Proposed Registration Decision PRD2018-08

Helicoverpa armigera nucleopolyhedrovirus isolate BV-0003 and Helicovex

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Overview

Proposed Registration Decision for *Helicoverpa armigera* Nucleopolyhedrovirus isolate BV-0003

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of HearNPV Technical and Helicovex, containing the technical grade active ingredient *Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003, as an insecticide to provide suppression of corn earworm in sweet corn.

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

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of HearNPV Technical and Helicovex.

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 the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of the Canada.ca website at https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management.html.

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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 *Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003 and Helicovex, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on *Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003 and Helicovex, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

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

What Is *Helicoverpa armigera* Nucleopolyhedrovirus Isolate BV-0003?

Helicoverpa armigera nucleopolyhedrovirus isolate BV-0003 is an insect virus that can act as an insecticide. Originally isolated from the cotton bollworm (*Helicoverpa armigera*), this baculovirus is known to infect only closely related insect species. It must be ingested to cause infection, which is lethal to susceptible insects. It is the active ingredient in the commercial class end-use product Helicovex, which provides suppression of corn earworm (*Helicoverpa zea*) in sweet corn.

Health Considerations

Can Approved Uses of *Helicoverpa armigera* Nucleopolyhedrovirus Isolate BV-0003 Affect Human Health?

***Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003 is unlikely to affect your health when Helicovex is used according to the label directions.**

Potential exposure to *Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003 may occur when handling and applying Helicovex and from potential residues in water and food. 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.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Residues of *Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003 on the treated crops, at the time of harvest, are possible following foliar applications to agricultural crops. Although baculoviruses, including *Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003, are abundant in nature, no adverse effects from dietary exposure have been attributed to natural populations of *Helicoverpa armigera* nucleopolyhedrovirus. Moreover, no adverse effects have been reported in acute oral toxicity and tissue culture studies with other baculoviruses. In addition, the likelihood of residues contaminating drinking water supplies is considered to be low. Consequently, dietary risks are considered to be low and not of concern.

Risks in Residential and Other Non-Occupational Environments

Estimated risk for non-occupational exposure is not of concern.

Helicovex is proposed for use on agricultural field crops, i.e., sweet corn. There are no residential uses and the label has necessary measures to prevent bystander exposure, such as to prevent spray drift from applications and restricting access to the area by unprotected persons during application. Even in the event of exposure, risk to the general population is not a concern since there were no signs of disease or toxicity noted in toxicological studies with baculoviruses.

Occupational Risks From Handling Helicovex

Occupational risks are not of concern when Helicovex is used according to label directions, which include protective measures.

Workers handling Helicovex can come into direct contact with *Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003 on the skin, in the eyes, or by inhalation. For this reason, the product label will specify that workers must wear waterproof gloves, long-sleeved shirts, long pants, a mist filtering mask or respirator, eye goggles and socks with shoes. In addition, to minimize postapplication exposure, workers are restricted from entering areas treated with Helicovex for 4 hours following application or until sprays have dried.

Environmental Considerations

What Happens When *Helicoverpa armigera* Nucleopolyhedrovirus Isolate BV-0003 Is Introduced Into The Environment?

Environmental risks are not of concern.

Helicoverpa armigera nucleopolyhedrovirus isolate BV-0003 is a naturally occurring baculovirus that specifically infects lepidopteran insects. Baculoviruses are common and persistent in aquatic and terrestrial ecosystems.

Helicovex is a new end-use product that is proposed for use as an insecticide to suppress corn earworm in sweet corn and is not intended for aquatic applications. The field use of Helicovex is not expected to result in sustained increases of *Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003 in terrestrial and aquatic environments beyond natural background levels.

Based on animal studies and scientific rationales, no significant effects to birds, wild mammals, fish, terrestrial and aquatic non-target arthropods, and plants are expected when Helicovex is applied according to directions on the label.

Value Considerations

What Is the Value of Helicovex?

Helicovex will provide a new mode of action to suppress corn earworm larvae and the damage they cause to sweet corn, and may be suitable for use in organic production.

Applied as foliar spray to sweet corn, Helicovex provides suppression of corn earworm larvae and the damage they cause. It contains a new active ingredient with a new mode of action for this use, and may be applied in rotation with registered alternatives to aid in resistance management. In addition, it may be suitable for use against corn earworm in organic production of sweet corn, for which there are no alternatives currently registered.

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 HearNPV Technical and Helicovex to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

HearNPV Technical and Helicovex are considered eye irritants. In addition, all microorganisms, including *Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003, contain substances that are potential sensitizers and thus, respiratory and dermal sensitivity may possibly develop in individuals exposed to potentially large quantities of *Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003. Therefore, workers handling or applying Helicovex must wear appropriate waterproof gloves, long-sleeved shirts, long pants, eye goggles, a mist filtering mask or respirator, and socks with shoes. In addition, to minimize postapplication exposure, all workers are restricted from entering treated areas during application and for 4 hours following application or until sprays have dried.

A standard drift statement is also required on the Helicovex 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.

Environment

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

Next Steps

Before making a final registration decision on *Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003 and Helicovex, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on *Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003 and Helicovex (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Helicoverpa armigera nucleopolyhedrovirus isolate BV-0003 and Helicovex

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active microorganism	*Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003
Function	For the suppression of corn earworm on sweet corn
Binomial name	*Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003
Taxonomic designation	
Superkingdom	Viruses
Family	Baculoviridae
Genus	*Alphabaculovirus*
Species	*Helicoverpa armigera* nucleopolyhedrovirus
Isolate	BV-0003
Patent Status information	None identified by the applicant.
Nominal purity of active	HearNPV Technical (TGAI): minimum of 7.5×10^{12} occlusion bodies (OBs)/L Helicovex (EP): minimum of 7.5×10^{12} OBs/L
Identity of relevant impurities of toxicological, environmental and/or significance.	The technical grade active ingredient (TGAI) does not contain any impurities or micro contaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances. The product must meet microbiological contaminants release standards.

