Proposed Registration Decision PRD2022-04

Pyraziflumid and Parade Fungicide

(*publié aussi en français*)

28 February 2022

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

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: canada.ca/pesticides
pmra.publications-arla@hc-sc.gc.ca
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.info-arla@hc-sc.gc.ca

Canada

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

Catalogue number: H113-9/2022-XXE (print version)
H113-9/2022-XXE-PDF (PDF version)

Table of Contents

Overview

Proposed registration decision for Pyraziflumid

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 Pyraziflumid Technical and Parade Fungicide, containing the technical grade active ingredient pyraziflumid, to control powdery mildew and scab on apples.

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 pyraziflumid and Parade 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 pyraziflumid and Parade 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 Decision[4] on

---

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*.

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

pyraziflumid and Parade 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 pyraziflumid?

Pyraziflumid is a new conventional fungicide active ingredient that controls certain economically important diseases of apples.

Health considerations

Can approved uses of pyraziflumid affect human health?

Parade fungicide, containing pyraziflumid, is unlikely to affect your health when used according to proposed label directions.

Potential exposure to pyraziflumid may occur through the diet (food and drinking water), when handling and applying the end-use product, or when coming into contact with treated surfaces. When assessing health risks, two key factors are considered: the levels at which 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 doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, pyraziflumid was of low acute toxicity via the oral, dermal and inhalation routes. It was non-irritating to the eyes and skin. It did not cause an allergic skin reaction.

The acute toxicity of Parade Fungicide, containing pyraziflumid, was low via the oral, dermal and inhalation routes of exposure. Parade Fungicide was non-irritating to the eyes and skin, but caused an allergic skin reaction. Consequently, the hazard statement "POTENTIAL SKIN SENSITIZER" is required on the label.

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 pyraziflumid to cause neurotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on the liver and thyroid, changes in motor activity level, and abortions. There was no evidence to suggest that

pyraziflumid damaged genetic material. Pyraziflumid did, however, cause thyroid tumours in male rats at the highest dose level tested. An increase in lung tumours observed in mice could not clearly be attributed to treatment with pyraziflumid. Liver tumours observed in female rats at the highest dose level tested, which exceeded the maximum tolerable dose, are not relevant to human health risk assessment. 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 or equal to 3% of the acute reference dose, and are not of health concern. Children 1–2 years old 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 30% of the acceptable daily intake, and are not of health concern. Infants are the subpopulation expected to be subjected to the highest exposure relative to body weight.

On the strength of the overall information, it was determined that a threshold approach was appropriate for the cancer risk assessment based on the observed tumours. Overall, the endpoints selected for the non-cancer dietary risk assessment are considered protective of potential cancer risks.

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.* Given that dietary risks from the consumption of foods are shown to be acceptable when pyraziflumid is used according to the supported label directions, MRLs are being proposed as a result of this assessment (refer to PMRL2022-02, *Pyraziflumid*).

MRLs for pyraziflumid determined from acceptable residue trials conducted in the United States, including growing regions representative of Canada, on various crops can be found in the Science Evaluation section of this consultation document.

Occupational risks from handling Parade Fungicide

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

Workers mixing, loading or applying Parade Fungicide, and workers entering recently treated apple orchards can come in direct contact with pyraziflumid residues on the skin and through inhalation. Therefore, the label specifies that anyone mixing, loading and applying Parade

Fungicide must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Chemical-resistant gloves are not required during application within a closed cab. The label also requires that workers do not enter or be allowed into treated areas during the restricted-entry interval (REI) of 12 hours. Taking into consideration the label statements, the number of applications and the duration of exposure for handlers and postapplication workers, the risks to these individuals are not of health concern.

Health risks in residential and other non-occupational environments

Risks in residential and other non-occupational environments are not of health concern when Parade Fungicide is used according to the proposed label directions and restricted-entry intervals are observed.

Adults, youth and children involved in postapplication activities, such as pruning and hand harvesting, may come in direct contact with pyraziflumid residues on the skin when apple trees in residential areas are treated with Parade Fungicide by commercial applicators. Taking into consideration the label statements, the number of applications and the duration of exposure, the risks to homeowners and their family are not of health concern once the sprays have dried.

