-San product's protective effects against plant pathogens is known to be multifaceted. Upon drying on the leaf surface, the product has been shown to result in plasmolysis of pathogen cells. Also, the pH-altering effects of the organic acids found in Lacto-San, mainly lactic and citric acids, are believed to reduce pathogen cell membrane integrity. In addition, it appears that the Lacto-San products produce a physical barrier that prevents penetration by the pathogens by creating a film over the treated plant surface.

2.0 Methods of Analysis

2.1 Methods for Identification of the Microorganism

A strain-specific identification method for the MPCA is an outstanding requirement for the *Lactobacillus casei* Technical and is required as a condition of the full registration.

2.2 Methods for Establishment of Purity of Seed Stock

Refer to PRD2010-09.

2.3 Methods for Formulation Analysis of the End-Use Product

A validated method has been provided for the analysis of the active ingredients, citric and lactic acid, in the end-use products.

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

The presence of *Lactobacillus casei* strain LPT-111 in the end-use products is shown to be less than 1.0×10^5 CFU/mL by using valid microbiological techniques to enumerate total aerobic bacteria.

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

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.

The MPCA is a strain of bacterium commonly used in the food industry to produce dairy products such as cheese and yogurt, and citric and lactic acid are naturally found in fruit as well as used as additives in beverages such as soft drinks. The levels of the MPCA and these organic acids that would result on food crops from the proposed use of Lacto-San and Lacto-San-D are expected to be much lower than levels already consumed in the Canadian diet from other sources. Consequently, the PMRA has determined that setting an MRL is not required for *Lactobacillus casei* strain LPT-111, or for citric and lactic acid. As a result, no methods to determine and quantify the residues of MPCA and relevant metabolites are required.

2.6 Methods for Determination of Relevant Impurities in the Manufactured Material

The quality control procedures used to limit contaminating microorganisms during manufacture of *Lactobacillus casei* Technical, Lacto-San and Lacto-San-D are acceptable. Any product that does not meet the applicant's specifications for microbial contamination will be destroyed.

2.7 Methods to Show Absence of Any Human and Mammalian Pathogens

As noted in Section 2.6, quality control procedures are used to limit microbial contamination in *Lactobacillus casei* Technical, Lacto-San and Lacto-San-D. These procedures include contamination checks to detect contaminating microbes.

Acceptable microbial contaminant analysis data were submitted for five batches of Lacto-San and Lacto-San-D.

3.0 Impact on Human and Animal Health

3.1 Toxicity and Infectivity Summary

As *Lactobacillus casei* Technical, containing the MPCA *Lactobacillus casei* strain LPT-111, is currently registered, the toxicity and infectivity of the MPCA and the organic acids (citric and lactic acid), has already been addressed. Refer to PRD2010-09 for details. Note that PRD2010-09 discusses the toxicity and infectivity of five lactic acid bacteria, one of which is *Lactobacillus casei* strain LPT-111, the MPCA in Lacto-San and Lacto-San-D.

3.2 Occupational / Bystander Exposure and Risk Assessment

3.2.1 Occupational

Lacto-San and Lacto-San-D are commercial and domestic end-use products, respectively, that will be diluted and applied as a foliar spray to fruits, vegetables, and ornamental roses. As a domestic product, Lacto-San-D will be used in residential gardens, while the commercial product, Lacto-San, will be used for field-grown crops and in commercial greenhouses. When handled according to the proposed label instructions, the potential routes of worker exposure to *Lactobacillus casei* strain LPT-111 and to citric and lactic acid in Lacto-San and Lacto-San-D are dermal, pulmonary and to some extent ocular.

Since unbroken skin is a natural barrier to microbial invasion of the human body, dermal absorption could occur only if the skin were cut, or 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. This MPCA has not been identified as a wound pathogen and there is no indication that it could penetrate intact skin of healthy individuals.

The PMRA does not expect that the occupational exposure to the MPCA will pose a toxicological concern on the basis that *Lactobacillus casei* strains are part of the commensal microflora of humans and animals, and that *Lactobacillus casei* strain LPT-111 is widely used in the dairy industry, and on the assumption that the precautionary labelling instructions aimed at minimizing worker exposure are adhered to by users. However, all MPCAs are considered potential sensitizers. The PMRA assumes that all microorganisms contain substances that can elicit positive hypersensitivity reactions. Label restrictions and risk mitigation measures are required to protect populations that are likely to be primarily exposed to the products. Such exposure to loaders, handlers and other workers can be minimized if they wear waterproof gloves, long-sleeved shirts, long pants, shoes and socks.

