Proposed Registration Decision PRD2015-24

Prohydrojasmon

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Overview

Proposed Registration Decision for Prohydrojasmon

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 Prohydrojasmon Technical Plant Growth Regulator and Blush Plant Growth Regulator Solution, containing the technical grade active ingredient prohydrojasmon, for colour enhancement of red apples in Canada.

Plant growth regulators products are regulated under the *Pest Control Products Act* when the nature of the label claim is modification of the physiological, morphological and/or reproductive processes of plants. Such claims include, but are not limited to, the inhibition of sprouts or germination, fruit setting, sucker control, color enhancement, defoliation and the control of preharvest drop (Regulatory Directive DIR93-09, *Plant Growth Regulators*).

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 Prohydrojasmon Technical Plant Growth Regulator and Blush Plant Growth Regulator Solution.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). 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 Health Canada's website at healthcanada.gc.ca/pmra.

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

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

Before making a final registration decision on prohydrojasmon, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on prohydrojasmon, 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 Prohydrojasmon?

Prohydrojasmon, the active ingredient in Blush Plant Growth Regulator Solution, is a synthetically made plant growth regulator that is structurally similar and functionally identical to jasmonic acid, a naturally occurring plant growth regulator present in all vascular plants. Jasmonic acid is involved with fruit colour development in red apple varieties by enhancing accumulation of anthocyanin, which is a red pigment and found predominantly in outer cell layers such as the epidermis and mesophyll cells in flowers and fruits.

Anthocyanin production, and therefore apple colour, varies among apple varieties and is influenced by a range of environmental and management factors in orchards. Applications of Blush Plant Growth Regulator Solution applied at a rate of 100-200 ppm prior to the anticipated harvest date may enhance colour development in red apple varieties.

Health Considerations

Can Approved Uses of Prohydrojasmon Affect Human Health?

Prohydrojasmon is unlikely to affect human health when used according to label directions.

Potential exposure to prohydrojasmon, present in the end-use product Blush Plant Growth Regulator Solution, may occur when handling and applying the product, or coming into contact with treated surfaces. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

In laboratory animals, prohydrojasmon was of low acute toxicity via the oral, dermal and inhalation routes of exposure. Prohydrojasmon was also minimally irritating to the eyes, non-irritating to the skin, and not a dermal sensitizer.

[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 end-use product, Blush Plant Growth Regulator Solution, is also of low acute toxicity via the oral, dermal, and inhalation routes of exposure. It was moderately irritating to the eyes, minimally irritating to the skin, and not a dermal sensitizer. Based on these characteristics, the hazard signal words, "WARNING - EYE IRRITANT", are required on the label for the end-use product.

Submitted animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of prohydrojasmon to cause short-term toxicity, developmental effects, genotoxicity, and various other effects. Prohydrojasmon was determined to not be genotoxic and there was no indication that the young were more sensitive than the adult animal. The risk assessment protects against these and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in Food and Water

Dietary risks from food and water are not of concern.

Dietary risks from food and drinking water are not expected to be of concern given the low toxicity and dietary and drinking water exposure to prohydrojasmon. Prohydrojasmon is a synthetic analogue of the naturally occurring plant growth regulator, jasmonic acid. Prohydrojasmon is structurally similar to jasmonic acid and performs the same function in terms of stimulating fruit ripening. Jasmonic acid is present in plant leaves, flowers, and developing fruit. As such, it is a natural component of plant materials found in the human diet. Consequently, the specification of a maximum residue limit (MRL) for prohydrojasmon under the *Pest Control Products Act* is not required.

Risks in Residential and Other Non-Occupational Environments

Non-occupational risks from bystander dermal exposure are not of concern.

Risk to residential users of the end-use product is not expected to be of concern due to the low toxicity of prohydrojasmon and the low potential for exposure expected when the end-use product is applied according to label directions.

Occupational Risks from Handling Prohydrojasmon

Occupational risks are not of concern when used according to label directions.

Workers can come in direct contact with the commercial end-use product containing prohydrojasmon when handling the product, or coming into contact with treated crops when entering treated areas before sprays have dried. The label has adequate precautionary measures including the requirement of personal protective equipment and precautionary and hygiene statements to minimize exposure. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for workers, risk to these individuals are not a concern.

Environmental Considerations

What Happens When Prohydrojasmon Is Introduced Into the Environment?

Prohydrojasmon will enter the environment when applied as Blush Plant Growth Regulator Solution to apples. Prohydrojasmon is not expected to persist in the environment and does not pose an unacceptable risk to non-target aquatic and terrestrial organisms.

Prohydrojasmon, the active ingredient in Blush Plant Growth Regulator Solution, is a synthetically-produced jasmonate and is similar in function and chemical structure to jasmonic acid, which is produced naturally in plants. Jasmonates are a group of plant hormones that promote fruit colour development.

Prohydrojasmon is not expected to persist in the environment and is relatively nontoxic to the aquatic and terrestrial organisms that were tested. Blush Plant Growth Regulator Solution is not expected to pose a risk to non-target aquatic and terrestrial organisms in the environment when used according to the label directions.

Value Considerations

What is the Value of Blush Plant Growth Regulator Solution?

Blush Plant Growth Regulator Solution is the first product for colour enhancement of red apples in Canada, especially for apple varieties that generally do not develop good red colour or in regions or seasons when environmental factors are not favourable to red colour development.

Commercial value of red apple varieties is partially dependent upon fruit colour, thus grower's returns can be significantly reduced if red colouration is poor. There is value in a product that can increase red colour development in apples.

Blush Plant Growth Regulator Solution was granted registration in the United States in 2013. Products containing prohydrojasmon are registered in several other countries and regions, for example, Japan, Taiwan, and Korea, for colour enhancement of apples, grapes, and citrus fruits. The availability of Blush Plant Growth Regulator Solution in Canada will provide growers a tool for enhancement of red apple colouration; therefore increasing higher grade apple production and the competitiveness of Canadian growers in the marketplace.

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.

