Proposed Registration Decision PRD2024-01

Phthorimaea operculella granulovirus isolate GV-0019 and Tutavir

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Proposed registration decision for *Phthorimaea operculella* granulovirus isolate GV-0019 and Tutavir

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of PhopGV Technical and Tutavir, containing the technical grade active ingredient *Phthorimaea operculella* granulovirus isolate GV-0019, for control of tomato leafminer (*Tuta absoluta*) on greenhouse fruiting vegetables.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

This summary describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of *Phthorimaea operculella* granulovirus isolate GV-0019 and Tutavir.

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 individuals 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 precautionary measures on the product label to further reduce risk.

To reach its decisions, Health Canada's PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children). They also consider the unique characteristics of organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of the Canada.ca website.

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

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on *Phthorimaea operculella* granulovirus isolate GV-0019 and Tutavir, Health Canada's PMRA will consider any written comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration Decision[4] on *Phthorimaea operculella* granulovirus isolate GV-0019 and Tutavir, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

For more details on the information presented in this summary, please refer to the Science Evaluation of this consultation document.

What is *Phthorimaea operculella* granulovirus isolate GV-0019?

Phthorimaea operculella granulovirus isolate GV-0019 is an insect-specific baculovirus and is the active ingredient in the insecticide product, Tutavir. Tutavir infects only larvae of certain Lepidopteran species (for example, moths) and acts only on ingestion by larvae, not by contact.

Health considerations

Can approved uses of *Phthorimaea operculella* granulovirus isolate GV-0019 affect human health?

Phthorimaea operculella granulovirus isolate GV-0019 is unlikely to affect your health when Tutavir is used according to the label directions.

Potential exposure to *Phthorimaea operculella* granulovirus isolate GV-0019 may occur through the diet (food and water) or when handling and applying Tutavir. When assessing health risks, several key factors are considered:

- the microorganism's biological properties (for example, infection cycle);
- 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.

The levels used to assess risks are established 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. Only uses that are determined as having no health risks of concern are considered acceptable for registration.

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

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

Studies in laboratory animals describe potential health effects from large doses of exposure to a microorganism and identify any pathogenicity, infectivity and toxicity concerns.

Granuloviruses belong to the baculovirus group of insect viruses. When other baculoviruses were tested on laboratory animals and in tissue cultures, there were no signs of significant toxicity or disease. Furthermore, there have been no reported adverse effects despite the natural occurrence and prevalence of baculoviruses in the environment, and the limited host range associated with baculoviruses has been well documented. In the absence of eye irritation testing, the technical grade active ingredient and end-use product are assumed to be eye irritants.

All microorganisms, including *Phthorimaea operculella* granulovirus isolate GV-0019, contain substances that are potential sensitizers and thus, sensitivity may possibly develop in individuals exposed to large quantities of *Phthorimaea operculella* granulovirus isolate GV-0019.

Residues in water and food

Dietary risks from food and water are acceptable.

Residues of *Phthorimaea operculella* granulovirus isolate GV-0019 on treated agricultural crops are possible at the time of harvest. Although baculoviruses, including *Phthorimaea operculella* granulovirus, are abundant in nature, no adverse effects from dietary exposure have been attributed to natural populations of *Phthorimaea operculella* granulovirus. Furthermore, no signs of infectivity or toxicity were observed when baculoviruses were tested on laboratory animals and in tissue culture studies. In addition, the likelihood of residues of *Phthorimaea operculella* granulovirus isolate GV-0019 contaminating drinking water supplies is expected to be low, as the label has the necessary mitigation measures to limit contamination of drinking water from the proposed uses of Tutavir. Consequently, health risks from dietary exposure are acceptable for all segments of the population, including infants, children, adults and seniors.

Occupational risks from handling Tutavir

Occupational risks are acceptable when Tutavir is used according to label directions, which include protective measures.

Workers handling Tutavir can be exposed to *Phthorimaea operculella* granulovirus isolate GV-0019 through direct skin or eye contact or through inhalation. To protect workers from exposure to Tutavir, the label states that workers must wear personal protective equipment, including a long-sleeved shirt, long pants, protective eyewear (goggles), waterproof gloves, socks and shoes, and a NIOSH-approved particulate filtering facepiece respirator with any N, R or P filter. The product label includes measures to restrict access to the treated area for four hours or until sprays have dried.