Non-occupational exposure during pick-your-own fruit activities in treated orchards are also not of health concern since the postapplication occupational risk assessment, which represents a more conservative exposure scenario, demonstrates that there are no health risks of concern associated with dermal exposure to the patrons in a pick-your-own facility.

Aggregate health risks

When apple trees in residential settings or pick-your-own facilities are treated with Parade Fungicide, there is potential for individuals to be exposed to pyraziflumid via the dermal and oral routes of exposure concurrently. As such, aggregation of dermal and dietary exposure was assessed and no health risks of concern were identified.

Health risks to bystanders

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

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

Environmental considerations

What happens when Pyraziflumid is introduced into the environment?

When used according to label directions, risks associated with the use of pyraziflumid and its associated end-use product have been determined to be acceptable from the viewpoint of environmental protection.

Pyraziflumid can enter the environment through spray drift deposition or run-off when applied as a foliar spray to control fungal diseases on apples. When released into the terrestrial and aquatic systems, pyraziflumid primarily resides in the soil or sediment and can remain there for months or years, depending on the soil and sediment types and conditions. It does not break down easily, and when it does, it produces a few smaller molecules at very low levels. Pyraziflumid is expected to be taken up by plants and move inside the plants. Pyraziflumid has a potential to move through the soil and, therefore, may reach groundwater. Pyraziflumid is not expected to be found in air or travel long distances in the atmosphere from where it is applied. Pyraziflumid is not expected to build-up in the tissues of organisms.

Non-target terrestrial organisms may be exposed to pyraziflumid residues through direct contact with spray or spray drift, contact with sprayed surfaces or from ingestion of contaminated food. Non-target aquatic organisms may be exposed to pyraziflumid through spray drift or runoff. When used according to the label directions, pyraziflumid poses acceptable risk to non-target organisms, including wild mammals, birds, beneficial insects, earthworms, terrestrial and aquatic plants, freshwater and marine invertebrates, algae, fish, and amphibians.

Value considerations

What is the value of Parade Fungicide?

The registration of Parade Fungicide will provide Canadian growers with a new active ingredient to manage economically important fungal diseases on apple while mitigating the risk of resistance development.

Parade Fungicide is applied to apple trees as a foliar spray to control powdery mildew and scab that, if left unmanaged, reduce yield and marketability of harvested fruit.

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 Pyraziflumid Technical and Parade Fungicide to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human health

To reduce the potential of workers coming into direct contact with pyraziflumid on the skin or through inhalation, workers mixing, loading and applying Parade Fungicide and performing cleaning and repair activities must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Chemical-resistant gloves are not required during application within a closed cab. The label also requires that workers do not enter or be allowed entry into treated apple orchards during the REI of 12 hours. Furthermore, standard label statements to protect

against drift during application and to prevent the use of handheld airblast, misters and foggers are present on the label.

Environment

- Require a label statement indicating the potential for movement to groundwater.
- Require a general statement for reducing runoff from treated areas to aquatic habitats.
- Require a precautionary label statement indicating toxicity to non-target terrestrial plants and buffer zones of 1 to 2 metres as a precautionary measure to mitigate the potential risk.
- Require a precautionary label statement indicating toxicity to aquatic organisms.

Next steps

Before making a final registration decision on pyraziflumid and Parade 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

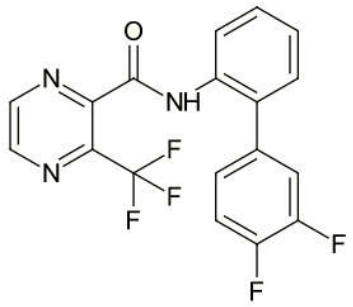
When the Health Canada makes its registration decision, it will publish a Registration Decision on pyraziflumid and Parade Fungicide (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection,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

Science evaluation

Pyraziflumid and Parade Fungicide

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active substance	Pyraziflumid
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	*N*-(3′,4′-difluorobiphenyl-2-yl)-3-(trifluoromethyl)pyrazine-2-carboxamide
2. Chemical Abstracts Service (CAS)	*N*-(3′,4′-difluoro[1,1′-biphenyl]-2-yl)-3-(trifluoromethyl)-2-pyrazinecarboxamide
CAS number	942515-63-1
Molecular formula	$C_{18}H_{10}F_5N_3O$
Molecular weight	379.29
Structural formula	
Purity of the active ingredient	98.8%

