Proposed Registration Decision PRD2020-10

Inpyrfluxam, Excalia Fungicide and Zeltera Fungicide

(publié aussi en français)

23 June 2020

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2020-10E (print version)
H113-9/2020-10E-PDF (PDF version)

Table of Contents

Overview

Proposed Registration Decision for Inpyrfluxam

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Inpyrfluxam Technical, Excalia Fungicide and Zeltera Fungicide, containing the technical grade active ingredient inpyrfluxam, to be applied foliarly and as a seed treatment on various crops.An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of inpyrfluxam, Excalia Fungicide and Zeltera Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

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

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of Canada.ca.

Before making a final registration decision on inpyrfluxam, Excalia Fungicide and Zeltera Fungicide, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration

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

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

3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

Decision[4] on inpyrfluxam, Excalia Fungicide and Zeltera Fungicide, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

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

What Is Inpyrfluxam?

Inpyrfluxam is a new conventional fungicide active ingredient that inhibits an enzyme involved in energy production in some fungi. It controls or suppresses economically important diseases of apple and field crops.

Health Considerations

Can Approved Uses of Inpyrfluxam Affect Human Health?

Excalia Fungicide and Zeltera Fungicide, containing inpyrfluxam, are unlikely to affect your health when used according to proposed label directions.

Potential exposure to inpyrfluxam may occur through the diet (food and drinking water) or when handling and applying the end-use products or when coming into contact with treated seeds. 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.

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

In laboratory animals, the technical grade active ingredient inpyrfluxam was of high acute toxicity by the oral route of exposure; consequently, the signal word and hazard statement "DANGER – POISON" are required on the label. It was of low acute toxicity dermally and through inhalation exposure. Inpyrfluxam was minimally irritating to the eyes and non-irritating to the skin, and did not cause an allergic skin reaction.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The acute toxicity of the end-use products Excalia Fungicide and Zeltera Fungicide containing inpyrfluxam was moderate via the oral route of exposure; consequently, the signal word and hazard statement "WARNING – POISON" are required on the labels. They were of low acute toxicity via the dermal and inhalation routes of exposure. They were non-irritating to the eyes and skin and did not cause allergic skin reactions.

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 inpyrfluxam to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on the liver and adrenal glands. There was no evidence of increased sensitivity of the young compared to adult animals. The risk assessment protects against the effects noted above and other potential effects by ensuring that the level of exposure to humans is well below the lowest dose level at which these effects occurred in animal tests.

Residues in Water and Food

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

Aggregate acute dietary (food plus drinking water) intake estimates for the general population and all population subgroups are expected to be less than 17% of the acute reference dose, and are not of health concern. Infants are the subpopulation expected to be subject to the highest exposure relative to body weight.

Aggregate chronic dietary (food plus drinking water) intake estimates for the general population and all population subgroups are expected to be less than or equal to 35% of the acceptable daily intake, and are not of health concern. Infants are the subpopulation expected to be subject to the highest exposure relative to body weight.

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.

MRLs for inpyrfluxam determined from the acceptable residue trials conducted throughout Canada and the United States on apples, canola, corn, peanuts, rice, sorghum, soybeans, and sugar beets can be found in the Science Evaluation of this consultation document.

Occupational Risks From Handling Excalia Fungicide

Occupational risks are not of concern when Excalia Fungicide, containing inpyrfluxam, is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Excalia Fungicide, as well as orchard or field workers entering freshly treated areas, may come in direct contact with inpyrfluxam residues on the skin and through inhalation. Therefore, the label of Excalia Fungicide specifies

that users must wear a long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair, unless specified otherwise. Gloves are not required during application within a closed-cab tractor. For application using handheld airblast/mistblower, workers must wear chemical-resistant coveralls with a chemical-resistant hood over long-sleeved shirt, long pants, chemical-resistant gloves, socks, chemical-resistant footwear and a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides or a NIOSH-approved canister approved for pesticides.

The label also requires that workers do not enter treated areas for 12 hours after application, and standard label statements to protect against drift during application are present on the label. Taking into consideration these label statements, the application timing, the number of applications and the duration of exposure for handlers and workers, health risks to these individuals are not of concern.

Occupational Risks From Handling Zeltera Fungicide

Occupational risks are not of concern when Zeltera Fungicide, containing inpyrfluxam, is used according to the proposed label directions, which include protective measures.

Workers treating seeds with Zeltera Fungicide in commercial facilities, with commercial mobile systems, or in on-farm settings, as well as workers planting or handling treated seeds, may come into direct contact with inpyrfluxam residues on the skin and through inhalation.

Therefore, the label of Zeltera Fungicide specifies that commercial handlers (including facility workers and mobile treaters) must use a closed-transfer system only, including closed mixing, loading, calibrating and closed treatment equipment, and must wear coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes during mixing, loading, treating, calibrating, bagging, sewing, stacking and cleaning.

For on-farm workers, the label of Zeltera Fungicide indicates that an open or closed transfer system can be used, and they must wear a long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes during mixing, loading, treating, calibrating, clean-up, repair and any other activities involving handling treated seeds. Planters of treated seeds must also wear a long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes. Open- or closed-cab tractors can be used while planting, and gloves are not required within a closed-cab tractor.

Taking into consideration these label statements, the number of applications and the duration of exposure for handlers and workers, health risks to these individuals are not of concern.

Risks in Residential and Other Non-Occupational Environments

Risks in residential and other non-occupational environments are not of concern when inpyrfluxam is used according to the proposed label directions.

Adults, youth and children, while pruning or maintaining apple trees, may come into direct contact with inpyrfluxam residues on foliage when apple trees in residential areas are treated with Excalia Fungicide by commercial applicators. However, when taking into consideration the label statements, the early application timing (in other words, no later than petal fall), the number of applications and the duration of exposure, health risks to these individuals are not of concern.

Non-occupational exposure in pick-your-own fruit scenarios in treated orchards are also not of health concern as the level of inpyrfluxam residues on foliage is expected to be negligible at the time of normal harvest in the fall when compared to the early timing of application in the spring.

Health Risks to Bystanders

Bystander risks are not of health concern when Excalia Fungicide and Zeltera Fungicide are used according to the proposed label directions and drift restrictions are observed.

A standard label statement to protect against drift during application is on both labels. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Inpyrfluxam Is Introduced Into the Environment?

When used according to label directions, the risks associated with the use of inpyrfluxam are acceptable from the viewpoint of environmental protection.

When inpyrfluxam is used as a foliar application or seed treatment to control fungal diseases, it can remain in the soil for months or years, depending on the soil type and conditions. Inpyrfluxam can move through the soil and, therefore, may reach groundwater. It may also move off the treatment area to reach surface waters such as ponds, streams and rivers. Transformation products of inpyrfluxam may move through soil more readily than the parent. Once in water, inpyrfluxam is expected to remain for a long period of time. Inpyrfluxam is not expected to be found in air, or travel long distances in the atmosphere from the location it is applied. Inpyrfluxam is not expected to accumulate in plant or animal tissue.

Inpyrfluxam does not present a risk to terrestrial invertebrates, bees, beneficial arthropods, aquatic invertebrates (including sediment dwelling invertebrates), algae and vascular aquatic plants. Inpyrfluxam may present a risk to birds, wild mammals and non-target plants adjacent to treated fields. In bodies of water, inpyrfluxam may present a risk to fish and amphibians. To minimize exposure to sensitive non-target species, spray buffer zones are required. In addition, precautionary statements and best management practices are required on the label. When inpyrfluxam is used in accordance with the label and the required precautions, the resulting environmental risk is considered to be acceptable.

Value Considerations

What Is the Value of Excalia Fungicide and Zeltera Fungicide?

Inpyrfluxam is the active ingredient in Excalia Fungicide and Zeltera Fungicide. The registration of these products will provide Canadian growers with a new option to manage important fungal diseases in several crops.

Excalia Fungicide is applied as a foliar spray to control or suppress various diseases of apple corn, soybean and sugar beet. Zeltera Fungicide is applied as a seed treatment to control or suppress certain seed and seedling diseases in particular cereal crops, corn, legume vegetables, soybean, rapeseed, including canola, and sugar beet, as well as sudden death syndrome in soybean and blackleg in canola.

Measures to Minimize Risk

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

The key risk-reduction measures being proposed on the label of Inpyrfluxam Technical, Excalia Fungicide and Zeltera Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is concern with users coming into direct contact with inpyrfluxam residues on the skin or through inhalation of spray mists, the label of Excalia Fungicide specifies that users must wear a long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair, unless specified otherwise. Gloves are not required during application within a closed-cab tractor. For application using handheld airblast/mistblower, workers must wear chemical-resistant coveralls with a chemical-resistant hood over long-sleeved shirt, long pants, chemical-resistant gloves, socks, chemical-resistant footwear and a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides or a NIOSH-approved canister approved for pesticides. The label also requires that workers do not enter treated areas for 12 hours after application, and standard label statements to protect against drift during application are present on the label.

The label of Zeltera Fungicide specifies that commercial handlers (including facility workers and mobile treaters) must use a closed-transfer system only, including closed mixing, loading, calibrating and closed treatment equipment, and must wear coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes during mixing, loading, treating, calibrating, bagging, sewing, stacking and cleaning.

For on-farm workers, the label of Zeltera Fungicide indicates that an open or closed transfer system can be used, and they must wear a long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes during mixing, loading, treating, calibrating, clean-up, repair and any other activities involving handling treated seeds. Planters of treated seeds must also wear a long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes. Open- or closed-cab tractors can be used while planting, and gloves are not required within a closed-cab tractor.

Furthermore, a standard label statement to protect against drift during application is present on the label.

Environment

To protect the environment, the following proposed risk mitigation measures are required:

- Label statements with spray buffer zones to reduce the risk of spray drift to terrestrial and aquatic ecosystems.
- Label statement indicating the potential for surface runoff from the soil surface is required when inpyrfluxam is used as foliar application.
- Label statement indicating the potential for movement to groundwater.
- Label statements indicating the toxicity to non target terrestrial plants, birds, mammals and aquatic organisms.

Next Steps

Before making a final registration decision on inpyrfluxam, Excalia Fungicide and Zeltera Fungicide, Health Canada's PMRA will consider any comments received from the public in response to this consultation document. Health Canada will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

Other Information

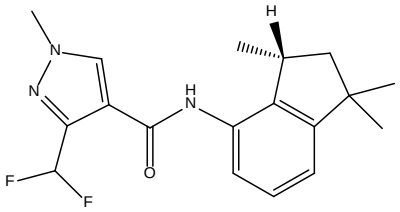
When Health Canada makes its registration decision, it will publish a Registration Decision on inpyrfluxam, Excalia Fungicide and Zeltera Fungicide (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for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

Science Evaluation

Inpyrfluxam, Excalia Fungicide and Zeltera Fungicide

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Inpyrfluxam
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	3-(difluoromethyl)-N-[(R)-2,3-dihydro-1,1,3-trimethyl-1H-inden-4-yl]-1-methyl-1H-pyrazole-4-carboxamide
2. Chemical Abstracts Service (CAS)	3-(Difluoromethyl)-N-[(3R)-2,3-dihydro-1,1,3-trimethyl-1H-inden-4-yl]-1-methyl-1H-pyrazole-4-carboxamide
CAS number	1352994-67-2
Molecular formula	$C_{18}H_{21}F_2N_3O$
Molecular weight	333.38 g/mol
Structural formula	
Purity of the active ingredient	97.4%

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

Technical Product—Inpyrfluxam Technical

Property	Result
Colour and physical state	Beige to white solid
Odour	No discernible odour
Melting range	104 ºC
Boiling point or range	No boiling point was determined below 237 ºC

Property	Result
Density	1.23 g/cm^3
Vapour pressure at 20 °C	3.8×10^{-8} kPa
Ultraviolet (UV)-visible spectrum	conditions / λ_{max} (nm) / ε (L/mol.cm) acidic / 242 / 1.05×10^4 290 / 1.31×10^3 neutral / 242 / 1.04×10^4 290 / 1.33×10^3 alkaline / 242 / 1.06×10^4 290 / 1.33×10^3
Solubility in water at 20 °C	1.64×10^{-2} g/L
Solubility in organic solvents at 20 °C	solvent / solubility (g/L) acetone / 645 dichloromethane / 366 ethyl acetate / 411 n-hexane / 1.02 methanol / 382 n-octanol / 87.8 toluene / 70.6
n-Octanol-water partition coefficient (K_{ow})	pH / log K_{ow} 7.1–7.3 / 3.6
Dissociation constant (pK_a)	No dissociative activity in the pH range 1 to 12
Stability (temperature, metal)	The technical grade active ingredient is stable to ~ 250 °C. The technical grade active ingredient is stable upon exposure to normal and elevated (54 ºC) temperatures, metals (iron and aluminium) and metal ions (iron II acetate and aluminium acetate) for 14 days.

End-Use Product—Excalia Fungicide

Property	Result
Colour	Off-white
Odour	Rancid odour
Physical state	Liquid
Formulation type	Suspension
Label concentration	31.25%
Container material and description	Plastic (HDPE) bottle, jug, drum, 500 mL to bulk
Density	1.08–1.09 g/cm^3 at 20 °C

Property	Result
pH of 1% dispersion in water	7.7–8.4
Oxidizing or reducing action	The product does not contain any oxidizing or reducing agents.
Storage stability	Stable when stored for one year at ambient temperature in HDPE bottles.
Corrosion characteristics	Not corrosive to the container material.
Explodability	Not explosive

End-Use Product—Zeltera Fungicide

Property	Result
Colour	Off-white
Odour	Rancid odour
Physical state	Liquid
Formulation type	Suspension
Label concentration	381 g/L
Container material and description	HDPE bottles.
Density	1.12 g/cm^3
pH of 1% dispersion in water	6.91–6.93
Oxidizing or reducing action	The product does not contain any oxidizing or reducing agents.
Storage stability	Stable when stored for one year at ambient temperature in HDPE bottles.
Corrosion characteristics	Not corrosive to the container material.
Explodability	Not explosive

1.3 Directions for Use

Excalia Fungicide is applied preventatively to apple, soybean and sugar beet to control or suppress specific diseases. In apple, Excalia Fungicide is applied at 146–219 mL/ha to control scab and powdery mildew, the latter disease for which an organosilicone surfactant is required at a concentration 0.0313–0.0625% v/v of the spray solution. In soybean, Excalia Fungicide is applied at 146 mL/ha for control of Asian soybean rust. In sugar beet, Excalia Fungicide is applied at 146 mL/ha in combination with a non-ionic surfactant at 0.125% v/v of the spray solution to suppress rhizoctonia crown and root rot. A minimum spray volume of 100 L water/ha is required for soybean and sugar beet.

Zeltera Fungicide is applied as a seed treatment in several cereal crops at 2.6–5.2 mL/100 kg seed, in corn, rapeseed and canola at 13 mL/100 kg seed, in legume vegetable crops and soybean at 6.5–13 mL/100 kg seed, and in sugar beet 0.13–0.26 mL/100,000 seeds to control or suppress multiple seed and seedling diseases as well as black leg in rapeseed and canola. For control of sudden death syndrome in soybean, Zeltera Fungicide is applied at 208 mL/100 kg seed.

1.4 Mode of Action

Inpyrfluxam inhibits the activity of succinate dehydrogenase, an enzyme of complex II within the fungal mitochondrial respiration chain (for energy production) and is classified as a Group 7 fungicide by the Fungicide Resistance Action Committee (FRAC).

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

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

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

High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; Methods RM-50C-1 in plant matrices and Methods RM-50AM-1 and RM-50E-1 in animal matrices) were developed and proposed for enforcement purposes. For data gathering purposes, HPLC-MS/MS analytical methods (Methods RM-50C-1 and RM-50C-2 in plant matrices and Methods 2814W and 2815W in animal matrices) were developed. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant and animal matrices. The proposed enforcement methods were successfully validated in plant and animal matrices by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled samples (rice straw, radish tops, milk, muscle, liver, and fat) analyzed with the respective enforcement methods.

HPLC-MS/MS methods were also developed and proposed for data generation and enforcement purposes in environmental matrices. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media.

Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Inpyrfluxam is a new succinate dehydrogenase inhibiting (SDHI) fungicide. A detailed review of the toxicological database for inpyrfluxam was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Mechanistic studies were also submitted to support a proposed mode of action for liver and

thyroid effects. The required 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 characterize the potential health hazards associated with inpyrfluxam.

In toxicokinetics studies in the rat, inpyrfluxam was rapidly and almost completely absorbed. Although there were sex-related differences in the timing of high-dose absorption, there were no major differences in maximum blood concentrations between males and females or between single and repeat doses. Plasma concentrations were relatively linear with dose level in males and supralinear in females. A slightly shorter half-life was noted in females after repeat dosing, but a longer half-life was noted in females after a single high dose. Excretion was more or less evenly divided between the urine and bile in males and females. Tissue distribution was extensive and tissues with concentrations above blood plasma levels included the thyroid, kidneys, adrenal glands, pituitary and lungs. Seven days following administration, quantifiable levels of radioactivity were only present in the gastro-intestinal tract and contents, liver, bone, and hair and skin. After14 days of repeat dosing, there was no evidence of tissue retention.

Toxicokinetic investigations were also performed in the long-term dietary toxicity studies in mice and rats and in the 12-month capsule study in dogs. In mice, blood plasma levels of unradiolabelled inpyrfluxam were below the limit of quantification (LOQ) at the low-dose level in males and around the LOQ at the mid-dose level in females. Females consistently had lower internal exposure levels than males. In rats, blood plasma levels of inpyrfluxam were only detectable in males at the highest dose level tested while levels were above the LOQ at all dose levels in females. Blood plasma levels were higher at the mid-dose level in females than at the high-dose level in males. These findings were consistent with toxicity effects, in that evidence of toxicity was only noted at the highest dose level tested in males. In dogs, blood plasma levels of inpyrfluxam were below the LOQ at the lowest dose tested and linear thereafter. There were no major sex-differences in plasma concentrations in dogs.

The metabolic pathway of inpyrfluxam in rats consists of N-demethylation, oxidation of the 1',1'-dimethyl group of the indane ring followed by further oxidation to carboxylic acid, and glucuronide conjugation, as well as 3'- and 7'-hydroxylation of the indane group as minor pathways. The main metabolites were: *N*-des-Me-1',1'-bis(CH_2OH)-S-2840; 1',1'-bis(CH_2OH)-S-2840; *N*-des-Me-1'-COOH-S-2840; and 1'-COOH-S-2840 found in urinary and fecal samples at low dose levels. These metabolites as well as *N*-des-Me-1'-CH_2OH-S-2840 were found in the urinary and fecal samples at high-dose levels and, additionally, the glucuronide of *N*-des-Me-1'-CH_2OH-S-2840 and glucuronide of 1'-CH_2OH-S-2840 found in all samples but at higher concentrations in the bile samples of the bile duct-cannulation study. No unchanged inpyrfluxam was present in urine or bile and less than 2% was present in feces. Identification of metabolites is found in Appendix I, Table 2.

In acute toxicity studies, inpyrfluxam was of high acute oral toxicity and low acute dermal and inhalation toxicity in rats. It was minimally irritating to the eyes and non-irritating to the skin of rabbits. It was not a dermal sensitizer in guinea pigs according to the maximization test.

Excalia Fungicide and Zeltera Fungicide were both of moderate acute oral toxicity and low acute dermal and inhalation toxicity in rats. They were non-irritating to the skin and eyes of rabbits and not dermal sensitizers in mice according to the local lymph node assay.

Following repeated oral exposure in mice, rats and dogs, effects on body weight, liver, kidney, and adrenal glands were observed. In addition, the thyroid was affected in mice and rats. Decreased body weights and body weight gains were observed in males and females at the highest dose levels in mice and down to the lowest dose levels in rats in long-term studies suggesting the rats were more sensitive. Generally, female rats had higher plasma concentrations at lower dose levels than males and more severe effects at similar internal dose levels. There was no impact of study duration on body weights in dogs. However, decreased body weights were only observed at higher dose levels in rats in the short-term studies when compared to longer term studies.

Liver effects consisted of increased organ weights, macroscopic changes, hepatocellular hypertrophy and clinical chemistry effects in mice, rats and dogs. Fatty change was noted in the 90-day dietary mouse toxicity study. Eosinophilic change was noted in the supplemental 28-day capsule dog toxicity study along with proliferation and/or dilation of the smooth endoplasmic reticulum and droplets found in the liver. In the 90-day capsule dog toxicity study, additional liver effects consisted of single cell necrosis, brown pigment deposition in the Kupffer cells, and eosinophilic inclusion bodies, as well as extrahepatic bile duct inflammation at the highest dose level tested.

In short-term studies, adrenal gland vacuolation occurred in all species. In the mouse at a high-dose level, there was an increase in accessory adrenocortical tissue and adrenal weights. In dogs, adrenal weights were increased in females only at the highest dose level tested.

Effects in the kidney were observed in the mouse, rat and dog. In a supplemental 28-day dietary toxicity study in mice, kidney weights were decreased and there was an increase in pelvic mononuclear cell infiltration and hyaline casts. In the long-term dietary mouse toxicity study, there was an increase in papillar necrosis and amyloid nephropathy at the mid-dose level and macroscopic changes and diffuse luminal dilatation of the proximal tubules occurred at the high-dose level. In rats, a decrease in urinary pH, increased basophilic tubules and α2μ-globin hyaline droplets in the proximal tubules and increased kidney mineralization. Kidney effects in the dog consisted of increased proximal tubular cell hypertrophy and eosinophilic inclusion bodies of proximal tubular cells, as well as decreased urinary pH at a higher dose level.

Thyroid effects noted in the mouse and rat included focal mononuclear cell infiltration in mice and increased thyroid weights, follicular cell hypertrophy and focal infiltration of the inflammatory cells in rats. Special studies were performed in rats and mice in order to characterize changes in the liver and thyroid; the results of these studies suggest that the thyroid effects observed were secondary to induction of hepatic enzymes.

No systemic toxicity occurred in rats following daily dermal application of the limit dose of testing for 28 days. Additionally, there were no signs of localized irritation at the application site.

Inpyrfluxam was tested for potential genotoxic activity in a standard battery of in vitro and in vivo assays. It was concluded that inpyrfluxam was not genotoxic based on the uniformly negative results of the studies.

Results from the 2-year dietary chronic combined toxicity/carcinogenicity study in rats indicated that there was an increase in treatment-related ovarian tumours in females. There was no evidence of tumourgenicity in mice or male rats. The rat ovarian tumours occurred at the high dose level following 92–105 weeks of treatment. At week 46, the high dose level was reduced due to excessive toxicity indicated by a decrease in body weight of 20–23% compared to controls. Following the reduction in dose level, body weight remained decreased compared to controls; however, body weight changes stabilized. Given the stress to the animals observed during the first 46 weeks of the study and lack of recovery of body weight, it is clear that the high-dose level exceeded the maximum tolerated dose (MTD). As such, the ovarian tumours were not considered relevant to the human risk assessment as they were observed at a dose level resulting in excessive toxicity.

In a dietary 2-generation reproductive toxicity study in rats, there was no evidence of sensitivity of the young. Systemic effects in the parental animals consisted of decreased body weights and increased liver weights in both sexes, hepatocellular hypertrophy, increased kidney weights and hyaline droplet deposition in males, and increased thyroid weights, follicular cell hypertrophy and loss of fur in females at the highest dose level tested. Toxicity in the offspring was limited to decreased body weights at the highest dose level tested in both generations. Reproductive toxicity consisted of isolated increases in luminal dilatation of the uterus and was consistent with decreased uterus weights in adult females and atrophy of the seminiferous tubules and glandular epithelial cells in adult males, also at the highest dose level tested. At higher dose levels in the supplemental one-generation range-finding reproductive toxicity study in rats, there was a decrease in pup viability, implantation sites and offspring born alive in groups given doses almost twice those of the main study. At the dose level similar to the top dose level in the main study, but in much smaller group numbers, body weight was decreased in both male and female pups and there was a delay in sexual maturation in females.

In the rat gavage developmental toxicity study, maternal toxicity consisted of decreased body weight gain throughout treatment and decreased body weight at the end of the gestation period at the highest dose level tested. At the same dose level, fetal body weights were decreased. In a supplemental study, maternal body weights, body weight gains and feed consumption were decreased along with fetal body weights at a similar dose level to the high dose level in the main study. In the rabbit gavage developmental toxicity study, there were two abortions, body weight loss and decreased body weight gain, food consumption and gravid uterine weights in does at the highest dose level tested. As the abortions occurred in does that had experienced significantly decreased body weight and body weight gain in the days before the abortions, concern for the offspring was lessened. At the same dose level, there were no additional signs of developmental toxicity in the fetuses.

In an acute neurotoxicity study, there were decreases in muscle tone and activity counts in females only. In males, there were no signs of toxicity up to the highest dose level tested. In a subchronic neurotoxicity study, there was no evidence of selective neurotoxicity. Systemic toxicity consisted of decreased body weights and food consumption in both sexes at the mid-dose level and above.

A waiver rationale was submitted for a subchronic inhalation study based on adequate characterization of the oral toxicity, high acute oral toxicity, low acute dermal and inhalation toxicities and low irritation potential to the eye and skin. The waiver was considered acceptable based on the applicant's proposal of assuming 100% absorption using the inhalation routes of exposure and defaulting to the oral toxicity endpoints.

Additional toxicology information was generated for the metabolites, 3'-OH-S-2840 and 1'-COOH-S-2840. Both metabolites were determined to be of low acute oral toxicity in rats and were negative in bacterial reverse mutation, in vitro mammalian cell forward mutation and in vitro mammalian clastogenicity assays.

The identification of select inpyrfluxam metabolites is presented in Appendix I, Table 2. Results of the toxicology studies conducted on laboratory animals with inpyrfluxam technical and its associated end-use products, are summarized in Appendix I, Table 3 and 4. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 5.

Health Incident Reports

Inpyrfluxam is a new active ingredient pending registration for use in Canada, and as of 2 December 2019, no health incident reports had been submitted to the PMRA.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the full complement of required studies including oral gavage developmental toxicity studies in rats and rabbits, and a dietary 2-generation reproductive toxicity study in rats. A supplemental gavage developmental toxicity study in the rat was also available, as well as several dose-finding range studies.

With respect to potential prenatal and postnatal toxicity, there was no evidence of increased sensitivity of the fetus or offspring compared to parental animals in either the developmental toxicity or reproductive toxicity studies. In the main reproductive toxicity study, decreased fetal body weights were observed at the same dose levels as decreased parental body weights and liver

and kidney changes. In the range-finding one-generation study, a delay in sexual maturation in female offspring in the presence of decreased maternal body weights and a decrease in viability in the presence of parental toxicity in both sexes were observed. In the developmental toxicity study in rats, fetal body weights were decreased at the same dose level as decreased maternal body weights and food consumption. In the main developmental toxicity study in rabbits, abortions were noted in the presence of excessive maternal toxicity. In the range-finding developmental toxicity study in rabbits, there was an increase in the percentage of resorptions and fetal deaths in the presence of excessive maternal toxicity.

Overall, the database is adequate for determining the sensitivity of the young. There is a low level of concern for sensitivity of the young as effects on the young are well characterized and occurred in the presence of maternal toxicity. Therefore, the *Pest Control Products Act* factor (PCPA factor) was reduced to onefold.

3.2 Determination of Acute Reference Dose

To estimate acute dietary risk, the point of departure for early findings in the 12-month oral dog toxicity study was selected for risk assessment. Although the overall study NOAEL was 6 mg/kg bw/day, the acute finding of vomiting within the first few days of treatment occurred at 160 mg/kg bw/day, resulting in a NOAEL of 30 mg/kg bw/day for this effect. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold. The composite assessment factor (CAF) is thus 100.

The acute reference dose (ARfD) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{30 \text{ mg/kg bw/day}}{100} = 0.3 \text{ mg/kg bw of inpyrfluxam}$$

3.3 Determination of Acceptable Daily Intake

To estimate risk following repeated dietary exposure, the NOAEL of 6 mg/kg bw/day from the 12-month oral toxicity study in the dog was selected. At the LOAEL of 30 mg/kg bw/day, effects included liver and adrenal gland findings in both sexes, as well as increased vomiting in females. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold. The CAF is thus 100.

The acceptable daily intake (ADI) is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{6 \text{ mg/kg bw/day}}{100} = 0.06 \text{ mg/kg bw/day of inpyrfluxam technical}$$

Cancer Assessment

An increased incidence of ovarian tumours was observed in rats following chronic dosing. However, the tumours occurred in animals that had clearly exceeded the maximum tolerated dose as evidenced by body weights that were decreased by 20% compared to controls and that did not completely recover after the dose was reduced at week 46. Therefore, these tumours were not considered relevant for the human health risk assessment and a cancer assessment is not required.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicology Reference Values

Occupational exposure to inpyrfluxam is characterized as short- to intermediate-term in duration and is predominantly by the dermal and inhalation routes.

Short- and Intermediate-term Dermal

For short- and intermediate-term dermal risk assessment, a NOAEL of 1000 mg/kg bw/day from the 28-day dermal toxicity study in rats was selected. At the highest dose level tested, 1000 mg/kg bw/day, there were no signs of toxicity noted. This study is of the appropriate route and duration for this exposure scenario, as there was no indication of increased toxicity with duration of exposure in the oral toxicity studies.

The target margin of exposure (MOE) for this scenario is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short- and Intermediate-term Inhalation

For short- and intermediate- term inhalation exposures, the NOAEL of 32 mg/kg bw/day from the 90-day oral rat toxicity study was selected for risk assessment. Toxicity was observed in the form of decreased body weight and liver effects at the LOAEL of 123 mg/kg bw/day. Although the NOAELs from the 2-generation reproductive toxicity study and rat developmental study were slightly lower at 28 and 25 mg/kg bw/day, respectively, the effects observed in all three studies were similar, and in all studies occurred at a higher dose level than the NOAEL in the 90-day rat toxicity study. A repeat-dose inhalation toxicity study was not available and thus, use of a NOAEL from an oral toxicity study was appropriate.

The target MOE for this scenario is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Cumulative Assessment

The *Pest Control Products Act* requires that the PMRA considers the cumulative exposure to pesticides with a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for inpyrfluxam. Inpyrfluxam is an SDHI fungicide. Currently, there are 22 SDHI pesticides, 13 of which are registered for use in Canada, not including inpyrfluxam. There is evidence of a similar spectrum of toxicological effects among SDHI pesticides, such as decreased body weight, and effects on the liver and thyroid gland. Additionally, oncogenicity in the liver and thyroid appears in multiple SDHI toxicological databases. Investigations into the mode of action for tumour formation have determined that the oncogenicity, in addition to the thyroid and liver toxicity related to the mode of action, are based on metabolic pathways in the laboratory animals that are not relevant to humans. Other effects on the liver and body weight are considered to represent a more generalized toxicity, and a common mechanism of toxicity has not been identified. Therefore, a cumulative health risk assessment is not required at this time.

3.4.1.1 Dermal Absorption

Chemical-specific dermal absorption studies were not submitted for inpyrfluxam and were not required as the toxicological dermal reference value is based on a dermal toxicity study.

3.4.2 Occupational Exposure and Risk for Excalia Fungicide

Excalia Fungicide is a suspension concentrate commercial-class product to be applied by ground equipment as a postemergent broadcast spray on apple trees from green tip to petal fall; on soybeans between the V3 and R5 growth stages; and on sugar beets between the 2- to 8-leaf growth stages. After application, workers may enter the treated areas to perform various tasks, such as hand harvesting, thinning, pruning, training, weeding or scouting.

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment for Excalia Fungicide

Individuals, such as workers, farmers and commercial applicators, have the potential for exposure to inpyrfluxam during mixing, loading, application, clean-up and repair activities involving Excalia Fungicide.

Exposure to inpyrfluxam from the use of Excalia Fungicide is expected to be mainly via the dermal and inhalation routes for mixers, loaders and applicators. Based on the use pattern and timings of application, exposure is expected to be of short-term duration (in other words, ≤ 30 days) for workers or farmers, and custom applicators.

Exposure estimates were derived for workers mixing and loading a liquid with an open-transfer system; applicators using an airblast sprayer or handheld airblast/mistblower equipment in apple orchards; and applicators using a groundboom sprayer in fields of soybeans and sugar beets.

The exposure estimates are based on all workers wearing the following personal protective equipment (PPE): a single layer of clothing, consisting of a long-sleeved shirt, long pants, socks and shoes, as well as chemical-resistant gloves, during mixing, loading and application. Only during application within a closed-cab tractor are gloves not required.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted for inpyrfluxam. As such, unit exposure estimates derived from the Agricultural Handlers Exposure Task Force (AHETF) or the Non-Dietary Exposure Task Force (NDETF) databases, of which the applicant is member, were used to conduct the mixer/loader/applicator risk assessment.

Daily dermal or inhalation exposure was calculated by coupling unit exposure estimates with the amount of product handled per day (derived from the maximum application rate and the default area treated per day for each crop) with 100% dermal or inhalation absorption. Exposure was normalized to mg/kg bw/day by using the default adult body weight of 80 kg. Daily exposure estimates were then compared to the toxicology reference values (in other words, no observed adverse effects levels (NOAELs) of 1000 mg/kg bw/day for dermal exposure and 32 mg/kg bw/day for inhalation exposure) to obtain the margins of exposure (MOEs). The target MOE is 100 for both dermal and inhalation exposures. The daily dermal and inhalation exposure values and calculated MOEs were not combined since the dermal and inhalation toxicology reference values were generated from the different studies and that the observed clinical effects are different.

As presented in Appendix I, Table 8, calculated MOEs were greater than the target MOE of 100 for all exposure scenarios related to Excalia Fungicide. As such, there are no health risks of concern when mixers/loaders and applicators using airblast sprayers or groundboom sprayers wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Gloves are not required within a closed-cab tractor. However, for applicators using handheld airblast/mistblower, the required level of PPE is higher and they must wear chemical-resistant coveralls with a chemical-resistant hood over long-sleeved shirt, long pants, chemical-resistant gloves, socks, chemical-resistant footwear and a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides or a NIOSH-approved canister approved for pesticides.

3.4.2.2 Postapplication Exposure and Risk Assessment for Workers Entering Fields and Orchards Treated with Excalia Fungicide

There is potential for exposure to workers entering orchards or fields treated with Excalia Fungicide when conducting postapplication activities, such as hand harvesting, thinning, pruning, training, weeding or scouting. Given the nature of activities performed, contact with treated foliage is expected to be primarily via the dermal route of exposure. Inhalation exposure is not considered to be a significant route of exposure for workers entering treated areas compared to the dermal route as inpyrfluxam is considered non-volatile with a vapour pressure of 3.8×10^{-8} kPa at 20 °C, which is less than the NAFTA criterion for non-volatile products for outdoor uses (in other words, 1×10^{-4} kPa at 20–30 °C).

As such, a quantitative inhalation risk assessment was not required for postapplication exposure scenarios. Inhalation risk is not of health concern for postapplication workers as inpyrfluxam is considered to be non-volatile and the restricted-entry interval of 12 hours will allow residues to dry, suspended particles to settle and vapours to dissipate.

A postapplication dermal risk assessment was conducted for Excalia Fungicide for each postapplication activity associated with each labelled crop at the maximum rate per application, maximum number of applications per season and minimum retreatment interval (RTI).

Given that no chemical-specific dislodgeable foliar residue (DFR) data for inpyrfluxam were submitted, the risk assessment used the current default DFR values, in other words, 25% of the maximum application rate on the day of the last application (Day 0) and 10% dissipation per day for the following days. Dermal exposure to workers entering treated areas was estimated by coupling the DFR values with activity-specific transfer coefficients from the Agricultural Re-entry Task Force (ARTF), of which the applicant is a member and has full access to the data. Exposure was normalized to mg/kg bw/day by using the default adult body weight of 80 kg and an 8-hour workday. Exposure estimates were then compared to the dermal toxicology reference value (in other words, the NOAEL of 1000 mg/kg bw/day for dermal) to obtain the MOEs. The target MOE is 100 for dermal exposure.

As presented in Table 9 of Appendix I, calculated MOEs were greater than the target MOE of 100 for all postapplication exposure scenarios on Day 0. As such, there are no health risks of concern and the default restricted-entry interval (REI) of 12 hours is adequate to protect workers.

3.4.3 Non-Occupational/Residential Exposure and Risk for Excalia Fungicide

The end-use product Excalia Fungicide is a commercial-class product for use on apple trees, as well as fields of soybeans and sugar beets. Non-occupational and residential exposures are not applicable to the use on soybeans and sugar beets, but for apple trees there is potential for non-occupational postapplication exposure to harvesters in apple orchards (in other words, pick-your-own (PYO) scenarios) and for residential postapplication dermal exposure to homeowners and their family when a commercial applicator is hired to treat apple trees in a residential area.

3.4.3.1 Non-Occupational Postapplication Exposure and Risk Assessment for Pick-Your-Own Activities in Apple Orchards Treated with Excalia Fungicide

For treated apple trees in a public orchard, non-occupational postapplication dermal exposure from pick-your-own activities was considered; however, based on the early timing of application to apple trees (in other words, before petal fall in the spring), the level of inpyrfluxam residues left on the foliage is expected to be negligible at the time of normal harvest in the fall. As such, a quantitative risk assessment was not conducted.

3.4.3.2 Residential Postapplication Exposure and Risk Assessment for Individuals Following Application of Excalia Fungicide to Apple Trees

Although Excalia Fungicide is not a domestic-class product, when commercial applicators are hired to treat apple trees in residential gardens, there is potential for residential postapplication dermal exposure to homeowners and their family.

The residential postapplication dermal risk assessment was conducted for Excalia Fungicide for postapplication activities associated with apple trees that are conducted early in the season after the applications (in other words, in the spring and summer), such as pruning or other orchard maintenance activities. Hand harvesting was not considered since, as explained previously, the amount of inpyrfluxam residues on foliage at the time of harvest in the fall is expected to be minimal. The maximum rate per application on apples, maximum number of applications per season and minimum RTI were also used.

