Proposed Registration Decision PRD2018-04

Autographa californica Nucleopolyhedrovirus FV11 and Loopex FC

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Overview

Proposed Registration Decision for *Autographa californica* nucleopolyhedrovirus FV11

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 AcMNPV Technical and new end use product, Loopex FC containing the technical grade active ingredient *Autographa californica* nucleopolyhedrovirus FV11, to control cabbage looper and alfalfa looper in specific field crops.

Autographa californica nucleopolyhedrovirus FV11 is currently registered in Canada for use in specific greenhouse vegetable crops for the control of cabbage looper and alfalfa looper. The detailed review for AcMNPV Technical and Loopex can be found in Proposed Registration Decision PRD2015-09, *Autographa californica* Nucleopolyhedrovirus.

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 AcMNPV Technical and new end use product, Loopex FC to control cabbage looper and alfalfa looper in specific field crops.

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

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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."

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 Canada.ca website at https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management.html.

Before making a final registration decision on *Autographa californica* nucleopolyhedrovirus FV11, 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 *Autographa californica* nucleopolyhedrovirus FV11, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

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

What is *Autographa californica* nucleopolyhedrovirus FV11?

Autographa californica nucleopolyhedrovirus FV11 is a naturally occurring virus that infects the larvae of cabbage looper and alfalfa looper when ingested by the larvae. Infected larvae die and release new virus particles which can then infect other larvae. *Autographa californica* nucleopolyhedrovirus FV11 is a registered microbial pest control agent (MCPA) in Canada.

Loopex FC is a new end use product containing this microbial pest control agent that is proposed for use as a commercial class biological insecticide for the control of cabbage looper (*Trichoplusia ni*) and alfalfa looper (*Autographa californica*) larvae on field grown crops when applied as a foliar spray.

Health Considerations

Can Approved Uses of *Autographa californica* nucleopolyhedrovirus FV11 Affect Human Health?

Autographa californica nucleopolyhedrovirus FV11 is unlikely to affect your health when Loopex FC is used according to the label directions.

Potential exposure to *Autographa californica* nucleopolyhedrovirus FV11 may occur when handling and applying Loopex FC, and when ingesting treated produce. When assessing health risks, several key factors are considered:

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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*.

- 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.

Studies in laboratory animals describe potential health effects from large doses in order to identify any potential pathogenicity, infectivity and toxicity concerns. When other strains of *Autographa californica* nucleopolyhedrovirus or other baculoviruses were tested on laboratory animals and tissue cultures, there were no signs that it caused any 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

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 that the food Canadians eat is safe.

Residues of *Autographa californica* nucleopolyhedrovirus FV11 on treated food crops, at the time of harvest, are possible following foliar applications to agricultural field crops. Baculoviruses are abundant in nature; however, no adverse effects from dietary exposure have been attributed to natural populations of *Autographa californica* nucleopolyhedrovirus. Moreover, no adverse effects have been reported in acute oral toxicity and tissue culture studies with other strains of *Autographa californica* nucleopolyhedrovirus or with other studied 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. Therefore, the Pest Management Regulatory Agency (PMRA) has determined that specification of an MRL under the *Pest Control Products Act* is not required for *Autographa californica* nucleopolyhedrovirus FV11.

Risks in Residential and Other Non-Occupational Environments

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

Loopex FC is proposed for use on agricultural field crops, there are no residential uses and the label has necessary mitigation measures to prevent bystander exposure, such as to prevent spray drift from application and restricting access to the area during application by unprotected persons. Consequently, it is unlikely that adults, youths and toddlers will be exposed to *Autographa californica* nucleopolyhedrovirus FV11. 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 other strains of *Autographa californica* nucleopolyhedrovirus or other baculoviruses.

Occupational Risks From Handling Loopex FC

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

Workers handling Loopex FC can come into direct contact with *Autographa californica* nucleopolyhedrovirus FV11 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, all unprotected workers are restricted from entering areas during application and for 4 hours following application or until sprays have dried.

Environmental Considerations

What Happens When *Autographa californica* nucleopolyhedrovirus FV11 Is Introduced Into the Environment?

Environmental risks are not of concern.

Autographa californica nucleopolyhedrovirus FV11 is a naturally occurring baculovirus that specifically infects lepidoteran insects. Baculoviruses are common and persistent in aquatic and terrestrial ecosystems.