The health risks to workers are acceptable when the precautionary statements on the label are observed.

Risks in residential and other non-occupational environments

Estimated risk for non-occupational exposure is acceptable.

Tutavir is being proposed for commercial use in greenhouses only and there are no residential uses. Residential and non-occupational exposure to Tutavir is therefore expected to be low when the label directions are observed. Consequently, the health risk to residents and the general public is acceptable.

Environmental considerations

What happens when *Phthorimaea operculella* granulovirus isolate GV-0019 is introduced into the environment?

Environmental risks are acceptable.

Phthorimaea operculella granulovirus isolate GV-0019 is a naturally occurring baculovirus that specifically infects Lepidopteran insects. Baculoviruses are common and persistent in aquatic and terrestrial ecosystems. Tutavir is a new end-use product that is proposed for use as an insecticide to control tomato leafminer larvae on greenhouse Solanaceous crops (for example, tomato or eggplant), and is not intended for outdoor uses. *Phthorimaea operculella* granulovirus isolate GV-0019 may be introduced to the environment through disposal of treated plant material. However, the greenhouse use of Tutavir is not expected to result in sustained increases of *Phthorimaea operculella* granulovirus isolate GV-0019 in terrestrial and aquatic environments beyond natural background levels.

Based on a critical review of animal studies, scientific rationales and information from public sources, no significant effects to birds, wild mammals, fish, terrestrial and aquatic non-target arthropods, and plants are expected when Tutavir is applied according to directions on the label.

Value considerations

What is the value of Tutavir?

Tutavir can be used as a foliar spray to control tomato leafminer (*Tuta absoluta*), which has the potential to become a major economic pest within Canada on greenhouse fruiting vegetables.

The registration of Tutavir will provide Canadian greenhouse fruiting vegetable growers, including organic growers, a new alternative microbial product with a novel mode of action to combat the greenhouse pest, tomato leafminer (*Tuta absoluta*). The narrow host range of the active ingredient makes the product a suitable component in integrated pest management.

Measures to minimize risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the labels of PhopGV Technical and Tutavir to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human health

The signal words “POTENTIAL SENSITIZER” and “CAUTION EYE IRRITANT” will appear on the primary display panel of the labels.

The end-use product and technical grade active ingredient are considered potential sensitizers. In turn, workers handling or applying Tutavir must wear a long-sleeved shirt, long pants, protective eyewear (goggles), waterproof gloves, socks and shoes and a NIOSH-approved particulate filtering facepiece respirator with any N, R or P filter. Furthermore, all unprotected workers are restricted from entering treated areas during application and for four hours following application or until sprays have dried.

Environment

The end-use product label will include environmental precaution statements that prevent the runoff and contamination of aquatic systems from the use of Tutavir.

Next steps

Before making a final registration decision on *Phthorimaea operculella* granulovirus isolate GV-0019 and Tutavir, Health Canada’s PMRA will consider any written comments received from the public in response to this consultation document up to 45 days from the date of publication of this document. Please forward all comments to Publications. Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada’s response to these comments.

Other information

When Health Canada makes its registration decision, it will publish a Registration Decision on *Phthorimaea operculella* granulovirus isolate GV-0019 and Tutavir (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. For more information, please contact the PMRA's Pest Management Information Service.

Science evaluation

Phthorimaea operculella granulovirus isolate GV-0019 and Tutavir

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active microorganism	*Phthorimaea operculella* granulovirus (PhopGV) isolate GV-0019
Function	Biological Insecticide – for the control of tomato leafminer (*Tuta absoluta*) on greenhouse fruiting vegetables in the family Solanaceae
Binomial name	*Phthorimaea operculella* granulovirus (PhopGV) isolate GV-0019
Taxonomic designation	
Superkingdom	Viruses
Family	Baculoviridae
Genus	*Betabaculovirus*
Species	*Phthorimaea operculella* granulovirus (PhopGV)
Isolate	GV-0019
Patent Status information	None
Nominal purity of active	PhopGV Technical (technical grade active ingredient): minimum of 2×10^{13} occlusion bodies (OBs)/L Tutavir (end-use product): minimum of 2×10^{13} OBs/L
Identity of relevant impurities of toxicological and/or environmental significance.	The technical grade active ingredient does not contain any impurities or micro contaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances. The product must meet microbiological contaminants release standards.