For citric and lactic acid, however, dermal irritation has been noted. Furthermore, the pH of Lacto-San and Lacto-San-D is likely to cause dermal, eye, and to a lesser extent, pulmonary irritation, particularly with repeated or prolonged exposure. Risk mitigation measures and label statements are required to protect populations that are likely to be exposed to Lacto-San and Lacto-San-D. Hazard statements to be included on the principal display panel will mirror end-use products with a similar pH and similar degree of irritancy. The pH of both Lacto-San

and Lacto-San-D (pH 4.1) is expected to be severely irritating to the eyes as well as mildly irritating to the skin, but is not considered corrosive.

The potential for dermal and ocular irritation is expected to be highest under prolonged exposure scenarios such as those encountered by commercial applicators, mixer-loaders, handlers, and early-entry workers. Therefore, to minimize dermal and ocular exposure to citric and lactic acid, commercial users will be required to wear waterproof gloves, long-sleeved shirts, long pants, shoes and socks and eye goggles. To minimize inhalation exposure, a label statement directing users to avoid inhaling the product and its mists will be required on the Lacto-San label. Furthermore, to reduce early-entry worker exposure, the commercial label will restrict workers from re-entering treated areas until the spray has dried.

The potential and frequency for dermal and ocular exposure is considerably lower for the domestic product. Therefore, standard precautionary label statements for domestic products are adequate to alert domestic users of the potential for skin and eye irritation without the need for personal protective equipment.

3.2.2 Bystander

As Lacto-San-D is a domestic end-use product, there is a potential for bystander exposure to adults, infants and children. Overall, the PMRA does not expect that bystander exposures will pose an undue risk on the basis of the low toxicity/pathogencity profile of *Lactobacillus casei* strain LPT-111, and citric and lactic acid. Furthermore, precautionary label statements to minimize off-target spray drift are present on the Lacto-San and Lacto-San-D labels.

3.3 Incident Reports Pertaining to Human and Animal Health

Since April 26, 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. Incidents from Canada and the United States were searched and reviewed for products containing the active ingredient *Lactobacillus casei*, as well as for the organic acids/fermentation products, citric and lactic acid.

As of May 18, 2011 there were no incident reports submitted to the PMRA for products containing *Lactobacillus casei*, or citric and lactic acid.

There has, however, been 52 human incident reports summarized by the California Department of Pesticide Regulation (CalDPR) for products containing citric acid for which the causality is established as possible, probable, or definite.

All the incidents were non-agricultural related, occurring in the workplace involving accidental exposure (i.e. spray/splash, inhalation) to disinfectants /cleaning products. All but one of the products contained more than just citric acid as the active ingredient (for example, phosphoric acid, sodium hypochlorite, hydrogen chloride, etc). The most common effects reported from exposure were minor symptoms such as eye irritation, respiratory symptoms (for example, cough, difficulty breathing, shortness of breath, or throat discomfort), gastrointestinal discomfort

(for example, nausea and/or vomiting), headaches, dizziness or skin rashes. Ten incidents reported more serious symptoms such as a persistent skin rash, wheezing, fainting, and moderate eye irritation.

There was also one incident summarized by the CalDPR for a non-agricultural product containing lactic acid. Following exposure to a disinfecting solution, an asthmatic laboratory technician reported difficulty breathing.

The effects reported to the CalDPR are consistent with exposure to citric and lactic acid which is known to cause skin, eye and pulmonary irritation. The PMRA has concluded that the information from the incident reports supports the current toxicity database for citric and lactic acid, however, it did not impact the risk assessment for LactoSan and LactoSan-D.

3.4 Dietary Exposure and Risk Assessment

3.4.1 Food

While 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 the MPCA is a strain of bacterium commonly used in the food industry to produce dairy products such as cheese and yogurt, and citric and lactic acid are naturally found in fruit as well as used as additives in beverages such as soft drinks. The levels of the MPCA and these organic acids that would result on food crops from the proposed use of Lacto-San and Lacto-San-D are expected to be much lower than levels already consumed in the Canadian diet from other sources. Consequently, dietary risks are minimal to non-existent.

Higher tier subchronic and chronic dietary exposure studies were not required because of the low toxicity of the MPCA, citric acid, and lactic acid, and because the technical grade active ingredient, and the organic acids, are already commonly used in the dairy industry at much higher concentrations in products intended for human consumption. Therefore, the dietary exposure to these commodities from the use of Lacto-San and Lacto-San-D is not expected to pose a concern for chronic risks to the general population and sensitive subpopulations, such as infants and children.

