Proposed Registration Document PRD2013-24

Streptomyces acidiscabies strain RL-110^{T} and Thaxtomin A

(publié aussi en français)

20 December 2013

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

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6604-E2
Ottawa, Ontario K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

Canada

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

Catalogue number: H113-23/2013-24E (print version)
H113-23/2013-24E-PDF (PDF version)

Table of Contents

Overview 1
Proposed Registration Decision for *Streptomyces acidiscabies* strain RL-110^{T} and Thaxtomin A 1
What Does Health Canada Consider When Making a Registration Decision? 1
What Is MBI-005 EP and MBI-005 TGAI? 2
Health Considerations 3
Environmental Considerations 4
Value Considerations 5
Measures to Minimize Risk 5
Next Steps 6
Other Information 6
Science Evaluation 7
1.0 The Active Ingredient, Its Properties and Uses 7
1.1 Identity of the Active Ingredient 7
1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product 8
1.3 Directions for Use 9
1.4 Mode of Action 9
2.0 Methods of Analysis 9
2.1 Methods for Identification of the Microorganisms 9
2.2 Methods for Establishment of Purity of Seed Stock 10
2.3 Methods to Define the Content of the Microorganism in the Manufactured Material Used for the Production of Formulated Products 10
2.4 Methods to Determine and Quantify Residues (Viable or Non-viable) of the Active Microorganism and Relevant Metabolites 10
2.5 Methods for Determination of Relevant Impurities in the Manufactured Material 10
2.6 Methods to Determine Storage Stability, Shelf-life of the Microorganism 11
3.0 Impact on Human and Animal Health 11
3.1 Toxicology Summary 11
3.2 Occupational / Bystander Exposure and Risk Assessment 13
3.2.1 Occupational 13
3.2.2 Bystander 14
3.3 Incident Reports Related to Human and Animal Health 14
3.4 Dietary Exposure and Risk Assessment 15
3.4.1 Food 15
3.4.2 Drinking Water 15
3.4.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations 15
3.5 Maximum Residue Limits 15
3.6 Aggregate Exposure 15
3.7 Cumulative Effects 16

4.0 Impact on the Environment 16
4.1 Fate and Behaviour in the Environment 16
4.2 Effects on Non-Target Species 17
4.2.1 Effects on Terrestrial Organisms 18
4.2.2 Effects on Aquatic Organisms 20
4.3 Incident Reports related to the Environment 22
5.0 Value 22
5.1 Effectiveness Against Pests 22
5.2 Non-Safety Adverse Effects 22
5.3 Consideration of Benefits 22
5.3.1 Social and Economic Impact 22
5.3.2 Survey of Alternatives 23
5.3.3 Compatibility with Current Management Practices Including Integrated Pest Management 23
5.3.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance 23
5.3.5 Contribution to Risk Reduction 23
5.4 Supported Uses 24
6.0 Pest Control Product Policy Considerations 24
6.1 Toxic Substances Management Policy Considerations 24
6.2 Formulants and Contaminants of Health or Environmental Concern 25
7.0 Summary 25
7.1 Methods for Analysis of the Micro-organism as Manufactured 25
7.2 Human Health and Safety 26
7.3 Environmental Risk 26
7.4 Value 27
8.0 Proposed Regulatory Decision 27
List of Abbreviations 29
Appendix I Tables and Figures 31
Table 1 Toxicity and Infectivity of MBI-005 TGAI and its associated EP, MBI-005 EP 31
Table 2 Toxicity to Non-Target Species 35
References 49

Overview

Proposed Registration Decision for *Streptomyces acidiscabies* strain RL-110^{T} and Thaxtomin A

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 MBI-005 TGAI and MBI-005 EP, containing the active ingredient *Streptomyces acidiscabies* strain RL-110^{T} and Thaxtomin A, for the partial suppression of dandelions on turf grass (Kentucky bluegrass and fescue turf).

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 MBI-005 TGAI and MBI-005 EP, containing the active ingredient *S. acidiscabies* strain RL-110^{T} and Thaxtomin A.

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.

---

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 *S. acidiscabies* strain RL-110^T and Thaxtomin A, 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 *S. acidiscabies* strain RL-110^T and Thaxtomin A, 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 MBI-005 EP and MBI-005 TGAI?

The technical grade active ingredient (TGAI), MBI-005 TGAI, and the end-use product (EP), MBI-005 EP, contain killed, non-viable *S. acidiscabies* strain RL-110^T and spent fermentation media as the active ingredient. During the fermentation process, *S. acidiscabies* strain RL-110^T produces a phytotoxin, Thaxtomin A, which is the basis for the mode of action of the active ingredient.

It is believed that Thaxtomin A produces phytotoxic effects through alterations in calcium and sodium ion transport in cells as well as inhibiting cellulose biosynthesis. The toxicity in plants is similar to the effects caused by known cellulose biosynthesis inhibitors, such as dichlobenil and isoxaben.

MBI-005 EP is a commercial herbicide that is to be used for the control of dandelions on Kentucky bluegrass and fescue turf.

---

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 *Streptomyces acidiscabies* strain RL-110^T and Thaxtomin A Affect Human Health?

S. acidiscabies strain RL-110^T and Thaxtomin A is unlikely to affect your health when MBI-005 EP is used according to the label directions.

People could be exposed to *S. acidiscabies* strain RL-110^T and Thaxtomin A when handling and applying MBI-005 EP. When assessing health risks, several key factors are considered:

The microorganism's biological properties (for example, production of toxic by-products); 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 MBI-005 EP and *S. acidiscabies* strain RL-110^T were tested on laboratory animals, there were no signs that it caused any significant toxicity or disease. Furthermore, *S. acidiscabies* strain RL-110^T is not viable in the EP.

Residues in Water and Food

Dietary risks from food and water are not of concern

S. acidiscabies are common bacteria found in agricultural soils of North America that cause plant disease. When MBI-005 EP was 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 *S. acidiscabies*.

The EP has not been approved for food uses, therefore, as no residues of MBI-005 EP are expected on agricultural commodities and the establishment of an MRL is not required for *S. acidiscabies* strain RL-110^T and Thaxtomin A. 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 MBI-005 EP

Occupational risks are not of concern when MBI-005 EP is used according to label directions, which include protective measures

Workers handling MBI-005 EP can come into direct contact with *S. acidiscabies* strain RL-110^{T} and Thaxtomin A on the skin or by inhalation. For this reason, the product label will specify that workers exposed to the EP 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.

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 MBI-005 EP Is Introduced Into the Environment?

Environmental risks are not of concern.

S. acidiscabies is a bacterium that occurs naturally in soils. This bacterium is a plant pathogen that causes scab (i.e. cork-like lesions) on tuber crops. The microorganism's ability to infect plants is achieved through the production of a plant toxin called Thaxtomin A.

No environmental exposure to viable cells of *S. acidiscabies* strain RL-110T are expected following the proposed use of MBI-005 EP because the bacterium is killed prior to formulation. Based on the proposed use of MBI-005 EP as a spot treatment for dandelions, environmental exposure to Thaxtomin A is expected to be minimal.

Studies were conducted to determine the effects of MBI-005 TGAI or MBI-005 EP on birds, fish, bees, terrestrial and aquatic arthropods, aquatic plants and algae. These studies showed that MBI-005 TGAI was not toxic to birds, fish, bees, or arthropods. As expected, MBI-005 EP was toxic to terrestrial and aquatic plants, and algae.

Although terrestrial non-arthropod invertebrate, and microorganism toxicity/pathogenicity testing were not assessed in the review, adequate information was available to determine that significant adverse effects to these non-target organisms are not expected.

Value Considerations

What Is the Value of MBI-005 EP?

The registration of MBI-005 EP provides another non-conventional control option for dandelion in turf grass.

There are a number of conventional herbicides currently registered in Canada for the control of dandelion in turfgrass, including 2,4-D, dicamba, mecoprop-p, etc. However, there are fewer herbicides available to users in certain provinces and jurisdictions that have enacted legislation restricting pesticide availability for non-essential or cosmetic use. Corn gluten, chelated iron (FeHEDTA) and *Phoma macrostoma* strain 94-44B are non-conventional herbicides that are not included on the list of pesticides prohibited for sale by many provincial and municipal legislations. It is conceivable that MBI-005 EP could also be permitted for use in jurisdictions that have enacted legislation restricting pesticide availability, thereby providing a viable alternative in the control of dandelion in lawns.

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 MBI-005 EP to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

In individuals exposed to large quantities of MBI-005 EP, respiratory and dermal sensitivity could possibly develop upon repeated exposure to the product since all microorganisms, including *S. acidiscabies* strain RL-110^{T}, contain substances that are potential sensitizers. Therefore, anyone handling or applying MBI-005 EP 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. Also, the signal words, “POTENTIAL SENSITIZER” are required on the principal display panel of MBI-005 TGAI and MBI-005 EP; and the precautionary statements: “Avoid contact with eyes, skin and clothing.”, “Avoid inhaling/breathing mists.” and “May cause sensitization.” are required on the secondary display panel of the label for MBI-005 EP.

Environment

The EP label will include environmental precaution statements that prevent the contamination of aquatic systems from the use of MBI-005 EP.

Next Steps

Before making a final registration decision on *S. acidiscabies* strain RL-110^{T} and Thaxtomin A, 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 *S. acidiscabies* strain RL-110^{T} and Thaxtomin A (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

Streptomyces acidiscabies strain RL-110^{T} and Thaxtomin A

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active ingredient	Killed, non-viable *S. acidiscabies* strain RL-110^{T} and Thaxtomin A
Function	To control of dandelions (*Taraxicum*) on Kentucky bluegrass (*Poa pratensis*) and fescue (*Festuca spp*.) turf.
Binomial name	*Streptomyces acidiscabies* strain RL-110^{T}
Taxonomic designation[1]	
Kingdom	Bacteria
Phylum	Actinobacteria
Class	Actinobacteria
Subclass	Actionobacteridae
Order	Actionmycetales
Suborder	Streptomycineae
Family	Streptomycetaceae
Genus	*Streptomyces*
Species	*acidiscabies*
Strain	RL-110^{T}
Patent Status information	The applicant has not yet filed for a Canadian patent.
Minimum purity of active	TGAI: Killed, non-viable *S. acidiscabies* strain RL-110^{T} cells and spent fermentation media containing 21.46 mg/L Thaxtomin A EP: Killed, non-viable *S. acidiscabies* strain RL-110^{T} cells and spent fermentation media – 17% w/w; EP contains 7.8 g/L Thaxtomin A

Identity of relevant impurities of toxicological, environmental and/or significance.	The TGAI 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. *S. acidiscabies* strain RL-110^T produces the phytotoxin, Thaxtomin A, but is not known to produce any toxic secondary metabolites.

[1] http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=42234

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

Technical Grade Active Ingredient–MBI-005 TGAI

Property	Result
Colour	Amber
Physical state	Liquid
Odour	Grass-like
pH	7.44
Density/Relative Density/Bulk Density	0.999 g/mL
Viscosity	4.96 cP
Storage stability	Stable for up to 1 year at 4ºC
Corrosion characteristics	None

End-Use Product–MBI-005 EP

Property	Result
Colour	Black
Physical state	Liquid
Odour	Rancid sweet odour
Miscibility	Miscible with water
pH	6.6
Density/Relative Density/Bulk Density	1.02 g/mL
Viscosity	63.8 cP
Storage stability	Stable for up to 2 years at 25ºC
Corrosion characteristics	None

1.3 Directions for Use

MBI-005 EP is a selective, contact post-emergent herbicide that can provide partial suppression of dandelions infesting turfgrass (Kentucky bluegrass and fescues). The concentrate of MBI-005 EP must be mixed with water at a rate of 100 to 200 mL/L of total spray volume and applied as a foliar spray with hand-held equipment. The lower rate is to be used on newly germinated dandelions and the higher rate on more mature dandelions. Thorough coverage of weed foliage is necessary for effective control. For a longer period of dandelion suppression, additional applications may be necessary after the initial application. Repeat applications at 21 day intervals as required. Overspray of surrounding turf should be avoided to limit possible injury to turfgrass.