1.2 Physical and chemical properties of the end-use product

End-use product—Tutavir

Property	Result
Colour	Light brown
Physical State	Liquid
Odour	Weak organic odour
pH	6–7

Property	Result
Viscosity	449.0–567.8 mPa·s at 20°C and 269.4–350.9 mPa·s at 40°C
Relative Density	1.16

1.3 Directions for use

Tutavir is a suspension concentrate that is proposed for the control of tomato leafminer (*Tuta absoluta*) on greenhouse fruiting vegetables (Crop Group 8–09) at a rate range of 50–200 mL/ha as a foliar spray in a minimum spray volume of 300 L/ha with a re-application interval of 4–7 days. Plants must be sprayed when eggs or first instar larvae are present.

1.4 Mode of action

After oral intake by the larvae, the viral particles are released from occlusion bodies and infect cells of the insect gut. Infection results in viral replication, distribution of viral particles through the hemocoel, tissue swelling, and liquefaction of larval body contents. Larval death ensues approximately six days post-infection. Insect viruses like *Phthorimaea operculella* granulovirus generally have a narrow host range, infecting only one or a suite of closely related Lepidopteran species.

2.0 Methods of analysis

2.1 Methods for identification of the microorganisms

Acceptable methodologies for detection, isolation and enumeration of the active ingredient, *Phthorimaea operculella* granulovirus (PhopGV) isolate GV-0019, were submitted by the applicant. *Phthorimaea operculella* granulovirus isolate GV-0019 has been fully characterized with respect to the origin of the isolate, natural occurrence and biological properties. *Phthorimaea operculella granulovirus* isolate GV-0019 can be identified to the isolate level by whole-genome sequencing.

2.2 Methods for establishment of purity of seed stock

Phthorimaea operculella granulovirus isolate GV-0019 is deposited in the German Collection of Microorganisms and Cell Cultures (DSMZ) under accession code GV-0019. The isolate is maintained in an acceptable manner in order to maintain purity, viability and genetic stability.

2.3 Methods to define the content of the microorganism in the manufactured material used for the production of formulated products

The guarantees of the technical grade active ingredient and the end-use product are expressed in units of occlusion bodies (OBs)/L. Representative data on five batches of end-use products, consisting of both potency data and OB counts, were submitted. The methods for potency testing and for determining the concentration of OBs were adequately described.

2.4 Methods to determine and quantify residues (viable or non-viable) of the active microorganism and relevant metabolites

As noted above, appropriate methods are available to enumerate OBs and to distinguish this microbial pest control agent (MPCA) from other isolates of PhopGV and other closely related baculoviruses.

2.5 Methods for determination of relevant impurities in the manufactured material

The quality assurance procedures used to limit contaminating microorganisms during the manufacture of PhopGV Technical and Tutavir are acceptable. These procedures include good hygienic practices for the maintenance, sanitation and cleaning of all laboratories and sterilization of all equipment used in the manufacturing process.

The absence of human pathogens and below-threshold levels of contaminating microorganisms were shown in the microbial screening of batches of Tutavir using standard microbiological methods as well as by results of mouse toxicity testing. All batches of Tutavir conform to the limits set out in the Organisation for Economic Co-operation and Development (OECD) issue paper on microbial contaminants for microbial pest control products [ENV/JM/MONO(2011)43/REV1].

2.6 Methods to determine storage stability, shelf-life of the microorganism

Storage stability data were provided for Tutavir. Results support a storage period of two years at lower than or equal to 5°C.