1.2 Physical and Chemical Properties of the End-use Product

End-use Product–Helicovex

Property	Result
Colour	Grey-brown
Physical state	Liquid
Odour	Typical organic odour
Miscibility	n/a; not emulsifiable
pH	6.43 (undiluted at 23.4°C); 6.92 (diluted 1% w/v at 24.1°C)
Viscosity	690.1 cSt at 20°C; 405 cSt at 40°C

Property	Result
Density	1.163 g/mL

1.3 Directions for Use

Helicovex provides suppression of corn earworm larvae and the damage they cause to sweet corn through foliar application. It is applied at 50-200 mL/ha (3.75×10^{11} to 1.5×10^{12} viral occlusion bodies per hectare), diluted in sufficient water to obtain uniform coverage. The application rate used depends on pest pressure. Applications are timed to target eggs or first-instar larvae, with reapplication intervals of 3-5 days. For optimal efficacy, 3-5 applications are recommended, and application is allowed up to and including the day of harvest.

1.4 Mode of Action

Helicoverpa armigera nucleopolyhedrovirus (HearNPV) is a baculovirus originally isolated from the cotton bollworm, *Helicoverpa armigera*. Baculoviruses infect only arthropods, and members of the genus *Alphabaculovirus*, which includes HearNPV, infect only Lepidoptera. HearNPV is known to infect only larvae of *Heliothis* and *Helicoverpa* species in the family Noctuidae.

HearNPV must be ingested to be effective. Once ingested by a susceptible host insect, the alkaline environment of the host gut dissolves the protein matrix of the viral occlusion bodies, releasing the virus to infect gut cells. The virus is replicated within the gut cells and then budded off to infect other tissues within the host. Systemic infection is lethal to the host, and the cadaver eventually ruptures, releasing the virus to potentially infect additional hosts.

2.0 Methods of Analysis

2.1 Methods for Identification of the Microorganisms

Acceptable methodologies for detection, isolation and enumeration of the active ingredient, HearNPV isolate BV-0003, were submitted by the applicant. HearNPV isolate BV-0003 can be identified to the species level by restriction endonuclease analysis of the viral deoxyribonucleic acid (DNA).

2.2 Methods for Establishment of Purity of Seed Stock

HearNPV isolate BV-0003 has been preserved and maintained at -20°C since its isolation. HearNPV isolate BV-0003 is also deposited in the German Collection of Microorganisms and Cell Cultures (DSMZ) under reference number BV-0003.

The inoculum used for the production of Helicovex was produced by amplification of the purified virus through *H. armigera* larvae via oral passage. The resulting virus inoculum is stored at -18°C in order to maintain its activity.

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 product, 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 strains of HearNPV 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 HearNPV Technical and Helicovex 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 Helicovex by certified test facilities using standard methods for detecting and enumerating microbial contaminants of concern as well as by results of mouse toxicity testing. In addition, all batches of Helicovex must conform to the limits set out in the Organization 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

Storage stability data were provided for Helicovex. Results support a maximum storage period of 24 months at 5°C.

3.0 Impact on Human and Animal Health

3.1.1 Testing

No human health and safety studies were conducted for HearNPV Technical and Helicovex. Instead, the applicant cited numerous human health and safety studies with other baculoviruses.

Some of the studies included numerous acute oral, acute pulmonary, acute injection, acute dermal, dermal sensitization and tissue culture studies which were previously assessed in support of the registration of *Autographa californica* nucleopolyhedrovirus (AcMNPV) strain Fraser Valley #11 (FV11) and *Abietiv Neodiprion abietis* nucleopolyhedrovirus (NeabNPV) Newfoundland strain. Information relevant to AcMNPV FV11 and NeabNPV Newfoundland strain are applicable to HearNPV isolate BV-0003 as these baculoviruses are sufficiently similar

with respect to their limited host specificity (restricted to arthropods) and mode of action. For descriptions of these studies, see PRD2015-09 *Autographa californica* Nucleopolyhedrovirus FV11 and REG2006-10 *Abietiv Neodiprion abietis* Nucleopolyhedrovirus Newfoundland Strain.

The applicant also provided several additional acute oral, acute pulmonary, acute injection and tissue culture studies where various hosts (guinea pigs, mice, rhesus monkeys, hamsters, pigs, cows, lambs, rabbits and rats) or cell lines (human, monkey, rabbit, hamster and rat cell lines) were administered or exposed to various baculovirus preparations [for example, *Lymantria dispar* NPV(LdNPV), *Orgyia pseudotsugata* NPV, a *Heliothis* sp. NPV, *N. lecontei* NPV (NeleNPV), *N. sertifer* NPV (NeseNPV), *Prodenia litura* NPV, *Mamestra brassicae* NPV, *Pieris rapae* granulovirus (GV) and *Laspeyresia pomonella* GV]. No treatment-related abnormalities or signs of virus replication were observed. These findings are consistent with the previously assessed studies. Based on the results of these studies, it can be concluded that baculoviruses do not infect cells from non-permissive hosts.

3.1.2 Additional Information

In addition to the studies on other baculoviruses, a general scientific waiver rationale was provided to address exposure through various routes.