1.4 Mode of Action

The precise mode of action is unclear. Phytotoxic effects have been reported to be a result of various factors including the inhibition of cellulose biosynthesis as well as the alteration of calcium and sodium ion transport in cells. Reported phytotoxic effects include growth inhibition and necrosis.

2.0 Methods of Analysis

2.1 Methods for Identification of the Microorganisms

S. acidiscabies strain RL-110^{T} can be distinguished from other potato scab-causing *Streptomyces* species based on internally transcribed (ITS) and 16S rRNA sequences, and Biolog metabolic fingerprinting. *S. acidiscabies* has been historically differentiated by its ability to induce potato scab in lower pH soils than other scab-causing species such as *S. scabiei* and through phenotypic characterization (for example, spore morphology, pigment production, carbohydrate utilization, etc.).

S. acidiscabies strain RL-110^{T} can be distinguished from other strains of *S. acidiscabies* through its ability to use L-phenylalanine as a sole nitrogen source and its degree of pigment production.

Based on a comparison of phenotypic characteristics for scab-causing *Streptomyces* species, *S. acidiscabies* appears to be more closely related to *S. setonii* and *S. tendae* (80%) than to *S. scabiei* (64%). From a comparison of cellular fatty acid profiles, *S. acidiscabies* only has a low level of similarity (54%) with deep-pitted scab inducing strains of *Streptomyces*. Finally, using DNA-DNA hybridization, *S. acidiscabies* RL-110^{T} had a DNA relatedness of 74–85% with other *S. acidiscabies* strains, but only 13–21% DNA relatedness with other scab-causing *Streptomyces* species (for example, *S. europaeiscabiei, S. scabiei, S. stelliscabiei*, *S. reticuliscabiei*, etc.).

2.2 Methods for Establishment of Purity of Seed Stock

Cultures of *S. acidiscabies* strain RL-110^T are kept in sterile 25% glycerol and maintained as frozen vials. At least 100 vials are produced at a time and stored at -80°C.

To replenish the stock, a liquid growth medium is inoculated with an aliquot of the *S. acidiscabies* strain RL-110^T seed stock and incubated. Once the incubation period has elapsed, 100% sterile glycerol is added to the liquid culture to make a 25% (v/v) solution. A sample of liquid culture is then withdrawn for dry cell weight analysis and culture purity check. The seed stock is then dispensed in cryovials and kept frozen at -80°C.

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 TGAI is expressed as the concentration of Thaxtomin A present which is determined by high performance liquid chromatography (HPLC) analysis with photodiode array (PDA) detection. An analysis of five batches of MBI-005 TGAI for Thaxtomin A concentrations was submitted.

The guarantee of the EP is expressed as the concentration of Thaxtomin A present which is determined by HPLC analysis with PDA detection. An analysis of five batches of MBI-005 EP for Thaxtomin A concentrations was submitted.

Cell and spore viability testing is conducted on the TGAI to confirm inactivation of the active ingredient. Cell and spore viability data were submitted for one batch of the TGAI and a sample of heat-inactivated TGAI stored for one year at 2–8ºC in plastic containers. Cell and spore viability data were also submitted for six fermentation culture lots of *S. acidiscabies* RL-110^T that were heat inactivated at temperatures up to 60ºC for durations up to 90 minutes. Based on the submitted data, heat inactivation at 60ºC for 30 minutes is expected to adequately inactivate the cells and spores of *S. acidiscabies* RL-110^T.

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

MBI-005 EP is not intended for use on food crops. Therefore, the establishment of an MRL is not required for *S. acidiscabies* strain RL-110^T and Thaxtomin A.

2.5 Methods for Determination of Relevant Impurities in the Manufactured Material

The quality control procedures used to limit contaminating microorganisms during manufacture of MBI-005 TGAI and MBI-005 EP are acceptable. Any product that does not meet the applicant's specifications for microbial contamination is destroyed.

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

Based on the results of two year storage stability and corrosion characteristics testing, the EP is stable when stored at 25ºC for two years and is not corrosive. Based on the results of similar testing for a period of one year, the TGAI is stable when stored at 4ºC for one year.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

The PMRA conducted a detailed review of the toxicological database for the TGAI (MBI-005 TGAI), and the EP (MBI-005 EP). The database is complete, consisting of laboratory animal (in vivo) toxicity studies (acute oral toxicity, acute inhalation toxicity, acute intravenous infectivity, acute dermal toxicity/irritation, dermal sensitization, and eye irritation) that were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices and data waiver rationales. The scientific quality of the data is high and the database is considered sufficient to characterize the toxicity and infectivity of this pest control agent and product.

The applicant submitted acute oral, inhalation and dermal toxicity studies as well as eye and dermal irritation, and dermal sensitization studies on an alternate TGAI (MOI 005). However, these studies were not considered in the health risk assessment because the Thaxtomin A level was well below the level present in the proposed EP.

In an acute oral toxicity study, one group of three female fasted 8-week old Sprague-Dawley rats were given a single oral dose of MBI-005 EP (10350 mg/L Thaxtomin A) at doses of 5000 mg/kg bw (equivalent to 4.85 mL/kg bw). There were no treatment related clinical signs, body weight or necropsy signs during the study. Based on the results of this study, MBI-005 EP is of low toxicity.

Data waiver rationales were submitted to waive the requirements for acute oral pathogenicity and acute pulmonary pathogenicity testing for *S. acidiscabies* strain RL-110^T. MBI-005 TGAI is a selective biological herbicide containing fermentation solids of killed, non-viable *S. acidiscabies* strain RL-110^T cells. The waivers are based on the rationale that there was no pathogenicity or infectivity observed in rats when acutely exposed by intravenous injection to a high dose of viable *S. acidiscabies* strain RL-110^T. As well, there are no incidents of pathogenicity/infectivity, or other deleterious effects, to mammalian species from *S. acidiscabies* reported in the public scientific literature. The review of the cited study concluded that it had not been shown that *S. acidiscabies* strain RL-110^T was not pathogenic or infective to the rat when exposed intravenously. Although no signs of pathogenicity or infectivity were observed, *S. acidiscabies* strain RL-110^T was not successfully recovered from any tissue at any point during the study nor was the microbial enumeration method validated. The study is of limited utility in the risk assessment. However, further infectivity testing is not required since it has been shown that *S. cidiscabies* strain RL-110^T is not viable in the EP.

In an acute dermal toxicity study, one group of 10-week old Sprague-Dawley albino rats (5♀; 5♂) were dermally exposed to MBI-005 EP (10350 mg/L Thaxtomin A) at a dose of 5050 mg/kg bw for 24 hours to an area of approximately 10% of body surface area. There were no treatment related clinical signs, body weight or necropsy signs during the study. Two females lost weight from Day 0 to Day 7 but gained weight overall by Day 14. Based on the results of this study, MBI-005 EP is of low toxicity.

In a primary dermal irritation study, young adult New Zealand White rabbits (2♂; 1♀) were dermally exposed to 0.5 mL of MBI-005 EP (10350 mg/L Thaxtomin A) for 4 hours. Irritation was scored by the method of Draize. Very slight erythema was present only at the 1 hour observation interval. There were no other signs of dermal irritation during the study. In this study, MBI-005 EP is slightly irritating to the skin based on a mean irritation score (MIS) at 1 hour of 1 out of maximum possible score of 8.

In an acute inhalation toxicity study, one group of 10-week old Sprague-Dawly rats (5♀; 5♂) was exposed by nose-only inhalation route to MBI-005 EP (10350 mg/L Thaxtomin A) at a dose of 5.32 mg/L for four hours. There were no treatment related clinical signs or necropsy signs during the study. One male animal lost weight between Day 7 and Day 14. Based on the results of this study, MBI-005 EP is of low toxicity.

In a skin sensitization study with MBI-005 EP (10350 mg/L Thaxtomin A), 6-week old Hartley albino guinea pigs (10♂; 10♀) were tested using a challenge treatment that followed three induction treatments. All treatments given consisted of an undiluted 0.4 mL dose of test substance to bare skin. No irritation was observed at any point during the study.

In a primary eye irritation study, 0.1 mL of MBI-005 EP (10350 mg/L Thaxtomin A) was instilled into the conjunctival sac of the right eye of young adult New Zealand white rabbits (2♂; 1♀) for 24 hours. Eyes were washed with de-ionized water for 1 minute after the 24-hour observation. All rabbits had redness and chemosis of the conjunctivae 1 hour after treatment and one male and one female had discharge from the conjunctivae 1 hour after treatment. In this study, MBI-005 EP is minimally irritating to the eye based on a mean irritation score of 6.0 (out of a possible score of 110) in the rabbit.

In an acute intravenous infectivity study, one group of 8 week old Sprague-Dawley albino rats (15 ♀; 15 ♂) were injected with a subculture of MOI 005 *S. acidiscabies* (9.0×10^7 colony forming units [CFU]/mL) at a dose of 0.1 mL/animal (equivalent to 9.0×10^6 CFU/animal). There were no treatment related effects in any animal. The microbial enumeration method was not validated nor was *S. acidiscabies* strain RL-110^T successfully recovered from any blood or tissue sample. Although it is possible that *S. acidiscabies* strain RL-110^T may not be recoverable from animal blood or tissues, it was not demonstrated in this study. However, the absence of signs of pathogenicity or infectivity in this study corroborates the rationale to waive further pathogenicity testing

Further testing for pathogenicity/infectivity is not required since, in addition to the absence of signs of pathogenicity or infectivity during the intravenous infectivity testing, it has been shown that viable *S. acidiscabies* strain RL-110^T is not contained in the EP. Furthermore, there are no incidents of pathogenicity/infectivity, or other deleterious effects, to mammalian species from *S. acidiscabies* reported in the public scientific literature.

Although species belonging to the genus *Streptomyces* are well known to produce biologically active secondary metabolites, the species *S. acidiscabies* has only been reported to produce secondary metabolites belonging to the group of chemicals known as thaxtomins. In the published scientific literature, thaxtomins are not reported to be toxic or cause ill effect to mammals. However, they are known to facilitate pathogenesis in the bacterial infection of plants by inhibiting cellulose biosynthesis. Furthermore, no treatment related effects were observed in mammals that had been acutely exposed to MBI-005 EP (containing 10350 mg/L Thaxtomin A) in the studies detailed above.

Higher tier subchronic and chronic toxicity studies were not required because of the low acute toxicity of the EP, and no conclusive indications of infectivity, toxicity or pathogenicity of *S. acidiscabies* strain RL-110^T in the test animals treated in the Tier I acute oral and pulmonary toxicity/infectivity tests.

Within the available scientific literature, there are no reports that suggest *S. acidiscabies* strain RL-110^T or Thaxtomin A 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 *S. acidiscabies* strain RL-110^T or Thaxtomin A.