3.0 Impact on human and animal health

3.1 Toxicity and infectivity summary

3.1.1 Testing

No new human health and safety studies were conducted for PhopGV Technical and Tutavir. Instead, numerous human health and safety studies with other baculoviruses, which were previously assessed and found to be acceptable to support the registrations of *Autographa californica* nucleopolyhedrovirus (AcMNPV) FV11 and *Neodiprion abietis* nucleopolyhedrovirus (NeabNPV) Newfoundland strain, were cited. Information relevant to AcMNPV FV11 and NeabNPV Newfoundland strain are applicable to PhopGV isolate GV-0019, as these baculoviruses are similar with respect to their limited host specificity (restricted to arthropods) and mode of action. These studies included numerous acute oral, inhalation, intravenous injection, acute dermal, dermal irritation and tissue culture studies. For descriptions of these studies, see PRD2015-09, *Autographa californica* Nucleopolyhedrovirus FV11 and REG2006-10, Abietiv *Neodiprion abietis* Nucleopolyhedrovirus Newfoundland Strain.

3.1.2 Additional information

No new additional information was submitted to address human health and safety requirements for PhopGV Technical and Tutavir. A previously submitted waiver rationale was used to address the potential infectivity of the MPCA and the potential toxicity and irritation of the formulation ingredients. The rationale was based on the limited host range associated with baculoviruses, the blocks to infection in non-permissive cells, and the lack of documented adverse effects despite the natural occurrence and prevalence of baculoviruses in the environment. The formulation ingredients in Tutavir are widely used in pharmaceuticals, cosmetics, food and drinks, or are present at very low concentrations and are considered to be of minimal concern for the proposed use of Tutavir. For additional information on these waiver rationales, see PRD2015-09, *Autographa californica* Nucleopolyhedrovirus FV11 and PRD2023-04, Plutella xylostella granulovirus (PlxyGV) isolate GV-0020 and Plutex.

3.1.3 Health incident reports

As of 19 September 2023, no human and domestic animal incidents involving *Phthorimaea operculella* granulovirus isolate GV-0019 had been submitted to the PMRA.

3.1.4 Hazard analysis

The data package submitted in support of registering PhopGV Technical and Tutavir was reviewed from the viewpoint of human health and safety and was determined to be acceptable.

Based on all the available information, the technical grade active ingredient, PhopGV Technical, is expected to be of low toxicity by the oral, pulmonary and dermal routes of exposure and is not a dermal irritant. Tutavir does not contain any formulants of human health concern. The available information also indicates that the MPCA is not infective or pathogenic. While baculovirus uptake has been demonstrated in non-permissive cells, such as those of vertebrates, infection will not occur, as there is no viral DNA replication or expression of viral proteins.

Similarly, the end-use product, Tutavir, is of low toxicity by the oral, inhalation and dermal routes and is not a dermal irritant.

Being an MPCA, PhopGV isolate GV-0019 is considered to be a potential sensitizer. Consequently, the hazard statement “POTENTIAL SENSITIZER” will appear on the principal display panels of the technical grade active ingredient and the end-use product labels. The statement “May cause sensitization. Avoid contact with skin, eyes or clothing.” is also required on the secondary display panel under the “PRECAUTIONS” sections of the technical grade active ingredient and end-use product labels. The statement “Avoid inhaling/breathing spray mist.” is required on the secondary panel under the “PRECAUTIONS” section of the end-use product label.

Since an eye irritation study was not submitted and no information was available in the scientific waiver rationale, the technical grade active ingredient and end-use product labels must also

include the hazard statements “CAUTION EYE IRRITANT” on the principal display panels and “May irritate eyes” and “Avoid contact with eyes” on the secondary display panels under the “PRECAUTIONS” sections.

Higher tier subchronic and chronic toxicity studies were not required because of the anticipated low toxicity of the end-use product, and the lack of infectivity, toxicity or pathogenicity when various baculoviruses were administered to test animals via the oral, pulmonary, intravenous and dermal routes of exposure.

Within the available scientific literature, there are no reports that suggest PhopGV isolate GV-0019 or other baculoviruses have the potential to cause adverse effects on the endocrine system of animals. Based on the weight of evidence of available data, no adverse effects to the endocrine or immune systems are anticipated for this MPCA.

3.2 Occupational, residential and bystander risk assessment

3.2.1 Occupational and postapplication exposure and risk

When handled according to the label instructions, occupational exposure is expected to occur by the dermal and inhalation routes for handlers, mixer/loaders and applicators. Ocular exposure is expected to be minimal.

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. *Phthorimaea operculella* granulovirus isolate GV-0019 has not been identified as a dermal wound pathogen, there is no indication that it could penetrate intact skin of healthy individuals, and it does not produce any known toxic secondary metabolites.