Next Steps

Before making a final registration decision on prohydojasmon, the PMRA will consider all 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

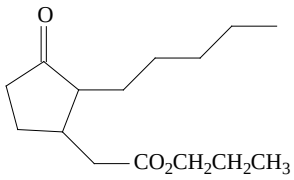
When the PMRA makes its registration decision, it will publish a Registration Decision on prohydrojasmon (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the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

Science Evaluation

Prohydrojasmon

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Prohydrojasmon
Function	Plant Growth Regulator
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	propyl (1*RS*,2*RS*)-(3-oxo-2-pentylcyclopentyl)acetate containing 10 ± 2% propyl (1*RS*,2*SR*)-(3-oxo-2-pentylcyclopentyl)acetate
2. Chemical Abstracts Service (CAS)	propyl (1*R*,2*R*)-*rel*-3-oxo-2-pentylcyclopentaneacetate
CAS number	158474-72-7
Molecular formula	$C_{15}H_{26}O_3$
Molecular weight	254.37
Structural formula	
Purity of the active ingredient	97.98%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product— Prohydrojasmon Technical Plant Growth Regulator

Property	Result
Colour and physical state	Light yellow liquid
Odour	Odourless
Melting range	N/A
Boiling point or range	318°C
Density at 20°C	0.974 g/cm^3
Vapour pressure at 25°C	16.7 mPa
Ultraviolet (UV)-visible spectrum	λ_{max} around 210 and 293 nm not pH dependent

Property	Result
Solubility in water at 25°C	60.2 mg/L
Solubility in organic solvents at 25°C	Reported to be soluble in acetone, DMSO, methanol, hexane, ethyl acetate, and acetonitrile in amounts greater than 100 g/L.
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 4.1
Dissociation constant (pK_a)	No dissociable moiety
Stability (temperature, metal)	Reported to degrade at temperatures above 342°C, may oxidize at room temperature and it may become unstable when stored for greater than 7 days under conditions where metals such as zinc, aluminum or iron are present. The stability of the active ingredient is diminished when the temperature is elevated to 54°C.

End-Use Product—Blush Plant Growth Regulator Solution

Property	Result
Physical state	Liquid
Formulation type	Solution
Guarantee	5.25%
Container material and description	HDPE (high density polyethylene) jugs, 3.78 L and 9.46 L
Specific gravity	0.955 at 20°C
pH of 1% dispersion in water	6.1
Oxidizing or reducing action	Not compatible with strong oxidizers, nitric acid, hydrogen peroxide, hydrazine, and hydroxylamine.
Storage stability	Stable when stored up to 36 months in polyethylene containers in the dark at room temperature.
Corrosion characteristics	Not corrosive to polyethylene containers.
Explodability	Not expected to be explosive.

1.3 Directions for Use

Blush Plant Growth Regulator Solution at a rate of 100-200 ppm is to be applied once or twice with a 7-14 day interval to red apple varieties between 7 and 28 days before anticipated harvest. Applications should be made using conventional spray equipment in a sufficient amount of water to ensure thorough coverage of the tree canopy.

Blush Plant Growth Regulator Solution works best in apple varieties that generally do not develop good red colour and in regions or seasons when climatic conditions are unfavourable to apple colouration. Otherwise, applications of Blush Plant Growth Regulator Solution may not result in significant additional red colour.

Best results are achieved by applying Blush Plant Growth Regulator Solution under slow drying conditions (for example, early morning or late afternoon).

1.4 Mode of Action

Prohydrojasmon is a synthetically made plant growth regulator that is structurally similar and functionally identical to jasmonic acid, a naturally occurring plant growth regulator present in all vascular plants. Jasmonic acid is involved with fruit colour development in red apple varieties by enhancing accumulation of anthocyanin, which is a red pigment and found predominantly in outer cell layers such as the epidermis and mesophyll cells in flowers and fruits.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

The technical grade active ingredient, Prohydrojasmon Technical Plant Growth Regulator, contains 97.98% w/w of the active ingredient. The submitted database of toxicology studies for prohydrojasmon along with published information on a close structural analogue chemical were considered adequate to address the non-conventional pest control product information requirements for a technical grade active ingredient. Similarly, the database of toxicology studies submitted for the end-use product, Blush Plant Growth Regulator Solution, was considered adequate to address the non-conventional pest control product information requirements for an end-use product. Results of the toxicity studies conducted on laboratory animals with prohydrojasmon and Blush Plant Growth Regulator Solution are summarized in Appendix I, Tables 1 and 2, respectively.

No information was submitted or identified in the published literature on the metabolism of prohydrojasmon. Based on a published review of the metabolism of methyl dihydrojasmonate, a close structural analogue, prohydrojasmon that is absorbed following oral exposure could potentially be metabolized by oxidation of the side chain to a carboxylic acid followed by conjugation and excretion. In addition, the aliphatic side chain could also be hydrolyzed to an alcohol and then a carboxylic acid followed by fatty acid metabolism or passage through the tricarboxylic acid cycle.

In laboratory animals prohydrojasmon was of low acute toxicity via the oral, dermal and inhalation routes of exposure. Prohydrojasmon was also minimally irritating to the eyes, non-irritating to the skin, and not a skin sensitizer. Blush Plant Growth Regulator Solution is also of low acute toxicity via the oral, dermal, and inhalation routes of exposure. It was moderately

irritating to the eyes and minimally irritating to the skin. The results of a dermal sensitization study were negative, but the study was noted to have a number of deficiencies. Despite these deficiencies, based on the skin sensitization testing results for prohydrojasmon, and the composition of the formulants, the Blush Plant Growth Regulator Solution is not expected to be a skin sensitizer.

In a short-term oral toxicity study, prohydrojasmon was administered to male and female rats at levels of 0, 1000, 3000 or 10000 ppm in the diet for 13 weeks. The lowest observed adverse effect level (LOAEL) was 3000 ppm (in other words, equivalent to 166 mg/kg bw/day in males or 176 mg/kg bw/day in females), based on decreased body weights and food consumption, increased liver weights, and changes in selected hematological, clinical chemistry, and urinalysis parameters observed in males and females. The no-observed-adverse-effect-level (NOAEL) was 1000 ppm (56.9 mg/kg bw/day in males or 58.5 mg/kg bw/day in females).

Prohydrojasmon was administered to pregnant female rats by gavage at dose levels of 0, 30, 120, and 500 mg/kg bw/day from days 6 through 15 of gestation in a prenatal developmental toxicity study. The maternal LOAEL was 120 mg/kg bw/day based on reduced body weight gain and food consumption. The maternal NOAEL was 30 mg/kg bw/day. The developmental LOAEL was 500 mg/kg bw/day, based on a significantly increased incidence of a skeletal variation (14th rib) in fetuses. The developmental NOAEL was 120 mg/kg bw/day.

Prohydrojasmon was negative for mutagenicity when tested in a bacterial reverse mutation assay using multiple strains of *Salmonella typhimurium* and *Eschericia coli* WP2uvrA with and without metabolic activation. Similarly, the compound did not induce chromosomal aberrations in an *in vitro* assay in Chinese Hamster Lung Fibroblast cells.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Health Canada website. Since prohydrojasmon is a new active ingredient pending registration for use in Canada, there are no incident reports. Once products containing prohydrojasmon are registered, the PMRA will monitor for incident reports.

