Proposed Re-evaluation Decision PRVD2019-08

# Streptomyces strain K61 and Its Associated End-use Product

*Consultation Document*

*(publié aussi en français)*

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# Proposed Re-evaluation Decision

Under the authority of the *Pest Control Products Act*, all registered pesticides must be regularly re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental safety standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports, and other regulatory agencies. Health Canada applies internationally accepted risk assessment methods as well as current risk management approaches and policies to all re-evaluations.

*Streptomyces* strain K61 is a bacterium that is used as a microbial pest control agent for the suppression of damping-off, root and crown rot, and wilt in various greenhouse ornamentals, vegetables, and herbs caused by common pathogenic fungi. The commercial end-use product is formulated as a wettable powder and is applied as a water suspension directly to the root zone/growing media of greenhouse plants. It can also be used as a seed treatment and is applied as a powder directly to seeds.

This document presents the proposed regulatory decision for the re-evaluation of *Streptomyces* strain K61 and includes the proposed label updates, as well as the science evaluation on which the proposed decision was based. All products containing *Streptomyces* strain K61 registered as a fungicide in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period, during which the public, including the pesticide manufacturers and stakeholders, may submit written comments and additional information to the Health Canada. The final re-evaluation decision will be published taking into consideration the comments and information received.

## Outcome of Science Evaluation

*Streptomyces* strain K61 has value in providing an additional disease management option for greenhouse vegetables and ornamentals.

*Streptomyces* strain K61 is a widely distributed and naturally occurring soil bacterium. Previous human exposure to natural populations of it and other soilborne species of *Streptomyces* are expected, and *Streptomyces* strain K61 has a long history of use with no known reports of adverse effects. When *Streptomyces* strain K61 was tested on laboratory animals, there were no signs that it caused any adverse disease, but it was considered to be toxic when inhaled.

With respect to human health, *Streptomyces* strain K61 has a low toxicity and infectivity profile. When the current label directions are followed, occupational and residential exposures to *Streptomyces* strain K61 are expected to be minimal and potential occupational and residential risk is considered to be acceptable for all populations. Likewise, with current label directions, food and drinking water residues of *Streptomyces* strain K61 are expected to be minimal. Combined with a long history of dietary exposure from natural populations and the low toxicity and infectivity profile of *Streptomyces* strain K61, the potential dietary risk (from food and drinking water) is considered to be acceptable for all populations.

*Streptomyces* strain K61 is not expected to be pathogenic or toxic to non-target organisms, and based on the current conditions of use in greenhouses, environmental exposure to *Streptomyces* strain K61 is expected to be minimal. As such, the potential risk to non-target organisms (aquatic and terrestrial) from the use of *Streptomyces* strain K61 is considered to be acceptable under the current conditions of use.

No additional information is required. No additional risk mitigation measures are proposed. However, updated label statements are proposed for further clarity and to meet the current labelling standards (Appendix II).

## Proposed Regulatory Decision for *Streptomyces* strain K61

Under the authority of the *Pest Control Products Act* and based on the evaluation of currently available scientific information, Health Canada is proposing that products containing *Streptomyces* strain K61 are acceptable for continued registration for use and sale in Canada.

Registered pesticide product labels include specific instructions for use. Directions include risk mitigation measures to protect human health and the environment that must be followed by law. As a result of the re-evaluation of *Streptomyces* strain K61, no additional risk mitigation measures are proposed by the PMRA. To meet current labelling standards, the following label updates and clarifications are proposed (Refer to the details in Appendix II):

- Clarification for use in greenhouses only;
- Updated personal protective equipment label statement;
- Updated warning label statements; and
- Restricted-entry interval label statement.

## International Context

*Streptomyces* strain K61 is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including the European Union, the United States, and Switzerland.

No decision by an OECD-member country to prohibit all uses of this microbial for health or environmental reasons has been identified.

## Next Steps

The public, including the registrants and stakeholders, are encouraged to submit comments during the 90-day public consultation period[1] upon publication of this proposed re-evaluation decision.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of re-evaluation decision document.[2] The re-evaluation decision

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

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

document will include the final re-evaluation decision, the reasons for it, and a summary of comments received on the proposed re-evaluation decision along with the PMRA's responses.