3.2 Occupational / Bystander Exposure and Risk Assessment

3.2.1 Occupational

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. *S. acidiscabies* has not been identified as a dermal wound pathogen, is not viable in the EP, there is no indication that it could penetrate intact skin of healthy individuals, and does not contain any known toxic secondary metabolites. Furthermore, dermal toxicity studies in animals demonstrated no signs of systemic toxicity to MBI-005 EP and MOI 005 (a version of MBI-005 TGAI containing viable *S. acidiscabies* strain RL-110^T).

The toxicity testing with the MBI-005 EP showed no significant signs of toxicity via the oral, dermal, or pulmonary routes of exposure. The submitted eye and dermal irritation studies with the EP demonstrated minimal eye and skin irritation.

Although dermal toxicity or toxicity from inhalation exposure is considered minimal from the proposed EP 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 MBI-005 EP 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. Also, the signal words, "POTENTIAL SENSITIZER" are required on the principal display panel of MBI-005 TGAI and MBI-005 EP; and the precautionary statements: "Avoid contact with eyes, skin and clothing.", "Avoid inhaling/breathing mists." and "May cause sensitization." are required on the secondary display panel of the label for MBI-005 EP.

Label warnings, restrictions and risk mitigation measures are adequate to protect users of MBI-005 EP, and no significant occupational risks are anticipated for this product.

3.2.2 Bystander

Overall, the PMRA does not expect that bystander exposures will pose an undue risk on the basis of the low toxicity/pathogenicity profile for *S. acidiscabies* strain RL-110^{T} and Thaxtomin A and the understanding that precautionary label statements will be followed by commercial applicators in the use of MBI-005 EP.

Although the label does allow applications to turf, residential or recreational areas; dermal and inhalation exposure to the general public will be very low since re-entry to into treated areas (i.e. turf, residential and recreational) is to be restricted until spray has dried. Therefore, non-occupational dermal exposure and risk to adults, infants and children are low. Also because the re-entry to treated sites is to be restricted until the product has dried, exposure to infants and children in school, residential and daycare facilities is likely to be minimal. Consequently, no adverse effects are anticipated due to the minimal exposure to bystanders and because MBI-005 EP demonstrated no oral or dermal toxicity at the maximum dose tested in the Tier I acute oral and acute dermal toxicity studies.

3.3 Incident Reports Related 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. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website www.healthcanada.gc.ca/pesticideincident. Incidents from Canada and the Unites States were searched and reviewed for *S. acidiscabies* strain RL110^{T} and Thaxtomin A.

As of August 22, 2013, there have been no incidents related to health or the environment reported to the PMRA, nor summarized by the UPEPA or the California Department of Pesticide Regulation (CalDPR), for products containing *S. acidiscabies* strain RL110^{T} or Thaxtomin A.

3.4 Dietary Exposure and Risk Assessment

3.4.1 Food

There are no proposed uses to food or feed crops and dietary exposure is not expected from the proposed use of the MBI-005 EP.

3.4.2 Drinking Water

The likelihood of *S. acidiscabies* strain RL110^T or Thaxtomin A entering neighbouring aquatic environments or surface water run-off from the proposed use of MBI-005 EP as a spot treatment on turf is considered very low.

No risks are expected from exposure to this active ingredient via drinking water because exposure will be minimal and there were no harmful effects observed in animals that were exposed orally in Tier I acute oral toxicity. The EP label instructs users not to contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes. Therefore, potential exposure to residues of *S. acidiscabies* strain RL110^T or Thaxtomin A in drinking water is negligible.

3.4.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

As there are no proposed uses to food or feed crops and given that the potential exposure to residues of *S. acidiscabies* strain RL-110^T and Thaxtomin A in drinking water is negligible, there is no concern for risks posed by dietary exposure of the general population, including infants and children, or animals to *S. acidiscabies* strain RL-110^T and Thaxtomin A.

3.5 Maximum Residue Limits

S. acidiscabies are common phytopathogenic bacteria found in agricultural soils of North America. Residues of *S. acidiscabies* strain RL-110^T and Thaxtomin A are not expected on agricultural commodities based on the turf use. In addition, the likelihood of residues contaminating drinking water supplies is negligible to non-existent. Therefore, the PMRA has determined that an MRL does not need to be established for *S. acidiscabies* strain RL-110^T and Thaxtomin A.

3.6 Aggregate Exposure

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 *S. acidiscabies* strain RL-110^T and Thaxtomin A to the general Canadian population, including infants and children, when the EP is used as labeled. 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, no adverse effects from exposure to other isolates of phytopathogenic streptomycetes (for example, *S. acidiscabies*, *S. scabies*, and *S. turgidiscabies*) encountered in the environment have been reported. Even if

there is an increase in exposure to this active ingredient from the use of MBI-005 EP, there should not be any increase in potential human health risk.

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 naturally occurring strains of phytopathogenic streptomycetes in the environment, the PMRA is not aware of any other microorganisms, or other substances that share a common mechanism of toxicity with *S. acidiscabies* strain RL-110^T and Thaxtomin A. No cumulative effects are anticipated if the residues of *S. acidiscabies* RL-110^T interact with related strains of this microbial species.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

S. acidiscabies is a Gram positive bacterium that occurs naturally in soils. Similar to *S. scabies*, this bacterium is a plant pathogen that causes scab (i.e. cork-like lesions) on tuber crops. *S. acidiscabies* has been historically recognized for its acid tolerance and its ability to induce potato scab in lower soil pH than other scab-causing species. Like other scab-producing *Streptomyces* species, pathogenicity is achieved through the production of phytotoxins called thaxtomins (4-nitroindol-3-yl-containing 2,5-diopiperazines). Although several kinds of Thaxtomin have been identified, Thaxtomin A is the predominant compound produced by *S. acidiscabies*. Strain RL-110^T was one of several strains of *S. acidiscabies* originally isolated from potato tuber samples with common scab disease collected from soils with pH under 5.2, in Maine and New York.

Following the proposed use of MBI-005 EP to control dandelions on turf, no environmental exposure to viable *S. acidiscabies* strain RL-110^T is expected because the bacterium is killed prior to formulation. Environmental exposure to Thaxtomin A is expected to be minimal based on the proposed use of MBI-005 EP as a spot treatment for dandelions.

The environmental fate of Thaxtomin A has not been fully characterized. Based on a number of published studies, it appears that this phytotoxin is at least partially degraded by soil bacteria and fungi. The identified microorganisms include common members of the soil microbial community, such as *Ralstonia pickettii*, *Penicillium* species, *Trichoderma* species, and *Streptomyces* species. Other studies showed that some of the phytotoxic activity of Thaxtomin A could be detoxified by some plants and by soil microorganisms through a process of glucosylation. In one study, *Aspergillus niger* was shown to transform Thaxtomin A to much less phytotoxic metabolites through a process of cyclodehydration. None of these studies demonstrated the complete degradation of Thaxtomin A. However, the microbial degradation of nitroaromatic compounds, such as Thaxtomin A, by various soil microorganisms is documented in published literature.

Based on physical and chemical properties, Thaxtomin A is expected to have a low potential for mobility in soil, be stable to hydrolysis in aquatic environments and degrade by photolysis in the environment. The solubility of Thaxtomin A in water is 23 ppm which classifies it as slightly soluble in water. Thaxtomin A has an octanol water partition coefficient (log K_{ow}) of 1.51 at pH 7 therefore its mobility in soil would be very high. The applicant has also noted that the photodegradation of Thaxtomin A is dependent on environmental conditions. In aqueous and dry conditions, it was observed that 64% and 3% of active compound remained after 1 day of UV exposure, respectively; however, no studies were submitted to support these values.

4.2 Effects on Non-Target Species

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

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

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

4.2.1 Effects on Terrestrial Organisms

Several studies and scientific rationales were submitted to address the hazards of the TGAI to terrestrial non-target organisms. These studies included non-target avian species, arthropods and plants.

The acute oral toxicity of MBI-005 TGAI (killed whole cell broth of *S. acidiscabies* strain RL-110^T) to mallard duck (*Anas platyrhynchos*; 30 ducks) was assessed over 30 days. MBI-005 TGAI was administered to the birds by oral gavage at 10 mL/kg body weight (equivalent to 63 mg dry cell/kg bw and 0.6273 mg/kg bw Thaxtomin A) for 5 consecutive days. The 30-day acute oral LD_{50} was greater than 63 mg dry cell/kg bw for 5 consecutive days or greater than 0.6273 mg Thaxtomin A/kg bw for 5 consecutive days and the no-observed effect level (NOEL) was 63 mg dry cell/kg bw for 5 consecutive days or 0.6273 mg Thaxtomin A/kg bw for 5 consecutive days. There were no treatment-related findings or mortalities.

In a 20-day dietary toxicity study, adult honeybees (*Apis mellifera*; 200 bees/group) were fed MBI-005 TGAI (killed concentrated whole cell broth of *S. acidiscabies* strain RL-110^T) in a 30% w/v sucrose suspension at a concentration of 500 µg dry cell/mL (equivalent to 21.5 µg/mL Thaxtomin A). The study was terminated on Day 20 when mortality in the negative control group reached 30%. At study termination, mortality in the MBI-005 TGAI treatment group was 16.5%. There were no toxic symptoms observed in the test groups during the test period. The 20-day LC_{50} was greater than 500 µg dry cells/mL or greater than 21.5 µg/mL Thaxtomin A, and the no-observed effect concentration (NOEC) was 500 µg dry cells/mL or 21.5 µg/mL Thaxtomin A.

In a 10-day dietary toxicity study, 1-day old green lacewing larvae (*Chrysoperla rufilabris*; 30/test group) were fed MBI-005 TGAI (killed concentrated whole cell broth of *S. acidiscabies* strain RL-110^T) in moth egg water meal at concentrations of 510, 5100 and 51000 ppm (equivalent to approximately 0.53, 5.3 and 53 ppm Thaxtomin A). The study was terminated on Day 10 after mortality in the negative control group exceeded 20% (13/59). At termination, mortality in the groups treated with 510, 5100 and 51000 ppm was 30% (9/30), 30% (9/30) and 33% (10/30), respectively. There were no sublethal effects noted during the study. The 10-day LC_{50} was greater than 51000 ppm MBI-005 TGAI or greater than 53 ppm Thaxtomin A, and the NOEC was 51000 ppm MBI-005 TGAI or 53 ppm Thaxtomin A.

In a 17-day dietary toxicity study, adult ladybird beetles (*Hippodamia convergens*; 75/test group) were fed MBI-005 TGAI (killed concentrated whole cell broth of *S. acidiscabies* strain RL-110^T) in a 30% honey and water suspension at concentrations of 510, 5100 and 51000 ppm or (equivalent to approximately 0.53, 5.3 and 53 ppm Thaxtomin A). The study was terminated on Day 17 after mortality in the negative control group exceeded 20% (16/75). At termination, mortality in the groups treated with 510, 5100 and 51000 ppm was 24% (18/74), 25% (19/75) and 32% (24/74), respectively. Lethargy and immobility was noted sporadically in both treatment and control groups, however, surviving beetles were generally normal in appearance and behaviour. The 17-day LC_{50} was greater than 51000 ppm MBI-005 TGAI or greater than 53 ppm Thaxtomin A and the NOEC was 5100 ppm MBI-005 TGAI or 5.3 ppm Thaxtomin A.