Loopex FC is a new end-use product that is proposed for use as an insecticide to control cabbage and alfalfa looper larvae in field-grown crops and is not intended for aquatic applications. This field use of Loopex FC is not expected to result in sustained increases of *Autographa californica* nucleopolyhedrovirus FV11 in terrestrial and aquatic environments beyond natural background levels.

Based on a critical review of information in acceptable scientific rationales, no significant effects to birds, wild mammals, fish, terrestrial and aquatic non-target arthropods, and plants are expected when Loopex FC is applied according to directions on the label.

Value Considerations

What Is the Value of Loopex FC?

Loopex FC controls cabbage looper and alfalfa looper larvae in leafy vegetables (Crop Group 4-13), cucurbit vegetables (Crop Group 9), *Brassica* head and stem vegetables (Crop Group 5-13), alfalfa and canola.

Loopex FC is the first product containing AcMNPV FV11 for use on crops which are not grown in the greenhouse. A similar product is registered to control cabbage looper in various greenhouse crops. Loopex FC is a commercial class product applied as a foliar spray that provides growers with a new management tool and a new mode of action to control these pests on the listed crops.

Measures to Minimize Risk

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

The key risk-reduction measures being proposed on the label(s) of AcMNPV Technical and Loopex FC to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

AcMNPV Technical and Loopex FC are considered eye irritants. In addition, all microorganisms, including *Autographa californica* nucleopolyhedrovirus FV11, contain substances that are potential sensitizers and thus, respiratory and dermal sensitivity may possibly develop in individuals exposed to potentially large quantities of *Autographa californica* nucleopolyhedrovirus FV11. In turn, workers handling or applying Loopex FC must wear appropriate waterproof gloves, a long-sleeved shirt, long pants, eye goggles, a mist filtering mask or respirator, and socks and shoes. In addition, all unprotected workers are restricted from entering treated areas during application and for four hours following application until sprays have dried.

A standard drift statement is also required on the Loopex FC 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 Loopex FC.

Next Steps

Before making a final registration decision on *Autographa californica* nucleopolyhedrovirus FV11, 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 *Autographa californica* nucleopolyhedrovirus FV11 (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

Autographa californica Nucleopolyhedrovirus FV11

1.0 The active substance, its properties and uses

1.1 Identity of the Active Ingredient

Active ingredient	Polyhedral inclusion bodies (PIBs)* of *Autographa californica* nucleopolyhedrovirus FV11 (AcMNPV FV11)
Function	Biological Insecticide – To control cabbage looper larvae (*Trichoplusia ni*) and alfalfa looper (*Autographa californica*) on field grown crops
Binomial name	*Autographa californica* multicapsid nucleopolyhedrovirus FV11
Taxonomic designation	
Superkingdom	Viruses
Family	Baculoviridae
Genus	*Alphabaculovirus*
Species	*Autographa californica* nucleopolyhedrovirus (AcMNPV)
Strain	FV11 (Fraser Valley #11)
Patent Status information	None.
Nominal purity of active	Technical Grade Active Ingredient (TGAI): minimum of 1×10^9 PIBs/mL End-Use Product (EP): minimum of 5×10^8 PIBs/mL
Identity of relevant impurities of toxicological, environmental and/or significance.	The TGAI does not contain any impurities or micro contaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances. The product must meet microbiological contaminants release standards.

*PIBs are also referred to as occlusion bodies (OBs)

1.2 Physical and Chemical Properties of the End-Use Product

Property	Result
Colour	Light-medium brown
Physical State	Liquid, flowable
Odour	Undetectable
Miscibility	n/a; not emulsifiable
Corrosion Characteristics	Non-corrosive

Property	Result
pH	6.0–7.0
Viscosity	12.64 cSt at 20°C and 5.86 cSt at 40°C
Density	1.2 g/mL

1.3 Directions for Use

Loopex FC controls cabbage looper larvae and alfalfa looper larvae in leafy vegetables (Crop Group 4-13), cucurbit vegetables (Crop Group 9), *Brassica* head and stem vegetables (Crop Group 5-13), alfalfa and canola by foliar application. Application rates are 50 – 200 mL of Loopex FC/ha and a water volume of 800 L/ha is recommended. Applications may be repeated every 7-14 days if monitoring indicates it is necessary.