Since no chemical-specific DFR data for inpyrfluxam were submitted, the risk assessment used the current default DFR values. Dermal exposure to individuals entering treated areas was estimated by coupling the DFR values with activity-specific transfer coefficients from the USEPA Residential 2012 SOPs. Exposure was normalized to mg/kg bw/day by using the default body weight of 80 kg and a 1-hour exposure period for adults, as well as the default body weight of 32 kg and a 0.5-hour exposure period for children. Exposure estimates were then compared to the dermal toxicology reference value of 1000 mg/kg bw/day to obtain the MOEs. The target MOE is 100 for dermal exposure.

As presented in Appendix I, Table 10 calculated MOEs were greater than the target MOE of 100 for all residential postapplication exposure scenarios on Day 0. As such, there are no health risks of concern when individuals enter the treated residential orchards on the same day as the applications once the sprays have dried.

3.4.4 Occupational Exposure and Risk for Zeltera Fungicide

Zeltera Fungicide is a suspension-formulated seed treatment product for commercial and on-farm use. Commercial seed treatment, which also includes seed treatment by mobile treaters, is permitted for all labelled seeds: corn (sweet, field and pop), rapeseed/canola, legume vegetables of crop group 6, (including soybeans), barley, buckwheat, millet (pearl and proso), oats, rye, teosinte, triticale and wheat. On-farm seed treatment is restricted to legume vegetables of crop group 6 (including soybeans), and the listed small grain cereals. In addition, although not treated in Canada, sugar beet seeds treated with Zeltera Fungicide outside of Canada can also be imported for planting.

Workers have the potential for exposure to inpyrfluxam while treating seeds in commercial seed treatment facilities or by using commercial mobile treaters, both equipped with a closed transfer system, as well as during bagging, sewing and stacking bags of treated seeds, and during calibration, cleaning and repair of equipment. Potential exposure can also occur during on-farm seed treatment and planting of treated seeds.

Occupational exposure to inpyrfluxam is expected to occur predominantly via the dermal and inhalation routes for mixers, loaders, other seed treatment workers and planters. Exposure duration is characterized as short-term for on-farm workers and planters, and intermediate-term for commercial workers.

3.4.4.1 Dust-off Study

The submitted dust-off study (PMRA# 2819646) was conducted to compare the dust-off potential of various seeds (corn, wheat, barley, oats, canola, soybean and sugar beet) untreated or treated with Zeltera Fungicide, or treated with several known surrogate seed treatment formulations or their substitutes. The seeds were treated with a slurry of each seed treatment formulation and dust-off levels from untreated and treated seed samples were measured using a Heubach dust measurement apparatus in grams of dust/100 kg seeds.

With regard to the seed-type effect of untreated and treated seeds, the general trend identified sugar beet seeds as being the dustiest of all tested seeds, with the following level of dustiness: sugar beets > oats > wheat > barley > corn > canola > soybeans.

However, it was noted that sugar beet seeds, either untreated or treated, always had an average dust-off level higher than any other seed type since they were pelleted with a talc-containing filler, but that no sticker or polymer was used to coat the seeds and reduce the amount of dust, as it is usually done in the industry. As such, the sugar beet seed dust-off results from this study are not representative of real-life scenarios. Nonetheless, the trend for the other seed types was comparable to typical observations.

With regard to the formulation effect, the treatment with Zeltera Fungicide decreased or had no significant influence on the dust-off levels from all seed types when compared to untreated seeds or seeds treated with any of the surrogate formulations or their substitutes.

Therefore, based on the submitted dust-off data generated with Zeltera Fungicide, the use of unit exposure estimates from the selected surrogate passive dosimetry exposure studies is not expected to underestimate occupational exposure of seed treatment workers and planters.

3.4.4.2 Commercial Seed Treatment Exposure and Risk Assessment for Zeltera Fungicide

Zeltera Fungicide can be used for the commercial treatment, including treatment by mobile treaters, of seeds of corn (sweet, field and pop), rapeseed/canola, legume vegetables of crop group 6 (including soybeans), barley, buckwheat, millet (pearl and proso), oat, rye, teosinte, triticale and wheat.

As chemical-specific unit exposure data were not submitted for Zeltera Fungicide, surrogate passive dosimetry exposure studies owned by the AHETF, of which the applicant is a member and has full access to the data, were used to estimate the worker exposure.

The choice of surrogate exposure study was based on results of the dust-off study, and also on various key factors influencing the exposure scenario, such as the formulation type, the seed type, the facility, the mixing/loading and treating equipment, the workers' tasks, the exposure duration, the PPE and engineering controls, as well as the quality of the data, such as the number of replicates, the validation recoveries and the unit exposure results.

To assess the exposure of mixers/loaders and cleaners involved in the treatment of cereal seeds, the unit exposure estimates from the AH809 2003a study, which was conducted with barley seeds, was used. The study adequately represents the scenario of treating cereal seeds in commercial facilities and had the highest unit exposure estimates for these tasks when compared to other surrogate exposure studies.

For baggers, sewers and stackers of treated cereal seeds, the AH817 2009 study, conducted in a commercial facility treating wheat seeds, was selected since it has the highest unit exposure estimates and the highest number of monitored workers and sites for these tasks when compared to other surrogate exposure studies on cereals.

Based on the dust-off study results, oat seeds were dustier than barley and wheat seeds. Therefore, unit exposure estimates from these surrogate exposure studies conducted with barley or wheat seeds, may underestimate exposure to workers handling oat seeds. Nonetheless, in the absence of a surrogate exposure study conducted with oat seeds, these studies were used and the magnitude of the calculated MOEs were considered in the final recommendations.

To assess the exposure of non-cereal grain seeds, in other words, corn, rapeseed/canola, legume vegetable or soybean seeds, the AH806 2010 study is the most appropriate since it was conducted in a commercial facility and separately monitored the treatment of corn and canola seeds. As such, the unit exposure estimates derived from the corn data were used in the risk assessments for corn and teosinte seeds, whereas the unit exposure estimates derived from the canola data were used in the risk assessments for rapeseed/canola, soybean and other legume vegetable seeds. It is noted that although teosinte seeds are to be treated at the same application rate as other small grain cereal seeds, the shape, size and physical properties of teosinte seeds are more similar to corn seeds.

Based on the dust-off study results, canola seeds generally produce more dust than soybean seeds. Therefore, the use of canola data is not expected to underestimate exposure to workers handling canola, soybean and other legume vegetable seeds. In addition, corn seeds generally produce more dust than both soybean and canola seeds. As such, the use of corn data is not expected to underestimate exposure to corn and teosinte seeds.

In addition to the unit exposure estimates from surrogate exposure studies, the risk assessment was conducted using the maximum supported application rate for each seed type, current default commercial throughput values, the default adult body weight of 80 kg, and the toxicology reference values presented in Section 3.4.1. No dermal absorption adjustment was needed since the dermal toxicological reference value is based on a dermal study.

Daily dermal or inhalation exposure was calculated by coupling the dermal or inhalation unit exposure estimates with the amount of active ingredient handled per day obtained from the active ingredient application rate and the amount of seeds treated in a day (in other words, commercial throughput). The daily dermal and inhalation exposures were normalized to mg/kg bw/day by using the default adult body weight. Dermal and inhalation exposures were not combined since the toxicology reference values are based on different studies and do not share common toxicological effects. To assess health risks, exposure estimates were compared to the toxicological reference value to obtain the MOEs. The target MOE for both dermal and inhalation exposure was 100.

As presented in Appendix I, Table 11, the dermal and inhalation MOEs obtained are well above the target MOE of 100. Hence, no health risks of concern are expected for commercial seed treatment workers and mobile treaters handling Zeltera Fungicide provided that they use closed transfer equipment as well as wear the most conservative of the PPE specified in the respective surrogate exposure studies for each task and seed type. Appendix I, Table 12 summarizes these PPE requirements.

Due to the very high calculated MOE for the dermal exposure of cleaners following the treatment of the cereal seeds (refer to Appendix I, Table 11), it is recommended that cleaners be allowed to wear cotton coveralls rather than chemical-resistant ones. Based on all conservatisms included in the risk assessment; the fact that the calculated dermal MOE is 1.88×10^5 times higher than the target MOE of 100; and that no toxicological effects were observed at the NOAEL of 1000 mg/kg bw/day in the 28-day dermal rat toxicity study, no health risks of concern are expected from this change and commercial workers conducting any task would always be required to wear the same PPE, in other words, cotton coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes.

3.4.4.3 On-Farm Seed Treatment Exposure and Risk Assessment for Zeltera Fungicide

Zeltera Fungicide can be used on-farm to treat seeds of legume vegetables of crop group 6, including soybeans, as well as the following cereal seeds: barley, buckwheat, pearl millet, proso millet, oats, rye, teosinte, triticale and wheat.

As chemical-specific unit exposure data were not submitted for Zeltera Fungicide, unit exposure estimates from the AH803 2006 surrogate passive dosimetry exposure study, owned by the AHETF, were used to estimate the exposure of on-farm workers. This is a well conducted study for the on-farm treatment and planting of wheat seeds.

Although the submitted dust-off study was not conducted with the consideration that unit exposure estimates from the AH803 2006 study would be used in the risk assessment for on-farm scenarios, the experiment included the product Gaucho 600 FS which is very similar to Gaucho 480 SC that was used in the AH803 2006 study. The following trend was observed with the dust-off levels of Gaucho-treated seeds: oats > wheat > barley > corn > soybean. In addition, the Gaucho-treated seeds always had higher dust-off levels than the Zeltera-treated seeds. Hence, based on these results, the use of unit exposure values generated from wheat seeds in the AH803 2006 study is not expected to underestimate exposure for workers handling soybean seeds, other

legume vegetable seeds, and any of the labelled cereal seeds, except oat seeds, which have been demonstrated to be dustier than wheat seeds. Nonetheless, as mentioned previously for commercial seed treatment, in the absence of a surrogate exposure study conducted with oat seeds, the AH803 2006 study is considered acceptable based on the high magnitude of the calculated MOEs as presented in Appendix I, Table 13.

In addition to the unit exposure estimates from the AH803 2006 surrogate exposure study, the on-farm risk assessment was conducted using the maximum supported application rate for each seed type; current default values for on-farm seeds treated/planted per day for cereal and legume seeds; the applicant's suggested value of 12 600 kg seeds handled per day for soybeans since it is higher and more conservative than the PMRA's default value of 9000 kg seeds/day; the default adult body weight of 80 kg; and the toxicological reference values presented in Section 3.4.1. No dermal absorption adjustment was needed since the dermal toxicology reference value is based on a dermal study.

Daily dermal or inhalation exposure was estimated by coupling the dermal or inhalation unit exposure values with the amount of active ingredient handled per day obtained from the active ingredient application rate and the amount of seeds treated/planted in a day in an on-farm setting. The daily dermal and inhalation exposures were normalized to mg/kg bw/day by using the default adult body weight. Dermal and inhalation exposures were not combined since the toxicology reference values are based on different studies and do not share common toxicological effects. To assess health risks, exposure estimates were compared to the toxicology reference value to obtain MOEs. The target MOE for both dermal and inhalation exposure was 100.

As presented in Appendix I, Table 13, the dermal and inhalation MOEs obtained are well above the target MOE of 100. Hence, no health risks of concern are expected for on-farm workers handling Zeltera Fungicide and planting the treated seeds provided that they use the PPE and engineering controls specified in the surrogate exposure study. Based on the AH803 2006 study, a closed or open transfer system can be used, and a single layer of clothing and chemical-resistant gloves must be worn. Planting of treated seeds must be done with a closed-cab tractor. However, since the calculated MOEs are all higher than 25-fold the target MOE of 100, the closed-cab tractor requirement can be waived.

3.4.4.4 Exposure and Risk Assessment for Planting Seeds Commercially Treated with Zeltera Fungicide

Commercially treated seeds are either bagged or stored in bulk. During planting, workers load the treated seeds into a planter from bags or from bulk containers using an auger. As such, workers have the potential for exposure to Zeltera Fungicide while loading and planting treated seeds.

Commercially treated seeds of cereals, soybeans and legume vegetables are typically stored in bulk containers, while the majority of commercially treated seeds of canola and corn are stored in bags. Sugar beets seeds, which are pelletized and treated outside of Canada, are boxed or bagged for transport and importation into Canada.

To assess the exposure scenarios of planting treated seeds of corn, teosinte, rapeseed/canola, legume vegetables, soybeans and sugar beets, the PMRA selected the AH825 2007 surrogate exposure study, which is owned by the AHETF. This is a well conducted study with no major limitations. It monitored workers opening paper bags of treated corn seeds; manually loading them in the planter; unloading the remaining seeds; planting using a closed-cab tractor and performing small repairs. The use of unit exposure values from this study is not expected to underestimate exposure to workers loading seeds from bulk containers since the exposure from this scenario is lower than the exposure from loading seeds from bags. Furthermore, it is recognized that corn seeds are dustier than canola, legume vegetable and soybean seeds. Corn seeds are also expected to be dustier than pelletized sugar beet seeds, which are usually coated with a dust-reducing polymer (although this was not done in the submitted dust-off study as explained above).

To assess the exposure scenario of planting treated cereal seeds (in other words, barley, buckwheat, pearl and proso millet, oats, rye, triticale and wheat), the PMRA selected the AHETF study AH823 2013. This is a recent and well conducted study with no major limitations. It was conducted on wheat seeds and professional farm employees or farmers were monitored while manually loading bags of treated seeds (only one worker was transferring treated seeds from a bulk container); planting using a closed-cab tractor; and cleaning. The use of unit exposure values from this study is thus considered adequate to cover the exposure of workers planting treated seeds from bags or bulk since the latter leads to a lower level of exposure. Unit exposure values from the AH823 2013 study are higher than from another cereal surrogate exposure study, which was solely conducted with bulk loading by auger or by vacuum transfer.

Since the AH823 2013 study was conducted on wheat seeds, it is not expected to underestimate exposure for workers planting Zeltera-treated seeds of all proposed cereal seeds, except oats, since it is well known that oat seeds are generally the dustiest type of cereal seeds. The submitted dust-off study also demonstrated this fact: apart from sugar beet seeds, which were always the dustier due to the presence of talk in the filler used for pelletizing, oat seeds had a higher dust-off level than any other seed type in all untreated and treated scenarios assessed during the experiment. As such, the use of unit exposure values from the AH823 2013 study may underestimate exposure for workers planting treated oat seeds. However, since a surrogate exposure study conducted with oat seeds is not available, the AH823 2013 study was used and the magnitude of the calculated MOEs will be considered in the final recommendations.

In addition to the unit exposure estimates from the AH825 2007 or AH823 2013 surrogate exposure studies, the risk assessment for planting treated seeds was conducted using the maximum supported application rate for each seed type; current default values for seeds planted per day for rapeseed/canola, legume vegetable and cereal seeds; the applicant’s suggested values for corn, soybean and sugar beet seeds since they are higher than the PMRA’s default values and based on more recent information from the AHETF 2013 seed treatment survey; the default adult body weight of 80 kg; and the toxicology reference values presented in section 3.4.1. No dermal absorption adjustment was needed since the dermal toxicology reference value is based on a dermal study.

Daily dermal or inhalation exposure was estimated by coupling the dermal or inhalation unit exposure values with the amount of active ingredient handled per day obtained from the active ingredient application rate and the amount of seeds planted in a day. The daily dermal and inhalation exposures were normalized to mg/kg bw/day by using the default adult body weight. Dermal and inhalation exposures were not combined since the toxicology reference values are based on different studies and do not share common toxicological effects. To assess health risks, exposure estimates were compared to the toxicology reference value to obtain the MOEs. The target MOE for both dermal and inhalation exposure was 100.

As presented in Appendix I, Table 14, the dermal and inhalation MOEs obtained are well above the target MOE of 100. Hence, no health risks of concern are expected for planters of Zeltera Fungicide-treated seeds provided that they use the PPE and engineering controls recommended based on the two surrogate exposure studies. The AH825 2007 and the AH823 2013 studies were both conducted with closed-cab planters for the most part. However, since the calculated MOEs are all higher than 25-fold the target MOE of 100, this requirement can be waived.

As for the PPE requirements, when considering the very high calculated dermal MOE when compared to the target MOE of 100, it is recommended to lower the PPE to a single layer of clothing, rather than cotton coveralls over a single layer of clothing, for planters of commercially-treated cereal seeds. Based on all conservatisms included in the risk assessment; the fact that the calculated dermal MOE is 1.55×10^3 times higher than the target MOE of 100; that even when waiving the closed-cab planter requirement based on a factor of 25-fold, the calculated MOE is still 62-fold higher than the target of 100; and that no toxicological effects were observed at the NOAEL of 1000 mg/kg bw/day in the 28-day dermal rat toxicity study, no health risks of concern are expected from this change.

3.4.5 Bystander Exposure and Risk

For the foliar product Excalia Fungicide, bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

For the seed treatment product Zeltera Fungicide, bystander exposure should be negligible since the product will be used in commercial seed treatment facilities or in on-farm settings, and there are minimal chances for drift during the treatment of seeds.

3.5 Exposure from Drinking Water

Drinking water modelling follows a tiered approach consisting of progressive levels of refinement. Level 1 EECs are conservative values intended to screen out pesticides that are not expected to pose any concern related to drinking water. These are calculated using conservative inputs with respect to application rate, application timing, and geographic scenario. Level 2 EECs are based on a narrower range of application timing, methods, and geographic scenarios, and are not considered conservative values that cover all regions of Canada.

Estimated environmental concentrations (EECs) in drinking water were calculated for groundwater and surface water using the Pesticide Water Calculator (PWC), version 1.52. For surface water, PWC calculates the amount of pesticide entering the water body by runoff and drift, and the subsequent degradation of the pesticide in the water system. EECs are calculated by modelling a total land area of 173 ha draining into a 5.3 ha reservoir with a depth of 2.7 m. Groundwater EECs are calculated by simulating leaching through a layered soil profile and reporting the average concentration in the top 1 m of a water table.

Modelling for inpyrfluxam was performed at Level 1. EECs for surface water were calculated based on a single standard scenario. EECs in groundwater were calculated for several scenarios representing different regions of Canada. The highest EECs from these regions are reported. All scenarios were run for 50 years.

Inpyrfluxam is a fungicide proposed for use on soybean, sugar beet and apple as foliar application. It is also proposed for use as seed treatment for multiple crops, including cereal grains, corn, soybean, rapeseed and sugar beet. Two use-patterns were selected for the modelling to encompass the highest proposed single and annual application rates: (i) two applications of 75 g a.i./ha (foliar application) and (ii) one application of 87.2 g a.i./ha (seed treatment) followed by two applications of 50 g a.i./ha (foliar application). The most conservative method of application and application timing across all proposed uses were applied to the modelling of both these use patterns. Successive airblast applications were used for the surface water modelling and successive seed treatment applications (at depth) were used for the groundwater modelling, with application intervals of 10 days. It is recognized that these assumptions do not reflect label instructions for the individual crop uses; however, this simple approach was considered adequate for the Level 1 modelling given its conservative nature.

Residues for drinking water modelling were defined as the combined residue of inpyrfluxam and two of its major transformation products, 3’-OH-S-2840 and 1’-COOH-S-2840. For each model input parameter, the most conservative value of all three compounds was used. The definition of the residue for drinking water modelling was determined based on their likely presence in drinking water sources and potential human health effects.

Model input parameters used for the ecological and drinking water modelling are outlined in Appendix I, Table 15.

Level 1 EECs, expressed as parent equivalent, are reported as follows:

Level 1 Estimated Environmental Concentrations of the combined residue (inpyrfluxam, 3'-OH-S-2840 and 1'-COOH-S-2840) in potential sources of drinking water, reported as parent equivalent

Use pattern	Groundwater (µg a.i./L)		Surface Water (µg a.i./L)	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
2 × 75 g a.i./ha at an interval of 10 days	222	222	8.1	1.5
1 × 87.2 + 2 × 50 g a.i./ha at an interval of 10 days	277	277	8.2	1.8

[1] 90th percentile of daily concentrations
[2] 90th percentile of 365-day moving average concentrations
[3] 90th percentile of 1-day concentrations from each year
[4] 90th percentile of yearly average concentrations

3.6 Food Residues Exposure Assessment

3.6.1 Residues in Plant and Animal Foodstuffs

The residue definition for enforcement in plant products and animal commodities is inpyrfluxam. For risk assessment, the residue definition is inpyrfluxam and *N*-des-Me-DFPA in plants and inpyrfluxam in animal commodities. The data gathering/enforcement analytical methods are valid for the quantitation of inpyrfluxam residues in crop and livestock matrices. Similarly, the data gathering method for *N*-des-Me-DFPA for crops is valid. The residues of inpyrfluxam are stable in potatoes, apples, corn (grain, forage, and stover), and soybeans for up to ~630 days when stored in a freezer at -20 °C. Under similar conditions, residues of inpyrfluxam were stable in processed potatoes (flakes and chips), corn (starch and oil), apples (pomace), soybeans (hulls), peanuts (meal), rice (bran, polished rice, and hulls), wheat (germ), and sugar beets (dried pulp, sugar, and molasses) for up to ~250 days of frozen storage. Therefore, inpyrfluxam residues are considered stable in all crop matrices, except high-acid crops, for up to ~630 days. Furthermore, inpyrfluxam is considered stable in a variety of processed crop fractions, not including those from high-acid crops, for up to ~250 days. Due to the absence of 0-day data in the freezer storage stability studies for the raw agricultural commodities (RACs), future expansions of use may trigger additional supporting data. Inpyrfluxam residues concentrated in the following processed commodities: apple pomace (2.9-fold), rice bran (1.3-fold), soybean oil (1.2-fold), sugar beet dried pulp (3.2-fold), and sugar beet molasses (2.0-fold). Adequate feeding studies were carried out to assess the anticipated residues in livestock matrices resulting from the current uses, and quantifiable residues are not expected to occur in livestock commodities. Crop field trials conducted throughout Canada and the United States using end-use products containing inpyrfluxam at approved or exaggerated rates in or on apples, canola, corn, peanuts, rice, sorghum, soybeans, and sugar beets are sufficient to support the proposed maximum residue limits. Field rotational crop studies were conducted in/on canola, cotton, field pea, sorghum, and wheat.

The data are adequate to demonstrate that a 9-month plant-back interval (PBI) is appropriate for cereals, legumes, and oilseeds not appearing on the Excalia Fungicide label. The confined crop rotation study supports a one-year PBI for all other crops not listed on the Excalia Fungicide label.

3.6.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 4.02, 05-10-c), which incorporates consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the year 2005–2010.

3.6.2.1 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the basic acute analysis for inpyrfluxam: 100% crop treated, default processing factors (where available), and residues in/on crops and animal commodities at MRL levels. The refined acute dietary exposure (food alone) for all supported inpyrfluxam registered commodities is estimated to be 0.15% (<0.0002 mg/kg bw) of the ARfD for the general population (95^{th} percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable at 5% of the ARfD for the general population, where the highest exposure and risk estimate is for all infants (<1 year) at 17% (0.05 mg/kg bw) of the ARfD.

3.6.2.2 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic analysis for inpyrfluxam: 100% crop treated, default and experimental processing factors (where available), and residues in/on crops and animal commodities at MRL levels. The basic chronic dietary exposure from all supported inpyrfluxam food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 1.2% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to inpyrfluxam from food and drinking water is 9.6% (<0.006 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants (< 1 year) at 35% (0.02 mg/kg bw/day) of the ADI.

3.6.3 Aggregate Exposure and Risk

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). For inpyrfluxam, the aggregate assessment consisted of combining food and drinking water exposure only, as there was no evidence of systemic toxicity in the repeat-dose dermal toxicity study, up to the limit dose. The most relevant toxicological endpoints and assessment factors for acute and chronic oral aggregate exposure are the same as those selected for the ARfD (see section 3.2) and ADI (see section 3.3), respectively.

3.6.4 Maximum Residue Limits

MRL (ppm)	Food Commodity
0.01	Rapeseeds (revised) Crop Subgroup 20A; Cereal Grains Crop Group 15; Legume Vegetables (succulent or dried) Crop Group 6; Apples; Peanuts; Sugar beet roots
	Eggs; Fat, meat, and meat byproducts of cattle, goats, horses, hogs, sheep, and poultry; Milk

MRLs are proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides section of the Canada.ca website.

For additional information on maximum residue limits (MRLs) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodologies, freezer storage stability, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 6 and 7.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Environmental fate properties of inpyrfluxam and its transformation products are summarized in Appendix I, Tables 16 and 17.

Air: Inpyrfluxam has low vapour pressure, low Henry's law constant, and it is soluble in water (Appendix I, Table 15). These intrinsic physico-chemical properties suggest that inpyrfluxam is not likely to volatilize from moist soil or water surfaces under field conditions.

Terrestrial Environment: In the terrestrial environment, inpyrfluxam is persistent. Laboratory studies show that transformation processes including hydrolysis, phototransformation, and aerobic/anaerobic biotransformation are generally slow and their contribution to the overall dissipation will not be important (Appendix I, Table 16). Inpyrfluxam is unlikely to hydrolyse under environmentally relevant conditions and does not phototransform on soil surfaces (half-life of 259 days under continous light). Laboratory studies of aerobic biotransformation of inpyrfluxam in four soils indicated that inpyrfluxam is moderately persistent to persistent in soil (DT_{50} = 66.9–241 d). The DT_{90s} were long (402–4004 d) indicating that inpyrfluxam may remain in soil for some time. At the end of the 120-d laboratory studies, the concentrations of inpyrfluxam in soil were similar (47.7, 46.0 and 41.8% of applied radioactivity). Under anaerobic conditions inpyrfluxam is persistent (DT_{50} >1212 d).

Observations from terrestrial field dissipation studies complement the interpretation of the laboratory results. Three studies on bare soil in Canadian relevant ecoregions resulted in DT_{50}s of 10.9 d, 24 d and 37.8 d. As in the laboratory studies, the DT_{90s} were long (244–950 d)

suggesting that inpyrfluxam is likely to persist under field conditions. In all three field studies, inpyrfluxam dissipated more rapidly at the beginning of the study, compared to the laboratory studies. Overall results suggest that inpyrfluxam is moderately persistent to persistent under field conditions. Despite the persistence of inpyrfluxam, this active ingredient does not meet the carryover criteria.

Two major transformation products, 3'-OH-S-2840 and 1'-COOH-S-2840, were observed in laboratory aerobic soil biotransformation studies with inpyrfluxam as well as a number of minor transformation products. An additional aerobic soil biotransformation study with the major transformation product 3'-OH-S-2840 indicated that it is persistent, with estimated DT_{50}s in three soils ranging from 276 to 369 days. A similar study performed with major transformation product 1'-COOH-S-2840 indicated it is moderately persistent, with estimated DT_{50}s ranging from 24.5 to 148 days. In this study with 1'-COOH-S-2840, a major transformation product 1'-keto-S-2840, was identified. Several minor compounds were also detected. In the field studies with inpyrfluxam, 3'-OH-S-2840 and 1'-COOH-S-2840 were detected down to a depth of 45 cm in a Washington field. In the other field studies, only 3'-OH-S-2840 was detected at low levels in the top layer of soils.

Laboratory experiments show that inpyrfluxam has low mobility in soil with the average adsorption coefficients (K_{oc}) ranging between 500 and 913 L/kg. However, primarily due to its persistence in soil, inpyrfluxam is predicted to be a borderline leacher to leacher. Soils of coarser texture or lower organic carbon content would be more susceptible to leaching. Fewer data were available to assess the leaching potential of the major transformation products. Based on the studies reviewed on aerobic biotransformation and adsorption/desorption in soil, their potential for leaching would be higher than for inpyrfluxam, with 1'-COOH–S-2840 having a very high mobility in soil (K_{oc} of 11 to 44 L/kg) and the highest potential for leaching. In one field dissipation study from Washington, inpyrfluxam and 3'-OH-S-2840 were detected consistently down to the 45-cm layer and 1'-COOH-S-2840 was also detected at the same depth. No soil samples were analysed below 45 cm.

Aquatic Environment: In the aquatic environment, hydrolysis and phototransformation are not expected to be major routes of transformation. In a buffer solution at pH 7, inpyrfluxam is stable to photolysis. Transformation was observed, albeit slow, in natural water with half-lives of 87 and 188 days. In aerobic water/sediment systems, inpyrfluxam partitioned relatively quickly to the sediment over the first few days and was persistent, with total system DT_{50} values ranging from 318 to 1610 days. No major transformation products were identified. Most transformation products produced from the biotransformation of inpyrfluxam in aerobic soil were also identified in the aerobic water/sediment systems, including 3'-OH-S-2840 and 1'-COOH-S-2840. In anaerobic water/sediment systems, inpyrfluxam partitioned to the sediment and was persistent, with DT_{50} values of 3367 and 3421 days in total systems. As in the aerobic water/sediment systems, no major transformation product were observed. The transformation product 3'-OH-S-2840 was found consistently as a minor compound.

The log K_{ow} of 3.6 for inpyrfluxam suggests a potential for bioaccumulation. A bioconcentration study conducted with bluegill sunfish resulted in low value steady-state bioconcentration factors (BCF_S). After three days of depuration, almost all radioactivity present in whole fish at steady-

state was eliminated. Several uncertainties were noted in that study and thus, quantitative results were not considered reliable. However, the study provided sufficient information to conclude that bioaccumulation was not observed to a great extent under laboratory conditions and is not expected to be of concern.

4.2 Environmental Risk Characterization

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

Initially, a screening level risk assessment is performed to identify specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application to the exposure medium at a maximum cumulative seasonal application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/(toxicity/uncertainty factor)), and the RQ is then compared to the level of concern (LOC). If the screening level risk quotient is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the LOC, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on refined exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or the available information does not allow for further refinement.

The environmental risk of inpyrfluxam and its related end-use products to non-target organisms was generally assessed based upon the maximum annual application rate to soybean from seed treatment (maximum 80 g a.i./100 kg seed and maximum 109 kg seeds/ha) combined with two foliar applications, for a total seasonal application rate of 187.2 g a.i./ha.

For certain non-target terrestrial organisms, the risk was assessed according to their specific exposure pathway from either seed treatment (maximum of 87.2 g a.i./ha on soybean) or foliar applications (2 × 75 g a.i./ha on apple by airblast sprayer and 2 × 50 g a.i./ha on soybean by ground boom sprayer).

4.2.1 Risks to Terrestrial Organisms

In determining the risk to terrestrial organisms, uncertainty factors are applied to acute toxicity endpoints (for example, LC_{50} or LD_{50}) to generate endpoint values that are used in calculating risk quotients (RQ = exposure/endpoint value). No uncertainty factors are applied to chronic endpoints (for example, NOEC). For earthworms, the acute endpoint is divided by the uncertainty factor of 2.0 and the resulting RQ is compared to the Level of Concern (LOC) of 1. For beneficial arthropods, no uncertainty factor is applied to acute endpoints and the resulting RQ is compared to the LOC of 2 for the two indicator species *T. pyri* and *A. rhopalosiphi* tested on glass plates. For birds and mammals, the acute toxicity endpoint (LC_{50} or LD_{50}) is divided by the uncertainty factor of 10 and the resulting RQ is compared to the LOC of 1. For bees, the acute endpoint is typically used directly without the uncertainty factor to calculate the RQ, which is compared to the LOC of 0.4. With terrestrial plants, the acute endpoint (for example, ER_{25}) is used directly without an uncertainty factor to calculate the RQ, which is then compared to the LOC of 1.

A summary of the effects on terrestrial organisms considered in the selection of toxicity endpoints is provided in Appendix I, Table 18. Endpoints used in the risk assessment are provided in Appendix I, Table 20, with their respective uncertainty factor. Resulting RQs for terrestrial organisms are presented in Appendix I, Tables 21 to 29.

The LOC was not exceeded for the following terrestrial organisms when inpyrfluxam is applied as a seed treatment or as a foliar application according to approved label directions and, the risks are acceptable:

- Earthworms
- Pollinators
- Non-target arthropods

The LOC is exceeded for the following organisms potentially exposed to inpyrfluxam when applied as a seed treatment or as a foliar application in the absence of mitigation measures. With the observance of preventative measures and use restrictions to reduce exposure, the risks are acceptable:

- Wild birds and mammals
- Terrestrial vascular plants

4.2.1.1 Screening Level Risk Assessment for Terrestrial Organisms

Appendix I, Tables 21 to 29 provide the results of the quantitative screening level risk assessment for terrestrial plants and non-target terrestrial invertebrates from exposure to inpyrfluxam and its two major transformation products 3'-OH-S-2840 and 1'-COOH-S-2840. In Table 21, exposure to inpyrfluxam was based on:

- the cumulative maximum application rate of 87.2 g a.i./ha from seed treatment plus two ground applications of 50 g a.i./ha (seasonal maximum 187.2 g a.i./ha), considering a half-life of 1242 days in soil for soil living organisms and plants,
- the same cumulative maximum application rate as above (total of 187.2 g a.i./ha) but using a foliar half-life of 15.9 days for beneficial arthropods living on plants, and
- a single maximum foliar application rate of 75 g a.i./ha for honeybees.

In Table 29, the screening level risk from major transformation products of inpyrfluxam was based on the exposure of soil organisms to inpyrfluxam (187.2 g a.i./ha). The estimated concentration in soil (0.082 mg a.i./kg soil) was converted to the respective concentrations of the transformation products based on the ratio of their molecular weight compared to inpyrfluxam, assuming 100% transformation into each transformation product.

Appendix I, Tables 22 to 24 provide the screening level risk assessment for terrestrial vertebrates (birds and mammals) consuming food containing inpyrfluxam from foliar applications and treated seeds, respectively. The exposure from foliar application was based on the cumulative maximum foliar application of 150 g a.i./ha on apple and the exposure from treated seeds was based on one maximum application rate of 80 g a.i./100 kg soybean seed (87.2 g a.i./ha).

When the LOC was exceeded at the screening level, further characterization of the risk was completed and presented in Section 4.2.1.2.

Terrestrial Invertebrates: The LOC was not exceeded for any of the species tested, including earthworm, springtail, honeybee (adult and larva), predatory mites and parasitic wasp on acute and chronic exposure basis. Therefore, further characterization of risk for those groups of organisms was not required. In addition, the LOC was not exceeded for the three species of soil invertebrates tested with the two major transformation products of inpyrfluxam, 3'-OH-S-2840 and 1'-COOH-S-2840. The risks associated with the use of inpyrfluxam are acceptable for terrestrial invertebrates.

Non-Target Terrestrial Plants: For non-target vascular plants, the most sensitive crop species (tomato) was considered in a study that examined the effects of an inpyrfluxam formulated product on seedling emergence. The resulting RQ of 27.8 exceeds the LOC based on reduction in the plant dry weight of emerged seedlings. The LOC was also marginally exceeded (RQ = 1.2) for the seedling emergence of oilseed rape, based on plant dry weight. The potential risk to non-target plants was then further characterized and is presented in Section 4.2.1.2.

Terrestrial Vertebrates: For birds and mammals, the risk was assessed considering two different exposure scenarios: foliar application and seed treatment exposure scenarios associated with the respective end-use products Excalia Fungicide and Zeltera Fungicide. Acute oral and chronic reproduction screening level risk assessment on birds and mammals were performed for both exposure scenarios. An acute dietary endpoint for birds was also included at the screening level risk assessment, as it was the most sensitive endpoint for birds.

For the foliar exposure scenario, the maximum application rate of 75 g a.i./ha on apple, applied twice at 10-day interval was used, with a foliar half-life of 15.9 days to estimate concentrations of inpyrfluxam in various food guilds for a range of bird and mammal species represented by a set of generic body weights.

The seed treatment scenario was conducted using the highest application rate of 80 g a.i./100 kg seed for soybean, for up to 109 kg seeds/ha or 87.2 g a.i./ha. The exposure of birds and mammals to inpyrfluxam through consumption of treated seed is a function of the amount of pesticide on the seed, the body weight and food ingestion rate of the animal, and the number of seeds available for consumption. The resulting inpyrfluxam intake corresponds to the estimated daily exposure (EDE). A set of generic bird and mammal body weights is used to represent a range of bird and mammal species and soybean seed treated with inpyrfluxam is the most conservative seed treatment exposure estimate.

The risk to birds at the screening level from the foliar application exposure exceeded the level of concern for all sizes of birds for one to two food guilds each, based on the acute dietary endpoint for zebra finch. For small and medium-size insectivore birds, RQs were 2.6 and 2.1, exceeding the LOC. For large herbivorous birds, RQs were 1.3 and 1.2 (Appendix I, Table 22). For mammals, the level of concern was not exceeded for any mammal size or endpoint, with the foliar application exposure scenario. The potential risk to birds from foliar application was then further characterized and is presented in Section 4.2.1.2.

The results of the screening level risk assessment for an exposure to soybean seeds treated with 80 g a.i./100 kg seed exceeded the LOC for small, medium and large birds from acute dietary exposure. RQs were 53.3, 41.9 and 12.2, respectively (Appendix I, Table 24). The LOC for reproductive effects was also exceeded for small, medium and large birds, with respective RQs of 4.4, 3.4 and 1.0. For mammals, the LOC was exceeded from both acute and chronic exposure to small, medium and large mammals, with RQs up to 6.4. The potential dietary and reproductive risks to birds and mammals from treated seeds was then further characterized and is presented in Section 4.2.1.2.

4.2.1.2 Further Characterization of Risk Assessment for Terrestrial Organisms

For those organisms where the LOC was exceeded, further characterization of exposure was conducted which considered off-target spray drift when inpyrfluxam is applied as a broadcast spray using airblast and field sprayers (Appendix I, Table 25). For this characterization, exposure of terrestrial plants to inpyrfluxam was based on the cumulative maximum foliar applications of 150 g a.i./ha on apple with airblast sprayer and 100 g a.i./ha on soybean with field sprayer, as opposed to 187.2 g a.i./ha at the screening level.

