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Proposed Registration Decision

PRD2019-10

Mild Pepino mosaic virus strain LP, isolate VX1, mild Pepino mosaic virus strain CH2, isolate VC1, and V10

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Overview

Proposed Registration Decision for mild Pepino mosaic virus strain LP, isolate VX1, mild Pepino mosaic virus strain CH2, isolate VC1, and the End-use Product V10

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the [Pest Control Products Act](#), is proposing registration for the sale and use of VX1 Technical, containing the active mild Pepino mosaic virus strain LP, isolate VX1, VC1 Technical, containing the active mild Pepino mosaic virus strain CH2, isolate VC1, and the end-use product V10, containing the technical grade active ingredients mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1, for use on greenhouse tomato to protect against Pepino mosaic virus (PepMV).

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

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of mild Pepino mosaic virus strain LP, isolate VX1, mild Pepino mosaic virus strain CH2, isolate VC1, and the end-use product V10.

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 acceptable¹ 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 value² 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 Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the [Pesticides](#) section of Canada.ca.

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 mild Pepino mosaic virus strain LP, isolate VX1, mild Pepino mosaic virus strain CH2, isolate VC1, and the end-use product V10, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.³ Health Canada will then publish a Registration Decision⁴ on mild Pepino mosaic virus strain LP, isolate VX1, mild Pepino mosaic virus strain CH2, isolate VC1, and V10, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

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

What are mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1?

Pepino mosaic virus (PepMV) isolates VX1 and VC1 are mild forms of PepMV. These mild forms protect greenhouse tomatoes against aggressive forms of the virus through cross-protection, which is a plant defence mechanism against viral infection.

Health Considerations

Can Approved Uses of mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 Affect Human Health?

Mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 are unlikely to affect your health when V10 is used according to the label directions.

Potential exposure to mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 may occur when handling and applying V10 or by ingesting treated produce. 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.

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 VX1 Technical and VC1 Technical were tested on laboratory animals, there was low toxicity following oral and inhalation exposures, and there was no toxicity or irritation following dermal exposure. Also, VX1 Technical and VC1 Technical were not corrosive to the skin when these products were tested in a human skin cell culture. Pepino mosaic virus is a plant virus. Plant viruses are not related to any animal or human pathogen, and there are no reports of adverse effects in published scientific literature despite the natural occurrence and prevalence of plant viruses in the environment.

Residues in Water and Food

Dietary risks from food and water are acceptable

Residues of mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 on treated food crops are possible at the time of harvest. As already noted Pepino mosaic virus is a plant virus. Plant viruses are not related to any mammalian or human pathogen, and there are no reports of adverse effects in published scientific literature despite the natural occurrence and prevalence of plant viruses in the environment. Moreover, no signs of infectivity and low toxicity were observed when mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 were tested on laboratory animals. In addition, the likelihood of residues of mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 contaminating drinking water supplies from the proposed application of V10 on greenhouse tomato crops is low. Consequently, dietary risks are acceptable.

Risks in Residential and Other Non-Occupational Environments

Estimated risk for non-occupational exposure is acceptable

V10 is proposed for use in the greenhouse only. Consequently, it is unlikely that adults, youths and toddlers will be exposed to mild Pepino mosaic virus strain LP, isolate VX1 or mild Pepino mosaic virus strain CH2, isolate VC1. Even in the event of exposure, risk to the general population is acceptable since VX1 Technical and VC1 Technical are of low toxicity and there were no signs that they caused any disease in studies on laboratory animals.

Occupational Risks from Handling V10

Occupational risks are not of concern when V10 is used according to label directions, which include protective measures

Workers handling V10 can come into direct contact with mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 on the skin or in the eyes. For this reason, the product label will specify that workers must wear personal protective equipment, including waterproof gloves, long-sleeved shirt, long pants, goggles and socks with shoes.

Environmental Considerations

What Happens When mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 Are Introduced into the Environment?

Environmental risks are acceptable.

V10 is a new end-use product that is proposed for use on greenhouse tomato and is not intended for outdoor uses. The greenhouse use of V10 is not expected to result in sustained increases of mild Pepino mosaic virus strain LP, isolate VX1 or mild Pepino mosaic virus strain CH2, isolate VC1 in terrestrial and aquatic environments beyond natural background levels.

Mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 belong to the genus *Potexvirus* in the family Alphaflexiviridae. The Potexviruses are exclusively plant pathogens with global distribution. Contact with infected plants through tools, workers, or bumblebees is necessary for transmission to healthy plants. Infection of healthy plants occurs by contact to contaminated surfaces with damaged surfaces on the plant.

Based on a critical review of applicant-submitted information from public sources, no significant effects to birds, wild mammals, fish, terrestrial and aquatic arthropods, terrestrial and aquatic non-arthropod invertebrates, or non-target terrestrial and aquatic plants are expected when V10 is applied according to directions on the label.

Value Considerations

What Is the Value of V10?

V10 protects greenhouse tomatoes against some aggressive strains of Pepino mosaic virus.

Pepino mosaic virus is a pathogen that causes a serious disease of greenhouse-grown tomatoes, which results in reduced crop yield, quality and marketability. V10 is compatible with current greenhouse integrated pest management practices and will serve as an additional option to protect greenhouse tomato against this increasingly widespread disease problem.

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.

Key Risk-Reduction Measures

The key risk-reduction measures being proposed on the labels of the VX1 Technical, VC1 Technical and V10 to address the potential risks identified in this assessment are as follows.