In a 22-day toxicity study, adult parasitic wasps (*Aphidius matricariae*) were exposed to MBI-005 TGAI (killed concentrated whole cell broth of *S. acidiscabies* strain RL-110^T)-treated plants artificially infested with green peach aphids at a rate of approximately 10× the application rate (not defined). At study termination, adult wasp emergence in autoclaved MBI-005 TGAI control, sterile filtrate control, negative control and MBI-005 TGAI groups were 75 (51 mummies removed), 35 (35 mummies removed), 55 (34 mummies removed), and 20 (11 mummies removed), respectively. The number of mummies was undercounted because parasitized aphids were present on leaves containing mummies. There were no observed abnormalities on plants or aphids. The 22-day EC_{50} was greater than 10× the application rate. This study was acceptable; however, its utility in the risk assessment is limited because the application rate was not clearly defined in the study report.

In a terrestrial plant toxicity study, the effect of MBI-005 EP (17% inactive *S. acidiscabies* strain RL-110^T) was evaluated on wheat (*Triticum aestivum* v. PR1404), corn (*Zea mays* v. Early Sunglow), sorghum (*Sorghum bicolor*), rice (*Oryza sativa* v. M104), kentucky bluegrass (*Poa pratensis*), creeping bentgrass (*Agrostis stolonifera*), chives (*Allium schoenoprasum*), onions (*Allium cepa* v. Yellow), soybean (*Glycine max* v. Beer Friend), barley (*Hordeum vulgare*), tomato (*Lycopersicon esculentum* v. Brandywine), lettuce (*Lactuca sativa* v. Celtuce), bean (*Phaseolus vulgaris* v. Blue Lake), broccoli (*Brassica oleracea* v. Packman), cucumber (*Cucumis sativus* v. SMR58 Pickling), peas (*Pisum sativum* v. Dwarf Grey), redstem (*Ammania robusta*), smallflower umbrella sedge (*Cyperus difformis*), redroot pigweed (*Amaranthus retroflexus*), and mustard (*Brassica juncea* v. Florida Broadleaf). Treatments consisted of MBI-005 EP groups at 40×, 20×, and 10× dilutions (equivalent to 0.2, 0.39 and 0.79 mg/mL Thaxtomin A). After 8 days, very mild to moderate symptoms of phytotoxicity were observed in monocots at all test concentrations with the exception of onions. Some severe symptoms of phytotoxicity were observed in onions. In dicots, very mild to severe symptoms were also observed, however, the frequency of moderate and severe phytotoxicity was much greater. Based on these results, MBI-005 EP is toxic to non-target plants, especially broadleaf plants. The scope of the study, however, was limited since it did not include standard plant parameters such as percent germination, seedling emergence, root weight, root length, shoot weight and shoot length. Consequently, the utility of this study in the risk assessment is limited.

From the data submitted under the Part M4 Human Health and Safety Testing, it was determined that MBI-005 TGAI and MBI-005 EP were not toxic to mammals via the oral, pulmonary or dermal routes. The infectivity and pathogenicity results via the pulmonary and intravenous routes were of limited utility in the health risk assessment; however, negligible environmental exposure to the live bacterium is expected since it is killed prior to formulation. Furthermore, no reports of adverse effects to mammals were found in PubMed using the keywords “Streptomyces acidiscabies” or “Thaxtomin” and minimal exposure is expected from the proposed use of MBI-005 EP, i.e. spot treatment on turf. Consequently, the risk to wild mammals is expected to be low. No further data are required to assess the risk of harm to non-target wild mammals.

No toxicity or pathogenicity data were considered to address the potential for harm to non-target terrestrial non-arthropod invertebrates or microorganisms. No infectivity or pathogenicity concerns were identified with the proposed use of MBI-005 EP since the bacterium will be killed in the end-use product. Also, a search in the PubMed database using the keywords "Streptomyces acidiscabies" or "Thaxtomin" found no reports of adverse effects to any non-target terrestrial organism other than plants.

Based on all the available data and information on the effects of *S. acidiscabies* strain RL-110^T to non-target terrestrial organisms, there is reasonable certainty that no harm will be caused to birds, wild mammals, terrestrial arthropods, terrestrial non-arthropod invertebrates, and microorganisms from the proposed use of MBI-005 EP. The proposed use of Thaxtomin A in MBI-005 EP could, however, harm non-target terrestrial plants but these effects should be minimal based on the proposed use of this end use product, i.e. spot treatments on turf.

4.2.2 Effects on Aquatic Organisms

Four studies and scientific rationales were submitted to address the hazards of the TGAI to aquatic non-target organisms. These studies included non-target fish species, arthropods, plants and algae.

In a 30-day toxicity study, bluegill sunfish (*Lepomis macrochirus*; 10 fish/group) were exposed to MBI-005 TGAI (killed concentrated whole cell broth of *S. acidiscabies* strain RL-110^T) under static/renewal. Test fish were exposed aquatically to 1.1, 11 and 28 mg dry cell/L (equivalent to 0.19, 1.9 and 4.8 ppm Thaxtomin A). Test fish were also fed feed containing 110 mg dry cells/kg (equivalent to 18.9 mg Thaxtomin A/kg) at a rate of 0.03 g/aquarium/day. None of the fish died and no signs of toxicity were observed throughout the study. At necropsy, there were no significant findings. The 30-day LC_{50} for bluegill sunfish was greater than 28 mg dry cell/L or greater than 4.8 ppm Thaxtomin A and the NOEC was 28 mg dry cells/L or 4.8 ppm Thaxtomin A.

In a 21-day toxicity study, daphnia (*Daphnia magna*; 20 daphnids/group) were exposed to MBI-005 TGAI (killed concentrated whole cell broth of *S. acidiscabies* strain RL-110^T) under static renewal. Daphnids were exposed aquatically to concentrations of 1.1, 11 and 28 mg dry cell/L (equivalent to 0.19, 1.9 and 4.8 ppm Thaxtomin A). At study termination, mortalities in the negative control, sterile filtrate control, 1.1 mg dry cell/L, 11 mg dry cells/L, and 28 mg dry cells/L were 10%, 45%, 5%, 35%, and 20%, respectively. Daphnids in the groups treated with 11 mg dry cells/L and 28 mg dry cells/L were pale and small relative to negative control daphnids. The mean cumulative number of offspring per female observed for daphnids exposed to negative control, sterile filtrate control, 1.1 mg dry cells/L, 11 mg dry cells/L and 28 mg dry cells/L was 130, 118, 151, 80, and 20, respectively. The 21-day LC_{50} for MBI-005 TGAI was greater than 28 mg dry cells/L or greater than 4.8 ppm Thaxtomin A and the NOEC was 1.1 mg dry cell/L or 0.19 mg/L Thaxtomin A.

In a 21-day toxicity study, third instar amphipods (*Hyalella Azteca*; 40 amphipods/group) were exposed to MOI-005 (killed concentrated whole cell broth of *S. acidiscabies* strain RL-110^T; equivalent to MBI-005 TGAI) under static renewal. Amphipods were exposed aquatically to concentrations of 11.0, 110.4 and 1104 mg dry cells/L (equivalent to 4.14, 41.4 and 414 mg/L Thaxtomin A). Survival rates at study termination were 100% and 93% for the negative control and sterile filtrate control groups, and 98%, 95% and 98% for the groups treated with MOI-005 at 11.0 mg/L, 110.4 mg/L, and 1104 mg/L MOI-005. A mean biomass of 0.130 mg per amphipod was observed in the negative control organisms as well as amphipods treated with MOI-005 at 11.04 mg/L. A mean biomass of 0.074 mg per organism was observed in amphipods exposed to sterile filtrate. Mean biomasses of 0.121 and 0.063 mg per organism were observed in groups treated with MOI-005 at 110.4 and 1104 mg/L, respectively. The LC_{50} was determined to be greater than 1104 mg dry cells/L or greater than 414 mg Thaxtomin A/L. An EC_{50} for growth was determined to be 1057 mg/L or ~396 mg/L Thaxtomin A (calculated value) and the NOEC was determined to be 110.4 mg dry cell/L or 41.4 mg/L Thaxtomin A.

In an aquatic vascular plant study, the effect of MBI-005 EP was determined on duckweed, *Lemna minor*, over a period of 7 days. Plants were exposed to MBI-005 EP in Steinberg medium at 1714×, 1000×, 600×, 333×, 188×, 107×, 60×, 30× and 20× dilutions (equivalent to 4.6, 7.8, 13, 23, 41, 73, 130, 260 and 390 mg/L Thaxtomin A). The growth of duckweed was markedly affected by MBI-005 EP. The number of fronds was significantly reduced and the percent bleaching of fronds was approximately 50%. At 600× dilution and above, 100% bleaching of fronds was observed. This study is classified as acceptable, but is of limited utility for the risk assessment purposes due to a general lack of detail.

In an algal growth inhibition study, the effect of MBI-005 EP was determined on the alga, *Pseudokirchneriella subcapitata*. Algae were exposed to MBI-005 EP in nutrient broth at 14000×, 2800×, 1400×, 560×, 280×, 140×, 47×, 28× and 20× dilutions (equivalent to 0.6, 2.8, 5.6, 14, 28, 56, 166, 279 and 390 mg/L Thaxtomin A). Algal growth was inhibited at all test concentrations. This study was classified as acceptable, but is of limited utility for the risk assessment purposes due to a general lack of detail.

No toxicity/pathogenicity data were considered to address the potential for harm to aquatic non-target non-arthropod invertebrates. No infectivity or pathogenicity concerns were identified with the proposed use of MBI-005 EP since the bacterium will be killed in the end-use product. As previously noted, MBI-005 EP contains a known phytotoxin, Thaxtomin A, but a search in the PubMed database using the keywords “Streptomyces acidiscabies” or “Thaxtomin” found no reports of adverse effects to aquatic non-arthropod invertebrates.

Based on all the available data and information on the effects of *S. acidiscabies* strain RL-110^T to non-target aquatic organisms, there is reasonable certainty that no harm will be caused to fish, aquatic arthropods, and aquatic non-arthropod invertebrates. MBI-005 EP could harm aquatic plants, however, these effects should be negligible based on the proposed use of this end use product, i.e. spot treatments on turf. As a precaution, standard label statements will prohibit handlers and applicators from contaminating aquatic habitats during application, clean-up and repair.

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/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 August 22, 2013, 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 *S. acidiscabies* strain RL-110^{T} or Thaxtomin A for use as pesticides.

5.0 Value

5.1 Effectiveness Against Pests

To support the registration of MBI-005 EP, the applicant submitted data from a total of five trials conducted on dandelion in California (1), Michigan (1), North Carolina (1) and New York (2) in 2010 (2) and 2011 (3). The data that were provided demonstrated that a 5x and 10x dilution of MBI-005 EP can have activity against dandelion in turf when applied as a spot treatment (as proposed). The activity on dandelion observed in the trials for which data were provided was quite variable, with poor to moderate activity noted. Two applications of MBI-005 EP were shown to improve activity against dandelion (compared to one application), with no increase in turfgrass injury observed.

5.2 Non-Safety Adverse Effects

To support the registration of MBI-005 EP, the applicant submitted data from a total of five trials conducted on turfgrass in California (1), Michigan (1) and New York (3) in 2010 (2) and 2011 (3). The provided trial data showed less activity being observed on the fescue / bluegrass than on the dandelion, suggesting that MBI-005 EP has differential selectivity for dandelion. Although MBI-005 EP was observed to have less activity against fescue / bluegrass than dandelion, one trial showed a level of turfgrass injury with the 5x dilution that might be considered unacceptable. Accordingly, the inclusion of precautionary statements on the label is warranted regarding the potential for turfgrass injury.

5.3 Consideration of Benefits

5.3.1 Social and Economic Impact

There are no priorities listed in the Canadian Grower Priority Database for dandelion control in turf.