Baculoviruses are naturally occurring and ubiquitous in the environment. *Autographa californica* NPV OB counts on random samples of cabbage taken from store shelves or collected from the field vary between 3.1×10^5 OBs/cm^2 to 1.1×10^7 OBs/cm^2. Based on these numbers, it is estimated that a typical serving of cole slaw contains an average of 1×10^8 OBs. Despite the close interaction between baculoviruses and humans, no reports of adverse effects have been noted.

The host range associated with baculoviruses is limited to arthropods. Baculoviruses are considered to be highly host specific, infecting only one or a few closely related species within the same order from which they were initially isolated. The active ingredient in Helicovex is in the form of OBs which consist of occlusion derived virions (ODVs) embedded in a proteinaceous matrix. The ODVs are released only when the proteinaceous matrix is dissolved in the alkaline environment (pH 8–11) of the larval midgut. Organisms in which the digestive tract or other ports of entry are not alkaline would not be susceptible to viral OBs. Although non-occluded forms of baculoviruses (i.e., alkaline-liberated virus, pre-occluded virus or budded virus) can enter cells from non-permissive hosts, the viral DNA does not reach the nuclei in an expressible form. As a result, no cytopathic effects, evidence of virus replication or viral gene expression have been noted even at high multiplicities of infection.

In addition to the lack of infection and replication in vertebrate cells, no evidence of baculovirus-induced cytogenic, carcinogenic, mutagenic or teratogenic effects has been observed.

The results of numerous safety studies with baculoviruses have been extensively reviewed. Baculoviruses have been administered to a wide range of vertebrates, including mammals, at doses many times higher than that acquired in the field through all possible routes of exposure (for example, oral, inhalation, intravenous, intracerebral, intramuscular and dermal). There were

no instances of toxicity, allergic response or evidence of pathogenicity. In long-term oral and parenteral studies on rats, no baculovirus-related deaths or neoplasia were observed. Baculoviruses are also classified by the European Union as being low risk biocontrol agents. Laboratories in which baculoviruses are studied are rated as BioSafety Level 1 (BSL-1) which is reserved for the lowest risk microbial organisms that are not known to consistently cause disease in healthy adults. Work is typically conducted on open benches using standard microbiological practices. Special containment equipment or facility design is not required.

The formulation ingredient in Helicovex is associated with low dermal toxicity and dermal irritation potential. It is widely used in industrial and consumer products including pharmaceuticals, cosmetics, food and drinks, paints, resins and paper.

3.1.3 Incident Reports Related to Human and Animal Health

As of 20 November 2017, no human, domestic animal or environment incident reports involving a baculovirus have been submitted to the PMRA.

3.1.4 Hazard Analysis

The database submitted by the applicant in support of the registrations of HearNPV Technical and Helicovex was reviewed from the viewpoint of human health and safety and was determined to be sufficiently complete.

Based on all the available information, the technical grade active ingredient, HearNPV Technical is of low toxicity by the oral, pulmonary, intravenous and dermal routes of exposure and is not a dermal irritant. The information also indicates that the MPCA is not infective or pathogenic. While virus uptake can occur 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. However, the MPCA is considered to be a potential sensitizer. Consequently, the hazard statement "POTENTIAL SENSITIZER" will appear on the principal display panel of the technical grade active ingredient. The statement "May cause sensitization. Avoid contact with skin and clothing. Avoid inhaling/breathing mist." is also required on the secondary panel of the label under the "PRECAUTIONS" section.

Similarly, the EP, Helicovex is of low toxicity by the oral, inhalation and dermal routes and is not a dermal irritant. As noted for the technical grade active ingredient, the end-use product is considered to be a potential sensitizer therefore the hazard statement "POTENTIAL SENSITIZER" will appear on the principal display panel of the end-use product label. The statement "May cause sensitization. Avoid contact with skin and clothing. Avoid inhaling/breathing mist." is also required on the secondary panel under the "PRECAUTIONS" section.

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" and "Avoid contact with eyes."

Higher tier subchronic and chronic toxicity studies were not required because there are no indications of infectivity, toxicity or pathogenicity in the test animals treated in the Tier I acute oral, pulmonary and intravenous toxicity/infectivity tests.

Within the available scientific literature, there are no reports that suggest HearNPV isolate BV-0003 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 HearNPV isolate BV-0003.

3.2 Occupational, Residential and Bystander Risk Assessment

3.2.1 Occupational Exposure and Risk

When handled according to the label instructions, the potential for dermal, eye and inhalation exposure for applicators, mixer/loaders, and handlers exists, with the primary exposure route being dermal. 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. *Helicoverpa armigera* NPV isolate BV-0003 has not been identified as a dermal wound pathogen and does not contain any known toxic secondary metabolites. There is no indication that it could penetrate intact skin of healthy individuals. Furthermore, toxicity testing with various baculoviruses showed no significant signs of toxicity via the oral, pulmonary or dermal routes of exposure. No evidence of skin irritation was noted in the submitted dermal irritation studies conducted with various baculovirus preparations. As an eye irritation study was not submitted, Helicovex must be considered an eye irritant. Also, the PMRA assumes that all microorganisms contain substances that can elicit positive hypersensitivity reactions, regardless of the outcome of sensitization testing.

Risk mitigation measures such as personal protective equipment, including waterproof gloves, eye goggles, long-sleeved shirts, long pants, a NIOSH-approved mist filtering respirator or NIOSH-approved mist filtering mask, and socks with shoes are required to minimize exposure and protect commercial applicators, mixer/loaders and handlers that are likely to be exposed. In addition, all unprotected workers and users are prohibited from entering treated areas where Helicovex 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 Helicovex and no significant occupational risks are anticipated for this product.