3.4.2 Drinking Water

The likelihood that the Lacto-San end-use products could enter neighbouring aquatic environments as a result of run-off from outdoor foliar spray applications, or from greenhouse uses, is negligible. No risks are expected from exposure to this microorganism via drinking water because: exposure will be minimal and the level of *Lactobacillus casei* strain LPT-111, citric and lactic acid in drinking water from the use of Lacto-San and Lacto-San-D is expected to be much lower than levels already consumed in the Canadian diet from other sources given that *Lactobacillus casei* strain LPT-111, and the organic acids, are routinely used in food production. Moreover, the Lacto-San and Lacto-San-D labels instruct users not to contaminate irrigation or drinking water supplies or aquatic habitats through equipment cleaning or waste disposal. Users

are also required not to allow effluent or runoff from greenhouses containing this product to enter lakes, streams, ponds or other waters. Municipal treatment of drinking water is also expected to remove the transfer of residues to drinking water. Therefore, potential exposure to *Lactobacillus casei* strain LPT-111, and to its fermentation products (citric and lactic acid) in surface and drinking water is negligible.

3.4.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

Calculations of acute reference doses and acceptable daily intakes 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 (i.e. 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 MPCA 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 microorganisms 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 this MPCA to human health.

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.

The MPCA is a strain of bacterium commonly used in the food industry to produce dairy products such as cheese and yogurt, and citric and lactic acid are naturally found in fruit as well as used as additives in beverages such as soft drinks. The levels of the MPCA and these organic acids that would result on food crops from the proposed use of Lacto-San and Lacto-San-D are expected to be much lower than levels already consumed in the Canadian diet from other sources. Therefore, the establishment of an MRL is not required for *Lactobacillus casei* strain LPT-111, citric acid, or lactic acid.

3.6 Aggregate Exposure

Based on the waiver rationales 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 *Lactobacillus casei* strain LPT-111 to the general Canadian population, including infants and children, when the microbial pest control 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.

Although the commercial and domestic uses of Lacto-San and Lacto-San-D, respectively, on outdoor and greenhouse crops carry the potential for dermal and inhalation exposure to the general public, few adverse effects are expected based on evidence from the safe history of use of *Lactobacillus casei* strain LPT-111, and of citric and lactic acid in the food industry and in natural health products.

3.7 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 *Lactobacillus casei* strain LPT-111 found in food and natural health products and in the commercial herbicide product OrganoSol (Registration Number 29603), the PMRA is not aware of any other microorganisms, or other substances that share a common mechanism of toxicity with this active ingredient. No cumulative effects are anticipated if the residues of *Lactobacillus casei* strain LPT-111 interact with related strains of this microbial species.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

As *Lactobacillus casei* Technical, containing the MPCA *Lactobacillus casei* strain LPT-111, is currently registered, the fate and behaviour or the MPCA, citric and lactic acid have already been addressed. Refer to PRD2010-09 for details. Note that PRD2010-09 discusses the fate and behaviour of five lactic acid bacteria, one of which is *Lactobacillus casei* strain LPT-111, the MPCA in Lacto-San and Lacto-San-D.

4.2 Effects on Non-Target Species

As *Lactobacillus casei* Technical, containing the MPCA *Lactobacillus casei* strain LPT-111, is currently registered, the effects of the MPCA, citric and lactic acid on non-target terrestrial organisms have already been addressed. Refer to PRD2010-09 for details. Note that PRD2010-09 discusses the effects of five lactic acid bacteria, one of which is *Lactobacillus casei* strain LPT-111, the MPCA in Lacto-San and Lacto-San-D.

4.2.1 Effects on Terrestrial Organisms

For effects on terrestrial organisms from *Lactobacillus casei* strain LPT-111, refer to PRD2010-09 for a discussion on the potential effects of *Lactobacillus casei* strain LPT-111 on non-target terrestrial organisms. Note that PRD2010-09 discusses the potential effects of five lactic acid bacteria, one of which is Lactobacillus casei strain LPT-111, the MPCA in Lacto-San and Lacto-San-D, on non-target terrestrial organisms.

With respect to the end-use products, all raw materials in Lacto-San and Lacto-San-D are food-grade ingredients commonly used in the food industry for the manufacturing of food for humans (i.e. fermentation of dairy by-products) and animals.

Lactobacillus casei strain LPT-111 is present in Lacto-San and Lacto-San-D at a level of ~1.0×10^5 CFU/mL and the use of Lacto-San and Lacto-San-D will be limited to foliar applications to fruit, vegetables, and ornamental roses in fields and in greenhouses. Given the widespread but occasional exposure to functionally equivalent strains of *Lactobacillus casei* as commensal organisms in humans and animals, and in the environment, and based on the lack of persistence of *Lactobacillus casei* strain LPT-111 in non-dairy environments, the proposed uses of Lacto-San and Lacto-San-D are not expected to result in a considerable increase in exposure of non-target terrestrial animals.

Based on these considerations, exposure to *Lactobacillus casei* strain LPT-111, citric and lactic acid from the use of Lacto-San and Lacto-San-D is not expected to result in an unacceptable risk to non-target terrestrial organisms.

For effects on terrestrial organisms from citric and lactic acid, refer to PRD2010-09 for a discussion on the potential effects of citric and lactic acid on non-target terrestrial organisms.