There are a number of conventional herbicides currently registered in Canada for the control of dandelion in turfgrass. However, there are fewer herbicides available to users in certain provinces and jurisdictions that have enacted legislation restricting pesticide availability for non-essential or cosmetic use. Corn gluten, chelated iron (FeHEDTA) and *Phoma macrostoma* strain 94-44B are non-conventional herbicides that are not included on the list of pesticides prohibited for sale by many provincial and municipal legislations. It is conceivable that MBI-005 EP could also be permitted for use in jurisdictions that have enacted legislation restricting pesticide availability, thereby providing a viable alternative in the control of dandelion in lawns.

5.3.2 Survey of Alternatives

There are a number of conventional chemicals currently registered for the control of dandelion in turfgrass, many of which are classified as Group 4 Herbicides; examples include 2,4-D, dicamba, mecoprop-p etc. There are also a variety of non-conventional herbicides registered for dandelion control on turfgrass, including corn gluten, chelated iron (FeHEDTA), and *Phoma macrostoma*.

5.3.3 Compatibility with Current Management Practices Including Integrated Pest Management

MBI-005 EP offers an alternative to the use of traditional chemical herbicides for the control of dandelions in turf. The availability of MBI-005 EP will allow the possibility to develop and implement sustainable turf management practices, especially in areas where the application of chemical herbicides is undesirable or prohibited by law.

The application of MBI-005 EP is compatible with all the integrated pest management practiced in turf such as adequate fertilization of the lawn, irrigation, overseeding, manual removing of weeds, etc.

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

It is unknown at this time if and to what degree MBI-005 EP would contribute to resistance management given that the precise mode of action is unclear (phytotoxic effects have been reported to be a result of various factors including the inhibition of cellulose biosynthesis as well as the alteration of calcium and sodium ion transport in cells). At present, there are no cellulose biosynthesis inhibiting herbicides registered for use in turf in Canada and very few cases of reported resistance to cellulose biosynthesis inhibitors worldwide.

5.3.5 Contribution to Risk Reduction

MBI-005 EP is a non-conventional product that offers an alternative to the use of traditional chemical herbicides in turf, especially where the use of traditional herbicides is not desirable or prohibited by law. As such, these products may contribute to a reduction in the use of chemical herbicides in turf.

5.4 Supported Uses

A claim of partial suppression of dandelion in turfgrass (Kentucky bluegrass and fescues) with repeat application every 21 days, as required, is supported.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

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

MBI-005 TGAI and MBI-005 EP were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track I criteria. The PMRA has reached the following conclusions:

- MBI-005 TGAI 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.

[5] 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*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- MBI-005 EP and MBI-005 TGAI do not contain any other formulants or contaminants of environmental concern identified in the *Canada Gazette,* Part II, Volume 139, Number 24, pages 2641-2643: *List of Pest Control Product Formulants of Health or Environmental Concern*.

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

7.0 Summary

7.1 Methods for Analysis of the Micro-organism as Manufactured

The product characterization data for MBI-005 TGAI and MBI-005 EP were judged to be adequate to assess their potential human health and environmental risks. The TGAI was characterized and the specifications of the EP were supported by the analyses of a sufficient number of batches. Storage stability data were sufficient to support a shelf life of two years for the EP when stored at 25ºC and one year for the TGAI when stored at 4ºC.

---

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

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

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

7.2 Human Health and Safety

The acute toxicity and infectivity studies and other relevant information submitted in support of *S. acidiscabies* strain RL-110^T and Thaxtomin A were determined to be sufficiently complete to permit a decision on registration. Submitted information suggests, MBI-005 EP was of low toxicity by the oral, pulmonary, and dermal routes, and the risk from pathogenicity or infectivity is negligible since *S. acidiscabies* strain RL-110^T is not viable in the EP. The TGAI and the EP are considered to be potential sensitizers.

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 MBI-005 EP, respiratory and dermal sensitivity could possibly develop upon repeated exposure to the product since all microorganisms, including *S. acidiscabies* strain RL-110^T, contain substances that are potential sensitizers. Therefore, anyone handling or applying MBI-005 EP 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. Also, the signal words, "POTENTIAL SENSITIZER" are required on the principal display panel of MBI-005 TGAI and MBI-005 EP; and the precautionary statements: "Avoid contact with eyes, skin and clothing.", "Avoid inhaling/breathing mists." and "May cause sensitization." are required on the secondary display panel of the label for MBI-005 EP.

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.

7.3 Environmental Risk

The non-target organism tests, scientific rationales and supporting published scientific literature submitted in support of MBI-005 TGAI and MBI-005 EP were determined to be sufficiently complete to permit a decision on registration. The use of MBI-005 EP containing *S. acidiscabies* strain RL-110^T 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 MBI-005 EP 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.

No other environmental fate studies or non-target organism studies are required to consider a decision on the registration of MBI-005 EP for use against dandelions on turf.

7.4 Value

The data submitted to register MBI-005 EP are sufficient to support the following claims:

- One or more post-emergence applications of MBI-005 EP for the partial suppression of dandelion in turfgrass (Kentucky bluegrass and fescues).

- Repeat applications every 21 days as required.

MBI-005 EP offers an alternative to the use of chemical herbicides for the control of dandelion in turfgrass, especially where the use of traditional chemical herbicides is not desirable or prohibited by law.

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 MBI-005 TGAI and MBI-005 EP, containing the active ingredient *Streptomyces acidiscabies* strain RL-110^{T} and Thaxtomin A, for the partial suppression of dandelion in turfgrass (Kentucky bluegrass and fescues).

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
µg	micrograms
bw	body weight
CalDPR	California Department of Pesticide Regulation
cP	centepoise
CFU	colony forming unit
DNA	deoxyribonucleic acid
EIIS	Ecological Incident Information System
EP	end-use Product
EC_{50}	median effect concentration
FDA	*Food and Drugs Act*
g	gram
HPLC	high performance liquid chromatography
ITS	internally transcribed
kg	kilogram
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOC	level of concern
mg	milligram
mL	millilitre
MIS	mean irritation score
MCC	maximum challenge concentration
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
PDA	photodiode array
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RQ	risk quotient
rRNA	ribosomal ribonucleic acid
TGAI	technical grade of the active ingredient
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume
w/v	weight per volume
w/w	weight per weight

Appendix I Tables and Figures

Table 1 Toxicity and Infectivity of MBI-005 TGAI and its associated EP, MBI-005 EP

Study Type	Species, Strain, and Doses	Results	Comments	Reference(s)
Acute Toxicity/Infectivity of MOI 005 (viable form of TGAI)				
Acute Oral Toxicity (14-Day study)	Rat- Sprague-Dawley 3♀, Singal oral dose, 5000 mg/kg bw (5.02 mL/kg bw; containing 27.2 mg/L Thaxtomin A), Body weight measured on Days 0, 7 and 14.	LD_{50}> 5000 mg/kg bw	**LOW TOXICITY LIMITED UTILITY**	PMRA 1973027
Acute Oral Pathogenicity (waiver)	In lieu of acute oral pathogenicity testing, the registrant submitted a waiver rationale. There was no pathogenicity or infectivity observed in rats when acutely exposed by intravenous injection to a high dose of viable *S. acidiscabies* strain RL-110^T. As well, there are no incidents of pathogenicity/infectivity, or other deleterious effects, to mammalian species from *S. acidiscabies* reported in the public scientific literature. Although the intravenous pathogenicity study did not meet the guideline requirements, no further pathogenicity/infectivity data are required since no viable *S. acidiscabies* strain RL-110^T is contained in MBI-005 EP. **WAIVER ACCEPTED**			PMRA 1973038
Acute Dermal Toxicity (14-Day study)	Rat- Sprague-Dawley 5/sex, 24 hour dermal exposure, 5050 mg/kg bw (5.17 mL/kg bw; containing 83.0 mg/L Thaxtomin A; dry cell weight *S. acidiscabies* strain RL-110^T 5.0 mg/mL). Body weight measured on Days 0, 7 and 14.	LD_{50}> 5050 mg/kg bw	**LOW TOXICITY LIMITED UTILITY**	PMRA 1973032

Study Type	Species, Strain, and Doses	Results	Comments	Reference(s)
Acute Inhalation Toxicity (14-Day study)	Rat- Sprague-Dawley 5/sex, 4 hour nose-only exposure, 2.21 mg/L (containing 83.0 mg/L Thaxtomin A; dry cell weight *S. acidiscabies* strain RL-110^T 5.0 mg/mL). Body weight measured on Days 0, 7 and 14.	LC_{50} > 2.21 mg/L Reduced activity and piloerection at 4.5 and 6 hours in all animals. Significant body weight loss between Day 7 and 14 in, and pink and swollen lungs in 5 ♂ and 4 ♀ animals; red lungs in 1♀ animal.	**LOW TOXICITY** **LIMITED UTILITY**	PMRA 1973036
Acute Inhalation Pathogenicity (waiver)	In lieu of acute inhalation pathogenicity testing, the registrant submitted a waiver rationale. There was no pathogenicity or infectivity observed in rats when acutely exposed by intravenous injection to a high dose of viable *S. acidiscabies* strain RL-110^T. As well, there are no incidents of pathogenicity/infectivity, or other deleterious effects, to mammalian species from *S. acidiscabies* reported in the public scientific literature. Although the intravenous pathogenicity study did not meet the guideline requirements, no further pathogenicity/infectivity data are required since no viable *S. acidiscabies* strain RL-110^T is contained in MBI-005 EP. **WAIVER ACCEPTED**			PMRA 1973038
Acute Intravenous Infectivity (21-Day study)	Rat- Sprague-Dawley 15/sex, Intravenous injection, 0.1 mL/aninmal (9.0×10^7 CFU/mL); equivalent to 9.0×10^6 CFU/animal. Body weights measured and interim sacrifices, necropsy, organ weight measurement, and microbial enumeration performed on Days 0, 7, 14 and 21. Inactivated test substance control: (15 ♀; 15 ♂). Untreated control: (15 ♀; 15 ♂).	No signs of infection or pathogenicity were observed. One treated male and one treated female had lost weight on Day 7. *S. acidiscabies* strain RL-110^T was not recovered from animal blood or tissue.	**NOT PATHOGENIC** **LIMITED UTILITY**	PMRA 1973030

Study Type	Species, Strain, and Doses	Results	Comments	Reference(s)
Acute Irritation/Sensitization of MOI 005 (viable form of TGAI)				
Dermal Irritation	Rabbit-New Zealand 1 ♂; 2 ♀, 4 hour dermal exposure, 0.5 mL/animal (containing 83.0 mg/L Thaxtomin A; dry cell weight *S. acidiscabies* strain RL-110^T 5.0 mg/mL). Observed for 72 hours.	No signs of irritation observed.	**NON-IRRITATING** **LIMITED UTILITY**	PMRA 1973033
Eye Irritation	Rabbit-New Zealand 1 ♂; 2 ♀, 24 hour ocular exposure, 0.1 mL/animal (containing 83.0 mg/L Thaxtomin A; dry cell weight *S. acidiscabies* strain RL-110^T 5.0 mg/mL). Observed for 72 hours	MIS= 2.7/110 (1 hour) All animals experienced conjunctival redness; corneal opacity in 1 ♀.	**MINIMALLY IRRITATING** **LIMITED UTILITY**	PMRA 1973035
Skin Sensitization	Guinea Pig-Hartley 10/sex 3 induction treatments (1 week intervals) followed by challenge treatment (2 weeks after last induction), 0.4 mL/animal (containing 83.0 mg/L Thaxtomin A; dry cell weight *S. acidiscabies* strain RL-110^T 5.0 mg/mL) for each treatment.	No signs of irritation observed.	**NEGATIVE FOR SKIN SENSITIZATION** **LIMITED UTILITY**	PMRA 1973034
Acute Toxicity of MBI-005 EP				
Acute Oral Toxicity (14-Day study)	Rat- Sprague-Dawley 3♀, Singal oral dose, 5000 mg/kg bw (4.85 mL/kg bw; containing 10350 mg/L Thaxtomin A). Body weight measured on Days 0, 7 and 14.	LD_{50}> 5000 mg/kg bw	**LOW TOXICITY** **ACCEPTABLE**	PMRA 2325403