1.2 Physical and chemical properties of the active ingredient and end-use product

Technical product—Pyraziflumid technical

Property	Result
Colour and physical state	Yellow solid
Odour	None
Melting range	119°C
Boiling point or range	Decomposition at 300 °C

Property	Result
Density	1.514 g/cm^3
Vapour pressure at 20°C	$\leq 3.5 \times 10^{-6}$ Pa
Ultraviolet (UV)-visible spectrum	pH / λ_{max} (nm) / ε (L/(mol cm)) Neutral 204.2 34427 Acidic 203.4 36944 Basic 218.6 21497
Solubility in water at 20°C	2.32 mg/L
Solubility in organic solvents at 20°C	Solvent / Solubility (g/L) Heptane 0.490 Methanol 63.7 Xylene 95.7 1,2-Dichloroethane > 250 Acetone > 250 Ethyl acetate > 250
n–Octanol-water partition coefficient (K_{ow})	pH / log K_{ow} 6.18 3.51
Dissociation constant (pK_a)	pK_a = 11.36
Stability (temperature, metal)	No decomposition was observed below 150 °C

End-use product—Parade Fungicide

Property	Result
Colour	Pale yellow
Odour	Paint-like
Physical state	Liquid
Formulation type	Suspension
Label concentration	Pyraziflumid … 220 g/L
Container material and description	0.5–1000 L plastic bottle, jug, or tote
Density	1.07–1.10 g/mL
pH of 1% dispersion in water	5.98
Oxidizing or reducing action	No oxidizing or reducing action
Storage stability	Stable when stored in an HDPE container at ambient temperature for 12 months.
Corrosion characteristics	Not corrosive to its HDPE packaging
Explodability	Not explosive

1.3 Directions for use

Parade Fungicide is applied to apple trees prior to the onset of disease and when conditions favour disease development. Using airblast or vertical boom sprayers, Parade Fungicide is applied at 227–340 mL/ha in a spray volume of 375–2000 L water/ha to control powdery mildew caused by *Podosphaera leucotricha* and scab caused by *Venturia inaequalis*. A maximum of three applications may be made per year with a minimum of seven days between applications.

In provinces other than British Columbia, Parade Fungicide is only applied as a tank mix with another fungicide of a different mode of action.

1.4 Mode of action

Pyraziflumid, belonging to the pyrazine carboxamide chemical family, inhibits succinate-dehydrogenase in susceptible fungi. As succinate dehydrogenase is an enzyme that is critical to cell respiration, its inhibition ultimately leads to cell death. Pyraziflumid 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 spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes in environmental media, and in plant matrices (Method GLP-MTH-096). 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 environmental media and in plant matrices. The proposed enforcement method was successfully validated in plant matrices by an independent laboratory. Extraction solvents used in the method were similar to those used in the metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled crops was not required for the enforcement method.

Methods for residue analysis are summarized in Appendix I, Tables 1a and 1b.

3.0 Impact on human and animal health

3.1 Hazard assessment

3.1.1 Toxicology summary

Pyraziflumid is a succinate dehydrogenase inhibitor fungicide that contains a pyrazine-carboxamide group.

A detailed review of the toxicology database for pyraziflumid was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Additional studies included mechanistic studies to support a proposed mode of action (MOA) for thyroid tumours, and a study assessing the genotoxicity of a metabolite of pyraziflumid. 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 acceptable and the database is considered adequate to characterize the potential health hazards associated with pyraziflumid.

Metabolism and toxicokinetics following single oral dose administration in the rat were investigated using pyraziflumid radiolabelled at the pyrazinyl, aniline or difluorophenyl ring. Pyraziflumid was well and quickly absorbed at low dose levels, with peak plasma concentrations occurring between 3 and 24 hours post-dosing. The absorption of pyraziflumid following oral dosing was estimated to be 91–93% of the administered dose (AD). Absorption as a percentage of the AD decreased with increasing dose level, which was evident by unchanged pyraziflumid being the major component identified in the feces at the high dose level. The highest residues were found in the gut and gut contents, liver, kidney, fat, and adrenal glands. Radioactivity levels in tissues 48 hours after single oral dose administration were low and there was no evidence of retention within tissues. Elimination of orally-administered pyraziflumid was rapid. The major route of excretion was via the feces, representing up to 87% of the AD for the low dose and 93% of AD for the high dose. The majority of the AD was recovered in the excreta within 72 hours post-dosing. Recovered radiolabel in bile accounted for 85% of the AD. Radiolabel recovery in urine was 13–16% of the AD for the low dose and 6–11% of AD for the high dose. There were no significant qualitative differences in absorption, distribution, or elimination between sexes or dose levels.

