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Proposed Registration Decision

PRD2018-07

Flupyradifurone; BCS 2960 Insecticide; Altus Insecticide

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Overview

Proposed Registration Decision for Flupyradifurone

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 Flupyradifurone TC, and the end-use products BCS 2960 Insecticide and Altus Insecticide, containing the technical grade active ingredient flupyradifurone, to control aphids, whiteflies and leafhoppers on greenhouse vegetables, ornamental crops and outdoor ornamentals, and to control aphids on Christmas trees.

Flupyradifurone is currently registered for the control of various insect pests on various fruit, vegetable and field crops, and as a seed treatment on soybeans. For further details, see Proposed Registration Decision PRD2014-20, *Flupyradifurone*, and Registration Decision RD2015-24, *Flupyradifurone*.

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 flupyradifurone, BCS 2960 Insecticide and Altus Insecticide.

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

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."

policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of the Canada.ca website.

Before making a final registration decision on flupyradifurone, BCS 2960 Insecticide and Altus Insecticide, the PMRA will consider any comments received from the public in response to this consultation document.³ The PMRA will then publish a Registration Decision⁴ on flupyradifurone, BCS 2960 Insecticide and Altus Insecticide, 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 Flupyradifurone?

Flupyradifurone is an insecticide that interferes with the function of insect nerves. It is registered for use as a foliar spray on various field vegetable, fruit and nut crops or by soil application to certain field vegetable and fruit crops to control insect pests. It is the active ingredient in the new commercial class end-use products BCS 2960 Insecticide and Altus Insecticide. Control of insect pests of greenhouse-grown crops, outdoor ornamental plants and Christmas trees are new uses for this active ingredient.

Health Considerations

Can Approved Uses of Flupyradifurone Affect Human Health?

BCS 2960 Insecticide and Altus Insecticide, containing flupyradifurone, are unlikely to affect your health when used according to label directions.

Potential exposure to flupyradifurone may occur through the diet (food and water), when handling and applying the end-use products, or when re-entering treated areas. 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. The dose 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 for which the exposure is well below levels that cause no effects in animal testing 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*.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, flupyradifurone was slightly acutely toxic via the oral route; therefore the signal word and hazard statement “CAUTION – POISON” are required on the label. Flupyradifurone was of low acute toxicity via the dermal and inhalation routes, non-irritating to skin, and minimally irritating to eyes. The potential for flupyradifurone to cause an allergic skin reaction could not be ruled out based on the information provided; therefore, the hazard statement “POTENTIAL SKIN SENSITIZER” is required on the label for flupyradifurone.

BCS 2960 Insecticide and Altus Insecticide, end-use products containing flupyradifurone, were considered to be of low acute toxicity via the oral, dermal and inhalation routes, as well as non-irritating to the skin and minimally irritating to the eye. The products were considered to cause an allergic skin reaction; therefore, the hazard statement “POTENTIAL SKIN SENSITIZER” is required on the labels for these end-use products.

Registrant-supplied short-, and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature were assessed for the potential of flupyradifurone to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment included general signs of toxicity as well as effects on body weight and skeletal muscle. In addition, an effect on fetal survival was also noted; however, there was no evidence to suggest that the young animal was more sensitive than the adult animal to flupyradifurone. The risk assessment protects against the effects noted above 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 test animals.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Aggregate chronic dietary intake estimates (food plus drinking water) revealed that the general population and infants less than one year old, the subpopulation which would ingest the most flupyradifurone relative to body weight, are expected to be exposed to less than 34% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from flupyradifurone is not of health concern for all population subgroups.

Acute dietary (food plus drinking water) intake estimates for females 13 to 49 years old and all population subgroups were less than 35% and 22% of the acute reference dose, respectively and are not of health concern. The highest exposed subpopulation was children 1 to 2 years old.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States, using flupyradifurone on greenhouse grown tomato, cucumber, pepper, and lettuce are acceptable. The use of BCS 2960 Insecticide and Altus Insecticide on these crops will not result in residues of flupyradifurone exceeding the currently established MRLs for leafy greens (crop group 4-13A), fruiting vegetables (crop group 8-09) and cucurbit vegetables (crop group 9).

Risks in Residential and Other Non-Occupational Environments

Estimated risks from residential exposure are not of concern provided that directions specified on the label are followed.

The exposure assessments conducted for adults and children when contacting landscape ornamentals treated with BCS 2960 Insecticide and Altus Insecticide, including when aggregated with dietary exposure, did not identify risks of concern when the label directions are followed.

Occupational Risks From Handling BCS 2960 Insecticide and Altus Insecticide

Occupational risks are not of concern when BCS 2960 Insecticide and Altus Insecticide are used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix and load BCS 2960 Insecticide and Altus Insecticide and apply as a foliar or soil treatment and workers re-entering treated greenhouses, nurseries and Christmas tree farms can come in direct contact with flupyradifurone residues on the skin and/or through inhalation. Therefore, the label specifies that anyone mixing/loading and applying flupyradifurone must wear long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks. The label also requires that workers not enter treated fields for 12 hours after application.

Taking into consideration these label statements, precautionary measures, and the exposure duration for handlers and workers, it was determined that the risks to these individuals are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Flupyradifurone Is Introduced Into the Environment?

When used according to label directions, Altus Insecticide and BCS 2960 Insecticide containing flupyradifurone are not expected to pose risks of concern to the environment.

Altus Insecticide and BCS 2960 Insecticide, containing flupyradifurone, can enter land and water habitats through spray drift and can enter water bodies through run-off when used as a foliar spray and soil drench for greenhouse vegetables, greenhouse ornamentals, outdoor ornamentals and Christmas trees. Although flupyradifurone can be broken down by microorganisms into two breakdown products, the rate of breakdown is very slow. As a consequence, flupyradifurone may build up in the soil and has the potential to move through soil to reach groundwater. In surface water, flupyradifurone mixes with water quickly and then breaks down slowly through reaction with sunlight. Breakdown by microorganisms in water is negligible. Therefore, flupyradifurone has a potential to remain in water and sediment over time. Flupyradifurone is not expected to build up in animal tissues. Flupyradifurone is not expected to move into the air and be transported long distances from where it was applied.

Flupyradifurone and its major breakdown products do not present risks of concern to plants, birds, small wild mammals, earthworms, algae, fish and amphibians when applied by foliar and soil drench applications. However, as an insecticide, flupyradifurone may pose risks to some species of non-target aquatic insects if they come in contact with high enough concentrations; therefore, preventative measures such as spray drift buffer zones, prohibiting the release of greenhouse effluent into water and advising users about the potential risk from run-off are required on the product labels. While flupyradifurone is unlikely to pose a risk to bee colonies, it may have short-term effects on adult foraging bees when applied during full bloom by foliar application. To protect bees and other non-target insects, risk reduction measures are in place and proper directions for use are outlined on product labels.

Value Considerations

What Is the Value of BCS 2960 Insecticide and Altus Insecticide?

BCS 2960 and Altus Insecticides will provide a new active ingredient for control of insect pests on greenhouse vegetables and ornamentals, outdoor ornamentals and Christmas trees.

Both BCS 2960 Insecticide and Altus Insecticide control aphids, leafhoppers and whiteflies in greenhouse tomato, pepper, cucumber, lettuce and ornamental crops and on outdoor ornamental plants, and BCS 2960 Insecticide also controls aphids on Christmas trees. The active ingredient in these products was identified by Canadian growers as a priority to register for several of these uses.

Measures to Minimize Risk

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

The key risk-reduction measures being proposed on the labels of BCS 2960 Insecticide and Altus Insecticide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

As direct contact with flupyradifurone on the skin or through inhalation of spray mists can occur, anyone mixing, loading and applying BCS 2960 Insecticide and Altus Insecticide as a foliar or soil application through ground application equipment must wear long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks. Any worker entering greenhouses, nurseries and farms treated with flupyradifurone must comply by the restricted-entry interval (REI) of 12 hours.

To reduce dermal contact with flupyradifurone for adults and children contacting treated plants in residential areas, statements will be included on the labels of BCS 2960 Insecticide and Altus Insecticide.

Environment

Altus Insecticide and BCS 2960 Insecticide are similar to Sivanto Prime Insecticide, a registered product. All three products contain flupyradifurone as the active ingredient. Both new products are proposed to be used in a similar manner as Sivanto Prime Insecticide, and thus, slight differences in crops and use sites between the two new products and the previously registered Sivanto Prime Insecticide do not affect the overall level of environmental exposure. The risk mitigation measures required for the previously registered Sivanto Prime Insecticide are applicable for the new products. Additional label statements are required for greenhouse uses of Altus Insecticide and BCS 2960 Insecticide for protecting pollinators and other beneficial insects used in greenhouse production and preventing the release of greenhouse effluent into aquatic systems.

Next Steps

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

Other Information

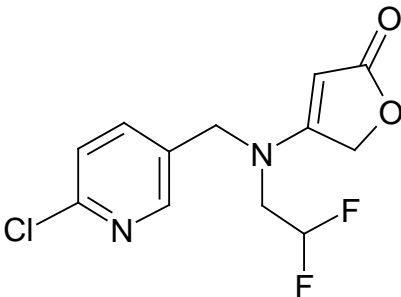
When the PMRA makes its registration decision, it will publish a Registration Decision on flupyradifurone (based on the Science Evaluation section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application,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

Science Evaluation

Flupyradifurone BCS 2960 Insecticide Altus Insecticide

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Flupyradifurone
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	4-[[[(6-chloropyridin-3-yl)methyl](2,2-difluoroethyl)amino]furan-2(5H)-one <i>OR</i> 4-[(6-chloro-3-pyridylmethyl)(2,2-difluoroethyl)amino]furan-2(5H)-one
2. Chemical Abstracts Service (CAS)	4-[[[(6-chloro-3-pyridinyl)methyl](2,2-difluoroethyl)amino]-2(5H)-furanone
CAS number	951659-40-8
Molecular formula	C ₁₂ H ₁₁ ClF ₂ N ₂ O ₂
Molecular weight	288.68
Structural formula	
Purity of the active ingredient	99.9%

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

Technical Product - Flupyradifurone TC

Additional chemistry data were received, reviewed and found to be acceptable to support the registration of the technical product. For all other chemistry data, refer to the Proposed Registration Decision, PRD2014-20, *Flupyradifurone*.