Human Health

In the absence of an eye irritation study, VX1 Technical, VC1 Technical and V10 are considered eye irritants. In addition, all microorganisms, including mild Pepino mosaic virus strain LP, isolate VX1 or mild Pepino mosaic virus strain CH2, isolate VC1, contain substances that are potential sensitizers and thus, dermal sensitivity may possibly develop in individuals exposed to potentially large quantities of mild Pepino mosaic virus strain LP, isolate VX1 or mild Pepino mosaic virus strain CH2, isolate VC1. In turn, workers handling or applying V10 must wear waterproof gloves, long-sleeved shirt, long pants, goggles, and shoes with socks.

Environment

The end-use product label will include environmental precaution statements that reduce contamination of aquatic systems from the use of V10.

Next Steps

Before making a final registration decision on mild Pepino mosaic virus strain LP, isolate VX1, mild Pepino mosaic virus strain CH2, isolate VC1, and V10, Health Canada's PMRA will consider any comments received from the public in response to this consultation document. Health Canada will accept written comments on this proposal up to 45 days from the date of publication of this document.

Please forward all comments to Publications (contact information on the cover page of this document). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

Other Information

When the Health Canada makes its registration decision, it will publish a Registration Decision on mild Pepino mosaic virus strain LP, isolate VX1, mild Pepino mosaic virus strain CH2, isolate VC1, and V10 (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

Mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1

1.0 The Active Substance, Its Properties And Uses

1.1 Identity of the Active Ingredients

Active microorganisms	Mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1
Function	For the protection against Pepino mosaic virus on greenhouse tomato
Binomial names	Mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1
Taxonomic designation⁵	
Superkingdom	Viruses
Family	Alphaflexiviridae
Genus	Potexvirus
Species	Pepino mosaic virus
Isolates	VX1 and VC1
Patent Status information	None identified by the applicant.
Minimum purity of active	Technical grade active ingredient: VX1 Technical: 10–50 mg mild Pepino mosaic virus strain LP, isolate VX1/L; VC1 Technical: 10–50 mg mild Pepino mosaic virus strain CH2, isolate VC1/L; End-Use Product: V10 : 5–25 mg mild Pepino mosaic virus strain LP, isolate VX1/L; and 5–25 mg mild Pepino mosaic virus strain CH2, isolate VC1/L
Identity of relevant impurities of toxicological, environmental and/or significance.	The technical grade active ingredients do 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.

⁵ National Center for Biotechnology Information - Taxonomy Browser
(<https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=112229>)

1.2 Physical and Chemical Properties of the Technical Grade Active Ingredient and the End-use Products

Technical Grade of the Active Ingredient–VX1 Technical

Property	Result
Colour	Yellow; opaque
Physical State	Liquid at room temperature
Odour	grassy
Dynamic viscosity	1.104 cSt
pH	7.45
Density	1.020 g/cm ³

Technical Grade of the Active Ingredient–VC1 Technical

Property	Result
Colour	Yellow; opaque
Physical State	Liquid at room temperature
Odour	grassy
Dynamic viscosity	1.104 cSt
pH	7.45
Density	1.020 g/cm ³

End-use Product–V10

Property	Result
Colour	Yellow; opaque
Physical State	Liquid at room temperature
Odour	grassy
Dynamic viscosity	1.104 cSt
pH	7.45
Density	1.020 g/cm ³

1.3 Directions for Use

V10 is applied once per crop cycle to young tomato plants either before or after transplanting from the 3-true leaf to the first visible flower buds stage. Tomato plants must be free of Pepino mosaic virus at the time of application. V10 is applied as a 10% v/v water-based solution with synthetic sand as an abrasive. This solution is applied at 8 L/ha using a clean scouring pad moistened with this solution to rub the top side of a leaf at mid-plant height.

1.4 Mode of Action

V10 protects tomato plants by means of cross-protection, which is essentially based on the similarity of nucleotide sequences and coat proteins of the mild PepMV isolates, VX1 and VC1 and related aggressive forms of PepMV. Once tomato plants are infected with VX1 and VC1, it is thought that multiplication of RNA by aggressive forms of the virus is prevented.

2.0 Methods of Analysis

2.1 Methods for Identification of the Microorganisms

Acceptable methodologies for detection and enumeration of the active ingredients, mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1, were submitted by the applicant. Mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 can be identified to the isolate level using whole genome sequencing and analysis.

2.2 Methods for Establishment of Purity of Seed Stock

Acceptable methods for establishment of purity of seed stock were fully described for the microbial pest control agents (MPCA). Mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 are stored in plant tissue at temperatures below -15°C. The integrity of the MPCA is assessed by genomic sequence analysis prior to the production cycle.

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

The guarantees of VX1 Technical, VC1 Technical and V10 are expressed in units of mg of virus particles/L. Representative data on five batches of VX1 Technical and VC1 Technical were submitted. The methods for estimating potency and for determining the concentration of active ingredient 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, acceptable methods are available to quantify the MPCA in VX1 Technical and VC1 Technical and to distinguish these MPCAs from other isolates of Pepino mosaic virus.

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 VX1 Technical, VC1 Technical, and V10 are acceptable. These procedures include good hygienic practices for the maintenance, disinfection and cleaning of equipment used in the manufacturing process.