Unchanged pyraziflumid was identified only in feces. The pyrazinyl-, aniline- or difluorophenyl-labelled pyraziflumid assays yielded nine to ten identified metabolites in urine, bile, or feces, indicating extensive metabolism. The major component identified in the feces was BC-01, which is a hydroxylated metabolite, and in bile was BC-01-glucuronide. The major metabolic transformation routes for pyraziflumid involved hydroxylation and subsequent conjugation with glucuronic acid. Metabolite profiles were qualitatively similar between male and female rats. Based on the results of a comparative in vitro study with liver microsomes from rats, mice, rabbits, goats, dogs and humans, there were no significant species- or sex-related qualitative differences in the metabolic profile of pyraziflumid.

In acute toxicity testing, pyraziflumid was of low acute toxicity via the oral, dermal and inhalation routes in rats. It was non-irritating to the eyes and skin of rabbits. Pyraziflumid was

negative for skin sensitization in mice when tested using the local lymph node assay (LLNA) method.

Parade Fungicide was of low acute toxicity in rats via the oral, dermal and inhalation routes of exposure. It was non-irritating to the eyes and skin of rabbits. It was positive for skin sensitization when tested in guinea pigs using the Buehler method.

Repeat-dose dietary toxicity studies with pyraziflumid were available in mice, rats, and dogs. The liver was identified as a target of toxicity for pyraziflumid following repeated oral exposure in mice, rats, and dogs. Liver effects observed among mice, rats, and dogs included increased weight, hepatocyte hypertrophy, vacuolation, fatty degeneration, elevated liver enzymes, and clinical chemistry alterations. Additional effects in the dog included increased hepatocellular degeneration, necrosis, and oval cell hyperplasia. The thyroid was also affected in multiple studies in the rat. Thyroid effects included increased weight and follicular cell hypertrophy or hyperplasia in rats in short- and long-term dietary studies. Thyroid hormone levels were also affected in multiple short-term mechanistic studies in rats. The most common effects were increased thyroid stimulating hormone (TSH) and decreased thyroxine (T4) hormone. Other effects observed in mice and rats were usually confined to a single study or occurred at dose levels near the limit dose. The most sensitive species for toxicity was the rat, in which the main targets of toxicity were the liver and thyroid, with increased incidences of hepatocellular hypertrophy and thyroid follicular cell hypertrophy in both sexes after short- and long-term exposure.

In a 90-day dermal toxicity study in rats, systemic effects were observed at the highest dose tested. These included decreased total bilirubin levels in males and increased gamma-glutamyl transpeptidase levels and thyroid weight in females.

There was no evidence of genotoxicity in a battery of in vitro and in vivo genotoxicity studies conducted with pyraziflumid. An increased incidence of thyroid follicular cell adenomas was observed in males of the high-dose group in the rat dietary combined chronic toxicity/carcinogenicity study. An MOA for the development of the thyroid tumours in rats was proposed by the applicant in conjunction with supplied mechanistic studies to support this proposed MOA. For the thyroid tumours in males, a constitutive androstane receptor (CAR)- and pregnane X receptor (PXR)-mediated MOA was proposed. This MOA proposes that administration of the test substance induces hepatic drug-metabolizing enzymes resulting in increased clearance of circulating T4 hormones. The pituitary increases TSH production to counter this effect, which leads to increased thyroid stimulation, resulting in hypertrophy and hyperplasia, and eventually progressing to tumours. The provided mechanistic data included plasma thyroid hormone measurements in multiple studies, a thyroid peroxidase activity study, and a hepatic enzyme induction study. Although the initial key event of CAR/PXR induction was not demonstrated, these mechanistic data, in conjunction with the full toxicity database, were supportive of the proposed MOA. Other possible tumourigenic MOAs, including genotoxicity and inhibition of thyroid peroxidase, were considered to be inconsistent with the available data. Although rats have been shown to be considerably more sensitive to the thyroid tumour precursor events than humans, this tumourigenic MOA has not been excluded from being relevant to humans. Overall, the weight of evidence supported the proposed MOA and a threshold approach for risk assessment was considered appropriate for the thyroid tumours.