1.4 Mode of Action

The mode of action associated with AcMNPV FV11 is infection leading to larval death. Larval infection begins with ingestion of viral OBs which consist of occlusion derived virions (ODVs) embedded in a proteinaceous matrix. In the alkaline environment of the larval midgut, the protein matrix is dissolved. The released ODVs infect the midgut epithelial cells in which progeny nucleocapsids are produced and bud from the cellular plasma membrane (budded virus or BV). Budded viruses initiate secondary infections in other cells and tissues. At late stages of infection, proteins involved in forming OBs are produced and enclose the virus particles leading to hypertrophy of the infected cells and tissues. As virus replication proceeds, the cells lyse and release progeny OBs into the environment for subsequent ingestion and infection of new hosts.

2.0 Methods of analysis

2.1 Methods for Identification of the Microorganisms

Acceptable methods for identification of the microorganism were fully described for the microbial pest control agent (MPCA) in support of the initial registration decision. For additional information on these methods, see PRD2015-09, *Autographa californica* Nucleopolyhedrovirus FV11.

2.2 Methods for Establishment of Purity of Seed Stock

Acceptable methods for establishment of purity of seed stock were fully described for the MPCA in support of the initial registration decision. For additional information on these methods, see PRD2015-09.

2.3 Methods to Define the Content of the Microorganism in the Manufactured Material Used for the Production of Formulated Products

Acceptable methods to define the content of the microorganism in the manufactured material were fully described for the MPCA in support of the initial registration decision. For additional information on these methods, see PRD2015-09.

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

While there are appropriate methods available to enumerate PIBs, and to distinguish this MPCA from other strains of AcMNPV and other closely related baculoviruses, no methods are required to quantify viable or non-viable residues of AcMNPV FV11 in food as it is a ubiquitous microorganism in nature and has been isolated from a wide variety of environments.

2.5 Methods for Determination of Relevant Impurities in the Manufactured Material

Acceptable methods for the determination of relevant impurities in the manufactured material have been fully described for the initial registration decision. For additional information on these methods, see PRD2015-09.

The absence of human pathogens and below-threshold levels of contaminating microorganisms were shown in the microbial screening of batches of Loopex FC 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 AcMNPV Technical 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

The storage stability of Loopex FC has been assessed at 5°C or less for up to 15 months.

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 provided for AcMNPV Technical and Loopex FC to support the proposed use expansion to field crops. In the initial registration review, the results of numerous safety studies with other baculoviruses were assessed. In these studies, baculoviruses were 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. For additional information on these studies with other baculoviruses, see PRD2015-09.

3.1.2 Additional Information

No new additional information was submitted to address human health and safety requirements for AcMNPV Technical and Loopex FC. A previously submitted waiver rationale was used to address the potential infectivity of the MPCA and the potential toxicity 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, as well as the widespread use of the formulation ingredients in industrial and consumer products including pharmaceuticals, cosmetics, food and drinks, paints, resins and paper. For additional information on this additional information, see PRD2015-09.

3.1.3 Incident Reports Related to Human and Animal Health

As of 5 September 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 previously submitted in support of registering AcMNPV Technical and its associated end-use product (Loopex) was reviewed from the viewpoint of human health and safety and was determined to be sufficiently complete to permit a decision on registration for the proposed uses for Loopex FC.

Based on all the available information, the TGAI, AcMNPV 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 TGAI. 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, Loopex FC, is of low toxicity by the oral, inhalation and dermal routes, and is not a dermal irritant. As noted for the TGAI, the EP is considered to be a potential sensitizer therefore the hazard statement “POTENTIAL SENSITIZER” will appear on the principal display panel of the EP label. 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.

Since an eye irritation study was not submitted and no information was available in the scientific waiver rationale, the TGAI and EP 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 of the anticipated low acute toxicity of the EP, 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 AcMNPV FV11 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 AcMNPV FV11.

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. AcMNPV FV11 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 previously submitted dermal irritation studies conducted with various baculovirus preparations. As an eye irritation study was not submitted, Loopex FC 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 mist filtering respirator/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 Loopex FC 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 Loopex FC and no significant occupational risks are anticipated for these products.

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 Loopex FC, the low infectivity/pathogenicity profile for AcMNPV FV11, and the assumption that precautionary label statements will be followed by commercial applicators in the use of Loopex FC. As well, AcMNPV is a species that is common in the environment and the use of Loopex FC 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 residues in or on agricultural commodities, dietary risk is expected to be low and not of concern to 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 AcMNPV FV11 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 EP 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 (i.e., 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 AcMNPV FV11 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, 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 AcMNPV FV11 to human health.