End-Use Products - BCS 2960 Insecticide and Altus Insecticide

Property	Result
Colour	Clear brown to pink
Odour	Weak characteristic odour
Physical state	Liquid
Formulation type	Solution
Guarantee	200 g/L
Container material and description	HDPE bottles, 1 – 20 L
Relative density	1.174
pH of 1% dispersion in water	5.4
Oxidizing or reducing action	No oxidizing properties
Storage stability	The active substance content is stable for one year at ambient temperature (mean 22.3°C) in HDPE.
Corrosion characteristics	The product is not corrosive to its HDPE packaging material.
Explosibility	Not explosive

1.3 Directions for Use

Applied as a foliar spray, BCS 2960 Insecticide controls aphids on Christmas trees at rates of 500-750 mL/ha (100-150 g a.i./ha), and both BCS 2960 and Altus Insecticides control aphids and leafhoppers at rates of 500-750 mL/ha (100-150 g a.i./ha) and whiteflies at rates of 750-1000 mL/ha (150-200 g a.i./ha) in greenhouse tomato, pepper, cucumber, lettuce and ornamental crops and on outdoor nursery and landscape ornamentals. Applied as a soil drench, both BCS 2960 and Altus Insecticides control aphids and leafhoppers at rates of 750-1000 mL/ha (150-200 g a.i./ha) and whiteflies at rates of 1500-2000 mL/ha (300-400 g a.i./ha) in greenhouse tomato, pepper, cucumber, lettuce and ornamental crops. For either application method, reapplication intervals are 10 days for peppers and 7 days for all other crops. The maximum application rate for all crops is 2000 mL/ha (400 g a.i./ha) per year outdoors or per crop cycle for greenhouse crops.

1.4 Mode of Action

Flupyradifurone is a nicotinic acetylcholine receptor competitive modulator (IRAC Mode of Action Group 4) in the butenolide class of chemistry (Sub-group 4D). It is active both on contact and through ingestion, but is more potent when ingested. It has systemic activity in plants when

applied as a soil drench and translaminar activity when applied as a foliar spray. Although all Group 4 insecticides act on the same receptor in the insect nervous system, there is evidence to suggest that the different chemical classes interact with the receptor differently. In addition, studies have shown that insects resistant to active ingredients in one sub-group (4A) are susceptible to those in others (4C or 4D), indicating a lack of cross-resistance to active ingredients in different sub-groups.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

Refer to the Proposed Registration Decision, PRD2014-20, *Flupyradifurone*.

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.

2.3 Methods for Residue Analysis

Refer to the Proposed Registration Decision, PRD2014-20, *Flupyradifurone*.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Flupyradifurone belongs to the butenolide class of pesticides.

A detailed review of the toxicological database for flupyradifurone was conducted previously and is summarized in the Proposed Registration Decision, PRD2014-20, *Flupyradifurone*. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. With the exception of the dermal sensitization study conducted with the active ingredient flupyradifurone, the studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to flupyradifurone.

The results of acute toxicity studies conducted with the EP Sivanto 200 SL, and summarized in Table 2 of the Proposed Registration Decision, PRD2014-20, *Flupyradifurone*, were used to characterize the acute hazards of the EPs BCS 2960 Insecticide and Altus Insecticide. Sivanto 200 SL was of low acute toxicity via the oral, dermal and inhalation routes in rats. In rabbits, Sivanto 200 SL was non-irritating to the skin and minimally irritating to the eyes. A positive dermal sensitization reaction was documented in a local lymph node assay in mice.

Results of the toxicology studies conducted on laboratory animals with flupyradifurone, as well as the toxicology reference values for use in human health risk assessment, are summarized in the Proposed Registration Decision, PRD2014-20, *Flupyradifurone*. These reference values are

presented in Appendix I, Table 1 of this document. Based on the current petitioned uses, aggregate exposure to flupyradifurone may occur through food, drinking water, and residential exposures. The reference values selected for use in aggregate risk assessment are summarized below and are included in Appendix I, Table 1.

A request to waive the requirement for a repeated-exposure inhalation toxicity study for the petitioned uses was accepted. This acceptance was based on the low volatility of flupyradifurone and the achieved margins of exposure (MOE), which exceeded 1000 for all inhalation exposure scenarios, when using a toxicological endpoint from an oral toxicity study.

Incident Reports

As of October 31, 2017, no human or domestic animal incident reports involving flupyradifurone were submitted to the PMRA.

3.2 Aggregate Risk Assessment

For short-, intermediate- and long-term aggregate risk assessment of the general population (including pregnant women, infants and children), the selected toxicological endpoint was body weight. For all routes of exposure, the results from both the one-year dietary toxicity study in the dog and the two-generation dietary reproductive toxicity study in the rat were considered co-critical. The effect levels established in the one-year dog study and the two-generation reproductive toxicity study were similar, and both studies revealed decreases in body weight. In the one-year dog study, the no observed adverse effect level (NOAEL) of 7.8 mg/kg bw/day was established based on reduced body weight that was observed in females at the lowest observed adverse effect level (LOAEL) of 28 mg/kg bw/day. Similar body weight effects were also noted in dogs at a comparable dose level after 90 days of dosing. In the two-generation reproductive toxicity study in the rat, the NOAEL of 7.8 mg/kg bw/day was established in offspring, with reduced body weights in the F2 generation occurring towards the end of the lactation period at the LOAEL of 39 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The target MOE is 100 for all scenarios. As discussed in the *Pest Control Products Act* Hazard Characterization section of the Proposed Registration Decision, PRD2014-20, *Flupyradifurone*, the *Pest Control Products Act* factor was reduced to 1-fold for all exposure scenarios other than those for which the point of departure was selected from the rabbit developmental toxicity findings. The selection of the endpoint for aggregate risk assessment and the MOE is considered protective of sensitive sub-populations, such as women of reproductive age, pregnant women, and unborn children.

Cumulative Assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. For the current evaluation, the PMRA did not identify information indicating that flupyradifurone shares a common mechanism of toxicity with other pest control products. Therefore, there is no requirement for a cumulative risk assessment at this time.

3.3 Occupational and Residential Risk Assessment

3.3.1 Toxicological Endpoints

Occupational exposure to flupyradifurone is characterized as short- to long- term in duration and by dermal and inhalation routes for workers mixing/loading and applying and by the dermal route for post-application workers. Residential exposure to treated foliage is via the dermal route and is expected to be short-term in duration.

3.3.1.1 Dermal Absorption

A dermal absorption value of 28% has been previously established for mixer/loader/applicators based on a rat in vivo dermal absorption study. Similarly, a 9% dermal absorption value for people who may come in contact with surfaces treated with the end-use product has been previously established based on a Triple Pack of rat in vivo and in vitro and human in vitro studies. Refer to the Proposed Registration Decision, PRD2014-20, *Flupyradifurone* for additional details.

3.3.2 Occupational Exposure and Risk

3.3.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have the potential to be exposed to BCS 2960 Insecticide and Altus Insecticide during mixing, loading and application. Exposure is expected to be of short- to long-term in duration (depending on the location of use and the crop treated) and to occur primarily by the dermal and inhalation routes.

Dermal and inhalation exposure estimates were derived for mixers/loaders/applicators applying flupyradifurone to a variety of greenhouse crops, outdoor ornamentals and Christmas trees via chemigation and backpack, hand-held (manually- and mechanically-pressurized), groundboom and airblast sprayers using unit exposure values from the Pesticide Handlers Exposure Database (PHED) and the Agricultural Handlers Exposure Task Force (AHETF) database. All exposure estimates are based on mixers/loaders/applicators wearing personal protective equipment (PPE) that is in keeping with label instructions.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 28% dermal absorption. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using an 80 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (NOAELs) to obtain the MOE; the target combined MOE is 100.

Dermal and inhalation risks to workers mixing, loading and applying flupyradifurone were not of concern (MOEs were above the target MOE; Appendix I, Table 2).

3.3.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers entering areas treated with flupyradifurone when completing tasks such as hand harvesting, pruning, scouting, setting irrigation lines, etc. Inhalation exposure is not of concern as the vapour pressure of flupyradifurone indicates it is not volatile indoors or outdoors at 25°C. The duration of exposure is considered to be short- to intermediate-term for workers completing tasks outdoors in nurseries and with Christmas trees and long-term for workers in greenhouses. The primary route of exposure for workers re-entering treated areas would be through the dermal route.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients. Activity transfer coefficients are based on data from the Agricultural Re-entry Task Force (ARTF). No data were submitted for outdoor ornamentals or Christmas trees so the default dislodgeable foliar residue value of 25% of the application rate and a daily dissipation rate of 10% were used in the exposure assessment. Chemical-specific dislodgeable foliar residue data were provided for greenhouse tomatoes and greenhouse roses.

Greenhouse Tomatoes

A dislodgeable foliar residue study was designed to collect data to calculate dislodgeable foliar residue dissipation curves for BYI 02960 (flupyradifurone, 200 g a.i./L nominal guarantee) on greenhouse tomatoes at a single test site in Seville, Spain during the 2011 season. BYI 02960 was applied twice by backpack sprayer at a rate of 246 g a.i./ha with an application interval of 10 days. Since the study was conducted in a greenhouse setting, geographical and climatic conditions had no impact on the acceptability of the study. The end-use product tested is relevant to the products proposed for registration in Canada.

Dislodgeable foliar residue (DFR) samples were collected on days -1, 0, 1, 3, and 7 after the first application. For the second application, samples were collected on days -1, 0, 1, 3, 7, 10, and 14 after application. At each collection period, using a Birkestrand leaf punch sampler, 40 samples at 10 cm² each were collected from each treated subplot for a total leaf surface area of 400 cm² per replicate. Untreated leaves to be used for control and field fortification samples were collected from the subplots prior to application.