The off-target spray drifts considered were 74, 59 and 3% of the application rate at one metre downwind from the point of application for early and late season airblast, and for ground boom sprayer using droplet size of ASAE Coarse,[5] respectively. The resulting off target drift EECs for airblast are 110.7 and 88.3 g a.i./ha, respectively, and for field sprayer is 3.0 g a.i./ha.

For terrestrial vertebrates (birds and mammals) exposed to food sources containing inpyrfluxam following foliar application on crops, the risk is further characterized by considering maximum and mean residues that may occur in food item on-field or off-field. For exposure from treated seeds, the number of seeds needed to reach the endpoint and the area required depending on the species and its size are considered. Further characterization of the risk from foliar application to birds and treated seeds to birds and mammals is provided in Appendix I, Table 26 to 28.

Non-Target Terrestrial Plants: The LOC was exceeded for the seedling emergence from the spray drift of early and late season airblast spraying of inpyrfluxam (RQ = 16.6 (early season); RQ = 13.3 (late season)) but was not exceeded from applications via ground boom sprayer. Therefore, spray buffer zones will be required to mitigate the risk from airblast applications and a default 1 m buffer zone for application with ground boom sprayer.

Birds and Mammals: For the foliar application scenario, the LOC was exceeded at the screening level with the acute dietary reproduction endpoints for all sizes of birds. Appendix I, Table 26 shows that when considering mean residues or maximum residues from off-field, RQs for large birds are at or below the LOC. For small and medium-size birds, the RQs slightly decreased close to the LOC threshold of 1 or just above for insectivores. This assessment assumes that 100% of the diet consists of contaminated food, which is unlikely. Therefore, the risk is considered acceptable for foliar uses. Precautionary label statements will be required to mitigate the risks due to the high inherent acute toxicity of inpyrfluxam to birds.

For the seed treatment exposure scenario, as the level of concern was exceeded at the screening level, based on acute dietary and chronic reproduction endpoints for birds of all sizes and on acute oral and chronic reproduction for mammals (Appendix I, Table 24), the risk was further characterized. At the screening level, the size of soybean seeds was not considered. Given the size of soybean seeds, this will likely limit the consumption by a small (20 g) bird or mammal (15 g). Thus, risk quotients for small bird and small mammals are considered less realistic as it is unlikely that they would be exposed to inpyrfluxam by consuming a soybean seed. In addition, untreated soybean seeds were shown not to be attractive to birds. As for treated seeds, regurgitation observed in Mallard duck in the acute oral study indicate that the formulation may be repulsive for certain species. For medium- and large-sized animals, the number of seeds needed to reach the endpoint shown in Appendix I, Tables 27 and 28 are plausible as all amounts fall within the limits of food ingestion rates for medium and large birds and mammals. The area required to find the respective number of seeds is also realistic.

[5] Droplet size classification system of the American Society of Agricultural Engineers (ASAE) based on the volume median diameter (VMD) of spray droplets.

However, the risk assessment assumes that the diet of the bird consists of 100% treated seed, which is a conservative assumption. Additionally, for seeds using precision drilling there is limited evidence to suggest that a bird or mammal will remove the seed from the soil after it is planted.

In order to provide a better exposure scenario for small animals, the risk was further assessed by considering the use of other treated seed crops of various sizes, more palatable than soybean, which may be more realistically consumed by various sizes of birds and mammals, including the small species. Additional calculations using rapeseed, corn and peas succulent seeds were performed to determine RQs. The application rate for these crops is the second highest to soybean at 5 g a.i./100 kg seeds. The highest RQ was 10.6 for dietary exposure of corn to small bird. The associated RQ calculated for rapeseed was 3.3. For mammals, this exposure resulted in RQs not exceeding 1.3. For all these additional assessments, the number of seeds needed to reach the endpoint are plausible as all amounts fall within the limits of food ingestion rates. The areas required to find the respective number of seeds are also realistic. However, these RQs assume a diet of 100% treated seed, which is unlikely. Calculations for wheat treated seed were also performed and the level of concern was not exceeded anywhere at the screening level.

In addition, the dietary endpoint associated with the exceeded LOCs is based on a 5-day dietary study looking at bird mortality after 5 days, which is an unlikely exposure scenario for exposure to seed treatments, that results in a one-time exposure. To mitigate the risk to birds and mammals from exposure to seed treatments, label statement requiring the clean-up of spilled seeds will be required.

Overall, following a refined risk assessment, the risks to birds and mammals associated with foliar and seed treatment application of inpyrfluxam are acceptable when labels are followed.

4.2.2 Risks to Aquatic Organisms

In determining the risk to aquatic organisms, uncertainty factors are applied to acute toxicity endpoints (for example, LC_{50}) that are used in calculating risk quotients (RQ = exposure/endpoint value). No uncertainty factors are applied to chronic endpoints (for example, NOEC). For aquatic invertebrates, algae and aquatic vascular plants, the acute endpoint is divided by the uncertainty factor of 2.0 and the resulting RQ is compared to the LOC of 1. For fish and amphibians, the acute endpoint is divided by the uncertainty factor of 10 and the resulting RQ is also compared to the LOC of 1.

A summary of the effects on aquatic organisms considered in the selection of assessment endpoints is provided in Appendix I, Table 19. Aquatic endpoints used in the risk assessment are provided in Appendix I, Table 20.

When used according to approved label directions, the risks are acceptable to the following aquatic organisms from the use of inpyrfluxam:

- Freshwater and marine invertebrates
- Freshwater and marine algae
- Aquatic vascular plants

The level of concern for inpyrfluxam applied as a seed treatment followed by two foliar applications was exceeded for the following aquatic organisms. However, with the addition of preventative measures to reduce drift and precautionary measures to inform users of the potential for surface runoff, the risks are acceptable for:

- Fish and Amphibians.

4.2.2.1 Screening Level Risk Assessment for Aquatic Organisms

The results of the screening level risk assessment are provided in Appendix I, Table 30. At the screening level, the exposure scenario is a direct application to a body of water (15 cm deep 1 ha pond for amphibian habitat and 80 cm 1-ha pond for other aquatic organisms). To calculate the screening level EECs, the following parameters were used, resulting in a maximum application rate of 187.2 g a.i./ha:

- maximum seed treatment rate of 80 g a.i./100 kg soybean seed and maximum recommended seeding rate of 109 kg seeds/ha, followed by two foliar applications of 50 g a.i./ha, and
- foliar application intervals of 30 days following the seed treatment and 14 days between foliar applications.

The screening level EECs resulted in 0.124 mg a.i./L (15 cm deep pond) and 0.023 mg a.i./L (80 cm deep pond), using a half-life in water systems of 2424 days. When the level of concern was exceeded, further characterization of the risk was completed and presented in Section 4.2.2.2.

Aquatic invertebrates: The screening level RQs for freshwater and marine invertebrates (RQ from < 0.02 to 0.16) did not exceed the LOC, hence, the risks to aquatic invertebrates from the use of inpyrfluxam are acceptable and no further refinement is necessary.

Algae and aquatic plants: The LOC was not exceeded for freshwater and marine algae and vascular aquatic plants (RQ range of < 0.002 to 0.08). As a result, the risk was acceptable and no further refinement to the risk assessment was considered for these organisms.

Aquatic vertebrates (fish and amphibians): For freshwater fish, the LOC was exceeded on an acute basis for four out of seven species tested (RQ exceeded range of 3.5 to 7.4) and was exceeded on a chronic exposure basis (RQ = 14.4) for the only tested species. For marine fish, the LOC was also exceeded on an acute (RQ = 1.5) and chronic basis (RQ = 2.6). For amphibians, fish endpoints were used as surrogates and the LOC was exceeded on both acute and chronic exposure basis (RQ = 40–77.5). In addition, one fish species was tested with the two

major transformation products of inpyrfluxam, 3'-OH-S-2840 and 1'-COOH-S-2840. The LOC for these transformation products was not exceeded for fish and amphibian exposure scenarios. As a result, further refinement to the risk assessment resulting from inpyrfluxam exposure was considered for aquatic vertebrates and is presented in Section 4.2.2.2.

4.2.2.2 Further Characterization of Risk Assessment for Aquatic Organisms

For those organisms where the LOC was exceeded, further characterization of exposure was conducted for when inpyrfluxam is applied as a seed treatment and by broadcast spray using field sprayers. Two separate exposure scenarios are considered for the risk assessment: off-target spray drift scenario and surface runoff scenario. The refined risk to aquatic organisms is provided in Appendix I, Tables 31 and 33.

For this characterization, inpyrfluxam exposure to freshwater organisms considered off-target spray drift when inpyrfluxam is applied as a broadcast spray using airblast and field sprayers (Appendix I, Table 31). Exposure from drift was based on two foliar applications of 75 g a.i./ha on apple with airblast sprayer at 10-day interval and two foliar applications of 50 g a.i./ha on soybean with field sprayer at 14-day interval (cumulative maximum application scenarios). Drift percentages of 74, 59 and 3% of the application rate at one metre downwind from the point of application for airblast, early and late season and, ground boom sprayer if the spray quality (droplet size distribution) used is classified as ASAE Coarse,[6] were considered, respectively. Resulting application rates to water were converted to concentrations in water, considering a half-life in water of 2424 days and assuming water depths of 80 cm for all organisms, except for amphibians, for which a 15 cm deep pond was assumed. The exposure from spray drift to marine organisms was based on a single application for each type of use (75 and 50 g a.i./ha), as tides and dilution are expected to make concentrations in the marine environment negligible at the time of subsequent applications. The resulting EECs were used to further assess the risk.

Surface runoff EECs for use in the ecological risk assessments were calculated using the Pesticide in Water Calculator (PWC) version 1.52. The model is based on a 10 ha field adjacent to a 1 ha water body 15 cm deep (amphibian habitat) or 80 cm deep (shallow pond). It calculates the amount of pesticide entering the water body by runoff and the subsequent degradation of the pesticide in the water and sediment. Yearly applications are modelled over a 50-year period. The parameters used for the modelling are presented in Appendix I, Table 15.

A subset of use patterns was considered for the modelling, intended to represent all proposed uses, which were modelled taking into consideration regional rates and application timing information. The ecological modelling was conducted on the parent inpyrfluxam alone. Although their presence is expected in water systems, available fish toxicity data for the two major transformation products, 3'-OH-S-2840 and 1'-COOH-S-2840, indicate a lower toxicity than the parent. In addition, as the parent is mostly persistent across all media, the ecoscenario modelling of the parent only was considered sufficient to cover the risk. Several representative scenarios

[6] Droplet size classification system of the American Society of Agricultural Engineers (ASAE) based on the volume median diameter (VMD) of spray droplets.

are selected for modelling different regions of Canada. The highest EECs from all modelled scenarios are reported in Appendix I, Table 32, for each use pattern and water depth. Appropriate values were chosen from Table 32 to assess the risk from runoff, according to the type of exposure and endpoint value.

For example, the maximum 96-h EEC in 80 cm water depth was used for the acute pelagic fish risk assessment and the maximum 21 day EEC in 15 cm water depth was used for the chronic amphibian risk assessment. The chosen EECs for runoff are reported in Appendix I, Table 33 along with the resulting RQs for relevant species.

Aquatic vertebrates (fish and amphibians): For the risk to freshwater fish from spray drift, the LOC on an acute basis was exceeded for the four species (RQ exceeded range of 1.69 to 4.52) and on a chronic exposure basis (RQ = 8.75 and 6.87 for early and late season airblast applications) for the one tested species. The LOC was not exceeded for the crops sprayed by ground boom sprayer (RQ range of 0.06 to 0.25). For marine fish, the LOC was not exceeded on acute or chronic exposure basis (RQ range of 0.01 to 0.78). The LOC for amphibians was exceeded on both acute and chronic exposure basis (RQ range of 1.25 to 46.25). Spray drift buffer zones are required to mitigate the identified risk from drift of inpyrfluxam to freshwater environments.

For the risk to freshwater fish from runoff, the LOC on an acute basis was exceeded for the four species (RQ exceeded range of 3.08 to 6.45) and on a chronic exposure basis (RQ = 12.5) for one tested species. For marine fish, the LOC was exceeded on acute (RQ = 1.33) and chronic (RQ = 2.22) exposure basis. The LOC for amphibians was exceeded on both acute (RQ = 10.97) and chronic (RQ = 18.75) exposure basis. In this characterization, the highest RQs are for amphibians (fish endpoints were used as surrogate data). The remaining RQs, range from close to the LOC of 1 up to 12.5.

Although there are instances where risk quotients exceed the level of concern, the risk from runoff is acceptable for inpyrfluxam when considering some of the assumptions made in the ecological modelling. Specifically for this compound, it is noted that EECs generated from modelling were not much lower than those calculated at the screening level from a direct overspray; this is an atypical situation, as amounts of pesticide entering water bodies are expected to be lower from runoff than for a direct application to water. In this case, the standard assumption that there is no water flowing in or out of the modelled pond is an important factor to consider when interpreting the results. Given the persistence of inpyrfluxam, an increase in concentrations was predicted over the modelled 50 years. However, most water bodies have flowing water and an accumulation would not occur under more typical conditions. In light of this, and also given that a pesticide is not likely to be applied yearly on a same area for a period of 50 years, risks to aquatic systems are not expected. The PMRA will nonetheless require label statements to warn users of the potential for runoff when using the foliar product (Excalia Fungicide). The risk assessment using the modelled EECs for seed treatment indicated that the runoff label statement is not warranted for the seed treatment product (Zeltera Fungicide) as the EECs are lower for this use and the treated seeds will be buried, therefore runoff is generally not expected.

Overall, the PMRA concludes that the risks to aquatic organisms resulting from the use of inpyrfluxam as a foliar application and seed treatment are acceptable from the viewpoint of environmental protection when label directions are followed.

4.2.3 Environmental Incident Reports

Inpyrfluxam is a new active ingredient pending registration for use in Canada, and as of 2 December 2019, no environmental incident reports had been submitted to the PMRA.

5.0 Value

The registration of Excalia Fungicide and Zeltera Fungicide will each constitute an additional option within the FRAC group 7 mode of action classification for growers to manage economically important diseases of multiple crops.

Excalia Fungicide

Field studies were conducted on apple, soybean and sugar beet to assess the efficacy of Excalia Fungicide in controlling scab and powdery mildew in apple, Asian soybean rust in soybean and crown and root rot in sugar beet. Applications were made to apple and soybean prior to natural infection with the respective causal pathogens while in sugar beet, most trials were inoculated with the causal pathogen, *Rhizoctonia solani* to encourage development of adequate crown and root rot disease pressure. Data were generated for disease incidence and severity in each crop, as well as stand counts (plant populations), crop vigour and marketable root yield in sugar beet. The data collectively support the efficacy claims summarized in Appendix I, Table 35. Excalia Fungicide did not cause any crop injury.

Zeltera Fungicide

The efficacy of Zeltera Fungicide for control of these diseases was assessed at one or more rates in field, greenhouse and controlled environment studies conducted on multiple cereal and legume crops, corn, soybean, canola and sugar beet. Greenhouse, growth room and several field studies were inoculated with the causal disease pathogen while other field trials were situated on sites with a known history of the particular disease, such as for soybean sudden death syndrome. Data for crop stand, crop vigour, disease incidence and severity, and overall disease damage, along with extrapolation-based rationales, demonstrated that Zeltera Fungicide can be expected to achieve the claims summarized in Appendix I, Table 36. Zeltera Fungicide did not affect germination or early seedling growth of any of the tested crops in seed germination tests. Crop injury was not evident in Zeltera Fungicide treatments in the field studies.

Details of the supported uses are summarized in Appendix I, Tables 35 and 36.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

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

During the review process, inpyrfluxam and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[7] and evaluated against the Track 1 criteria.

The PMRA concludes that inpyrfluxam does not meet all Track 1 criteria. Please refer to Appendix I, Table 34 for further information on the TSMP assessment of inpyrfluxam.

Limited data were available for the transformation products. Toxicity studies indicated they would both be less toxic than inpyrfluam to terrestrial invertebrates and fish (Appendix I, Table 18 and 19). Soil biotransformation studies indicated 3'-OH-S-2840 would meet the Track 1 criteria for soil. For 1'-COOH-S-2840, Track 1 criteria for soil persistence was met in one soil but not in two other soils (Appendix I, Table 16). Without available information on bioaccumulation for the transformation products, with their respective molecular structures similar to inpyrfluxam, their bioaccumulation profile is also assumed to be similar to inpyrfluxam. Therefore, the PMRA concludes that inpyrfluxam and its transformation products do not meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette.*[8]

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

8 SI/2005-114, last amended on June 25, 2008. See Justice Laws website, *Consolidated Regulations, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

The list is used as described in the PMRA Notice of Intent NOI2005-01[9] and is based on existing policies and regulations including the Toxic Substances Management Policy[1] and the Formulants Policy,[10] and taking into consideration the *Ozone-depleting Substances and Halocarbon Alternatives Regulations* under the *Canadian Environmental Protection Act*, 1999,(substances designated under the Montreal Protocol).

The PMRA has reached the conclusion that inpyrfluxam and its end-use products Zeltera Fungicide and Excalia Fungicide do not contain any formulants in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

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

7.0 Summary

7.1 Human Health and Safety

Toxicology

The toxicology database is adequate to characterize the potential health hazards associated with inpyrfluxam. In short-term and chronic studies in laboratory animals, the primary targets of toxicity were the liver, kidney, thyroid, and adrenal glands. There was no evidence to indicate that inpyrfluxam is selectively neurotoxic or genotoxic. There was no evidence of increased sensitivity of the young in reproductive or developmental toxicity studies. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose level at which these effects occurred in animal tests.

Occupational and Residential exposure

Occupational exposure and risks are acceptable for mixers, loaders and applicators handling Excalia Fungicide and Zeltera Fungicide, as well as for postapplication workers entering freshly treated orchards and fields or planting and handling treated seeds when these inpyrfluxam-containing end-use products are used according to proposed label directions.

The PPE on the label of the foliar product Excalia Fungicide states that workers must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair, unless otherwise specified. Only during application within a closed-cab tractor are the gloves not required. For application using handheld airblast/mistblower, workers must wear chemical-resistant coveralls with a chemical-resistant hood over long-sleeved shirt, long pants, chemical-resistant gloves, socks, chemical-resistant footwear and a respirator with a NIOSH-approved organic-vapour-removing cartridge with a

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9 PMRA's Notice of Intent NOI2005-01, *"List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act"*.

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

prefilter approved for pesticides OR a NIOSH-approved canister approved for pesticides. Postapplication workers are not allowed to enter the treated areas during the REI of 12 hours.

The PPE on the label of the seed treatment product Zeltera Fungicide states that commercial handlers (including facility workers and mobile treaters) must use a closed transfer system only and must wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, treating, calibrating, bagging, sewing, stacking and cleaning. The label also specifies that on-farm seed treatment can be performed with open or closed transfer system and that workers must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, treating, calibrating, clean-up, repair and any other activities involving handling of treated seeds. Planters of treated seeds can use an open-or closed-cab tractor and must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Gloves are not required within a closed-cab tractor.

Non-occupational/residential exposure and risks are acceptable for individuals involved in pick-your-own activities in apple orchards treated with Excalia Fungicide, or performing tasks around treated apple trees in residential areas when this product is used according to proposed label directions.

Dietary exposure

The nature of the residues in plants and animals is adequately understood. The residue definition for enforcement is inpyrfluxam in plant products and in animal matrices. The proposed use of inpyrfluxam in Canada (apples, soybeans, succulent or dried legume vegetables, sugar beets, corn, canola, barley, buckwheat, pearl millet, proso millet, oat, rye, teosinte, triticale, and wheat) and the importation of treated crops (rice, sorghum, peanuts, and all crops other than canola that belong to rapeseed crop subgroup 20A) do not constitute a health risk of concern for acute or chronic 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 to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues of inpyrfluxam.

MRL (ppm)	Food Commodity
0.01	Rapeseeds (revised) Crop Subgroup 20A; Cereal Grains Crop Group 15; Legume Vegetables (succulent or dried) Crop Group 6; Apples; Peanuts; Sugar beet roots
	Eggs; Fat, meat, and meat byproducts of cattle, goats, horses, hogs, sheep, and poultry; Milk

7.2 Environmental Risk

The risks associated with the use of Excalia Fungicide and Zeltera Fungicide at the proposed application rates are acceptable from the viewpoint of environmental protection, provided that the use restrictions and precautions on the product label are followed.

In the terrestrial environment, the risks posed by inpyrfluxam were acceptable for earthworms, beneficial arthropods and pollinators (bees). Inpyrfluxam may pose a risk to terrestrial plants, birds and mammals. To mitigate the risk of spray drift to non-target terrestrial plants, the observance of spray buffer zones is required according to label directions. With the standard precautionary label statements required to warn users of the potential risk from foliar application along with statements requiring the clean up of spilled seed, the risks to birds and mammals are acceptable.

In the aquatic environment, the risks posed by inpyrfluxam were acceptable for freshwater invertebrates, algae and aquatic vascular plants and marine invertebrates and algae. Inpyrfluxam may pose a risk to freshwater fish and amphibians and marine fish. Risks from drift at the time of application can be mitigated using spray buffer zones. Standard precautionary label statements alerting users of the potential for runoff and leaching are also required on the product label to mitigate the risk. With these measures, the risk is considered acceptable for all aquatic organisms.

7.3 Value

The submitted value information is adequate to demonstrate the value of Excalia Fungicide applied to the foliage of apple, soybean and sugar beet, and of Zeltera Fungicide for use as a seed treatment in some cereal crops, corn, legume vegetables, soybean, rapeseed, including canola, and sugar beet for the control or suppression of certain seed and seedling diseases, blackleg in rapeseed and canola, and sudden death syndrome in soybean.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Inpyrfluxam Technical, Excalia Fungicide and Zeltera Fungicide, containing the technical grade active ingredient inpyrfluxam, to control or suppress economically important diseases of apple and listed field crops.

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

Additional Information Being Requested

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

List of Abbreviations

↑	increased
↓	decreased
♂	male
♀	female
µg	micrograms
1/n	exponent for the Freundlich isotherm
abs	absolute
a.i.	active ingredient
AD	administered dose
ADME	absorption, distribution, metabolism and elimination
ADI	acceptable daily intake
A/G	albumin/globulin ratio
AHETF	Agricultural Handler Exposure Task Force
ALB	albumin
ALP	alkaline phosphatase
ALS	acetolactate synthase
ALT	alanine aminotransferase
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
AST	aspartate aminotransferase
ASAE	American Society of Agricultural Engineers
atm	atmosphere
ATPD	Area Treated Per Day
BAF	bioaccumulation Factor
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BCF	bioconcentration factor
BCFss	bioconcentration factor at steady-state
bili	bilirubin
BUN	blood urea nitrogen
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CG	Crop Group
CHO	Chinese hamster ovary
chol	cholesterol
cm	centimetres
C_{max}	maximum blood concentrations
CR	Chemical-Resistant
CYP	cytochrome P
d	day(s)
DALA	days after last application
DEEM-FCID	Dietary Exposure Evaluation Model

DF	dry flowable
DFR	Dislodgeable Foliar Residue
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
EC_3	concentration required to induce a threshold positive sensitization response (SI=3)
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental concentration
ER_{25}	effective rate for 25% of the population
F1	first generation
F2	second generation
fc	food consumption
FIR	food ingestion rate
FOB	functional observational battery
FRAC	Fungicides Resistance Action Committee
g	gram
GD	gestation day
GGT	gamma-glutamyl transpeptidase
gluc	glucose
ha	hectare(s)
HAFT	highest average field trial
Hb	hemoglobin
HC	historical control
Hct	hematocrit
HDPE	high-density polyethylene
HDT	highest dose tested
Hg	mercury
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
hr	Hour
ILV	Independent laboratory validation
Inc.	Incorporated
IUPAC	International Union of Pure and Applied Chemistry
i.v.	intravenous
kg	kilogram
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
km	kilometre
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
kPa	Kilopascal
L	litre

LAFT	lowest average field trial
LC_{50}	lethal concentration 50%
LD	lactation day
LD_{50}	lethal dose 50%
LDH	lactate dehydrogenase
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOEC	low observed effect concentration
LOD	limit of detection
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
LSC	liquid scintillation counting
mg	milligram
mL	millilitre
m/z	mass-to-charge ratio of an ion
MAS	maximum average score
MBD	more balanced diet
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
M/L	Mixer/Loader
M/L/A	Mixer/Loader/Applicator
MOA	mode of action
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
MTD	maximum tolerated dose
N/A	not applicable
nb	number
NAFTA	North American Free Trade Agreement
NDETF	Non-Dietary Exposure Task Force
NHANES/WWEIA	National Health and Nutrition Examination Survey/What We Eat in America
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
NR	not reported
N/R	not required
NZW	New Zealand white
OC	organic carbon content
OM	organic matter content
P	parental generation
PBI	plantback interval
PHED	Pesticide Handler Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant

PMRA	Pest Management Regulatory Agency
PND	postnatal day
ppb	parts per billion
PCV	packed cell volume
PPE	Personal Protective Equipment
ppm	parts per million
PWC	Pesticide Water Calculator
PYO	Pick-Your-Own
q_1*	cancer potency factor
QSAR	quantitative structure-activity relationship
RAC	raw agricultural commodity
RBC	red blood cells
RD	residue definition
REI	Restricted-Entry Interval
rel	relative
retic	reticulocytes
RQ	risk quotient
RSD	relative standard deviation
RTI	Retreatment Interval
SC	soluble concentrate
SDEV	standard deviation
SER	smooth endoplasmic reticulum
SI	stimulation index
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TC	Transfer Coefficient
TGAI	technical grade active ingredient
T_{max}	time to peak blood concentration
TP	transformation product
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
TWA	time-weighted average
UAN	urea ammonium nitrate
UDP-GT	uridine diphosphate glucuronyltransferase
UF	uncertainty factor
US 40°N	40 degree latitude North in the United States
USEPA	United States Environmental Protection Agency
UV	ultraviolet
VMD	volume median diameter
v/v	volume per volume dilution
WBC	white blood cells
wk	week
wt	weight
yrs	Years

Appendix I Tables and Figures

Table 1 Residue Analysis

Analytical Methods	Matrix	Analytes	Method ID/ Type	LOQ	Reference
Livestock Commodities					
Enforcement Method	Beef liver and cream Eggs	Inpyrfluxam (S-2399), 1'-COOH-S-2840-A, 1'-COOH-S-2840-B, 1'-CH_2OH-S-2840-A and 1'-CH_2OH-S-2840-B (including conjugates of 1'-CH_2OH-S-2840-A and 1'-CH_2OH-S-2840-B converted to their aglycones)	RM-50AM-1: Beef liver and cream RM-50E-1: Eggs Both LC-MS/MS	Both methods: 0.010 ppm for each analyte	PMRA# 2819370
Data-Gathering Method	Dairy cattle milk, liver, kidney, muscle and fat Laying hen eggs, liver, muscle and fat	Inpyrfluxam (S-2399), 1'-COOH-S-2840-A, 1'-COOH-S-2840-B, 1'-CH_2OH-S-2840-A and 1'-CH_2OH-S-2840-B (including free and conjugated forms)	Method 2814W - Dairy cattle Method 2815W Laying hen Both LC-MS/MS	Both methods: 0.010 ppm for S-2399 and 0.005 ppm for metabolites	PMRA#s 2819574, 2819575
ILV of Enforcement Method	2814W: Bovine milk RM-50AM-1: Bovine liver and chicken breast muscle	Inpyrfluxam (S-2399), 1'-COOH-S-2840-A, 1'-COOH-S-2840-B, 1'-CH_2OH-S-2840-A and 1'-CH_2OH-S-2840-B (including conjugates of 1'-CH_2OH-S-2840-A and 1'-CH_2OH-S-2840-B)	2814W RM-50AM-1 Both LC-MS/MS	2814W: 0.010 ppm for S-2399 and 0.005 ppm for metabolites RM-50AM-1: 0.010 ppm for each analyte	PMRA# 2819369
Radiovalidation	2814W: Goat milk, muscle, liver and fat from metabolism study (2452W)	Inpyrfluxam (S-2399), 1'-COOH-S-2840-A, 1'-COOH-S-2840-B, 1'-CH_2OH-S-2840-A and 1'-CH_2OH-S-2840-B (including free and conjugated forms)	NA	NA	PMRA# 2819574

Analytical Methods	Matrix	Analytes	Method ID/ Type	LOQ	Reference
Plant Commodities					
Enforcement Method and Data-Gathering	Validated for corn grain, soybean seed, apples, and corn stover.	Inpyrfluxam, 3'-OH-S-2840, 1'COOH-S-2840A, 1'COOH-S-2840B 1'-CH_2-OH-S-2840A, 1'-CH_2-OH-S-2840B, and DFPA-$CONH_2$ (free forms). 1'COOH-S-2840A, 1'COOH-S-2840B 1'-CH_2-OH-S-2840A, and 1'-CH_2-OH-S-2840B (aglycones)	Method RM-50C-1 LC-MS/MS	0.01 ppm in crops 0.02 ppm in livestock feed items	PMRA# 2819567
Data-Gathering Methods	Validated for apples, soybean seed, corn grain, and corn stover.	Free and conjugated forms of *N*-des-Me-DFPA	Methods RM-50C-2 and RM 50C-2a LC-MS/MS	RM-50C-2: 0.010 ppm RM-50C-2a: 0.020 ppm	PMRA# 2819566
	Validated for canola seed sorghum stover	Inpyrfluxam, 1'-CH_2OH-S-2840-B, and DFPA (aglycones)	Method RM-50RC LC-MS/MS	0.010 ppm for canola 0.020 ppm for sorghum stover	PMRA# 2819568
ILV of Enforcement Method	Validated by an independent laboratory for corn stover, corn grain, and corn forage.	Inpyrfluxam, 3'-OH-S-2840, 1'-CH_2-OH-S-2840A, 1'-CH_2-OH-S-2840B, and DFPA-$CONH_2$ (free forms). 1'COOH-S-2840A, 1'COOH-S-2840B 1'-CH_2-OH-S-2840A, and 1'-CH_2-OH-S-2840B (aglycones)	Method RM-50C-1 LC-MS/MS	Corn grain: 0.010 ppm. Corn stover and forage: 0.020 ppm.	PMRA#: 2819572, 2819570, and 2819569

Analytical Methods	Matrix	Analytes	Method ID/ Type	LOQ	Reference
	Validated by an independent laboratory for apple, soybean seed, and soybean oil.	Inpyrfluxam	Method RM-50C-1a LC-MS/MS	0.010 ppm for apple, soybean seed, and soybean oil	PMRA# 2819573
Radiovalidation	Rice straw from metabolism study (PMRA# 2819362) and radish tops from confined crop rotation study (PMRA# 2819589)	Inpyrfluxam, 3'-OH-S-2840, 1'COOH-S-2840A, 1'COOH-S-2840B 1'-CH_2-OH-S-2840A, 1'-CH_2-OH-S-2840B, and DFPA-$CONH_2$ (free forms). 1'COOH-S-2840A, 1'COOH-S-2840B 1'-CH_2-OH-S-2840A, and 1'-CH_2-OH-S-2840B (aglycones)	Method RM-50C-1 LC-MS/MS	0.020 ppm for rice straw 0.010 ppm for radish tops	PMRA# 2819571
Environmental Media					
Data generation and enforcement	Soil, sediment	Parent, 3'-OH-S-2840, 1'-COOH-S-2840-A, 1'-COOH-S-2840-B	HPLC-MS/MS	0.01 mg/kg	PMRA# 2819389, 2819364
	Water	Parent, 3'-OH-S-2840, 1'-COOH-S-2840-A, 1'-COOH-S-2840-B	HPLC-MS/MS	1.0 µg/L	PMRA# 2819368, 2819391

Table 2 Identification of Select Metabolites of Inpyrfluxam

Code	Chemical Name
N-des-Me-1',1'-bis(CH_2OH)-S-2840	*N*-des-Me-1',1'-bis(N-[(1RS,3RS)-(1RS,3SR)--2,3-dihydro-1-(hydroxymethyl)-1,3-dimethyl-1H-inden-4-yl)]-1-methyl-3-(difluoromethyl)-1H-pyrazole-4-carboxamide)
1',1'-bis(CH_2OH)-S-2840	1',1'-bis(N-[(1RS,3RS)-(1RS,3SR)--2,3-dihydro-1-(hydroxymethyl)-1,3-dimethyl-1H-inden-4-yl)]-1-methyl-3-(difluoromethyl)-1H-pyrazole-4-carboxamide)
N-des-Me-1'-COOH-S-2840	*N*-des-Me-(1RS,3RS)-(1RS,3SR)-2,3-dihydro-1,3-dimethyl-4-{[1-methyl-3-(difluoromethyl)-1H-pyrazole-4-ylcarbonyl] amino}-1H-indene-1-carboxylic acid
N-des-Me-1'-CH_2OH-S-2840	*N*-des-Me-N-[(1RS,3RS)-(1RS,3SR)--2,3-dihydro-1-(hydroxymethyl)-1,3-dimethyl-1H-inden-4-yl)]-1-methyl-3-

Code	Chemical Name
	(difluoromethyl)-1H-pyrazole-4-carboxamide
glucuronide of *N*-des-Me-1'-CH_2OH-S-2840	glucuronide of *N*-des-Me-N-[(1RS,3RS)-(1RS,3SR)--2,3-dihydro-1-(hydroxymethyl)-1,3-dimethyl-1H-inden-4-yl)]-1-methyl-3-(difluoromethyl)-1H-pyrazole-4-carboxamide
glucuronide of 1'-CH_2OH-S-2840	glucuronide of N-[(1RS,3RS)-(1RS,3SR)--2,3-dihydro-1-(hydroxymethyl)-1,3-dimethyl-1H-inden-4-yl)]-1-methyl-3-(difluoromethyl)-1H-pyrazole-4-carboxamide
3'-OH-S-2840	3-(Difluoromethyl)-*N*-[3'-hydroxy-(3'S)-1',1',3'-trimethyl-2',3'-dihydro-1'*H*-inden-4'-yl]-1-methyl-1*H*-pyrazole-4-carboxamide; 3-(Difluoromethyl)-*N*-[3'-hydroxy-(3'R)-1',1',3'-trimethyl-2',3'-dihydro-1'*H*-inden-4'-yl]-1-methyl-1*H*-pyrazole-4-carboxamide
1'-COOH-S-2840	(1RS,3RS)-(1RS,3SR)-2,3-dihydro-1,3-dimethyl-4-{[1-methyl-3-(difluoromethyl)-1H-pyrazole-4-ylcarbonyl] amino}-1H-indene-1-carboxylic acid

Table 3 Toxicity Profile of End-use Product(s) Containing Inpyrfluxam Technical

Study Type/Animal/PMRA#	Study Results
Acute Toxicity Studies – End-use Product -Excalia Fungicide	
Acute Oral Toxicity Sprague-Dawley rats PMRA# 2819554	LD_{50}(♀) = 550 mg/kg bw 550 mg/kg bw: one mortality with abnormal gait, irregular respiration, hypoactivity and/or writhing, surviving animal with abnormal gain and irregular respiration 174 mg/kg bw: hypoactivity, irregular respiration, hunched posture **Moderate acute toxicity**
Acute Dermal Toxicity Sprague-Dawley rats PMRA# 2819555	LD_{50} (♂/♀) > 5000 mg/kg bw Erythema at dose site **Low acute toxicity**
Acute Inhalation Toxicity Sprague-Dawley rats PMRA# 2819556	LC_{50} (♂/♀)> 2.10 mg/L One mortality (♀) with hunched posture, prone posture, red oral discharge; surviving animals with hypoactivity **Low acute toxicity**

Study Type/Animal/PMRA#	Study Results
Primary Eye Irritation New Zealand White rabbits PMRA# 2819557	MAS = 0/110 MIS= 4/110 @ 24 hrs **Non-irritating**
Primary Dermal Irritation New Zealand White rabbits PMRA# 2819558	MAS = 0/8 **Non-irritating**
Dermal Sensitization (LLNA) CBA/J mouse PMRA# 2819559	**Negative**
Acute Toxicity Studies – End-use Product - Zeltera Fungicide	
Acute Oral Toxicity Sprague-Dawley rats PMRA# 2819633	LD_{50} (♀) = 550 mg/kg bw 550 mg/kg bw: one death with ataxia, irregular respiration, hypoactivity and hunched posture 1750 mg/kg bw: prone posture, irregular respiration, clear oral discharge, ataxia, and/or hypoactivity 5000 mg/kg bw: mortality with no clinical signs prior to death **Moderate acute toxicity**
Acute Dermal Toxicity Sprague-Dawley rats PMRA# 2819634	LD_{50} (♂/♀) > 5000 mg/kg bw **Low acute toxicity**
Acute Inhalation Toxicity Sprague-Dawley rats PMRA# 2819635	LC_{50} (♂/♀) > 2.19 mg/L Irregular respiration, hyperactivity, ataxia **Low acute toxicity**

Study Type/Animal/PMRA#	Study Results
Primary Eye Irritation New Zealand White rabbits PMRA# 2819636	MAS = 0/110 MIS = 0.67/110 @ 1hr **Non-irritating**
Dermal Irritation New Zealand White rabbits PMRA# 2819637	$MAS_{(24\text{-}72hrs)}$ = 0/8 **Non-irritating**
Dermal Sensitization (LLNA) CBA/J mouse PMRA# 2819638	**Negative**

Table 4 Toxicity Profile of Technical Inpyrfluxam

Effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Study Type/Animal/PMRA#	Study Results
Metabolism (gavage) PMRA# 2819342/2819343	Absorption, distribution, metabolism and excretion were investigated in Wistar rats with pyrazolyl-4-^{14}C and phenyl-4-^{14}C labels. Single dose studies were performed using dose levels of 1 mg/kg bw with the pyrazolyl-4-^{14}C and phenyl-4-^{14}C labels and 150 mg/kg bw with the pyrazolyl-4-^{14}C label. The repeat-dose study was performed with pyrazolyl-4-^{14}C-labelled compound at 1 mg/kg bw/day administered for 14 days. **Absorption** Absorption was rapid with T_{max} values of 1 hr in single low-dose ♂ and ♀ and repeat-dose ♂, 2 hrs in repeat-dose ♀, 8 hrs in high-dose ♂ and 24 hrs in high-dose ♀. There were no major differences in low-dose group Cmax values in males (0.161 µg eq. of inpyrfluxam/g) or females (0.144 µg eq. of inpyrfluxam/g) or in single or repeat doses (0.198 and 0.214 µg eq. of inpyrfluxam/g in males and females, respectively). Cmax values in high-dose group animals were 8.0 and 7.2 µg eq. of inpyrfluxam/g in males and females, respectively.