3.2.2 Residential and Bystander Exposure and Risk

Overall, the PMRA does not expect that residential and bystander exposures will pose a health risk of concern on the basis of the low toxicity profile for Helicovex, the low infectivity/pathogenicity profile for HearNPV isolate BV-0003, and the assumption that precautionary label statements will be followed by commercial applicators in the use of Helicovex. As well, HearNPV is a species that is common in the environment and the use of

Helicovex is not expected to cause sustained increases in exposure to bystanders beyond natural levels. Consequently, the health risk to infants and children is expected to be low.

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, dietary risk is expected to be low and not of concern for the general population and sensitive subpopulations such as infants and children, or to animals because various baculoviruses demonstrated no pathogenicity, infectivity or oral toxicity in acute oral toxicity and tissue culture studies. Furthermore, higher tier subchronic and chronic dietary exposure studies were not required because of the anticipated low toxicity and lack of infectivity or pathogenicity associated with the MPCA.

3.3.2 Drinking Water

Health risks are not expected from exposure to HearNPV isolate BV-0003 via drinking water because exposure will be minimal from operational applications and because there are no anticipated harmful effects for this microorganism as evidenced by acute oral toxicity testing and tissue culture studies using other baculoviruses. The end-use product label instructs users not to contaminate irrigation or drinking water supplies or aquatic habitats through equipment cleaning or waste disposal. Aerial application is also prohibited. Furthermore, municipal treatment of drinking water is expected to remove the transfer of residues to drinking water.

3.3.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

Calculations of acute reference doses (ARDs) and acceptable daily intakes (ADIs) are not usually possible for predicting acute and long term effects of microbial agents in the general population or to potentially sensitive subpopulations, particularly infants and children. The single (maximum hazard) dose approach to testing MPCAs is sufficient for conducting a reasonable general assessment of risk if no significant adverse effects (in other words, no acute toxicity, infectivity or pathogenicity endpoints of concern) are noted in acute toxicity and infectivity tests. Based on all the available information and hazard data, the PMRA concludes that HearNPV isolate BV-0003 is of low toxicity, is not pathogenic or infective to mammals, and that infants and children are likely to be no more sensitive to the MPCA than the general population. Thus there are no threshold effects of concern and, as a result, there is no need to require definitive (multiple dose) testing or apply uncertainty factors to account for intra- and interspecies variability, safety factors or margins of exposure. Further factoring of consumption patterns among infants and children, special susceptibility in these subpopulations to the effects of the MPCA, including neurological effects from pre- or post-natal exposures, and cumulative effects on infants and children of the MPCA and other registered microorganisms that have a common mechanism of toxicity, does not apply to this MPCA. As a result, the PMRA has not used a margin of exposure (safety) approach to assess the risks of HearNPV isolate BV-0003 to human health.

3.3.4 Aggregate Exposure and Risk

Based on the toxicity and infectivity test data submitted and other relevant information in the PMRA's files, there is reasonable certainty that no harm will result from aggregate exposure of residues of HearNPV isolate BV-0003 to the general Canadian population, including infants and children, when the end-use product is used as labelled. This includes all anticipated dietary (food and drinking water) exposures and all other non-occupational exposures (dermal and inhalation) for which there is reliable information. Dermal and inhalation exposure to the general public will be low since the product is not allowed for use on turf, residential or recreational areas and the label will include mitigation measures to reduce spray drift. Furthermore, few adverse effects from exposure to other baculoviruses encountered in the environment have been reported. Even if there is an increase in exposure to this active ingredient from the use of Helicovex, there should not be any increase in potential human health risk.

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 HearNPV isolate BV-0003 on treated food crops, at the time of harvest, are anticipated following foliar applications to agricultural crops. Consequently, the PMRA has applied a hazard-based approach for determining whether an MRL is required for this microorganism. The risks anticipated for dietary exposure are considered low as no adverse effects from dietary exposure have been attributed to natural populations of HearNPV, 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 negligible to non-existent. Therefore, the PMRA has determined that specification of an MRL under the *Pest Control Products Act* is not required for HearNPV isolate BV-0003.

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. For the current evaluation, the PMRA has determined that HearNPV shares a common mechanism of toxicity with other registered isolates of baculoviruses. The PMRA is not aware of any other registered microorganism or pesticide that shares a common mechanism of toxicity with HearNPV. The potential health risks from cumulative exposure of HearNPV isolate BV-0003 and other registered baculoviruses are not of concern given the low toxicity and pathogenicity of baculoviruses.

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.

Helicoverpa armigera nucleopolyhedrovirus belongs to the genus *Alphabaculovirus* 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 (pH 1 to 7) 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 insects 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 Polyhedral inclusion bodies or PIBs/cm^3), ground litter (4×10^5 PIBs/cm^3) and tree bark (5×10^6 PIBs/cm^3) can persist for at least one year following natural epizootics of the host. Spray applications, at the maximum label rate of 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 or PIBs.

Therefore, while no studies were submitted to address the environmental fate and behaviour of HearNPV isolate BV-0003 based on the assessment, the field use of Helicovex is not expected to result in sustained increases of HearNPV isolate BV-0003 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 some safety factor. Tier II studies consist of environmental fate (persistence and dispersal) studies as well as additional acute toxicity testing of MPCAs. Tier III studies consist of chronic toxicity studies, i.e. life cycle studies, as well as definitive toxicity testing, for example, LC_{50}, LD_{50}. Tier IV studies consist of experimental field studies on toxicity and fate, and are required to determine whether adverse effects are realized under actual use conditions.