3.2 Occupational and Bystander Risk Assessment

3.2.1 Dermal Absorption

Although the physical and chemical properties of prohydrojasmon (water solubility at 25°C = 60.2 mg/L and Log K_{ow} = 4.1) suggest that the dermal absorption is moderate, the absence of a dermal absorption study means that the default value of 100 % dermal absorptivity must be assumed.

3.2.2 Use Description

The end-use product is proposed for fruit colour enhancement in commercial apple orchards. Blush Plant Growth Regulator Solution is to be applied by airblast and with conventional spray equipment (groundboom and handheld sprayer). The end-use product is diluted with water (100 to 200 ppm active ingredient) and then applied until fruit and foliage are thoroughly covered, once or twice per season with a 7 to 14 day reapplication interval.

3.2.3 Mixer, Loader, and Applicator Exposure and Risk

Exposure to workers mixing, loading, and applying Blush Plant Growth Regulator Solution is expected to be short-term in duration and to occur primarily by the dermal and inhalation routes, as well as accidental exposure of the eyes.

Based on the toxicological profile for Blush Plant Growth Regulator Solution, the risk due to occupational exposure is considered to be acceptable when workers follow the label directions, which includes wearing appropriate Personal Protective Equipment (in other words, long pants, a long-sleeved shirt, shoes plus socks, chemical-resistant gloves, and goggles or a face shield).

3.2.4 Post-application Exposure and Risk

There is a potential for exposure to workers re-entering areas treated with Blush Plant Growth Regulator Solution. Given the nature of the post-application activities typically performed (for example, scouting treated areas, pruning, harvesting, etc.), dermal and accidental eye contact with treated surfaces is possible. The degree of exposure will be related to the time of re-entry and the duration of the activities. Once the treated area has dried, the potential risk due to exposure resulting from post-application work is not a concern, regardless of the type and duration of the activity.

In order to minimize exposure of workers or other individuals, re-entry into a treated area should be restricted until the area is dry.

3.2.5 Residential and Bystander Exposure and Risk

The application of Blush Plant Growth Regulator Solution near residential areas may result in the exposure of residents. A residential area is defined as a location where bystanders, including children, may be exposed during or after application. These locations include around homes, schools, parks, playgrounds, playing fields, public buildings or any other area where the general public, including children, could be exposed.

In order to minimize drift, and subsequent risk due to bystander exposure, when applying Blush Plant Growth Regulator Solution, wind speed, wind direction, temperature inversions, application equipment, and sprayer settings should be considered.

3.3 Food Residue Exposure Assessment

3.3.1 Food and Drinking Water

Crop residue trials were not performed with Blush Plant Growth Regulator Solution because they were not identified by the Pest Management Regulatory Agency as a basic tier I data requirement to support the registration of prohydrojasmon. However, because NOAEL values were identified in a short-term oral toxicity study, the potential maximum level of prohydrojasmon expected on apples treated with Bush Plant Growth Regulator Solution was calculated to assess potential dietary intake.

Maximum expected crop residue levels were calculated following a conservative, worst case approach as follows: Assuming all of the applied product is deposited on the apples, the maximum residue level of prohydrojasmon expected on the fruit would be 0.0644 g a.i./kg apple. This value assumes no dissipation or metabolism of the parent compound and a combined maximum rate of application of 1.58 kg a.i./ha/season (in other words, the prohydrojasmon from two applications is considered additive).

The potential dietary intake of prohydrojasmon was then calculated in various age subpopulations (see Appendix I, Table 3) and was found to range between 2.98 mg/kg bw/day for infants (0 to 1 year old) to 0.43 mg/kg bw/day for adults (>16 years). These calculated dietary intakes are below the short-term oral NOAEL values (56.9 mg/kg bw/day and 58.5 mg/kg bw/day in male and female rats respectively). Thus, consumption of foods treated with Blush Plant Growth Regulator Solution is not expected to be of concern.

In addition, consideration was given to the fact that prohydrojasmon is a synthetic analogue of the naturally occurring plant growth regulator, jasmonic acid. It is structurally similar to jasmonic acid and performs the same function in terms of stimulating fruit ripening. Jasmonic acid is present in plant leaves, flowers, and developing fruit. As such, it is a natural component of plant materials found in the human diet.

A pre-harvest interval (PHI) is not required. However, as a 7 to 28 day before harvest (DBH) interval is being recommended by PMRA to optimize fruit colouration, this period will further reduce the potential residue levels of prohydrojasmon present on apples on the day of harvest.

Based on the proposed use pattern and a 10.7 day aquatic biotransformation half-life, a 57.8 hour phototransformation half-life in water, and a 1.6 to 2.3 hour biotransformation half-life in aerobic soil, it is not anticipated that levels of prohydrojasmon in drinking water will be of concern.

3.3.2 Maximum Residue Limits

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine that 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 adulteration provision of the *Food and Drugs Act*. Health Canada specifies science-based MRLs to ensure the food Canadians eat is safe.

Based on a weight of evidence consideration of the structural and functional similarities between prohydrojasmon and jasmonic acid, the low toxicity of prohydrojasmon, and the relatively short half-lives of the compound in water and soil, the dietary risks from food and drinking water are not expected to be of concern. Consequently, the specification of an MRL under the *Pest Control Products Act* is not required.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

For chemicals that are submitted under Regulatory Directive DIR2012-01 *Guidelines for the Registration of Non-Conventional Pest Control Products*, the data requirements follow a tiered approach. If information requested in the first tier demonstrates that the technical grade active ingredient is of low acute toxicity to the non-target organisms potentially exposed to the proposed product(s), then further information, which includes detailed information on the fate of the chemical, is not routinely required. This was the case for Prohydrojasmon Technical Plant Growth Regulator; however, some information on the fate of prohydrojasmon in laboratory studies was available and is reported here.

Prohydrojasmon is soluble in water and is expected to volatilize from moist soil and water surfaces. Prohydrojasmon has a 1.6–2.3 hour half-life in aerobic soil and is also expected to degrade rapidly in aquatic systems through microbial transformation. Thus, prohydrojasmon is not expected to persist in the environment when exposed to microbially-active media. Prohydrojasmon is, however, stable to hydrolysis at environmentally relevant pH (although a half-life at pH 9 of 10.7 days is reported). Hydrolysis and phototransformation in water are not expected to be a significant route of transformation of prohydrojasmon in the environment (Appendix I, Table 4).

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models, which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications (where possible). For prohydrojasmon, the ecotoxicology information includes acute toxicity data, or rationales for waiving particular toxicity studies, for various organisms or groups of organisms from both terrestrial and aquatic habitats, including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessment may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. For characterizing acute risk, acute toxicity values (such as LC_{50} and LD_{50}) are divided by an uncertainty factor. The uncertainty factor is used to account for differences in inter- and intra-species sensitivity as well as varying protection goals (for example, community, population, individual). Thus, the magnitude of the uncertainty factor depends on the group of organisms that are being evaluated (for example, 10 for fish, 2 for aquatic invertebrates).