Study Type/Animal/PMRA#	Study Results
	Elimination Toxicokinetics were relatively linear in ♂ ($t_{1/2}$ = 13 and 14 hrs at low and high dose levels, respectively, and 12 hrs following repeat dosing) and supralinear in ♀ ($t_{1/2}$ = 12 hrs at low dose level) with a relatively shorter $t_{1/2}$ of elimination after repeat dosing ($t_{1/2}$ = 9 hrs), but a relatively longer $t_{1/2}$ of elimination in ♀ after a single high dose ($t_{1/2}$ = 17 hrs). In non-bile-duct cannulated rats, excretion was slightly higher in urine (60–61% AD) than feces (41–42% AD) in low-dose groups and skewed slightly towards urine in females in high-dose groups (49 and 53% AD in urine and 49 and 44% AD in feces in males and females, respectively). In bile-duct cannulated rats, urine residues consisted of 27 and 48% of the AD in males and females, respectively, bile residues consisted of 69 and 47% of the AD in males and females, respectively, and fecal residues consisted of 3% of the AD in both males and females. **Distribution** Tissue distribution was extensive although quantifiable levels were only present in the G.I. tract and contents, liver, bone and hair and skin at 7 days following administration in the single dose studies or the last administered dose in the repeat dose study. At the previous time points, other organs where residual concentrations were above those of blood plasma were the thyroid, kidneys, adrenal glands, pituitary glands, and lungs. There was no evidence of tissue retention. **Metabolism** The metabolic pathway consists of N-demethylation, oxidation of the 1',1'-dimethyl group of the indane ring followed by further oxidation to carboxylic acid, and glucuronide conjugation, as well 3'- and 7'-hydroxylation, of the indane group as minor pathways. The main metabolites were *N*-des-Me-1',1'-bis(CH_2OH)-S-2840 (up to 11% of the AD), 1',1'-bis(CH_2OH)-S-2840 (up to 11% of the AD), *N*-des-Me-1'-COOH-S-2840 (up to 21% of the AD) and 1'-COOH-S-2840 (up to 15% of the AD) found in urinary and fecal samples at low doses. The aforementioned metabolites and *N*-des-Me-1'-CH_2OH-S-2840 (up to 8% of the AD) were detected in the urinary and fecal samples of the high-dose groups and, additionally, the glucuronide of *N*-des-Me-1'-CH_2OH-S-2840 and glucuronide of 1'-CH_2OH-S-2840 were found in urine, feces and bile samples but at higher concentrations in the bile samples of the bile duct cannulation study (up to 21 and 30% of AD in the bile samples, respectively).
Acute Toxicity Studies	
Acute Oral Toxicity Wistar rats	50 mg/kg bw < LD_{50} (♀) < 300 mg/kg bw 300 mg/kg bw: 2 mortalities with prone or lateral position and/or loss of righting reflex, ↓ spontaneous activity, ↑ ataxic gait

Study Type/Animal/PMRA#	Study Results
PMRA# 2819306	50 mg/kg bw: single incidence of decreased spontaneous activity **High acute toxicity**
Acute Oral Toxicity Wistar rats PMRA# 2819308	LD_{50} (♀) = 180 mg/kg bw 570 mg/kg bw: death, ↓ spontaneous activity 180 mg/k bw: death, ↓ spontaneous activity, ataxic gait **High acute toxicity**
Acute Dermal Toxicity Wistar rats PMRA# 2819310	LD_{50} (♂/♀) > 2000 mg/kg bw **Low acute toxicity**
Acute Inhalation Toxicity Wistar rats PMRA# 2819311	LC_{50} (♂/♀) > 2.61 mg/L Wet fur (♂♀); death with no symptoms, surviving animals with decreased spontaneous activity, ataxic gait, lateral position (♀) **Low acute toxicity**
Eye Irritation New Zealand White rabbits PMRA# 2819312	MAS = 1.33/110 MIS = 4/110 at 24 hrs **Minimally irritating**
Dermal Irritation New Zealand White rabbits PMRA# 2819313	MAS = 0/8 **Non-irritating**
Dermal Sensitization (Guinea Pig Maximization) Slc:Hartley Guinea Pigs PMRA# 2819314	**Negative**

Study Type/Animal/PMRA#	Study Results
Short-Term Toxicity Studies	
28-Day Oral Toxicity (diet) CD1 mice PMRA# 2879424	Supplemental – range-finding NOAEL and LOAEL not established ≥ 54/60 mg/kg bw/day: ↓ total bili (♂) ≥ 170/200 mg/kg bw/day: ↑ centrilobular hepatocellular hypertrophy (♂♀); ↑ abs liver wt (♂); ↓ abs kidney wt,↑ atretic follicle/interstitial gland (♀) ≥ 610/840 mg/kg bw/day : ↑ dark liver (♂♀); ↑ APTT, ↑ rel liver wt, ↑ enlarged liver (♂); ↓ total bili, ↑ total gluc, K, ↑ liver and abs adrenal wt, ↓ ovarian and rel kidney wt (♀) 1110/1180 mg/kg bw/day: ↑ accessory adrenocortical tissue, fine vacuolation of zona fasciculata/reticularis and glomerulosa, ↑ mononuclear cell pelvic infiltration kidney, papilla mineralization, ↑ granulocytic infiltration of submandibular lymph node sinus (♂♀); ↓ kidney, heart, lung wt, ↑ focal mononuclear cell infiltration of thyroid (♂); ↑ total chol, ↑ rel adrenal wt, ↑ enlarged liver, ↑ hyaline casts of kidney, ↑swelling of salivary gland submandibular acinar cell, ↑ focal glandular dilatation of stomach, ↑ mononuclear cell infiltration of submucosa of urinary bladder (♀)
90-Day Oral Toxicity (diet) CD1 mice PMRA# 2819315	NOAEL = 111/130 mg/kg bw/day (♂/♀) LOAEL = 491/559 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ globulin, ↑ liver wt (♂♀); ↑ centrilobular hepatocellular hypertrophy, ↑ centrilobular hepatocellular fatty change (♂); ↓ A/G ratios, ↑ diffuse hepatocellular hypertrophy (♀)
28-Day Oral Toxicity (diet) Wistar rats PMRA# 2879425	Supplemental – range-finding NOAEL and LOAEL not established ≥ 86/91 mg/kg bw/day: ↑ total chol, ↑ phospholipid, ↑ fine vacuolation of zona granulosa of adrenal (♂); ↑ trig, ↑ interstitial gland ovary (♀) ≥ 250/260 mg/kg bw/day: ↓ bw/bwg, fc, ↓ urinary pH, ↑ GGT, ↑ diffuse hepatocellular hypertrophy ↑ follicular cell hypertrophy of thyroid (♂♀); ↑ rel liver wt, ↓ thymus wt, ↑ fine vacuolation of zona fascicualata of adrenal, ↑ basophilic tubules, hyaline droplets proximal tubules kidneys (♂); ↑ total chol, ↑ phospholipid, ↑ liver wt, ↓ rel ovary, uterine wt, ↑ fine vacuolation of zona granulosa of adrenal, ↑ fatty infiltration bone marrow, ↑ vacuolation of ovarian interstitial gland, ↑ uterine atrophy (♀) 410/380 mg/kg bw/day: dark, enlarged liver (♂♀); ↑ RBC, ↑ alb, A/G ratio, ↓ gluc, ↑ LDH, ↑ abs liver wt, ↑ rel thyroid wt, ↓ rel epididymis, ↑ abnormal

Study Type/Animal/PMRA#	Study Results
	protrusion liver, ↑ dark, red focus on thymus, ↑ fatty infiltration bone marrow, ↑ kidney mineralization, ↑ focal mononuclear cell prostate interstitial cell infiltration, thymic atrophy (♂); ↑ ovarian cyst, ↑ thymic tangible macrophage, focal cell infiltration of thyroid inflammatory cell (♀)
90-Day Oral Toxicity (diet) Wistar rats PMRA# 2819316	NOAEL = 32/38 mg/kg bw/day (♂/♀) LOAEL = 123/144 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ GGT, ↑ rel. liver wt, ↑ hepatocellular hypertrophy (♂♀); ↑ α2μ-globin hyaline droplets kidney (♂); ↓ open field rearing, ↓ bw, ↓ bwg, ↓ fc, ↑ platelets, ↑ ALP, ↑ TG, ↑ chol, ↓ bili, ↑ ovary interstitial gland vacuolation, ↑ hypertrophy thyroid follicular cells, ↑ adrenal cortical cell vacuolation (♀)
28-Day Oral Toxicity (capsule) Beagle Dogs PMRA# 2879426	Supplemental – range-finding NOAEL and LOAEL not established ≥ 100 mg/kg bw/day: ↑ soft/mucous stool (♂♀); ↑ diffuse hepatocellular eosinophilic change (♀) ≥ 500 mg/kg bw/day: ↑ vomiting, ↑ focal hepatocellular necrosis (♂♀); ↓ phospholipid, ↑ ALP, ↑ SER proliferation (♂); ↑ liver wt (♀) 1000 mg/kg bw/day: ↑ salivation, ↓ bwg, ↑ diffuse hepatocellular eosinophilic inclusion, ↑ concentric membranous bodies of ER, ↑ atrophy/involution of thymus (♂♀); ↓ total chol, ↑ liver wt, diffuse hepatocellular hypertrophy, ↑ focal atrophy of seminiferous tubule (♂); 1 mortality, ↓ fc, ↓ blood gluc, ↑ AST, ALT, GGT, ↓ thymus wts, ↑ fatty inclusion in bone marrow, ↑ SER dilatation, ↑ lipid droplet liver, ↑ atrophy acinar cell of submandibular salivary gland (♀)
90-Day Oral Toxicity (capsule) Beagle dogs PMRA# 2819318	NOAEL = 40 mg/kg bw/day (♂/♀) LOAEL = 160 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ vomiting, ↓retic, ↓ TP, alb, total chol, ↑ dark, enlarged liver (♂/♀); ↓ bw/fc, ↑ ALP, ↑ gallbladder calculi, single cell necrosis (diffuse and/or periportal), ↑ brown pigment deposition in Kupffer cells, calculi in the gallbladder, ↑ proximal tubular cell hypertrophy, ↑ eosinophilic inclusion bodies of proximal tubular cell of kidneys, ↑ vacuolation of zona fasciculata in adrenals (♂); ↑ GGT, ↓ A/G ratio, ↑ eosinophilic inclusion bodies of liver (♀)
12-Month Oral Toxicity (capsule)	NOAEL = 6 mg/kg bw/day (♂/♀) LOAEL = 30 mg/kg bw/day (♂/♀)

Study Type/Animal/PMRA#	Study Results
Beagle dogs PMRA# 2919320	Effects at the LOAEL: ↑ ALP, GGT, ↑ liver wts, ↑ vacuolation of zona fasciculata in adrenals (♂♀); ↑ BUN, ↓ ALB, A/G, ↑ hepatocellular hypertrophy (♂); ↑ vomiting (♀) 160 mg/kg bw/day: ↑ vomiting first few days of treatment (♀) Toxicokinetics: Plasma concentrations of inpyrfluxam displayed dose-response and were below the LOQ at 2 mg/kg bw/d. There were few sex-related differences
28-Day Dermal Toxicity Sprague Dawley rats PMRA# 2819321	NOAEL = 1000 mg/kg bw/day LOAEL = undetermined No treatment-related effects.
90-Day Inhalation Toxicity Waiver request PMRA 2819322	The waiver request was accepted based on the low acute inhalation toxicity compared to the acute oral toxicity and on the applicant's proposal of assuming 100% absorption using the inhalation routes of exposure and defaulting to the oral toxicity endpoints.
Chronic Toxicity/Oncogenicity Studies	
18-Month Oral Carcinogenicity (diet) CD1 mice PMRA# 2819323	NOAEL = 77/69 mg/kg bw/day (♂/♀) LOAEL = 224/210 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ amyloidosis various organs (♂♀); ↑ centrilobular hypertrophy (♂); ↑ dark colouration of liver, ↑ necrosis of renal papilla, amyloid nephropathy (♀) **No evidence of oncogenicity** Toxicokinetics: According to toxicokinetic investigations of the plasma at 52 weeks of treatment, plasma concentrations of inpyrfluxam were below the LOQ at 77/69 mg/kg bw/day and around the LOQ at 210 mg/kg bw/d in ♀. Systemic exposure was lower in ♀than in ♂.
24-Month Oral Chronic Toxicity/Carcinogencity (diet) Wistar rats PMRA# 2819324	NOAEL = 19/7.5 mg/kg bw/day (♂/♀) LOAEL = 78/25 mg/kg bw/day (♂/♀) Effects at the LOAEL (♀): ↓ bw/bwg (♀) Effects at the LOAEL (♂): ↓ bw/bwg, fc,↑ GGT, ↑ glob, A/G, ↑ T. bili, ↑ chol, ↑ triglycerides, ↑ pancreatic acinar cell hyperplasia (♂)

Study Type/Animal/PMRA#	Study Results
	Effects at the HDT of 66 mg/kg bw/day in ♀ included: ↓ fc, ↓ neut, mono, ↑ GGT, BUN, ↓ T. bili, ↑ chol, ↓ triglycerides, ↑ ovarian cysts and masses, ↑ increase in overall ovarian tumours (1, 0, 1, 4) According to toxicokinetic investigations of the plasma at 13, 25 and 51 weeks of treatment, plasma concentrations were above the LOQ at all dose levels in ♀ and only at the high-dose level in males. (2000 ppm ♂ had lower systemic exposures than ♀ dosed at 500 ppm.) **MTD exceeded for ♀** **Evidence of carcinogenicity above the MTD**
Developmental/Reproductive Toxicity Studies	
1-Generation Reproductive Toxicity (diet) Wistar rats PMRA# 2819325	No NOAEL or LOAEL established Supplemental – range-finding **Parental:** ≥ **64/68 mg/kg bw/day**: ↓ bwg/fc wk 0–1 premating (♀) ≥ **131/132 mg/kg bw/day**: ↑ liver wt, ↑ dark colouration liver (♂); ↓ bwg premating, GD 0–20, ↓ fc wk 0–1 and LD 0–7 (♀) **232/137 mg/kg bw/day**: ↓ bw/fc (♂/♀) **Reproductive**: **232/237 mg/kg bw/day**: ↓ implantation sites and offspring born alive, ↓ ovary and uterine wts **Offspring**: ≥ **20 mg/kg bw/day**: ↓ rel spleen ♂ ≥ **68 mg/kg bw/day**: ↓ abs spleen ♂ ≥ **132 mg/kg bw/day**: ↓ bw, ↑ eye enlargement (♂/♀); ↓ abs/rel spleen, ↑ delayed sexual maturation, synechia, haemorrhage, cataract ♀ **237 mg/kg bw/day**: ↓ viability, ↑ lost and/or found dead, ↑ eye opacity (♂/♀); ↑ synechia, haemorrhage, cataracts ♂; ↑ retinal atrophy ♀
2-Generation Reproductive Toxicity (diet) Wistar rats	**Parental Toxicity** NOAEL = 28/35 mg/kg bw/d (♂/♀) LOAEL = 113/86 mg/kg bw/d

Study Type/Animal/PMRA#	Study Results
PMRA# 2819326	Effects at the LOAEL: ↓ bw/bwg F_1, ↑ rel liver wt P, ↑ diffuse hepatocellular hypertrophy P/F_1, ↑ kidney wt F_1, ↑ deposition hyaline droplets in proximal tubular cells P/F_1 ♂; ↓ bw/bwg P/F_1, ↓ fc P, ↑ liver wt P/F_1, ↑ thyroid wt, ↑ follicular cell hypertrophy P/F_1, ↑ loss of fur P ♀ **Offspring Toxicity** NOAEL = 35 mg/kg bw/d LOAEL = 86 mg/kg bw/d Effects at the LOAEL: ↓ bw F_1/F_2 ♂♀ **Reproductive Toxicity** NOAEL = 28/35 mg/kg bw/d LOAEL = 113/86 mg/kg bw/d Effects at the LOAEL (♀): ↑ luminal dilatation uterus P, ↓ abs uterine wt F_1, abs/rel uterine wts F_2 ♀ Effects at the LOAEL (♂): ↑ atrophy of seminiferous tubules P/F_1, ↑ atrophy glandular epithelial cells in prostate F_1♂ **No evidence of sensitivity of the young**
Developmental Toxicity (gavage) Wistar rats PMRA# 2819327	No NOAEL or LOAEL established Supplemental – range-finding **Maternal** ≥ **40 mg/kg bw/d**: ↓bwg starting day 6-9, ↓ fc at day 6-9 and day 9-12 ≥ **80 mg/kg bw/d**: ↓ adjusted final bw, ↓ bwg starting day 6-9, ↓ fc starting day 6-9 **Developmental:** **≥ 40 mg/kg bw/d**: ↓ fetal bw
Developmental Toxicity (gavage) Wistar rats PMRA# 2819328	**Maternal** NOAEL = 25 mg/kg bw/d LOAEL = 80 mg/kg bw/d Effects at the LOAEL: ↓ bw GD 18 and 20, ↓ adj final bw, ↓ bwg GD 6-9, GD 6-12, GD 6-15, GD 6-18, ↓ fc starting day 6-9 **Developmental** NOAEL = 25 mg/kg bw/d LOAEL = 80 mg/kg bw/d Effects at the LOAEL: ↓ fetal bw

Study Type/Animal/PMRA#	Study Results
	No evidence of treatment-related malformations No evidence of sensitivity of the young
Developmental Toxicity (gavage) Wistar rats PMRA# 2819349	No NOAEL or LOAEL established Supplemental – only one dose conducted to investigate malformations **Maternal** **90 mg/kg bw/d**: ↓ bw, ↓ bwg ,↓ fc **Developmental** **90 mg/kg bw/d**: ↓ fetal bw
Developmental Toxicity (gavage) Japanese White rabbits PMRA 2819329	No NOAEL or LOAEL established Supplemental – range-finding **Maternal:** **≥ 50 mg/kg bw/d:** ↓ bwg **≥ 150 mg/kg bw/d:** ↓ fc **Offspring:** None
Developmental Toxicity (gavage) Japanese White rabbits PMRA# 2819330	No NOAEL or LOAEL established Supplemental – range-finding **Increase in found dead and killed in extremis at doses ≥ 500 mg/kg bw/d** **Maternal toxicity:** **≥ 300 mg/kg bw/d:** ↑ lateral and/or prone position, convulsions, loose stool, ↑ abortion, ↓ bw/bwg, fc, ↑ stomach spot, slight ↑ in % resportions/fetal deaths **≥ 500 mg/kg bw/d:** ↑ killed in extremis/found dead, ↑ stomach ulcers, liquid contents in large intestine **1000 mg/kg bw/d:** ↓ spontaneous activity, ↑ bradypnea **Offspring:** **300 mg/kg bw/d:** ↓ fetal bw, slight ↑ in % resportions/fetal deaths

Study Type/Animal/PMRA#	Study Results
	≥ 500 mg/kg bw/d: Developmental toxicity could not be assessed due to an insufficient number of litters
Developmental Toxicity (gavage) Japanese White rabbits PMRA# 2819331	**Maternal** NOAEL = 60 mg/kg bw/d LOAEL = 200 mg/kg bw/d Effects at the LOAEL**:** 2 abortions, bw loss, ↓ bwg, ↓ fc, ↓ gravid uterine wt **Developmental** NOAEL = 60 mg/kg bw/d LOAEL = 200 mg/kg bw/d Effects at the LOAEL: 2 abortions **No evidence of sensitivity of the young or treatment-related malformations**
Genotoxicity Studies	
Reverse mutation assay *Salmonella typhimurium* and *Escherichia coli* PMRA# 2819332	**Negative ± metabolic activation** Tested up to the limit concentration
In vitro mammalian cell assay Chinese Hamster V79 Cells PMRA# 2819337	**Negative ± metabolic activation** Tested up to the cytotoxic concentration
In vitro mammalian clastogenicity Chinese Hamster Lung cells (CHL/IU) PMRA# 2819338	**Negative ± metabolic activation** Tested up to the cytotoxic concentration
In vivo cytogenetics CD-1 Mice PMRA# 2819341	**Negative**

Study Type/Animal/PMRA#	Study Results
Neurotoxicity Studies	
Acute Neurotoxicity (gavage) Wistar rats PMRA# 2819346	No NOAEL or LOAEL established Supplemental **One female from the 200 and 400 mg/kg bw/d dose groups, respectively, found dead** ≥ 200 mg/kg bw/d: ↓ alertness, ↑ staggering gait, ↓ muscle tone ♀ 400 mg/kg bw/d: ↑ prone position, bradypnea, laboured respiration, tremors, paleness, nasal secretions, ↓ co-ordination of movement, ↑ hypothermia, ananastasia, ↓ motor activity ♀
Acute Neurotoxicity (gavage) Wistar rats PMRA# 2819344	NOAEL = 200/100 mg/kg bw (♂/♀) LOAEL = undetermined/200 mg/kg bw/d Effects at the LOAEL: ↓ muscle tone, activity counts ♀ **Evidence of non-selective neurotoxicity**
Subchronic neurotoxicity study [BrlHan:WIST@Jcl(GALAS)] rats PMRA# 2819347	NOAEL = 30/35 mg/kg bw/d (♂/♀) LOAEL = 119/68 mg/kg bw Effects at the LOAEL: ↓ bw, ↓ fc (sporadic) ♀ **No evidence of selective neurotoxicity**
Special Studies (non-guideline)	
Immunotoxicity study Waiver PMRA# 2819348	Waiver is based on lack of immunological effects in the database. Acceptable
Mode of Action Studies	
Liver and thyroid time course toxicity study HarlanRccHanTM:WIST rats PMRA# 2819351	No NOAEL or LOAEL established Supplemental No quality assurance ↓ bw, ↑ liver wts, ↑ hepatocellular hypertrophy, ↑ thyroid hypertrophy, ↑ hepatic CYP and UGT mRNA expression levels; ↑ enlarged liver ♂; ↑ hepatic enzyme activity ♀

Study Type/Animal/PMRA#	Study Results
Liver and thyroid time course toxicity study Crlj:CD1 (ICR) mice PMRA# 2819352	No NOAEL or LOAEL established Supplemental No quality assurance 7-day: ↑ liver wts, enlarged liver, hepatocellular hypertrophy, ↓ hepatic enzyme activity, ↑ hepatic CYP and UGT mRNA expression level, ↓ T3 and/or T4 levels; ↑ bw ♂; ↓ bw, fc, ↓ TSH ♀ 14-day: ↑ liver wts, enlarged liver, hepatocellular hypertrophy, ↑ hepatic CYP and UGT mRNA expression level, ↓ T3 and/or T4 levels; ↑ hepatic enzyme activity, ↓ TSH ♀
Metabolite Studies	
3'-OH-S-2840	
Acute oral toxicity study RccHan:WIST rats PMRA# 2819307	LD_{50} (♀) > 2000 mg/kg bw **Low acute toxicity** Clinical signs: none
Reverse mutation assay *Salmonella typhimurium* and *Escherichia coli* PMRA# 2819333	Negative Tested up to limit concentrations
In vitro mammalian cell assay Chinese Hamster V79 Cells PMRA# 2819335	Negative Tested up to limit of solubility

Study Type/Animal/PMRA#	Study Results
In vitro mammalian clastogenicity Chinese Hamster Lung cells (CHL/IU) PMRA# 2819339	Negative
1'-COOH-S-2840	
Acute Oral Toxicity Study RccHan:WIST rats PMRA# 2819309	LD_{50} (♀) > 2000 mg/kg bw **Low acute toxicity** Clinical signs: single incidences of abdomen and anogenital staining
Reverse mutation assay *Salmonella typhimurium* and *Escherichia coli* PMRA# 2819334	Negative Tested up to limit concentrations
In vitro mammalian cell assay Chinese Hamster V79 Cells PMRA# 2919336	Negative Tested up to limit concentration/limit of solubility
In vitro mammalian clastogenicity Chinese Hamster Lung cells (CHL/IU) PMRA# 2819340	Negative

Table 5 Toxicology Reference Values for Use in Health Risk Assessment for Inpyrfluxam Technical

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	12-month Dog	NOAEL(Acute) = 30 mg/kg bw Vomiting within the first few days of treatment	100
	ARfD = 0.3 mg/kg bw		
Repeated dietary	12-month Dog	NOAEL = 6 mg/kg bw/d Liver and adrenal changes in males and females and vomiting in females.	100
	ADI = 0.06 mg/kg bw/d		
Short- and intermediate-term dermal	Short-term dermal rat	NOAEL = 1000 mg/kg bw/d	100
Short- and intermediate-term inhalation[2]	90-day oral rat	NOAEL = 32 mg/kg bw/d Liver changes in males and females, kidney changes in males and decreased open field rearing, decreased body weight, body weight gain and food consumption, vacuolation of the ovary and adrenal glands and hypertrophy of the thyroid follicular cells in females.	100
Cancer	A cancer risk assessment was not required. Evidence of ovarian tumours in rats above the MTD.		

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

Table 6 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN LAYING HEN	PMRA# 2819356
Species and Numbers	20 laying hens (*Gallus gallus domesticus*) – 10 for each radiolabel
Radiolabel position	[^{14}C-4-Pyrazolyl]-Inpyrfluxam (specific activity: 1.51×10^8 dpm/mg) and [^{14}C-Phenyl]-Inpyrfluxam (specific activity: 1.49×10^8 dpm /mg)
Average dose	[^{14}C-4-Pyrazolyl]-label: 14.12 mg a.i./kg feed (corresponding to 0.862 mg/kg bw/day) [^{14}C-Phenyl]-label: 14.89 mg a.i./kg feed (corresponding to 0.827 mg a.i./kg bw/day)
Treatment Regimen	Once a day by gelatin capsule
Study period	7 consecutive days
Collection time	Eggs: 2/day (morning and evening); Excreta: 2/day
Tissues collected	Liver, thigh muscle, breast muscle, abdominal fat, subcutaneous fat, as well as gastrointestinal (GI) tract and its contents.
Interval from last dose to sacrifice	6 hours
Plateau of residues in eggs	0.030 ppm on Day 7
Extraction solvents	Muscle, liver, eggs and excreta: twofold acetonitrile/water (1/1, v/v) and onefold acetonitrile Fat: onefold hexane/acetone (4/1, v/v) and twofold acetone

Matrices	Pyrazolyl-^{14}C Label		Phenyl-^{14}C Label	
	TRRs (ppm)	% of Administered Dose	TRRs (ppm)	% of Administered Dose
Excreta	119.91	80.25	135.95	81.70
Cage Wash	0.510	1.33	0.594	1.57
GI Tract and Contents	2.124	0.78	2.478	1.12
Pooled Egg Composite (Day 2 AM–7 PM)	0.025	0.06	0.020	0.06
Liver	0.526	0.22	0.268	0.11
Abdominal fat	0.069	0.01	0.107	0.03
Subcutaneous fat	0.109	0.01	0.086	0.01
Thigh muscle	0.013	0.01	0.012	0.01
Breast muscle	0.012	0.01	0.022	0.02

Summary of Major Identified Metabolites in Hen Matrices	
Radiolabel Position	[Pyrazolyl-4-^{14}C], [Phenyl-U-^{14}C]
Metabolites Identified	Major Metabolites
Liver	None
Eggs (Day 2 AM–Day 7 PM)	Inpyrfluxam, 1'-CH_2OH-S-2840B
Thigh muscle	DFPA-$CONH_2$, 1'-CH_2OH-S-2840B
Breast muscle	None
Abdominal fat	Inpyrfluxam
Subcutaneous fat	Inpyrfluxam

NATURE OF THE RESIDUE IN LACTATING GOAT	**PMRA# 2819357**
Species and Numbers	2 lactating goats (*Capra hircus*) – 1 for each radiolabel
Radiolabel position	[^{14}C-4-Pyrazolyl]-Inpyrfluxam (specific activity: 1.57×10^8 dpm/mg) and [^{14}C-Phenyl]-Inpyrfluxam (specific activity: 1.61×10^8 dpm /mg)
Average dose	[^{14}C-4-Pyrazolyl]-label: 13.74 mg a.i./kg feed (corresponding to 0.505 mg/kg bw/day) [^{14}C-Phenyl]-label: 15.74 mg a.i./kg feed (corresponding to 0.636 mg a.i./kg bw/day)
Treatment Regimen	Once a day by gelatin capsule
Study period	5 consecutive days
Collection time	Milk: 2/day (morning and evening); Urine and feces: 2/day
Tissues collected	Liver, kidney, flank muscle, loin muscle, omental fat, subcutaneous fat, renal fat, gastrointestinal (GI) tract and its contents, bile and blood
Interval from last dose to sacrifice	6–8 hours
Plateau of residues in milk	0.013–0.016 ppm (AM), 0.040 ppm (PM) both on Day 5
Extraction solvents	Muscle, liver, kidney and feces: twofold acetonitrile/water (1/1, v/v) and 1x acetonitrile. Fats (including omental, subcutaneous and renal fat): onefold hexane/acetone (4/1, v/v) and twofold acetone. Milk fat: twofold hexane/acetone (4/1, v/v) and onefold acetone. Skim milk: onefold acetone, onefold acetone/water (1/1, v/v), and onefold acetone.

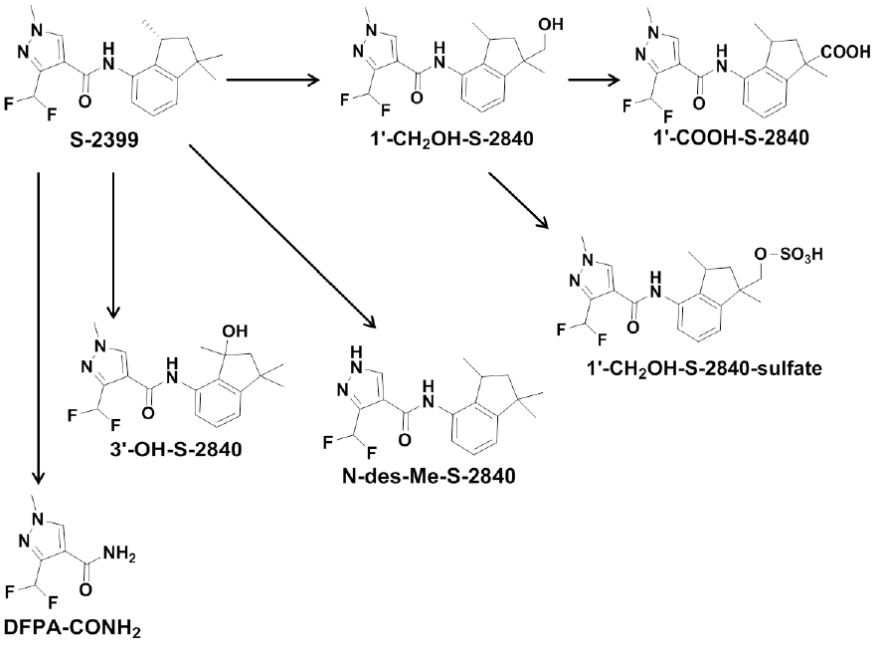
Matrices	**Pyrazolyl-^{14}C Label**	**Phenyl-^{14}C Label**

	TRRs (ppm)	% of Administered Dose	TRRs (ppm)	% of Administered Dose
Urine	4.336	35.37	6.184	33.38
Feces	5.880	41.12	6.007	44.61
Cage Wash	0.541	0.09	0.437	0.07
GI Tract and Contents	1.678	19.80	1.893	18.61
Pooled skim milk (Day 1–5)	0.240	0.11	0.238	0.08
Pooled milk fat (Day 1–5)	0.178	0.01	0.232	0.01
Liver	0.334	0.24	0.350	0.26
Kidney	0.169	0.02	0.166	0.02
Omental fat	0.007	≤0.01	0.024	≤0.01
Subcutaneous fat	0.017	≤0.01	0.029	≤0.01
Renal fat	0.009	≤0.01	0.040	≤0.01
Flank muscle	0.015	≤0.01	0.024	≤0.01
Loin muscle	0.011	≤0.01	0.016	0.01

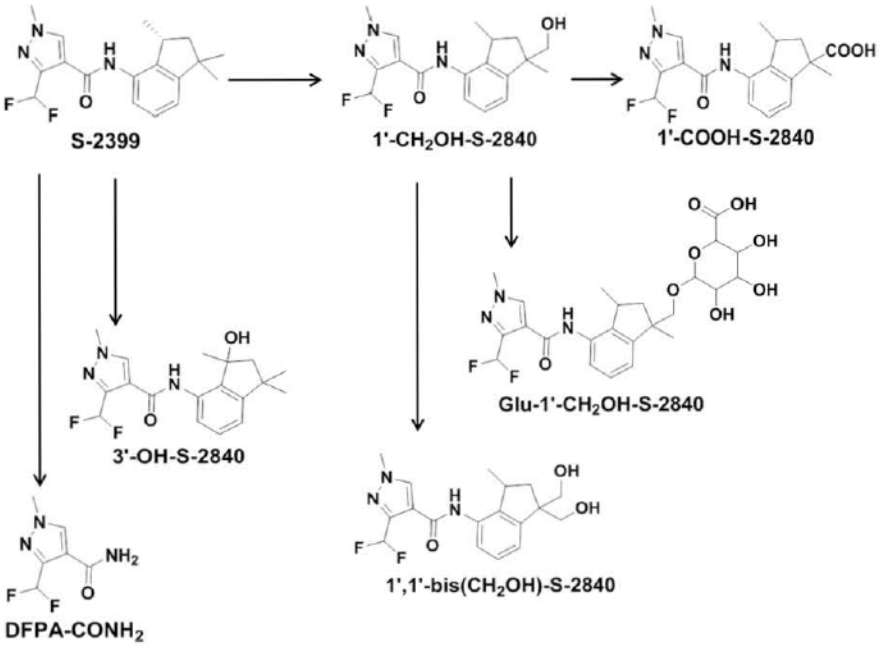
Summary of Major Identified Metabolites in Goat Matrices	
Radiolabel Position	[Pyrazolyl-4-^{14}C], [Phenyl-U-^{14}C]
Metabolites Identified	Major Metabolites
Liver	1'-COOH-S-2840A, Glu-1'-CH_2OH-S-2840
Kidney	1'-COOH-S-2840A, 1'-COOH-S-2840B, Glu-1'-CH_2OH-S-2840
Flank muscle	DFPA-$CONH_2$, 1'-COOH-S-2840A, 1'-COOH-S-2840B, Glu-1'-CH_2OH-S-2840
Loin muscle	1'-COOH-S-2840A, 1'-COOH-S-2840B, Glu-1'-CH_2OH-S-2840
Subcutaneous fat	1'-COOH-S-2840A, 1'-CH_2OH-S-2840A
Omental fat	Inpyrfluxam, 1'-COOH-S-2840A
Renal fat	Inpyrfluxam, 1'-COOH-S-2840A
Skim milk	1'-COOH-S-2840A
Milk fat	1'-COOH-S-2840A

Proposed Metabolic Scheme in Livestock

Laying Hen



Lactating Goat



FREEZER STORAGE STABILITY IN ANIMAL MATRICES		
Tested Matrices	**Analytes**	**Tested Intervals (days)**
Muscle	Inpyrfluxam, 1'-COOH-S-2840A, 1'-COOH-S-2840B, 1'-CH_2OH-S-2840A, and 1'-CH_2OH-S-2840B	Hen: 0, 21, and 40 Cattle: 0 and 29
Liver		Hen: 0, 21, and 40 Cattle: 0 and 29
Kidney		Cattle: 0 and 29
Fat		Hen: 0, 30, and 49 Cattle: 0 and 31

Milk		0, 29, and 75
Eggs		0, 29, 49, and 90

LIVESTOCK FEEDING – Dairy cattle **PMRA# 2819549**

Lactating dairy cows were administered inpyrfluxam at dose levels of 2, 6, and 20 ppm in the feeds for 28 consecutive days. The dose levels of 2, 6, and 20 ppm represent 100-fold, 300-fold, and 10000fold, respectively, the estimated more balanced diet (MBD) to beef cattle and 50-fold, 150-fold, and 500-fold, respectively, for dairy cattle. Animals were sacrificed 18–23 hours after the last dose. A depuration study was conducted using the 20 ppm feeding level and selected animals were sacrificed at 3, 7, and 14 days after the last dose. Results from the depuration study indicate residues of inpyrfluxam were <LOQ (<0.01 ppm) in all samples analyzed.