With respect to the end-use products, Lacto-San and Lacto-San-D both contain citric and lactic acid at 21.37 g/L and 10.73 g/L, respectively. The use of Lacto-San and Lacto-San-D will be limited to foliar applications to fruit, vegetables, and ornamental roses in fields and in greenhouses. Given the ubiquitous nature of citric and lactic acid in animals, plants, edible food commodities and industrial chemicals, the proposed uses of Lacto-San and Lacto-San-D is not expected to result in a considerable increase in exposure to non-target terrestrial animals to citric and lactic acid. Furthermore, reports in published literature of cases of adverse effects from citric and lactic acid, as well as published toxicological endpoints for citric and lactic acid, do not suggest that that exposure of non-target terrestrial animals to the levels of citric and lactic acid in Lacto-San and Lacto-San-D will pose a concern with respect to toxicity. Given that citric and lactic acid are expected to undergo biotransformation and have very high mobility in soil, these acids are not expected to persist in the terrestrial environment. Based on these considerations exposure to citric and lactic acid from the use of Lacto-San and Lacto-San-D is not expected to result in an unacceptable risk to non-target terrestrial organisms.

Due to the low level of the MPCA in Lacto-San and Lacto-San-D (<1.0×10^5 CFU/mL), and that foreign *Lactobacillus casei* strain LPT-111 is not expected to persist in non-dairy environments, toxicity testing for effects on non-target soil microorganisms was not required. Furthermore, the

use of Lacto-San and Lacto-San-D to control plant diseases on fruits, vegetables and ornamental roses is not expected to affect environmentally or economically important microbial species or microbiologically-mediated biogeochemical processes.

4.2.2 Effects on Aquatic Organisms

Refer to PRD2010-09 for a discussion on the potential effects of *Lactobacillus casei* strain LPT-111 on non-target aquatic organisms. Note that PRD2010-09 discusses the potential effects of five lactic acid bacteria, one of which is Lactobacillus casei strain LPT-111, the MPCA in Lacto-San and Lacto-San-D, on non-target aquatic organisms.

With respect to the end-use products, *Lactobacillus casei* strain LPT-111 is present in Lacto-San and Lacto-San-D at a level of ~1.0×10^5 CFU/mL, and the use of Lacto-San and Lacto-San-D will be limited to foliar applications at 1.5–12% solutions to fruit, vegetables, and ornamental roses in fields and in greenhouses, with no direct applications to aquatic systems. Given the lack of persistence of *Lactobacillus casei* strain LPT-111 in non-dairy environments, and that the use of Lacto-San and Lacto-San-D is limited to fields and greenhouses, run-off into aquatic environments is expected to be minimal. Moreover, foreign *Lactobacillus casei* strain LPT-111 are not expected to persist in or on fish for more than a couple weeks, nor in aquatic systems for any prolonged period of time due to rapid biotransformation. Furthermore, a literature search revealed no reports of adverse effects in aquatic organisms from *Lactobacillus casei*.

Based on these considerations, exposure to *Lactobacillus casei* strain LPT-111 from the use of Lacto-San and Lacto-San-D is not expected to result in an unacceptable risk to non-target aquatic organisms.

For effects on aquatic organisms from citric and lactic acid, refer to PRD2010-09 for a discussion on the potential effects from citric and lactic acid on non-target aquatic organisms. With respect to the end-use products, Lacto-San and Lacto-San-D both contain citric and lactic acid at 21.37g/L, and 10.73 g/L, respectively, and the use of Lacto-San and Lacto-San-D will be limited to foliar applications to fruit, vegetables, and ornamental roses in fields and in greenhouses, with no direct applications to aquatic systems. Citric and lactic acid are expected to undergo biotransformation in terrestrial environments but are also expected to redistribute into the aquatic environment based on their high mobility in soil. However, based on the levels of acids in Lacto-San and Lacto-San-D and the use pattern of the products, run-off and leaching into aquatic environments is expected to be minimal. In the aquatic environment, citric acid and lactic acid are expected to undergo rapid and complete biotransformation, and the potential for bioconcentration in aquatic organisms is low. Furthermore, reports in published literature of cases of adverse effects from citric and lactic acid, as well as published toxicological endpoints for citric and lactic acid do not indicate that exposure of non-target aquatic organisms to the levels of citric and lactic acid in Lacto-San and Lacto-San-D will pose a concern.

Based on these considerations, exposure to citric and lactic acid from the use of Lacto-San and Lacto-San-D is not expected to result in an unacceptable risk to non-target aquatic organisms.

4.3 Incident Reports related to the Environment

Since April 26, 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/index-eng.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 May 20, 2011, there were no environmental incidents reported in the PMRA Incident reporting database nor in the USEPA's Ecological Incident Information System (EIIS) for products containing *Lactobacillus casei*, or citric and lactic acid.