The type of environmental risk assessment conducted on MPCAs varies depending on the tier level that was triggered during testing. For many MPCAs, Tier I studies are sufficient to conduct environmental risk assessments. Tier I studies are designed to represent "worst-case" scenarios where the exposure conditions greatly exceed the expected environmental concentrations. The absence of adverse effects in Tier I studies are interpreted as minimal risk to the group of non-

target organisms. However, higher tiered studies will be triggered if significant adverse effects on non-target organisms are identified in Tier I studies. These studies provide additional information that allows 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 level of concern, 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

Acceptable scientific rationales and studies were submitted in support of Tier I testing requirements for terrestrial non-target organisms. The rationales were based on a previously reviewed extensive database of the published scientific literature including the results of ecotoxicological testing conducted on various baculoviruses in support of the registrations of AcMNPV FV11. Information relevant to AcMNPV FV11 is applicable to HearNPV isolate BV-003 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 impact of baculoviruses 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, does not increase virus levels beyond those that would occur naturally.

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

The applicant also submitted three non-target toxicity studies conducted with HearNPV isolate BV-0003 on aphid parasitoids, predatory mites and honey bees.

In two of these toxicity studies, aphids parasitoid (*Aphidius rhopalosiphi*) and predatory mites (*Typhlodromus pyri*) were exposed by contact to dried surface residues remaining from application at 6 times the maximum labelled rate of 1.5×10^{12} OBs/ha or 50–200 mL of Helicovex/ha. There were no adverse effects on mortality or reproduction reported for either beneficial arthropod. Similarly, no behavioural effects were observed for honey bees (*Apis milifera*) in 72-hour contact and 48-hour dietary acute toxicity testing conducted with Helicovex at the maximum labelled application rate. The LD_{50} or LC_{50} for the studies were greater than the single maximum applied rate of 1.5×10^{12} OBs/ha or 50–200 mL Helicovex/ha. Although these three toxicity studies were not required, they were considered to be acceptable as additional information, i.e., these studies further demonstrate the lack of adverse effects expected to non-target terrestrial arthropods from the proposed field use of Helicovex.

While the host range of baculoviruses is restricted to terrestrial arthropods (primarily larval stages), only three orders in the class Insecta are confirmed hosts of baculoviruses. All baculoviruses are restricted to a specific order, and within that order, most are restricted to a single family and usually to a single species or only to few closely related species. Single Nucleopolyhedrovirus (SNPV) alphabaculoviruses and gammabaculoviruses (for example, AcMNPV and *M. brassicae* NPV) can infect greater than 50 species crossing over 13 families of Lepidoptera. Only Lepidotera (*Alphabaculovirus*, *Betabaculovirus*), hymenopteran sawflies (*Gammabaculovirus*) and a few species of Diptera (*Deltabaculovirus*) have been confirmed to host baculoviruses. There is no cross infection of baculoviruses between these orders. Baculoviruses do not infect cockroaches, grasshoppers, aphids, nor have they been shown to infect non-phytophagous beneficial and predatory insects such as lady beetles, parasitoids and honeybees. Although not infectious to parasitoids, baculoviruses can cause premature death of larval host and competition for resources that can affect the fitness and survival of parasitoids. Parasitoids are often generalists and while a depletion of virally-treated insect populations will occur, the lack of non-target effects on other potential hosts would likely provide alternate hosts for the parasitoids. In addition studies suggest that some parasitoids transmit baculoviruses (for example, LdMNPV) and contribute to viral epizootics without adverse effects to themselves.

No deleterious effects of various baculoviruses (including *Heliothis zea* NPV) on honeybees have been reported in the published scientific literature. Treatments of whole colonies have never revealed any abnormalities in egg production, brood rearing, worker and queen mortality, and general colony behaviour. Even when hymenopteran specific NPV such as NeseNPV and NeleNPV were applied to control *Neodiprion sertifer* and *N. lecontei*, respectively, no adverse effects on bee colonies was reported. Similarly, *Galleria mellonella* NPV was used to control *G. mellonella* in bee hives without reported effects to bees.

An independent search of published scientific literature through 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 biological properties of HearNPV isolate BV-0003 and its anticipated effects on non-target terrestrial organisms, there is reasonable certainty that no harm will be caused to birds, wild mammals, terrestrial non-target arthropod invertebrates, non-arthropod invertebrates, and terrestrial plants from the proposed agricultural uses of Helicovex.

4.2.2 Effects on Aquatic Organisms

Acceptable scientific rationales were submitted in lieu of Tier I testing requirements for aquatic non-target organisms. The rationales were based on a previously reviewed extensive database of the published scientific literature including the results of ecotoxicological testing conducted on various baculoviruses in support of the registration of AcMNPV FV11. Information relevant to AcMNPV FV11 is applicable to HearNPV isolate BV-0003 as these baculoviruses are sufficiently similar with respect to their limited host specificity (restricted to arthropod) 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, supported by a lack of adverse effects to these non-target organisms reported in the scientific literature;
- 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 impact of baculoviruses 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. The current findings are consistent with the studies and information that was previously assessed by the PMRA.

An independent search of published scientific literature through PubMed yielded no reports of adverse effects to fish, aquatic arthropods and non-arthropod invertebrates, and aquatic plants.

Based on all the available information on the effects of HearNPV to non-target aquatic organisms there is reasonable certainty that no harm will be caused to fish, aquatic arthropods and non-arthropod invertebrates, and aquatic plants from the proposed field use of Helicovex. As a general precaution no aerial application is permitted. The label will also prohibit the direct application of Helicovex to aquatic habitats, estuaries or marine habitats, and direct handlers to not contaminate surface water by disposal of equipment wash waters. The label also instructs users to reduce runoff to aquatic environments.

4.3 Incident Reports related to the Environment

As of 20 November 2017, no human, domestic animal or environment incident reports involving a baculovirus have been submitted to the PMRA.