Commodity/Collection Day	Actual Feeding Level (ppm)	Highest Residues Inpyrfluxam (ppm)	Mean Residues Inpyrfluxam (ppm)
Whole milk (days -1, 1, 3, 7, 10, 14, 17, 21, 24, 28)	2	<0.01	<0.01
	6	<0.01	<0.01
	20	<0.01	<0.01
Skim milk and cream (days 14, 28)	2	<0.01	<0.01
	20	<0.01	<0.01
Fat (perirenal, omental, subcutaneous) Day 28	2	<0.01	<0.01
	6	<0.01	<0.01
	20	<0.01	<0.01
Liver Day 28	2	<0.01	<0.01
	6	<0.01	<0.01
	20	<0.01	<0.01
Kidney Day 28	2	<0.01	<0.01
	6	<0.01	<0.01
	20	<0.01	<0.01
Muscle (flank, loin) Day 28	2	<0.01	<0.01
	6	<0.01	<0.01
	20	<0.01	<0.01

Anticipated Residues in Animal Matrices

Matrices	Residue Definition	Dietary Burden (ppm)	Anticipated Residues of Inpyrfluxam (ppm)
Beef/Dairy Cattle			
Whole milk	Inpyrfluxam	0.04	<0.01
Fat		0.02	
Liver			
Kidney			
Muscle			
Swine			
Fat	Inpyrfluxam	0.01	<0.01
Liver			
Kidney			
Muscle			

LIVESTOCK FEEDING – Laying hens	PMRA# 2819595

Laying hens were administered inpyrfluxam at dose levels of 1 ppm, 3 ppm and 10 ppm in the feeds for 28 consecutive days. The dose levels of 1, 3, and 10 ppm represent 100-fold, 300-fold, and 1000-fold, respectively, the estimated MBD to poultry. Animals were sacrifices approximately 6 hours after the last dose. A depuration study was conducted using the 10 ppm feeding level and selected animals were sacrificed at 3, 7, and 14 days after the last dose. Results from the depuration study indicate residues of inpyrfluxam were <LOQ (<0.01 ppm) in all samples analyzed..

Commodity/Collection Day	Actual Feeding Level (ppm)	Highest Residues (ppm)	Mean Residues (ppm)
Whole Eggs Days 14, 28	1	<0.01	<0.01
	3	<0.01	<0.01
	10	<0.01	<0.01
Egg yolk Days 14, 28	1	<0.01	<0.01
	3	<0.01	<0.01
	10	<0.01	<0.01
Egg white Days 14, 28	1	<0.01	<0.01
	3	<0.01	<0.01
	10	<0.01	<0.01
Fat Day 28	1	<0.01	<0.01
	3	<0.01	<0.01
	10	<0.01	<0.01
Liver Day 28	1	<0.01	<0.01
	3	<0.01	<0.01
	10	<0.01	<0.01
Muscle Day 28	1	<0.01	<0.01
	3	<0.01	<0.01
	10	<0.01	<0.01

Anticipated Residues in Poultry Matrices

Matrices	Residue Definition	Dietary Burden (ppm)	Anticipated Residues of Inpyrfluxam (ppm)
Eggs	Inpyrfluxam	0.01	<0.01
Fat			
Liver			
Muscle			

NATURE OF THE RESIDUE IN POTATO (treated seed pieces)	PMRA# 2819358
Radiolabel Position	Pyrazolyl-4-^{14}C]-Inpyrfluxam (specific activity: 99,300 dpm/µg) and [Phenyl-U-^{14}C]-Inpyrfluxam (specific activity: 98,300 dpm/µg)
Treatment	
Test Site	Planted in boxes and grown outdoors.
Treatment	Treated seed pieces.
Total Rate	[Pyrazolyl-4-^{14}C]-Inpyrfluxam: 5 g a.i./100 kg seed. [Phenyl-U-^{14}C]-Inpyrfluxam: 5 g a.i./100 kg seed
Formulation	Potato seed pieces were first treated with a Flowable Suspension (FS) formulation blank (3.2 FS), followed by dosing with radiolabelled material (described in previous cell).
Harvest	Potato foliage was collected 70 days after planting (BBCH 48), and mature potatoes were collected 83 days after planting (BBCH 49).
Extraction solvents	2 × acetone and 2 × acetone:water (60:40, v/v)

Matrices	PHI (days)[1]	Pyrazolyl-^{14}C Label	Phenyl-^{14}C Label
		TRR (ppm)	TRR (ppm)
Mature potato tuber	83	0.040	0.012
Potato foliage foliage	70	0.385	0.151
[1]Days after planting treated seed pieces			
Summary of Major Identified Metabolites in Potato (seed piece treatment) Plant Matrices			
Radiolabel Position	[Pyrazolyl-4-^{14}C], [Phenyl-U-^{14}C]		
Metabolites Identified	Major Metabolites		
Mature potato tubers	Inpyrfluxam, 1'-COOH-S-2840A, DFPA, *N*-des-Me-DFPA		

NATURE OF THE RESIDUE IN CORN AND SORGHUM (seed treatment)	**PMRA# 2819647**
Radiolabel Position	[Pyrazolyl-4-^{14}C]-Inpyrfluxam (specific activity: 98,343 dpm/µg) and [Phenyl-U-^{14}C]-Inpyrfluxam (specific activity: 99,280 dpm/µg)
Treatment	
Test Site	Planted in contained boxes and grown outdoors.
Treatment	Seed treatment.
Total Rate	[Pyrazolyl-4-^{14}C]-Inpyrfluxam: 5 g a.i./100 kg seed. [Phenyl-U-^{14}C]-Inpyrfluxam: 5 g a.i./100 kg seed
Formulation	Radiolabelled material was formulated as a Flowable Suspension (3.2 FS).
Harvest	For corn, forage (late dough/early dent stage), kernel plus cob with husks removed (milk/succulent stage), mature grain, and stover (grain free cob and stalks) were collected. For sorghum, forage (soft to hard dough stage), mature grain, and stover (stalks with grain removed) were collected.
Extraction solvents	Extractions were not carried out.

Matrices	Pyrazolyl-^{14}C Label	Phenyl-^{14}C Label
	TRR (ppm)	TRR (ppm)
Corn – forage	<0.005	<0.005
Corn – kernels plus cob with husks removed	<0.005	<0.005
Corn – mature grain	<0.005	<0.005
Corn – stover	<0.005	<0.005
Sorghum – forage	<0.005	<0.005
Sorghum – stover	<0.005	<0.005
Sorghum – mature grain	<0.005	<0.005
TRRs were too low for further identification/characterization.		

NATURE OF THE RESIDUE IN CANOLA (seed treatment)	**PMRA# 2819649**
Radiolabel Position	[Pyrazolyl-4-^{14}C]-Inpyrfluxam (specific activity: 101 000 dpm/µg) and [Phenyl-U-^{14}C]-Inpyrfluxam (specific activity: 99 900 dpm/µg)
Treatment	
Test Site	Planted in contained boxes and grown outdoors.
Treatment	Seed treatment.
Total Rate	[Pyrazolyl-4-^{14}C]-Inpyrfluxam: 5 g a.i./100 kg seed. [Phenyl-U-^{14}C]-Inpyrfluxam: 5 g a.i./100 kg seed
Formulation	Radiolabelled material was formulated as a Flowable Suspension (3.2 FS).
Harvest	Mature canola seeds were harvested ~5.3 months after planting.
Extraction solvents	Extractions were not carried out.

Matrices	Pyrazolyl-^{14}C Label	Phenyl-^{14}C Label
	TRR (ppm)	TRR (ppm)
Mature canola seeds	<0.005	<0.005
TRRs were too low for further identification/characterization.		
NATURE OF THE RESIDUE IN APPLES (foliar treatment)		**PMRA# 2819359**
Radiolabel Position	[Pyrazolyl-4-^{14}C]-Inpyrfluxam (specific activity: 150 000 dpm/µg) and [Phenyl-U-^{14}C]-Inpyrfluxam (specific activity: 150 000 dpm/µg)	
Treatment		
Test Site	Grown outdoors with plastic sheeting covering soil with 2 m barriers around each plot.	
Treatment	Foliar treatment.	
Total Rate	[Pyrazolyl-4-^{14}C]-Inpyrfluxam: 3 × 200 g a.i./ha, 35, 24, and 14 days before harvest of mature fruit (total rate of 600 g a.i./ha). [Phenyl-U-^{14}C]-Inpyrfluxam: 3 × 200 g a.i./ha, 35, 24, and 14 days before harvest of mature fruit (total rate of 600 g a.i./ha).	
Formulation	Radiolabelled materials were formulated as 40% SC formulations.	
Harvest	Mature fruit and leaves were sampled at a 14-day PHI. Leaves were not further analyzed.	
Extraction solvents	Mature fruit was rinsed with acetonitrile. Peel and pulp were extracted as follows: 2 × acetonitrile:H_2O (1:1, v/v) and 1 × acetonitrile	

Matrices	Pyrazolyl-^{14}C Label	Phenyl-^{14}C Label
	TRR (ppm)	TRR (ppm)
Rinses	0.192	0.145
Apple peel	0.424	0.526
Apple pulp	0.017	0.011
Summary of Major Identified Metabolites in Apples (foliar treatment) Plant Matrices		
Radiolabel Position	[Pyrazolyl-4-^{14}C], [Phenyl-U-^{14}C]	
Metabolites Identified	Major Metabolites	
Rinsate from whole fruit	Inpyrfluxam, 3'-OH-S-2840	
Peel	Inpyrfluxam, 3'-OH-S-2840, 1'-CH_2OH-S-2840B	
Pulp	Inpyrfluxam, 1'-CH_2OH-S-2840B	
NATURE OF THE RESIDUE IN RICE (foliar treatment)		**PMRA# 2819360**
Radiolabel Position	[Pyrazolyl-4-^{14}C]-Inpyrfluxam (specific activity: 150 000 dpm/µg) and [Phenyl-U-^{14}C]-Inpyrfluxam (specific activity: 151 100 dpm/µg)	
Treatment		
Test Site	Grown outdoors in above ground wooden boxes.	
Treatment	Foliar treatment.	
Total Rate	[Pyrazolyl-4-^{14}C]-Inpyrfluxam: 1 × 100 g a.i./ha, 28 days before harvest of mature crop. [Phenyl-U-^{14}C]-Inpyrfluxam: 1 × 100 g a.i./ha, 28 days before harvest of mature crop.	
Formulation	Radiolabelled materials were formulated as 40% SC formulations.	
Harvest	Immature rice plants were harvested 14 days after treatment, and mature straw, grain, and hulls were harvested at a 28-day PHI.	
Extraction solvents	2 × acetonitrile:H_2O (1:1, v/v) and 1 × acetonitrile	

Matrices	Pyrazolyl-^{14}C Label	Phenyl-^{14}C Label
	TRR (ppm)	TRR (ppm)
Immature rice plants (14-day PHI)	0.323	0.391
Straw (28-day PHI)	0.848	0.805
Grain (28-day PHI)	0.053	0.044
Hulls (28-day PHI)	1.576	1.430
Summary of Major Identified Metabolites in (rice foliar) Plant Matrices		
Radiolabel Position	[Pyrazolyl-4-^{14}C], [Phenyl-U-^{14}C]	
Metabolites Identified	Major Metabolites	
Immature plants (14-day PHI)	Inpyrfluxam	
Rice straw (28-day PHI)	Inpyrfluxam, 3'-OH-S-2840	
Grain / Brown rice (28-day PH)	Inpyrfluxam, Gly-CH_2OH-S-2840	
Hulls (28-day PHI)	Inpyrfluxam, 1'-CH_2OH-S-2840A, 1'-CH_2OH-S-2840B	
NATURE OF THE RESIDUE IN RICE (granular soil treatment)		**PMRA# 2819362**
Radiolabel Position	[Pyrazolyl-4-^{14}C]-Inpyrfluxam (specific activity: 150,000 dpm/µg) and [Phenyl-U-^{14}C]-Inpyrfluxam (specific activity: 151,000 dpm/µg)	
Treatment		
Test Site	Grown outdoors in above ground wooden boxes.	
Treatment	Granular treatment to the soil surface.	
Total Rate	[Pyrazolyl-4-^{14}C]-Inpyrfluxam: 1 × 400 g a.i./ha, at 3-4 leaf stage of plant development 132 days before harvest. [Phenyl-U-^{14}C]-Inpyrfluxam: 1 × 400 g a.i./ha, at 3-4 leaf stage of plant development 132 days before harvest.	
Formulation	Radiolabelled materials were formulated as 4% GR (granulated product) formulations.	
Harvest	Immature rice plants were harvested 30 days after treatment, and mature straw, grain, and hulls were harvested at a 132-day PHI.	
Extraction solvents	2 × acetonitrile:H_2O (1:1, v/v) and 1 × acetonitrile	

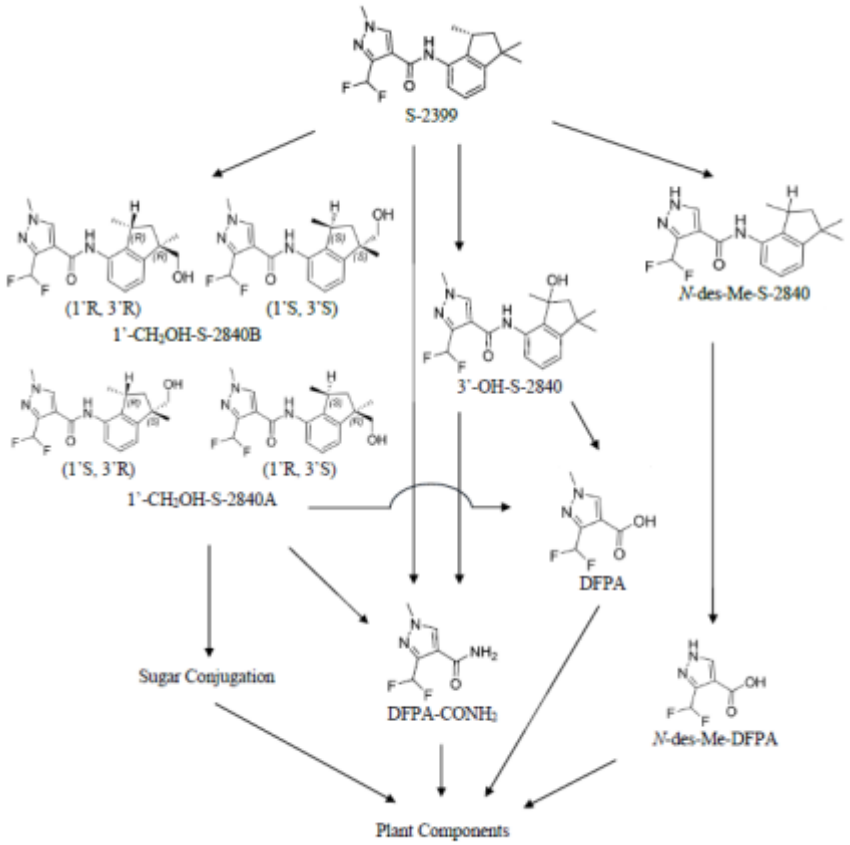
Matrices	Pyrazolyl-^{14}C Label	Phenyl-^{14}C Label
	TRR (ppm)	TRR (ppm)
Immature rice plants (30-day PHI)	3.783	1.909
Straw (132-day PHI)	1.548	1.095
Grain (132-day PHI)	0.010	0.015
Hulls (132-day PHI)	0.171	0.158
Summary of Major Identified Metabolites in Rice (granular soil treatment) Plant Matrices		
Radiolabel Position	[Pyrazolyl-4-^{14}C], [Phenyl-U-^{14}C]	
Metabolites Identified	Major Metabolites	
Immature plants (30-day PHI)	Inpyrfluxam, Sugar conjugates of 1'CH_2OH-S-2840A/B	
Rice straw (132-day PHI)	Sugar conjugates of 1'CH_2OH-S-2840A/B, 1'-CH_2OH-S-2840A, 1'-CH_2OH-S-2840B	
Grain / Brown rice (132-day PH)	1'-CH_2OH-S-2840A, N-des-Me-DFPA, DFPA	
Hulls (132-day PHI)	1'-CH_2OH-S-2840A, DFPA-$CONH_2$	
NATURE OF THE RESIDUE IN SOYBEANS (foliar treatment)		**PMRA# 2819361**
Radiolabel Position	[Pyrazolyl-4-^{14}C]-Inpyrfluxam (specific activity: 150,500 dpm/µg) and [Phenyl-U-^{14}C]-Inpyrfluxam (specific activity: 150,500 dpm/µg)	

Treatment	
Test Site	Grown outdoors in above ground wooden boxes.
Treatment	Foliar treatment.
Total Rate	[Pyrazolyl-4-^{14}C]-Inpyrfluxam: 2 × 100 g a.i./ha, at BBCH 60 and 36 days later at BBCH 75. [Phenyl-U-^{14}C]-Inpyrfluxam: 2 × 100 g a.i./ha, at BBCH 60 and 36 days later at BBCH 75.
Formulation	Radiolabelled materials were formulated as 40% SC formulations.
Harvest	Harvest of immature foliage and hay occurred 20 and 33 days, respectively, following the first application. Harvest of edamame (in other words, immature) and mature soybeans occurred 11 and 53 days, respectively, following the second application.
Extraction solvents	2 × acetonitrile:H_2O (1:1, v/v) and 1 × acetonitrile

Matrices	**Pyrazolyl-^{14}C Label**	**Phenyl-^{14}C Label**
	TRR (ppm)	**TRR (ppm)**
Foliage (20 days after 1st treatment)	1.652	1.878
Hay (33 days after 1st treatment)	2.088	1.942
Edamame (11 days after 2nd treatment) Immature seeds Immature pods	 0.120 0.715	 0.024 0.703
Mature Soybeans (53 days after 2nd treatment) Mature seeds Mature pods (unrinsed) Mature pods (rinsed)	 0.210 1.250 1.120	 0.038 0.781 0.657

Summary of Major Identified Metabolites in Soybean Plant Matrices	
Radiolabel Position	[Pyrazolyl-4-^{14}C], [Phenyl-U-^{14}C]
Metabolites Identified	Major Metabolites
Foliage (20 DAA1)	Inpyrfluxam, 3'-OH-S-2840
Hay (33 DAA1)	Inpyrfluxam, 3'-OH-S-2840
Edamame seed (11 DAA2)	-
Edamame pod (11 DAA2)	Inpyrfluxam
Mature seed (53 DAA2)	*N*-glycoside conjugate of *N*-des-Me-DFPA
Mature pod (53 DAA2)	Inpyrfluxam, 3'-OH-S-2840

Proposed Metabolic Scheme in Plants



FREEZER STORAGE STABILITY IN PLANT MATRICES				**PMRA# 2819579, 2819577**
Tested Matrices	**Analytes**	**Tested Intervals (months)**	**Temperature (°C)**	**Category**
Apple fruit, corn forage, and corn stover	Inpyrfluxam, 3'OH-S-2840, 1'-CH2OH-S-2840 (A&B), DFPA-CONH2 and 1'-COOH-S-2840 (A&B)	17–19	-20°C	High-water
Soybean seeds		19		High-protein & High-oil
Potato tubers and corn grain		21		High-starch
-		-		High-acid
Corn starch		3		NA
Potato flakes		8		
Potato chips		8		
Rice bran		6		
Polished rice		6		
Wheat germ		10		
Rice hulls		6		
Sugar beet dried pulp		9		
Sugar beet sugar		3		
Sugar beet molasses		3		
Apple pomace		5		

Soybean hulls		2		
Corn oil		4		
Peanut meal		4		

CROP FIELD TRIALS and RESIDUE DECLINE ON APPLES **PMRA# 2819581, 2819582**

Crop field trials for apples were conducted in 2014–2015 in Canada and the United States. Trials were conducted in North American growing regions 1 (4 trials), 2 (2 trials), 5 (6 trials), 9 (1 trial), 10 (1 trial), and 11 (5 trials) for a total of 19 trials. Excalia Fungicide was applied twice as foliar broadcast sprays at rates of 94–102 g a.i./ha/application at full bloom and at petal fall for total seasonal application rates of 190–206 g a.i./ha. The applications were made at 6- to 14-day intervals with the last application occurring 111–185 days before harvest.

Adjuvants were used in/on apples at all field trial sites. The number and geographic distribution of trials were generally in accordance with Health Canada's SPN2017-02. At two trials, harvest dates were varied to evaluate residue decline. Data show that residues of inpyrfluxam were <0.01 ppm on all samples analyzed, including additional samples taken to assess residue decline. Adequate storage stability data are available in/on apples to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

Crop	**Total Application Rate (g a.i./ha)**	**PHI (days)**	**Inpyrfluxam Residues (ppm)**					
			n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
Apples	190–206	111–185	19	<0.01	<0.01	<0.01	<0.01	-

n = number of independent trials.
For computation, values <LOQ are assumed to be at the LOQ.

CROP FIELD TRIALS AND RESIDUE DECLINE ON PEANUTS **PMRA# 2819586**

Crop field trials for peanuts were conducted in 2015 in the United States. Trials were conducted in North American growing regions 2 (6 trials), 3 (1 trial), 6 (1 trial), and 8 (2 trials) for a total of 10 trials. Excalia Fungicide SC was applied once as foliar broadcast sprays at rates of 198-206 g a.i./ha 38–42 days before harvest.

Adjuvants were used in/on peanuts at all field trial sites. The number and geographic distribution of trials were generally in accordance with the USEPA's OPPTS 860.1500. Data show that residues of inpyrfluxam were <0.01 ppm on all samples analyzed. Adequate storage stability data are available in/on soybeans to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

Crop	**Total Application Rate (g a.i./ha)**	**PHI (days)**	**Inpyrfluxam Residues (ppm)**					
			n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
Peanut nutmeat	198–206	38–42	10	<0.01	<0.01	<0.01	<0.01	-

n = number of independent trials.
For computation, values <LOQ are assumed to be at the LOQ.

CROP FIELD TRIALS AND RESIDUE DECLINE ON SUGAR BEETS **PMRA# 2819588, 2819583**

Crop field trials for sugrabeets were conducted in 2014–2015 in Canada and in the United States. Trials were conducted in North American growing regions 5 (6 trials), 7 (1 trial), 7A (5 trials), 8 (1 trial), 9 (1 trial), 10 (2 trials), and 11 (2 trials) for a total of 18 trials. Excalia Fungicide was applied twice as foliar broadcast sprays at rates of 99-107 g a.i./ha/application, for total seasonal application rates of 197-212 g a.i./ha, to plants grown from seeds treated with Zeltera Fungicide at 0.1 g a.i./100 000 seeds. Foliar applications were made ~71 and ~50 days before harvest, with PHIs of 49 to 51-days.

Adjuvants were used in/on sugar beets at all field trial sites for the foliar applications. The number and geographic distribution of trials were generally in accordance with Health Canada's SPN2017-02. At two trials, harvest dates were varied to evaluate residue decline. Data show that residues of inpyrfluxam were <0.01 ppm on all samples analyzed, including additional samples taken to assess residue decline. Adequate storage stability data are available in/on corn grain and potatoes to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

Crop	Total Application Rate (g a.i./ha)	PHI (days)	Inpyrfluxam Residues (ppm)					
			n	LAFT	HAFT	Median	Mean	SDEV
Sugar beet roots	197–2121	49–51	18	<0.01	<0.01	<0.01	<0.01	-

[1] = Includes foliar and seed treatment rates.
n = number of independent trials.
For computation, values <LOQ are assumed to be at the LOQ.

CROP FIELD TRIALS AND RESIDUE DECLINE ON SOYBEANS **PMRA# 2819584**

Crop field trials for soybeans were conducted in 2014–2015 in the United States. Trials were conducted in North American growing regions 2 (2 trials), 4 (3 trials), and 5 (16 trials) for a total of 21 trials. Excalia Fungicide was applied twice as foliar broadcast sprays at rates of 98-106 g a.i./ha/application, for total seasonal application rates of 204-214 g a.i./ha, to plants grown from seeds treated with Zeltera Fungicide at 10 g a.i./100 kg seed. Foliar applications were made at 10–21 day RTIs, and with PHIs of 26 to 84-days.

Adjuvants were used in/on soybeans at all field trial sites for the foliar applications. The number and geographic distribution of trials were generally in accordance with Health Canada's SPN2017-02. Data show that residues of inpyrfluxam were <0.01 ppm on all samples analyzed. Adequate storage stability data are available in/on soybeans to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

Crop	Total Application Rate (g a.i./ha)	PHI (days)	Inpyrfluxam Residues (ppm)					
			n	LAFT	HAFT	Median	Mean	SDEV
Soybean seed	204–2141	26–84	21	<0.01	<0.01	<0.01	<0.01	-

[1] = Includes foliar and seed treatment rates.
n = number of independent trials.
For computation, values <LOQ are assumed to be at the LOQ.

CROP FIELD TRIALS AND RESIDUE DECLINE ON CORN **PMRA# 2819583**

Crop field trials for corn (sweet and field) were conducted in 2015–2016 in Canada and in the United States. For sweet corn, trials were conducted in North American growing regions 1 (2 trials), 2 (1 trial), 4 (1 trial), 5 (7 trials), 10 (1 trial), 11 (1 trial), and 12 (1 trial) for a total of 14 trials. For field corn, trials were conducted in North American growing regions 1 (2 trials), 2 (1 trial), 4 (1 trial), 5 (17 trials), 6 (1 trial), 10 (1 trial), 11 (1 trial), 12 (1 trial), and 14 (1 trial) for a total of 26 trials. Excalia Fungicide was applied once as an in-furrow application at rates of 49–53 g a.i./ha, to plants grown from seeds treated with Zeltera Fungicide at 5 g a.i./100 kg seed. Corn grain and stover were harvested at 112 to 179-day PHIs, corn forage at 80 to 124-day PHIs, and K+CWHR at 70 to 95-day PHIs.

Adjuvants were not used in any of the in-furrow applications. The number and geographic distribution of trials were generally in accordance with Health Canada's SPN2017-02. At one trial, harvest dates were varied to evaluate residue decline in corn forage. Data show that residues of inpyrfluxam were <0.01 ppm on all samples analyzed, including additional samples taken to assess residue decline. Adequate storage stability data are available in/on corn grain, forage, and stover to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

Crop	Total Application Rate (g a.i./ha)	PHI (days)	Inpyrfluxam Residues (ppm)					
			n	LAFT	HAFT	Median	Mean	SDEV
K+CWHR	50–541	70–95	14	<0.01	<0.01	<0.01	<0.01	-
Corn forage		80–124	26	<0.02	<0.02	<0.02	<0.02	-
Corn grain		112–179	26	<0.01	<0.01	<0.01	<0.01	-
Corn stover		112–179	26	<0.02	<0.02	<0.02	<0.02	-

[1] = Includes foliar and seed treatment rates.
n = number of independent trials.
For computation, values <LOQ are assumed to be at the LOQ.

CROP FIELD TRIALS AND RESIDUE DECLINE ON RICE	PMRA# 2819587

Crop field trials for rice were conducted in 2015-2016 and 2017 in in the United States. Trials were conducted in North American growing regions 4 (11 trials), 5 (1 trial), 6 (2 trials), and 10 (2 trials) for a total of 16 trials. Excalia Fungicide was applied once as foliar broadcast sprays at rates of 102-123 g a.i./ha to plants grown from seeds treated with Zeltera Fungicide at 10 g a.i./100 kg seed. Rice grain was harvested at 35 to 71-day PHIs.

Adjuvants were used in all foliar applications. The number and geographic distribution of trials were generally in accordance with the USEPA's OPPTS 860.1500. Data show that residues of inpyrfluxam were <0.01 ppm on all samples analyzed. Adequate storage stability data are available in/on corn grain and potato tubers to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

Crop	Total Application Rate (g a.i./ha)	PHI (days)	Inpyrfluxam Residues (ppm)					
			n	LAFT	HAFT	Median	Mean	SDEV
Rice grain	102–1231	35–71	16	<0.01	<0.01	<0.01	<0.01	-

[1] = Includes foliar and seed treatment rates.
n = number of independent trials.
For computation, values <LOQ are assumed to be at the LOQ.

PROCESSED FOOD AND FEED – APPLES	PMRA# 2819581

A processing study was conducted in a representative North American growing region using Excalia Fungicide at 980 g a.i./ha (6.5-fold of maximum single seasonal use rate) in/on apples. Adequate storage stability data are available for apples and wet pomace to support the storage intervals of the RAC and the RAC and the processed food and feed. Samples were analyzed using a validated analytical method.

RAC	Processed Fractions	HAFT[RAC] (ppm)	Processing Factor of Inpyrfluxam	Anticipated Residues of Inpyrfluxam (ppm)
Apples	Apple juice	<0.01	0.1-fold	<0.01
	Apple wet pomace		2.9-fold	0.03

PROCESSED FOOD AND FEED – RICE	PMRA# 2819587

A processing study was conducted in a representative North American growing region using Zeltera Fungicide at 50 g a.i./100 kg seed for seed treatment and Excalia Fungicide at 490 g a.i./ha for foliar treatment (5-fold of maximum single seasonal use rate) in/on rice imported into Canada. Adequate storage stability data are available for corn grain, potato tubers, and rice (bran, hulls, and polished rice) to support the storage intervals of the RAC and the processed food and feed. Samples were analyzed using a validated analytical method.

RAC	Processed Fractions	HAFT[RAC] (ppm)	Processing Factor of Inpyrfluxam	Anticipated Residues of Inpyrfluxam (ppm)
Rice grain	Rice bran	<0.01	1.3-fold	<0.013
	Polished rice		-	-

A processing factor could not be calculated for inpyrfluxam in polished rice since residues were <LOQ (<0.01 ppm) in both the RAC and in this processed fraction.

PROCESSED FOOD AND FEED - SUGAR BEETS	PMRA# 2819585

A processing study was conducted in a representative North American growing region using Zeltera Fungicide at 0.1 g a.i./100 000 seeds for seed treatment and Excalia Fungicide at 1000 g a.i./ha for foliar treatment (20-fold of maximum single seasonal use rates for seed and foliar treatment combined) in/on sugar beets. Adequate storage stability data are available for corn grain, potato tubers, and sugar beets (sugar, molasses, and dried pulp) to support the storage intervals of the RAC and the processed food and feed. Samples were analyzed using a validated analytical method.

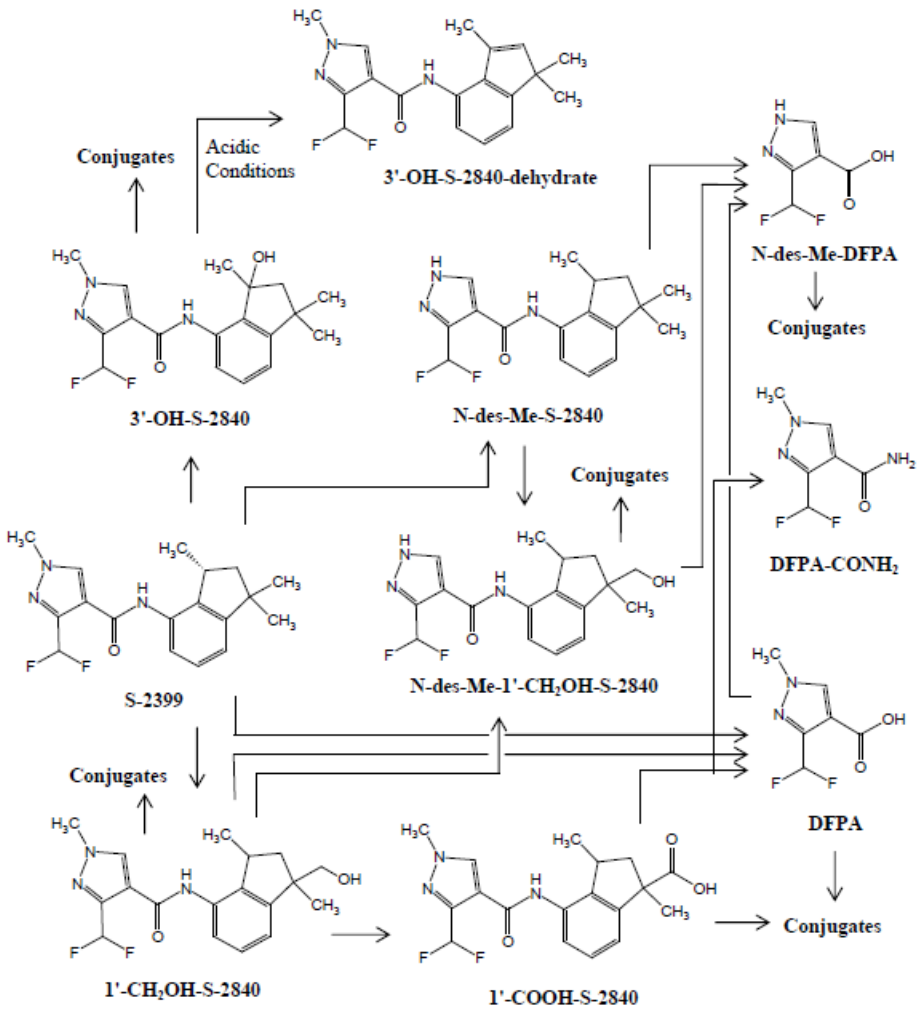
RAC	Processed Fractions	HAFT[RAC] (ppm)	Processing Factor of Inpyrfluxam	Anticipated Residues of Inpyrfluxam (ppm)
Sugar beet roots	Sugar beet sugar	<0.01	-	-
	Sugar beet molasses		2.0-fold	<0.02
	Sugar beet dried pulp		3.2-fold	<0.032
A processing factor could not be calculated for inpyrfluxam in sugar beet sugar since residues were <LOQ (<0.01 ppm) in both the RAC and in this processed fraction.				
PROCESSED FOOD AND FEED – PEANUTS				**PMRA# 2819586**
A processing study was conducted in a representative North American growing region using Excalia Fungicide at 1500 g a.i./ha for foliar treatment (7.5-fold of maximum single seasonal use rate) in/on peanuts imported into Canada. Adequate storage stability data are available for soybean seeds, peanut meal, and corn oil to support the storage intervals of the RAC and the processed food and feed. Samples were analyzed using a validated analytical method.				
RAC	**Processed Fractions**	**HAFT[RAC] (ppm)**	**Processing Factor of Inpyrfluxam**	**Anticipated Residues of Inpyrfluxam (ppm)**
Peanut nutmeat	Peanut meal	<0.01	0.4-fold	<0.01
	Peanut refined oil		0.4-fold	<0.01
PROCESSED FOOD AND FEED – SOYBEANS				**PMRA# 2819584**
A processing study was conducted in a representative North American growing region using Zeltera Fungicide at 50 g a.i./100 kg seed for seed treatment and Excalia Fungicide at 1040 g a.i./ha for foliar treatment (6.3-fold of maximum single seasonal use rates for seed and foliar treatment combined) in/on soybeans. Adequate storage stability data are available for soybean (seed and hulls), peanut meal, and corn oil to support the storage intervals of the RAC and the processed food and feed. Samples were analyzed using a validated analytical method.				
RAC	**Processed Fractions**	**HAFT[RAC] (ppm)**	**Processing Factor of Inpyrfluxam**	**Anticipated Residues of Inpyrfluxam (ppm)**
Soybeans	Soybean meal	<0.01	-	<0.01
	Soybean hulls		-	<0.01
	Soybean refined oil		1.2-fold	<0.012
Processing factors could not be calculated for inpyrfluxam in soybean meal and hulls since residues were <LOQ (<0.01 ppm) in both the RAC and in these two processed fractions.				
PROCESSED FOOD AND FEED – CORN				**PMRA# 2819583**
A processing study was conducted in a representative North American growing region using Zeltera Fungicide at 10 g a.i./100 kg seed for seed treatment and Excalia Fungicide at 510 g a.i./ha for foliar treatment (10-fold of maximum single seasonal use rates for seed and foliar treatment combined) in/on corn imported into Canada. Adequate storage stability data are available for corn grain, starch, and oil to support the storage intervals of the RAC and the processed food and feed. Samples were analyzed using a validated analytical method.				
RAC	**Processed Fractions**	**HAFT[RAC] (ppm)**	**Processing Factor of Inpyrfluxam**	**Anticipated Residues of Inpyrfluxam (ppm)**
Corn grain	Corn flour	<0.01	-	<0.01
	Corn grit		-	<0.01
	Corn meal		-	<0.01
	Corn starch		-	<0.01
	Corn oil		-	<0.01
Processing factors could not be calculated for inpyrfluxam in all corn processed fractions since residues were <LOQ (<0.01 ppm) in both the RAC and processed fractions.				
CONFINED ACCUMULATION IN ROTATIONAL CROPS – Lettuce, radish and sorghum				**PMRA# 2819589**
Radiolabel Position	[Pyrazolyl-4-14C]-inpyrfluxam (specific activity: 122 mCi/mmol) and [Phenyl-U-14C]-inpyrfluxam (specific activity: 57 mCi/mmol)			

Treatment			
Test Site	In contained plots outdoors		
Soil Type	Sandy loam		
Treatment	Bare soil was treated at 235 g a.i./ha, and aged for 30, 120 and 365 days.		
Formulation	Suspension concentrate (SC) formulation of inpyrfluxam (guarantee: 40 %)		
Extraction solvent(s)	2 × ACN, 2 × water, 1 × can		
Matrices	**PBI (days)**	**Pyrazolyl-14C Label**	**Phenyl-14C Label**
		TRR (ppm)	**TRR (ppm)**
Immature Lettuce	30	0.045	0.080
Mature Lettuce		0.094	0.074
Immature Radish Tops		0.112	0.139
Immature Radish Roots		0.033	0.040
Mature Radish Tops		0.136	0.228
Mature Radish Roots		0.044	0.065
Sorghum Forage		0.102	0.209
Sorghum Stover		0.692	0.703
Sorghum Grain		0.012	0.048
Immature Lettuce	120	0.052	0.103
Mature Lettuce		0.069	0.093
Immature Radish Tops		0.106	0.230
Immature Radish Roots		0.029	0.059
Mature Radish Tops		0.117	0.367
Mature Radish Roots		0.030	0.108
Sorghum Forage		0.135	0.180
Sorghum Stover		1.074	0.945
Sorghum Grain		0.012	0.058
Immature Lettuce	365	0.023	0.039
Mature Lettuce		0.012	0.025
Immature Radish Tops		0.088	0.101
Immature Radish Roots		0.021	0.024
Mature Radish Tops		0.092	0.073
Mature Radish Roots		0.028	0.022
Sorghum Forage		0.035	0.047
Sorghum Stover		0.133	0.236
Sorghum Grain		0.014	0.014

Summary of Major Identified Metabolites in Rotated Crops			
Plant-back Intervals (PBI)	**1st Rotation (30-day PBI)**	**2nd Rotation (120-day PBI)**	**3rd Rotation (365-day PBI)**
Radiolabel Position	**[14C-X], [14C-Y]**		
Metabolites Identified	**Major Metabolites**		
Immature lettuce	Inpyrfluxam, 3'OH-S-2840, 1'CH2OH-S-2840 (A+B), DFPA	Inpyrfluxam, 3'OH-S-2840, 1'CH2OH-S-2840 (A+B), DFPA	Inpyrfluxam, DFPA, N-des-Me-DFPA

Mature lettuce	Inpyrfluxam, 3'OH-S-2840 1'CH2OH-S-2840 (A+B), DFPA	Inpyrfluxam, 3'OH-S-2840, 1'CH2OH-S-2840 (A+B), 1'COOH-S-2840 (A+B), DFPA	Inpyrfluxam, DFPA, N-des-Me-DFPA
Immature radish tops	Inpyrfluxam, N-des-Me-S-2840, N-des-Me-1'CH2OH-S-2840 (A+B), DFPA, DFPA-CONH2	N-des-Me-S-2840, N-des-Me-1'CH2OH-S-2840 (A+B), DFPA-CONH2	N-des-Me-S-2840, 1'COOH-S-2840 (A+B), DFPA, DFPA-CONH2
Mature radish tops	Inpyrfluxam, N-des-Me-S-2840, 3'-OH-S-2840, N-des-Me-CH2OH-S-2840 (A+B), DFPA, DFPA-CONH2	1'COOH-S-2840 (A+B), N-des-Me-1'CH2OH-S-2840 (A+B), N-des-Me-S-2840, 1'CH2OH-S-2840 (A+B)	N-des-Me-S-2840, 1'COOH-S-2840 (A+B), DFPA
Immature radish roots	Inpyrfluxam, 1'COOH-S-2840 (A+B), DFPA	Inpyrfluxam, 3'OH-S-2840, DFPA	Inpyrfluxam, 1'CH2OH-S-2840 (A+B), DFPA
Mature radish roots	Inpyrfluxam	Inpyrfluxam, 3'OH-S-2840, 1'COOH-S-2840 (A+B), DFPA	Inpyrfluxam, 3'OH-S-2840, 1'CH2OH-S-2840 (A+B), DFPA
Sorghum forage	1'CH2OH-S-2840 (A+B), DFPA	1'CH2OH-S-2840 (A+B), N-des-Me-1'CH2OH-S-2840 (A+B), DFPA	N-des-Me-1'CH2OH-S-2840 (A+B), DFPA
Sorghum stover	1'CH2OH-S-2840 (A+B), DFPA	3'OH-S-2840, 1'CH2OH-S-2840 (A+B), N-des-Me-1'CH2OH-S-2840 (A+B), DFPA	3'OH-S-2840
Sorghum grain	DFPA	-	-

Proposed Metabolic Scheme in Rotational Crops



RESIDUE DATA IN ROTATIONAL CROPS								**PMRA# 2819591, 2819590, 2819593, 2819592**
Nine trials (2 trials for wheat, 2 trials for sorghum, 2 trials for canola, 1 trial for field peas, and 2 trials for cotton) were conducted during the 2015 growing season in North American growing regions 6, 7, and 14. One broadcast application was made to wheat or soybeans as primary crops with Excalia Fungicide at rates of ~100 and ~200 g a.i./ha. Adjuvants were used on primary crops at all trial sites. Adequate storage stability data are available on soybean seed, corn grain, and potato tuber to support the storage intervals of the rotational crop field trials. Samples were analyzed using a validated analytical method.								
Commodity	**Total Application Rate (g a.i./ha)**	**PBI (days)**	**Residue Levels (ppm)**					
			n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
Inpyrfluxam								
Wheat forage	100-117	312–328	2	<0.02	<0.02	-	<0.02	-
Wheat hay				<0.02	<0.02	-	<0.02	-
Wheat grain				<0.01	<0.01	-	<0.01	-
Wheat straw				<0.02	<0.02	-	<0.01	-

Canola seed	100–117	328-339	2	<0.01	<0.01	-	<0.02	-
Field pea vines	100	328	1	<0.02	<0.02	-	-	-
Field pea hay				<0.02	<0.02	-	-	-
Field pea seed				<0.01	<0.01	-	-	-
Sorghum forage	209–220	267-273	2	<0.02	<0.02	-	<0.02	-
Sorghum grain				<0.01	<0.01	-	<0.01	-
Sorghum stover				<0.02	<0.02	-	<0.02	-
Undelinted cottonseed	209–220	267-273	2	<0.01	<0.01	-	<0.01	-
Cotton gin trash				<0.02	<0.02	-	<0.02	-
Values based on per-trial averages. For computation, values <LOQ are assumed to be at the LOQ. n = number of independent field trials.								
Based on the results of the field accumulation studies, a plant-back interval of 9 months is required for cereals, legumes, and oilseeds that are not listed on the Excalia Fungicide label as primary crops. Based on the results of the confined crop rotation study which showed that all analytes were <0.01 ppm in edible crop matrices (i.e. mature lettuce, mature radish roots, and sorghum grain) planted at the 365-day PBI, a 12-month PBI is required for all other crops that are not on the Excalia Fungicide label.								