The difference in value of the uncertainty factors reflects, in part, the ability of certain organisms at a certain trophic level (feeding position in a food chain) to withstand, or recover from, a stressor at the level of the population. Also, data for the most sensitive fish species is used as a surrogate for amphibians, as no amphibian data are typically generated.

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 = 1 for most species, 0.4 for pollinators). 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 (such as drift to non-target habitats) and might consider different toxicity endpoints.

Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

Based on the available ecotoxicity data, prohydrojasmon is relatively non-toxic to the organisms that were tested. Nevertheless, as exposure to the environment will occur through application to apples/tree canopies via a conventional airblast sprayer, a screening level risk assessment (Section 4.2.1) was conducted to characterize the potential risk.

4.2.1 Risks to Non-Target Species

The use of Blush Plant Growth Regulator Solution on red apple varieties, which is applied to foliar surfaces (single or multiple applications), may result in the release of prohydrojasmon to the environment through spray drift and/or overland runoff.

The submitted studies did not show any adverse effects to the non-target organisms tested. Prohydrojasmon Technical Plant Growth Regulator was shown to be relatively non-toxic to the honeybee (*Apis mellifera*), bobwhite quail (*Colinius virginianus*) and Japanese quail (*Coturnix coturnix japonica*) on an acute contact, oral and dietary basis, respectively, at the highest concentrations that were tested. Prohydrojasmon Technical Plant Growth Regulator was moderately toxic to daphnids (*Daphnia magna*) and common carp (*Cyprinus carpio)* with LC_{50} values of 2.13 and 3.33 mg a.i./L, respectively (Appendix I, Table 5).

Waiver requests were submitted in lieu of studies with algae, aquatic vascular plants and effects on the vegetative vigour of terrestrial vascular plants. These waiver requests were found to be acceptable, and were based on a lack of demonstrated phytotoxicity in the seedling emergence/growth study, mode of action of active ingredient (for fruit colour and plant defense), and structural similarity to jasmonic acid which is found naturally in the actively-growing plant parts of many species.

The risk quotients, estimated environmental concentrations for each non-target group of organisms, and LOC values are reported in Appendix I, Tables 6 and 7.

The risk quotients for bees, birds and non-target terrestrial plants (all < 1) were below the LOC. The risk quotients for fish and *Daphnia* were 0.3 and 0.09, respectively, and the risk quotient was 1.6 for amphibians. Thus, the risk quotients did not exceed the level of concern for any organisms tested, except for amphibians where the level of concern was marginally exceeded. However, given that prohydrojasmon is not expected to persist in the environment (in other words, it is volatile and susceptible to transformation by microbes), exposure to amphibians is not expected to be of concern. Overall, when applied to red apple varieties at a proposed concentration range of 100-200 ppm, twice a year (equivalent to a maximum seasonal cumulative rate of 400 ppm or 800 g a.i./ha based on spray volumes used in apple orchards typically ranging from 500 - 2000 L/ha), Blush Plant Growth Regulator Solution will not pose an unacceptable risk to terrestrial and aquatic environments.

5.0 Value

5.1 Effectiveness

Value information submitted included data from 28 field research trials conducted in New York, Washington, Massachusetts, North Carolina, Michigan, and Ohio between 2007 and 2011. These studies were carried out by Northwest Contract Research, Fine Americas, Reality Research, Washington Tree Fruit Research Commission, North Carolina State University, New England Fruit Consultations, Michigan State University, and Ohio State University. Each of these organizations conducted unique studies in terms of experimental design and value assessments.

In summary, all studies submitted were scientifically designed with 4 to 11 replicates. Efficacy of one and two applications of Blush Plant Growth Regulator Solution at 100, 150, and 200 ppm made between 7 and 31 days before harvest was assessed for 14 apple varieties. Ages of apple trees ranged from three to 20+ years. Treatments were applied using a handgun or airblast sprayer with a spray volume of 460-1870 L/ha.

Red colour enhancement, expressed as (1) % apples with greater red surface, (2) % higher grade apples, (3) average red surface (%) per fruit, and/or (4) hue angle over an untreated control, was assessed in each study.

5.1.1 Support for Efficacy Claims

The applications of Blush Plant Growth Regulator Solution significantly or numerically increased the percentage of the first and second grade apples or apples with greater red surface in 32 of the 44 variety-trials (73%), whereas the applications of Blush Plant Growth Regulator Solution did not have any impact in 12 of the 44 variety-trials (27%).

Since apple varieties genetically vary in red colour development, they respond to the application of Blush Plant Growth Regulator Solution differently. For instance, Red Delicious apples (with dark red colour) were assessed in two trials and they did not respond to the application of Blush Plant Growth Regulator Solution in either trial. Gala apples that are usually red with a portion being greenish or yellow-green were assessed in eight trials, in seven of which the red colour development was enhanced.

Temperature, irradiance, and light quality are environmental factors that impact accumulation of anthocyanins. Optimal temperature for accumulation of anthocyanins is generally between 20 and 25°C daytime temperature, following by 10 to 15°C nighttime temperature. Orchard pruning and training practices influence fruit light exposure.

Mineral nutrients, chemicals, and plant hormones also alter anthocyanin synthesis. Nitrogen is important for anthocyanin formation; however, excess nitrogen can adversely affect red colour development. Potassium application can reduce the effects of excess nitrogen on red colour development. Auxin and ethylene promote apple colouration/ripening while advancing maturity.

Given the number of variables that can influence colour development, it is important that the use pattern be flexible to allow growers to adapt it to their orchard. Therefore, the range in application concentration (100-200 ppm) and timing (between 7 and 28 days before harvest) and number of applications (one and two applications) are supported. It is clearly indicated on the label that:

"*Blush Plant Growth Regulator Solution can promote fruit colouration in red apples; however, apple variety and environmental factors, for example, temperature, fruit light exposure, light quality, etc., can impact the efficacy of Blush PGR Solution. Under conditions where red colour development is acceptable (for example, cultivars or strains that develop good red colour, orchards that typically produce apples with sufficient red colour development, environmental conditions in which red colour development is satisfactory), use of Blush PGR Solution may not result in significant additional red colour*".

This statement is similar to that appearing on the American label (United States Environmental Protection Agency Reg. No. 62097-29).

5.2 Non-Safety Adverse Effects

Phytotoxicity expressed as % tree injury, apple yield measured by yield per tree or single fruit weights, and fruit quality expressed as fruit maturity, firmness, Brix, or acid content, were assessed for the same Blush Plant Growth Regulator Solution treatments in the same trials.