Complete microbial contaminant analysis data were submitted for five batches each of VX1 Technical and VC1 Technical using standard methods for detecting and enumerating microbial contaminants of concern. The data demonstrated the absence of human pathogens and below-threshold levels of contaminating microorganisms in the technical grade active ingredients. All batches of VX1 Technical and VC1 Technical must be screened for the microbial contaminants and 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

Submitted storage data support the claim that the technical grade active ingredients are stable for a period of six months when stored at -15°C. Acceptable storage stability data were not provided for V10, however, it was stated that the end-use product is unstable once thawed and has a shelf life of 7 days. This instability is reflected in the storage statement on the V10 product label that states that the product must be stored between 4 and 10°C, and used within 3 days of receipt by users from the manufacturer.

3.0 Impact On Human And Animal Health

3.1 Toxicity and Infectivity Summary

3.1.1 Testing

The PMRA conducted a detailed review of the toxicological studies submitted in support of VX1 Technical, VC1 Technical and V10.

3.1.1.1 VX1 Technical (containing mild Pepino mosaic virus strain LP, isolate VX1)

Test data submitted to fulfil the requirements for the health hazard assessment of VX1 Technical included acute oral toxicity, acute inhalation toxicity, acute dermal toxicity, and in vitro human skin cell corrosivity studies. All studies were conducted using former preparations of VX1 Technical. These preparations were accepted as being equivalent to the current technical grade active ingredient preparation.

In an acute oral toxicity study, two groups of three fasted, 8–9 week old female Wistar rats were given a single oral dose of VX1 Technical (18 mg mild Pepino mosaic virus strain LP, isolate VX1/L) undiluted at doses of 2000 mg/kg body weight (bw). The animals were then observed for a period of up to 14 days. Effects included choreoathetoid movements, pruritus, piloerection, reduced spontaneous activity, half eyelid closure and catalepsis. All symptoms resolved within 2 days post dosing. One animal lost weight during the second week. There were no mortalities.

In an acute inhalation toxicity study, one group of 8–9 week old Sprague-Dawley rats (5/sex) were exposed by the inhalation route to VX1 Technical (18 mg mild Pepino mosaic virus strain LP, isolate VX1/L) for 4 hours to nose only at a concentration of 5.08 mg/L. Animals then were observed for 14 days.

All animals exhibited irregular respiration; three animals exhibited moist or dry rales; and one exhibited hunched posture during the first 24 hours. All animals lost weight at Day 1, however, all animals showed a continued weight gain thereafter through Day 14. There were no mortalities.

In an in vitro human skin corrosivity study, 50 µL of VX1 Technical (18 mg mild Pepino mosaic virus strain LP, isolate VX1/L) was applied to human skin model EpiDerm tissues in 2 groups (6 replicates/group). Following treatment, the groups were measured for tissue viability, relative to a negative control, using an MTT (3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) reduction assay 3 and 60 minutes postapplication. The mean relative tissue viability was 105% (greater than 50%) after 3 minutes and 76% (greater than 15%) after 60 minutes. VX1 Technical was not corrosive in the in vitro human skin model under the parameters of the test.

In an acute dermal toxicity study, groups of 8–9 week old Wistar Crl rats (5/sex) were dermally exposed to undiluted VX1 Technical (18 mg mild Pepino mosaic virus strain LP, isolate VX1/L) at doses of 2000 mg/kg bw for 24 hours to an area of approximately 10% of body surface area. Following exposure, the animals were observed for a period of 14 days. There were no treatment related clinical signs, necropsy findings, changes in body weight, or signs of skin irritation. There were no mortalities.

Test results are summarized in Appendix I, Table 1.1.

3.1.1.2 VC1 Technical (containing mild Pepino mosaic virus strain CH2, isolate VC1)

Test data submitted to fulfil the requirements for the health hazard assessment of VC1 Technical included acute oral toxicity, acute inhalation toxicity, acute dermal toxicity, and in vitro human skin cell corrosivity studies. All studies were conducted using former preparations of VC1 Technical. These preparations were accepted as being equivalent to the current technical grade active ingredient preparation.

In an acute oral toxicity study, two groups of three fasted, 8–9 week old female Wistar rats were given a single oral dose of VC1 Technical (22 mg mild Pepino mosaic virus strain CH2, isolate VC1/L) undiluted at doses of 2000 mg/kg bw. The animals were then observed for a period of up to 14 days. Effects included pruritus, piloerection, reduced spontaneous activity, half eyelid closure and catalepsis. All symptoms resolved within 2 days post dosing. There were no mortalities.

In an acute inhalation toxicity study, one group of 11 week old Sprague-Dawley rats (5/sex) were exposed by the inhalation route to VC1 Technical (22 mg mild Pepino mosaic virus strain CH2, isolate VC1/L) for 4 hours to nose only at a concentration of 5.04 mg/L. Animals then were observed for 14 days. All animals exhibited irregular respiration. All animals had recovered at Day 5. Nine animals lost or failed to gain weight at Day 1 and one female also failed to gain weight from Day 3 through Day 7. All animals showed a continued weight gain thereafter through Day 14, with the exception of one female that lost weight from Day 7. There were no mortalities.

In an in vitro human skin corrosivity study, 50 µL of VC1 Technical (22 mg mild Pepino mosaic virus strain CH2, isolate VC1/L) was applied to human skin model EpiDerm tissues in 2 groups (6 replicates/group). Following treatment, the groups were measured for tissue viability, relative to a negative control, using an MTT reduction assay 3 and 60 minutes postapplication. The mean relative tissue viability was 105% (greater than 50%) after 3 minutes and 81% (greater than 15%) after 60 minutes. VC1 Technical was not corrosive in the in vitro human skin model under the parameters of the test.