## Additional Scientific Information

No additional data are required.

# Science Evaluation

## 1.0 Introduction

*Streptomyces* strain K61 is a biological fungicide used to supress the effects such as damping-off, root and crown rot, and wilt caused by pathogenic fungi (including the species *Fusarium*, *Pythium*, and/or *Phytophthora*) in greenhouse ornamentals, vegetables, and herbs. *Streptomyces* strain K61 is a naturally occurring soil bacterium. It produces an extracellular anti-fungal metabolite (aromatic heptane); however, it is unclear if this metabolite is involved in pathogenic fungi control.

The end-use product is registered as a commercial-class product and is formulated as a wettable powder. It is registered for use in greenhouses only and is applied as a water suspension directly to the root zone/growing media of plants by spraying, soil drenching, drip irrigation, and/or dip treatment. It can also be used as a seed treatment applied as a powder directly to seeds. Greenhouse crops can be treated multiple times throughout the growing season with a three to six week interval between treatments. All currently registered products containing *Streptomyces* strain K61 are listed in Appendix I.

To improve the clarity of the end-use product label, and in particular for treated seeds, an additional label statement is proposed to limit use of *Streptomyces* strain K61 to greenhouse environments only (Appendix II).

## 2.0 Identity of the Technical Grade Active Ingredient

| | |
|---|---|
| **Active ingredient** | Dried spores and mycelium of *Streptomyces* strain K61 |
| **Function** | Biological Fungicide – To supress fungal diseases on greenhouse food and ornamental crops |
| **Binomial name** | *Streptomyces* strain K61 |
| **Taxonomic designation**[3] | |
| **Super kingdom** | Bacteria |
| **Phylum** | Actinobacteria |
| **Class** | Actinobacteria |
| **Order** | Streptomycetales |
| **Family** | Streptomycetaceae |
| **Genus** | *Streptomyces* |
| **Strain** | K61: originally isolated from Sphagnum peat moss in Finland |

[3] National Center for Biotechnology Information - Taxonomy Browser (https://www.ncbi.nlm.nih.gov/taxonomy)

| | |
|---|---|
| **Registration No.** | 26264 |
| **Minimum concentration of active in TGAI** | $1.0 \times 10^8$ colony forming units/g |

The *Streptomyces* strain K61 used in the pesticide products has not been genetically modified or engineered through recombinant nucleic acid procedures.

# 3.0 Human Health

Based on the registered use pattern, exposure to *Streptomyces* strain K61 from use as a fungicide can occur through consuming food and drinking water, through working as commercial mixer, loader, applicator, or by performing postapplication activities as both a worker and a residential consumer. When assessing health risks of microorganisms, the following 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 the microorganism.

Studies in laboratory animals describe potential health effects from large doses of exposure to a microorganism, and they identify any potential pathogenicity, infectivity, and toxicity concerns. The levels used to assess human risks are established from these studies to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Continued registration is only supported for uses that are determined as having acceptable human health risks.

## 3.1 Toxicity and Infectivity Summary

*Streptomyces* strain K61 is a widely distributed and naturally occurring soil bacterium: previous exposures to natural populations of it and other soilborne species of *Streptomyces* are expected in most populations. From animal studies, *Streptomyces* strain K61 is not toxic, pathogenic, or infective via the oral exposure route. It is not pathogenic or infective following intraperitoneal injection in mice, and via the dermal route, it is not toxic. *Streptomyces* strain K61 is considered to be toxic, but not pathogenic or infective, via the inhalation exposure route. It is considered to be mildly irritating to the eyes and a moderate skin sensitizer. Regardless of the outcome of sensitization testing, the PMRA assumes that all microorganisms contain substances that can elicit positive hypersensitivity reactions. For more details, refer to REG2000-04, PRDD2003-07, and the 2009 evaluation report.

*Streptomyces* strain K61 produces low-levels of a secondary metabolite (a polyene compound/aromatic heptane). This metabolite can potentially bind to sterols of mammalian cell membranes and influence ion permeability; however, these polyenes are expected to be absorbed very poorly from the gastrointestinal tract due to their physiochemical properties (for example, amphiphilic, relatively high molecular weight compounds, with a polar part due to their sugar moiety and hydrophilic groups of the lactone ring).