Since the recoveries for the field fortification level closest to the residues found in the test samples were below 95%, data were corrected, and corrected data after the first and second application were both used for the linear regression analysis. The equations of the line from the analysis had r^2 values of 0.991 and 0.947 for the first and second application, respectively, indicating that residues dissipate according to a log-linear regression. The half-life is estimated to be $t_{1/2} = 7.73$ and 7.45 days for the first and second application, respectively. The predicted peak DFR value from the linear regression analysis was calculated as 0.238 µg/cm² which is lower than the actual field sample taken one day after the first application (0.243 µg/cm²). For the second application, the predicted peak DFR value from the linear regression analysis was calculated as 0.322 µg/cm² which is lower than the actual field sample (0.368 µg/cm²).

The slope of the line was used to calculate a percent dissipation per day value of 8.6% and 8.9% for the first and second application, respectively. These dissipation values refine the PMRA's default dissipation value of 0% for greenhouse vegetable uses.

There are limitations with the study such as there was only a single field fortification event. However, the study is still considered acceptable for risk assessment purposes for greenhouse tomatoes. As well, the results are applicable to other greenhouse vegetables such as cucumbers, peppers and lettuce.

Greenhouse Roses

A dislodgeable foliar residue study was designed to collect data to calculate dislodgeable foliar residue dissipation curves for BYI 02960 (flupyradifurone, 200 g a.i./L nominal guarantee) on greenhouse Grandprix roses at a single test site in Zwaagdijk, Netherlands during the 2011 season. BYI 02960 was applied by backpack sprayer at a rate of 148.9 g a.i./ha for four applications with an application interval of 7 days. Since the study was conducted in a greenhouse setting, geographical and climatic conditions had no impact on the acceptability of the study. Furthermore, the EP (BYI 02960, 200 g/L) used in the study was relevant to the proposed Canadian products.

DFR samples were collected on days -1, 0, 1, 3, and 7 after the first, second, and third application. After the fourth application, samples were collected on days -1, 0, 1, 3, 7, 10, 14, and 21. At each collection period, using a Birkestrand leaf punch sampler, 40 samples, at 10 cm² each, were collected from each treated subplot with a total leaf surface area of 400 cm². Control samples were collected from the subplots prior to application.

Since the recoveries from the field fortification level closest to the residues found in the test samples were below 95%, data were corrected using the closest field fortification level recovery. The corrected data after each application were used for the linear regression analysis. The equations of the line from the analysis had r^2 values ranging from 0.94 to 0.97, indicating that residues dissipate according to a log-linear regression. The predicted peak DFR value from the linear regression analysis of the data after the first application was calculated as 0.297 µg/cm² which was very similar to the actual field sample taken immediately after application (0.313 µg/cm²). For the second application, the predicted peak DFR value from the linear regression analysis was calculated as 0.364 µg/cm² which was very similar to the actual field sample (0.386 µg/cm²). For the third application, the predicted peak DFR value from the linear regression analysis was calculated as 0.366 µg/cm² which was higher than the actual field sample (0.352 µg/cm²). For the fourth application, the predicted peak DFR value from the linear regression analysis was calculated as 0.252 µg/cm² which is lower than the actual field sample (0.322 µg/cm²). The slope of the line for each application was used to calculate a percent dissipation per day value which ranged from 11 to 24%. Each application exhibited higher daily dissipation than the PMRA's current default daily dissipation value for greenhouse ornamental of 2.3%.

Overall, while the study has limitations, such as there was only a single field fortification event, it is considered acceptable for risk assessment purposes for greenhouse roses. The study is also acceptable to use for all greenhouse cut and potted flowers.

Exposure estimates for greenhouse vegetables and ornamentals, outdoor ornamentals and Christmas trees were compared to the toxicological endpoint to obtain the MOE. Dermal risks of post-application workers to flupyradifurone were not of concern (MOEs were above the target MOE; Appendix I, Table 3).

3.3.2.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal for greenhouse uses. For field and residential uses, appropriate label statements will be added to ensure that the products will only be applied when there is low risk of drift when taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.3.3 Residential Exposure and Risk Assessment

3.3.3.1 Handler Exposure and Risk

The end-use products are commercial marketing-class products so a residential handler exposure assessment is not required.

3.3.3.2 Postapplication Exposure and Risk

Short-term dermal exposure was calculated for adults (16+ years) and youth (6<11 years). Postapplication exposure can result from conducting activities in previously treated areas such as gardening or picking fruits following pesticide applications by professional pesticide applicators. Adults (16+ years) and children (6<11 years) are considered the index lifestages for this exposure scenario as it is assumed that younger children (< 6 years old) would not utilize these areas for playing nor engage in the types of activities associated with these areas (for example, gardening or picking fruits) to the extent that older children will. Children aged 6 < 11 years will be representative of older children (11+ years) because of their larger surface area/body weight ratio.

Postapplication exposure assessments for landscape ornamentals in outdoor residential areas are considered to be representative of non-residential (office buildings, public spaces, commercial areas, etc.) outdoor areas.

The assessment for adults and children used the PMRA's default values of 25% dislodgeable residues and 10% daily dissipation rate per day to determine dermal exposure after two applications applied at a 7-day retreatment interval (RTI). The transfer coefficients (cm²/hr) and exposure time (hr/day) for adults and children are derived from the 2012 USEPA Residential SOP, Section 4 – Gardens and Trees.

Based on the exposure inputs listed above, dermal MOEs were calculated for adults and children when in contact with treated gardens, trees and plants. The calculated MOEs immediately after the second application exceeded the target MOE of 100 and so no risks of concern were identified (Appendix I, Table 4).

3.3.3.3 Aggregate Exposure and Risk

The aggregate exposure of flupyradifurone to adults and children when in dermal contact with treated ornamentals and through the dietary (food + water) route was calculated. The aggregate endpoint used to determine the risk of aggregate exposure is 7.8 mg/kg bw/day. The chronic dietary exposure for adults and children is 0.008555 mg/kg bw/day and 0.006744 mg/kg bw/day, respectively. When the dermal and dietary exposures are aggregated, the target MOE of 100 was exceeded for both adults and children so risks are not of concern (Appendix I, Table 5).

3.4 Food Residues Exposure Assessment

3.4.1 Residues in Plant and Animal Foodstuffs

Refer to the Proposed Registration Decision, PRD2014-20, *Flupyradifurone*.

3.4.2 Dietary Risk Assessment

Acute and chronic (non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™).

3.4.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the refined chronic non-cancer analysis for flupyradifurone: 100% crop treated, default and experimental processing factors (where available), residues of greenhouse grown tomatoes, bell peppers, non-bell peppers, cucumbers, and lettuce based on supervised trial median residue (STMdR) values (where applicable), and anticipated residues for all animal commodities.

The refined chronic dietary exposure from all supported flupyradifurone food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 18% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to flupyradifurone from food and drinking water is 12% (0.009652 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants less than one year old at 33% (0.026497 mg/kg bw/day) of the ADI.

3.4.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the refined acute analysis for flupyradifurone: 100% crop treated, default and experimental processing factors (where available), residues of greenhouse grown tomatoes, bell peppers, non-bell peppers, cucumbers, and lettuce based on highest average field trial residue (HAFT) values (where applicable), and anticipated residues for

all animal commodities. The refined acute dietary exposure (food alone) for all supported flupyradifurone registered commodities is estimated to be 25% (0.025160 mg/kg bw/day) of the acute reference dose (ARfD) for females 13–49 years old (95th percentile, deterministic), and 18% (0.073301 mg/kg bw/day) for all other population subgroups. Aggregate exposure from food and drinking water is considered acceptable: 35% (0.034590 mg/kg bw) of the ARfD for females 13–49 years old, and 21% (0.085606 mg/kg bw) for all other population subgroups.

3.4.3 Aggregate Exposure and Risk

The dietary exposure values [food plus drinking water chronic exposure for specific subpopulations] for flupyradifurone and difluoroacetic acid (DFA) were aggregated with the residential exposure (residential areas on gardens and trees).

3.4.4 Maximum Residue Limits

Please refer to the Maximum Residue Limit Database in the Pesticides and Pest Management section of the Canada.ca website for the established MRLs for flupyradifurone.

The field trial data, acute and chronic dietary risk estimates are summarized in Appendix I, Tables 6 and 7.

4.0 Impact on the Environment

An environmental assessment for Altus Insecticide and BCS 2960 Insecticide containing flupyradifurone for foliar and soil drench applications on greenhouse vegetables, indoor and outdoor ornamentals and outdoor Christmas trees was conducted as these represent major new uses for flupyradifurone. Previously, an environmental risk assessment for flupyradifurone and the flupyradifurone-containing product, Sivanto Prime Insecticide, was conducted for similar use patterns on various field crops and the results are reported in the Proposed Registration Decision, PRD2014-20, *Flupyradifurone*, and the Registration Decision, RD2015-24, *Flupyradifurone*. Altus Insecticide and BCS 2960 Insecticide are similar to Sivanto Prime Insecticide.

4.1 Fate and Behaviour in the Environment

The properties of flupyradifurone and its environmental behaviour have been thoroughly characterized and presented in the Proposed Registration Decision, PRD2014-20, *Flupyradifurone*, and the Registration Decision, RD2015-24, *Flupyradifurone*. There are no additional environmental fate data available and none are required for further consideration.

4.2 Environmental Risk Characterization

The new flupyradifurone-containing products, Altus Insecticide and BCS 2960 Insecticide, are similar to Sivanto Prime Insecticide and are to be used at the same application rates with the same application methods and timing, i.e., similar exposure scenarios. Therefore, the previous environmental risk assessment and the majority of the required risk mitigation measures are applicable to the proposed new products.

The only exception is the requirement for greenhouse specific label statements that preclude the release of treated effluent into aquatic systems on the labels of Altus Insecticide and BCS 2960 Insecticide.

In addition, pollinator risk assessments were revisited since new data were submitted.