5.0 Value

Helicovex is an insecticide with a new mode of action for use against corn earworm in sweet corn. There are no pest control products currently registered in Canada for corn earworm that are suitable for organic production of sweet corn, and Helicovex has the potential to address this gap.

Registered alternatives for corn earworm in sweet corn are limited to active ingredients in IRAC Mode of Action Groups 1A (carbaryl, malathion and methomyl), 3A (lambda-cyhalothrin, cypermethrin, deltamethrin and permethrin), 15 (novaluron) and 28 (chlorantraniliprole). However, use of carbaryl on sweet corn is to be cancelled and must be removed from product labels no later than 31 March 2018 (RVD2016-02, *Carbaryl*), and this use of lambda-cyhalothrin also has been proposed for cancellation (PRVD2017-03, *Lambda-cyhalothrin*). In addition, resistance to cypermethrin, deltamethrin and permethrin, as well as to carbaryl and methomyl, has been reported for corn earworm.

Applied using conventional spray equipment, Helicovex is compatible with current management practices. It is also well-suited to Integrated Pest Management (IPM), the active ingredient HearNPV infecting only species of *Heliothis* and *Helicoverpa*. Helicovex can be used in rotation with conventional chemical insecticides, and this may reduce reliance on conventional chemicals and aid in the management of resistance to those products, which is a known problem with corn earworm, as noted above.

Efficacy data from four field trials of Helicovex demonstrated significant reductions in corn earworm numbers and/or damage to sweet corn. Those data were sufficient to support a claim of suppression of corn earworm in sweet corn through foliar application of 50-200 mL/ha, with a reapplication interval of 3-5 days and 3-5 applications recommended for optimal efficacy.

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 [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*.

HearNPV Technical and Helicovex were assessed in accordance with the PMRA Regulatory Directive DIR99-03.[5]

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

- HearNPV Technical does not meet the Track 1 criteria because the active ingredient is a biological organism and hence is not subject to the criteria used to define persistence, bioaccumulation and toxicity properties of chemical control products.
- There are also no formulants, contaminants or impurities present in the end-use product that would meet the TSMP Track-1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette.*[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- The technical grade active ingredient, HearNPV Technical, does not contain formulants of health or environmental concern as identified in the *Canada Gazette,* Part II, Volume 139, Number 24, pages 2641-2643: *List of Pest Control Product Formulants of Health or Environmental Concern.*
- The end-use product, Helicovex, does not contain formulants of health or environmental concern as identified in the *Canada Gazette,* Part II, Volume 139, Number 24, pages 2641-2643: *List of Pest Control Product Formulants of Health or Environmental Concern.*

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

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

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

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

7.0 Summary

7.1 Methods for Analysis of the Microorganism as Manufactured

The product characterization data for HearNPV Technical and Helicovex were judged to be adequate to assess their potential human health and environmental risks. The technical grade active ingredient was characterized and the specifications of the end-use product were supported by the analyses of a sufficient number of batches. All batches of Helicovex must conform to the limits set out in the OECD issue paper on microbial contaminants for microbial pest control products [ENV/JM/MONO(2011)43]. Storage stability data support storage at 5°C for up to 24 months for HearNPV Technical and Helicovex.

7.2 Human Health and Safety

The scientific waiver rationales and acute toxicity and infectivity studies using other baculoviruses submitted in support of HearNPV isolate BV-0003 were determined to be sufficiently complete to permit a decision on the registration of HearNPV Technical (TGAI) and Helicovex (EP). Based on all the available information, the technical grade active ingredient, HearNPV Technical, is of low toxicity and not infective or pathogenic by the oral, pulmonary, intravenous and dermal routes of exposure. This information also indicates that Helicovex will not be irritating to the skin. HearNPV Technical and Helicovex, however, are considered eye irritants and the signal words “CAUTION – EYE IRRITANT” must appear on the principal display panel of the label. Since HearNPV isolate BV-0003 is considered to be a potential sensitizer, the signal words, “POTENTIAL SENSITIZER”, are also required on the principal display panels of the end-use product and technical grade active ingredient.

When handled according to prescribed label instructions, the potential for dermal, eye and inhalation exposure for mixer/loaders, applicators, and handlers exists, with the primary source of exposure to workers being dermal. Respiratory and dermal sensitivity could possibly develop upon repeated exposure to the product since all microorganisms, including HearNPV isolate BV-0003, contain substances that are potential sensitizers. Therefore, anyone handling or applying Helicovex must wear waterproof gloves, eye goggles, a long-sleeved shirt, long pants, a NIOSH approved mist filtering mask or NIOSH approved mist filtering respirator, and socks with shoes. In addition, to further minimize postapplication exposure, workers are restricted from entering areas treated with Helicovex for 4 hours or until sprays have dried.

The health risk to the general population, including infants and children, as a result of bystander exposure and/or chronic dietary exposure is low and of no concern due to the low toxicity/pathogenicity profile for HearNPV isolate BV-0003, HearNPV Technical and Helicovex as well as the absence of sustained increases in exposure to bystanders beyond natural levels. The specification of an MRL under the *Pest Control Products Act* is not required for HearNPV isolate BV-0003.

7.3 Environmental Risk

The scientific studies, rationales and supporting published scientific literature submitted in support of HearNPV Technical and its associated end-use product, Helicovex, were determined to be sufficiently complete to permit a decision on registration. The field use of Helicovex containing HearNPV isolate BV-0003 is not expected to pose a risk to non-target organisms when the directions for use on the label are followed. The proposed field use of Helicovex on sweet corn is not expected to result in sustained increases of HearNPV isolate BV-0003 in terrestrial and aquatic environments.