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

PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (potatoes, rice, apples, and soybeans)** **Rotational crops**		Inpyrfluxam	
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops** **Rotational crops**		Inpyrfluxam and *N*-des-Me-DFPA	
METABOLIC PROFILE IN DIVERSE CROPS		Similar in potatoes, rice, apples, and soybeans.	
ANIMAL STUDIES			
ANIMALS		**Ruminant and Poultry**	
RESIDUE DEFINITION FOR ENFORCEMENT		Inpyrfluxam	
RESIDUE DEFINITION FOR RISK ASSESSMENT		Inpyrfluxam	
METABOLIC PROFILE IN ANIMALS **(goat, hen, rat)**		Metabolism is similar in all animals tested	
FAT SOLUBLE RESIDUE		Yes	
DIETARY RISK FROM FOOD AND DRINKING WATER			
Basic acute dietary exposure analysis, 95th percentile **ARfD = 0.3 mg/kg bw**	**POPULATION**	**ESTIMATED RISK** **% of ACUTE REFERENCE DOSE (ARfD)**	
		Food Alone	**Food and Drinking Water**
	All infants <1 year	0.3	17.0

Estimated acute drinking water concentration = 0.277 ppm	Children 1–2 years	0.5	7.3
	Children 3–5 years	0.3	5.8
	Children 6–12 years	0.2	4.5
	Youth 13–19 years	0.1	4.2
	Adults 20–49 years	0.1	4.8
	Adults 50+ years	0.1	4.2
	Females 13-49 years	0.1	4.9
	Total population	0.2	5.0

	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Drinking Water**
Basic chronic dietary exposure analysis **ADI = 0.06 mg/kg bw/day** **Estimated chronic drinking water concentration = 0.277 ppm**	All infants <1 year	0.5	35.3
	Children 1–2 years	1.2	14.0
	Children 3–5 years	0.8	11.2
	Children 6–12 years	0.4	8.2
	Youth 13–19 years	0.2	6.8
	Adults 20–49 years	0.2	9.4
	Adults 50+ years	0.1	9.2
	Females 13-49 years	0.2	9.3
	Total population	0.2	9.6

Table 8 Mixer/Loader/Applicator Risk Assessment for Workers Handling Excalia Fungicide

Exposure Scenario (Crop and Tasks)		**Unit Exposure (µg/kg a.i. handled)[1]**		**ATPD (ha/day)[2]**	**Rate (kg a.i./ ha)**	**Daily Exposure (mg/kg bw/day)[3]**		**MOE[4]**	
		Dermal	**Inhal.**			**Dermal**	**Inhal.**	**Dermal**	**Inhal.**
PPE[5]: Single layer and CR gloves for mixing/loading/application									
Soybeans and Sugar Beets	**Farmers:** Open mixing/ loading a liquid + open-cab groundboom application	83.9	2.31	107	0.050	5.61×10^{-3}	1.54×10^{-4}	1.78×10^{5}	2.07×10^{5}
	Custom Applicators: Open mixing/ loading a liquid + open-cab groundboom application	83.9	2.31	360	0.050	1.89×10^{-2}	5.20×10^{-4}	5.30×10^{4}	6.16×10^{4}

Exposure Scenario (Crop and Tasks)		Unit Exposure (µg/kg a.i. handled)[1]		ATPD (ha/day)[2]	Rate (kg a.i./ ha)	Daily Exposure (mg/kg bw/day)[3]		MOE[4]	
		Dermal	Inhal.			Dermal	Inhal.	Dermal	Inhal.
PPE[5]: Single layer and CR gloves for mixing/loading/application									
Apple Trees	**Orchard Workers:** Open mixing/loading a liquid + open-cab airblast application	3827.8	9.71	20	0.075	7.18×10^{-2}	1.82×10^{-4}	1.39×10^{4}	1.76×10^{5}
PPE[5]: Single layer with chemical-resistant gloves for mixing/loading and CR coveralls with a CR hood over a single layer with CR gloves and a respirator for application									
Apple Trees	**Orchard Workers:** Open mixing/loading a liquid + Handheld airblast/ Mistblower application	32 619.5	3 940.63	2	0.075	6.12×10^{-2}	7.39×10^{-3}	1.64×10^{4}	4.33×10^{3}

[1] Total unit exposure based on data from the AHETF and the NDETF databases.
[2] PMRA Default Area Treated per Day table.
[3] Daily exposure = (Unit exposure × ATPD × Rate × 100% dermal/inhalation absorption) / (80 kg bw × 1000 µg/mg).
[4] Margins of Exposure (MOEs) based on a dermal NOAEL of 1000 mg/kg bw/day, an inhalation NOAEL of 32 mg/kg bw/day and a target MOE of 100 for both dermal and inhalation exposure.
[5] PPE: personal protective equipment; CR: chemical-resistant; single layer: long-sleeved shirt, long pants, socks and shoes; respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH-approved canister approved for pesticides.

Table 9 Postapplication Dermal Exposure and Risk Estimate for Inpyrfluxam on Day 0

Crop (Max. Rate; No. App.; RTI[1])	Postapplication Activity	Peak DFR (µg/cm²)[2]	Transfer Coefficient (cm²/hr)[3]	Dermal Exposure (mg/kg bw/day)[4]	Day 0 MOE[5]	REI[6]
Apples (75 g a.i./ha; 2/season; 10-day RTI)	Fruit thinning	0.2529	3000	0.0759	1.32×10^{4}	12 hours
	Scouting, hand pruning and training		580	0.0147	6.82×10^{4}	
	Hand weeding, propping and orchard maintenance		100	0.0025	3.95×10^{5}	
Soybeans (50 g a.i./ha; 2/season; 14-day RTI)	Scouting	0.1536	1100	0.0169	5.92×10^{4}	12 hours
	Hand weeding		70	0.0011	9.30×10^{5}	
Sugar beets (50 g a.i./ha; 1/season)	Hand harvesting	0.1250	1100	0.01238	7.27×10^{4}	12 hours
	Scouting		210	0.0026	3.81×10^{5}	
	Hand weeding and thinning		70	0.0009	1.14×10^{6}	

[1] RTI = retreatment interval
[2] Calculated using the default 25% dislodgeable on the day of the last application and 10% dissipation per day.
[3] Transfer coefficients obtained from PMRA Agricultural TCs Table based ARTF data.
[4] Dermal exposure = (Peak DFR [µg/cm²] × TC [cm²/hr] × 8 hours × 100% dermal absorption) / (80 kg bw × 1000 µg/mg)

[5] Based on a dermal NOAEL of 1000 mg/kg bw/day and a target MOE of 100.
[6] Minimum REI is 12 hours to allow residues to dry, suspended particles to settle and vapours to dissipate.

Table 10 Residential Postapplication Dermal Exposure and Risk Estimate for Inpyrfluxam on Day 0

Crop (Max. Rate; No. App.; RTI[1])	**Life Stage**	**Postapplication Activities**	**Peak DFR (µg/cm²)[2]**	**Transfer Coefficient (cm²/hr)[3]**	**Dermal Exposure (mg/kg bw/day)[4]**	**Day 0 MOE[5]**
Apples (75 g a.i./ha; 2/season; 10-day RTI)	Adults	Pruning and/or other related activities	0.2529	1700	5.37×10^{-3}	1.86×10^{5}
	Children (6 < 11 yrs)			930	3.67×10^{-3}	2.72×10^{5}

[1] RTI = retreatment interval
[2] Calculated using the default 25% dislodgeable on the day of the last application and 10% dissipation per day.
[3] Transfer coefficients obtained from the PMRA memo entitled 'Review of USEPA Residential SOPs (2012) Section 4: Gardens and Trees, and from the 2012 USEPA SOP for Residential Pesticide Exposure Assessment.
[4] Dermal exposure = (Peak DFR [µg/cm²] × TC [cm²/hr] × Exposure duration [1 hour for adults; 0.5 hour for children] × 100% dermal absorption) / (Body weight [80 kg for adults; 32 kg for children] × 1000 µg/mg)
[5] Based on a dermal NOAEL of 1000 mg/kg bw/day and a target MOE of 100.

Table 11 Exposure Risk Assessment for Commercial Workers Treating Various Seeds Types with Zeltera Fungicide

Worker's Tasks	**Unit Exposures (µg/kg a.i. handled)[1]**		**App. Rate (g a.i./ 100 kg seed)**	**Commercial Throughput[2] (kg seeds/ day)**	**Daily Exposures[3,4] (mg/kg bw/day)**		**MOE**	
	Dermal	**Inhal.**			**Dermal**	**Inhal.**	**Dermal[5]**	**Inhal.[6]**
Corn Seeds – Corn Unit Exposures from the AH806 2010 Study; PPE[7]: Single layer + CR gloves; closed M/L								
Mixer/loader	256	3.72	5	125 000	2.00×10^{-2}	2.91×10^{-4}	5.00×10^{4}	1.10×10^{5}
Bagger/ sewer/stacker	114	18.7	5	125 000	8.91×10^{-3}	1.46×10^{-3}	1.12×10^{5}	2.19×10^{4}
Cleaner[4] (µg/g a.i./100 kg seed)	127	24.1	5	---	7.94×10^{-3}	1.51×10^{-3}	1.26×10^{5}	2.12×10^{4}
Teosinte Seeds[8] - Corn Unit Exposures from the AH806 2010 Study; PPE: Single layer + CR gloves; closed M/L								
Mixer/loader	256	3.72	2	125 000	8.00×10^{-3}	1.16×10^{-4}	1.25×10^{5}	2.75×10^{5}
Bagger/ sewer/stacker	114	18.7	2	125 000	3.56×10^{-3}	5.84×10^{-4}	2.81×10^{5}	5.48×10^{4}
Cleaner[4] (µg/g a.i./100 kg seed)	127	24.1	2	---	3.18×10^{-3}	6.03×10^{-4}	3.15×10^{5}	5.31×10^{4}
Legume Vegetable Seeds (CG 6) - Canola Unit Exposures from the AH806 2010 Study; PPE: Cotton coveralls + Single layer + CR gloves; closed M/L								
Mixer/loader	53.5	1.12	5	216 000	7.22×10^{-3}	1.51×10^{-4}	1.38×10^{5}	2.12×10^{5}
Bagger/ sewer/stacker	7.33	1.5	5	216 000	9.90×10^{-4}	2.03×10^{-4}	1.01×10^{6}	1.58×10^{5}
Cleaner[4] (µg/g a.i./100 kg seed)	56.2	12.7	5	---	3.51×10^{-3}	7.94×10^{-4}	2.85×10^{5}	4.03×10^{4}
Canola Seeds - Canola Unit Exposures from the AH806 2010 Study; PPE: Cotton coveralls + Single layer + CR gloves; closed M/L								
Mixer/loader	53.5	1.12	5	67 000	2.24×10^{-3}	4.69×10^{-5}	4.46×10^{5}	6.82×10^{5}
Bagger/ sewer/stacker	7.33	1.5	5	67 000	3.07×10^{-4}	6.28×10^{-5}	3.26×10^{6}	5.09×10^{5}

Worker's Tasks	Unit Exposures (µg/kg a.i. handled)[1]		App. Rate (g a.i./ 100 kg seed)	Commercial Throughput[2] (kg seeds/ day)	Daily Exposures[3,4] (mg/kg bw/day)		MOE	
	Dermal	Inhal.			Dermal	Inhal.	Dermal[5]	Inhal.[6]
Cleaner[4] (µg/g a.i./100 kg seed)	56.2	12.7	5	---	3.51×10^{-3}	7.94×10^{-4}	2.85×10^{5}	4.03×10^{4}
Soybeans Seeds - Canola Unit Exposures from the AH806 2010 Study; PPE: Cotton coveralls + Single layer + CR gloves; closed M/L								
Mixer/loader	53.5	1.12	80	63 000	3.37×10^{-2}	7.06×10^{-4}	2.97×10^{4}	4.54×10^{4}
Bagger/ sewer/stacker	7.33	1.5	80	63 000	4.62×10^{-3}	9.45×10^{-4}	2.17×10^{5}	3.39×10^{4}
Cleaner[4] (µg/g a.i./100 kg seed)	56.2	12.7	80	---	5.62×10^{-2}	1.27×10^{-2}	1.78×10^{4}	2.52×10^{3}
Cereal Seeds (except teosinte) - Wheat Unit Exposures from the AH809 2003a Study PPE for mixer/loader: Cotton coveralls + single layer + CR gloves; closed M/L PPE for cleaner: CR coveralls + single layer + CR gloves; closed M/L								
Mixer/loader	83.06	6.04	2	92 000	1.91×10^{-3}	1.39×10^{-4}	5.23×10^{5}	2.30×10^{5}
Cleaner[9] (µg/g a.i./100 kg seed)	2.13	0.102	2	---	5.33×10^{-5}	2.55×10^{-6}	1.88×10^{7}	1.25×10^{7}
Cereal Seeds (except teosinte) – Wheat Unit Exposures from the AH817 2009 Study PPE: Single layer + CR gloves; closed M/L								
Bagger/ sewer/stacker	17.67	0.89	2	92 000	4.06×10^{-4}	2.05×10^{-5}	2.46×10^{6}	1.56×10^{6}

[1] Dermal and inhalation unit exposure estimates (arithmetic means) are from the specified surrogate exposure studies. All selected studies were conducted with a closed mixing/loading system. Unit exposure estimates for mixers/loaders and baggers/sewers/stackers are in µg/kg a.i. handled, while unit exposure estimates for cleaners are in µg/g a.i./100 kg seeds.
[2] Commercial throughput values are from the PMRA's memo "Commercial Seed Treatment Throughput Values".
[3] For mixers/loaders and baggers/sewers/stackers: dermal/inhalation daily exposure (mg/kg bw/day) = [kg a.i. handled/day × dermal/inhalation unit exposure (µg/kg a.i. handled)] / [80 kg bw × 1000 µg/mg].
[4] For cleaners: dermal/inhalation daily exposure (mg/kg bw/day) = [dermal/inhalation unit exposure (µg/g a.i. /100 kg seed) × application rate in g a.i./100 kg seed] / [80 kg bw × 1000 µg/mg].
[5] Based on a dermal NOAEL of 1000 mg/kg bw/day and a dermal target MOE of 100.
[6] Based on an oral NOAEL of 32 mg/kg bw/day and an inhalation target MOE of 100.
[7] PPE: personal protective equipment; CR: chemical-resistant; M/L: mixing/loading
[8] For teosinte seeds, the corn unit exposure estimates from the AH806 2010 study are used because the size and shape of this cereal grain seed is more similar to corn than wheat. In addition, the default commercial throughput value for corn seeds was used for teosinte seeds.
[9] In PMRA's review of the AH809 2003a study, the units for cleaners' exposure estimates are in µg/hour/kg a.i./1000 kg seed; however, for the purpose of the current submission, they were converted to the same units as the other surrogate studies, i.e., µg/g a.i./100 kg seed, using the original calculation spreadsheet for this study.

Table 12 Summary of the PPE Requirements for Commercial Seed Treatment Based on the Selected Surrogate Exposure Studies

Tasks / Seed Types	Mixers/Loaders	Baggers/Sewers/Stackers	Cleaners
Corn (sweet, field, pop)	Single layer + CR[1] gloves	Single layer + CR gloves	Single layer + CR gloves
Teosinte	Single layer + CR gloves	Single layer + CR gloves	Single layer + CR gloves
Legume vegetables of CG 6 (except soybeans)	Cotton coveralls + single layer + CR gloves	Cotton coveralls + single layer + CR gloves	Cotton coveralls + single layer + CR gloves
Soybeans	Cotton coveralls + single layer + CR gloves	Cotton coveralls + single layer + CR gloves	Cotton coveralls + single layer + CR gloves

Rapeseed/Canola	Cotton coveralls + single layer + CR gloves	Cotton coveralls + single layer + CR gloves	Cotton coveralls + single layer + CR gloves
Labelled Cereals	Cotton coveralls + single layer + CR gloves	Single layer + CR gloves	CR coveralls + single layer + CR gloves
Most Conservative PPE	Cotton coveralls + single layer + CR gloves	Cotton coveralls + single layer + CR gloves	CR coveralls + single layer + CR gloves

[1] CR: chemical-resistant

Table 13 Exposure Risk Assessment for On-Farm Workers Treating and Planting Legume Vegetable, Soybean and Cereal Seeds with Zeltera Fungicide

Task and Seed Type	Unit Exposures (µg/kg a.i. handled)[1]		App. Rate (g a.i./ 100 kg seed)	Amount of Seeds Treated/ Planted[2] (kg seeds/day)	Daily Exposures[3] (mg/kg bw/day)		MOE	
	Dermal	Inhal.			Dermal	Inhal.	Dermal[4]	Inhal.[5]
Wheat Unit Exposures from the AH803 2006 Study; PPE[6]: Single layer + CR gloves; open M/L; closed-cab Mixer/loader/operator/cleaner/planter								
Legume vegetable of CG 6 (except soybeans)	145.22	7.61	5	19 000	1.72×10^{-3}	9.04×10^{-5}	5.80×10^{5}	3.54×10^{5}
Soybeans	145.22	7.61	80	12 600	1.83×10^{-2}	9.59×10^{-4}	5.47×10^{4}	3.34×10^{4}
Cereals (except teosinte)	145.22	7.61	2	22 000	7.99×10^{-4}	4.19×10^{-5}	1.25×10^{6}	7.65×10^{5}
Teosinte	145.22	7.61	2	1 688	6.13×10^{-5}	3.21×10^{-6}	1.63×10^{7}	9.96×10^{6}

[1] Dermal and inhalation unit exposure estimates (arithmetic means) are from the AH803 2006 study, which was conducted with closed-cab tractors for planting.
[2] For soybean and teosinte seeds, the seed treating capacities proposed by the applicant was used in the on-farm risk assessment since they are higher than PMRA's default values and based on more recent information from the seed treatment industry.
[3] Dermal/inhalation daily exposure (mg/kg bw/day) = [kg a.i. handled/day × dermal/inhalation unit exposure (µg/kg a.i. handled)] / [80 kg bw × 1000 µg/mg].
[4] Based on a dermal NOAEL of 1000 mg/kg bw/day and a dermal target MOE of 100.
[5] Based on an oral NOAEL of 32 mg/kg bw/day and an inhalation target MOE of 100.
[6] PPE: personal protective equipment; CR: chemical-resistant.

Table 14 Exposure Risk Assessment for Workers Planting Seeds Commercially Treated with Zeltera Fungicide

Seed Type	Unit Exposures (µg/kg a.i. handled)[1]		App. Rate (g a.i./ 100 kg seed)	Amount of Seeds Planted[2] (kg seeds/day)	Daily Exposures[3] (mg/kg bw/day)		MOE	
	Dermal	Inhal.			Dermal	Inhal.	Dermal[4]	Inhal.[5]
Corn Unit Exposures from the AH825 2007 Study (bagged seeds) PPE[6]: Single layer + CR gloves; closed-cab								
Teosinte seeds	1515	82.83	2	1 688	6.39×10^{-4}	3.50×10^{-5}	1.56×10^{6}	9.15×10^{5}
Corn seeds	1515	82.83	5	1 688	1.60×10^{-3}	8.74×10^{-5}	6.26×10^{5}	3.66×10^{5}
Canola seeds	1515	82.83	5	600	5.68×10^{-4}	3.11×10^{-5}	1.76×10^{6}	1.03×10^{6}
Legume seeds	1515	82.83	5	19 000	1.80×10^{-2}	9.84×10^{-4}	5.56×10^{4}	3.25×10^{4}
Sugar beet seeds	1515	82.83	10	160	3.03×10^{-4}	1.66×10^{-5}	3.30×10^{6}	1.93×10^{6}
Soybean seeds	1515	82.83	80	12 600	1.91×10^{-1}	1.04×10^{-2}	5.24×10^{3}	3.07×10^{3}
Wheat Unit Exposures from AH823 2013 Study (mostly bagged seeds) PPE[6]: Cotton coveralls over a single layer + CR gloves; closed-cab								
Cereal seeds (except teosinte)	1171.83	360.04	2	22 000	6.45×10^{-3}	1.98×10^{-3}	1.55×10^{5}	1.62×10^{4}

[1] Dermal and inhalation unit exposure estimates (arithmetic means) are from the AH825 2007 and AH823 2013 studies, which were conducted with closed-cab tractors for planting.
[2] For rapeseed/canola, legume vegetable and cereal seeds, the amounts of seeds planted per day (kg seed/day) are from PMRA's 'Seed Treated Planted Per Day-2018' table. For corn, soybean and sugar beet seeds, the seed planting rates proposed by the applicant in the DACO 5.2 document were used as they were higher than PMRA's default values and based on more recent information from the seed treatment industry.
[3] Dermal/inhalation daily exposure (mg/kg bw/day) = [kg a.i. handled/day × dermal/inhalation unit exposure (µg/kg a.i. handled)] / [80 kg bw × 1000 µg/mg].
[4] Based on a dermal NOAEL of 1000 mg/kg bw/day and a dermal target MOE of 100.
[5] Based on an oral NOAEL of 32 mg/kg bw/day and an inhalation target MOE of 100.
[6] PPE: personal protective equipment; CR: chemical-resistant.

Table 15 Model Input Parameters for aquatic eco-scenario and drinking water assessment

Parameter	Drinking water	Ecological
	Combined residue	Inpyrfluxam
Molecular weight (g/mole)	333.38	333.38
Vapour pressure (mm Hg) at 20 °C	2.85E-10	2.85E-10
Solubility (mg/L) in water at pH 5.5–5.8	16.4	16.4
Henry's law constant (unitless)	3.12E-10	3.12E-10
Photolysis half-life (day) at 40° latitude	Stable	Stable
Hydrolysis at pH 7	Stable	Stable
Koc (L/kg)	12.5*	571
Soil half-life (day) at 20 °C	1.65E+5**	1242
Aerobic aquatic half-life (day) at 20 °C	3119	2424
Anaerobic aquatic half-life (day) at 20 °C	3641	3421

Parameter	Drinking water	Ecological
	Combined residue	**Inpyrfluxam**
Chemical application method	Airblast (SW)/Seed treatment (GW)	Ground foliar and seed treatment
Application efficiency	0.99 (foliar)/1.0 (seed)	0.99 (foliar)/1.0 (seed)
Seeding depth (^{cm})	8.0***	NA
Vapour phase diffusion coefficient (cm^2/day)	3.53E+3	3.53E+3
Heat of Henry (Joule/mole)	54872	54872

* Mean of 20th percentile for the K_{oc} values of two isomers of 1'-COOH-S-2840 (1'-COOH-S-2840-A and 1'-COOH-S-2840-B).

** 90% upper confidence bound on the mean of half-lives from four soils (461, 345, 6980 and 249000 days).

*** The deepest seeding depth for all listed crop seed treatments

Table 16 Fate and Behaviour in the Environment

Fate Process	Substance	Value		Major TPs	Comments	PMRA#
Abiotic transformation						
		DT_{50} / DT_{90}	**$t_{1/2}$ representative**			
Hydrolysis	Inpyrfluxam	Stable		None	Not a route of transformation	2819372
Phototransformation on soil	Inpyrfluxam	SFO DT_{50} irrad: 99.3 d DT_{50} dark: 161 d DT_{90} irrad: 330 d DT_{90} dark: 535 d	SFO 259 d (or 627 d of natural sunlight in summer at latitude 40 °N)	None	Not an important route of transformation	2819373
Phototransformation in water	Inpyrfluxam	Stable		None	Not a major route of transformation	2819374
		SFO DT_{50} irrad: 37.6 d DT_{50} dark: 499 d DT_{90} irrad: 125 d DT_{90} dark: 1658 d	SFO 41 d (or 87 d of natural sunlight in summer at latitude 40°N)	None	Not a major route of transformation	2819375
		SFO DT_{50} irrad: 88.5 d DT_{90} irrad: 294 d Dark samples not calculable	SFO 88.5 d (or 188 d of natural sunlight in summer at latitude 40°N)			
Biotransformation						
		DT_{50} / DT_{90}	**$t_{1/2}$ representative**			
Aerobic soil	Inpyrfluxam	Loam	Loam	3'-OH-	Persistent in aerobic soil	2819377

Fate Process	Substance	Value		Major TPs	Comments	PMRA#
		DFOP DT_{50}: 241 d DT_{90}: 1182 d	DFOP 413 d	S-2840		
		Sandy Loam SFO DT_{50}: 121 d DT_{90}: 402 d Silt Loam DFOP DT_{50}: 66.9 d DT_{90}: 4004 d Loam Soil DFOP DT_{50}: 87.2 d DT_{90}: 805 d	Sandy Loam SFO 121 d Silt Loam DFOP 1720 d Loam Soil DFOP 331 d	3'-OH-S-2840 1'-COOH-S-2840	Moderately persistent to persistent in aerobic soil	2819378
	3'-OH-S-2840	Sandy Loam SFO DT_{50}: 369 d DT_{90}: 1226 d Silt Loam SFO DT_{50} = 303 d DT_{90} = 1006 d Loamy Sand SFO DT_{50} = 276 d DT_{90} = 917 d	Sandy Loam SFO 369 d Silt Loam SFO 303 d Loamy Sand SFO 276 d	None	Persistent in aerobic soil	2819392
	1'-COOH-S-2840	Sandy Loam SFO DT_{50}: 91.3 d DT_{90}: 303 d Silt Loam DFOP DT_{50} = 24.5 d DT_{90} = 631 d Loamy Sand SFO DT_{50} = 148 d DT_{90} = 492 d	Sandy Loam SFO 91.3 d Silt Loam DFOP 270 d Loamy Sand SFO 148 d	1'-keto-S-2840	Moderately persistent in aerobic soil	2819393

Fate Process	Substance	Value		Major TPs	Comments	PMRA#
Anaerobic soil	Inpyrfluxam	Stable		None	Persistent in anaerobic soil	2819379
		Silt Loam SFO DT_{50} = 1212 d DT_{90} = 4027 d Loam SFO DT_{50} = 1858 d DT_{90} = 6172 d Loamy Sand SFO DT_{50} = 2975 d DT_{90} = 9883 d	Silt Loam SFO 1212 d Loam SFO 1858 d Loamy Sand SFO 2975 d	1'-COOH-S-2840	Persistent in anaerobic soil	2819380
Aerobic water / sediment systems	Inpyrfluxam	Water/Loamy Sand IORE DT_{50} = 423 d DT_{90} = 18869 d Water/ Sandy Loam SFO DT_{50} = 1610 d DT_{90} = 5348 d	Water/Loamy Sand IORE 5680 d Water/ Sandy Loam SFO 1610 d	None	Persistent in aerobic aquatic systems	2819381
		Water/ Clay Loam SFO DT_{50} = 318 d DT_{90} = 1057 d Water/ Clay SFO DT_{50} = 561 d DT_{90} = 1862 d Water/ Sand SFO DT_{50} = 705 d DT_{90} = 2341	Water/ Clay Loam SFO 318 d Water/ Clay SFO 561 d Water/ Sand SFO 705 d	None	Persistent in aerobic aquatic systems	2819382

Fate Process	Substance	Value		Major TPs	Comments	PMRA#
		d				
Aerobic surface water	Inpyrfluxam	0.01 mg a.i./L SFO DT_{50} = 2973 d DT_{90} = 9875 d 0.1 mg a.i./L SFO DT_{50} = 2866 d DT_{90} = 9519 d	0.01 mg a.i./L SFO 2973 d 0.1 mg a.i./L SFO 2866 d	None	Persistent in aerobic aquatic systems	2819394
Anaerobic water /sediment systems	Inpyrfluxam	Water/ Clay SFO DT_{50} = 3367 d DT_{90} = 11186 d Water/ Sand SFO DT_{50} = 3421 d DT_{90} = 11365 d	Water/ Clay SFO 3367 d Water/ Sand SFO 3421 d	None	Persistent in anaerobic aquatic systems	2819383
Mobility						
Adsorption / desorption in soil	Inpyrfluxam	K_{oc} = 500–913			Low mobility in soil	2819384
	3'-OH-S-2840	K_{oc} = 365–568			Low to moderate mobility in soil	2819385
	1'-COOH-S-2840	K_{oc} = 11–44			Very high mobility in soil	2819386
Bioaccumulation						
Bioconcentration in fish	Inpyrfluxam	BCF_{SS} = 173–190			Low potential for bioaccumulation	2819456
Field studies						
		DT_{50} / DT_{90}	**$t_{1/2\ rep}$**			
Terrestrial field dissipation	Inpyrfluxam	Sandy Loam IORE DT_{50} = 24 d DT_{90} = 244 d	Sandy loam IORE DT_{50} = 73.3 d	3'-OH-S-2840 detected at low levels	Rapid dissipation during the first few months under field conditions. Sharp decrease of the dissipation rate afterward. All reported concentrations were within the 15 cm depth.	2819397
		Loamy Sand IORE DT_{50} = 37.8 d DT_{90} = 950 d	Loamy Sand IORE 286 d	3'-OH-S-2840 detected at low levels	Rapid dissipation during the first few months under field conditions. Afterward, soil concentrations remain stable. Inpyrfluxam, 3'-OH-S-2840 and 1'-COOH-S-	2819398

Fate Process	Substance	Value		Major TPs	Comments	PMRA#
					2840 detected down to 45 cm depth.	
		Sandy Loam DFOP DT_{50} = 10.9 d DT_{90} = 560 d	Sandy loam DFOP 279 d	3'-OH-S-2840 detected at low levels	Rapid dissipation during the first few months under field conditions. Sharp decrease of the dissipation rate afterward. All reported concentrations were within the 15 cm depth.	2819399
Foliar Washoff from Apple Tree Leafs	Inpyrfluxam	SFO DT_{50} = 15.9 d DT_{90} = 52.7 d	SFO 15.9 d	N/A	From leaf punch samples collected pre-rainfall simulation.	2819402

Table 17 Major Transformation Products of Inpyrfluxam and their Occurrence

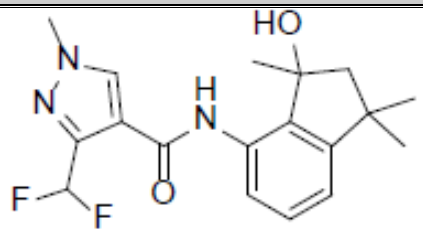
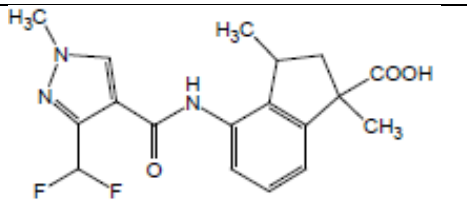
Code / name	Molecular Formula / Molecular Weight	Structure	Matrix occurrence (at > 10% AR)
3'OH-S-2840 / 3-(Difluoromethyl)-*N*-[3'-hydroxy-(**3'S**)/(**3'R**)-1',1',3'-trimethyl-2',3'-dihydro-1'*H*-inden-4'-yl]-1-methyl-1*H*-pyrazole-4-carboxamide	$C_{18}H_{21}F_2N_3O_2$ 349.38 g/mol		Aerobic soil Max of 22.5%AR at the end of the study (120 days). Also seen as a minor compound in most studies.
1'-COOH-S-2840B / (1RS,3RS)-(1RS,3SR)-2,3-dihydro-1,3-dimethyl-4-{[1-methyl-3-(difluoromethyl)-1H-pyrazole-4-ylcarbonyl] amino}-1H-indene-1-carboxylic acid	$C_{18}H_{19}F_2N_3O_3$ 363.36 g/mol	 (2 enantiomers: 1´R,3´R and 1´S,3´S)	Aerobic soil Max of 26.2% AR at study end (120 days). Anaerobic soil Max of 17.9% AR at study end (125 days) Also seen as a minor compound in other laboratory biotransformation studies.