Risk to pollinators

A number of pollinator toxicity studies were submitted since the initial registration of flupyradifurone and Sivanto Prime Insecticide (Appendix I, Table 8). The PMRA reviewed these studies in support of the major new use, compared the toxicity endpoints with those previously reported (Appendix I, Table 8) and made the following conclusions:

1. The newly submitted acute oral and contact tests on bumblebees showed that bumblebees were less sensitive to flupyradifurone than honeybees (i.e., lower levels of ecotoxicity were observed). Therefore, the risk mitigation measures required for honeybees are also expected to be protective of bumblebees. Further refinements to the risk assessment based on bumblebees are not required.
2. The 10-day chronic feeding study resulted in a less sensitive endpoint than that used in the previous risk assessment. Therefore, further refinements to the risk assessment are not required.
3. The acute contact toxicity test with a mixture of Sivanto Prime Insecticide and Tebuconazole EW 250C G at 1:3.3 a.i. ratio showed an enhanced toxicity to bees when compared to either product used alone. Compared to results obtained from a previous study conducted with the same mixture but at 1:7.5 a.i. ratio, it appears that an increase in tebuconazole concentration in the mixture increases the synergistic effect on honeybees. The semi-field study conducted with the same mixture at 4:3 a.i. ratio showed that on the day of application, a moderate, short-term increase in mortality occurred when compared to the controls. During the rest of the study up to 21 days, no adverse effects were observed on foraging activity, behaviour, nectar and pollen storage, brood-abundance and brood-development, colony strength, nor on queen survival. The results were similar to those observed in the previous semi-field studies with Sivanto Prime Insecticide alone. It is noted, however, that the amount of tebuconazole in the mixture was lower than those used in the laboratory studies where a synergistic effect was observed. This provides further support for having the label statement “Do not tank mix with azole fungicides during bloom”. No further evaluation is required.
4. In acute contact toxicity tests conducted with Sivanto Prime Insecticide mixed with one other non-azole fungicide (Fluopyram SC 500B G, Trifloxystrobin WG 50 W, Propineb WG 70A W or Pyrimethanil SC 300 G), no statistically significant increases in mortality were observed at comparable concentrations of Sivanto Prime Insecticide alone. Therefore, no additional mitigation measures are required when used with these tank mix products up to the tested concentrations (Appendix I, Table 8).

5. A residue study measured concentrations of flupyradifurone in pollen and nectar collected by forager bees and in comb after two spray applications on phacelia at 200 g a.i./ha each (maximum Canadian registered rate) and 10 days apart. The first application occurred at 7 days before hive setup in the tunnel and just before onset of flowering at BBCH 58-60 and the second application occurred at 3 days after hive setup in the tunnel when phacelia were at full bloom (BBCH 65) and honeybees were actively foraging. Results showed that the majority of flupyradifurone residues were detected in the pollen samples taken from forager bees within the initial hours. Measured residues declined rapidly and were only 23% of the peak concentration after 1 day. Flupyradifurone residues in the nectar samples taken from forager bees followed the same trend, only the highest concentration was less than 5% of that in pollen at any given time. Flupyradifurone residues in the pollen samples taken from combs were considerably lower than those measured from forager bees and concentration peaked after 4 days, followed by a slower declining trend. Flupyradifurone residues in the nectar samples taken from combs were at least two orders of magnitude lower than that from forager bees at any time.

Compared to previous studies conducted with Sivanto Prime Insecticide whereby residues were measured in bees and plants, the peak residue levels measured in pollen and nectar sampled by forager bees in the new study were higher within 4 hours after application but were within the range of previously detected residues after 1 day (note, no samples were taken hours after application in the previous studies). Consequently, a risk assessment was conducted using the new residue data and the endpoints reported in the Proposed Registration Decision, PRD2014-20, *Flupyradifurone*. For the acute oral risk assessment, individual maximum concentrations measured at sampling intervals of 1, 2, 4 and 24 hours were used to calculate risk quotients (RQ). Results show that initially RQ values exceeded 0.4, the level of concern (LOC) for acute risk (Appendix I, Table 9); however, as the residue levels declined rapidly, so did the RQ values. One day after application, the RQ values reduced to 0.23, below the LOC. Furthermore, previous laboratory, semi-field and field studies showed that the effects from direct spray application at the maximum rate to blooming crops while bees were actively foraging were transient with no long-term effect on the colony through overwintering (Proposed Registration Decision, PRD2014-20, *Flupyradifurone*). This suggests that the potential adverse acute effects are temporary and the risk can be mitigated by limiting applications in early morning or in the evening when most bees are not actively foraging. On a chronic basis, the average residue concentrations in pollen and nectar detected in forager bees in the 10-day exposure period were used for RQ calculations. The resulting RQ values were 0.51 and 0.25 for adult bees and larvae, respectively, which did not exceed the chronic LOC of 1 (Appendix I, Table 9).

Based on these findings, the PMRA has concluded that although these studies provided further insight for its potential effects on pollinators, the results do not alter the risk profile of flupyradifurone and the proposed end-use products.

4.3 Incident reports

As of 31 October 2017, no environment incident reports involving flupyradifurone had been submitted to the PMRA.

5.0 Value

Flupyradifurone is a new active ingredient for control of aphids, leafhoppers and whiteflies in greenhouse tomato, pepper, cucumber, lettuce and ornamental crops and on outdoor ornamentals and Christmas trees. It was identified by Canadian growers as a high priority for registration to control aphids on greenhouse lettuce, peppers and tomatoes and whiteflies on greenhouse peppers, tomatoes and ornamentals, as well as a medium priority for registration to control aphids and whiteflies on greenhouse cucumbers and lettuce.

Support for registration of BCS 2960 Insecticide and Altus Insecticide for these new uses of flupyradifurone was provided by data from 11 efficacy trials and by scientific rationales based on pest grouping and crop grouping principles. The efficacy trials included aphids on greenhouse cucumber (both foliar and drench applications) and Christmas trees, and whiteflies on greenhouse tomato, lettuce and ornamentals. Scientific rationales extrapolated claims for leafhoppers and for aphids and whiteflies on the other crops from the data provided and from registered uses of Sivanto Prime Insecticide, which contains the same amount of flupyradifurone as BCS 2960 and Altus Insecticides, and is registered for control of aphids, leafhoppers and whiteflies in a variety of field vegetable, fruit and nut crops.

No phytotoxicity was noted in any of the efficacy trials, except in cucumber where the applicant indicated that the damage did not exceed acceptable industry standards and there was no significant reduction in yield. The labels of both BCS 2960 Insecticide and Altus Insecticide include statements warning that leaf yellowing or mottling may occur in cucumber. Although no phytotoxicity was observed in ornamentals, very few species were assessed. Due to the extensive diversity of plants represented by “ornamentals”, it is not possible to evaluate a sufficient number of species and varieties to rule out the occurrence of any phytotoxicity. Therefore, a statement guiding the user to test a small number of plants for sensitivity prior to treatment of an entire crop will be included on the labels of both end-use products.

Numerous alternative active ingredients, including some in Mode of Action Sub-group 4A, are registered in commercial class products for most of the uses on the labels of BCS 2960 and Altus Insecticides. However, there are relatively few alternatives for some uses (for example, aphids on Christmas trees and leafhoppers on ornamentals) and these products will be the first registered for control of leafhoppers on greenhouse vegetables. As described previously (Section 1.4), there is evidence for a lack of cross-resistance to active ingredients in different sub-groups of insecticide Mode of Action Group 4, so BCS 2960 and Altus Insecticides may contribute to resistance management even for uses with Sub-group 4A alternatives registered. Two instances of resistance to flupyradifurone have been reported, both in sweetpotato whitefly in Florida, indicating that there is potential for insects to develop resistance to this active ingredient. Appropriate resistance management recommendations have been included on the labels of both end-use products.

The value information provided was sufficient to support label claims for control of aphids on Christmas trees with foliar application of BCS 2960 Insecticide, control of aphids, leafhoppers and whiteflies on outdoor nursery and landscape ornamentals with foliar application of either BCS 2960 Insecticide or Altus Insecticide, and control of aphids, leafhoppers and whiteflies in greenhouse tomato, pepper, cucumber, lettuce and ornamental crops with either foliar or drench application of either BCS 2960 Insecticide or Altus Insecticide.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

Flupyradifurone and its transformation products were previously assessed in accordance with Regulatory Directive DIR99-03⁵, and were found not to meet all the Track 1 criteria, as discussed in the Proposed Registration Decision, PRD2014-20, *Flupyradifurone*.

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 EPs were 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 NOI2005-01⁷ 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 flupyradifurone and the end-use products Altus Insecticide and BCS 2960 Insecticide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

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

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

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*.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for flupyradifurone is adequate to identify the potential health hazards associated with this active ingredient. There was no evidence of carcinogenicity in rats or mice after long-term dosing. In short- and long-term studies with adult animals, the targets of toxicity were the liver, thyroid gland, kidney, and skeletal muscle. There was no evidence of dysregulation of the immune system. Neurotoxicity was evident after acute gavage dosing, but not after repeated dietary exposures. There was no evidence of increased susceptibility of the young in the rat. In the rabbit, fetal deaths, considered a serious endpoint, were observed in the presence of maternal toxicity. Effects on the reproductive system were noted at a dose level higher than that which resulted in systemic toxicity to parental animals. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixer, loader applicators handling BCS 2960 Insecticide and Altus Insecticide and workers re-entering treated areas are not expected to be exposed to levels of flupyradifurone that will result in human health concerns when the products are used according to label directions. The personal protective equipment on the product labels, of a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks, is adequate to protect workers.

Residential exposure to contacting treated areas is not expected to result in human health concerns when BCS 2960 Insecticide and Altus Insecticide are used according to label directions.

The nature of the residues in plants and animals is adequately understood. The residue definition for enforcement is flupyradifurone in plant products and in animal matrices. The residue definition for risk assessment is flupyradifurone and the metabolite difluoroacetic acid (DFA) in plant products and in animal matrices. The proposed use of flupyradifurone on greenhouse grown tomatoes, bell peppers, non-bell peppers, cucumbers, and lettuce does not constitute a risk of concern for chronic or acute dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors.

Sufficient crop residue data have been reviewed for foliar and drench application to greenhouse grown tomatoes, cucumbers, bell peppers, non-bell peppers, and lettuce to confirm that the use of BCS 2960 Insecticide and Altus Insecticide will not result in residues of flupyradifurone exceeding the currently established MRLs.

7.2 Environmental Assessment

When used for treatments on greenhouse vegetables, indoor or outdoor ornamentals and outdoor Christmas trees, the environmental risks of Altus Insecticide and BCS 2960 Insecticide are acceptable when the proposed labels with mitigation measures are followed.