An increased incidence of liver adenomas was observed in females of the high-dose group in the rat dietary combined chronic toxicity/carcinogenicity study. A mechanistic study of liver enzyme induction was provided which indicated induction of pentoxyresorufin o-dealkylase (PROD) and 7-ethoxyresorufin O-dealkylase (EROD) suggesting a potential MOA of tumour formation. However, a full MOA was not elucidated since the increase in tumour incidence occurred only at the high dose level, which exceeded the maximum tolerated dose (MTD) based on significant decreases in body weight. As such, the liver tumours were not considered relevant to the risk assessment.

In the mouse dietary carcinogenicity study, an increased incidence of lung adenomas was observed in males of the high-dose group. This increase was considered equivocal based on lack of clear dose-response trend and consideration of the historical control data. Further, the tumours were of low concern as they occurred near the limit dose of testing.

In the range-finding 2-generation reproductive dietary toxicity study, a decreased number of animals with normal estrous cycle was observed, but this effect was not repeated in a more robust guideline study described below. Increased liver weight and incidences of hepatocyte hypertrophy in both sexes, and decreased ovary and uterus weights in females from both generations, as well as increased thyroid follicular cell hypertrophy in males in P generation were observed along with decreased pup body weights in both generations. In a 2-generation dietary reproductive toxicity study in rats, no treatment-related reproductive toxicity was observed. In parental rats from both generations, increased incidences of hepatocyte hypertrophy in both sexes and of liver fatty degeneration and thyroid follicular cell hypertrophy in males were observed. In offspring, increased liver weight and incidence of hepatocellular hypertrophy were observed in male and female pups from both generations. There was no evidence of sensitivity of the young.

In the gavage developmental toxicity studies, there was no evidence of sensitivity of the young in rabbits or rats. Decreased body weight gain and food consumption were observed in maternal rats. No evidence of developmental toxicity was observed in rat fetuses. In maternal rabbits, decreased body weight gain and food consumption were observed along with a slight increase in abortions at the highest dose tested.

In an acute oral neurotoxicity study in rats, decreased total and ambulatory motor activity was observed at the time of peak effect in females at the lowest dose tested. Increased defecation was observed in males at the highest dose tested.

A waiver rationale was provided for the conditionally required immunotoxicity study. The waiver was accepted based on the absence of immunotoxic effects in the database.

There was no evidence of genotoxicity when a metabolite of pyraziflumid, BC-08 (pyraziflumid-amine metabolite and minor environmental transformation product), was tested in an in vivo micronucleus assay.

The identification of select metabolites is presented in Appendix I, Table 2. Results of the toxicology studies conducted on laboratory animals with pyraziflumid along with a relevant metabolite, and with its associated end-use product are summarized in Appendix I, Tables 3 and

4, respectively. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 5.

3.1.2 *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.[5]

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.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of fetuses or offspring compared to parental animals in the dietary reproductive and gavage prenatal developmental toxicity studies. In the 2-generation rat reproductive toxicity study, increased liver weight and hypertrophy were observed in the offspring at the highest dose tested; however, this occurred in the presence of maternal toxicity (hepatocellular hypertrophy and liver fatty degeneration). In the 2-generation range-finding rat reproductive toxicity study, similar liver effects were observed in offspring, along with changes in organ weights and a slight decrease in mean implantation site at the highest dose. All these effects occurred in the presence of parental toxicity. No developmental effects were observed in the rat developmental toxicity study; however, a serious effect, abortions, was observed in the rabbit developmental toxicity study in the presence of maternal toxicity.

Overall, the database is adequate for determining the sensitivity of the young. There is a low level of concern (LOC) for sensitivity of the young as effects in the young were well-characterized and occurred in the presence of maternal toxicity. The abortions in the rabbit were considered a serious endpoint, although the concern was tempered by the presence of maternal toxicity. Therefore, the *Pest Control Products Act* factor (PCPA factor) was reduced to threefold when using the rabbit developmental toxicity study to establish the point of departure for human health risk assessment. For all other exposure scenarios, the PCPA factor was reduced to onefold.