Toxicity testing with various baculoviruses showed no notable signs of toxicity or infectivity via the oral, pulmonary, intravenous or dermal routes of exposure. Dermal irritation studies using various baculovirus preparations showed no dermal irritation and the formulants contained in Tutavir are not dermal irritants. In lieu of testing, the PMRA considers all microorganisms as ocular irritants; therefore, the technical grade active ingredient and end-use product may cause eye irritation. The PMRA also assumes that all microorganisms contain substances that can elicit positive hypersensitivity reactions.

Risk mitigation measures, such as personal protective equipment (PPE), including a long-sleeved shirt, long pants, protective eyewear (goggles), waterproof gloves, socks and shoes, and a NIOSH-approved particulate filtering facepiece respirator with any N, R or P filter are required to minimize exposure and protect applicators, mixer/loaders and handlers that are likely to be exposed.

There is a potential for post-application exposure to workers entering areas treated with Tutavir. Therefore, all unprotected workers and users are prohibited from entering treated areas where

Tutavir has been applied for four hours or until the sprays have dried. If early entry is required, workers must wear the appropriate PPE as specified on the label.

Label warnings, restrictions and risk mitigation measures are adequate to protect users of Tutavir. Overall, health risks to workers are acceptable when the precautionary statements on the label are followed, which include PPE.

3.2.2 Residential and bystander exposure and risk

Tutavir is proposed for use in greenhouses only. There are no residential uses. This use is not expected to result in significant residential and bystander exposure due to drift. Bystander exposure will be mitigated by the inclusion of a statement on the label, requiring all unprotected workers to remain out of treated areas until sprays have dried. Also, Tutavir is considered to be of low toxicity via the oral, dermal and inhalation routes and baculoviruses are not infective or pathogenic to non-target hosts.

Consequently, the health risk to bystanders and individuals in residential areas from the use of Tutavir is acceptable when label directions are observed.

3.3 Dietary exposure and risk assessment

3.3.1 Food

While the proposed use pattern may result in dietary exposure with possible residues in or on agricultural commodities, the risks from consuming crops treated with Tutavir are acceptable because various baculoviruses demonstrated no notable toxicity, pathogenicity or infectivity in acute oral toxicity and tissue culture studies. Furthermore, no adverse effects from dietary exposure have been attributed to natural populations of PhopGV. Consequently, there is no health risk from dietary exposure for the general population, including infants and children, or domestic animals.

3.3.2 Drinking water

Dietary exposure from drinking water is expected to be low, as the label has the necessary mitigation measures to limit contamination of drinking water from the proposed greenhouse use of Tutavir. The end-use product label will instruct users not to contaminate irrigation or drinking water supplies or aquatic habitats through equipment cleaning or waste disposal and to not allow effluent or runoff from greenhouses containing this product to enter lakes, streams, ponds or other waters. Municipal treatment of drinking water is also expected to further reduce the transfer of residues to drinking water. Furthermore, there are no anticipated harmful effects for PhopGV isolate GV-0019 as evidenced by acute oral toxicity testing and tissue culture studies using other baculoviruses.

Health risks from residues of PhopGV isolate GV-0019 in drinking water are acceptable.

3.3.3 Acute and chronic dietary risks for sensitive subpopulations

As noted above, when the end-use product is applied as directed by the label, the health risk is acceptable for the general population, including infants and children, and domestic animals.

3.3.4 Aggregate exposure and risk

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation).

In an aggregate risk assessment, the combined potential risk associated with food, drinking water and various residential exposure pathways is assessed. A major consideration is the likelihood of co-occurrence of exposures. Additionally, only exposures from routes that share common toxicological endpoints can be aggregated.

Tutavir is considered to be of low toxicity by the oral, dermal and inhalation routes and no adverse effects from exposure to other baculoviruses encountered in the environment have been reported. Tutavir will not be applied near or to drinking water. Furthermore, non-occupational exposure will be low when Tutavir is used as directed on the label. When the end-use product is used as labelled, there is reasonable certainty that no harm will result from aggregate exposure of residues of PhopGV isolate GV-0019.