As a general precaution, the product label will prohibit aerial application or the direct application of Helicovex to aquatic habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs, and wetlands), estuaries or marine habitats, and direct handlers to not contaminate surface water by disposal of equipment wash waters and to limit runoff from treated areas.

7.4 Value

Helicovex provides suppression of corn earworm larvae and the damage they cause to sweet corn. It contains a new active ingredient with a new mode of action for this use, and may be applied in rotation with registered alternatives to aid in resistance management. In addition, it may be suitable for use against corn earworm in organic production of sweet corn, for which there are no alternatives currently registered.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of HearNPV Technical and Helicovex, containing the technical grade active ingredient *Helicoverpa armigera* nucleopolyhedrovirus isolate BV-0003, as an insecticide to provide suppression of corn earworm in sweet corn.

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

List of Abbreviations

°C	degree(s) Celsius
AcMNPV	*Autographa californica* (multiple) nucleopolyhedrovirus
ADI	acceptable daily intake
ARD	acute reference dose
BSL	bio-safety level
BV	budded virus
cm	centimetre
cST	centistoke
DNA	deoxyribonucleic acid
DSMZ	German Collection of Microorganisms and Cell Cultures
EP	end-use product
FV	Fraser Valley
g	gram
GV	granulovirus
ha	hectare
HearNPV	*Helicoverpa armigera* nucleopolyhedrovirus
IRAC	Insecticide Resistance Action Committee
L	litre
LC_{50}	median lethal concentration
LdNPV	*Lymantria dispar* nucleopolyhedrovirus
LOC	level of concern
LR_{50}	median lethal residue
MCC	maximum challenge concentration
mL	millilitre
MPCA	microbial pest control agent
MRL	maximum residue limit
NeabNPV	*Neodiprion abietis* nucleopolyhedrovirus
NeleNPV	*Neodiprion lecontei* nucleopolyhedrovirus
NeseNPV	*Neodiprion sertifer* nucleopolyhedrovirus
NIOSH	National Institute for Occupational Safety and Health
NPV	nucleopolyhedrovirus
OB	occlusion body
ODV	occlusion derived virus
OECD	Organization for Economic Co-operation and Development
PMRA	Pest Management Regulatory Agency
SNPV	single nucleopolyhedrovirus
TGAI	technical grade of the active ingredient
TSMP	Toxic Substances Management Policy
w/v	weight volume percent

Appendix I Tables and Figures

Table 1 Toxicity to Non-Target Species

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
Arthropods				
Terrestrial Arthropods	Contact Residue– *Aphidius rhopalosiphi*, adult	Wasps (40) were exposed for 48 hours to a test arena previously sprayed with a solution of Helicovex containing 7.5×10^{12} (HearNPV isolate BV-0003 OBs)/mL at 2400 mL/ha or 6 times the maximum application rate. Two other groups of wasps (40/group) were administered water, and Perfekthion (positive control). After the exposure period, 17 females from each of the treatment groups were removed and confined individually over pots of aphid-infested barley plants for 24 hours. The aphids developed on the plants for 12 days after which the number of parasitized aphids that developed to pupae was assessed.	Cumulative mortality after 48 hours was 0.0% in Helicovex - treated groups and the water control. Mean number of parasitized aphids per wasp in the water control and Helicovex-treated groups was 15.7 and 17.2, respectively and was not considered significant LR_{50} > 2400mL Helicovex/ha **NOT TOXIC**	PMRA 2814190
Terrestrial Arthropods	Contact – *Typhlodromus pyri* (protonymphs maximum 24 hours old)	*Typhlodromus pyri* (80) were exposed for 7 days to a test arena previously sprayed with a solution of Helicovex containing 7.5×10^{12} (HearNPV isolate BV-0003 OBs)/mL at 2400 mL/ha or 6 times the maximum application rate.	Cumulative mortality on Day 7 in the water and Helicovex-treatment groups was 3% and 1%, respectively. No sublethal effects were observed. Total number of	PMRA 2814192

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		Two other groups of wasps (80/group) were administered water, and Perfekthion (positive control). Mortality was assessed on Day 3 and Day 7 of exposure. Reproduction was assessed on Days 9, 11 and 14.	eggs/female produced by the water and Helicovex-treated groups was 9.4 and 10.4, respectively. No statistical difference in reproduction was found for the Helicovex treated groups compared to the control. LR_{50} > 2400mL Helicovex/ha **NOT TOXIC**	
Terrestrial Arthropods	72h Contact – *Apis mellifera* (honeybee), young worker bees	A Helicovex suspension of 0.58 mg/mL (guarantee > 7.5×10^{12} HearNPV isolate BV-0003 OBs/mL) was administered to the dorsal surface of the thorax of each honeybee (50 per group) at the following doses 0.7, 1.3, 2.5, 5 and 10 µL test solution/bee Two other groups of bees (50/group) were administered water, and Perfekthion (positive control). Mortality was reported for the 24, 48 and 72 hour time points.	Cumulative mortality of 20% was recorded at the highest dose level of 10 µL test solution /bee after 72 hours. The maximum mortality of 22.0% was recorded in the second highest dose level of 5 µL test solution/ bee 48 hours following treatment. No behavioural effects were observed in the contact toxicity tests throughout the 48 and 72 hour observation period, respectively. No mortality occurred in the negative control group during the study. The 72-hour contact LC_{50} was >10µL test solution/bee or	PMRA 2814191