In an acute dermal toxicity study, groups of 8–9 week old Wistar Crl rats (5/sex) were dermally exposed to undiluted VC1 Technical (22 mg mild Pepino mosaic virus strain CH2, isolate VC1/L) at doses of 2000 mg/kg bw for 24 hours to an area of approximately 10% of body surface area. Following exposure, the animals were observed for a period of 14 days. There were no treatment related clinical signs, necropsy findings, changes in body weight, or signs of skin irritation. There were no mortalities.

Test results are summarized in Appendix I, Table 1.2.

3.1.1.3 V10 (containing mild Pepino mosaic virus isolates VX1 and VC1)

The end-use product requirement for dermal irritation study was waived because no signs of dermal irritation were observed in the acute dermal toxicity studies testing the technical grade active ingredients. VX1 Technical and VC1 Technical are considered toxicologically equivalent to V10.

3.1.2 Additional Information

A scientific rationale was accepted to waive the technical grade active ingredient requirements for intravenous infectivity and tissue culture testing on the basis that VX1 Technical and VC1 Technical were of low toxicity and arguments that scientific literature on the biological properties of plant viruses have not demonstrated them to be infective to animals.

Pepino mosaic virus is a Potexvirus belonging to the order of Tymovirales and family of Alphaflexiviridae, which include single-stranded positive sense RNA plant viruses only. Human exposure to plant viruses in general is very large. In general, plant pathogenic viruses are considered to be pathogenic towards plant species only and not towards other organisms.

A literature search was performed by the applicant to investigate acute intravenous/intraperitoneal infectivity of mild Pepino mosaic virus strain CH2, isolate VC1 and mild Pepino mosaic virus strain LP, isolate VX1 to animals and humans. The publications found in this literature search did not show adverse effects to mammals or multiplication in mammals after intravenous application of plant viruses. No publications describing infections of mammals after intravenous application of plant viruses were found. Plant viruses of different genera are used in studies for the design of new vaccination strategies in humans. The results of this literature search support the general assumption that plant pathogenic viruses are not considered pathogenic toward mammals and humans.

Furthermore, a survey of published literature on the [National Center for Biotechnology Information search engine](#) performed by the PMRA using the keyword ‘Pepino virus’ has found no incidents, adverse or otherwise, involving the Pepino mosaic virus related to humans or other mammals.

3.1.3 Incident Reports Related to Human and Animal Health

Mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 are a new active ingredients pending registration in Canada. As of 12 March 2019, no incident reports were submitted to the PMRA.

3.1.4 Hazard Analysis

The data package submitted in support of the registration of mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 was reviewed from the viewpoint of human health and safety and determined to be acceptable.

Based on all the available information, the technical grade active ingredients, VX1 Technical and VC1 Technical, are of low toxicity by the oral, inhalation and dermal routes of exposure and are not dermal irritants. The information also indicates that mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 are not infective or pathogenic. However, mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 are considered to be potential sensitizers. Consequently, the hazard statement “POTENTIAL SENSITIZER” will appear on the principal display panel of the VX1 Technical and VC1 Technical. The statement “May cause sensitization. Avoid contact with skin and clothing.” is also required on the secondary display panel of the label under the “PRECAUTIONS” section.

Similarly, the end-use product, V10, is considered to be of low toxicity by the oral, inhalation and dermal routes and not a dermal irritant. As noted for VX1 Technical and VC1 Technical, V10 is also considered to be a potential sensitizer, therefore the hazard statement “POTENTIAL SENSITIZER” will appear on the principal display panel of the V10 label. The statement “May cause sensitization. Avoid contact with skin and clothing.” is also required on the secondary display panel of the label under the “PRECAUTIONS” section.

In the absence of studies, all microorganisms are considered to be mild eye irritants and thus, the labels for VX1 Technical and VC1 Technical, and V10 will include the signal words “CAUTION – EYE IRRITANT” and the precautionary statement “Avoid contact with eyes”.

Higher tier subchronic and chronic toxicity studies were not required because VX1 Technical and VC1 Technical were not acutely toxic by the oral, dermal or inhalation routes of administration. Furthermore, there were no indications of infectivity or pathogenicity in any animals tested in the Tier I studies.

Within the available scientific literature, there are no reports that suggest mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 or other plant viruses 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 system are anticipated for these MPCAs.

3.2 Occupational, Residential and Bystander Risk Assessment

3.2.1 Occupational Exposure and Risk

When V10 is used according to the label instructions, inhalation exposure is not anticipated, however, the potential for dermal and eye 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. Mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 have not been identified as dermal wound pathogens and there is no indication that they could penetrate the intact skin of healthy individuals. Furthermore, toxicity testing with the technical grade active ingredients showed low toxicity via the oral, inhalation and dermal routes of exposure. No evidence of skin irritation was noted in the submitted dermal toxicity studies. As an eye irritation study was not submitted, V10 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, goggles, long-sleeved shirt, long pants, and socks with shoes are required to minimize exposure and protect applicators, mixer/loaders and handlers that are likely to be exposed.

Label warnings, restrictions and risk mitigation measures are adequate to protect users of V10 when applied to greenhouse tomato; consequently occupational risks are acceptable.

3.2.2 Residential and Bystander Exposure and Risk

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 V10, the low infectivity/pathogenicity profile for mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1, the expectation that the label will be followed by commercial applicators in the use of V10, and that V10 will be applied only inside commercial greenhouses. As well, Pepino mosaic virus is a common viral disease in commercially grown tomatoes and the use of V10 is not expected to cause sustained increases in exposure to bystanders beyond natural levels. Consequently, the health risk to infants and children is acceptable.