3.3.5 Maximum residue limits

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether dietary risks are acceptable from the consumption of foods treated with the pesticide when used according to the supported label directions. If acceptable, this means food containing that amount of residue is safe to eat, and maximum residue limits (MRLs) may be proposed. MRLs are the maximum amount of pesticide residue legally permitted to remain in/on food sold in Canada and are specified under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act.*

Residues of PhopGV isolate GV-0019 on treated food crops are possible at the time of harvest. Dietary risk to humans from the proposed use of Tutavir is acceptable as no adverse effects from dietary exposure have been attributed to natural populations of PhopGV, and no adverse effects were observed in the acute oral toxicity and tissue culture studies with other baculoviruses. In addition, the likelihood of residues contaminating drinking water supplies is low. Therefore, the PMRA has determined that specification of an MRL under the *Pest Control Products Act* is not required for PhopGV isolate GV-0019.

3.4 Cumulative assessment

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 mechanism of

toxicity, the PMRA considers both the taxonomy of the MPCAs and the production of any potentially toxic metabolites. For the current evaluation, the PMRA has determined that PhopGV isolate GV-0019 shares a common mechanism of toxicity with the MPCAs nucleopolyhedrovirus of Douglas-fir tussock moth, nuclear polyhedrosis virus of red-headed pine sawfly, *Cydia pomonella* granulosis virus (strain CMGv4), *Neodiprion abietis* nucleopolyhedrovirus, *Cydia pomonella* granulovirus (strain M), *Cydia pomonella* granulovirus isolate V-22, *Autographa californica* nucleopolyhedrovirus FV11, *Helicoverpa armigera* nucleopolyhedrovirus BV-0003, and *Plutella xylostella* granulovirus GV-0020, all of which are baculoviruses. Although co-exposure to PhopGV isolate GV-0019 and these other MPCAs may occur through consumption of treated crops or residential exposure, all of these MPCAs are of low toxicity and are not pathogenic, are naturally-occurring in the environment, and their uses are not anticipated to result in sustained increases of baculoviruses beyond natural background levels. Thus, cumulative risks are acceptable.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

Environmental fate data (Tier II/III) are not normally required at Tier I, and are only triggered if significant toxicological effects in non-target organisms are noted in Tier I testing.

Phthorimaea operculella granulovirus isolate GV-0019 belongs to the genus *Betabaculovirus* in the family Baculoviridae. Baculoviruses are ubiquitous and persistent in aquatic and terrestrial ecosystems. The host range of baculoviruses is restricted to terrestrial arthropods primarily of the larval stage. The crystalline structure of the OBs has been shown to assist in the dispersal of the virus by vertebrates. The acidic pH of the stomach of vertebrates helps to preserve the integrity of the OBs. Excreted OBs, recovered from the digestive tracts of non-host invertebrate and vertebrate animals, were found to remain infectious to their insect larval hosts, leading to the suggestion that the consumption of baculovirus-infected larvae by various non-target animals plays a role in the dissemination of OBs. Baculoviruses are a natural component of the host insect's habitat, and environmental concentrations reported in soil (1.55×10^5 OBs/cm^3), ground litter (4×10^5 OBs/cm^3) and tree bark (5×10^6 OBs/cm^3) can persist for at least one year following natural epizootics of the host. Greenhouse spray applications, at the maximum label rate of 4×10^{12} OBs/ha, introduce relatively little virus into the environment compared to natural baculovirus epizootics in which a single late instar larvae can release 10^9 to 10^{10} OBs.

Therefore, while no studies were submitted to address the environmental fate and behaviour of PhopGV isolate GV-0019, the greenhouse use of Tutavir is not expected to result in sustained increases of PhopGV isolate GV-0019 in terrestrial and aquatic environments beyond background levels.

4.2 Effects on non-target species

The PMRA has a four-tiered approach to environmental testing of microbial pesticides.

Tier I studies consist of acute studies on up to seven broad taxonomic groups of non-target organisms exposed to a maximum hazard or Maximum Challenge Concentration (MCC) of the MPCA. The MCC is generally derived from the amount of the MPCA or its toxin expected to be available following application at the maximum recommended label rate multiplied by a safety factor. Tier II studies consist of environmental fate (persistence and dispersal) studies as well as additional acute toxicity testing of MPCAs. Tier III studies consist of chronic toxicity studies (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 is 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 risk quotient is then compared to the level of concern (LOC).