7.3 Value

BCS 2960 Insecticide and Altus Insecticide will provide users with a new active ingredient to control aphids, leafhoppers and whiteflies in greenhouse tomato, pepper, cucumber, lettuce and ornamental crops and on outdoor ornamental plants, and to control aphids on Christmas trees. Registration of flupyradifurone for several of those uses was identified as a priority by Canadian growers. These products will be the first registered for leafhoppers in greenhouse vegetable crops and may aid in resistance management of the other pests, for which there are registered alternatives.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Flupyradifurone TC and the EPs BCS 2960 Insecticide and Altus Insecticide, containing the technical grade active ingredient flupyradifurone, to control aphids, whiteflies and leafhoppers on greenhouse vegetables and ornamental crops, and on outdoor ornamentals, and to control aphids on Christmas trees.

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
a.i.	active ingredient
ADI	acceptable daily intake
AHETF	Agricultural Handlers Exposure Task Force
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
ATPD	area treated per day
BBCH	Biologische Bundesanstalt, Bundessortenamt und Chemische Industrie
bw	body weight
CAF	composite assessment factor
cm	centimetre(s)
cm ²	square centimetre(s)
DFA	difluoroacetic acid
DFR	dislodgeable foliar residue
EP	end-use product
FDA	<i>Food and Drugs Act</i>
g	gram(s)
ha	hectare(s)
HAFT	highest average field trial
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
IRAC	Insecticide Resistance Action Committee
kg	kilogram(s)
L	litre(s)
LAFT	lowest average field trial
LC ₅₀	lethal concentration 50%
LD ₅₀	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOQ	limit of quantitation
Max	maximum
mg	milligram(s)
Min	minimum
mL	millilitre(s)
MOE	margin of exposure
MRL	maximum residue limit
n	number of trials
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
PCPA	<i>Pest Control Products Act</i>
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million

Reg. No.	registration number
REI	restricted-entry interval
RQ	risk quotient
RTI	retreatment interval
SDEV	standard deviation
SOP	standard operating procedure
STMdR	supervised trial median residue
TC	transfer coefficients
TSMP	Toxic Substances Management Policy
USA	United States
USEPA	United States Environmental Protection Agency

Appendix I Tables and Figures

Table 1 Toxicology Reference Values for Use in Human Health Risk Assessment for Flupradifurone

Exposure Scenario	Study	Point of Departure and Endpoint	CAF or Target MOE ¹
Acute dietary – general population	Acute oral neurotoxicity study in the rat	NOAEL = 35 mg/kg bw/day Piloerection, dilated pupils	100
	ARfD (general population) = 0.4 mg/kg bw		
Acute dietary – females 13-49 years of age	Oral developmental toxicity studies in the rabbit	Developmental NOAEL = 40 mg/kg bw/day, based on increased fetal deaths and reduced fetal body weight	300 ²
	ARfD (females 13-49 years) = 0.1 mg/kg bw		
Chronic dietary	Two co-critical studies: Two-generation dietary reproductive toxicity study in the rat One-year dietary study in the dog	NOAEL = 7.8 mg/kg bw/day Offspring NOAEL = 7.8 mg/kg bw/day in the two-generation reproductive toxicity study in rats, based on reduced offspring body weights NOAEL = 7.8 mg/kg bw/day in the one-year dietary study in the dog, based on reduced body weight and skeletal muscle myofiber degeneration	100
	ADI = 0.08 mg/kg bw/day		
Short-term, intermediate-term, long-term dermal ³ and inhalation ⁴	Two co-critical studies: Two-generation dietary reproductive toxicity study in the rat One-year dietary study in the dog	NOAEL = 7.8 mg/kg bw/day Offspring NOAEL = 7.8 mg/kg bw/day in the two-generation reproductive toxicity study in rats, based on reduced offspring body weights NOAEL = 7.8 mg/kg bw/day in the one-year dietary study in the dog, based on reduced body weight and skeletal muscle myofiber degeneration	100
Short-term, intermediate-term, long-term aggregate risk assessment (all routes)	Two co-critical studies: Two-generation dietary reproductive toxicity study in the rat One-year dietary study in the dog	NOAEL = 7.8 mg/kg bw/day Offspring NOAEL = 7.8 mg/kg bw/day in the two-generation reproductive toxicity study in rats, based on reduced offspring body weights NOAEL = 7.8 mg/kg bw/day in the one-year dietary study in the dog, based on reduced body weight	100
Cancer	A cancer risk assessment was not required as there was no evidence on oncogenic potential.		

¹ CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments.

² Includes a 3-fold PCPA factor to account for a serious endpoint (fetal death) observed in the presence of maternal toxicity.

³ Since an oral NOAEL was selected, a dermal absorption factor of 9% was used in a route-to-route extrapolation.

⁴ Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 2 Dermal and Inhalation Exposure and Risk for Mixer/Loader/Applicators Handling Flupyradifurone

Scenario (Unit Exposure Database)	Application Rate	ATPD	Dermal			Inhalation			Combined MOE ⁵
			Unit Exposure Value (µg/kg a.i. handled)	Exposure (mg/kg bw/day) ³	MOE ⁴	Unit Exposure Value (µg/kg a.i. handled)	Exposure (mg/kg bw/day) ³	MOE ⁴	
Airblast (AHETF)	0.2 kg a.i./ha ¹	20 ha/day	3827.8	0.05358	146	9.71	0.0004855	16100	144
Groundboom (AHETF)		360 ha/day	83.9	0.02114	369	2.31	0.002079	3750	336
Drench Chemigation	0.4 kg a.i./ha ¹	2 ha/day	58.50	0.00016	47600	0.63	0.0000063	1240000	45900
Mechanically-pressurized handgun (PHED)	0.0004 kg a.i./L ²	3800 L/day	5585.49	0.02971	262	151.00	0.002869	34900	239
Manually-pressurized handwand (PHED)		150 L/day	943.37	0.00020	39400	45.20	0.0000339	8260	33600
Backpack (PHED)		150 L/day	5445.85	0.00114	6820	62.10	0.00004658	1930	6550

¹ Application Rate (kg a.i./ha) = Maximum Application Rate (g a.i./ha) x Conversion Factor (kg/1000g)

² Application Rate (g a.i./L) = Maximum Application Rate (g a.i./ha) ÷ Minimum Spray Volume (500 L/ha) x Conversion Factor (kg/1000g)

³ Exposure (mg/kg bw/day) = Application Rate x ATPD x Unit Exposure (µg/kg a.i. handled) x Conversion Factor (mg/1000 µg) x Absorption Factor ÷ Body Weight (80 kg)

⁴ Calculated MOE = NOAEL of 7.8 mg/kg bw/day ÷ Exposure (mg/kg bw/day); Target MOE = 100

⁵ Combined MOE = NOAEL of 7.8 mg/kg bw/day ÷ Exposure (Dermal + Inhalation (mg/kg bw/day)); Target MOE = 100

Table 3 Post-application Exposure and Risk Estimate for Flupyradifurone on Day 0 After the Last Application

Crop/Re-entry activity	Peak DFR ($\mu\text{g}/\text{cm}^2$)	Transfer coefficient (cm^2/hr) ²	Dermal exposure ($\text{mg}/\text{kg bw}/\text{day}$) ³	MOE ⁴	REI (days) ⁵
Christmas Trees – Handset irrigation	0.554 ¹	1750	0.0087	893	0.5
Outdoor Nursery and Landscape Ornamentals – Handset irrigation	0.739 ¹	1750	0.0116	670	0.5
Greenhouse Tomatoes & Cucumbers – All	0.365 ⁶	1400	0.0046	1700	0.5
Greenhouse Peppers – All	0.368 ⁷	1400	0.0046	1680	0.5
Greenhouse Lettuce – All	0.365 ⁶	230	0.0008	10300	0.5
Greenhouse Ornamentals, Cut flowers - Hand harvesting, pruning	0.518 ⁸	4000	0.0187	418	0.5
Greenhouse Ornamentals, potted flowers - Hand harvesting, pruning	0.518 ⁸	230	0.0011	7270	0.5

¹ Calculated using the default 25% fraction dislodgeable on the day of application and 10% dissipation per day.

² SPN2014-02

³ Dermal Exposure = (Peak DFR [$\mu\text{g}/\text{cm}^2$] \times TC [cm^2/hr] \times 8 hours \times 9% dermal absorption / (80 kg bw \times 1000 $\mu\text{g}/\text{mg}$)

⁴ Based on a NOAEL of 7.8 mg/kg bw/day, target MOE = 100

⁵ Minimum REI is 12 hours (0.5 days) to allow residues to dry.

⁶ The predicted peak DFR value at Day 0 after the second application from the DFR study on greenhouse tomatoes with a 7-day RTI.

⁷ The study peak DFR value at Day 0 after the second application from the DFR study on greenhouse tomatoes with a 10-day RTI.

⁸ The study peak DFR value at Day 0 after the second application multiplied by the ratio of the use pattern and study application rates.

Table 4 Residential Post-application Dermal Exposure and Risk Immediately After 2 Applications¹

Lifestage	DFR ($\mu\text{g}/\text{cm}^2$) ²	Transfer Coefficient (cm^2/hr)	Exposure Time (hr/day)	Dermal Exposure ($\text{mg}/\text{kg bw}/\text{day}$)	Dermal MOE
Gardens					
Adult	0.739	8,400	2.2	0.0154	508
Children	0.739	4,600	1.1	0.0105	742
Trees and Retail Plants					
Adult	0.739	1,700	1	0.00141	5520
Children	0.739	930	0.5	0.000967	8070

¹ Refer to the 2012 USEPA Residential SOP – Section 4 for a full explanation of the algorithms calculating dermal exposure to treated ornamentals.

² The DFR value is based on the Peak DFR for Outdoor Nursery and Landscape Ornamentals from Table 3.

Table 5 Aggregate Risk from Chronic Dietary Exposure and Dermal Exposure to Treated Gardens

Lifestage	Dermal Exposure (mg/kg bw/day) ¹	Dietary Exposure (mg/kg bw/day) ²	Aggregate Exposure (mg/kg bw/day)	Aggregate MOE
Adult (16 – 80 years)	0.0154	0.008555	0.0239	326
Children (6 < 11 years)	0.0105	0.006744	0.0173	452

¹ Refer to exposure calculation to treated gardens presented in Table 4

² Refer to Food Residue section of this proposed regulatory decision document.