Study Type	Species, Strain, and Doses	Results	Comments	Reference(s)
Acute Dermal Toxicity (14-Day study)	Rat- Sprague-Dawley 5/sex, 24 hour dermal exposure, 5050 mg/kg bw (4.89 mL/kg bw; containing 10350 mg/L Thaxtomin A). Body weight measured on Days 0, 7 and 14.	LD_{50}> 5050 mg/kg bw	**LOW TOXICITY ACCEPTABLE**	PMRA 2325404
Acute Inhalation Toxicity (14-Day study)	Rat- Sprague-Dawley 5/sex, 4 hour nose-only exposure, 5.32 mg/L (containing 10350 mg/L Thaxtomin A). Body weight measured on Days 0, 7 and 14.	LC_{50} > 5.32 mg/L One male lost weight between Day 7 and 14.	**LOW TOXICITY ACCEPTABLE**	PMRA 2325409
Acute Irritation/Sensitization of MBI-005 EP				
Dermal Irritation	Rabbit-New Zealand 2 ♂; 1 ♀, 4 hour dermal exposure, 0.5 mL/animal (containing 10350 mg/L Thaxtomin A). Observed for 72 hours.	MIS = 1.0/8.0 (1 hour) Very slight erythema (1 hour).	**SLIGHTLY IRRITATING ACCEPTABLE**	PMRA 2325405
Eye Irritation	Rabbit-New Zealand 2 ♂; 1 ♀, 24 hour ocular exposure, 0.1 mL/animal (containing 10350 mg/L Thaxtomin A). Observed for 72 hours.	MIS = 6.0/110 (1 hour) All rabbits had redness and chemosis of the conjunctivae (1 hour) and one male and one female had discharge from the conjunctivae (1 hour).	**MINIMALLY IRRITATING ACCEPTABLE**	PMRA 2325407

Study Type	Species, Strain, and Doses	Results	Comments	Reference(s)
Skin Sensitization	Guinea Pig-Hartley 10/sex 3 induction treatments (1 week intervals) followed by challenge treatment (2 weeks after last induction), 0.4 mL/animal (containing 10350 mg/L Thaxtomin A) for each treatment.	No signs of irritation observed.	**NEGATIVE FOR SKIN SENSITIZATION ACCEPTABLE**	PMRA 2325406

Table 2 Toxicity to Non-Target Species

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
Terrestrial Organisms				
Vertebrates				
Birds	Oral – *Anas platyrhynchos*, 14 days old	Six replicates of birds (5/replicate) were gavaged with MBI-005 TGAI at a dose of 10 mL/kg bw (equivalent to 63 mg dry cell mass/kg bw or 0.6273 mg Thaxtomin A/kg/bw) for 5 consecutive days. Two replicates of birds (5/replicate) were gavaged with MBI-005 Sterile Filtrate Media at at 10 mL/kg bw. Two replicates of birds (5/replicate) were gavaged with sterile saline at a dose of 10 mL/kg bw. 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. Pathogenicity and infectivity were not assessed. 30-day acute oral LD_{50} >10 mL/kg bw per day for five days (equivalent to > 0.6273 mg Thaxtomin A/kg bw per day for five days or >63 mg cells/kg bw per day for five days). 30-day NOEL 10 mL/kg bw per day for five days (equivalent to 0.6273 mg Thaxtomin A/kg bw per day for five days or 63 mg cells/kg bw per day for five days). **ACCEPTABLE (Toxicity only)**	PMRA 1973040, 2075046

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
	Pulmonary	A request to waive the requirement for test data was submitted. No adverse effects were observed in the avian acute oral toxicity study and no reports of adverse effects were found in published scientific literature. The requirement for avian pulmonary testing has been waived.		PMRA 1973038
Wild Mammals	From the data submitted under the Part M4 Human Health and Safety Testing, it was determined that MBI-005 TGAI and MBI-005 EP were not toxic to mammals via the oral, pulmonary or dermal routes. The infectivity and pathogenicity results via the pulmonary and intravenous routes were of limited utility in the health risk assessment, however, negligible environmental exposure to the live bacterium is expected since the it is killed prior to formulation. Furthermore, no reports of adverse effects to mammals were found in PubMed using the keywords "Streptomyces acidiscabies" or "Thaxtomin" and minimal exposure is expected from the proposed use of MBI-005 EP, i.e. spot treatment on turf. No further data are required to assess the risk of harm to non-target wild mammals.			PMRA 1973038
Invertebrates				
Arthropods				
Terrestrial Arthropods	Dietary – *Apis mellifera*, adult	Four replicates (50/replicate) were fed MBI-005 TGAI in a 30% w/v sucrose/distilled water suspension at 500 µg dry cell mass/mL (equivalent to 21.5 µg/mL Thaxtomin A). Four replicates (50/replicate) were fed 30% w/v sucrose/distilled water suspension (Negative Control). Four replicates (50/replicate) were fed 100 µg/mL potassium arsenate in a 30% w/v sucrose/ distilled water suspension (Positive Control).	There were no behavioural or morphological abnormalities observed. The study was terminated on Day 20 after mortality in the negative control group exceeded 30%. At termination, mortality in the negative control, positive control and MBI-005 TGAI treatment groups was 30%, 100% and 16.5%, respectively. Pathogenicity and infectivity were not assessed. 22-day dietary LC_{50} > 500 µg dry cell/mL (equivalent to >21.5 µg Thaxtomin A/mL). 22-day NOEC 500 µg dry cell/mL (equivalent to 21.5 µg Thaxtomin A/mL). **ACCEPTABLE (Toxicity only)**	PMRA 1973042, 2075046

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		Diets were renewed every 48 hours. Bees were observed over a period of 20 days.		
	Dietary – *Chrysoperla rufilabris*, larvae	A group of larvae (30) was fed MBI-005 TGAI in moth eggs at 510, 5100, or 51000 ppm (equivalent to 0.53, 5.3 or 53 ppm Thaxtomin A). Another group of larvae (60) was fed moth eggs only (Negative Control). Diets were renewed on Days 0 and 7. Larvae were observed over a period of 10 days.	There were no treatment-related harmful sublethal effects or mortality. The study was terminated on Day 10 when mortality in the negative control group exceeded 20%. At termination, mortality in the negative control, 510 ppm, 5100 ppm and 51000 ppm groups was 24% (14 of 59), 30% (9 of 30), 30% (9 of 30), and 33% (10 of 30), respectively. Pathogenicity and infectivity were not assessed. 10-day LC_{50} was >51000 ppm (equivalent to >53 ppm Thaxtomin A). NOEC was 51000 ppm (equivalent to 53 ppm Thaxtomin A). **ACCEPTABLE (Toxicity only)**	PMRA 1973044, 2075046
	Dietary – *Hippodamia convergens*, adults	Three replicates (25/replicate) were fed MBI-005 TGAI in a 30% honey in water diet at 510, 5100, or 51000 ppm (equivalent to 0.53, 5.3 or 53 ppm Thaxtomin A). Three replicates (25/replicate) were fed 30% honey in water diet (Negative	Surviving beetles in the negative control and MBI-005 TGAI treatment groups appeared mostly normal throughout the study period. Sporadic observations of lethargy and immobility were observed in MBI-005 TGAI treated groups. Lethargy was also occasionally observed in the negative control group. The study was terminated on Day 17 after mortality in the negative control group exceeded 20%.	PMRA 1973043, 2075046

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		Control). Diets were renewed at least twice weekly. Beetles were observed over a period of 17 days.	At test termination, percent mortality in the negative control group was 21% (16 of 75). In the 510, 5100 and 51000 ppm treatment groups, mortality was 24% (18 of 74), 25% (19 of 75) and 32% (24 of74), respectively. Pathogenicity and infectivity were not assessed. 17-day LC_{50} was >51000 ppm (equivalent to >53 ppm Thaxtomin A). NOEC was 5100 ppm (equivalent to 53 ppm Thaxtomin A). **ACCEPTABLE (Toxicity only)**	
	Contact – *Aphidius matricariae*, adult	Parasitic wasps (403 in total) were divided evenly between 4 groups of dusty miller plants that were artificially infested with green peach aphids: i. one group of plants was treated with MBI-005 TGAI* at 10× field application rate (rate not provided); ii. another group was treated with MBI 005 Sterile Filtrate at rate that is equivalent to 10× field application rate; iii. another group was treated with inactivated MBI-005 TGAI at rate that is equivalent	There were no observed abnormalities among the plants or aphids. The total number of mummies removed and wasps emerged were as follows: Removed Emerged i. MBI-005 TGAI 11 20 ii. Inactivated MBI-005 TGAI 51 75 iii. MBI 005 Sterile Filtrate 35 35 iv. Water 34 55 The number of mummies removed and placed in petri dished was undercounted since some parasitized aphids were on the leaves containing mummified aphid(s). Pathogenicity and infectivity were not assessed. EC_{50} > 10× field application rate.	PMRA 1973045, 2075046

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		to 10× field application rate; and iv. last group was treated with water only (Negative Control). Wasps were removed from containers on Day 1. On Day 8, parasitized aphids (mummies) were removed, placed in petri dishes and observed daily for emergence. Plants and aphids were assessed daily for signs of toxicity or pathogenicity. *contained 1.05 mg/mL Thaxtomin A	**ACCEPTBALE but of LIMITED UTILITY (Toxicity only)**	
Non-arthropods				
Terrestrial Non-Arthropod Invertebrates	A request to waive the requirement for test data was not submitted. No infectivity or pathogenicity concerns are expected since the bacterium will be killed in the end-use product. Also, a search in the PubMed database using the keywords "Streptomyces acidiscabies" or "Thaxtomin" found no reports of adverse effects to any non-target terrestrial organism other than plants despite their presence in soil environments. No further data are required to assess the risk of harm to terrestrial non-arthropod invertebrates.			
Plants				
Plants	Foliar – Wheat (*Triticum aestivum* v. PR1404), Corn (*Zea mays* v. Early Sunglow), Sorghum (*Sorghum bicolor*), Rice (*Oryza sativa* v. M104), Kentucky Bluegrass (*Poa pratensis*), Creeping Bentgrass (*Agrostis stolonifera*),	The following treatments were performed for each host plant (3 replicates per group): - MBI-005 EP in distilled water at 10× dilution, 20× dilution and 40× dilution (equivalent to 0.78, 0.39 and 0.2	<u>Monocots</u> Wheat Very mild symptoms of phytotoxicity (0.5–1) in 10× and 20× dilutions. Plants initially showed minimal evidence of phytotoxicity in the form of burned blade edges and yellowing blotches; however, after 8 days, the effects were no longer observable in all but one plant.	PMRA 1975391