Table 18 Effects on Terrestrial Species

Organism	Exposure	Test substance[1]	Endpoint value	Degree of toxicity	PMRA#
Invertebrates					
Earthworm *(Eisenia fetida)*	14-d Acute	S-2399 TG (95.0%)	LC_{50} = 235.9 mg a.i./kg soil	N/A	2819406
	56-d Reproduction	S-2399 TG (95.5%)	NOEC = 6.3 mg a.i./kg soil (number of juveniles)	N/A	2819408
		3'-OH-S-2840	NOEC = 100 mg/kg soil (highest	N/A	2819407

Organism	Exposure	Test substance[1]	Endpoint value	Degree of toxicity	PMRA#
		(99.5%)	concentration tested)		
		1'-COOH-S-2840 (100%)	NOEC = 50 mg/kg soil (nb of juveniles) EC_{50} > 100 mg a.i./kg soil	N/A	2819409
Collembola *Folsomia candida*	28-d Reproduction	S-2399 TG (95.5%)	NOEC = 100 mg a.i./kg soil (highest concentration tested)	N/A	2819427
		3'-OH-S-2840 (99.5%)	NOEC = 100 mg/kg soil (highest concentration tested)	N/A	2819428
		1'-COOH-S-2840 (100%)	NOEC = 100 mg/kg soil (highest concentration tested)	N/A	2819429
Honey Bee (*Apis mellifera* L.)	48h-acute	S-2399 TG (95.0%)	Oral LD_{50} > 111.3 µg a.i./bee Contact LD_{50} > 100 µg a.i./bee	Practically non-toxic	2819411
	10-d Oral	40 SC (37.31% w/w)	LD_{50} > 116.6 µg a.i./bee/day NOEL = 116.6 µg a.i./bee/day		2819417
	10-d Oral	2.84 SC (30.8%)	LD_{50} > 129.2 µg a.i./bee/day NOEL = 129.2 µg a.i./bee/day		2819419
Honey Bee Larva (*Apis mellifera* L.)	72-h Acute	S-2399 TG (95.0%)	LD_{50} > 100 µg a.i./larva		2819412
	22-d Chronic oral	2.84 SC (30.8% w/w)	NOEL = 1.5 µg a.i./larva/day		2819416
	22-d Chronic oral	40 SC (37.31% w/w)	NOEL = 1.2 µg a.i./larva/day		2819414
Bumble Bees (*Bombus terrestris* L.)	48h-acute	S-2399 TG (95.5%)	Oral LD_{50} > 95.1 µg a.i./bee Contact LD_{50} > 100 µg a.i./bee		2819410
Predatory Mite *(Typhlodromus pyri)*	7-day Acute 14-d Reproduction on Glass plates	40 SC (38.61% w/w)	7-d LR_{50} > 1000 g a.i./ha 7-d NOER: 1000 g a.i./ha (mortality at highest concentration tested) 14-d NOER: 1000 g a.i./ha (cumulative nb of eggs/♀)	N/A Harmless (based on IOBC)	2819422
Predatory Mite *(Hypoaspis aculeifer)*	14-d Reproduction	S-2399 TG (95.5%)	NOEC = 100 mg a.i./kg soil (mortality and nb of juveniles at highest concentration tested)	N/A	2819421
		3'-OH-S-2840 (99.5%)	NOEC = 100 mg/kg soil (mortality and nb of juveniles at highest concentration tested)	N/A	2819426
		1'-COOH-S-2840 (100%)	NOEC = 100 mg/kg soil (mortality and nb of juveniles at highest concentration tested)	N/A	2819425
Parasitoid *(Aphidius rhopalosiphi)*	14-d Acute on Glass Plates	40 SC (38.61% w/w)	7-d LR_{50} > 1000 g a.i./ha (highest tested concentration) NOER: 1000 g a.i./ha	N/A Harmless (based on IOBC)	2819423

Organism	Exposure	Test substance[1]	Endpoint value	Degree of toxicity	PMRA#
Birds					
Northern bobwhite quail *(Colinus virginianus)*	14-d single dose oral	S-2399 TG (95.0%)	LD_{50} > 2250 mg a.i./kg bw	Practically non-toxic	2819457
	5-d Dietary	S-2399 TG (95.0%)	LC_{50} > 6210 mg a.i./kg dw of diet (highest mean measured concentration tested) Equivalent to: LD_{50} > 1490 mg a.i./kg bw/d	Practically non-toxic	2819460
	One generation dietary Reproduction	S-2399 TG (95.0%)	NOEC = 539 mg a.i./kg dw of diet (eggs laid/pen/day) Equivalent to: NOEL = 46.4 mg a.i./kg bw/d	N/A	2819464
Mallard duck *(Anas platyrhynchos)*	14-d single dose oral	S-2399 TG (95.0%)	LD_{50} > 486 mg a.i./kg bw (regurgitation/sublethal effects at higher concentrations)	N/A	2819458
	5-d Dietary	S-2399 TG (95.0%)	LC_{50} > 6145 mg a.i./kg dw of diet (highest mean measured concentration) Equivalent to: LD_{50} > 2336 mg a.i./kg bw/d	Practically non-toxic	2819461
	One generation dietary Reproduction	S-2399 TG (95.0%)	NOEC = 1017 mg a.i./kg dw of diet (highest concentration tested) Equivalent to: NOEL = 132 mg a.i./kg bw/d	N/A	2819465
Zebra finch (*Taeniopygia guttata*)	5-d Dietary	S-2399 TG (95.5%)	LC_{50} = 359 mg a.i./kg diet Equivalent to: LD_{50} = 38.09 mg a.i./kg bw/d	Highly toxic	2819462
Mammals					
Wister Rat	Acute oral	S-2399 TG (95.0%)	50 mg a.i./kg bw < LD_{50}(♀) < 300 mg a.i./kg bw	Moderately toxic	2819306
			LD_{50}(♀)= 180 mg a.i./kg bw	Moderately toxic	2819308
Sprague-Dawley Rat	Acute oral	2.84 SC (31%)	LD_{50}(♀) = 550 mg equiv. a.i./kg bw	Slightly toxic	2819554
		3.2 FS (34.6%)	LD_{50}(♀) = 550 mg equiv.a.i./kg bw	Slightly toxic	2819633
Wistar Rat	Two-Generation Reproduction	S-2399 TG (95.0%)	Parent: NOAEL = 28/35 mg/kg bw/day (♂/♀) Offspring: NOAEL = 35 mg/kg bw/day LOAEL = 86 mg/kg bw/day (↓ bw F_1/F_2 ♂♀) Reproductive Toxicity NOAEL = 28/35 mg/kg bw/day	N/A	2819326
Vascular plants					
Vascular plant	14-d Seedling emergence	2.84 SC (31.0%)	ER_{25} = ND (dry weight tomato) LOER ≤ 13.3 g a.i./ha (42% effects) NOER < 13.3 g a.i./ha (lowest tested application rate)	N/A	2819473

Organism	Exposure	Test substance[1]	Endpoint value	Degree of toxicity	PMRA#
			ER_{25} = 151 g a.i./ha (dry weight oilseed rape)	N/A	2819495
	21-d Vegetative vigour		ER_{25} > 207 g a.i./ha (highest tested application rate)	N/A	2819484

1 S-2399 TG is the inpyrfluxam active ingredient, 2.84 SC (30.8%) is the inpyrfluxam formulation Excalia Fungicide, 40 SC (37.31% w/w) is a different inpyrfluxam formulation and 3.2 FS (34.6%) is the seed treatment inpyrfluxam formulation Zeltera Fungicide.

Table 19 Effects on Aquatic Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity	PMRA#
Freshwater species					
Water flea *(Daphnia magna)*	48-h Acute	S-2399 TG (95.0%)	LC_{50} = 1.1 mg a.i./L	Highly toxic	2819430
	21-d Chronic	S-2399 TG (95.0%)	NOEC = 0.14 mg a.i./L (live offspring, succesful birth rate and time to first brood)	N/A	2819431
Midge *(Chironomus dilutus)*	62-d Chronic	S-2399 TG (95.0%)	NOEC = 1.1 mg a.i./L (survival at 20 days and emergence at 62 days, TWA pore water concentration)	N/A	2819432
Freshwater Amphipod (*Hyalella azteca*)	42-d Chronic	S-2399 TG (95.0%)	NOEC = 0.21 mg a.i./L (TWA pore water concentration; 35-d survival)	N/A	2819436
Rainbow trout (*Oncorhynchus mykiss)*	96-h Acute	S-2399 TG (95.0%)	LC_{50} = 0.031 mg a.i./L	Very highly toxic	2819443
	96-h Acute	3'-OH-S-2840 (99.5%)	LC_{50} > 6.2 mg TP/L (highest mean measured concentration)	Not toxic up to the highest concentration tested	2819444
	96-h Acute	1'-COOH-S-2840 (100%)	LC_{50} > 50 mg TP/L (mean measured concentration at the limit of solubility under test conditions)	Not toxic to the highest concentration tested	2819445
Bluegill sunfish (*Lepomis macrochirus)*	96-h Acute	S-2399 TG (95.0%)	LC_{50} = 0.055 mg a.i./L (mean measured concentration)	Very highly toxic	2819446
Carp (*Cyprinus carpio*)	96-h Acute	S-2399 TG (95.0%)	LC_{50} = 0.065 mg a.i./L	Very highly toxic	2819451

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity	PMRA#
Fathead Minnow (*Pimephales promelas*)	96-h Acute	S-2399 TG (95.0%)	LC_{50} = 0.047 mg a.i./L (mean measured concentration)	Very highly toxic	2819447
	28-d Early life stage	S-2399 TG (95.0%)	NOEC = 0.0016 mg a.i./L (mean measured concentration; larval survival)	N/A	2819453
Guppy *(Poecilia reticulata)*	96-h Acute	S-2399 TG (95.5%)	LC_{50} = 0.35 mg a.i./L (mean measured concentration)	Highly toxic	2819448
Japanese medaka *(Oryzias latipes)*	96-h Acute	S-2399 TG (95.5%)	LC_{50} = 0.80 mg a.i./L (mean measured concentration)	Highly toxic	2819449
Zebrafish *(Danio rerio)*	96-h Acute	S-2399 TG (95.5%)	LC_{50} = 0.31 mg a.i./L (mean measured concentration)	Highly toxic	2819450
Freshwater green algae (*Pseudokirchneriella subcapitata*)	96-h Acute	S-2399 TG (95.0%)	EBC_{50} = 7.1 mg a.i./L (mean measured concentration) NOEC = 1.3 mg a.i./L (biomass, growth rate and area under the growth curve)	N/A	2819470
Blue-green algae *A. flos-aquae*	96-h Acute	S-2399 TG (95.0%)	EBC_{50} > 27 mg a.i./L (mean measured concentration; biomass) NOEC = 6.1 mg a.i./L	N/A	2819468
Diatom *N. pelliculosa*	96-h Acute	S-2399 TG (95.0%)	EC_{50} = 3.93 mg a.i./L (mean measured concentration; area under the growth curve) NOEC = 0.25 mg a.i./L (mean measured concentration; yield)	N/A	2819466
Vascular plant (*L. gibba*)	7-d	S-2399 TG (95.0%)	EC_{50} > 24 mg a.i./L (TWA measured concentration) EC_{20} = 5.7 mg a.i./L NOEC = 2.8 mg a.i./L (frond dry weight)	N/A	2819496
Marine species					
Mysid (*A. bahia*)	96-h Acute	S-2399 TG (95.0%)	LC_{50} = 1.1 mg a.i./L (mean measured concentration)	Moderately toxic	2819438

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity	PMRA#
	32-d Life-cycle	S-2399 TG (95.0%)	NOEC = 0.18 mg a.i./L (mean measured concentration; F_0 male length)	N/A	2819441
Mollusk shell deposition (*C. virginica*)	96-h Acute	S-2399 TG (95.0%)	EC_{50} > 0.99 mg a.i./L (mean measured concentration)	Not toxic up to highest concentration tested	2819439
Estuarine Amphipod (*Leptocheirus plumulosus*)	28-d Chronic	S-2399 TG (95.0%)	NOEC = 0.42 mg a.i./L (TWA pore water concentration; ♂ dw)	N/A	2819442
Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute	S-2399 TG (95.0%)	LC_{50} = 0.15 mg a.i./L (mean measured concentration)	Highly toxic	2819452
	28d-ELS	S-2399 TG (95.0%)	NOEC = 0.009 mg a.i./L (mean measured concentration; post-hatch survival)	N/A	2819454
Marine algae *S. costatum*	96-h Acute	S-2399 TG (95.0%)	EC_{50} = 0.56 mg a.i./L (initial measured concentrations) NOEC = 0.32 mg a.i./L	N/A	2819471

Table 20 Endpoints used in the risk assessment

Organism	Test Substance	Exposure	Endpoint	Value	Study #	Uncertainty factor	Level of Concern
Earthworm (*Eisenia fetida*)	Inpyrfluxam	Acute	14-d LC_{50}	235.9 mg a.i./kg soil	2819406	2	1
		Chronic	56-d NOEC (number of juveniles)	6.3 mg a.i./kg soil	2819408	1	1
	3'-OH-S-2840	Chronic	56-d NOEC (number of juveniles)	100 mg TP/kg soil	2819407	1	1
	1'-COOH-S-2840	Chronic	56-d NOEC (number of juveniles)	50 mg TP/kg soil	2819409	1	1

Organism	Test Substance	Exposure	Endpoint	Value	Study #	Uncertainty factor	Level of Concern
Springtail (*Folsomia candida*)	Inpyrfluxam	Chronic	28-d NOEC (mortality / reproduction)	100 mg a.i./kg soil	28194 27	1	1
	3'-OH-S-2840	Chronic	28-d NOEC (mortality / reproduction)	100 mg TP/kg soil	28194 28	1	1
	1'-COOH-S-2840	Chronic	28-d NOEC (mortality / reproduction)	100 mg TP/kg soil	28194 29	1	1
Honey Bee (*Apis mellifera L.*)	Inpyrfluxam	Acute oral	48-h Oral LD_{50}	> 111.3 µg a.i./bee	28194 11	1	0.4
		Acute contact	48-h-Contact LD_{50}	> 100 µg a.i./bee		1	0.4
	40 SC	Chronic adult	10-d NOAEL (mortality)	116.6 µg a.i./bee/day	28194 17	1	1
	Excalia (2.84 SC)	Chronic adult	10-d NOAEL (mortality)	129.2 µg a.i./bee/day	28194 19	1	1
	Inpyrfluxam	Acute larvae	72h-LD_{50}	> 100 µg a.i./larva	28194 12	1	0.4
	Excalia (2.84 SC)	Chronic larvae	22-d larvae NOEL (adult emergence; repeat dose on days 3-6)	1.5 µg a.i./larva/day	28194 16	1	1
	40 SC	Chronic larvae	22-d larvae NOEL (adult emergence; repeat dose	1.2 µg a.i./larva/day	28194 14	1	1

Organism	Test Substance	Exposure	Endpoint	Value	Study #	Uncertainty factor	Level of Concern
			on days 3-6)				
Bumble Bee (*Bombus terrestris L.*)	Inpyrfluxam	Acute oral	48-h Oral LD_{50}	LD_{50} > 95.1 µg a.i./bee	28194 10	N/A	N/A
		Acute contact	48-h Contact LD_{50}	LD_{50} > 100 µg a.i./bee		N/A	N/A
Predatory mite (*Typhlodromus pyri)*	40 SC	Acute contact (glass surface)	7-d LR_{50}	> 1000 g a.i./ha	28194 22	1	2
		Chronic	14-d NOER (mortality, cumulative nb eggs/♀)	1000 g a.i./ha		1 (glass plates)	1
Predatory mite (*Hypoaspis aculeifer)*	Inpyrfluxam	Acute contact	14-d LC_{50}	> 100 mg a.i./ kg soil	28194 21	1	1
		Chronic	14-d NOEC (mortality, nb of juveniles)	100 mg a.i./kg soil		1 (soil)	1
	3'-OH-S-2840	Chronic	14-d NOEC (mortality, nb of juveniles)	100 mg TP/kg soil	28194 26	1 (soil)	1
	1'-COOH-S-2840	Chronic	14-d NOEC (mortality, nb of juveniles)	100 mg TP/kg soil	28194 25	1 (soil)	1
Parasitic wasp (*Aphidius rhopalosiphi*)	40 SC	Acute contact (glass surface)	48h LR_{50}	> 1000 g a.i./ha	28194 23	1	2
		Chronic	14-d	1000 g		1 (plant	1

Organism	Test Substance	Exposure	Endpoint	Value	Study #	Uncertainty factor	Level of Concern
		(barley plants)	NOER	a.i./ha		surfaces)	
Bobwhite quail *(Colinus virginianus)*	Inpyrfluxam	Acute oral	14-d LD_{50}	> 2250 mg a.i./kg bw	28194 57	10	1
		Dietary	5-d LD_{50}	> 1490 mg a.i./kg bw/day	28194 60	10	1
		Reproduction	21-wk NOEL (eggs laid/pen/day)	46.4 mg a.i./kg bw/day	28194 64	1	1
Mallard Duck *(Anas platyrhynchos)*	Inpyrfluxam	Acute single dose oral	14-d LD_{50}	> 486 mg a.i./kg bw	28194 58	10	1
		Dietary	5-d LD_{50}	> 2336 mg a.i./kg bw/day	28194 61	10	1
		Reproduction	NOEL	132 mg a.i./kg bw/day	28194 65	1	1
Zebra Finch (*Taeniopygia guttata*)	Inpyrfluxam	Dietary	5-d LD_{50}	38.09 mg a.i./kg bw/day	28194 62	10	1
Mammals (Rat)	Inpyrfluxam	Acute oral	LD_{50}	180 mg/kg bw	28193 08	10	1
		Reproduction	NOEL	28 mg/kg bw/day	28193 26	1	1
Terrestrial vascular plants	Excalia (2.84 SC)	Seedling emergence	14-d LOER (42% effects) (dry weight)	13.3 g a.i./ha	28194 73	2	1
			14-d ER_{25} (dry weight)	151 g a.i./ha	28194 95	1	1
		Vegetative vigour	21-d ER_{25}	> 207 g a.i./ha	28194 84	1	1

Organism	Test Substance	Exposure	Endpoint	Value	Study #	Uncertainty factor	Level of Concern
Water flea *(Daphnia magna)*	Inpyrfluxam	Acute	48-h LC_{50}	1.1 mg a.i./L	28194 30	2	1
		Chronic	21-d NOEC (live offspring, birth rate, time to first brood)	0.14 mg a.i./L	28194 31	1	1
Midge *(Chironomus dilutus)*	Inpyrfluxam	Chronic	62-d NOEC (survival at 20 days, pore water concentration)	1.1 mg a.i./L	28194 32	1	1
Freshwater amphipod *(Hyalella azteca)*	Inpyrfluxam	Chronic	42-d NOEC (pore water concentration)	0.21 mg a.i./L	28194 36	1	1
Rainbow trout *(Oncorhynchus mykiss)*	Inpyrfluxam	Acute	96-h LC_{50}	0.031 mg a.i./L	28194 43	10	1
	3'-OH-S-2840	Acute	96-h LC_{50}	> 6.2 mg TP/L	28194 44	10	1
	1'-COOH-S-2840	Acute	96-h LC_{50}	> 50 mg TP/L	28194 45	10	1
Bluegill Sunfish *(Lepomis macrochirus)*	Inpyrfluxam	Acute	96-h LC_{50}	0.055 mg a.i./L	28194 46	10	1
Carp *(Cyprinus carpio)*	Inpyrfluxam	Acute	96-h LC_{50}	0.065 mg a.i./L	28194 51	10	1
Fathead minnow *(Pimephales promelas)*	Inpyrfluxam	Acute	96-h LC_{50}	0.047 mg a.i./L	28194 47	10	1
		Chronic ELS	28-d NOEC (larval survival)	0.0016 mg a.i./L	28194 53	1	1

Organism	Test Substance	Exposure	Endpoint	Value	Study #	Uncertainty factor	Level of Concern
Guppy *(Poecilia reticulata)*	Inpyrfluxam	Acute	96-h LC_{50}	0.35 mg a.i./L	28194 48	10	1
Japanese medaka *(Oryzias latipes)*	Inpyrfluxam	Acute	96-h LC_{50}	0.80 mg a.i./L	28194 49	10	1
Zebrafish *(Danio rerio)*	Inpyrfluxam	Acute	96-h LC_{50}	0.31 mg a.i./L	28194 50	10	1
Amphibians (Rainbow trout and fathead minnow as surrogates)	Inpyrfluxam	Acute	96-h LC_{50}	0.031 mg a.i./L		10	1
		ELS	NOEC (larval survival)	0.0016 mg a.i./L		1	1
Aquatic vascular plant (*Lemna gibba*)	Inpyrfluxam	Acute	7-d EC_{20} (frond dry weight)	5.7 mg a.i./L	28194 96	1	1
Green algae (*Pseudokirchneriella subcapitata)*	Inpyrfluxam	Acute	96-h EC_{50}	7.1 mg a.i./L	28194 70	2	1
Blue-green algae *(A. flos-aquae)*	Inpyrfluxam	Acute	96-h EC_{50}	> 27 mg a.i./L	28194 68	2	1
Diatom *(N. pelliculosa)*	Inpyrfluxam	Acute	96-h EC_{50}	3.93 mg a.i./L	28194 66	2	1
Mysid *(A. bahia)*	Inpyrfluxam	Acute	96-h LC_{50}	1.1 mg a.i./L	28194 38	2	1
		Chronic	28-d NOEC (male length)	0.18 mg a.i./L	28194 41	1	1
Eastern oyster *(C. virginica)*	Inpyrfluxam	Acute	96-h EC_{50} (shell deposition)	> 0.99 mg a.i./L	28194 39	2	1
Estuarine amphipod *(Leptocheirus plumulosus)*	Inpyrfluxam	Chronic	28-d NOEC (♂ dry weight, pore water concentration)	0.42 mg a.i./L	28194 42	1	1

Organism	Test Substance	Exposure	Endpoint	Value	Study #	Uncertainty factor	Level of Concern
Sheepshead minnow *(Cyprinodon variegatus)*	Inpyrfluxam	Acute	96-h LC_{50}	0.15 mg a.i./L	28194 52	10	1
		Chronic	28-d NOEC ELS	0.009 mg a.i./L	28194 54	1	1
Saltwater algae (*Skeletonema costatum*)	Inpyrfluxam	Acute	96-h EC_{50} (yield)	0.56 mg a.i./L	28194 71	2	1

Table 21 Screening level risk from inpyrfluxam exposure to terrestrial organisms other than birds and mammals

Organism	Exposure	Endpoint value	EEC[1]	RQ[2]	LOC[3] exceeded
Earthworm	Acute	$LC_{50}/2$ = 118 mg a.i./kg soil	0.082 mg a.i./kg soil	< 0.001	No
	Chronic	NOEC = 6.3 mg a.i./kg soil	0.082 mg a.i./kg soil	0.013	No
Springtail	Chronic	NOEC = 100 mg a.i./kg soil	0.082 mg a.i./kg soil	0.001	No
Honey bee	Adult oral acute	LD_{50} > 111.3 µg a.i./bee	2.15 µg a.i./bee	< 0.019	No
	Adult contact acute	LD_{50} > 100 µg a.i./bee	0.18 µg a.i./bee	< 0.002	No
	Adult oral chronic	NOEL = 116.6 µg a.i./bee	2.15 µg a.i./bee	0.018	No
		NOEL = 129.2 µg a.i./bee	2.15 µg a.i./bee	0.017	No
	Larvae oral acute	LD_{50} > 100 µg a.i./larva	0.91 µg a.i./larva	< 0.009	No
	Larvae oral chronic	NOEL = 1.5 µg a.i./larva	0.91 µg a.i./larva	0.61	No
		NOEL = 1.15 µg a.i./larva	0.91 µg a.i./larva	0.79	No
Predatory mite (foliar exposure)	Acute contact	LR_{50} > 1000 g a.i./ha (glass plates)[a]	90.0 g a.i./ha	< 0.09	No
	Chronic	NOER = 1000 g a.i./ha	90.0 g a.i./ha	0.09	No
Predatory mite	Acute	LC_{50} > 100 mg a.i./kg soil	0.082 mg a.i./kg soil	< 0.001	No

Organism	Exposure	Endpoint value	EEC[1]	RQ[2]	LOC[3] exceeded
(soil exposure)	Chronic	NOEC = 100 mg a.i./kg soil	0.082 mg a.i./kg soil	0.001	No
Parasitic wasp	Acute contact (glass plates)	LR_{50} > 1000 g a.i./ha (glass plates)[a]	90.0 g a.i./ha	< 0.09	No
	Chronic (barley plants)	NOER = 1000 g a.i./ha	90.0 g a.i./ha	0.09	No
Vascular plants	Seedling emergence	LOER (42% effects)/2 = 6.65 g a.i./ha	184.7 g a.i./ha	**27.77**	**Yes**
		ER_{25} = 151 g a.i./ha	184.7 g a.i./ha	**1.22**	**Yes**
	Vegetative vigour	ER_{25} > 207 g a.i./ha	184.7 g a.i./ha	0.89	No

[1]EEC = Estimated Environmental Concentration. The EEC in soil was determined using the maximum application rate of 87.2 g a.i./ha (soybean seed treatment), 30-d interval followed by 2 applications of 50 g a.i./ha with a 14-d interval, considering a half-life in soil of 1242 days, assuming a soil bulk density of 1.5 g/cm^3 and a soil depth of 15 cm. EEC for bees = maximum single foliar application rate (75 g a.i./ha) × adjustment factor (2.4 µg a.i./bee/kg a.i./ha for adult contact; 0.18 µg a.i./bee and, 98 µg a.i./g diet/kg a.i./ha with consumption of 0.292 g diet/adult/day and 0.124 g diet/larva/day; 2.15 µg a.i./bee/day for adult oral and 0.91 µg a.i./larva/day for larvae. From seed treatment exposure, EEC for bees assuming 1 mg a.i./kg in pollen and nectar = 0.292 µg a.i./bee/day for adult and 0.124 µg a.i./bee/day for larva. EEC for predatory mite and parasitic wasp from foliar exposure = 87.2 g a.i./ha (calculated with the same maximum application rate as for EEC in soil BUT using a foliar half-life of 15.9 days).

[2]RQ = Risk Quotient. The RQ is calculated by dividing the EEC by the endpoint value (RQ = EEC/endpoint value)

[3]LOC = Level of Concern. The RQ is compared to the LOC. The LOC = 2 for predatory mites and parasitic wasp tested on glass plates (otherwise LOC = 1). The LOC =1.0 for earthworms, chronic exposure in bees and vascular plants. The LOC = 0.4 for acute exposure in bees. If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary.

Table 22 Screening level risks to birds exposed to inpyrfluxam foliar applications

Bird size/endpoint	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)[1]	EDE (mg a.i./kg bw)[2]	RQ[3]	LOC[4] Exceeded
Small Bird (0.02 kg)					
Acute	225.00	Insectivore	10.05	0.0	No
	225.00	Granivore (grain and seeds)	1.56	0.0	No
	225.00	Frugivore (fruit)	3.11	0.0	No
Dietary	3.81	Insectivore	10.05	2.6	**Yes**
	3.81	Granivore (grain and seeds)	1.56	0.4	No
	3.81	Frugivore (fruit)	3.11	0.8	No
Reproduction	46.40	Insectivore	10.05	0.2	No
	46.40	Granivore (grain and seeds)	1.56	0.0	No
	46.40	Frugivore (fruit)	3.11	0.1	No
Medium Sized Bird (0.1 kg)					
Acute	225.00	Insectivore	7.85	0.0	No
	225.00	Granivore (grain and seeds)	1.21	0.0	No
	225.00	Frugivore (fruit)	2.43	0.0	No
Dietary	3.81	Insectivore	7.85	2.1	**Yes**
	3.81	Granivore (grain and seeds)	1.21	0.3	No
	3.81	Frugivore (fruit)	2.43	0.6	No

Bird size/endpoint	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)[1]	EDE (mg a.i./kg bw)[2]	RQ[3]	LOC[4] Exceeded
Reproduction	46.40	Insectivore	7.85	0.2	No
	46.40	Granivore (grain and seeds)	1.21	0.0	No
	46.40	Frugivore (fruit)	2.43	0.1	No
Large Sized Bird (1 kg)					
Acute	225.00	Insectivore	2.29	0.0	No
	225.00	Granivore (grain and seeds)	0.35	0.0	No
	225.00	Frugivore (fruit)	0.71	0.0	No
	225.00	Herbivore (short grass)	5.07	0.0	No
	225.00	Herbivore (long grass)	3.09	0.0	No
	225.00	Herbivore (Broadleaf plants)	4.69	0.0	No
Dietary	3.81	Insectivore	2.29	0.6	No
	3.81	Granivore (grain and seeds)	0.35	0.1	No
	3.81	Frugivore (fruit)	0.71	0.2	No
	3.81	Herbivore (short grass)	5.07	1.3	**Yes**
	3.81	Herbivore (long grass)	3.09	0.8	No
	3.81	Herbivore (Broadleaf plants)	4.69	1.2	**Yes**
Reproduction	46.40	Insectivore	2.29	0.0	No
	46.40	Granivore (grain and seeds)	0.35	0.0	No
	46.40	Frugivore (fruit)	0.71	0.0	No
	46.40	Herbivore (short grass)	5.07	0.1	No
	46.40	Herbivore (long grass)	3.09	0.1	No
	46.40	Herbivore (Broadleaf plants)	4.69	0.1	No

[1]Specialized feeding guilds are considered for each category of animal weights to help determine exposure (herbivore, frugivore, insectivore and granivore).
[2]EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where: FIR: Food Ingestion Rate, BW: Body Weight, EEC: Estimated Environmental Concentration. For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used: Passerine Equation (BW < or = 200 g): FIR (g dry weight/day) = 0.398(BW in g) $^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) $^{0.651}$.
[3]RQ = Risk Quotient. The RQ is calculated by dividing the EDE by the endpoint value (RQ = EDE/endpoint value).
[4]LOC = Level of Concern. The RQ is then compared to the level of concern (LOC = 1).

Table 23 Screening level risks to mammals exposed to inpyrfluxam foliar applications

Mammal size/endpoint	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)[1]	EDE (mg a.i./kg bw)[2]	RQ[3]	LOC[4] Exceeded
Small Mammal (0.015 kg)					
Acute	18.00	Insectivore	5.78	0.32	No
Reproduction	28.00	Insectivore	5.78	0.21	No
Medium Sized Mammal (0.035 kg)					
Acute	18.00	Herbivore (short grass)	11.21	0.62	No
Reproduction	28.00	Herbivore (short grass)	11.21	0.40	No
Large Sized Mammal (1 kg)					

Mammal size/endpoint	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)[1]	EDE (mg a.i./kg bw)[2]	RQ[3]	LOC[4] Exceeded
Acute	18.00	Herbivore (short grass)	5.99	0.33	No
Reproduction	28.00	Herbivore (short grass)	5.99	0.21	No

[1]Specialized feeding guilds are considered for each category of animal weights to help determine exposure (herbivore, frugivore, insectivore and granivore).
[2]EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where: FIR: Food Ingestion Rate, BW: Body Weight, EEC: Estimated Environmental Concentration. For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(BW in g) $^{0.822}$
[3]RQ = Risk Quotient. The RQ is calculated by dividing the EDE by the endpoint value (RQ = EDE/endpoint value).
[4]LOC = Level of Concern. The RQ is then compared to the level of concern (LOC = 1).

Table 24 Screening level risks to birds and mammals exposed to inpyrfluxam treated seeds

	Study Endpoint (mg a.i./kg bw/day / UF)	EDE[1] (mg a.i./kg bw/day)	RQ	LOC Exceeded
Small bird (0.02 kg)				
Acute	225.0	203.2	0.9	No
Dietary	3.8	203.2	53.3	**Yes**
Reproduction	46.4	203.2	4.4	**Yes**
Medium bird (0.10 kg)				
Acute	225.0	159.6	0.7	No
Dietary	3.8	159.6	41.9	**Yes**
Reproduction	46.4	159.6	3.4	**Yes**
Large bird (1.00 kg)				
Acute	225.0	46.5	0.2	No
Dietary	3.8	46.5	12.2	**Yes**
Reproduction	46.4	46.5	1.0	**Yes**
Small mammals (0.015 kg)				
Acute	18.0	116.1	6.4	**Yes**
Reproduction	28.0	116.1	4.1	**Yes**
Medium mammals (0.035 kg)				
Acute	18.0	99.8	5.5	**Yes**
Reproduction	28.0	99.8	3.6	**Yes**
Large mammals (1.00 kg)				
Acute	18.0	55.0	3.1	**Yes**
Reproduction	28.0	55.0	2.0	**Yes**

[1]EDE = FIR × number of seeds/g
EDE: Estimated Dietary Exposure, expressed as the number of seeds consumed per day.
FIR: Food ingestion rate, in g dry weight per day.

Table 25 Further characterization of risk to terrestrial organisms other than birds and mammals

Organism	Exposure	Endpoint value (g a.i./ha)	EEC - Spray drift (g a.i./ha)[1]	RQ[2]	LOC[3] exceeded
Vascular plants	Seedling emergence	LOER (42% effects)/2 = 6.65	110.7 (Airblast - early season)	**16.65**	**Yes**
			88.3 (Airblast - late season)	**13.27**	**Yes**
			3.0 (Ground Boom Sprayer)	0.45	No
		ER_{25} = 151	110.7 (Airblast - early season)	0.73	No
			88.3 (Airblast - late season)	0.58	No
			3.0 (Ground Boom Sprayer)	0.02	No

[1]EEC = Estimated Environmental Concentration. The EEC resulting from spray drift from foliar applications was determined by using the cumulative maximum foliar application rate on apple by airblast sprayer (two times 75 g a.i./ha at 10-day interval) on soybean by ground boom sprayer (two times 50 g a.i./ha at 14-day interval), considering a half-life in soil of 1242 days (90% of upper confidence bound on the mean of $t_{1/2}$ representative values from four soils). Spray drift at one metre downwind from the point of application was determined by assuming approximately 74, 59 and 6% of the application rate for airblast (early and late season) and ground boom sprayers, respectively, if the spray quality (droplet size distribution) used is classified as ASAE fine (airblast) and medium (ground boom sprayer).
[2]RQ = Risk quotient. The RQ is calculated by dividing the EEC from spray drift by the endpoint value (RQ = EEC/endpoint value).
[3]LOC = Level of concern. The RQ is compared to the LOC (LOC = 1.0).

Table 26 Further characterization of risks to birds through consumption of inpyrfluxam-contaminated food sources from foliar application

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)										
Acute	225.0	Insectivore	10.1	0.0	7.4	0.0	6.9	0.03	5.1	0.02
	225.0	Granivore (grain and seeds)	1.6	0.0	1.2	0.0	0.7	0.00	0.6	0.00
	225.0	Frugivore (fruit)	3.1	0.0	2.3	0.0	1.5	0.01	1.1	0.00
Dietary	3.8	Insectivore	10.1	2.6	7.4	2.0	6.9	1.82	5.1	1.35
	3.8	Granivore (grain and seeds)	1.6	0.4	1.2	0.3	0.7	0.19	0.6	0.14
	3.8	Frugivore (fruit)	3.1	0.8	2.3	0.6	1.5	0.39	1.1	0.29
Reproduction	46.4	Insectivore	10.1	0.2	7.4	0.2	6.9	0.15	5.1	0.11
	46.4	Granivore (grain and seeds)	1.6	0.0	1.2	0.0	0.7	0.02	0.6	0.01
	46.4	Frugivore (fruit)	3.1	0.1	2.3	0.0	1.5	0.03	1.1	0.02
Medium-Sized Bird (0.1 kg)										
Acute	225.0	Insectivore	7.9	0.0	5.8	0.0	5.4	0.02	4.0	0.02
	225.0	Granivore (grain and seeds)	1.2	0.0	0.9	0.0	0.6	0.00	0.4	0.00
	225.0	Frugivore (fruit)	2.4	0.0	1.8	0.0	1.2	0.01	0.9	0.00

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Dietary	3.8	Insectivore	7.9	2.1	5.8	1.5	5.4	1.42	4.0	1.05
	3.8	Granivore (grain and seeds)	1.2	0.3	0.9	0.2	0.6	0.15	0.4	0.11
	3.8	Frugivore (fruit)	2.4	0.6	1.8	0.5	1.2	0.30	0.9	0.22
Reproduction	46.4	Insectivore	7.9	0.2	5.8	0.1	5.4	0.12	4.0	0.09
	46.4	Granivore (grain and seeds)	1.2	0.0	0.9	0.0	0.6	0.01	0.4	0.01
	46.4	Frugivore (fruit)	2.4	0.1	1.8	0.0	1.2	0.02	0.9	0.02
Large Sized Bird (1 kg)										
Acute	225.00	Insectivore	2.29	0.0	1.69	0.0	1.6	0.01	1.2	0.01
	225.00	Granivore (grain and seeds)	0.35	0.0	0.26	0.0	0.2	0.00	0.1	0.00
	225.00	Frugivore (fruit)	0.71	0.0	0.52	0.0	0.3	0.00	0.3	0.00
	225.00	Herbivore (short grass)	5.07	0.0	3.75	0.0	1.8	0.01	1.3	0.01
	225.00	Herbivore (long grass)	3.09	0.0	2.29	0.0	1.0	0.00	0.8	0.00
	225.00	Herbivore (Broadleaf plants)	4.69	0.0	3.47	0.0	1.6	0.01	1.2	0.01
Dietary	3.81	Insectivore	2.29	0.6	1.69	0.4	1.6	0.42	1.2	0.31
	3.81	Granivore (grain and seeds)	0.35	0.1	0.26	0.1	0.17	0.04	0.13	0.03
	3.81	Frugivore (fruit)	0.71	0.2	0.52	0.1	0.34	0.09	0.25	0.07
	3.81	Herbivore (short grass)	5.07	1.3	3.75	1.0	1.80	0.47	1.33	0.35
	3.81	Herbivore (long grass)	3.09	0.8	2.29	0.6	1.01	0.27	0.75	0.20
	3.81	Herbivore (Broadleaf plants)	4.69	1.2	3.47	0.9	1.55	0.41	1.15	0.30
Reproduction	46.40	Insectivore	2.29	0.0	1.69	0.0	1.58	0.03	1.17	0.03
	46.40	Granivore (grain and seeds)	0.35	0.0	0.26	0.0	0.17	0.00	0.13	0.00
	46.40	Frugivore (fruit)	0.71	0.0	0.52	0.0	0.34	0.01	0.25	0.01
	46.40	Herbivore (short grass)	5.07	0.1	3.75	0.1	1.80	0.04	1.33	0.03
	46.40	Herbivore (long grass)	3.09	0.1	2.29	0.0	1.01	0.02	0.75	0.02
	46.40	Herbivore (Broadleaf plants)	4.69	0.1	3.47	0.1	1.55	0.03	1.15	0.02

[1]Specialized feeding guilds are considered for each category of animal weights to help determine exposure (herbivore, frugivore, insectivore and granivore).