5.2.1 Support for Host Claim

No phytotoxicity was reported for the applications of Blush Plant Growth Regulator Solution in any trials. Fruit yield and quality was not diminished as a result of the Blush Plant Growth Regulator Solution treatments.

Adequate information was submitted to demonstrate that apples exhibited an adequate margin of tolerance to applications of Blush Plant Growth Regulator Solution in accordance with the label directions.

5.3 Consideration of Benefits

5.3.1 Social and Economic Impact

Commercial value of red apples is partially dependent upon fruit colour. The red colour is due to accumulation of anthocyanin pigments in the vacuole of the fruit epidermal cells. Anthocyanin production, and therefore apple colour, varies among apple varieties and is as well influenced by

a range of environmental and management factors in orchards. Grower's returns can be significantly reduced if red colour coverage is poor. Thus, there is a value in a product that can increase red colour development in apples, especially apple varieties that do not develop good red colour and in regions or seasons where (when) environmental factors are not favourable to apple colouration.

Prohydrojasmon containing products have been registered in the United States and other countries and regions for colour enhancement in apples, grapes, and citrus fruits. The availability of Blush Plant Growth Regulator Solution in Canada will provide growers a tool for enhancement of red apple colouration; therefore increasing higher grade apple production and the competitiveness of Canadian growers in the marketplace.

5.3.2 Survey of Alternatives

There is no alternative registered in Canada for red apple colour enhancement.

5.3.3 Compatibility with Current Management Practices Including Integrated Pest Management

Use of Blush Plant Growth Regulator Solution for enhancement of red apple colouration is compatible with other apple production practices.

5.3.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Given that prohydrojasmon is structurally similar and functionally identical to jasmonic acid, a naturally occurring plant growth regulator present in all vascular plants, development of resistance is not expected.

5.4 Supported Uses

Colour enhancement in red apple varieties is supported for one or two applications of 100 to 200 ppm Blush Plant Growth Regulator Solution made between 7 and 28 days before anticipated harvest.

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: in other words, 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*].

During the review process, Prohydrojasmon Technical was assessed in accordance with the PMRA Regulatory Directive DIR99-03.[5] Prohydrojasmon Technical does not meet the TSMP criteria (Appendix I, Table 8).

6.2 Formulants and Contaminants of Health or Environmental Concern

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

> Technical grade prohydrojasmon and the end-use product Blush Plant Growth Regulator Solution do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

7.0 Summary

7.1 Human and Health Safety

The submitted database of toxicology studies for prohydrojasmon is adequate to characterize the majority of toxic effects that could result from exposure. Prohydrojasmon is of low acute toxicity via the oral, dermal, and inhalation routes. It is minimally irritating to the eye, and is not a skin irritant or skin sensitizer. Decreased body weights and food consumption, increased liver weights, and changes in selected hematological, clinical chemistry, and urinalysis parameters were observed in rats in a short-term oral toxicity study of prohydrojasmon. In a developmental toxicity study of prohydrojasmon, effects were limited to an increase in a skeletal variation which occurred at a dose that caused toxicity to the maternal animals. Based on the results of bacterial mutagenicity and in vitro mammalian cell clastogenicity assays, prohydrojasmon is not genotoxic. Blush Plant Growth Regulator Solution containing prohydrojasmon is of low acute toxicity via the oral, dermal, and inhalation routes. It is moderately irritating to the eye, minimally irritating to the skin, and is not expected to be a skin sensitizer.

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5 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/2005-114 (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 1 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 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

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

Worker, bystander and residential exposures to prohydrojasmon as a result of the proposed use patterns are not expected to result in unacceptable risk when the commercial end-use product is used according to label directions.

Dietary exposure to prohydrojasmon from the use of the proposed end-use product is not expected to result in unacceptable dietary risks when the product is used according to label directions. It is not necessary to specify a maximum residue limit (MRL) for prohydrojasmon.

7.2 Environmental Risk

Prohydrojasmon, the active ingredient in Blush Plant Growth Regulator Solution, is not expected to persist in the environment. No potential for concern for aquatic and terrestrial organisms was identified during the risk assessment. Standard environmental label statements for products that can be released into the environment will be used. Blush Plant Growth Regulator Solution will not pose an unacceptable risk to non-target organisms when used according to label instructions.

7.3 Value

The information submitted is adequate to characterize the efficacy of Blush Plant Growth Regulator Solution at 100 to 200 ppm for colour enhancement in red apple varieties. One application or two applications with 7-14 day interval should be made using conventional spray equipment with a sufficient amount of water to ensure a uniform coverage of fruit and foliage.

For best results, Blush Plant Growth Regulator Solution should be used on apple varieties that do not develop good red colour or in regions or seasons where (when) environmental factors are not favourable to apple colouration. Application should be made under slow-drying conditions (for example, early morning or late afternoon).

The information is also adequate to demonstrate that apples exhibit an adequate margin of tolerance to broadcast applications of Blush Plant Growth Regulator Solution in accordance with the label directions.

Prohydrojasmon containing products have been registered in the United States and other countries and regions for colour enhancement in apples, grapes, and citrus fruits. Blush Plant Growth Regulator Solution, as the first product for colour enhancement in red apple varieties in Canada, will increase higher grade apple production and the competitiveness of Canadian growers in the marketplace.

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 Prohydrojasmon Technical Plant Growth Regulator and Blush Plant Growth Regulator Solution, containing the technical grade active ingredient prohydrojasmom, for colour enhancement of red apples in Canada.

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

µg	micrograms
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
ADI	acceptable daily intake
ALS	acetolactate synthase
ARfD	acute reference dose
atm	atmosphere
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetres
DBH	days before harvest
DF	dry flowable
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{75}	dissipation time 75% (the dose required to observe a 75% decline in concentration)
EC_{10}	effective concentration on 10% of the population
EC_{25}	effective concentration on 25% of the population
EECs	environmental exposure concentrations
ER_{25}	effective rate for 25% of the population
g	gram
ha	hectare(s)
HDT	highest dose tested
Hg	mercury
HPLC	high performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
km	kilometre
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOEC	low observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
mg	milligram
mL	millilitre
MAS	maximum average score
MOE	margin of exposure

MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
N/R	not required
NZW	New Zealand white
OC	organic carbon content
OM	organic matter content
PBI	plantback interval
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RQ	risk quotient
RSD	relative standard deviation
SC	soluble concentrate
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UAN	urea ammonium nitrate
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution

Appendix I

Table 1 Toxicity Profile of Prohydrojasmon.