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
	Chives (*Allium schoenoprasum*), Onions (*Allium cepa* v. Yellow), Soybean (*Glycine max* v. Beer Friend), Barley (*Hordeum vulgare*), Tomato (*Lycopersicon esculentum* v. Brandywine), Lettuce (*Lactuca sativa* v. Celtuce), Bean (*Phaseolus vulgaris* v. Blue Lake), Broccoli (*Brassica oleracea* v. Packman), Cucumber (*Cucumis sativus* v. SMR58 Pickling), Peas (*Pisum sativum* v. Dwarf Grey), Redstem (*Ammania robusta*), Smallflower Umbrella Sedge (*Cyperus difformis*), Redroot Pigweed (*Amaranthus retroflexus*), Mustard (*Brassica juncea* v. Florida Broadleaf).	mg/mL Thaxtomin A) - water only (negative control) Each plant was sprayed with 0.66 mL of test suspension using a nozzle from a 2-ounce spray bottle. Observations were made 1, 3 and 8 days after treatment. Phytotoxicity rating: 0 – None 1 – Mild 2 – Mild to Moderate 3 – Moderate to Severe 4 – Severe 5 – Death	Corn After 8 days, mild symptoms of phytotoxicity (0.5–1.5) were observed at all concentrations. Barley Very mild symptoms of phytotoxicity (0.5) at all concentrations. Plants initially showed minimal evidence of phytotoxicity that was no longer observable after 8 days. Sorghum Starting on Day 3, very mild to moderate symptoms of phytotoxicity (0.5–2) were observed at all concentrations. Rice After 8 days, mild to moderate symptoms of phytotoxicity (1–2) were observed at all test concentrations. Note: mild to moderate symptoms were also noted in negative (untreated) control group. Kentucky Bluegrass Very mild symptoms of phytotoxicity (0.5) are observed in 10× and 20 × dilutions after Days 1 and 3. No symptoms are observed after 8 days. Creeping Bentgrass Starting on Day 3, very mild to mild symptoms of phytotoxicity (0.5–1) are observed in 10× and 20× dilutions. No symptoms are observed in 20× dilution after 8 days. Chives After 8 days, very mild to moderate symptoms of phytotoxicity (0.5–2) were	

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
			observed at all concentrations, including burned blade tips. Onions After 8 days, very mild to severe symptoms of phytotoxicity (0.5–3) were observed at all test concentrations, including yellowing blotches and general yellowing of plants. <u>Dicots</u> Soybean Starting on Day 3, moderate to severe symptoms of phytotoxicity (3–4) were observed at all test concentrations, including burned foliage and deformation of apical meristem. Tomato Starting on Day 3, mild to moderate symptoms of phytotoxicity (1–3) were observed at all test concentrations, including stunting. Lettuce Starting on Day 3, very mild to moderate symptoms of phytotoxicity (0.5–2.5) were observed at all test concentrations, including burned spots and leaf curling. Bean Starting on Day 3, moderate symptoms of phytotoxicity (2–2.5) were observed at all concentrations, including distortion of apical meristem, leaf discolouration and leaf drop. Broccoli Starting on Day 3, very mild to moderate symptoms of phytotoxicity (0.5–3) were	

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
			observed at all test concentrations, including stunting. Cucumber Starting on Day 3, mild to severe symptoms of phytotoxicity (1–3.5) were observed at all test concentrations, including burned foliage, yellow discolouration of foliage and deformation of apical meristem. Peas Starting on Day 3, mild to severe symptoms of phytotoxicity (1.5–3) were observed at all test concentrations, including warping foliage, possible tissue burning and a general plant yellowing. <u>Postive Controls (target plants)</u> Redstem Very mild symptoms of phytotoxicity (0.5) were observed in some plants at 10× and 20× dilutions after 3 days. After 8 days, moderate to severe symptoms of phytotoxicity (2.5–3) were observed. Smallflower Umbrella Sedge After 8 days, very mild symptoms of phytotoxicity (0.5) were observed in 20× and 40× dilutions. Redroot Pigweed After 8 days, plant death (5) is observed at all test concentrations. Mustard After 8 days, severe symptoms of phytotoxicity (3.5–4) were observed at all test concentrations.	

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
			Pathogenicity and infectivity were not assessed. **ACCEPTABLE but of LIMITED UTILITY (Toxicity only)**	
Microorganisms				
Micro-organisms	A request to waive the requirement for test data was not submitted. No infectivity or pathogenicity concerns are expected since the bacterium will be killed in the end-use product. Also, a search in the PubMed database using the keywords "Streptomyces acidiscabies" or "Thaxtomin" found no reports of adverse effects to any non-target terrestrial organism other than plants despite their presence in soil environments. No further data are required to assess the risk of harm to microorganisms.			
Aquatic Organisms				
Vertebrates				
Fish	Aqueous and Dietary –*Lepomis macrochirus*, juveniles, static renewal.	Fish (10) were exposed to MBI-005 TGAI in dilution water at 1.1, 11 and 28 mg dry cell mass/L (equivalent 0.19, 1.9 and 4.8 mg/L Thaxtomin A) and in feed at a rate of 0.35 mL per 20 g feed. One group of fish (10) were exposed to MBI-005 Sterile Filtrate in dilution water at 1.1, 11 and 28 mg dry cell mass/L and in feed at a rate of 0.35 mL per 20 g feed. Another group of fish (10) remained untreated (Negative Control). Test suspensions were renewed every other day. Treated feed was	There were no mortalities or signs of toxicity noted throughout the study period. No observable findings at necropsy. Pathogenicity and infectivity were not assessed. 30-day LC_{50} > 28 mg dry cell mass/L (equivalent to >4.8 mg/L Thaxtomin A). NOEC 28 mg dry cell mass/L (equivalent to 4.8 mg/L Thaxtomin A). **ACCEPTABLE (Toxicity only)**	PMRA 1973041, 2075046

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		prepared on Day 0 then refrigerated for entire study period. Fish were observed daily until Day 30.		
Invertebrates				
Aquatic Arthropods	Aqueous –*Hyalella azteca*, 13 days old (third instar), static renewal.	Three groups (40/group) were exposed to MOI 005 (equivalent to TGAI) in dilution water at 11.04, 110.4 or 1104 mg/L (equivalent to 4.14m 41.4 or 414 mg dry cell mass/L Thaxtomin A). A group (40) was exposed to MOI 005 Sterile Filtrate in dilution water at a rate equivalent to 1104 mg dry cell mass/L. Another group of amphipods (40) remained untreated (Negative Control). Test suspensions were renewed on Days 3, 6, 9, 12, 15 and 18. Amphipods were observed daily for 21 days.	There were no treatment-related mortalities. Mean biomass per total number of amphipods for negative control and sterile filtrate control groups was 0.130 and 0.074 mg, respectively. Mean biomass per total number of amphipods for 11.04, 110.4 and 1104 mg/L was 0.130, 0.121 and 0.063 mg, respectively. Pathogenicity and infectivity were not assessed. 21-day LC_{50} > 1104 mg dry cell mass/L (equivalent to 414 mg/L Thaxtomin A). 21-day EC_{50} (growth) 1057.3 mg dry cell mass/L (equivalent to approximately 396.5 mg/L Thaxtomin A). NOEC 110.4 mg dry cell mass/L (equivalent to 41.4 mg/L Thaxtomin A). **ACCEPTABLE (Toxicity only)**	PMRA 1973047, 2075046
	Aqueous –*Daphnia magna*, <24 hours old, static renewal.	Three groups (20/group) of daphnids were exposed to MBI-005 TGAI at 1.1, 11, or 28 mg dry	Mortality in the negative control and sterile filtrate control groups was 10 and 45%, respectively. Mortality in the groups	PMRA 1973046, 2075046

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		cell mass/L (equivalent to 0.19, 1.9 and 4.9 mg/L Thaxtomin A) A group (20) of daphnids was exposed to MBI-005 Sterile Filtrate at a rate equivalent to 28 mg dry cell mass/L. Negative control with 20 daphnids in untreated test culture. Test suspensions were renewed every 48 hours. Observed daily for mortality, toxicity and reproduction for 21 days.	treated with MBI-005 TGAI at 1.1, 11 and 28 mg dry cell mass/L was 5, 35 and 20%, respectively. During the course of the exposure, the sterile filtrate control was observed to be cloudy, indicating bacterial growth in the suspensions and possible contamination of the source fermentation broth. Daphnids treated with 11 mg dry cell/L or 28 mg dry cell/L MBI-005 TGAI were found to be smaller and/or pale compared to negative control daphnids. The mean cumulative number of offspring per female observed among daphnids exposed to 1.1, 11 and 28 mg dry cell mass/L was 151, 82 and 28, respectively. Pathogenicity and infectivity were not assessed. 21-day LC_{50} > 28 mg dry cell mass/L (equivalent to >4.9 mg/L Thaxtomin A) NOEC 1.1 mg dry cell mass/L (equivalent to >0.19 mg/L Thaxtomin A) **ACCEPTABLE (Toxicity only)**	
Aquatic Non-Arthropod Invertebrates	A request to waive the requirement for test data was submitted. No infectivity or pathogenicity concerns are expected since the bacterium will be killed in the end-use product. Furthermore, minimal aquatic exposure to MBI-005 EP is expected from its use as a spot treatment on turf and a search in the PubMed database using the keywords "Streptomyces acidiscabies" or "Thaxtomin" found no reports of adverse effects to any non-target terrestrial organism other than plants despite their presence in soil environments. No further data are required to assess the risk of harm to non-target aquatic non-arthropod invertebrates.			PMRA 1973038

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
Plants				
Aquatic Plants	Aqueous – *Lemna minor*, static.	Three replicates (3 mL in 12-well plate/replicate) were exposed to MBI-005 EP in Steinberg medium at 1714×, 1000×, 600×, 333× 188×, 107×, 60×, 30× and 20× dilutions (equivalent to 4.6, 7.8, 13, 23, 42, 73, 130, 260 and 390 mg/L Thaxtomin A) Three replicates (3 mL in 12-well plate/replicate) were exposed to KCl in Steinberg medium at 20 g/L (Positive Control). Three replicates (3 mL in 12-well plate/replicate) were exposed to Steinberg medium lone (Negative Control). Plates were incubated for 7 days at 22±1°C, 12 hour light/12 hour dark, and 60–120 µmol/(m2 s) light intensity.	MBI-005 EP had a toxic effect on *L. minor*. Even at the lowest test concentration of 1714× dilution, the growth of *L. minor* markedly affected and approximately 50% of fronds were bleached. Pathogenicity and infectivity were not assessed. **ACCEPTABLE but of LIMITED UTILITY (Toxicity only)**	PMRA 1975391
	Aqueous – *Pseudokirchneriella subcapita*, static.	Three replicates (7 mL in cell culture flask/replicate) were exposed to MBI-005 EP in nutrient medium at 14000×, 2800×, 1400×, 560× 280×, 140×, 47×, 28× and 20×	All MBI-005 EP treatments caused algal growth inhibition. Approximately 20% reduction in absorbance at 680 nm is observed for the 14000× dilution. Absorbance continued to decrease with increasing	PMRA 1975391

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		dilutions (equivalent to 0.6, 2.8, 5.6, 14, 28, 56, 166, 279 and 390 mg/L Thaxtomin A). Three replicates (3 mL in 12-well plate/replicate) were exposed to nutrient medium lone (Negative Control). Growth was measured by absorbance at 680 nm.	concentrations of MBI-005 EP. At concentrations of 1400× and above, absorbance at 680nm stabilized at approximately 65% below the untreated control group. **ACCEPTABLE but of LIMITED UTILITY (Toxicity only)**	