3.2 Toxicology reference values

3.2.1 Route and duration of exposure

For mixers, loaders and applicators, occupational exposure to Parade Fungicide is characterized as short- to intermediate-term in duration and is predominantly by the dermal and inhalation

---

[5] SPN2008-01. The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides.

routes. For postapplication workers and homeowners in residential areas, exposure to Parade Fungicide is also characterized as short- to intermediate-term in duration, while for patrons in pick-your-own facilities, postapplication exposure is expected to be of short-term duration. Postapplication exposure to all individuals is expected to be primarily by the dermal route.

3.2.2 Occupational and Residential Toxicology Reference Values

3.2.2.1 Short- and Intermediate-term Dermal

For short- and intermediate-term dermal risk assessment for adults, a NOAEL of 30 mg/kg bw/day from the gavage developmental toxicity study in rabbits was selected. At a dose level of 100 mg/kg bw/day, a slightly increased incidence of abortions was observed in the presence of maternal toxicity. The existing short-term dermal toxicity study did not address the endpoint of concern, thus necessitating the use of an oral study for risk assessment.

For residential scenarios, the target margin of exposure (MOE) selected for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As outlined in the *Pest Control Products Act* hazard characterization section, the PCPA factor was reduced to threefold to account for serious effects in the young in the presence of maternal toxicity. The selection of this study and target MOE is considered to be protective of all adults, as well as the unborn children of exposed women.

For occupational scenarios, the target MOE for this endpoint is 300. Tenfold factors were applied each for interspecies extrapolation and intraspecies variability. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus that may be exposed via its mother. In light of concerns regarding prenatal toxicity, as outlined in the *Pest Control Products Act* hazard characterization section, an additional threefold factor was applied to this endpoint to protect for a sensitive subpopulation, namely females 13–49 years of age. 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.

For short- and intermediate-term dermal risk assessment for children (6–11 years old), a NOAEL of 200 mg/kg bw/day from the 90-day dermal toxicity study in rats was selected. At dose levels of 1000 mg/kg bw/day, decreased total bilirubin, increased gamma-glutamyl transpeptidase (GGT) and increased thyroid weight were observed. This study was selected as the endpoint in the developmental toxicity study was not relevant to this age group, and it was conducted via the relevant route.

For residential scenarios, the target MOE selected for this endpoint is 100. Tenfold factors were applied each for interspecies extrapolation and intraspecies variability. As outlined in the *Pest Control Products Act* hazard characterization section, the PCPA factor was reduced to onefold. The selection of this study and target MOE is considered to be protective of children (6–11 years of age).

3.2.2.2 Short- and intermediate-term inhalation

For short- and intermediate-term occupational inhalation risk assessment, the parental NOAEL of 5.6 mg/kg bw/day from the 2-generation reproductive toxicity study in rats was selected. At a dose level of 17 mg/kg bw/day, effects on the liver were as observed in parental animals. With regards to the selection of reference values for inhalation risk assessment, a short-term or repeat-dose inhalation toxicity study was not available and thus, use of a NOAEL from an oral study was appropriate.

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

3.2.3 Acute reference dose (ARfD)

General population (including females 13–49 years of age)

To estimate acute dietary risk, the acute oral neurotoxicity study in the rat with a LOAEL of 500 mg/kg bw was selected for risk assessment. No NOAEL was established in this study as this value represented the lowest dose level tested. At 500 mg/kg bw, effects on motor activity in female rats were observed. These effects were the result of a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied.

An additional threefold factor was applied as a NOAEL was not established in this study. 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 300.**

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{LOAEL}}{\text{CAF}} = \frac{500 \text{ mg/kg bw}}{300} = 1.7 \text{ mg/kg bw of pyraziflumid}$$

3.2.4 Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, the NOAEL of 2.2 mg/kg bw/day from the 2-year dietary chronic toxicity/carcinogenicity study in the rat was selected. At the LOAEL of 4.3 mg/kg bw/day, increased incidence of hepatocellular vacuolation in male rats and increased thyroid follicular cell hypertrophy in female rats were observed. 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 ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2.2 \text{ mg/kg bw/day}}{100} = 0.02 \text{ mg/kg bw/day of pyraziflumid}$$

The ADI provides margins of greater than 11 000 to the NOAEL for the equivocal increase in lung adenomas in the mouse carcinogenicity study, 665 to the NOAEL for thyroid tumours in the rat chronic toxicity/carcinogenicity study, and 1500 to the NOAEL for abortions in the rabbit developmental toxicity study.