STUDY	SPECIES/STRAIN DOSES	RESULT	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE
Acute oral toxicity	Rat/Sprague Dawley strain 5 rats/sex/dose by gavage 5000 mg/kg bw (limit test)	LD_{50} ♂ & ♀: > 5000 mg/kg bw	No mortality or treatment-related clinical signs, necropsy findings or changes in body weight **Low acute oral toxicity**	2386004
Acute dermal toxicity	Rat/ Sprague Dawley strain 5 rats/sex/dose 2000 mg/kg bw applied (semi-occlusively) for 24 hr (limit test)	LD_{50} ♂ & ♀: > 2000 mg/kg bw	No mortality or treatment-related clinical signs, necropsy findings or changes in body weight **Low acute dermal toxicity**	2386005
Acute inhalation toxicity (whole body exposure)	Rat/Sprague-Dawley 5 rats/sex/dose Gravimetric chamber concentration of 2.8 mg/L, mass median aerodynamic diameter of 2.3 µm, and 4 hr exposure period	LC_{50} ♂ & ♀ > 2.8 mg/L	No mortality. Clinical signs included salivation and nasal discharge for one hour post exposure. No other clinical signs, or treatment-related necropsy findings or changes in body weight **Low acute inhalation toxicity**	2386006
Primary Eye irritation	Rabbit/Japanese White/9 ♂ Single dose of 0.1mL of test substance instilled into one eye of each rabbit Six rabbits' eyes left unwashed, three had eyes washed 2 min after exposure Ocular irritation scored at 1, 24, 48 and 72 hr post-instillation.	MAS [a] = 0.6/110 MIS[b] = 5/110 (unwashed eyes) MAS [a] = 0.6/110 MIS[b] = 11/110 (washed eyes)	Slight conjunctival redness and discharge at 1 hr (6/6 animals) with minor chemosis (2/6) and corneal opacity (2/6) in the unwashed group. All symptoms resolved by 48 hours. Corneal opacity and conjunctival redness at 1 hr (3/3 animals), chemosis at 1 hour (1/3), slight corneal opacity at 24 hr (1/3) in the washed group. All symptoms resolved by 48 hr.	2386011

STUDY	SPECIES/STRAIN DOSES	RESULT	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE
			Minimally irritating to the eye (Based on the MAS)	
Primary Dermal irritation	Rabbit/Japanese White /6 ♂ 0.5 ml of test substance applied to 6 cm^2 intact skin surface per animal for 4 hr using semi-occlusive dressing Skin irritation scored 1, 24, 48, and 72 hr after exposure	MAS [a] = 0/8 MIS [b] = 0/8	No signs of dermal irritation in any animal **Non-irritating to the skin**	2386015
Dermal Sensitization (Maximization test)	Guinea pig/Hartley strain/50 ♂ Treatment group: 20 animals Control group: 20 animals DNCB positive control: 5 animals Control for DNCB: 5 animals Intradermal induction: 0.05 mL undiluted test substance or control substances Topical induction (7 days later): 0.4 mL test substance or control substances All animals challenged 21 days after first induction with 0.4 mL of test substance or control substances and observed 24, 48, and 72 hr later	Negative	No skin irritation at skin sites in test substance group at any time point after challenge Skin irritation observed in all DNCB positive control group animals after challenge **Non-sensitizer**	2386016
Short-term Oral (13 week dietary)	Rat/F344/DuCrj 10 rats/sex/dose 0, 1000, 3000 or 10000 ppm in the diet (♂: 0, 56.9, 168 or 566 mg/kg bw/day; ♀: 0, 58.5, 176 or 587 mg/kg bw/day)	NOAEL = 1000 ppm (♂: 56.9 mg/kg bw/day; ♀: 58.5 mg/kg bw/day) LOAEL = 3000 ppm (♂: 166 mg/kg bw/day; ♀: 176 mg/kg	Effects at the LOAEL: ♂: ↓ body weight, ↓ food consumption, ↑ blood cholesterol, ↓ chloride ♀: ↑ liver weight, ↓ platelet counts, ↑ BUN	2386017

STUDY	SPECIES/STRAIN DOSES	RESULT	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE
		bw/day)		
Prenatal Developmental Toxicity	Rat/Crj: CD(SD) 20–22 ♀ (pregnant)/dose 0, 30, 120 or 500 mg/kg bw/day on GD 6–15	Maternal: NOAEL = 30 mg/kg bw/day LOAEL = 120 mg/kg bw/day Developmental: NOAEL = 120 mg/kg bw/day LOAEL = 500 mg/kg bw/day	Maternal: Effects at LOAEL: ↓ body weight gain, ↓ food consumption Developmental: Effects at LOAEL: ↑ incidence of 14th rib (skeletal variation)	2386020
Genotoxicity: Bacterial Reverse Mutation Assay	Without metabolic activation: *Salmonella typhimurium* strains TA100, TA1235, TA1537: 2.44–78.1 µg/plate; strain TA98 and *Escherichia coli strain* WP2uvrA: 2.44–156 µg/plate With metabolic activation (S9): *S. typhimurium* strains TA100 and TA1535: 9.77–625 µg/plate; strain TA98 and *E. coli* strain WP2uvrA: 39.1–2500 µg/plate; *S. typhimurium* strain TA1537: 39.1–1250 µg/plate	Negative	No increase in number of revertants with or without metabolic activation Cytotoxicity at ≥ 78.1 µg/plate without metabolic activation and ≥ 313 µg/plate with metabolic activation Positive controls induced appropriate responses in the strains tested	2386021
Genotoxicity: *In vitro* Mammalian Cell Assay (*In vitro* chromosomal aberration assay)	Chinese hamster lung fibroblasts (CHL/IU) Without metabolic activation: 0, 10, 20, 40, 80 µg/mL; 24 and 48 hour exposures With metabolic activation (S9): 0, 1250, 2500, 5000 µg/mL; 6 hour exposure	Negative	≤ 2% of cells had structural/numerical chromosomal aberrations at all concentrations with or without metabolic activation Evidence of cytotoxicity (reduced mitotic index) in tests without metabolic activation at 80 µg/mL for 24 and 48 hour exposures and solvent only control for 6 hour exposure Positive controls induced the appropriate response	2386022

[a] MAS = Maximum Average Score for 24, 48 and 72 hrs
[b] MIS = Maximum Irritation Score (average)

Table 2 Acute Toxicity Profile of Blush Plant Growth Regulator.