3.3 Dietary Exposure and Risk Assessment

3.3.1 Food

While the proposed use pattern may result in dietary exposure with possible residue in or on agricultural commodities, the dietary risk for the general population and sensitive subpopulations such as infants and children is acceptable because mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 demonstrated no pathogenicity or infectivity, and low toxicity in acute oral and acute inhalation toxicity studies.

3.3.2 Drinking Water

Health risks are not expected from exposure to VX1 Technical and VC1 Technical via drinking water because exposure will be low due to application being limited to greenhouses, where mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 are not likely to reach ground or surface water. The label for V10 prohibits aerial application and instructs users not to contaminate irrigation or drinking water supplies or aquatic habitats through equipment cleaning or waste disposal. Furthermore, municipal treatment of drinking water is expected to reduce the transfer of residues to drinking water.

3.3.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

Calculations of acute reference doses (ARfDs) 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 mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 are of low toxicity, not pathogenic or infective to mammals, and that infants and children are likely to be no more sensitive to the MPCAs 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 MPCAs, including neurological effects from pre- or post-natal exposures, and cumulative effects on infants and children of the MPCAs and other registered microorganisms that have a common mechanism of toxicity, do not apply to these MPCAs. As a result, the PMRA has not used a margin of exposure (safety) approach to assess the risks of mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 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 mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain

CH2, isolate VC1 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. Furthermore, adverse effects from exposure to other Pepino mosaic virus encountered in the environment have not been reported. Even if there is an increase in exposure to mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 from the use of V10, 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 mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 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 Pepino mosaic virus, and low toxicity was observed in the acute oral and acute inhalation toxicity studies. 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 mild Pepino mosaic virus strain LP, isolate VX1 or mild Pepino mosaic virus strain CH2, isolate VC1.

3.4 Cumulative Assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. In its assessment of common mechanism of toxicity, the PMRA considers both the taxonomy of MPCAs and the production of any potentially toxic metabolites. For the current evaluation, the PMRA has determined that mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 share a common mechanism of toxicity with one other strain of Pepino mosaic virus that is used as a pesticide; Pepino mosaic virus, CH2 strain, isolate 1906. The potential health risks from cumulative exposure of mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 and this other microbial pesticide are acceptable when used as labelled given their low toxicity and pathogenicity.

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 mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1; however, 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.

The occurrence of Pepino mosaic virus in tomato greenhouses is widespread. Like all viruses (both plant and animal) Pepino mosaic virus can only reproduce inside its host. Multiplication in soil, water and air, therefore, does not occur. The virus is transmitted between plants most effectively via mechanical plant-to-plant contact, contact between equipment and plants, and to a lesser extent via greenhouse recirculation water.

Pepino mosaic virus infections, symptomless or with mild symptoms, have been observed in weed species which are members of the families Amaranthaceae, Asteraceae, Boraginaceae, Brassicaceae, Chenopodiaceae, Compositae, Convolvulaceae, Malvaceae, Plantaginaceae, Polygonaceae and Solanaceae. Most of these infections were found in the vicinity of tomato greenhouses. It has not been observed that these species play a significant role in the epidemiology of the virus. Although the use of V10 is expected to increase levels of mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1 in and around the greenhouse, it is not expected to increase the overall level of Pepino mosaic virus in the environment due to the widespread occurrence of this plant pathogen.

Overall, it is not expected that the greenhouse use of V10 will result in sustained increases of mild Pepino mosaic virus strain LP, isolate VX1 or mild Pepino mosaic virus strain CH2, isolate VC1 in outdoor terrestrial and aquatic environments beyond naturally occurring background levels.

4.2 Effects on Non-Target Species

The PMRA has a four tiered approach to environmental testing of microbial pesticides. Tier I studies consist of acute studies on up to seven broad taxonomic groups of non-target organisms exposed to a maximum hazard or Maximum Challenge Concentration (MCC) of the MPCA. The MCC is generally derived from the amount of the MPCA, or its toxin, expected to be available following application at the maximum recommended label rate multiplied by a safety factor. Tier II studies consist of environmental fate (persistence and dispersal) studies as well as additional acute toxicity testing of MPCAs. Tier III studies consist of chronic toxicity studies (life cycle studies), as well as definitive toxicity testing (for example, LC₅₀, LD₅₀). 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 ($RQ = \text{exposure}/\text{toxicity}$), 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 based on published scientific literature were submitted in lieu of Tier I data on non-target birds, wild mammals, terrestrial arthropods, terrestrial non-arthropod invertebrates, terrestrial plants and microorganisms.

The scientific rationales were based on the biological properties of the Pepino mosaic virus and results of a literature search. Plant viruses such as Pepino mosaic virus are generally only pathogenic towards plant species. Organisms are naturally exposed to large quantities of plant viruses but there are no known adverse effects outside plants. A literature search for the pathogenicity of plant viruses to non-target terrestrial organisms found no reports of multiplication of these or other plant viruses in vertebrate or mammalian tissue.

Although plant pathogenic viruses are generally considered to be pathogenic toward plant species only and not toward other organisms, one known exception of a plant virus infecting an organism from a different kingdom is the tobacco ringspot virus which replicates in the honeybee and can also be found in association with the varroa mite. The presence of this virus correlated with weaker honeybee colony health. Pepino mosaic virus can be spread mechanically by bumblebees, however, no specific vector-plant virus relation is known and the virus is not known to be harmful to bumblebees or any other insects.