Combined with the low levels produced and the absence of adverse effects in test animals (topical and oral), the PMRA concluded that the potential risk to human health from the presence of heptanes is considered to be acceptable for all populations under the current conditions of use.

In general, *Streptomyces* strain K61 has a low toxicity and infectivity profile, and it has a long history of use with no known reports of adverse effects. Nonetheless, handling of the wettable powder may cause an allergic reaction, irritation, or sensitization if inhaled or exposed to the skin and eyes. As such, the PMRA is proposing updated standard label statements (for example, "CAUTION – EYE IRRITANT" and "May cause eye irritation. DO NOT get in eyes.") (Appendix II). No toxicological endpoints have been established for quantitative risk assessment by the PMRA, and, as such, a qualitative approach was used to assess the potential risks of *Streptomyces* strain K61 to human health.

## 3.2 Human Exposure and Risk

The *Streptomyces* strain K61 end-use product is formulated as a commercial wettable powder that is applied as a liquid directly to the root zone/growing media of plants by spraying, soil drenching, drip irrigation, and/or dip treatment. For seed treatment, *Streptomyces* strain K61 is applied as a powder directly to seeds. Workers can be exposed to *Streptomyces* strain K61 through mixing, loading, and/or applying the product as well as through clean-up and maintenance activities. Postapplication workers and residential consumers of greenhouse plants can also be exposed through soil residues when handling a treated plant to conduct activities such as transplanting. Direct residential exposure from application is not expected.

**Occupational Exposure and Risk:**

Given the current use pattern (direct application of liquid to the root zone/growing media of plants and /or as seed treatment), potential worker exposure is via the dermal, inhalation, and ocular route with the primary route being dermal (mixing, loading, applying, during clean up/repair, and during postapplication activities).

Since unbroken skin is a natural barrier to microbial invasion of the human body, dermal penetration and uptake could occur only if the skin were cut, or if the microbe were a pathogen equipped with mechanisms for entry through, or infection of, the skin. Species of bacteria belonging to the genus *Streptomyces* have not frequently been identified as dermal wound pathogens, and there is no indication that strain K61 specifically can penetrate intact skin of healthy individuals. Moreover, toxicity testing with *Streptomyces* strain K61 showed no toxicity via the oral or dermal routes and no signs of infectivity or pathogenicity via the pulmonary or intraperitoneal injection routes. *Streptomyces* strain K61, however, was toxic via the inhalation exposure route and mildly irritating to the eyes and a moderate skin sensitizer (Section 3.1).

To minimize potential exposure to workers, current label directions include personal protective equipment such as water-proof gloves, long-sleeved shirt and pants, eye goggles, socks with shoes, and a dust mask. When used as directed on the label, the potential occupational risk from *Streptomyces* strain K61 is considered acceptable.

No additional risk mitigation measures are proposed. However, to meet current labelling standards, updates to the personal protective equipment statement and the addition of a standard restricted-entry interval statement are proposed (Appendix II).

**Residential Exposure and Risk:**

There are no registered domestic-class products containing *Streptomyces* strain K61, and commercial class products are for greenhouse use only. Residential exposure to treated greenhouse plants and soils is expected to be equivalent to, or less than, greenhouse occupational exposure. As such and under the current conditions of use, the potential risk is considered to be acceptable for all residential populations. No additional risk mitigation measures are proposed.

## 3.3 Dietary Exposure and Risk

*Streptomyces* strain K61 is applied as soil-directed spray or seed treatment, and *Streptomyces* strain K61 does not colonize plant tissues above the soil. As such, residues of both *Streptomyces* strain K61 and its metabolite in food commodities are expected to be minimal. *Streptomyces* strain K61 is used in greenhouses only; therefore, exposure to the environment, including drinking water sources, is expected to be minimal under the current label directions. Given (1) the low exposure potential; (2) the low toxicity and infectivity profile; and (3) the lack of any known reports of adverse effects associated with the consumption of *Streptomyces* strain K61, the potential dietary risk (food and drinking water) from the use of *Streptomyces* strain K61 with current label directions is considered to be acceptable for all populations. No additional mitigation measures are proposed.

