Proposed Registration Decision PRD2023-04

Plutella xylostella granulovirus (PlxyGV) isolate GV-0020 and Plutex

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Overview

Proposed Registration Decision for *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020

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 PlxyGV Technical and Plutex, containing the technical grade active ingredient *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020, to control diamondback moth larvae on canola and field-grown Brassica Head and Stem Vegetables (Crop Group 5-13).

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 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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 and Plutex.

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.

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. 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 Canada.ca.

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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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 and Plutex, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration Decision[4] on *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 and Plutex, 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 Overview, please refer to the Science Evaluation of this consultation document.

What is *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020?

Plutella xylostella granulovirus (PlxyGV) isolate GV-0020 is an insect-specific virus that infects and kills larvae of the diamondback moth, an important insect pest of crop plants in the plant family Brassicaceae.

Health considerations

Can approved uses of *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 affect human health?

***Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 is unlikely to affect your health when Plutex is used according to the label directions.**

Potential exposure to *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 may occur through the diet (food and water) or when handling and applying Plutex. 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.

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.

The technical grade active ingredient, PlxyGV Technical, and the end-use product, Plutex, are considered potential sensitizers.

Residues in water and food

Dietary risks from food and water are acceptable.

Residues of *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 on treated agricultural crops are possible at the time of harvest. Although baculoviruses, including *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020, are abundant in nature, no adverse effects from dietary exposure have been attributed to natural populations of *Plutella xylostella* 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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 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 Plutex. Consequently, dietary risks are acceptable for all segments of the population, including infants, children, adults and seniors.

Occupational risks from handling Plutex

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

Workers handling Plutex can be exposed to *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 through direct skin or eye contact or through inhalation. To protect workers from exposure to Plutex, 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 occupational risks 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 acceptable.

Plutex is being proposed for use as a commercial insecticide on various outdoor food crops. There are no residential uses. The product label includes mitigation measures to prevent bystander exposure such as reducing spray drift. Residential and non-occupational exposure to Plutex is therefore expected to be low when the label directions are observed. Consequently, the risk to residents and the general public is acceptable.

Environmental considerations

What happens when *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 is introduced into the environment?

Environmental risks are acceptable.

Plutella xylostella granulovirus (PlxyGV) isolate GV-0020 is a naturally occurring baculovirus that specifically infects lepidopteran insects. Baculoviruses are common and persistent in aquatic and terrestrial ecosystems. Plutex is a new end-use product that is proposed for use as an insecticide to control diamondback moth on field-grown crops (Brassica Head and Stem Vegetables and canola), and is not intended for aquatic applications. The field use of Plutex is not expected to result in sustained increases of *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 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 Plutex is applied according to directions on the label.

Value considerations

What is the value of Plutex?

Plutex, containing *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 at a minimum concentration of 2.5×10^{13} occlusion bodies (OBs)/L, is a microbial bio-insecticide that specifically infects and kills larvae of the diamondback moth.

The development of resistance to insecticides is a considerable problem in the diamondback moth, which makes this pest a challenge for growers of canola, broccoli, Brussels sprouts, cabbage and cauliflower. Plutex will provide these growers with an additional microbial bio-pesticide active ingredient for use against the diamondback moth that may be used to manage diamondback moths that are resistant to other registered active ingredients. Because Plutex contains a narrow spectrum active ingredient, it will not infect natural enemies of the diamondback moth and, consequently, may allow a degree of biological control of this pest, a key goal of 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 PlxyGV Technical and Plutex 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 Plutex 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.

A standard drift statement is required on the Plutex label to minimize the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas as well as statements to limit contamination of water supplies through cleaning or waste disposal.

Environment

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

Next steps

Before making a final registration decision on *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 and Plutex, Health Canada’s PMRA will consider any comments received from the public in response to this consultation document. Health Canada 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). 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 the Health Canada makes its registration decision, it will publish a Registration Decision on *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 and Plutex (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

Plutella xylostella granulovirus (PlxyGV) isolate GV-0020 and Plutex

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active microorganism	*Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020
Function	Biological Insecticide – for the control of diamondback moth (*Plutella xylostella*) on Brassica Head and Stem Vegetables and canola crops
Binomial name	*Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020
Taxonomic designation	
Superkingdom	Viruses
Family	Baculoviridae
Genus	*Betabaculovirus*
Species	*Plutella xylostella* granulovirus (PlxyGV)
Isolate	GV-0020
Patent Status information	None
Nominal purity of active	PlxyGV Technical (technical grade active ingredient): minimum of 2.5×10^{13} occlusion bodies (OBs)/L Plutex (end-use product): minimum of 2.5×10^{13} OBs/L
Identity of relevant impurities of toxicological, environmental and/or significance.	The technical grade active ingredient does not contain any impurities or micro contaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances. The product must meet microbiological contaminants release standards.