5.0 Value

5.1 Effectiveness Against Pests

A total of 23 field and greenhouse trials conducted in Quebec and Ontario were submitted to demonstrate the efficacy of the Lacto-San end-use products against the labelled plant diseases. Two additional laboratory trials were accepted as supplementary data. All of the trials submitted were designed and conducted with due consideration of sound scientific principles (for example, replication, randomization, control treatments, statistical analyses, etc.). Low to moderate disease pressure was present in the majority of the trials with a few having high disease pressure.

5.1.1 Acceptable Efficacy Claims

Applications of the Lacto-San products at rates of 12 L/ha and 20 L/ha reduced bacterial canker incidence in greenhouse tomatoes by up to 72% under moderate disease pressure. The demonstrated levels of efficacy were deemed consistent with a claim for suppression.

Among the trials provided to demonstrate suppression of powdery mildew on cucumbers in greenhouses, four were selected and deemed to be sufficient to support this claim. Disease severity was reduced by up to 100% in younger unaffected leaves, contrary to older leaves with symptoms already present, which showed little response to the treatment. This observation provided evidence for supporting the use of the Lacto-San products as a preventative treatment. Efficacy was demonstrated against two different species that cause powdery mildew in cucumbers. In some instances, efficacy of the Lacto-San products were reported to be superior to a conventional commercial standard.

Two greenhouse trials were submitted to support the cucumber downy mildew claim. The highest level of disease reduction under moderate disease pressure was 79% at a concentration of 8% of the Lacto-San products. Based on the demonstrated efficacy of the Lacto-San products, the claim for suppression of downy mildew in greenhouse cucumbers at a concentration of 8% was deemed acceptable.

Six greenhouse and field trials were submitted to support the claim for powdery mildew on

strawberries. Disease pressure ranged from low to high across the trials. Reductions in disease severity reached 80% when the Lacto-San products were applied at a concentration of 12% in the field. In one trial, yield increases of 43% were attributed to the Lacto-San product treatment. Based on the efficacy demonstrated in the greenhouse and in the field, the claim for suppression of powdery mildew on strawberries at rates of 8 or 12% was deemed acceptable.

Claims of efficacy of the Lacto-San products against powdery mildew on squash and pumpkins were supported by two trials with moderate to high disease pressure. Under moderate disease pressure, disease severity was reduced by up to 73%. Based on the demonstrated efficacy, along with the evidence submitted in support of the greenhouse cucumber claim, the claim for suppression of powdery mildew on squashes and pumpkins at rates of 8 to 12% was deemed acceptable.

A single black spot trial on roses with high disease pressure was provided to demonstrate the Lacto-San product efficacy for this claim. Disease reduction by the Lacto-San products at a rate of 2.5% reached 84%. Good efficacy was also observed at the 1.5% rate; however, the level of disease reduction was maintained longer at the 2.5% rate. Based on the efficacy data from the submitted trial, the claim for suppression of black spot disease on roses at a rate of 1.5 to 2.5% was deemed acceptable.

A single greenhouse trial with moderate to high disease pressure was provided in support of the claim against powdery mildew on roses. Disease was measured based on a visual assessment index and by the average number of affected leaves on a plant. Improvements to the visual index of up to 88% and 56% were attributable to the Lacto-San product applied at the rates of 2.5% and 1.5%, respectively. The number of affected leaves was reduced by 55% and 48% by the 2.5% and the 1.5% rates, respectively. The claim was deemed acceptable based on the submitted efficacy data as well as the evidence showing the Lacto-San product efficacy against powdery mildew in other crops, including another species of the same genus. Since roses are potentially susceptible to black spot and powdery mildew under the same conditions, the same recommended rates were deemed acceptable for both diseases (i.e. 1.5-2.5%).

Data from a culture plate trial were reviewed to determine the value of the claim for angular leaf spot on strawberries. Although data from lab trials are generally only considered as supplementary data, complete inhibition of bacterial growth was observed on plates where 4-10% of the Lacto-San product was included in the growth media. To further demonstrate the value of this claim, a rationale was provided that asserted that because of the products putative mode of action (acidification and plasmolysis of pathogen cells), the causal bacterium of angular leaf spot would have similar susceptibility to the product as was demonstrated for the causal organism of tomato bacterial canker, for which efficacy data were provided. Based on demonstrated efficacy and considerations presented in the rationale justifying an application rate of 8 to 12%, this claim was deemed to be supported with conditions.

5.2 Phytotoxicity

Treatments with the Lacto-San end-use products within the recommended rate range did not show any negative effect on the growth and development of the tested plants relative to those in control treatments. Based on the submitted data, no phytotoxicity, phytopathogenicity, or any other negative effect on the growth of plants included in the label claims are expected following the application of Lacto-San products at the recommended rates.

5.3 Economics

No market analysis was done for these applications.