Pepino mosaic virus infections have been observed in weed species which are members of the families Amaranthaceae, Asteraceae, Boraginaceae, Brassicaceae, Chenopodiaceae, Compositae, Convolvulaceae, Malvaceae, Plantaginaceae, Polygonaceae and Solanaceae. These infections can be symptomless or with mild symptoms. Most of these infections were found in the vicinity of tomato greenhouses. These weed species do not seem to play a significant role in the epidemiology of the virus.

Based on all the available data and information on the effects of mild Pepino mosaic virus strain LP, isolate VX1 or mild Pepino mosaic virus strain CH2, isolate VC1 to terrestrial non-target organisms, there is reasonable certainty that no harm will be caused to birds, wild mammals, arthropods, non-arthropod invertebrates, or to other non-target microorganisms from the use of V10 in greenhouse tomato crops. While mild Pepino mosaic virus strain LP, isolate VX1 or mild Pepino mosaic virus strain CH2, isolate VC1 could potentially infect non-target plants, exposure to non-target plants is low due to the proposed use of V10 in greenhouses.

4.2.2 Effects on Aquatic Organisms

Acceptable scientific rationales based on published scientific literature were submitted in lieu of Tier I data on freshwater fish, aquatic arthropods, aquatic non-arthropod invertebrates and aquatic plants.

The scientific rationales were based on the biological properties of the Pepino mosaic virus and results of a literature search. As noted in Section 4.2.1 above, plant viruses such as Pepino mosaic virus are generally only pathogenic towards plant species. Organisms are naturally exposed to large quantities of plant viruses but there are no known adverse effects outside plants. A literature search for the pathogenicity of plant viruses to non-target aquatic organisms found no reports of multiplication of these or other plant viruses in vertebrate tissue.

Based on all the available data and information on the effects of mild Pepino mosaic virus strain LP, isolate VX1 or mild Pepino mosaic virus strain CH2, isolate VC1 to aquatic non-target organisms, there is reasonable certainty that no harm will be caused to fish, aquatic arthropods, aquatic non-arthropod invertebrates or aquatic plants from the use of V10 in greenhouse tomato crops. As a precaution, standard label statements will prohibit handlers from contaminating aquatic habitats.

4.3 Incident Reports related to the Environment

Mild Pepino mosaic virus strain LP, isolate VX1 or mild Pepino mosaic virus strain CH2, isolate VC1 are new active ingredients pending registration for use in Canada. As of 12 March 2019, no incident reports were submitted to the PMRA.

5.0 Value

Value information demonstrated that V10 applied in combination with synthetic sand is effective against aggressive isolates of the EU and CH2 PepMV strains, both present in Canada. V10 was not tested against any aggressive forms of the LP strain, which is not yet present in Canada. However, V10 is expected to protect tomato plants from this strain given that VX1 is a mild

isolate of the LP strain and since the degree of similarity among isolates within the LP strain is greater than that between the LP strain and the EU strain, which V10 protects against. While V10 may cause mild symptoms of PepMV, particularly on foliage, overall crop growth and vigour are improved. Applied in accordance with the use directions, V10 can be expected to protect tomato plants from the EU, CH2 and LP strains of PepMV.

V10 will serve as an additional option to inoculate greenhouse tomato against aggressive forms of commonly present strains of the Pepino mosaic virus, which causes serious fruit yield, quality and marketability losses. The use of V10 would be in conjunction with current practices to minimize and delay PepMV infection of tomato. These practices include greenhouse cleaning and disinfection procedures, and the use of virus-free tomato transplants.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

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

During the review process, VX1 Technical and VC1 Technical were assessed in accordance with the PMRA Regulatory Directive DIR99-03⁶ and evaluated against the Track 1 criteria. VX1 Technical, VC1 Technical and V10 did not meet TSMP criteria.

6.2 Formulants and Contaminants of Health Concern

During the review process, contaminants in the technical as well as formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.⁷ The list is used as described in the PMRA Notice of Intent NOI2005-01⁸ and is based on existing policies and regulations including: DIR99-03; and DIR2006-02⁹ 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:

⁶ Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*.

⁷ SI/2005-114.

⁸ Notice of Intent NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

⁹ Regulatory Directive DIR2006-02, *PMRA Formulants Policy and Implementation Guidance Document*.

- Technical grade VX1 Technical and VC1 Technical, and their end-use product do not contain formulants or contaminants identified in the *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 product characterization data for VX1 Technical and VC1 Technical and V10 were judged to be adequate to assess their potential human health and environmental risks. The technical grade active ingredients were characterized and the specifications were supported by the analyses of a sufficient number of batches. All batches of VX1 Technical and VC1 Technical 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 of V10 between 4 and 10°C, and application within 3 days of receipt by users from the manufacturer.

7.2 Human Health and Safety

The acute toxicity studies and other relevant information submitted in support of VX1 Technical, VC1 Technical, and V10 were determined to be acceptable. Based on all the available information, the technical grade active ingredients, VX1 Technical and VC1 Technical, are of low toxicity and not infective or pathogenic by the oral, inhalation, and dermal routes of exposure. This information also indicates that V10 will not be irritating to the skin.

VX1 Technical and VC1 Technical and V10, however, are considered as eye irritants and thus, the signal words “CAUTION – EYE IRRITANT” must appear on the principal display panel of the labels. Since mild Pepino mosaic virus strain LP, isolate VX1 or mild Pepino mosaic virus strain CH2, isolate VC1 are also considered to be potential sensitizers, the signal words, “POTENTIAL SENSITIZER”, are required on the principal display panels of V10 and VX1 Technical and VC1 Technical. The following precautionary statements are also required on the secondary panel of each technical grade active ingredient and the end-use product: “May cause sensitization”, “Avoid contact with skin and clothing”.