1.2 Physical and chemical properties of the end-use product

End-use product—Plutex

Property	Result
Colour	Grey-brown
Physical State	Liquid
Odour	Characteristic of organic compounds
pH	6.5

Property	Result
Viscosity	56.9–71.5 mPa·s at 20°C and 44.5–53.8 mPa·s at 40°C
Relative Density	1.15

1.3 Directions for use

Plutex is applied as a foliar spray to field-grown Brassica Head and Stem Vegetable crops (CG 5-13) and canola infested with diamondback moth eggs or larvae at a rate of 50–200 mL/ha with re-application every 6 to 8 days. Between 2 to 5 applications may be required per generation.

1.4 Mode of action

The Insecticide Resistance Action Committee (IRAC) classifies baculoviruses, including nucleopolyhedroviruses (NPVs) or granuloviruses (GVs), in Group 31. Baculoviruses generally have a narrow host range, infecting one or a small group of related insect species. When plant tissue that has been sprayed with Plutex is consumed by the larval diamondback moth, virus particles infect cells lining the insect gut. Replication of viruses within the larval body leads to the death of the larvae within approximately 6 days.

2.0 Methods of analysis

2.1 Methods for identification of the microorganisms

Acceptable methodologies for detection, isolation and enumeration of the active ingredient, *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020, were submitted by the applicant. *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 has been fully characterized with respect to the origin of the isolate, natural occurrence and biological properties. *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 can be identified to the isolate level by restriction endonuclease analysis of the viral deoxyribonucleic acid (DNA).

2.2 Methods for establishment of purity of seed stock

Plutella xylostella granulovirus (PlxyGV) isolate GV-0020 is deposited in the German Collection of Microorganisms and Cell Cultures (DSMZ) under accession code GV-0020. 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 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 PlxyGV 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 PlxyGV Technical and Plutex 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 Plutex using standard microbiological methods as well as by results of mouse toxicity testing. All batches of Plutex 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].

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

Information on the stability of other baculovirus products and interim storage stability data were provided for Plutex. The data and information support a storage period of 24 months at ≤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 PlxyGV Technical and Plutex. 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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 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 PlxyGV Technical and Plutex. 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 Plutex 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 Plutex. For additional information on these waiver rationales, see PRD2015-09, *Autographa californica* Nucleopolyhedrovirus FV11.

3.1.3 Health incident reports

Plutella xylostella granulovirus (PlxyGV) isolate GV-0020 is a new active ingredient pending registration for use in Canada, and as of 30 November 2022, no human or domestic animal incident reports have been submitted to the PMRA.

3.1.4 Hazard analysis

The data package submitted in support of registering PlxyGV Technical and Plutex 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, PlxyGV Technical is of low toxicity by the oral, pulmonary and dermal routes of exposure and is not a dermal irritant. Plutex 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, Plutex, is of low toxicity by the oral, inhalation and dermal routes and is not a dermal irritant.

Being an MPCA, *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 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 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 acute 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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 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 primarily 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. *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 has not been identified as a dermal wound pathogen, there is no indication that it could penetrate intact skin of healthy individuals, and 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 Plutex 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. Furthermore, all unprotected workers and users are prohibited from entering treated areas where Plutex has been applied for 4 hours or until the sprays have dried.

Label warnings, restrictions and risk mitigation measures are adequate to protect users of Plutex. Overall, occupational 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

Plutex is being proposed for use on brassica and canola crops. There are no residential uses. The product label includes mitigation measure to prevent bystander exposure such as reducing spray drift.

Plutex 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. As well, PlxyGV is a species that is common in the environment and the use of Plutex is not expected to cause sustained increases in exposure to bystanders beyond natural levels.

Consequently, the health risk to bystanders and individuals in residential areas from the use of Plutex 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 residue in or on agricultural commodities, the risks from consuming crops treated with Plutex 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 PlxyGV. Consequently, there is no health risk 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 uses of Plutex. 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. The label will also limit runoff containing this product from entering aquatic habitats. 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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 as evidenced by acute oral toxicity testing and tissue culture studies using other baculoviruses.