5.4 Sustainability

5.4.1 Survey of Alternatives

The chemical and other non-conventional/biological fungicidal active ingredients listed in Appendix 1, Table 1 are found in products that are registered for control or suppression of diseases on the crops found on the Lacto-San and Lacto-San-D labels.

Aside from treatments with fungicides, certain cultural practices are relied on to reduce disease pressure by the pathogens appearing on the Lacto-San and Lacto-San-D labels. Sanitation practices such as the removal and destruction of infected leaves when disease is first observed, good sanitation between crop cycles and prompt removal and destruction of culled material and old crop debris help reduce sources of inoculum for most of the labelled diseases. Whenever possible, maintaining uniform environmental conditions that favour plant health while discouraging disease development is also helpful in improving crop protection from the labelled diseases.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

The Lacto-San end-use product's mode of action is not directly linked to the presence of living microorganisms. Therefore, the risk of adverse effects on the Lacto-San product efficacy by a concurrent use of chemical pesticides should be limited. However, the Lacto-San products have not been specifically tested for compatibility with chemical products or with other microbial control organisms.

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

The Lacto-San products are reduced-risk biological fungicides with evidence to support multi-site nature of the product's mode of action. Consequently, development of pathogens that are resistant to the Lacto-San products is not expected.

5.4.4 Contribution to Risk Reduction and Sustainability

The Lacto-San products have the potential to reduce applications of chemical fungicides and bactericides on tomatoes, greenhouse cucumbers, squashes, pumpkins, grapes, roses, and strawberries. As a result, the Lacto-San products would contribute to the improvement of integrated pest management strategies and sustainable practices.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy (TSMP), which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

In its review of *Lactobacillus casei* strain LPT-111, the PMRA took into account the federal Toxic Substances Management Policy and followed its Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with its use were also considered, including microcontaminants in the technical product, *Lactobacillus casei* Technical, and formulants in the end-use products, Lacto-San and Lacto-San-D. The PMRA has reached the following conclusions:

Lactobacillus casei Technical does not meet the Track 1 criteria because the active ingredient is a biological organism and hence are not subject to the criteria used to define persistence, bioaccumulation and toxicity properties of chemical control products.

Furthermore, citric acid and lactic acid do not meet the Track 1 criteria and are not expected to form any transformation products which meet the Track 1 criteria. Citric acid and lactic acid are naturally occurring substances and are not expected to be persistent or bioaccummulative in the environment.

There are also no formulants, contaminants or impurities present in the end-use products that would meet the TSMP Track 1 criteria. Therefore, the use of *Lactobacillus casei* Technical and Lacto-San and Lacto-San-D are not expected to result in the entry of Track 1 substances into the environment.

6.2 Formulants and Contaminants of Health or Environmental Concern

The technical grade active ingredient *Lactobacillus casei* Technical does not contain any contaminants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

The end-use products, Lacto-San and Lacto-San-D, may contain unmodified milk protein (whey) 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*. Therefore the labels for Lacto-San and Lacto-San-D will include the precautionary statements: "WARNING – CONTAINS THE ALLERGEN MILK (WHEY PROTEIN)".

7.0 Summary

7.1 Methods for Analysis of the Microorganism as Manufactured

The product characterization data for *Lactobacillus casei* Technical, and the end-use products Lacto-San and Lacto-San-D, 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 products were supported by the analyses of a sufficient number of batches. The requirement for a strain-specific identification method for the MPCA is an outstanding requirement for *Lactobacillus casei* Technical.

7.2 Human Health and Safety

The human health and safety information and data submitted in support of the MPCA (*Lactobacillus casei* strain LPT-111) and fermentation products (citric and lactic acid) were determined to be sufficiently complete to permit a decision on registration.

At the concentrations present in Lacto-San and Lacto-San-D, *Lactobacillus casei* strain LPT-111 is not expected to pose a significant risk via the oral route of exposure. Literature searches did not yield reports of dermal toxicity or irritation, nor of eye irritation associated with *Lactobacillus casei*.

The active ingredients/fermentation products, citric and lactic acid, are of low acute toxicity by the oral route. Lactic acid is of low acute toxicity via the dermal route; however, both citric and lactic acid are slightly irritating to the skin. Eye irritation studies indicated that, at the concentrations found in Lacto-San and Lacto-San-D, citric and lactic acid are capable of producing moderate to severe injury to the eye, particularly with repeated or prolonged exposure.

Occupational exposure to *Lactobacillus casei*, citric and lactic acid from the commercial use of Lacto-San are expected to be minimal from the proposed use pattern if the recommended personal protective equipment and re-entry precaution statements on the product label are observed. For the domestic product, Lacto-San-D, precautionary label statements will warn

domestic users of the hazards, but personal protective equipment is not required based on the infrequency of application for domestic users compared to commercial applicators.