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
1973017	2009, MBI-005 Literature Review: Scab-causing Streptomyces, DACO: M1.2, M2.14, M2.7.1, M2.7.2, M9.9 CBI
1973019	2010, One Month Interim Report for Storage Stability and Corrosion Characteristics of MBI-005 TGA, DACO: M2.11 CBI
1973023	2010, Manufacturing Process for MBI-005 TGAI Heat Devitalization Process Supplemental to MRID 479468-01, DACO: M2.8 CBI
1973024	2009, Product Chemistry for MBI-005 TGAI, DACO: M2.10.1, M2.10.2, M2.10.3, M2.12, M2.8, M2.9.2, M2.9.3 CBI
1973025	2010, Secondary Metabolites of MBI-005 (*Streptomyces acidiscabies*), DACO: M2.9.3 CBI
1975368	2010, Product Name and Proposed Uses, DACO: M1.2, M10.4.1, M2.7.2 CBI
1975382	2010, Product Chemistry for MBI-005 EP, DACO: M2.10.1, M2.10.2, M2.11, M2.12, M2.8, M2.9.2, M2.9.3 CBI
1975383	2010, M2.6 Canadian Patent Status Information, DACO: M2.6 CBI
2075043	2011, MBI-005 Working Cell Bank Generation, DACO: M2.8 CBI
2075044	2011, Quantitative Analysis of Thaxtomin A (MBI-005), DACO: M2.9.2 CBI
2075046	2011, MBI-005 TGAI, containing *Streptomyces acidiscabies* strain RL-110T cells and spent fermentation media, TGAI, DACO: 4.5.2, 4.5.4, 4.5.5, 4.7.1, M2.7.1, M2.7.2, M2.8, M2.9.2, M4.2.2, M4.3.2, M4.4, M4.5.2, M4.6, M4.9, M8.0, M9.2.1, M9.4.1, M9.5.1, M9.5.2 CBI
2075073	2011, Quantitative Analysis of Thaxtomin A (MBI-005), DACO: M2.9.2 CBI
2112370	2011, MBI-005 Microbe Inactivation Confirmation Procedure, DACO: M2.8 CBI
2211869	2012, Two-year Storage Stability and Corrosion Characteristics Study, DACO: M2.11 CBI
2211874	2012, MBI-005 TGAI: One-year Storage Stability and Corrosion Characteristics Study, DACO: M2.11 CBI
2274639	2013, RESPONSE, DACO: 4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.3.4, 4.3.6, 4.5.2, 4.5.4, 4.5.5, M2.8, M2.9.1
2274642	2011, Heat Inactivation of MBI-005 TGAI (*Streptomyces acidiscabies* strain RL-110T), DACO: M2.8 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
1973026	2010, Tox Summary. DACO: M4.1, M4.2.1, M4.3.1, M4.5.1, M4.1, M4.2.1, M4.3.1, M4.5.1
1973027	2009, Acute Oral Toxicity Study (UDP) in Rats, DACO: M4.2.2
1973028	2009, Response to Tier 1 Microbial Pesticide Data Requirements for MBI-005 TGAI. DACO: M4.2.2, M4.2.3, M4.6, M9.2.2, M9.3, M9.4.2
1973029	2009, Acute Injection Toxicity/Pathogenicity Pilot Study in Mice, DACO: M4.3.2
1973030	2009, Acute Injection Toxicity/Infectivity Study, DACO: M4.3.2
1973032	2009, Acute Dermal Toxicity Study in Rats, DACO: M4.4
1973033	2009, Acute Dermal Irritation Study in Rabbits, DACO: M4.5.2
1973034	2009, Skin Sensitization Study in Guinea Pigs, DACO: M4.6
1973035	2009, Acute Eye Irritation Study in Rabbits, DACO: M4.9
1973036	2009, Acute Inhalation Toxicity Study in Rats, DACO: M4.9
1973037	2009, Subcutaneous Mouse Safety Study, DACO: M4.9
1973038	2009, Response to Tier 1 Microbial Pesticide Data Requirements for MBI-005 TGAI, DACO: M4.9, M9.9
2325403	2013, MBI-005 EP Acute Oral Toxicity Study (UDP) in Rats, DACO: M4.2.2
2325404	2013, MBI-005 EP Acute Dermal Toxicity Study in Rats, DACO: M4.4
2325405	2013, MBI-005 EP Acute Dermal Irritation in Rabbits, DACO: M4.5.2
2325406	2013, MBI-005 EP Skin Sensitization Study in Guinea Pigs, DACO: M4.6
2325407	2013, MBI-005 EP Acute Eye Irritation Study in Rabbits, DACO: M4.9
2325409	2013, MBI-005 EP Acute Inhalation Toxicity Study in Rats, DACO: M4.9

3.0 Environment

PMRA Document Number	Reference
1973038	2009, Response to Tier 1 Microbial Pesticide Data Requirements for MBI-005 TGAI, DACO: M4.9,M9.9
1973040	2009, An Avian Oral Pathogenicity and Toxicity Study in the Mallard, DACO: M9.2.1
1973041	2009, MBI 005 -30-Day Bluegill Sunfish (*Lepomis macrochirus*) Static-Renewal Toxicity, Infectivity and Pathogenicity Test Following OPPTS Guideline 885.4200, DACO: M9.4.1
1973042	2009, Evaluation of the Dietary Effect(s) of MBI 005 on Adult Honey Bees (*Apis mellifera* L.), DACO: M9.5.1
1973043	2009, MBI-005: A Dietary Pathogenicity and Toxicity Study with the Ladybird Beetle (*Hippodamia convergens*), DACO: M9.5.1
1973044	2009, MBI-005: A Dietary Pathogenicity and Toxicity Study with Green Lacewing Larvae (*Chrysoperla rufilabris*), DACO: M9.5.1
1973045	2010, Parasitic Wasp Non-Target Insect Microbial Testing, DACO: M9.5.1

1973046 2009, MBI 005 -21-Day Daphnid (*Daphnia magna*) Static-Renewal Toxicity, Infectivity and Pathogenicity Test Following OPPTS Guideline 885.4240, DACO: M9.5.2

1973047 2010, Microbial Pest Control Agent (MPCA) Freshwater Aquatic Invertebrate Test with *Hyalella azteca*, DACO: M9.5.2

1973048 2001, Glucosylation as a mechanism of resistance to Thaxtomin A in potatoes, DACO: M9.9

1973050 1998, Phenotypic, genotypic and pathogenic variation among streptomycetes implicated in common scrab disease, DACO: M9.9

1973051 1998, Selection and Characterization of Microorganisms Utilizing Thaxtomin A, a Phytotoxin Produced by *Streptomyces scabies*, DACO: M9.9

1973052 1992, Characterization of Actinomycetes Isolated from Common Scrab Lesions on Potato Tubers, DACO: M9.9

1973053 2000, Microbial Glucosylation of Thaxtomin A, a Partial Detoxification, DACO: M9.9

1973055 2004, Biotransformation of the *Streptomyces scabies* phytotoxin Thaxtomin A by the fungus *Aspergillus niger*, DACO: M9.9

1973056 1987, Plant Pathogenicity in the Genus *Streptomyces*, DACO: M9.9

1973057 2009, Endangered Species Evaluation for MBI-005, DACO: M9.9

1973061 2006, Evolution of Plant Pathogenicity in *Streptomyces*, DACO: M9.9

1973062 2006, Thaxtomin biosynthesis: the path to plant pathogenicity in the genus *Streptomyces*, DACO: M9.9

1973063 2006, Bacterial pathways for degradation of nitroaromatics, DACO: M9.9

1973064 2004, Field Isolates of *Streptomyces* Differ in Pathogenicity and Virulence on Radish, DACO: M9.9

1973066 2004, Biodegradation of nitroaromatics and other nitrogen-containing xenobiotics, DACO: M9.9

1973067 2009, Endangered Species Evaluation for MBI-005, DACO: M9.9

1975391 2010, MBI-005-Nontarget Plants, DACO: M9.8.1, M9.8.2

2075046 2011, MBI-005 TGAI, containing Streptomyces acidiscabies strain RL-110T cells and spent fermentation media, TGAI, DACO: 4.5.2, 4.5.4, 4.5.5, 4.7.1, M2.7.1, M2.7.2, M2.8, M2.9.2, M4.2.2, M4.3.2, M4.4, M4.5.2, M4.6, M4.9, M8.0, M9.2.1, M9.4.1, M9.5.1, M9.5.2 CBI

4.0 Value

PMRA Document Number **Reference**

1975368 2010, M1.2, M2.7.2, M10.4.1, DACO: M1.2,M10.4.1,M2.7.2 CBI

1975374 2010, Broadleaf Weed Control Marrone Bio And Solitare, DACO: M10.2.2,M10.3.1

1975380 2010, M10.4.2, M10.4.3, M10.4.4, DACO: M10.4.2,M10.4.3,M10.4.4

2120017 2011, Comparison of MBI-005 concentrations and spray volumes for postemergence control of common landscape weeds grown in containers, DACO: 10.2.3.3(B),10.3.2(A),M10.0

2120018 2011, Evaluation of MBI-005 Concentrations for Post-emergence Control of Dandelion in Turf, DACO: 10.2.3.3(B),10.3.2(A),M10.0
2120021 2011, Evaluation of MBI-005 Concentrations for Post-emergence Control of Broadleaf Weeds in Turf, DACO: 10.2.3.3(B),10.3.2(A),M10.0
2120022 2011, Evaluation of MBI-005 Concentrations for Crop Safety on Cool-season Turf Species, DACO: 10.2.3.3(B),10.3.2(A),M10.0
2120023 2010, MBI-005 in Turf, DACO: 10.2.3.3(B),10.3.2(A),M10.0

B. Additional Information Considered

i) Published Information

1.0 Chemistry

2043490 1968, Bonde, M.R. and McIntyre, G.A., Isolation and Biology of a *Streptomyces sp*. causing potato scab in soils below pH 5.0, American Potato Journal 45: 273-278, DACO: M2.7.1
2043491 1986, Loria, R., Kempter, A., and Jamieson, A.A., Characterization of *Streptomyces spp*. Causing Potato Scab in the Northeast, American Potato Journal 63: 440, DACO: M2.7.1
2043492 2001, Tóth, L., Maeda, M., Tanaka, F., and Kobayashi, K., Isolation and Identification of Pathogenic Strains of *Streptomyces acidiscabies* from Netted Scab Lesions of Potato Tubers in Hokkaido (Japan), Acta Microbiologica et Immunologica Hungarica 48(3-4): 575-585, DACO: M2.7.1
2043494 2006, Wanner, L.A., A Survey of Genetic Variation in *Streptomyces* Isolates Causing Potato Common Scab in the United States, Bacteriology 96(12): 1363-1371, DACO: M2.7.2
2043498 1991, Lambert, D.H., First Report of Additional Hosts for the Acid Scab Pathogen *Streptomyces acidiscabies*, Plant Disease 75:750, DACO: M2.7.2
2043502 2008, Kotiaho, M., Aittamaa, M., Andersson, M.A., Mikkola, R., Valkonen, J.P.T., and Salkinoja-Salonen, M., Antimycin A-producing nonphytopathogenic *Streptomyces turgidiscabies* from potato, Journal of Applied Microbiology 104: 1332-1340, DACO: M2.9.3
2043503 1980, Ikushima, H., Okamoto, M., Tanaka, H., Ohe, O., Kohsaka, M., Aoki, H., and Imanaka, H., New Anticoccidial Antibiotics, WS-5995 A and B I. Isolation and Characterization, The Journal of Antibiotics 33(10): 1107-1113, DACO: M2.9.3