³ Aggregate Exposure (mg/kg bw/day) = Dermal Exposure + Dietary Exposure

⁴ Aggregate MOE = NOAEL (7.8 mg/kg bw/day) ÷ Aggregate Exposure; Target MOE = 100

Table 6 Integrated Food Residue Chemistry Summary

For more information on residue chemistry, refer to the Proposed Registration Decision, PRD2014-20, *Flupyradifurone*.

Crop Field Trials with Flupyradifurone (BYI 02960)									
The applicant submitted greenhouse trials conducted in North America and in Europe (sweet peppers only) where tomatoes, peppers, cucumbers, and leaf lettuce received foliar and soil drench applications of EPs BYI 02960 200SL or Sivanto SL 200. For all trials, the applicant collected residue data for flupyradifurone, and difluoroacetic acid (DFA) using an adequate data collection method. Adequate storage stability data are available on diverse crop types. Average residues of flupyradifurone generally decreased with increasing PHI, but average residues of DFA often increased at longer pre-harvest intervals.									
Greenhouse Tomatoes – 2012 Growing Season							PMRA# 2588877		
Commodity	Total Application Rate, [g a.i./ha]	PHI (days)	n	Max.	LAFT	HAFT	Median	Mean	SDEV
Flupyradifurone Residues (ppm)									
Tomatoes	411-432	1	6	0.73	0.08	0.66	0.20	0.25	0.21
DFA Residues, expressed as parent equivalents (ppm)									
Tomatoes	411-432	1	6	0.05	0.02	0.05	0.02	0.02	0.01
Greenhouse Peppers in USA - 2013-2014 Growing Seasons							PMRA# 2588880		
Flupyradifurone Residues (ppm)									
Bell pepper	411-427	3	2	0.016	<0.010	0.014	--	0.012	--
Non-bell pepper		3	2	0.029	0.020	0.026	--	0.023	--
DFA Residues, expressed as parent equivalents (ppm)									
Bell pepper	411-427	3	2	<0.020	<0.020	<0.020	--	<0.020	--
Non-bell pepper		3	2	<0.020	<0.020	<0.020	--	<0.020	--
Greenhouse Sweet Peppers in EU- 2011 Growing Season							PMRA# 2588879		
Commodity	Total Application Rate, [g a.i./ha]	PHI (days)	n	Min.	Max.	Median	Mean	SDEV	
Flupyradifurone Residues (ppm)									
Sweet pepper	350-450	3	5	0.088	0.240	0.120	0.144	0.058	
DFA Residues, expressed as parent equivalents (ppm)									
Sweet pepper	350-450	3	5	<0.020	0.062	<0.020	0.030	0.018	

Greenhouse Cucumbers - 2012-2013 Growing Seasons							PMRA# 2588878		
Commodity	Total Application Rate, [g a.i./ha]	PHI (days)	n	Max.	LAFT	HAFT	Median	Mean	SDEV
Flupyradifurone Residues (ppm)									
Cucumber	402-417	1	5	0.250	0.135	0.225	0.175	0.181	0.036
DFA Residues, expressed as parent equivalents (ppm)									
Cucumber	402-417	1	5	0.190	0.045	0.175	0.100	0.112	0.066
Greenhouse Leaf Lettuce - 2013-2014 Growing Seasons							PMRA# 2588881		
Flupyradifurone Residues (ppm)									
Leaf lettuce	419-430	1	4	22.07	9.02	21.06	17.46	16.25	5.32
DFA Residues, expressed as parent equivalents (ppm)									
Leaf lettuce	419-430	1	4	0.057	0.020	0.055	0.033	0.035	0.016

Table 7 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT AND RISK ASSESSMENT Primary crops (Apples, cotton, paddy rice, tomatoes, potatoes) Rotational crops (Wheat, Swiss chard, turnips)	<u>Enforcement:</u> Flupyradifurone <u>Dietary Exposure:</u> Flupyradifurone and DFA, expressed as parent equivalents
METABOLIC PROFILE IN DIVERSE CROPS	<p>The metabolic pathways in the five crops, irrespective of application types (soil, foliar, seed) are qualitatively similar and well understood based on characterization and identification of the residues. The metabolic pathway in confined rotational crops is similar to that in primary crops. Flupyradifurone is generally the predominant residue, including DFA, which was observed in all plant metabolism studies. DFA is also a rat metabolite.</p>
ANIMAL STUDIES	
ANIMALS	Ruminant and Poultry
RESIDUE DEFINITION FOR ENFORCEMENT AND RISK ASSESSMENT	<u>Enforcement:</u> Flupyradifurone <u>Dietary Exposure:</u> Flupyradifurone and DFA, expressed as parent equivalents
METABOLIC PROFILE IN ANIMALS (goat, hen, rat)	<p>The metabolism in ruminants qualitatively mirrors that of plants. Metabolism is limited, with flupyradifurone as the predominant residue in all commodities. In milk, complete degradation of the parent (degradation of the furanone moiety) and reincorporation is indicated by the presence of radiolabeled lactose. Other metabolic pathways are indicated by the presence of 6-CNA from the cleavage of the pyridinylmethylamine bond and the presence of BYI 02960-OH-gluA from hydroxylation of the furanone moiety. The metabolism in poultry is much more extensive than in plants or ruminants, as evidenced by the low or no concentrations of flupyradifurone in eggs and tissues. The majority of the radiolabeled residue was characterized as fatty acids.</p>

	The majority of the minor metabolites found are consistent with metabolites found in the ruminant and in the rat.		
FAT SOLUBLE RESIDUE	No		
DIETARY RISK FROM FOOD AND WATER			
Refined chronic non-cancer dietary exposure analysis ADI = 0.08 mg/kg bw/day Estimated chronic drinking water concentration = 0.264 ppm	POPULATION	ESTIMATED RISK	
		% of ACCEPTABLE DAILY INTAKE (ADI)	
		Food Alone	Food and Water
	All infants	8.2	33.1
	Children 1–2 years	17.4	26.6
	Children 3 to 5 years	12.2	19.7
	Children 6–12 years	6.9	12.5
	Youth 13–19 years	3.8	8.5
	Adults 20–49 years	4.3	11.0
	Adults 50+ years	4.8	11.2
Females 13-49 years	4.4	10.9	
Total population	5.4	12.1	
Refined acute dietary exposure analysis, 95th percentile ARfD_{♀13-49} = 0.1 mg/kg bw/day ARfD_{Total} = 0.4 mg/kg bw/day Estimated acute drinking water concentration = 0.267 ppm	POPULATION	ESTIMATED RISK	
		% of ACUTE REFERENCE DOSE (ARfD)	
		Food Alone	Food and Water
	All infants	11.7	18.1
	Children 1–2 years	18.4	21.4
	Children 3 to 5 years	14.2	16.4
	Children 6–12 years	8.8	10.8
	Males 13-19 years	5.2	7.2
	Males 20-49 years	5.7	7.9
	Adults 50+ years	6.8	8.6
Females 13-49 years	25.2	34.6	

Table 8 Effects of flupyradifurone and Sivanto 200 SL formulations on bees

PMRA #	Test organism	Test substance	Test condition	Endpoint from new study data	Existing endpoint reported in PRD2014-20), comparison and comments	Degree of toxicity* (for new data)
2616174	Bumblebee	TGAI	48-h oral toxicity on bumblebee at 1.81, 2.77, 4.17, 5.69 or 8.52 µg a.i./bumblebee	48-h LD ₅₀ : > 8.52 µg a.i./ bumblebee, the highest test concentration	NA The 48-h acute oral and contact LD ₅₀ values show that bumblebees are less sensitive to flupyradifurone than honeybees; therefore the risk mitigation measures stated in RD2015-24 for honeybees are expected to be protective of bumblebees. Further refinements to the risk assessment are not required.	NA
2588821	Bumblebee	Sivanto	48-h contact toxicity on bumblebee at 6.25, 12.5, 25, 50 and 100 µg a.i./bumblebee	LD ₅₀ (24/48-h): >100 µg a.i./ bumble bee, the highest test concentration.		
2588890	Adult honeybee	TGAI	10-d continuous exposure test (chronic feeding) on adult bees: TGAI at 10, 16, 26, 41 and 66 mg a.i./kg diet.	NOEC = 26 mg a.i./kg diet (0.79 µg a.i./bee/d); LC ₅₀ = 61.1 mg a.i./kg diet (1.83 µg a.i./bee/d)	NOEC = 10 mg a.i./kg diet (0.464 µg a.i./bee/d) The previous study did not produce a definitive endpoint as there was no effect at the highest test concentration.	NA
2588822	Honeybee	Sivanto + Tebuconazole EW 250C G	48-h acute contact toxicity on honey bee with FPD alone at 110.2, 35.3, 11.0, 3.53, 1.10 and 0.35 µg FPD/bee; with mixture of FPD and TEU at 35.3 µg FPD+116.2 µg TEU/bee, 11.0 µg FPD+36.3 µg TEU/bee, 3.53 µg FPD+11.6 µg TEU/bee, 1.10 µg FPD+3.63 µg TEU/bee and 0.35 µg FPD+1.16 µg TEU/bee (1:3.3 ratio)	FPD alone: 48-h LD ₅₀ >110 µg a.i./bee (the highest dose tested) TEU alone: 48-h LD ₅₀ >176 µg a.i./bee (tested with TGAI, REG2006-11) FPD+TEU: 48-h LD ₅₀ -FPD = 11.0 µg a.i./bee (95% CI: 7.5-16.0 µg a.i./bee) FPD+TEU: 48-h LD ₅₀ -TEU = 36.2 µg a.i./bee (95% CI: 24.8-52.8 µg a.i./bee)	FPD+TEU at 1:7.5 a.i. ratio: 48-h oral LD ₅₀ -FPD = 0.2 µg a.i./ bee; 72-h contact LD ₅₀ -FPD = 1 µg a.i./bee Mixture was more than 10 and 4.8 times more toxic than FPD and TEU alone, respectively – synergistic effect. Comparing to previous results, it appears that an increase in tebuconazole in the mixture increases the synergistic effect on honeybees.	Relatively non-toxic either alone or in mixture