There is a potential for non-occupational exposure to adults, infants and children as the label allows applications in residential and public areas. The associated risk, however, is expected to be low based on the low acute toxicity/pathogenicity profile for *Lactobacillus casei* strain LPT-111, citric and lactic acid in Lacto-San and Lacto-San-D.

Negligible to no risk for the general population, including infants and children, or animals, is expected from dietary exposure to residues in or on agricultural commodities because of the low toxicity profile of *Lactobacillus casei* strain LPT-111 and lactic acid and citric acid, and because *Lactobacillus casei* strain LPT-111, and the organic acids are used in the food industry at much higher concentrations for products intended for human consumption, and no adverse effects have been attributed to dietary exposure.

7.3 Environmental Risk

The scientific rationales and published scientific literature submitted in support of *Lactobacillus casei* Technical, and Lacto-San and Lacto-San-D were determined to be sufficiently complete to permit a decision on registration.

Waiver rationales were submitted to address the hazards of citric acid, lactic acid, and *Lactobacillus casei* strain LPT-111 to non-target organisms. These rationales and other published information showed that the use of Lacto-San and Lacto-San-D does not pose a risk to birds, mammals, arthropods (including honeybees), fish, non-arthropod invertebrates, plants, or algae.

No additional studies were required to address the environmental fate and behaviour of citric acid, lactic acid or *Lactobacillus casei* strain LPT-111. Environmental fate data (Tier II/III) are not normally required in the absence of toxicological effects in non-target organisms in Tier I testing.

As a general precaution from adverse effects on plants from high concentrations of acids, a precautionary statement will be imposed on the commercial and domestic end-use product labels warning users to follow mixing instructions carefully to ensure the product is properly diluted prior to application.

7.4 Value

The data submitted to register Lacto-San and Lacto-San-D were sufficient to support the value of the products' uses for suppressing various fungal and bacterial diseases of tomatoes, greenhouse cucumbers, squashes, pumpkins, grapes, roses, and strawberries. In addition, the low risk profile of the products makes them useful additions to integrated pest management programs.

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 *Lactobacillus casei* Technical, Lacto-San-D and Lacto-San, containing the microbial pest control agent *Lactobacillus casei* strain LPT-111, to suppress various foliar diseases on field and greenhouse crops including roses, tomatoes, strawberries, cucumbers, squashes and pumpkins.

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

List of Abbreviations

^{o}C	degree(s) Celsius
CalDPR	California Department of Pesticide Regulation
CFU	colony forming unit
DACO	data code
ha	hectare(s)
g	gram
L	litre
mL	millilitre
mPa	milli-Pascals
MPCA	microbial pest control agent
MRL	maximum residue limit
PMRA	Pest Management Regulatory Agency
TSMP	Toxic Substances Management Policy
U.S.	United States
USEPA	United States Environmental Protection Agency

Appendix I Tables and Figures

Table 1 Alternative Fungicides Registered for Foliar Diseases on Tomatoes, Strawberries,Cucurbits, Grapes and Roses

Pests	Crop	Active Ingredient	Resistance Management Group
Bacterial canker	Tomatoes	Copper	M1
Powdery mildew	Greenhouse Cucumbers	Boscalid	7
		Myclobutanil	3
	Strawberries	Potassium bicarbonate	NC
		Pyraclostrobin	11
		Quinoxyfen	M2
		Streptomyces lydicus strain WYEC 108	NC
		Sulphur	M2
	Squashes and pumpkins	Chlorothalonil	M5
		Folpet	M4
		Potassium bicarbonate	NC
		Pyraclostrobin	11
		Bacillus subtilis strain QST 713	44
		Quinoxyfen	13
		Sulphur	M2
	Roses	Captan	M4
		Copper	M1
		Dodemorph	5
		Folpet	M4
		Myclobutanil	3
		Propiconazole	3
		Bacillus subtilis strain QST 713	44
		Sulphur	M2
		Thiophanate-methyl	1
		Trifloxystrobin	11
		Triforine	3

Pests	Crop	Active Ingredient	Resistance Management Group
Downy mildew	Greenhouse Cucumbers	*Bacillus subtilis* strain QST 713	44
	Grapes	Boscalid	7
		Captan	M4
		Copper	M1
		Kresoxim-Methyl	11
		Mancozeb	M3
		Mandipropamid	40
		Metalaxyl	4
		Metiram	M3
		Pyraclostrobin	11
		Zoxamide	22
Angular leaf spot	Strawberries	No products currently registered for this use	n/a
Black spot	Roses	Calcium polysulphide	M2
		Captan	M4
		Chlorothalonil	M5
		Copper	M1
		Folpet	M4
		Myclobutanil	3
		Propiconazole	3
		Sulphur	M2
		Thiophanate-methyl	1
		Triforine	M2