[2]EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where: FIR: Food Ingestion Rate, BW: Body Weight, EEC: Estimated Environmental Concentration. For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used: Passerine Equation (BW < or = 200 g): FIR (g

dry weight/day) = 0.398(BW in g)$^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g)$^{0.651}$.
[3]RQ = Risk Quotient. The RQ is calculated by dividing the EDE by the endpoint value (RQ = EDE/endpoint value).

Table 27 Further characterization of risks to birds through consumption of inpyrfluxam treated seeds

Study Endpoint (mg a.i./kg bw/day / UF)		EDE (mg a.i./kg bw/day)	RQ	Number of seeds needed to reach endpoint		Area required (m2)			
						No Drilling		Precision drilling	
				min	max	min	max	min	max
Small bird (0.02 kg)									
Acute	225.0	203.2	0.9	30.94	41.63	0.33	1.33	66.36	265.55
Dietary	3.8	203.2	53.3	0.52	0.70	0.01	0.02	1.12	4.50
Reproduction	46.4	203.2	4.4	6.38	8.58	0.07	0.27	13.69	54.76
Medium bird (0.10 kg)									
Acute	225.0	159.6	0.7	154.69	208.13	1.66	6.64	331.81	1327.75
Dietary	3.8	159.6	41.9	2.62	3.52	0.03	0.11	5.62	22.48
Reproduction	46.4	159.6	3.4	31.90	42.92	0.34	1.37	68.43	273.81
Large bird (1.00 kg)									
Acute	225.0	46.5	0.2	1546.88	2081.25	16.59	66.39	3318.05	13277.51
Dietary	3.8	46.5	12.2	26.19	35.23	0.28	1.12	56.17	224.77
Reproduction	46.4	46.5	1.0	319.00	429.20	3.42	13.69	684.26	2738.12

Table 28 Further characterization of risks to mammals through consumption of inpyrfluxam treated seeds

Study Endpoint (mg a.i./kg bw/day / UF)		EDE (mg a.i./kg bw/day)	RQ	Number of seeds needed to reach endpoint		Area required (m2)			
						No Drilling		Precision drilling	
				min	max	min	max	min	max
Small mammals (0.015 kg)									
Acute	18.0	116.1	6.4	1.86	2.50	0.03	0.06	5.36	11.84
Reproduction	28.0	116.1	4.1	2.89	3.89	0.04	0.09	8.33	18.42
Medium mammals (0.035 kg)									
Acute	18.0	99.8	5.5	4.33	5.83	0.06	0.14	12.50	27.63
Reproduction	28.0	99.8	3.6	6.74	9.07	0.10	0.21	19.44	42.98
Large mammals (1.00 kg)									
Acute	18.0	55.0	3.1	123.75	166.50	1.79	3.95	357.14	789.47
Reproduction	28.0	55.0	2.0	192.50	259.00	2.78	6.14	555.56	1228.07

Table 29 Screening level risk from major transformation products of inpyrfluxam to terrestrial and aquatic organisms

Organism	Exposure	Endpoint value	EEC[1]	RQ[2]	LOC[3] exceeded
Terrestrial organisms					
Earthworm	3'-OH-S-2840 Chronic	NOEC = 100 mg TP/kg soil	0.086 mg TP/kg soil	< 0.001	No
	1'-COOH-S-2840 Chronic	NOEC = 50 mg TP/kg soil	0.089 mg TP/kg soil	0.002	No
Springtail	3'-OH-S-2840 Chronic	NOEC = 100 mg TP/kg soil	0.086 mg TP/kg soil	< 0.001	No
	1'-COOH-S-2840 Chronic	NOEC = 100 mg TP/kg soil	0.089 mg TP/kg soil	< 0.001	No
Predatory mite (soil exposure)	3'-OH-S-2840 Chronic	NOEC = 100 mg TP/kg soil	0.086 mg TP/kg soil	< 0.001	No
	1'-COOH-S-2840 Chronic	NOEC = 100 mg TP/kg soil	0.089 mg TP/kg soil	< 0.001	No
Aquatic organisms					
Rainbow trout	3'-OH-S-2840 Acute	LC_{50}/10 > 0.62 mg TP/L	0.024 mg TP/L	< 0.039	No
	1'-COOH-S-2840 Acute	LC_{50}/10 > 5.0 mg TP/L	0.025 mg TP/L	< 0.005	No
Amphibians (Rainbow trout as surrogate)	3'-OH-S-2840 Acute	LC_{50}/10 > 0.62 mg TP/L	0.13 mg TP/L	< 0.21	No
	1'-COOH-S-2840 Acute	LC_{50}/10 > 5.0 mg TP/L	0.14 mg TP/L	< 0.03	No

[1]EEC = Estimated Environmental Concentration. The EECs for the major transformation products 3'-OH-S-2840 and 1'-COOH-S-2840 were calculated based on the ratios of their respective molecular weight (349.38 and 363.36 g/mol) to the molecular weight of inpyrfluxam (333.38 g/mol), using the EECs of inpyrfluxam in soil and freshwater (see Tables 7 and 14).
[2]RQ = Risk Quotient. The RQ is calculated by dividing the EEC by the endpoint value (RQ = EEC/endpoint value)
[3]LOC = Level of Concern. The RQ is compared to the LOC. The LOC = 1.0 for earthworms, predatory mites, parasitic wasp and aquatic organisms.

Table 30 Screening level risk to aquatic organisms

Organism	Exposure	Endpoint value (mg a.i./L)	EEC (mg a.i./L)[1]	RQ[2]	LOC exceeded[3]
Freshwater species					
Daphnia magna	Acute	LC_{50}/2 = 0.55	0.023	0.04	No
	Chronic	NOEC = 0.14	0.023	0.16	No
Chironomus dilutus	Chronic	NOEC = 1.1 (pore water concentration)	0.023	0.02	No
Freshwater amphipod	Chronic	NOEC = 0.21 (pore water concentration)	0.023	0.11	No
Rainbow trout	Acute	LC_{50}/10 = 0.0031	0.023	**7.42**	**Yes**
Blugill Sunfish	Acute	LC_{50}/10 = 0.0055	0.023	**4.18**	**Yes**
Carp	Acute	LC_{50}/10 = 0.0065	0.023	**3.54**	**Yes**
Fathead minnow	Acute	LC_{50}/10 = 0.0047	0.023	**4.89**	**Yes**
	Chronic	NOEC = 0.0016	0.023	**14.37**	**Yes**
Guppy	Acute	LC_{50}/10 = 0.035	0.023	0.66	No
Japanese medaka	Acute	LC_{50}/10 = 0.08	0.023	0.29	No
Zebrafish	Acute	LC_{50}/10 = 0.031	0.023	0.74	No
Amphibian	Acute	LC_{50}/10 = 0.0031	0.124	**40**	**Yes**
	Chronic	NOEC = 0.0016	0.124	**77.5**	**Yes**
Green algae	Acute	EC_{50}/2 = 3.55	0.023	0.006	No
Blue-green algae	Acute	EC_{50}/2 > 13.5	0.023	< 0.002	No

Organism	Exposure	Endpoint value (mg a.i./L)	EEC (mg a.i./L)[1]	RQ[2]	LOC exceeded[3]
Diatom	Acute	$EC_{50}/2 = 1.96$	0.023	0.01	No
Vascular plant	Acute	$EC_{20} = 5.7$	0.023	0.004	No
Marine species					
Mysid	Acute	$EC_{50}/2 = 0.55$	0.023	0.04	No
	Chronic	NOEC = 0.18	0.023	0.13	No
Mollusk	Acute	$EC_{50}/2 > 0.50$	0.023	< 0.05	No
Estuarine amphipod	Chronic	NOEC = 0.42 (pore water concentration)	0.023	0.05	No
Sheepshead minnow	Acute	$LC_{50}/10 = 0.015$	0.023	**1.53**	**Yes**
	Chronic	NOEC = 0.009	0.023	**2.56**	**Yes**
Marine alga	Acute	$EC_{50}/2 = 0.28$	0.023	0.08	No

[1]EEC = Estimated Environmental Concentration. The EEC in a 80-cm deep pond is 0.023 mg a.i./L and 0.124 mg a.i./L in a 15-cm pond. It is calculated by assuming a direct overspray to water with the maximum application rate of 87.2 g a.i./ha (soybean seed treatment), 30-d interval followed by 2 applications of 50 g a.i./ha with a 14-d interval, considering a half-life in water of 2424 days (80^{th} percentile of $t_{1/2}$ in five water/sediment systems), assuming 80-cm and 15-cm water depths for the respective ponds.

[2]RQ = Risk quotient. The RQ is calculated by dividing the EEC by the endpoint value (RQ = EEC/endpoint value).

[3]LOC = Level of concern. The RQ is compared to the LOC (LOC = 1.0). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary.

Table 31 Further characterization of risk from drift to aquatic organisms

Organism	Exposure	Endpoint value (mg a.i./L)	EEC - Spray drift (mg a.i./L)[1]	RQ[2]	LOC[3] exceeded
Rainbow trout	Acute	$LC_{50}/10 = 0.0031$	0.014 (Airblast - early season)	**4.52**	**Yes**
			0.011 (Airblast - late season)	**3.55**	**Yes**
			0.0004 (Ground Boom Sprayer)	0.13	No
Blugill Sunfish	Acute	$LC_{50}/10 = 0.0055$	0.014 (Airblast - early season)	**2.54**	**Yes**
			0.011 (Airblast - late season)	**2.00**	**Yes**
			0.0004 (Ground Boom Sprayer)	0.07	No
Carp	Acute	$LC_{50}/10 = 0.0065$	0.014 (Airblast - early season)	**2.15**	**Yes**
			0.011 (Airblast - late season)	**1.69**	**Yes**
			0.0004 (Ground Boom Sprayer)	0.06	No
Fathead minnow	Acute	$LC_{50}/10 = 0.0047$	0.014 (Airblast - early season)	**2.98**	**Yes**
			0.011 (Airblast - late season)	**2.34**	**Yes**
			0.0004 (Ground Boom Sprayer)	0.08	No
	Chronic	NOEC = 0.0016	0.014 (Airblast - early season)	**8.75**	**Yes**
			0.011 (Airblast - late season)	**6.87**	**Yes**

Organism	Exposure	Endpoint value (mg a.i./L)	EEC - Spray drift (mg a.i./L)[1]	RQ[2]	LOC[3] exceeded
			0.0004 (Ground Boom Sprayer)	0.25	No
Amphibian	Acute	$LC_{50}/10 = 0.0031$	0.074 (Airblast - early season)	**23.87**	**Yes**
			0.059 (Airblast - late season)	**19.03**	**Yes**
			0.002 (Ground Boom Sprayer)	0.65	**Yes**
	Chronic	NOEC = 0.0016	0.074 (Airblast - early season)	**46.25**	**Yes**
			0.059 (Airblast - late season)	**36.87**	**Yes**
			0.002 (Ground Boom Sprayer)	**1.25**	**Yes**
Sheepshead minnow	Acute	$LC_{50}/10 = 0.015$	0.007 (Airblast - early season)	0.47	No
			0.006 (Airblast - late season)	0.40	No
			0.0002 (Ground Boom Sprayer)	0.01	No
	Chronic	NOEC = 0.009	0.007 (Airblast - early season)	0.78	No
			0.006 (Airblast - late season)	0.67	No
			0.0002 (Ground Boom Sprayer)	0.02	No

[1]EEC = Estimated Environmental Concentration. The EEC in freshwater resulting from spray drift from foliar applications was determined by using the cumulative maximum foliar application rate on apple by airblast sprayer (two times 75 g a.i./ha at 10-day interval) on soybean by ground boom sprayer (two times 50 g a.i./ha at 14-day interval), considering a half-life in water of 2424 days and water depths of 15 cm (amphibians) and 80 cm (other aquatic organisms). Spray drift at one metre downwind from the point of application was determined by assuming approximately 74, 59 and 3% of the application rate for airblast (early and late season) and ground boom sprayers, respectively, if the spray quality (droplet size distribution) used is classified as ASAE fine (airblast) and coarse (ground boom sprayer). For the EEC in saltwater, only a single application for each type of use was considered (75 g a.i./ha on apple for airblast sprayer and 50 g a.i./ha on soybean for ground boom sprayer), as tides and dilution are expected to make concentrations in the marine environment negligible at the time of subsequent applications.
[2]RQ = Risk quotient. The RQ is calculated by dividing the EEC from spray drift by the endpoint value (RQ = EEC/endpoint value).
[3]LOC = Level of concern. The RQ is compared to the LOC (LOC = 1.0).

Table 32 Modeling data for inpyrfluxam EECs (µg/L) in water bodies resulting from surface runoff from various use pattern scenarios across Canada

Use	Water depth	Water column				Pore water	
		Peak	24 hour	96 hour	21 day	Peak	21 day
Apples airblast: 2 applications of 75 g/ha @ 10 day	80 cm	7.4	7.4	7.4	7.4	7.1	7.1
	15 cm	13	12	12	11	--	--
Soybeans foliar: 2 applications of 50 g/ha @ 14 day	80 cm	21	21	20	20	19	19
	15 cm	37	36	34	30	--	--
Sugar beets foliar: 1 application of 50 g/ha	80 cm	9.9	9.9	9.9	9.8	9.7	9.7
	15 cm	16	15	15	15	--	--
Soybeans seed treatment: 1 application of 87.2 g/ha	80 cm	1.9	1.9	**1.9**	**1.9**	1.8	1.8
	15 cm	3.9	3.8	**3.5**	**2.8**	--	--
Soybeans seed treatment followed by foliar applications: 1	80 cm	21	21	20	20	20	20
	15 cm	37	36	34	30	--	--

Use	Water depth	Water column				Pore water	
		Peak	24 hour	96 hour	21 day	Peak	21 day
application of 87.2 g/ha + 2 applications of 50 g/ha @ 14 day							
Peas seed treatment: 1 application of 15 g/ha	80 cm	0.86	0.86	0.85	0.83	0.77	0.77
	15 cm	1.8	1.7	1.6	1.3	--	--
Spring wheat seed treatment: 1 application of 3.5 g/ha	80 cm	0.14	0.14	0.14	0.14	0.13	0.13
	15 cm	0.26	0.25	0.23	0.21	--	--
Winter wheat seed treatment: 1 application of 3.5 g/ha	80 cm	0.15	0.15	0.15	0.14	0.14	0.14
	15 cm	0.26	0.26	0.25	0.22	--	--
Maximum EECs for all modelled foliar and seed treatment uses	**80 cm**	21	21	**20[1]**	**20[2]**	20	20
	15 cm	37	36	**34[3]**	**30[4]**	--	--

[1] The 96-h EEC of 20 µg a.i./L in an 80 cm water depth was used in the acute pelagic fish risk assessment.
[2] The 21-day EEC of 20 µg a.i./L in a 80 cm water depth was used in the chronic pelagic fish risk assessment.
[3] The 96-h EEC of 34 µg a.i./L in a 15 cm water depth was used in the acute amphibian risk assessment.
[4.] The 21-day EEC of 30 µg a.i./L in a 15 cm water depth was used in the chronic amphibian risk assessment.

Table 33 Further characterization of risk from runoff to aquatic organisms

Organism	Exposure	Endpoint value (mg a.i./L)	EEC in water (mg a.i./L)[1]	RQ[2]	Runoff – LOC exceeded[3]
Foliar application					
Rainbow trout	Acute	LC_{50}/10 = 0.0031	0.020	**6.45**	**Yes**
Blugill Sunfish	Acute	LC_{50}/10 = 0.0055	0.020	**3.64**	**Yes**
Carp	Acute	LC_{50}/10 = 0.0065	0.020	**3.08**	**Yes**
Fathead minnow	Acute	LC_{50}/10 = 0.0047	0.020	**4.26**	**Yes**
	Chronic	NOEC = 0.0016	0.020	**12.5**	**Yes**
Amphibian	Acute	LC_{50}/10 = 0.0031	0.034	**10.97**	**Yes**
	Chronic	NOEC = 0.0016	0.030	**18.75**	**Yes**
Sheepshead minnow	Acute	LC_{50}/10 = 0.015	0.020	**1.33**	**Yes**
	Chronic	NOEC = 0.009	0.020	**2.22**	**Yes**
Seed Treatment					
Rainbow trout	Acute	LC_{50}/10 = 0.0031	0.0019	0.61	No
Blugill Sunfish	Acute	LC_{50}/10 = 0.0055	0.0019	0.35	No
Carp	Acute	LC_{50}/10 = 0.0065	0.0019	0.29	No
Fathead minnow	Acute	LC_{50}/10 = 0.0047	0.0019	0.4	No
	Chronic	NOEC = 0.0016	0.0019	**1.19**	**Yes**
Amphibian	Acute	LC_{50}/10 = 0.0031	0.0035	**1.13**	**Yes**
	Chronic	NOEC = 0.0016	0.0028	**1.75**	**Yes**

[1]EEC = Estimated Environmental Concentration. The EECs were obtained from the inpyrfluxam ecomodeling (Table 18).
[2]RQ = Risk quotient. The RQ is calculated by dividing the EEC by the endpoint value (RQ = EEC/endpoint value).
[3]LOC = Level of concern. The RQ is compared to the LOC (LOC = 1.0). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary.

Table 34 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	DT_{50} = 66.9 – 241 days
	Water	Half-life ≥ 182 days	DT_{50} = 318 – 1610 days
	Sediment	Half-life ≥ 365 days	Stable
	Air	Half-life ≥ 2 days or evidence of long range transport	Unlikely to volatilize, base on physico-chemical properties. Model estimate from AOPWIN™ (v 1.92): 2.8 h in the gaseous phase.
Bioaccumulation[4]	Log K_{ow} ≥ 5		3.6
	BCF ≥ 5000		173–190
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

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

Table 35 List of Supported Use Claims for Excalia Fungicide

Supported Uses
Apple: Control of apple scab (Venturia inaequalis) and powdery mildew (Podosphaera leucotricha) at 146–219 mL/ha in a minimum spray volume of 500 L water/ha using ground sprayer equipment. Application is made prior to disease development and between green tip and petal fall. Up to two applications ten days apart may be made per year. Addition of a 100% organosilicone surfactant to the spray solution at 31.3–62.5 mL/100 L is required to achieve control of powdery mildew.

Soybean: Control of Asian soybean rust (Phakopsora pachyrhizi) at 146 mL/ha applied in a minimum of 100 L water/ha using ground sprayer equipment. Application is made prior to disease development and between the third unfolded trifoliate leaf stage (V3) and early seed development (R5). Up to two applications 14 days apart may be made per year.
Sugar beet: Suppression of rhizoctonia crown rot and rhizoctonia root rot at 146 mL/ha with a non-ionic surfactant at 125 mL/100 L water and in a minimum spray volume of 100 L water/ha. A maximum of one banded application over the row between the 2–8 leaf stage may be made per year.

Table 36 List of Supported Use Claims for Zeltera Fungicide

Supported Uses
Cereal grain crops: barley, buckwheat, pearl millet, proso millet, oat, rye teosinte, triticale and wheat: Control of seed decay/pre-emergence damping-off, post-emergence damping-off and seedling blight are suppression of root rot caused by *Rhizoctonia solani* at 2.6–5.2 mL/100 kg seed
Barley: Control of true loose smut caused by *Ustilago nuda* at 2.6–5.2 mL/100 kg seed
Wheat: Control of wheat loose smut caused by *Ustilago tritici* at 2.6–5.2 mL/100 kg seed
Corn (field, sweet, pop): Control of seed decay/pre-emergence damping-off, post-emergence damping-off and seedling blight caused by *R. solani* at 13 mL/100 kg seed
Legume vegetables, succulent or dried (Crop group 6, except soybean): Control of seed decay/pre-emergence damping-off, post-emergence damping-off and seedling blight, and suppression of root rot caused by *R. solani* at 6.5–13 mL/100 kg seed
Soybean: Control of seed decay/pre-emergence damping-off, post-emergence damping-off and seedling blight, and suppression of root rot caused by *R. solani* at 6.5–13 mL/100 kg seed; Control of sudden death syndrome caused by *Fusarium virguliforme* at 208 mL/100 kg seed; Maximum of 210 g inpyrfluxam/ha per year in soybean applied as both Zeltera Fungicide and Excalia Fungicide

Rapeseeed, including canola: Control of seed decay/pre-emergence damping-off, post-emergence damping-off, seedling blight, and root rot caused by *R. solani* at 13 mL/100 kg seed; Suppression of blackleg caused by *Leptosphaeria maculans* for varieties that possess some genetic resistance to this disease at 13 mL/100 kg seed
Sugar beet: Control of seed decay/pre-emergence damping-off and post-emergence damping-off caused by *R. solani* at 0.13–0.26 mL/100 000 seeds

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Inpyrfluxam is an active ingredient that is concurrently being registered in Canada and the United States for use on Rapeseeds (revised) Crop Subgroup 20A, Legume Vegetables (succulent or dried) Crop Group 6, Cereal Grains Crop Group 15, apples, peanuts, and sugar beets. The MRLs proposed for inpyrfluxam in Canada are the same as corresponding tolerances to be promulgated in the United States, except for certain commodities where American tolerances will not established because there is no expectation of residues (as described under DIR2003-02 for differences in regulatory framework for seed treatment).

Once established, the American tolerances for inpyrfluxam will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[11] listed for inpyrfluxam in or on any commodity on the Codex Alimentarius Pesticide Index website.

Table 1 compares the MRLs proposed for inpyrfluxam in Canada with corresponding American tolerances and Codex MRLs.[5] American tolerances are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs (where different)

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)	Codex MRL (ppm)
Legume Vegetables Crop Group 6	0.01	0.01 (soybeans only)	Not established
Cereal Grains Crop Group 15	0.01	0.01 (Corn: sweet, field, and pop; rice grain)	Not established
Rapeseeds (revised) Crop subgroup 20A	0.01	Not established	Not established

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

[11] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2819273	2017, S-2399 Technical: Product Identity and Composition, Description of Materials Used to Produce the Product, Description of Production Process and Discussion on Formation of Impurities, DACO: 2.1, 2.11.2, 2.11.3, 2.11.4, 2.13.4, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9
2819274	2017, Chemical Abstracts Registry Number, DACO: 2.1, 2.11.2, 2.11.3, 2.11.4, 2.13.4,2.2,2.3,2.4,2.5,2.6,2.7,2.8,2.9 CBI
2819275	2017, Certified Limits of S-2399 Fungicide Technical, DACO: 2.12.1
2819276	2017, Establishing Certified Limits, DACO: 2.12.1 CBI
2819277	2016, Enforcement Analytical Methods of S-2399 Technical Grade, DACO: 2.13.1
2819278	2016, Methodology/Validation, DACO: 2.13.1 CBI
2819279	2016, Enforcement Analytical Method of Intermediate A in S-2399 Technical Grade, DACO: 2.13.1
2819280	2016, Methodology/Validation, DACO: 2.13.1 CBI
2819281	2016, Characterization of Active Ingredient and Identification of Ingredients in S-2399 Technical Grade, DACO: 2.13.2
2819282	2016, Batch Analysis of S-2399 Technical Grade, DACO: 2.13.3
2819283	2016, Batch Data, DACO: 2.13.3 CBI
2819284	2016, Batch Analysis of S-2399 Technical Grade for [CBI removed], DACO: 2.13.3
2819285	2016, Batch Data, DACO: 2.13.3 CBI
2819286	2015, S-2399 PAI: Determination of Appearance, DACO: 2.14.1,2.14.2,2.14.3
2819287	2015, S-2399 TGAI: Determination of Appearance, DACO: 2.14.1, 2.14.2, 2.14.3
2819288	2016, S-2399 PAI: Determination of Physico-Chemical Properties, DACO: 2.14.13,2.14.4,2.14.5,2.14.6,2.16
2819289	2013, S-2399: Determination of Water Solubility, DACO: 2.14.7

2819290	2014, S-2399 PAI: Determination of Vapor Pressure, DACO: 2.14.9
2819291	2016, 3-OH-S-2840 (S-2399 Metabolite): Determination of Octanol: Water Partition Coefficient, DACO: 2.14.11
2819292	2013, S-2399: Determination of Partition Coefficient (n-Octanol/Water), DACO: 2.14.11
2819293	2016, 1-COOH-S-2840A and 1-COOH-S-2840B (S-2399 Metabolites): Determination of Octanol: Water Partition Coefficient and Effect of pH, DACO: 2.14.11
2819294	2014, S-2399 PAI: Determination of Infrared Spectrum and Ultraviolet/Visible Spectra, DACO: 2.14.12
2819295	2016, Stability of S-2399 Technical Grade to Normal and Elevated Temperatures, Metals and Metal Ions, DACO: 2.14.13
2819296	2016, Storage Stability and Corrosion Characteristics of S-2399 Technical Grade, DACO: 2.14.14
2819297	2016, S-2399 TGAI: Determination of Physico-Chemical Properties Report Amendment 1, DACO: 2.14.8,2.16
2819298	2017, S-2399: Submission of TGAI and PAI Samples, DACO: 2.15
2819299	2014, S-2399 PAI: Determination of NMR and Mass Spectra, DACO: 2.16
2819300	2016, S-2399 - Henry's Law Constant, DACO: 2.16
2819301	2017, S-2399 TGAI: Determination of Hazardous Physico-Chemical Properties, DACO: 2.16
2819302	2017, Request for Waiver: Group B Product Chemistry For S-2399 TGAI, DACO: 2.14.10,2.16
2819303	2016, Characterization of Impurity Standards for S-2399 Analysis, DACO: 2.16
2819304	2017, Mass Spectra of Impurity Standards for S-2399 Analysis, DACO: 2.16
2920728	2014, S-2399 PAI: Determination of NMR and Mass Spectra (Amended Final Report #1) (Amendments to Title Page Only), DACO: 2.16
2819503	2017, S-2399 - Product Chemistry Evaluation - Identity, Physical and Chemical Properties, Analytical Methods, Confidential Information (based on OECD Dossier Numbering), DACO: 12.7.2,Document J, Document M
2819504	2017, S-2399 - Product Chemistry Evaluation - Identity, Physical and Chemical Properties, Analytical Methods, Confidential Information (based on OECD Dossier Numbering), DACO: 12.7.2,Document J, Document M
2879430	2017, S-2399 - Document M-IIA, Point 4 - Analytical Methods, DACO: 12.7.2,12.7.7,12.7.8,Document J ,Document M, Document N

2879431	2017, S-2399 - Product Chemistry Evaluation - Identity, Physical and Chemical Properties, Analytical Methods, Confidential Information (based on OECD Dossier Numbering), DACO: 12.7.2,Document J, Document M
2879432	2017, S-2399 - Product Chemistry Evaluation - Identity, Physical and Chemical Properties, Analytical Methods, Confidential Information (based on OECD Dossier Numbering), DACO: 12.7.2,Document J, Document M
2911331	2017, S-2399 - Product Chemistry Evaluation - Identity, Physical and Chemical Properties, Analytical Methods, Confidential Information (based on OECD Dossier Numbering) , DACO: 12.7.2,Document J, Document M
2920729	2017, Amended Report (Non-GLP) S-2399 - Product Chemistry Evaluation - Identity, Physical and Chemical Properties, Analytical Methods, Confidential Information (based on OECD Dossier Numbering) , DACO: 12.7.2,Document J, Document M
2920730	2017, Amended Report (Non-GLP) S-2399 - Product Chemistry Evaluation - Identity, Physical and Chemical Properties, Analytical Methods, Confidential Information (based on OECD Dossier Numbering) , DACO: 12.7.2,Document J, Document M
2819547	2017, Summary of Product Identity for S-2399 2.84 SC Fungicide, DACO: 3.1.1,3.1.2,3.1.3,3.1.4,3.5.4,3.5.5,3.6
2819548	2017, S-2399 2.84SC Fungicide: Product Identity and Composition, Description of Materials Used to Produce the Product, Description of Production Process, Description of Formulation Process, Discussion of Formation of Impurities, Preliminary Analysis, Certified Limits, Enforcement Analytical Method, Submittal of Samples, DACO: 3.2.1,3.2.2,3.2.3,3.3.1,3.4.1,3.4.2
2819549	2017, S-2399 2.84SC Fungicide: Product Identity and Composition, Description of Materials Used to Produce the Product, Description of Production Process, Description of Formulation Process, Discussion of Formation of Impurities, Preliminary Analysis, Certified Limits, Enforcement Analytical Method, Submittal of Samples, DACO: 3.2.1,3.2.2,3.2.3,3.3.1,3.4.1,3.4.2 CBI
2819550	2016, Validation of Enforcement Analytical Method for Determination of S-2399 in S-2399 2.84 SC, DACO: 3.4.1 CBI
2819551	2016, Physical and Chemical Properties of S-2399 2.84 SC, DACO: 3.5.1, 3.5.11,3.5.12,3.5.13,3.5.15,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,3.5.9
2819552	2017, Shelf-Life Storage Stability and Corrosion Characteristics of S-2399 2.84 SC, DACO: 3.5.10,3.5.14
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2.0 Human and Animal Health

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3.0 Environment

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2819411	2015, Effects of S-2399 TG (Acute Contact and Oral) on Honey Bees (*Apis mellifera* L.) in the Laboratory, DACO: 9.2.4.1,9.2.4.2
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PMRA Document Number	Reference
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2819419	2017, S-2399 2.84 SC: 10-Day Oral Toxicity Test on the Honey Bee (*Apis mellifera* L.) in the Laboratory, DACO: 9.2.4
2819421	2016, S-2399 TG: Effects on Reproduction of the Predatory Mite *Hypoaspis aculeifer* in Artificial Soil with 5% Peat, DACO: 9.2.5
2819422	2016, S-2399 40 SC (formulation): Effects on the Predatory Mite *Typhlodromus pyri* in the Laboratory - Dose Response Test, DACO: 9.2.5
2819423	2016, S-2399 40 SC (formulation): Effects on the Parasitoid *Aphidius rhopalosiphi* in the Laboratory - Dose Response Test, DACO: 9.2.6
2819425	2016, 1-COOH-S-2840: Effects on Reproduction of the Predatory Mite *Hypoaspis aculeifer* in Artificial Soil with 5% Peat, DACO: 9.2.5
2819426	2016, 3-OH-S-2840: Effects on Reproduction of the Predatory Mite *Hypoaspis aculeifer* in Artificial Soil with 5% Peat, DACO: 9.2.5
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2819431	2014, S-2399 TG - Full Life-Cycle Toxicity Test with Water Fleas, *Daphnia magna*, Under Static- Renewal Conditions, Following OECD Guideline #211 and OPPTS Draft Guideline 850.1300, JMAFF 12 NohSan, No. 8147 Daphnia Reproduction Test (2-7-2-3) and the Official Journal of the European Communities L383A, Method C.20, *Daphnia magna* Reproduction Test, DACO: 9.3.3
2819432	2015, Life-Cycle Toxicity Test Exposing Midges (*Chironomus dilutus*) to S-2399 TG Applied to Sediment Under Static-Renewal Conditions Following EPA Test Methods, DACO: 9.3.4
2819436	2016, 42-Day Toxicity Test Exposing Freshwater Amphipods (*Hyalella azteca*) to S-2399 TG Applied to Sediment Under Static-Renewal Conditions Following EPA Test Methods, DACO: 9.3.4
2819438	2014, S-2399 TG: Acute Toxicity to Mysids (*Americamysis bahia*) Under Static Conditions, Following OCSPP Draft Guideline 850.1035, DACO: 9.4.2

PMRA Document Number	Reference
2819439	2016, S-2399 TG: Acute Toxicity to Eastern Oyster (*Crassostrea virginica*) Under Flow-Through Conditions Following OCSPP Guideline 850.1025, DACO: 9.4.2
2819441	2016, S-2399 T.G. - Life-Cycle Toxicity Test with Mysids (*Americamysis bahia*), DACO: 9.4.5
2819442	2016, S-2399 - 28-Day Toxicity Test Exposing Estuarine Amphipods (*Leptocheirus plumulosus*) to a Test Substance Applied to Sediment Following EPA Test Methods, DACO: 9.4.5
2819443	2014, S-2399 TG - Acute Toxicity Test with Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions Following OECD Guideline #203, OPPTS Draft Guideline 850.1075, JMAFF 12 NohSan, No. 8147 Fish, Acute Toxicity Test (2-7-1-1) and The Official Journal of the European Communities, L383A, Method C.1, Acute Toxicity for Fish, DACO: 9.5.2.1
2819444	2016, Acute Toxicity Study of 3-0H-S-2840 with Rainbow trout (*Oncorhynchus mykiss*), DACO: 9.5.2.1
2819445	2016, Acute Toxicity Study of 1-COOH-S-2840 with Rainbow trout (*Oncorhynchus mykiss*), DACO: 9.5.2.1
2819446	2014, S-2399 TG - Acute Toxicity Test with Bluegill Sunfish (*Lepomis macrochirus*) Under Static Conditions Following OECD Guideline # 203, OPPTS Draft Guideline 850.1075, JMAFF 12 NohSan, No. 8147 Fish, Acute Toxicity Test (2-7-1-1) and The Official Journal of the European Communities, L383A, Method C.1, Acute Toxicity for Fish, DACO: 9.5.2.2
2819447	2014, S-2399 - Acute Toxicity Test with Fathead Minnow (*Pimephales promelas*) Under Static Conditions Following OECD Guideline # 203, OPPTS Draft Guideline 850.1075, JMAFF 12 NohSan, No. 8147 Fish, Acute Toxicity Test (2-7-1-1) and The Official Journal of the European Communities, L383A, Method C.1, Acute Toxicity for Fish, DACO: 9.5.2.3
2819448	2016, Acute Toxicity Study of S-2399 TG with Guppy (*Poecilia reticulata*), DACO: 9.5.2.3
2819449	2016, Acute Toxicity Study of S-2399 TG with Japanese medaka (*Oryzias atipes*), DACO: 9.5.2.3
2819450	2016, Acute Toxicity Study of S-2399 TG with Japanese medaka (*Oryzias atipes*), DACO: 9.5.2.3
2819451	2014, S-2399 TG - Acute Toxicity Test with Common Carp (*Cyprinus carpio*) Under Static Conditions Following OECD Guideline #203, OPPTS Draft Guideline 850.1075, JMAFF 12 NohSan, No. 8147 Fish, Acute Toxicity Test (2-7-1-1) and The Official Journal of the European Communities, L383A, Method C.1, Acute Toxicity for Fish, DACO: 9.5.2.3
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PMRA Document Number	Reference
2819453	2014, S-2399 TG - Early Life-Stage Toxicity Test with Fathead Minnow, *Pimephales promelas*, Following OECD Guideline #210 and OPPTS Draft Guideline 850.1400, DACO: 9.5.3.1
2819454	2017, S-2399 T.G. - Early Life-Stage Toxicity Test with Sheepshead Minnow, *Cyprinodon variegatus*, DACO: 9.5.3.1
2819456	2015, [14C]S-2399 - Flow-Through Bioconcentration and Metabolism Study with Bluegill Sunfish (*Lepomis macrochirus*), DACO: 9.5.6
2819457	2014, S-2399 TG: An Acute Oral Toxicity Study with the Northern Bobwhite, DACO: 9.6.2.1
2819458	2016, S-2399: An Acute Oral Toxicity Study with the Mallard, DACO: 9.6.2.2
2819460	2014, S-2399 TG: A Dietary LC_{50} Study with the Northern Bobwhite, DACO: 9.6.2.4
2819461	2014, S-2399 TG: A Dietary LC_{50} Study with the Mallard, DACO: 9.6.2.5
2819462	2017, S-2399: A Dietary LC_{50} Study with the Zebra Finch, DACO: 9.6.2.6
2819464	2015, S-2399 TG: A Reproduction Study with the Northern Bobwhite, DACO: 9.6.3.1
2819465	2015, S-2399 TG: A Reproduction Study with the Mallard, DACO: 9.6.3.2
2819466	2015, S-2399 TG: Toxicity Test with the Freshwater Diatom, *Navicula pelliculosa*, DACO: 9.8.2
2819468	2015, S-2399 TG: Toxicity Test with the Freshwater Cyanobacterium, *Anabaena flosaquae*, DACO: 9.8.2
2819470	2015, S-2399 T.G. - 96-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, DACO: 9.8.2
2819471	2015, S-2399 TG: Toxicity Test with the Marine Diatom, *Skeletonema costatum*, DACO: 9.8.3
2819473	2016, S-2399: A Toxicity Test to Determine the Effects on Seedling Emergence of Ten Species of Plants, DACO: 9.8.4
2819484	2016, S-2399: A Toxicity Test to Determine the Effects on Vegetative Vigour of Ten Species of Plants, DACO: 9.8.4
2819495	2017, S-2399: A Toxicity Test to Determine the Effects on Seedling Emergence of Two Species of Plants, DACO: 9.8.4
2819496	2016, S-2399 TG: 7-Day Toxicity Test with Duckweed (*Lemna gibba*), DACO: 9.8.5
2819578	2017, S-2399: Freezer Storage Stability of S-2399, 3-OH-S-2840, 1-COOH-S-2840-A, and 1- COOH-S-2840-B in Soils, DACO: 8.6

4.0 Value

PMRA Document Number	Reference
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2819653	2017, Appendix I: Trial Reports for "Value Summary for S-2399 3.2 FS Fungicide, a Seed Protectant Containing Inpyrfluxam, for Control of Seed and Seedling Diseases of canola, cereals, legumes, corn, soybeans and sugar beets", DACO: 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3(D), 10.3.1, 10.5.1, 10.5.2, 10.5.3, 10.5.4
2879452	2018, Appendix I: References and Trial Reports for "Value Deficiency Response for S-2399 3.2 FS Fungicide", DACO: 10.1,10.2
2992728	2019, Appendix I: Trial Reports for "Value Clarification Response for Efficacy of Excalia Fungicide on Apples", DACO: 10.1, 10.2.3, 10.2.3.1, 10.2.3.2, 10.2.3.3, 10.5.3
2994786	Appendix I: Trial Reports for "Value Clarification Response for Efficacy of Zeltera Fungicide on Cereal Grains"