3.3.4 Aggregate Exposure and Risk

Based on the toxicity and infectivity test data previously 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 AcMNPV FV11 to the general Canadian population, including

infants and children, when the microbial pest control product is used as labeled. This includes all anticipated dietary (food and drinking water) exposures and all other non-occupational exposures (dermal and inhalation) for which there is reliable information. 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 and restrict access to the areas during application. Furthermore, few adverse effects from exposure to other isolates of AcMNPV or 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 Loopex FC, 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 AcMNPV FV11 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 AcMNPV, and no adverse effects were observed in the acute oral toxicity and tissue culture studies with other strains of AcMNPV or 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 AcMNPV FV11.

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 AcMNPV 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 AcMNPV. The potential health risks from cumulative exposure of AcMNPV FV11 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

No studies were submitted to address the environmental fate and behaviour of AcMNPV FV11. 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.

AcMNPV FV11 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 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 label rate of up to 10^{11} PIBs/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} PIBs. Given that *Autographa californica* nucleopolyhedrovirus is abundant in nature, the field use of Loopex FC is not expected to result in sustained increases of *Autographa californica* nucleopolyhedrovirus FV11 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 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 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 were previously submitted to waive Tier I testing requirements for strain FV11 to terrestrial non-target organisms based on extensive literature reviews including results of ecotoxicological testing conducted on various baculoviruses (see PRD2015-09 *Autographa californica* Nucleopolyhedrovirus FV11). 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; and
- no evidence of infection, toxicity or mortality was observed following exposure to direct deposit of contaminated material (insects, frass, etc.).

The host range of baculoviruses is restricted to terrestrial arthropods; primarily larval stages. In the class Insecta, only three orders are confirmed hosts of baculoviruses. All baculoviruses are restricted to 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. There is no cross infection of baculoviruses between these orders. However, 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.

Based on all the available information on the biological properties of AcMNPV FV11 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 Loopex FC.

4.2.2 Effects on Aquatic Organisms

Acceptable scientific rationales were previously submitted to waive Tier I testing requirements for aquatic non-target organisms based on an extensive review of the published scientific literature including the results of ecotoxicological testing conducted on various baculoviruses (see PRD2015-09 *Autographa californica* Nucleopolyhedrovirus FV11). 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.

Based on all the available information on the effects of AcMNPV FV11 to non-target aquatic organisms there is reasonable certainty that no harm will be caused to fish, aquatic arthropod and non-arthropod invertebrates, and aquatic plants from the proposed use of Loopex FC outdoors. As a general precaution no aerial application is permitted, the label will also prohibit the direct application of Loopex FC 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 September 5, 2017, no human, domestic animal or environment incident reports involving a baculovirus have been submitted to the PMRA.

5.0 Value

Loopex FC is the first product containing AcMNPV FV11 for use on crops which are not grown in the greenhouse. A similar product is registered to control cabbage looper in various greenhouse crops.

Active ingredients in several mode-of-action groups are registered for use against cabbage looper in the supported crops, including conventional chemistries (e.g., organophosphates) as well as insect growth regulators and *Bacillus thuringiensis*. In comparison, there are few alternatives registered for use against alfalfa looper and only on a small number of supported crops (e.g., alfalfa, canola). Loopex FC will provide growers access to a new product with a new mode of action to control cabbage looper and alfalfa looper in the supported crops.

Pest claims were supported by efficacy data for cabbage looper from three field trials and one laboratory trial conducted on bok choy, kale and broccoli in British Columbia. Rationales based on pest and crop grouping principles were provided to support extrapolation to alfalfa looper and other proposed crops. No phytotoxicity to the host crops was observed in any of the trials. The value information supported the use of Loopex FC on leafy vegetables (Crop Group 4-13), cucurbit vegetables (Crop Group 9), *Brassica* head and stem vegetables (Crop Group 5-13), alfalfa and canola to control cabbage looper larvae and alfalfa looper larvae.

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*.

AcMNPV Technical and Loopex FC were assessed in accordance with the PMRA Regulatory Directive DIR99-03.[5]

- AcMNPV 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 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

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

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*

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, AcMNPV 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, Loopex FC, 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 the PMRA formulant initiatives and DIR2006–02.