Health risks from residues of *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 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.

Plutex 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. Plutex will not be applied near or to drinking water. Furthermore, non-occupational exposure will be low when Plutex 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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020.

3.3.5 Maximum residue limits

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally specified as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada specifies science-based MRLs to ensure the food Canadians eat is safe.

Residues of *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 on treated food crops are possible at the time of harvest. Dietary risk to humans from the proposed use of Plutex is acceptable as no adverse effects from dietary exposure have been attributed to natural populations of PlxyGV, 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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020.

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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 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 and *Helicoverpa armigera* nucleopolyhedrovirus BV-0003 all of which are baculoviruses. Although co-exposure to *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 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.

Plutella xylostella granulovirus (PlxyGV) isolate GV-0020 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. Spray applications, at the maximum label rate of 2.5×10^{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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020, the field use of Plutex is not expected to result in sustained increases of *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 in terrestrial and aquatic environments beyond background levels.

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 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

A study performed with Plutex was submitted to address the hazards of *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 to honey bees. No other new studies were conducted for PlxyGV Technical and Plutex. Acceptable scientific rationales and studies were cited in support of Tier I testing requirements for terrestrial 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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 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 (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.

In a 10-day dietary toxicity and pathogenicity study, 10 honeybees (*Apis millifera)* per group were exposed to Plutex in the diet at a mean accumulated dose per bee of 1.32×10^8 OBs or 3.43×10^8 OBs and observed over a period of 30 days. Under the conditions of this study, there were no treatment-related toxic or pathogenic effects. *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 and Plutex is of low toxicity and the MPCA is not pathogenic to honeybees.

An independent search of published scientific literature including through Science Direct and PubMed 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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 to non-target terrestrial organisms and the precautionary measures required on the Plutex label, the risks to birds, wild mammals, non-target arthropods (including honeybees), non-arthropod invertebrates, microorganisms and plants from the proposed use of Plutex are acceptable.

4.2.2 Effects on aquatic organisms

No new studies were conducted for PlxyGV Technical and Plutex. 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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 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 *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020 to non-target aquatic organisms and the precautionary measures required on the Plutex label, the risks to fish, aquatic arthropod and non-arthropod invertebrates, and aquatic plants from the proposed use of Plutex are acceptable.

4.3 Incident reports related to the environment

Plutella xylostella granulovirus (PlxyGV) isolate GV-0020 is a new active ingredient pending registration for use in Canada, and as of 30 November 2022, no environment incident reports had been submitted to the PMRA.

5.0 Value

Resistance to a wide range of insecticides has been reported in diamondback moth populations globally and in Canada. Because the diamondback moth largely does not overwinter in Canada, Plutex would have limited utility for resistance management purposes. However, Plutex would be a valuable tool for the management of insecticide-resistant diamondback moths that are blown or fly into Canada each year. As a new active ingredient with a unique mode of action, widespread resistance to Plutex is unlikely.

Because Plutex is highly specific to the diamondback moth, this product is not likely to affect the natural enemies of the diamondback moth. Narrow-spectrum active ingredients allow pest control products to act in concert with natural enemies to reduce pest numbers and protect crops. Natural enemies, such as insect parasitoids and predators, can exert significant pressure on diamondback moth populations. For this reason, the use of Plutex will help to foster non-chemical means of diamondback moth management in Brassica Head and Stem Vegetable crop production in Canada.

Diamondback moth larvae damage or may completely destroy important vegetable and oilseed crops if left untreated. When Plutex was applied according to use directions, it reduced diamondback moth larvae infestations in canola, broccoli and cabbage field efficacy trials conducted in Ontario by ~80%, on average, and similarly to conventional and microbial bio-pesticide commercial standard products and that are registered with claims to control this pest.

Claims to control diamondback moth larvae on canola and Brassica Head and Stem Vegetables (CG 5-13) when applied at 50–200 mL product/ha as a full coverage spray with a re-application interval of 6–8 days and 2 to 5 applications per generation were supported by the submitted value information.