STUDY	SPECIES/STRAIN DOSES	RESULT	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCES
Acute oral toxicity	Rat/Sprague Dawley strain 5 rats/sex/dose by gavage 5000 mg/kg bw (limit test)	LD_{50} ♂ & ♀: > 5000 mg/kg bw	No mortality or treatment-related clinical signs, necropsy findings or changes in body weight **Low acute oral toxicity**	2385842
Acute dermal toxicity	Rat/ Sprague Dawley strain 5 rats/sex/dose 2000 mg/kg bw applied (semi-occlusively) for 24 hr (limit test)	LD_{50} ♂ & ♀: > 2000 mg/kg bw	No mortality or treatment-related clinical signs, necropsy findings or changes in body weight **Low acute dermal toxicity**	2385843
Acute inhalation toxicity (whole body exposure)	Rat/Sprague-Dawley 5 rats/sex/dose Gravimetric chamber concentration of 5.0 mg/L, mass median aerodynamic diameter of 1.96 µm, and 4 hr exposure period	LC_{50} ♂ & ♀ > 2.8 mg/L	No mortality. Clinical signs included decreased activity, increased salivation, and nasal discharge for two hours post exposure. No other clinical signs, or treatment-related necropsy findings or changes in body weight **Low acute inhalation toxicity**	2385844
Primary Eye irritation	Rabbit/Japanese White/9 ♂ Single dose of 0.1mL of test substance instilled into one eye of each rabbit Six rabbits' eyes left unwashed for 24 hr, three had eyes washed 2 min after exposure Ocular irritation scored at 1, 24, 48 and 72 hr, and 7 days post-instillation.	MAS [a] = 39.28/110 MIS[b] = 52/110 (unwashed eyes) MAS [a] = 24.56/110 MIS[b] = 40.67/110 (washed eyes)	Unwashed group: Maximum corneal opacity score of 2/4 and maximum conjunctival erythema score of 1/3 up to 4 days post exposure. No iritis in any animal at any time point. Maximum chemosis score of 3/4 up to 1 hr post exposure. Maximum discharge score of 3/3 up to 24 hr post exposure. All irritation for all animals resolved by 7 days. Washed group: Maximum corneal opacity score of 2/4 up to 48 hr post	2385845

STUDY	SPECIES/STRAIN DOSES	RESULT	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCES
			exposure. No iritis in any animal at any time point. Maximum conjunctival erythema score of 2/4 up to 4 days post exposure. Maximum chemosis score of 2/4 1 hr post exposure. Maximum discharge score 3/3 (1 animal) 24hr post exposure **Moderately irritating to the eye** (Based on the MAS)	
Primary Dermal irritation	Rabbit/Japanese White /6 ♂ 0.5 ml of test substance applied to 6 cm^2 intact skin surface per animal for 4 hr using semi-occlusive dressing Skin irritation scored 1, 24, 48, and 72 hr after exposure	MAS [a] = 0.056/8 MIS [b] = 0.5/8	Very slight erythema in 3/6 animals 1 hr post exposure and in 1/6 animals up to 24 hr. No edema in any animal at any time point. **Minimally irritating to the skin** (Based on the MAS)	2385846
Dermal Sensitization (Beuhler)	Guinea pig/Hartley strain/30 ♀ Treatment group: 10 animals Control group: 10 animals DNCB positive control: 5 animals Control for DNCB: 5 animals Topical induction: 0.04 mL 10% test substance in water or control substances for 6 hr (3 times with 1 wk between inductions) All animals challenged 14 days after first induction with 0.4 mL of 10% test substance in water or control substances for 6 hr. Sites observed 24 and	Negative	No skin irritation at skin sites in test substance group at any time point after challenge Skin irritation observed in all DNCB positive control group animals after challenge Insufficient number of animals used in treatment group (minimum 20) and induction concentration was not the highest concentration (10%) to cause mild irritation in a preliminary assay	2385847

STUDY	SPECIES/STRAIN DOSES	RESULT	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCES
	48 hr later			

[a] MAS = Maximum Average Score for 24, 48 and 72 hrs
[b] MIS = Maximum Irritation Score (average)

Table 3 Total Potential Dietary Intake of Prohydrojasmon from Apples and Apple Products[1,2]

AGE	BODY WEIGHT (kg)	TOTAL ACTIVE INGREDIENT CONSUMED[3] (mg a.i./kg bw/day)
0 < 1 month	4.8	2.98
1 < 3 months	5.9	2.42
3 < 6 months	7.4	1.93
6 < 11 months	9.2	1.77
1 < 2 yrs	11.4	1.34
2 < 3 yrs	13.8	1.12
3 < 6 yrs	18.6	0.89
6 < 11 yrs	31.8	0.4
11 < 16 yrs	56.8	0.21 – 0.31
16 < 80 yrs	80.0	0.1 – 0.43

[1] The marketed production of apples for Canada (2014) was 374,275 metric tonnes and the total apple bearing area was 15,265 hectares (Source: *Statistics Canada. Table 001-0009 – Area, production and farm gate value of fresh and processed fruits, by province, annual*, CANSIM (database). (accessed: 2015-03-16)). Thus, there was an average of 24,519 kg apples per bearing hectare.
[2] The daily consumption of apples (with and without the peel), apple juice, applesauce, and dried apples, for each age group, was obtained from the National Health and Nutrition Examination Surveys (NHANES) (Source: *Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data*. NHANES, 2006 (database). (accessed: 2015-03-16)).
[3] Age groups 0<1 month, 1<3 months, and 3<6 months, were limited to the consumption apple juice.

Table 4 Fate and Behaviour of Prohydrojasmon in the Environment

Property	Test Substance	Half-life or DT_{50}	Comments	PMRA#
Hydrolysis, 25°C	98.5% w/w n-propyl dihydrojasmonate; ^{14}C-labeled and unlabeled	pH 4, stable pH 7, stable pH 9, 10.7 days	Hydrolysis half-life for pH 9 was extrapolated from 50°C to 25°C using the Arrhenius equation.	2526386
Phototransformation in water, 25°C	98.5% w/w n-propyl dihydrojasmonate; ^{14}C-labeled and unlabeled	54.0 hrs (purified water) and 57.8 hrs (non-sterile river water) continuous irradiation, equivalent to 17.4 d and 18.6 d, respectively, when converted to sunlight hours/ intensity	pH 7.81; half-life converted under conditions of sunlight duration and irradiation at latitude 35 degrees north in spring (April to June). Half-life would be longer at Canadian latitudes.	2526387

Property	Test Substance	Half-life or DT_{50}	Comments	PMRA#
Biotransformation in aerobic soil, 30°C	98.5% w/w n-propyl dihydrojasmonate; ^{14}C-lableled and unlabeled	1.6 to 2.3 hrs; 80% elimination of test substance in 3.7 to 5.3 hrs.	Japanese soils, clay loam and sandy clay loam; transformation would be slower at 25°C, but active ingredient is not expected to persist for long periods of time in soil. No volatile substances were observed through the test period; $^{14}C0_2$ reached 72-76% after 30 d.	2526388