## 3.4 Aggregate Exposure Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources from all known or plausible exposure routes (oral, dermal, and inhalation). For *Streptomyces* strain K61, aggregate exposure is limited to residential and dietary exposure (See Section 3.2 and 3.3), and it is considered acceptable for all populations under the current conditions of use.

## 3.5 Cumulative Exposure and Risk

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. In its assessment of common mechanisms of toxicity, the PMRA considers both the taxonomy of microbial pest control agents as well as the production of any potentially toxic metabolites. For the current re-evaluation, the PMRA has determined that *Streptomyces* strain K61 shares a common mechanism of toxicity with other registered microbial pest control agents, namely *Streptomyces acidiscabies* strain RL-110T and *Streptomyces lydicus* strain WYEC 108. The potential health risks from cumulative exposure of *Streptomyces* strain K61 and these other registered microbial pest control agents are acceptable when used as directed on the label, given their low toxicity and pathogenicity.

## 4.0 Environment

*Streptomyces* strain K61 is a naturally occurring soil bacterium, and population numbers are highest near the plant-root interface.

*Streptomyces* strain K61 is not toxic or pathogenic to wild mammals and birds. It is practically non-toxic to honey bees, earthworms, and freshwater invertebrates, and it is slightly toxic to freshwater fish. No adverse effects in non-target terrestrial plants and other soil microorganisms have been observed in field trials. For further details, refer to REG2000-04, PRDD2003-07, and the 2009 evaluation report.

Based on the current use in greenhouses, negligible environmental exposure (in addition to natural soil populations) is expected from the use of *Streptomyces* strain K61, and the current label includes standard environmental statements for the management of greenhouse effluent. Considering the low exposure potential and combined with the low toxicity and infectivity profile of *Streptomyces* strain K61 to non-target organisms, the potential risk to the environment from *Streptomyces* strain K61 is considered to be acceptable when used according to label directions. No additional risk mitigation measures are proposed. Label clarification to indicate the end-use product is restricted to greenhouse use is proposed.

## 5.0 Value

*Streptomyces* strain K61 has value in providing a preventative option for suppression of damping-off, root and crown rot, and wilt in greenhouse ornamentals, vegetables, and herbs. *Streptomyces* strain K61, when used in an integrated pest management program, can play a valuable role in resistance management by potentially reducing the need for conventional chemical fungicides.

## 6.0 Pest Control Policy Considerations

### 6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, in other words, those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

During the review process, Mycostop Biofungicide Technical was assessed in accordance with the PMRA Regulatory Directive DIR99-03[4] and evaluated against the Track 1 criteria. Mycostop Biofungicide Technical did not meet TSMP criteria.

[4] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic SubstancesManagement Policy*

### 6.2 Formulants and Contaminants of Health Concern

During the review process, contaminants in the technical as well as 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*.[5] The list is used as described in the PMRA Notice of Intent NOI2005-01[6] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[7] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act*, 1999 (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Mycostop Biofungicide Technical, and its end-use product do not contain formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants 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 Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. As of 22 May 2019, no incident reports have been submitted to the PMRA for the active ingredient *Streptomyces* strain K61.

## 8.0 Conclusion

*Streptomyces* strain K61 has value in providing an additional disease management option for greenhouse vegetables, herbs, and ornamentals.

Streptomyces bacteria are naturally occurring and widespread in the environment, and there is a long history of human exposure to natural populations with no attributed adverse effects. With respect to human health, *Streptomyces* strain K61 has a low toxicity and infectivity profile, and when used according to label directions, potential risk to human health is considered to be acceptable for all populations.

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

6 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

7 DIR-2006-02, *Formulants Policy and Implementation Guidance Document.*

Under current conditions of use, limited environmental exposure to *Streptomyces* strain K61 is expected, and combined with the low ecotoxicity and infectivity profile, the potential risk of *Streptomyces* strain K61 to non-target organisms is considered to be acceptable.

On this basis, Health Canada's Pest Management Regulatory Agency, under the authority of the *Pest Control Products Act*, is proposing continued registration of products containing *Streptomyces* strain K61 for sale and use in Canada.

Updates to label directions are being proposed for clarification and to meet the current labelling standards.