PMRA #	Test organism	Test substance	Test condition	Endpoint from new study data	Existing endpoint reported in PRD2014-20), comparison and comments	Degree of toxicity* (for new data)
2588832	honeybee	Sivanto + Tebuconazole EW 250C G	Semi-field (tunnel) test at 200 g a.i. FPD and 150 g a.i. TEU/ha (4:3 a.i. mixing ratio). 7-d exposure and 21-d monitoring	No adverse effects on foraging activity, behaviour, nectar- and pollen storage, brood-abundance and brood-development, colony strength as well as on queen survival were observed throughout the entire duration of the study. On the day of application, a moderate, short-lived increase in mortality was observed in the test items treated group when compared to control.	NA This study has limited use as the mixing ratio was different than those used in the lab studies which showed enhanced toxicity with increasing concentrations of tebuconazole in the mixture.	NA
2588823	honeybee	Sivanto + Fluopyram SC 500B G	48-h acute contact toxicity on honey bee with FPD alone at 110.2, 35.3, 11.0, 3.53, 1.10 and 0.35 µg FPD/bee and with mixture of FPD and FPR at 35.3 µg FPD+47.5 µg FPR/bee, 11.0 µg FPD+14.9 µg FPR/bee, 3.53 µg FPD+4.75 µg FPR/bee, 1.10 µg FPD+1.49 µg FPR/bee and 0.35 µg FPD+0.48 µg FPR/bee	FPD alone: 48-h LD ₅₀ >110 µg a.i./bee (the highest dose tested) FPR (TGAI) alone: : 48-h LD ₅₀ >100 µg a.i./bee Luna Privilege G (FPR EP): 48-h LD ₅₀ >83.2 µg a.i./bee (ERC2014-02) FPD+FPR: 48-h LD ₅₀ -FPD >35.3 µg a.i./bee (the highest tested dose of FPD in the mixture)	NA No statistically significant increase of mortality was observed at comparable FPD concentration. The highest tested concentrations of FPD and FPR in the mixture were lower than the LD ₅₀ derived from tests with individual chemicals.	Relatively non-toxic either alone or in mixture

PMRA #	Test organism	Test substance	Test condition	Endpoint from new study data	Existing endpoint reported in PRD2014-20), comparison and comments	Degree of toxicity* (for new data)
2588824	honeybee	Sivanto + Trifloxystrobin WG 50 W	48-h acute contact toxicity on honey bee with FPD alone at 110.2, 35.3, 11.0, 3.53, 1.10 and 0.35 µg FPD/bee; with mixture of FPD and TFY at 35.3 µg FPD+40.0 µg TFY/bee, 11.0 µg FPD+12.5 µg TFY/bee, 3.53 µg FPD+4.00 µg TFY/bee, 1.10 µg FPD+1.25 µg TFY/bee and 0.35 µg FPD+0.40 µg TFY/bee	FPD alone: LD ₅₀ (24/48-h) >110 µg a.i./bee (the highest test dose); TFY TGAI alone: : 48-h LD ₅₀ >200 µg a.i./bee; Flint 50 WG (TFY EP): 48-h LD ₅₀ >200 µg EP/bee (>99.6 µg a.i./bee) (REG2004-03) FPD+TFY: LD ₅₀ (24/48-h) > 35.3 µg FPD/bee (the highest test dose of FPD in the mixture)	NA No statistically significant increase of mortality was observed at comparable FPD concentration. The highest tested concentrations of FPD and TFY in the mixture were lower than the LD ₅₀ derived from tests with individual chemicals.	Relatively non-toxic either alone or in mixture
2588825	honeybee	Sivanto + Propineb WG 70A W	48-h acute contact toxicity on honey bee with FPD alone at 110.2, 35.3, 11.0, 3.53, 1.10 and 0.35 µg FPD/bee and with mixture of FPD and PRP at 35.3 µg FPD+240.0 µg PRP/bee, 11.0 µg FPD+75.0 µg PRP/bee, 3.53 µg FPD+24.0 µg PRP/bee, 1.10 µg FPD+7.5 µg PRP/bee and 0.35 µg FPD+2.40 µg PRP/bee	FPD alone: LD ₅₀ (24/48-h) >110 µg a.i./bee (the highest test dose); FPD+PRP: LD ₅₀ (24/48-h) > 35.3 µg FPD/bee (the highest test dose of the mixture)	NA No statistically significant increase of mortality was observed at comparable FPD concentration. NOTE: Propineb is not registered in Canada.	Relatively non-toxic either alone or in mixture

PMRA #	Test organism	Test substance	Test condition	Endpoint from new study data	Existing endpoint reported in PRD2014-20), comparison and comments	Degree of toxicity* (for new data)
2588826	honeybee	Sivanto + Pyrimethanil SC 300 G	48-h acute contact toxicity on honey bee with FPD alone at 110.2, 35.3, 11.0, 3.53, 1.10 and 0.35 µg FPD/bee and with mixture of FPD and PYI at 35.3 µg FPD+225 µg PYI/bee, 11.0 µg FPD+70.4 µg PYI/bee, 3.53 µg FPD+22.5 µg PYI/bee, 1.10 µg FPD+7.04 µg PYI/bee and 0.35 µg FPD+2.25 µg PYI/bee	FPD alone: LD ₅₀ (24/48-h) >110 µg a.i./bee (the highest test dose); PYI (TGAI) alone: 48-h LD ₅₀ > 100 µg a.i./bee (REG2006-04) FPD+PYI: 48-h LD ₅₀ > 35.3 µg FPD/bee (the highest test dose of the mixture)	NA No statistically significant increase of mortality was observed at comparable FPD concentration. The highest tested concentrations of FPD and TFY in the mixture were lower than the LD ₅₀ derived from tests with individual chemicals. The Pyrimethanil EP used in the mixture was not registered in Canada.	Relatively non-toxic either alone or in mixture

PMRA #	Test organism	Test substance	Test condition	Endpoint from new study data	Existing endpoint reported in PRD2014-20), comparison and comments	Degree of toxicity* (for new data)
2588831	Residues in <i>phacelia</i> collected by forager bees	Sivanto (BYI 02960 SL 200 G)	Residue measurements in pollen and nectar of <i>phacelia</i> after two spray applications at 200 g a.i./ha each time and 10 days apart. The first application was 7 days before hive setup in the tunnel and just before onset of flowering at BBCH 58-60. The second application occurred 3 days after hive setup in the tunnel during full blooming (BBCH 65) and when honeybees were actively foraging.	Residue of TGAI in pollen from comb: 139-22529 µg a.i./kg and from forager bees: 138-70667 µg a.i./kg; residues in nectar from combs: <LOQ-186 µg a.i./kg and from forager bees: 4.8-3304 µg a.i./kg. The highest measured concentrations were measured within 1-2.5 hours after second application. Average residues in pollen from forager bees at 1, 2.5, 4 and 24 hours were 64743, 63271, 36126 and 10354 µg a.i./kg, respectively; and in nectar were 3048, 2265, 1435 and 752 µg a.i./kg, respectively. Residue of a major transformation product, DFEEAF, in pollen from comb: 1.6-46 µg/kg and from forager bees: 1.3-135 µg /kg; residues in nectar from combs: <LOD-9.4 µg /kg and from forager bees: <LOQ-122 µg /kg. Note: numbers quoted above are individual minimum and maximum detects. Over the 10-day study period, the mean residue concentrations in pollen from forager bees was 15 001 µg a.i./kg and in nectar from forager bees was 652.5 µg a.i./kg. The mean residue concentrations in pollen from combs was 4868 µg a.i./kg and in nectar from combs was 67.2 µg a.i./kg.	In a similar study where blooming apple trees were sprayed twice with Sivanto at 200 g a.i./ha each (PMRA # 2236665), the highest residues in pollen and nectar from forager bees were found at 39 ppm on honeybee legs and 1.5 ppm in nectar from forage bees one day after the second application. These residue levels were higher than that detected in the new study at the same sampling interval (10.4 and 0.75 ppm, respectively). No samples were taken hours after second application. Using the same endpoints reported in PRD2014-20 and the highest individually measured residue concentrations in pollen and nectar, the RQ values for adult honeybees was 0.94 on an acute basis, greater than the LOC of 0.4. However, residue concentrations in pollen and nectar declined rapidly to 36126 and 1435 µg a.i./kg after 4 hours and to 10354 and 752 µg a.i./kg (mean) after 1 day, respectively. The corresponding acute RQ values decreased to 0.54 and 0.23, respectively. On a chronic basis, the average residue concentrations in pollen and nectar detected in the 10-day exposure period in the tunnel were used to calculate the RQ, which resulted in RQ values of 0.51 and 0.25 for adult and larvae, both were below LOC.	

* According to Atkins *et al.* (1981) classification schemes.

Table 9 Risk Assessment for Honeybees using Pollen and Nectar Residues Obtained From Newly Reviewed Data

Application method	Application rate	Honeybee stage	Toxicity endpoint ¹	Residue from forager bees (ppb) ²		RQ	Does RQ exceed LOC ⁴ ?
Foliar spray	200 g a.i./ha	Adult	Acute oral LD ₅₀ : 1.2 µg a.i./bee	Max. in pollen after 1 hour	69 911	0.94	Yes
				Max. in nectar after 1 hour	3304		
				Max. in pollen after 2 hour	70 667	0.88	Yes
				Max. in nectar after 2 hour	2726		
				Max. in pollen after 4 hour	42 126	0.54	Yes
				Max. in nectar after 4 hour	1709		
				Max. in pollen after 24 hour	16 113	0.23	No
				Max. in nectar after 24 hour	871		
		Adult	Chronic oral NOEL: 0.464 µg a.i./bee	Mean in pollen ³	15 001	0.51	No
		Larvae	Chronic oral NOEL: 0.55 µg a.i./bee	Mean in nectar ³	652.5	0.25	No

¹ All endpoints on honeybees were obtained from PRD2014-20.

² Maximum concentration detected in individual samples during the sampling intervals after 2nd application.

³ Mean residue concentrations over 10-day exposure period in the tunnels.