3.2.5 Cancer assessment

There was adequate evidence to support a threshold-based mechanism for the thyroid follicular cell tumours in male rats in the dietary combined chronic toxicity/carcinogenicity study. The ADI and the selected reference values for occupational and residential exposure provide sufficient margins to these tumours.

As previously discussed, a slight increase in lung adenomas in male mice in the dietary carcinogenicity study was considered equivocal based on the weight of evidence, and the increased incidence of liver adenomas observed in high-dose female rats in the dietary combined chronic toxicity/carcinogenicity study was not considered relevant to the human health risk assessment since it was observed at a dose level exceeding the MTD. Overall, the toxicology reference values selected for the non-cancer risk assessment are protective of any residual concerns regarding the carcinogenic potential of pyraziflumid.

3.2.6 Aggregate toxicology reference values

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). Short- and intermediate-term aggregate exposure to pyraziflumid may be comprised of food, drinking water and residential exposure via the oral and dermal routes. The toxicology endpoint selected for aggregation was liver toxicity. For the dermal route, the NOAEL of 200 mg/kg bw/day from the 90-day dermal toxicity study in rats was selected with a target MOE of 100. The PCPA factor was onefold as set out in the *Pest Control Products Act* hazard characterization section. For the oral route, the toxicology endpoint and assessment factor are the same as that selected for the ADI (see Section 3.2.4). The selection of these toxicology endpoints for aggregate risk assessment is protective for effect observed in the rabbit developmental toxicity study (abortions).

3.3 Dermal absorption

A chemical-specific dermal absorption study was not submitted and is not on file for pyraziflumid. Therefore, the default dermal absorption value of 100% was used in the occupational exposure assessments and the residential exposure assessment for adults. In the residential exposure assessment for children and the aggregate risk assessment, the dermal toxicological reference values are based on a dermal study and a dermal absorption factor is not required.

3.4 Occupational and residential risk exposure assessment

3.4.1 Acute hazards of end-use product and mitigation measures

3.4.1.1 Parade fungicide

The acute hazard assessment indicated that Parade Fungicide is of low acute toxicity via the oral, dermal and inhalation routes. It is non-irritating to the eyes and skin of rabbits, but is a dermal sensitizer based on the Buehler test. Consequently, the hazard statement "POTENTIAL SKIN SENSITIZER" is required on the label. Based on these acute hazards, a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes are required for workers during mixing, loading, application, clean-up and repair. Chemical-resistant gloves are not required during application within a closed cab.

3.4.2 Occupational exposure and risk assessment

3.4.2.1 Mixer, loader and applicator exposure and risk assessment

Parade Fungicide is a suspension concentrate commercial-class product for postemergence foliar application to apple trees by ground equipment.

Individuals have the potential for exposure to pyraziflumid during mixing, loading, application, clean-up and repair. Dermal and inhalation exposure estimates were generated from the Agricultural Handler Exposure Task Force (AHETF) database, of which the applicant is a member and has full access to the data, for mixers, loaders and applicators applying Parade Fungicide to apple trees using an airblast sprayer. The unit exposure values in the risk assessment are based on handlers wearing a single layer of clothing and chemical-resistant gloves (Appendix I, Table 6).

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

Exposure estimates were compared to the selected toxicological reference value to obtain the MOE; the target MOE is 300 for dermal exposure and 100 for inhalation exposure. Dermal and inhalation exposures were not combined since the dermal and inhalation reference values are based on different studies and different toxicological effects. Calculated MOEs are greater than the target MOEs for all chemical handler scenarios in apple orchards and are therefore not of health concern (Appendix I, Table 7).

Taking into account both the acute toxicity of the end-use product and the risk assessment of pyraziflumid, workers are required to wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair. Chemical-resistant gloves are not required during application within a closed cab.