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

No new studies were conducted for PhopGV Technical and Tutavir. Acceptable scientific rationales and studies were cited in lieu of Tier I testing requirements for terrestrial non-target organisms. The rationales were based on an extensive database review of the published scientific literature, including the results of ecotoxicological testing conducted with various baculoviruses, that was previously reviewed in support of the registration of AcMNPV FV11 and *Plutella xylostella* granulovirus GV-0020. Information relevant to these MPCAs is applicable to PhopGV isolate GV-0019 as these baculoviruses are sufficiently similar with respect to their limited host specificity (restricted to arthropods) and mode of action.

The rationales were based on the following:

- baculoviruses are not toxic to vertebrate animals (birds and mammals), non-arthropod invertebrates, microorganisms and plants;
- baculoviruses are infectious only to insects of the same order from which they were initially isolated;
- baculoviruses are ubiquitous and persistent in aquatic and terrestrial ecosystems, yet there has been no report of negative impacts on ecosystems other than the effect on the target host insect;
- no evidence of infection, toxicity or mortality was observed following exposure to direct deposit of contaminated material (dead insects, frass, etc.); and
- field applications of baculoviruses into the environment do not result in sustained increases of baculovirus levels beyond those that would occur naturally.

For further details on the above information and its review, see PRD2015-09, *Autographa californica Nucleopolyhedrovirus FV11* and PRD2023-04, *Plutella xylostella granulovirus (PlxyGV) isolate GV-0020 and Plutex*.

An independent search of published scientific literature, including through Science Direct and PubMed, in August 2023 yielded no reports of adverse effects to birds, plants, wild mammals, arthropods (with the exception of known hosts) and non-arthropod invertebrates.

Based on all the available information on the effects of PhopGV isolate GV-0019 to non-target terrestrial organisms and the precautionary measures required on the Tutavir label, the risks to birds, wild mammals, non-target arthropods (including honeybees), non-arthropod invertebrates, microorganisms and plants from the proposed use of Tutavir are acceptable.

4.2.2 Effects on aquatic organisms

No new studies were conducted for PhopGV Technical and Tutavir. Acceptable scientific rationales were cited in support of Tier I testing requirements for aquatic non-target organisms. The rationales were based on an extensive database of the published scientific literature, including the results of ecotoxicological testing conducted with various baculoviruses, that was previously reviewed in support of the registration of AcMNPV FV11.

Information relevant to AcMNPV FV11 is applicable to PhopGV isolate GV-0019, as these baculoviruses are sufficiently similar with respect to their limited host specificity (restricted to arthropods) and mode of action.

The rationales were based on the following:

- baculoviruses are not toxic to aquatic vertebrate animals (fish), arthropods, non-arthropod invertebrates, and plants;
- baculoviruses are infectious only to insects of the same order from which they were initially isolated; and

- baculoviruses are ubiquitous and persistent in aquatic ecosystems, yet there has been no report of negative impacts on ecosystems other than the effect on the target host insect.

For further details on the above information and its review, see PRD2015-09, *Autographa californica* Nucleopolyhedrovirus FV11.

Based on all the available information on the effects of PhopGV isolate GV-0019 to non-target aquatic organisms, the anticipated minimal environmental exposure resulting from greenhouse use, and the precautionary measures required on the Tutavir label, the risks to fish, aquatic arthropod and non-arthropod invertebrates, and aquatic plants from the proposed use of Tutavir are acceptable.

4.3 Incident reports related to the environment

Phthorimaea operculella granulovirus isolate GV-0019 is a new active ingredient pending registration for use in Canada, and as of 19 September 2023, no environment incident reports had been submitted to the PMRA.

5.0 Value

Five greenhouse efficacy trials were conducted in Spain, Italy and the Netherlands, on greenhouse tomato against tomato leafminer (*Tuta absoluta*). The submitted trials, combined with a bridging rationale to expand the use to greenhouse fruiting vegetables (crop group 8-09) as well as use history information were sufficient to support the use of Tutavir for control of tomato leafminer (*Tuta absoluta*) on greenhouse fruiting vegetables (Crop Group 8-09) using an application rate of 50–200 mL/ha as a foliar spray in a minimum spray volume of 300 L/ha with a 4–7 day re-application interval. Tutavir provides a new active ingredient with a novel mode of action for control of tomato leafminer (*Tuta absoluta*) on solanaceous fruiting vegetables in greenhouses.