7.0 Summary

7.1 Methods for Analysis of the Microorganism as Manufactured

The applicant previously provided adequate data/information on the ecology, physiological properties and genetic make-up of the MPCA. The product characterization data for AcMNPV Technical and Loopex FC were judged to be adequate to assess their potential human health and environmental risks. The TGAI was characterized and the specifications of the EP were supported by the analyses of a sufficient number of batches. Storage stability data provided for the EP, can support the maximum storage period of 15 months at 5°C or less , proposed for the labels of AcMNPV Technical and Loopex FC

7.2 Human Health and Safety

The scientific waiver rationales and acute toxicity and infectivity studies using other baculoviruses previously submitted in support of AcMNPV FV11 were determined to be sufficiently complete to permit a decision on registration. Based on all the available information, ACMNPV FV11 is of low toxicity and not infective or pathogenic by the oral, pulmonary, intravenous and dermal routes of exposure. This information also indicates that Loopex FC will not be irritating to the skin. AcMNPV Technical and Loopex FC, however, are considered eye irritants and the signal words “CAUTION – EYE IRRITANT” must appear on the principal display panel of the label. Since AcMNPV FV11 is considered to be a potential sensitizer, the signal words, “POTENTIAL SENSITIZER”, are also required on the principal display panels of the EP and TGAI.

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

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 AcMNPV FV11, contain substances that are potential sensitizers. Therefore, anyone handling or applying Loopex FC must wear waterproof gloves, eye goggles, long-sleeved shirts, long pants, a mist filtering mask or respirator, and socks with shoes. In addition, all unprotected workers are restricted from entering areas where Loopex FC has been applied for 4 hours or until mists 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 AcMNPV FV11, AcMNPV Technical and Loopex FC 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 AcMNPV FV11.

7.3 Environmental Risk

The scientific rationales and supporting published scientific literature previously submitted in support of AcMNPV Technical and its associated end-use product (Loopex) were determined to be sufficiently complete to permit a decision on registration. The field use of Loopex FC containing AcMNPV FV11 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 Loopex FC is not expected to result in sustained increases of AcMPNV FV11 in terrestrial and aquatic environments.

As a general precaution, the product label will prohibit aerial application or the direct application of Loopex FC 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

Value information demonstrated that Loopex FC controls cabbage looper larvae and alfalfa looper larvae on leafy vegetables (Crop Group 4-13), cucurbit vegetables (Crop Group 9), *Brassica* head and stem vegetables (Crop Group 5-13), alfalfa and canola. There are few alternatives registered for use against alfalfa looper. Loopex FC will provide growers access to a new product with a new mode of action to control cabbage looper larvae and alfalfa looper larvae on the supported crops. Loopex FC is the first product containing AcMNPV FV11 for use on crops which are not grown in the greenhouse.

8.0 Proposed Regulatory Decision

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 AcMNPV Technical and new end use product, Loopex FC containing the technical grade active ingredient *Autographa californica* nucleopolyhedrovirus FV11, to control cabbage looper and alfalfa looper in specific field crops.

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
AcNPV	Autographa californica nucleopolyhedrovirus
CpGV	Cydia pomonella granulovirus
cSt	centistoke
DNA	deoxyribonucleic acid
EP	end-use product
FV	Fraser Valley
g	gram
ha	hectare
L	litre
LdNPV	Lymantria dispar nucleopolyhedrovirus
mL	millilitre
MPCA	microbial pest control agent
MRL	maximum residue limit
NeabNPV	Neodiprion abietis nucleopolyhedrovirus
NeleNPV	Neodiprion lecontei nucleopolyhedrovirus
NIOSH	National Institute for Occupational Safety and Health
NPV	nucleopolyhedrovirus
OB	occlusion body
ODV	occlusion derived virus
PIBs	polyhedral inclusion bodies
TGAI	technical grade of the active ingredient
TSMP	Toxic Substances Management Policy

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A. List of Studies/Information Submitted by Registrant

1.0 THE ACTIVE SUBSTANCE, ITS PROPERTIES AND USES

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2329612	2003, Can Host Susceptibility to Baculovirus Infection be Predicted from Host Taxonomy or Life History?, DACO: M1.2,M2.7.2,M9.5.1
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2329614	1997, Liquefaction of Autographa californica Nucleopolyhedrovirus-Infected Insects Is Dependent on the Integrity of Virus-Encoded Chitinase and Cathepsin Genes, DACO: M1.2,M2.7.2
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PMRA Document Number	Reference
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2706938	M2.11 Loopex 24 month Storage Stability and Corrosion Characteristics at 5°C

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B. Additional Information Considered

i) Published Information

1.0 IMPACT ON HUMAN AND ANIMAL HEALTH

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