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, PlxyGV Technical and Plutex 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 PlxyGV Technical and Plutex 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

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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*.

regulations, including the *Toxic Substances Management Policy* 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 conclusion that PlxyGV Technical and the end-use product, Plutex, 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 PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of PlxyGV Technical and Plutex, containing the technical grade active ingredient *Plutella xylostella* granulovirus (PlxyGV) isolate GV-0020, to control diamondback moth larvae on canola and field-grown Brassica Head and Stem Vegetables (Crop Group 5-13).

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.

Additional information being requested

Since the storage stability data provided thus far were interim results, the completed storage stability study will be required as post-market information after registration.

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

List of abbreviations

°C	degree(s) Celsius
CG	Crop Group
AcMNPV	Autographa californica nucleopolyhedrovirus
cm	centimetres
DNA	deoxyribonucleic acid
DSMZ	German Collection of Microorganisms and Cell Cultures
GV	granulovirus
ha	hectare(s)
kg	kilogram
L	litre
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOC	level of concern
MCC	maximum challenge concentration
mL	millilitre
mPa·s	milliPascal per second
MPCA	microbial pest control agent
MRL	maximum residue limit
NeabNPV	Neodiprion abietis nucleopolyhedrovirus
OB	occlusion body
OECD	Organisation for Economic Co-operation and Development
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
PlxyGV	*Plutella xylostella* granulovirus
RQ	risk quotient
TSMP	*Toxic Substances Management Policy*

Appendix I Tables and figures

Table 1 Toxicity of Plutex (end-use product) to non-target species

Organism	Exposure	Significant effect, comments	Reference
Terrestrial Organisms			
Invertebrates			
Arthropods			
Honey Bee (*Apis mellifera*), young adult	10 day dietary exposure to Plutex, then observed for 30 days. Dose concentration = 4.1×10^8OBs/mL (Accumulated 1.32×10^8 OBs per bee) Dose concentration= 8.0×10^8OBs/mL (Accumulated dose 3.43×10^8 OBs per bee) Attenuated control= 8.0×10^8 non-viable OBs/mL	There were no treatment related effects. At Day 19, the corrected mortality of bees that received an accumulated dose of 1.32×10^8 OBs per bee or 3.43×10^8 OBs/bee was -2.44 and 36.59 %, respectively. The corrected mortality was -9.76 % in the attenuated control group. Mortality in the treatment groups was not greater than 50%; therefore, an LD_{50} could not be determined. **LOW TOXICITY NOT PATHOGENIC**	PMRA# 3305107

References

A. List of studies/Information submitted by registrant

PMRA Document Number	References
	1.0 Product characterization and analysis
3305036	2021, M1.2 Product Profile and Proposed Use Pattern, DACO: M1.2
3305063	2021, M2.1 Name and Address of Applicant, DACO: M2.1 CBI
3305064	2021, M2.10.1 Active Ingredient or MPCA, DACO: M2.10.1 CBI
3305066	2021, M2.10.2 Appendix 1, DACO: M2.10.2 CBI
3305067	2021, M2.11 Storage Stability, DACO: M2.11 CBI
3305068	2021, 2nd interim Report: Plutex 2 year storage stability and Corrosion Characteristics at 5C, DACO: M2.11,M2.12 CBI
3305070	2021, Density and Viscosity assessment of the Microbial Pest Control Product Plutex, DACO: M2.12 CBI
3305071	2021, M2.2 Name and Address of Manufacturing Plant, DACO: M2.2 CBI
3305072	2021, M2.3 Name and Address of Formulation Plant, DACO: M2.3 CBI
3305073	2021, M2.4 Trade Name, DACO: M2.4 CBI
3305074	2021, M2.5 Binominal Name (MPCA), DACO: M2.5 CBI
3305075	2021, M2.6 Canadian Patent Status, DACO: M2.6 CBI
3305076	2021, M2.7.1 Origin, Derivation and Identification of the MPCA, DACO: M2.7.1 CBI
3305077	2021, M2.7.1 Appendix 1, DACO: M2.7.1 CBI
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3305079	2017, M2.7.1 Appendix 2, DACO: M2.7.1,M2.7.2,M2.8 CBI
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3305087	2021, Mouse IP Safety Study, DACO: M2.10.2,M2.8 CBI
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3305094	2021, M2.9.2 Potency Estimation and Product Guarantee, DACO: M2.9.2 CBI
3305095	2021, M2.9.3 Unintentional Ingredients, DACO: M2.9.3 CBI
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3345926	2022, M2.8.2 Appendix 1, DACO: M2.8 CBI

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