6.0 Pest control product policy considerations

6.1 Toxic Substances Management Policy considerations

The *Toxic Substances Management Policy* (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, 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, PhopGV Technical and Tutavir were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the conclusion that PhopGV Technical and Tutavir do 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.

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 Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.[6] The list is used as described in the PMRA Science Policy Note SPN2020-01[7] and is based on existing policies and regulations, including the *Toxic Substances Management Policy*[1] and *Formulants Policy*,[8] and taking into consideration the *Ozone-depleting Substance and Halocarbon Alternatives Regulations* under the *Canadian Environmental Protection Act, 1999,* (substances designated under the Montreal Protocol).

The PMRA has reached the following conclusions:

- PhopGV Technical and the end-use product, Tutavir, do not contain any 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 PMRA formulant initiatives and DIR2006-02.

7.0 Proposed regulatory decision

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of PhopGV Technical and Tutavir, containing the technical grade active ingredient *Phthorimaea operculella* granulovirus isolate GV-0019, for control of tomato leafminer (*Tuta absoluta*) on greenhouse fruiting vegetables.

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

6 SI/2005-114, last amended on June 25, 2008. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

7 PMRA's Science Policy Note SPN2020-01, *Policy on the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under paragraph 43(5)(b) of the Pest Control Products Act.*

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

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

List of abbreviations

°C	degree(s) Celsius
AcMNPV	*Autographa californica* nucleopolyhedrovirus
cm^3	cubic centimetres
DNA	deoxyribonucleic acid
DSMZ	German Collection of Microorganisms and Cell Cultures
GV	granulovirus
ha	hectare
IPM	Integrated Pest Management
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOC	level of concern
MCC	maximum challenge concentration
mL	millilitre
mPa	milliPascal
MPCA	microbial pest control agent
MRL	maximum residue limit
NeabNPV	*Neodiprion abietis* nucleopolyhedrovirus
NIOSH	National Institute for Occupational Safety and Health
OB	occlusion body
OECD	Organisation for Economic Co-operation and Development
PhopGV	*Phthorimaea operculella* granulovirus
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
RQ	risk quotient
s	second
TSMP	Toxic Substances Management Policy

References

A. List of studies/Information submitted by registrant

1.0 Product characterization and analysis

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2998589	Groner, A., 1986, Specificity and safety of baculoviruses. In R.R Granados and B.A Federici (eds.) The biology of Baculoviruses: Biological properties and molecular biology CRC Press pp. 1323-1337. DACO: M1.2,M2.7.2
2998598	R. Lapointe, et al., 2012, Recent advances in our knowledge of baculovirus molecular biology and its relevance for the registration of baculovirus-based products for insect pest population control. Pages 481-522 (Chapter 21) *in* S. Soloneski and M.L. Larramendy, editors. *Integrated pest management and pest control - current and future tactics.* InTech, Rijeka, Croatia. DACO: M1.2,M2.7.2
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3403149	2022, Origin, derivation and identification of the MPCA, DACO: M2.7.1 CBI
3403150	2022, Origin, derivation and identification of the MPCA, Appendix 1, DACO: M2.7.1 CBI

PMRA Document Number	Reference
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3403152	2018, Restriction enzyme analysis of PhopGV isolate and in silico comparison with sequenced PhopGV strains, DACO: M2.7.1 CBI
3403153	2022, Biological Properties of the MPCA, DACO: M2.7.2 CBI
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3403162	2022, Manufacturing methods and quality control, DACO: M2.8 CBI
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2.0 Human and animal health

PMRA Document Number	Reference
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3.0 Environment

PMRA Document Number	Reference
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3403225	1994, Gross, H.R., Hamn, J.J. and Carpenter, J.E., Design and Application of a hive-mounted device that uses honeybees (*Apis melifera*) to disseminate Heliothis nuclear polyhedrosis virus, DACO: M9.5.1. Envion. Entomol. 23(2):492-501

4.0 Value

PMRA Document Number	Reference
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