# Appendix I Registered Products Containing *Streptomyces* Strain K61

## Table 1 Registered Products Containing *Streptomyces* Strain K61 as of 22 May 2019

| Registration Number | Marketing Class | Registrant | Product Name | Formulation Type | Guarantee |
|---|---|---|---|---|---|
| 26264 | Technical | DANSTAR FERMENT AG | MYCOSTOP BIOFUNGICIDE TECHNICAL | Wettable Powder | $1 \times 10^8$ CFU /g |
| 26265 | Commercial | DANSTAR FERMENT AG | MYCOSTOP BIOFUNGICIDE | Wettable Powder | $1 \times 10^8$ CFU /g |

# Appendix II Label Amendments for Products Containing *Streptomyces* strain K61

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the label statements provided below.

The following label statements are proposed to be included on the end-use product label.

I) Under **PRECAUTIONS**, the following statement must be included:

*"**Restricted Entry Interval**: DO NOT enter or allow worker entry into treated areas for 4 hours or until sprays have dried, unless wearing personal protective equipment, including waterproof gloves, a long-sleeved shirt, long pants, and socks with shoes."*

II) Under **"PRECAUTIONS"**, complete the following:

Replace

*"May cause sensitization by inhalation and skin contact. Avoid breathing dust or spray mist. Avoid contact with skin and eyes. Wear a long sleeved shirt, long pants, shoes plus socks, chemical resistant gloves, eye goggles and a dust mask (minimum standard MSHA/NIOSH TC-21C) when handling this product and during all clean up/repair activities. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse."*

With

*"May cause eye irritation. DO NOT get in eyes. May cause sensitization. Avoid contact with skin or clothing. Avoid inhaling/breathing spray mist. Wear a long-sleeved shirt, long pants, eye goggles or face shield, water-proof gloves, shoes with socks, and a minimum of a NIOSH-approved particulate filtering face piece respirator with any N, R or P filter when handling, mixing/loading or applying the product, and during all clean-up/repair activities. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse."*

III) The following statements must be included in a section entitled **DIRECTIONS FOR USE:**

*"For greenhouse use only."*

V) On the **PRINCIPAL DISPLAY** panel, the following must be added:

*"**CAUTION - EYE IRRITANT**"*

# References

## A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT(S)

Unpublished information

| PMRA Document Number | Reference |
|---|---|
| 2849039 | 2018, ANALYSIS FOR MICROBIAL CONTAMINANTS, DACO: M2.10.1,M2.10.2,M2.2,M2.3,M2.7.1,M2.8,M2.9.2,M2.9.3 |
| 2868633 | 2018, ANALYSIS FOR MICROBIAL CONTAMINANTS, DACO: M2.10.2,M2.9.2,M2.9.3 |

## B. ADDITIONAL INFORMATION CONSIDERED

Published information

| PMRA Document Number | Reference |
|---|---|
| 652632 | Regulatory Note REG2000-04, Mycostop Biofungicide *Streptomyces griseoviridis.* Peat Management Regulatory Agency. March 22nd, 2000. |
| 655689 | Proposed Regulatory Decision Document PRDD2003-07, Mycostop Biofungicide *Streptomyces griseoviridis* strain K61. Pest Management Regulatory Agency. April 10, 2003. |
| 665798 | Regulatory Decision Document RDD2003-10, *Streptomyces griseoviridis* strain K61. Pest Management Regulatory Agency. September 8, 2003. |
| 2009627 | Evaluation Report for Category B, Subcategory 3.13 Application, *Streptomyces* griseoviridis strain K61. Pest Management Regulatory Agency, 2009 |
| 2835010 | European Commission, 2008. Review report for the active substance *Streptomyces* K61 (formerly *Streptomyces griseoviridis*) in view of the inclusion of *Streptomyces* K61 in Annex I of Directive 91/414/EEC. June 26th, 2008. |
| 2835011 | US EPA, 2011. *Streptomyces* Strain K61 Registration Review Final Decision. March, 2011. Docket ID: EPA-HQ-OPP-2009-0509 |
| 2835012 | European Commission, 2014. Review report for the active substance *Streptomyces* K61 (formerly *Streptomyces griseoviridis*) in view of the inclusion of *Streptomyces* K61 in Annex I of Directive 91/414/EEC. July 11th, 2014. |