Table 5 Toxicity of Prohydrojasmon to Non-Target Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a] and Comments	PMRA#
Invertebrates					
Honeybee (*Apis mellifera*)	48-hr acute contact	PDJ Technical[b]; 98.49% w/w	LD_{50}> 98.49µg a.i./bee	practically non-toxic	2386023
	acute oral	PDJ Technical	LC50 > 100 µg a.i./bee	practically non-toxic; study not provided to the PMRA.	2385869; USEPA BRAD
Daphnia magna	48-hr-acute	PDJ Technical; 98.0% w/w	48-hr EC_{50} = 2.13 mg a.i./L.	moderately toxic	2386024
Birds					
Northern Bobwhite (*Colinius virginianus*)	acute oral	PDJ Technical; 98.08% w/w	LD_{50}> 2000 mg a.i./kg bw	practically non-toxic	2386026
Japanese quail (*Coturnix coturnix japonica*)	5-d-acute dietary	PDJ Technical; 98.08% w/w	LD_{50}> 5000 mg a.i/kg diet (>4721 mg a.i./kg diet, mean measured)	practically non-toxic	2386027
Fish					
Common carp (*Cyprinus carpio)*	96-h-acute	PDJ Technical; 98.1% w/w	LC_{50} = 3.33 mg a.i./L	moderately toxic	2386025
Vascular plants					
Terrestrial Plants	Seedling emergence	PDJ Technical; 99.9% w/w	ER_{50} > 1,140 g a.i./hectare; based on emergence and height/dry weight of seedlings up to 21 d	N/A; highest concentration tested on ten species. *Cucumis sativus*, NOER = 380 g a.i./ha (based on height).	2526775
	Vegetative vigour	N/A	N/A	Study waived based on rationale: mode of action of a.i. and structural similarity to jasmonic acid, which is present in actively-	2386029; 2385869

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a] and Comments	PMRA#
				growing plant parts.	
Aquatic vascular plants	N/A	N/A	N/A	Study waived based on rationale: phytotoxicity not expected based on no effects reported for seedling emergence and growth of terrestrial vascular plants, mode of action of active ingredient, and similarity to jasmonic acid which is present naturally in plants.	2386030
Algae					
Algae	N/A	N/A	N/A	Study waived based on rationale: see aquatic vascular plants.	2386028 2385853

[a] Atkins et al.(1981) for bees and USEPA classification for others, where applicable.
[b] PDJ Technical: 3-oxo-2-pentylcyclopentaneacetic acid n-propyl ester or n-propyl dihydrojasmonate
*N/A, not available

Table 6 Screening Level Risk Assessment for Non-Target Species (except birds) Exposed to Prohydrojasmon

Organism	Exposure	Toxicity value	Toxicity value/ Uncertainity factor	EEC[a]	RQ	LOC Exceeded
Terrestrial invertebrates						
Honeybee (*Apis mellifera*)	Acute Contact	LD_{50}> 98.49 µg a.i./bee	NA*	0.96 µg a.i./bee[b]	<0.0097	No; LOC = 0.4
	Acute Oral	LC50 > 100 µg a.i./bee	NA	11.6 µg a.i./bee[c]	<0.116	No; LOC = 0.4
Aquatic organisms						
Daphnia magna	Acute	EC_{50} = 2.13 mg a.i/L.	2.13/2=1.065 mg a.i./L	0.1 mg a.i./L	0.09	No; LOC = 1
Common carp (*Cyprinus carpio)*	Acute	LC_{50} = 3.33 mg a.i./L	3.33/10=0.333 mg a.i./L	0.1 mg a.i./L	0.3	No; LOC = 1
Amphiban	Acute	LC_{50} = 3.33 mg a.i./L	3.33/10=0.333 mg a.i./L	0.53 mg a.i./L	**1.6**	Yes; LOC = 1
Vascular plants						
Vascular plant	Seedling emergence	ER_{50} > 1,140 g a.i./ha	NA	400 g a.i./ha	<0.35	No; LOC = 1

*NA: not applicable
[a] EECs in water were calculated for 15 cm (amphibians) and 80 cm (fish, daphnids) using a cumulative rate of 800 g a.i./ha.
[b]An EEC for contact toxicity to bees is calculated by multiplying the single application rate, in units of kg (0.400 kg a.i./ha) by a factor of 2.4 µg a.i./bee, which gives an EEC in units that match the toxicity endpoint (µg a.i./bee).
[c]An EEC for oral toxicity to bees is calculated by multiplying the single application rate, in units of kg (0.400 kg a.i./ha) by a factor of 29 µg a.i./bee, which gives an EEC in units that match the toxicity endpoint (µg a.i./bee)

Table 7 Screening Level Risk Assessment for Birds Exposed to a Maximum Seasonal Application Rate of 800 g a.i./ha of Prohydrojasmon Plant Growth Regulator

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE* (mg a.i./kg bw)	RQ	LOC Exceeded
Small Bird (0.02 kg)					
Acute	200.00	Insectivore (insects)	52.6	0.26	No
Medium Sized Bird (0.1 kg)					
Acute	200.00	Insectivore (insects)	41.05	0.21	No
Large Sized Bird (1 kg)					
Acute	200.00	Herbivore (short grass)	26.52	0.13	No

*EDE = Estimated dietary exposure is calculated using the following formula: (FIR/bw) × EEC

Toxicity endpoint used was for acute oral toxicity, northern bobwhite, divided by 10 (uncertainty factor).

For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used, as follows:

Passerine Equation (body weight <or = 200 g): FIR (g dry weight/day) = $0.398(\text{bw in g})^{0.850}$

All birds Equation (body weight >200 g): FIR (g dry weight/day) = $0.648\ (\text{bw in g})^{0.651}$

For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{bw in g})^{0.822}$

FIR: Food Ingestion Rate.
bw: Generic Body Weight
EEC: Concentration of pesticide on food item. At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

Table 8 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Prohydrojasmon Endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Aerobic biotransformation half-life =1.6 – 2.3 hours
	Water	Half-life ≥ 182 days	Not available
	Sediment	Half-life ≥ 365 days	Not available
	Air	Half-life ≥ 2 days or evidence of long range transport	Not available
Bioaccumulation[4]	Log $K_{OW} \geq 5$		3.96 (estimate)
	BCF ≥ 5000		Not available
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four			No, does not meet TSMP Track 1 criteria.

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Prohydrojasmon Endpoints
criteria must be met)?		

[1]All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (in other words, all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air), then the criterion for persistence is considered to be met.
[4]Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

Table 9 List of Supported Uses

Items	Proposed label claims	VRD supported use claims
Application rate	From 100 to 200 ppm	As proposed.
Efficacy claim	Red colour enhancement.	As proposed.
Host claim	Red colour apples	As proposed.
Application timing	Between 7 and 28 days before anticipated harvest.	As proposed.
Number of application	One or two times	As proposed.
Application method	Using conventional spray equipment with a sufficient amount of water to ensure thorough and uniform coverage of the tree canopy.	As proposed.

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