When handled according to prescribed label instructions, the potential for dermal and eye exposure for mixer/loaders, applicators, and handlers exists, with the primary source of exposure to workers being dermal. Dermal sensitivity could possibly develop upon repeated exposure to the product since all microorganisms, including mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1, contain substances that are potential sensitizers. Therefore, anyone handling or applying V10 must wear waterproof gloves, goggles, a long-sleeved shirt, long pants, and shoes with socks.

The health risk to the general population, including infants and children, as a result of bystander exposure and/or chronic dietary exposure is acceptable due to the low toxicity/pathogenicity profile for VX1 Technical, VC1 Technical and V10 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 mild Pepino mosaic virus strain LP, isolate VX1 or mild Pepino mosaic virus strain CH2, isolate VC1.

7.3 Environmental Risk

The scientific rationales and supporting published scientific literature in support of VX1 Technical and VC1 Technical, and its associated end-use product, V10, were determined to be acceptable. The greenhouse use of V10 containing mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1, is not expected to pose a risk to non-target organisms when the directions for use on the label are followed. The greenhouse use of V10 on tomato is not expected to result in sustained increases of mild Pepino mosaic virus strain LP, isolate VX1 or mild Pepino mosaic virus strain CH2, isolate VC1, in terrestrial and aquatic environments.

As a general precaution, the product label will direct handlers to not contaminate surface water by disposal of equipment wash waters.

7.4 Value

The information submitted to register V10 is adequate to demonstrate the value of its use to protect greenhouse tomato from particular aggressive strains of the Pepino mosaic virus when applied in accordance with the product label.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of VX1 Technical, containing the active mild Pepino mosaic virus strain LP, isolate VX1, VC1 Technical, containing the active mild Pepino mosaic virus strain CH2, isolate VC1, and the end-use product V10, containing the technical grade active ingredients mild Pepino mosaic virus strain LP, isolate VX1 and mild Pepino mosaic virus strain CH2, isolate VC1, for use on greenhouse tomato to protect against Pepino mosaic virus (PepMV).

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

Additional Information Being Requested

Since this technical product is manufactured only at pilot scale before registration, five-batch data representing commercial-scale production will be required as post-market information after registration.

List of Abbreviations

°C	degree(s) Celsius
µL	microlitre
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
cm ³	cubic centimeter
cSt	centistokes
g	gram
ha	hectare(s)
HPLC	high performance liquid chromatography
kg	kilogram
L	litre
LC ₅₀	lethal concentration 50%
LD ₅₀	lethal dose 50%
LOC	level of concern
mg	milligram
MCC	maximum challenge concentration
MPCA	microbial pest control agent
MRL	maximum residue limit
MS	mass spectrometry
MTT	3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide
OECD	Organization for Economic Co-operation and Development
PepMV	Pepino mosaic virus
PMRA	Pest Management Regulatory Agency
RNA	ribonucleic acid
RQ	risk quotient
TSMP	Toxic Substances Management Policy
v/v	volume per volume dilution
w/v	weight as a percentage of volume

Appendix I Tables and Figures

Table 1.1 Toxicity profile of VX1 Technical (surrogate)

Study Type/ Animal/ PMRA#	Study Results
14-Day Acute Oral Toxicity Wistar Rat PMRA# 2965600	<p>There were no mortalities.</p> <p>Treatment related clinical signs included choreoathetoid movements, pruritus, piloerection, reduced spontaneous activity, half eyelid closure and catalepsis.</p> <p>One animal lost weight during the second week; all other animals gained weight normally throughout the study.</p> <p>There were no abnormal necropsy findings.</p> <p>The oral LD₅₀ was ≥ 2000 mg/kg bw in female rats (low toxicity).</p>
14-Day Acute Dermal Toxicity Wistar Rat PMRA# 2749546	<p>There were no mortalities.</p> <p>There were no treatment related clinical signs, no abnormal necropsy findings and all animals gained body weight.</p> <p>The dermal LD₅₀ was ≥ 2000 mg/kg bw in male and female rats (low toxicity) and no signs of irritation were observed.</p>
14-Day Acute Inhalation Toxicity Sprague-Dawley Rat PMRA# 2965601	<p>There were no mortalities.</p> <p>Treatment related clinical signs included irregular respiration, moist or dry rales, and hunched posture. All animals recovered by Day 1.</p> <p>All animals lost weight by Day 1. All animals showed a continued weight gain thereafter through Day 14.</p> <p>There were no abnormal necropsy findings.</p> <p>The inhalation LC₅₀ was ≥ 5.08 mg/L in male and female rats (low toxicity).</p>
In vitro Human Tissue Culture – Corrosivity EpiDerm Tissues PMRA# 2965603	<p>Non-corrosive to the in vitro human skin model under the parameters of the test.</p>

Table 1.2 Toxicity profile of VC1 Technical (surrogate)