Table 2 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Proposed use claim	Supported Use
To suppress bacterial canker on tomatoes, apply Lacto-San or Lacto-San-D at a rate of 20 L/ha.	To suppress bacterial canker **(*Clavibacter michiganensis*)** on greenhouse and field tomatoes, apply Lacto-San at a rate of 12 L/ha or Lacto-San-D at a rate of 2.4% until runoff.
To suppress powdery mildew and downy mildew on greenhouse cucumbers, apply Lacto-San or Lacto-San-D at a rate of 8% or 12% in water solution until runoff.	To suppress powdery mildew **(*Podosphaera xanthii*)** and downy mildew **(*Pseudoperonospora cubensis*)** on greenhouse cucumbers, apply Lacto-San or Lacto-San-D at a rate of 8% or 12% water solution until runoff.
To suppress powdery mildew and angular leaf spot on strawberries, apply Lacto-San or Lacto-San-D at a rate of 8% or 12% in water solution until runoff.	To suppress powdery mildew **(*Sphaerotheca macularis f.sp. fragariae*)** and angular leaf spot **(*Xanthomonas fragariae*)** on strawberries, apply Lacto-San or Lacto-San-D at a rate of 8% or 12% in water solution until runoff.
To suppress powdery mildew on squashes & pumpkins, apply Lacto-San or Lacto-San-D at a rate of 8% in water solution until runoff.	To suppress powdery mildew **(*Podosphaera xanthii*)** on squashes & pumpkins, apply Lacto-San or Lacto-San-D at a rate of 8% or 12% in water solution until runoff.
To suppress black spot and powdery mildew on roses, apply Lacto-San or Lacto-San-D at a rate of 1.5 - 2.5% in water solution until runoff.	To suppress black spot **(*Diplocarpon rosae*)** and powdery mildew **(*Sphaerotheca pannosa*)** on roses, apply Lacto-San or Lacto-San-D at a rate of 1.5 - 2.5% in water solution until runoff.
To suppress powdery mildew and downy mildew on grapes, apply Lacto-San or Lacto-San-D at a rate of 8% or 12% in water solution until runoff.	To suppress downy mildew **(*Plasmopara viticola*)** on grapes, apply Lacto-San or Lacto-San-D at a rate of 8% or 12% in water solution until runoff.

References

A. List of Studies/Information Submitted by Registrant

1.0 Product Characterization and Analysis

PMRA Document Number	Reference
1788684	2009, DACO M2 Product characterization and analysis, DACO: M2.0 CBI
1788716	2009, Lacto-San Manufacturing and Quality Assurance Processes, DACO: M2.8 CBI
1788787	2009, Lacto-San Analysis (5 batches), DACO: M2.10.1,M2.10.2,M2.8 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
1788685	2009, DACO M4 Summary, human health and safety testing, DACO: M4.1
1788686	2009, DACO M5 Exposure assessment, DACO: M5.0
1788843	2007, Allergen Analysis Organo-San 2007, DACO: M10.0,M2.9.3,M7.0
1788844	2009, Allergen Analysis Organo-San 2008, DACO: M10.0,M2.9.3,M7.0
1788869	2007, Whey analysis, DACO: M2.8

3.0 Environment

PMRA Document Number	Reference
1788687	2009, DACO M9 Summary- Environmental toxicology, DACO: M9.1

4.0 Value

PMRA Document Number	Reference
1788706	2009. Efficacy and phytotoxicity of biofungicide Lacto-San in roses. DACO: M10.0

1788708 2009. Efficacy and phytotoxicity of biofungicide Lacto-San on bacterial canker in greenhouse tomatoes. DACO: M10.0

1788714 2008. Evaluation of efficacy of biofungicide Lacto-San to reduce powdery mildew in strawberry. DACO: M10.0

1788827 2006. OMAFRA - Abe Powdery Mildew Greenhouse Experiment 2005 report. DACO: M10.0

1788836 2009. Personal Communication. DACO: M10.0

1788848 2006. Report for Mildew Trial at Bergens Summer_06. DACO: M10.0

1788807 2009. McGill - May 2009 Final Report. DACO: M10.0

1788707 2009. Efficacy and phytotoxicity of biofungicide Lacto-San on bacterial canker in field tomatoes. DACO: M10.0

1788808 2008. McGill - Progress Report March 2008. DACO: M10.0

1788688 2009. DACO M10 Value (including efficacy). DACO: M10.1, M10.2, M10.2.1, M10.2.2, M10.3, M10.3.1, M10.3.2, M10.3.2.1, M10.3.2.2, M10.4, M10.4.1, M10.4.2, M10.4.3, M10.4.4

1788639 2009. Bacterial Canker and Angular Leaf Spot. DACO: M10.1, M10.2.1, M10.2.2

1788653 2009. Black Spot. DACO: M10.2.1

2011786 2008. HectAg Report on Grapes 2008. DACO: M10.0