⁴ Levels of concern (LOC) for acute and chronic risk are RQ values of 0.4 and 1.0, respectively.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2236628	2011, Physical, chemical and technical properties of BYI 02960 SL 200 (200 g/L) - BYI 02960 SL 200 G - Amendment no.: 1, DACO: 3.5.1,3.5.2,3.5.3,3.5.6,3.5.7,3.5.9,3.7,8.2.3.6,IIIA 2.1,IIIA 2.4.2,IIIA 2.5.1,IIIA 2.5.2,IIIA 2.5.3,IIIA 2.6.1,IIIA 2.8.2,IIIA 2.8.4 CBI
2236631	2012, Storage stability data of BYI 02960 SL 200 (200 g/L) - [Packaging material:HDPE], DACO: 3.5.10,3.5.14,3.5.5,IIIA 2.13,IIIA 2.14,IIIA 2.7.2 CBI
2236632	2012, Storage stability and shelf life of BYI 02960 SL 200 (200 g/L) - [Packaging material:HDPE] - Final report (2 years), DACO: 3.5.10,3.5.14,IIIA 2.13,IIIA 2.7.2 CBI
2236635	2012, Safety relevant technical properties of BYI 02960 SL 200 (200 g/L) - Final report -, DACO: 3.5.11,3.5.12,3.5.8,IIIA 2.2.1,IIIA 2.2.2,IIIA 2.3.1,IIIA 2.3.3 CBI
2236642	2012, Determination of BYI 02960 in formulations - Assay HPLC, external standard, DACO: 3.4.1,IIIA 5.2.1 CBI
2236643	2010, Validation of HPLC-method AM012609MF1 - Determination of BYI 02960 in formulations - BYI 02960 SL 200 (200 g/L), DACO: 3.4.1,IIIA 5.2.1 CBI
2236690	2012, Manufacturing procedure plant protection product flupyradifurone SL 200 (200 g/L) - BYI 2960SL 200, DACO: 3.2.2,IIIA 1.4.5.1 CBI
2762325	2017, Determination of [CBI REMOVED] on 6 batches of Flupyradifurone, DACO: 2.11.3 CBI
2762326	2017, Flupyradifurone (BYI 02960) Description of the Manufacturing Process of the Technical Grade Active Substance for Canada, DACO: 2.11.4 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
2768791	2017, Justification for Waiving the 90-Day Inhalation Study for BCS 2960 Insecticide and Altus Insecticide, DACO: 4.3.6
1913109	2009, Agricultural Handler Exposure Scenario Monograph: Open Cab Groundboom Application of Liquid Sprays, DACO: 5.3,5.4
2004944	2010, Agricultural Handler Exposure Scenario Monograph: Open Cab Airblast Application of Liquid Sprays, DACO: 5.3,5.4
2236641	2012, BYI 02960 (SL200) - In vivo dermal absorption study in the male rat, DACO: 5.8,IIIA 7.6.1

PMRA Document Number	Reference
2236650	2012, BYI 02960 (SL200) - Comparative in vitro dermal absorption study using human and rat skin, DACO: 5.8,IIIA 7.6.2
2588873	2012, Determination of the dislodgeable foliar residues (DFR) of BYI 02960 after spraying of BYI 02960 SL 200 on roses in the greenhouse in the Netherlands, DACO: 5.9
2588874	2012, Determination of the dislodgeable foliar residues (DFR) of BYI 02960 after spraying of BYI 02960 SL 200 on tomatos in the greenhouse in Spain, DACO: 5.9
2761179	2012, Analytical method 01204 for the determination of BYI 02960 in leaf punches washings solution by HPLC-MS/MS, DACO: 5.9(A)
2790272	2012, Determination of the dislodgeable foliar residues (DFR) of the BYI 02960 metabolite difluoroacetic acid (DFA) after spraying of BYI 02960 SL 200 on tomatos in the greenhouse in Spain, DACO: 5.9(A)
2588877	2015, BYI 02960 - Magnitude of the residue on tomato (greenhouse), DACO: 7.4.1,7.4.2
2588878	2015, BYI 02960 - Magnitude of the residue on cucumber (greenhouse), DACO: 7.4.1,7.4.2
2588879	2012, Determination of the residues of BYI 02960 in/on sweet pepper after spraying of BYI 02960 SL 200 in the greenhouse in France, Spain, Italy, Greece and the Netherlands, DACO: 7.4.1,7.4.2
2588880	2015, Flupyradifurone (BYI 02960): Magnitude of the residue on pepper (greenhouse), DACO: 7.4.1,7.4.2
2588881	2015, Flupyradifurone: Magnitude of the residue on lettuce, greenhouse, DACO: 7.4.1,7.4.2

3.0 Environment

PMRA Document Number	Reference
2588821	2012. Flupyradifurone SL 200 G: Acute contact toxicity to the bumblebee <i>Bombus terrestris</i> L. (Hymenoptera, Apidae) under laboratory conditions (multi doses test). DACO 9.2.4.1.
2588822	2012. Effects of a test item mix of BYI 02960 SL 200 G + tebuconazole (HWG 1608) EW 250C G (acute contact) on honey bees (<i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.4.1.
2588823	2012. Effects of a test item mix of flupyradifurone (BYI 02960) SL 200 G + fluopyram SC 500B G (acute contact) on honey bees (<i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.4.1.
2588824	2012. Effects of a test item mix of flupyradifurone (BYI 02960) SL 200 G + trifloxystrobin WG 50 W (acute contact) on honey bees (<i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.4.1.
2588825	2012. Effects of a test item mix of flupyradifurone (BYI 02960) SL 200 G + propineb WG 70A W (acute contact) on honey bees (<i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.4.1.

PMRA Document Number	Reference
2588826	2012. Effects of a test item mix of flupyradifurone (BYI 02960) SL 200 G + pyrimethanil SC 300 G (acute contact) on honey bees (<i>Apis mellifera</i> L.) in the laboratory. DACO 9.2.4.1.
2588831	2013. Determination of residues of BYI 02960 after application of BYI 02960 SL 200 G once before and once during flowering in a semi-field honeybee (<i>Apis mellifera</i> L.) study in <i>Phacelia tanacetifolia</i> in 2012. DACO 9.9.
2588832	2014. Toxicity testing of a tank mix of flupyradifurone (BYI 02960) SL 200 G + tebuconazole EW 250C G on honey bees (<i>Apis mellifera</i> L.) under semi-field conditions - Tunnel test. DACO 9.9.
2588890	2013. Assessment of chronic effects of BYI 02960 tech. to the honey bee, <i>Apis mellifera</i> L., in a 10 days continuous laboratory feeding test. DACO 9.9.
2616174	2016. Flupyradifurone (BYI 02960): Acute Oral Toxicity to the Bumble Bee, <i>Bombus terrestris</i> L. under Laboratory Conditions. DACO 9.2.4.2.

4.0 Value

PMRA Document Number	Reference
2588848	2015, Value assessment of Sivanto Prime insecticide (flupyradifurone) for aphid control on christmas trees, DACO: 10.1, 10.2.3.1, 10.2.3.3, 10.3.1, 10.3.2, 10.5.1, 10.5.2, 10.5.3, 10.5.4, 10.5.5
2588849	2015, BCS 2960 Insecticide for the control of leafhoppers in the greenhouse as a foliar spray application, DACO: 10.1, 10.2.3.1, 10.2.3.3, 10.3.2, 10.5.5
2588850	2015, Efficacy and tolerance of Sivanto 200 SL insecticide (Flupyradifurone) for whitefly management on greenhouse ornamentals (including cut flowers, perennials and annuals), DACO: 10.1, 10.2.3.1, 10.2.3.3(D), 10.3.1, 10.3.2
2588851	2015, Efficacy and tolerance of Sivanto 200 SL (flupyradifurone) for control of aphids and whiteflies in greenhouse lettuce, DACO: 10.1, 10.2.3.1, 10.2.3.3(D), 10.3.1, 10.3.2
2588852	2015, Efficacy and tolerance of Sivanto SL insecticide (flupyradifurone) for control of aphids and whiteflies in greenhouse tomato, pepper and cucumber, DACO: 10.1, 10.2.3.1, 10.2.3.3(D), 10.3.1, 10.3.2
2588853	2015, BCS 2960 Insecticide a 200 g/L formulation of the active ingredient flupyradifurone for the control of insect pests in the greenhouse as a drench application, DACO: 10.1, 10.2.3.1, 10.2.3.3(D), 10.3.1, 10.3.2, 10.5.1, 10.5.2, 10.5.3, 10.5.4, 10.5.5
2588854	2015, Efficacy and tolerance of Sivanto 200 SL insecticide (Flupyradifurone) for whitefly management on greenhouse ornamentals (including cut flowers, perennials and annuals), DACO: 10.2.3.1, 10.2.3.3(D), 10.3.2(B)

PMRA Document Number	Reference
2588855	2015, Efficacy and tolerance of Sivanto 200 SL (flupyradifurone) for control of aphids and whiteflies in greenhouse lettuce, DACO: 10.2.3.1, 10.2.3.3(D), 10.3.2(B)
2588856	2015, Efficacy and tolerance of Sivanto SL insecticide (flupyradifurone) for control of aphids and whiteflies in greenhouse tomato, pepper and cucumber, DACO: 10.2.3.1, 10.2.3.3(D), 10.3.2(B)
2588857	2015, BCS 2960 Insecticide - Rationale for Control of Aphids in Greenhouse Ornamentals, DACO: 10.2.3.1, 10.2.3.3(D), 10.3.2(B)
2588858	2015, BCS 2960 Insecticide - Rationale for Use in Outdoor Nursery and Landscape Ornamentals, DACO: 10.2.3.1, 10.2.3.3(D), 10.3.2(B)
2588862	2015, Value assessment of Sivanto Prime insecticide (flupyradifurone) for aphid control on christmas trees, DACO: 10.2.3.3(D), 10.3.2(B)
2588863	2015, BCS 2960 Insecticide a 200 g/L formulation of the active ingredient flupyradifurone for the control of insect pests in the greenhouse as a drench application, DACO: 10.2.3.3(D), 10.3.2(B)
2588864	2015, BCS 2960 Insecticide a 200 g/L formulation of the active ingredient flupyradifurone for the control of insect pests in the greenhouse as a drench application, DACO: 10.2.3.3(D), 10.3.2(B)
2658542	2016, BCS 2960 Insecticide - Deficiency Response, DACO: 10.2.3.1