Study Type/ Animal/ PMRA Document Number	Study Results
14-Day Acute Oral Toxicity Wistar Rat PMRA# 2750994	There were no mortalities. Treatment related clinical signs included pruritus, piloerection, reduced spontaneous activity, half eyelid closure and catalepsis. All animals gained weight normally throughout the study. There were no abnormal necropsy findings. The oral LD ₅₀ was ≥ 2000 mg/kg bw in female rats (low toxicity).
14-Day Acute Dermal Toxicity Wistar Rat PMRA# 2749545	There were no mortalities. There were no treatment related clinical signs, no abnormal necropsy findings and all animals gained body weight. The dermal LD ₅₀ was ≥ 2000 mg/kg bw in male and female rats (low toxicity) and no signs of irritation were observed.
14-Day Acute Inhalation Toxicity Sprague-Dawley Rat PMRA# 2750995	There were no mortalities. Treatment related clinical signs included irregular respiration. All animals recovered by Day 5. Nine of ten animals lost or failed to gain weight by Day 1 and one female also failed to gain weight from Day 3 through Day 7. All animals showed a continued weight gain thereafter through Day 14, with the exception of one female that lost weight from Day 7. There were no abnormal necropsy findings. The inhalation LC ₅₀ was ≥ 5.04 mg/L in male and female rats (low toxicity).
In vitro Human Tissue Culture – Corrosivity EpiDerm Tissues PMRA# 2750999	Non-corrosive to the in vitro human skin model under the parameters of the test.

Table 2 List of Supported Uses

Crop	Greenhouse tomato
Pest	Pepino mosaic virus (PepMV) strains EU, CH2, LP
Application rate	0.8 L/ha as a 10% solution that includes carborundum at 15 g/L for 8 L solution/ha
Application method	Manually applied to the top surface of a leaf at mid-plant height with a V10 solution-moistened scouring pad
Application timing	Before or after transplanting between the 3 true leaf stage and the first flower fully open stage
Number of applications	One per crop cycle
Other instructions	Prior to V10 application, plant samples must be submitted to a laboratory for analysis to confirm PepMV-free status

References

A. List of Studies/Information Submitted by Registrant

1.0 Product Characterization and Analysis

PMRA

Document

Number	Reference
2750563	2015, Confidential information - mild Pepino mosaic virus VX1, DACO: M2.10.1, M2.10.2, M2.10.3, M2.11, M2.7.2, M2.8, M2.9.1, M2.9.2, M2.9.3, M4.2.2, M4.2.3, M4.4, M4.6, M4.8, M4.9, M5.0 CBI.
2750565	2013, Operating procedure for the preparation of VX1 and VC1 batches, DACO: M2.10.1, M2.8, M2.9.2 CBI.
2750567	2013, Hygiene protocol during preparation of VX1 and VC1 batches, DACO: M2.10.1, M2.8, M2.9.2 CBI.
2750569	2012, Experimental protocol of inoculation with plant viruses on plants by rubbing on leaves, DACO: M2.10.1, M2.8, M2.9.2 CBI.
2750572	2012, Experimental protocol of inoculation with plant viruses on young plants by high-pressure spraying, M2.10.1, M2.8, M2.9.2 CBI.
2750576	2014, Five batch analysis for the identification of VX1 by using validated RT-qPCR sponsor's method, DACO: M2.10.2, M2.11, M2.8, M2.9.1 CBI.
2750578	2014, 5-batch analysis for the quantification of PepMV in VX1 by using validated quantitative ELISA method, DACO: M2.10.2, M2.11, M2.8, M2.9.1 CBI.
2750580	2014, Evaluation of ELISA analytical methods specificity on V10 placebo according to SANCO3030REV.4:1999 in order to quantify active ingredient content, DACO: M2.10.2, M2.11, M2.8, M2.9.1 CBI.
2750583	2014, Quality control data of VX1 batches, production date 19-02-2014, DACO: M2.10.2, M2.11, M2.8, M2.9.1 CBI.
2750585	2014, Five-batch analysis for the determination of CBI residues in VX1, DACO: M2.10.2, M2.11, M2.8, M2.9.1 CBI.
2750588	2014, Five-batch analysis for the determination of phosphate (PO ₄ 3-) and sulfite (SO ₃ 2-) in the test item VX1, DACO M2.10.2, M2.11, M2.8, M2.9.1 CBI.
2750590	2014, Set up and validation of two IC methods for the quantification of the anions PO ₄ 3-, SO ₃ 2-, and the cation K ⁺ in the test item "VX1", DACO: M2.10.2, M2.11, M2.8, M2.9.1 CBI.
2750592	2013, Validation of qRT-PCR-assays to identify mild variants of PepMV and to semi-quantify the ratio of mild variants relative to total PepMV, DACO: M2.10.1 CBI.
2750594	2012, Protocol for the determination of indices of VC1, VX1 and PepMV by qRT-PCR, DACO: M2.10.1 CBI.
2750596	2013, Validation of the analytical method for CBI quantification in plant extract by LC-MS/MS, DACO: M2.10.3, M2.8, M2.9.3 CBI.
2750598	2013, Quantification of CBI in water and other liquids using LCMS/MS (English translation of original document in Dutch: Bepaling van het CBI met behulp van LC-MS/MS in water en vloeibare producten), DACO: M2.10.3, M2.8, M2.9.3 CBI.

- 2750601 2012, Validation plan: Nicotine in liquid samples using UPLC-MS (English translation of original document in Dutch: Validatieplan: Nicotine in waterige monsters m.b.v. UPLC-MS), DACO: M2.10.3, M2.8, M2.9.3 CBI.
- 2750605 R.A.C. Jones, R. Koenig, and D.E. Lesemann, 1980, Pepino mosaic virus, a new potexvirus from pepino (*Solanum muricatum*) (Annals of Applied biology 94(1): 61-68), DACO: M2.7.1.
- 2750606 2013, Email - Checking of a strain deposited with the DMZ (VX1 and VC1), DACO: M2.7.1 CBI.
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2.0 Human And Animal Health

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Document

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3.0 Environment

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Document

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4.0 Value

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Document

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