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
			7.5×10^7 OBs of HearNPV isolate BV-0003 **NOT TOXIC**	
Terrestrial Arthropods	48-h Dietary–*Apis mellifera* (honeybee), young worker bees	Bees (50) were communally fed a Helicovex suspension of 0.58 mg/mL (guarantee > 7.5×10^{12} HearNPV isolate BV-0003 OBs/mL). Each bee received 10.37 µL test solution. Two other groups of bees (50/group) were fed 50% sucrose, and dimethoate (positive control). Mortality was assessed at 4, 24, and 48 hours.	No mortality was reported in the treated groups. Cumulative mortality of 2.0% occurred in the negative control No behavioural effects were observed in the dietary toxicity tests throughout the 48 observation period. The 48-hour dietary LC_{50} was >10.37µL test solution/bee or 7.8×10^7 OBs of HearNPV isolate BV-0003 **NOT TOXIC**	PMRA 2814191

References

A. List of Studies/Information Submitted by Registrant

1.0 The Active Substance, Its Properties and Uses

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2758109	Burges, H.D., Croizier, G. and Huber, J., 1980, A review of Safety tests on Baculoviruses, DACO: M1.2,M2.7.2,M9.2.1,M9.4.1,M9.5.1,M9.5.2
2758110	Cory, J.S, 2003, Ecological impacts of virus insecticides, DACO: M1.2,M2.8,M9.1
2758113	Groner, A., 1986, Specificity and safety of baculoviruses, DACO: M1.2,M2.7.2,M4.1,M4.3.2,M4.7,M9.2.1,M9.4.1,M9.5.1,M9.5.2
2758114	Ignoffo, C.M., 1975, Evaluation of in vivo specificity of insect viruses, DACO: M1.2,M10.3.2.2,M2.7.2,M4.1,M4.3.2,M9.1,M9.2.1,M9.5.1,M9.5.2
2758116	King, E.G. and Coleman, R.J., 1989, Potential for Biological Control of Heliothis species., DACO: M1.2,M2.7.2
2758118	Lapointe, R., Thumbi, D and Lucarotti, C.J., 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., DACO: M1.2,M2.7.2,M4.1,M4.3.2,M9.1
2758121	Moscardi, F., 1999, Assessment of the application of baculoviruses for control of Lepidoptera, DACO: M1.2,M2.8
2758122	Organization for Economic Co-operation and Development, 2002, Consensus Document on Information Used in the Assessment of Environmental Applications Involving Baculovirus, DACO: M1.2,M2.7.1,M2.7.2,M2.8,M4.1,M4.3.2,M8.0,M9.1,M9.8.1
2758128	2016, Binominal Name (MPCA), DACO: M2.5
2758131	2016, Origin, Derivation and Identification of MPCA(s), DACO: M2.7.1
2758133	2006, A declaration, DACO: M2.7.1,M2.8 CBI
2758134	2006, The identity of *Helicoverpa armigera* nuclear polyhedrosis virus, DACO: M2.10.1,M2.7.1 CBI
2758136	2006, The baculovirus preparation HANPV., DACO: M2.7.1 CBI
2758137	2016, Biological Properties of MPCA, DACO: M2.7.2
2758139	Evans, H.F. and Haarp, K.A., 1982, Persistence of Insect Virus, DACO: M2.7.2
2758140	Jaques, R.A., 1977, Stability of entomopathogenic viruses, DACO: M2.7.2
2758141	Krieg, A., Groner, A., Huber, J. and Zimmerman, G., 1981, Inactivation of certain insect pathogens by ultraviolet radiation, DACO: M2.7.2
2758142	Thomas, E.D., Reichelderfer, C.F. and Heimpel, A.M., 1973, The effect of soil pH on the persistence of cabbage looper nuclear polyhedrosis virus on soil., DACO: M2.7.2
2758147	2016, Manufacturing Methods and Quality Assurance, DACO: M2.8 CBI
2758150	2007, MSDS Formulant, DACO: M2.9.1 CBI
2758156	2016, Active Ingredient or MPCA, DACO: M2.10.1,

PMRA Document Number	Reference
2758161	2016, Analysis of Microbial contaminants/Analysis of sample, certification of limits, DACO: M2.10.2 CBI
2758163	2015, Helicovex (*Helicoverpa armigera* NPV) Intraperitoneal Acute Mouse Toxicity/Infectivity, DACO: M2.10.2
2758164	2015, Confirmation of Microbial Examination Methods, DACO: M2.10.2 CBI
2758165	2006, 3 Year Storage Stability of the Formulation Helicovex at 5C, DACO: M2.11,M2.12 CBI
2758166	2016, Summary of Physical and Chemical Properties, DACO: M2.12
2758167	2011, Physical-Chemical Properties pH, Viscosity and Relative Density of test item Helicovex, DACO: M2.12 CBI
2764710	2011, Comparative Restriction Analysis for Virus Max, Gemstar and Helicovex, DACO: M2.7.1 CBI
2764711	2006, Production of *Helicoverpa armigera* nucleopolyhedrovirus, DACO: M2.8 CBI
2816647	2017, M 2.8 Manufacturing Methods and Quality Assurance, DACO: M2.8 CBI
2816649	2006, M 2.10.2 Appendix 1, DACO: M2.10.2 CBI
2816650	2011, M 2.10.2 Appendix 2, DACO: M2.10.2 CBI
2816651	2009, M 2.10.2 Appendix 3, DACO: M2.10.2 CBI
2816652	2011, M 2.10.2 Appendix 4, DACO: M2.10.2 CBI
2816654	2012, M 2.10.2 Appendix 5, DACO: M2.10.2 CBI

2.0 Impact on Human and Animal Health

PMRA Document Number	Reference
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3.0 Environment

PMRA Document Number	Reference
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4.0 Value

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B. Additional Information Considered

i) Published Information

1.0 The Active Substance, Its Properties and Uses

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2.0 Impact on Human and Animal Health

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