3.4.2.2 Exposure and risk assessment for workers entering treated areas

There is potential for exposure to workers entering areas treated with Parade Fungicide to complete tasks such as hand thinning, hand harvesting, scouting, hand pruning, training, hand

weeding, propping and other apple orchard maintenance activities. Given the nature of activities performed, exposure should be primarily via the dermal route based on dermal contact with treated foliage. Inhalation exposure is not expected as pyraziflumid is considered non-volatile with a vapour pressure of approximately 8.1×10^{-9} kPa (at 25°C), which is less than the North American Free Trade Agreement (NAFTA) criterion for a non-volatile product for outdoor scenarios of 1×10^{-4} kPa (7.5×10^{-4} mmHg) at 20-30°C. As such, a quantitative inhalation risk assessment is not required. Inhalation risk is not of health concern for postapplication workers as pyraziflumid 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.

Chemical-specific dislodgeable foliar residue (DFR) data were reviewed. This study was designed to collect data to calculate DFR dissipation curves for pyraziflumid and the metabolite BC-01 from treated apple foliage at three test sites: New York (NY), Michigan (MI) and Washington (WA), representing the NAFTA Growing Regions 1, 5 and 11, respectively. Geographical and climatic conditions were relevant to Canadian growing regions. The formulation type, application method, application rates, frequency, including number and timing of application, as well as the monitoring times were relevant to the Canadian uses. A non-ionic surfactant was also added to the spray mixtures of all applications at the three sites. The three sites were monitored with three replicates per sampling time per site. Apple leaf samples were collected prior to each application (within up to one day), after each application as soon as the sprays had dried (within less than 3 hours), and then at 1, 3, 6-7, 10, 14, 20-21, 28 and 35 days after the third application.

In the study, DFR values were measured separately for pyraziflumid and the metabolite BC-01. Therefore, as a conservative measure, residues of pyraziflumid and the metabolite BC-01 (converted to pyraziflumid equivalent based on the ratio of their molecular weights) were combined for the purpose of the current assessment in order to determine DFR and dissipation values.

Dissipation rates were modelled utilizing pseudo first order kinetics to estimate the percents of daily dissipation and half-lives. The percents of dissipation per day were determined to be 6.2%, 7.4% and 4.6%, while the calculated half-lives were 10.8, 9.0 and 14.7 days, for the NY, MI and WA sites, respectively. R-squared values of the dissipation curves for combined residues of pyraziflumid and the metabolite BC-01 at these three sites were ≥ 0.9167.

Peak combined residues of pyraziflumid and the metabolite BC-01 were measured on Day 0 after the third application at the NY and MI sites (0.1512 and 0.1187 $\mu g/cm^2$), and on Day 0 after the first application at the WA site (0.1433 $\mu g/cm^2$). These peak DFR values represented 18.2%, 16.0% and 19.3% of the rate applied for the respective treatment at each site (Appendix I, Table 8).

The DFR values derived from the WA site were selected for use in the current postapplication risk assessment since they represent the most conservative exposure estimates: the peak DFR value, expressed in percent of the application rate, is the highest at 19.3% and the daily dissipation rate is the slowest at 4.6%. As such, with this scenario more residues are dislodged from the apple leaves following treatment and residues dissipate less quickly in the following

days. Furthermore, the R-squared (R2) value for the WA trial site is adequate and above 0.9 and the region is representative of Canadian-growing sites.

Dermal exposure to workers entering treated areas is estimated using DFR values with activity-specific transfer coefficients (TCs). Activity-specific TCs are based on data from the Agricultural Re-entry Task Force (ARTF). As chemical- and crop-specific DFR data were submitted, the experimental DFR values of 19.3% of the application rate dislodged on Day 0 and 4.6% daily dissipation of residues were used in the exposure assessment.

Exposure estimates were compared to the toxicological dermal reference value to obtain the MOE; the target dermal MOE is 300. Only exposures and risks to the activities with the highest TCs are presented as MOEs for these activities exceed the target MOE of 300, and are thus, not of health concern. For all postapplication activities, the REI of 12 hours is adequate (Appendix I, Table 9).

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk assessment

Parade Fungicide is not a domestic class product and is not permitted for use by homeowners in residential settings; therefore, a residential handler exposure assessment is not required.

3.4.3.2 Postapplication exposure and risk

Parade Fungicide is proposed for use on apple trees, which includes residential areas such as pick-your-own (PYO) settings or homeowners' gardens following application by a commercial applicator. Therefore, a postapplication residential risk assessment is required.

3.4.3.2.1 Pick-Your-Own activities

Given that apple trees can be treated with pyraziflumid, there is potential for exposure during pick-your-own activities. The postapplication occupational risk assessment, which represents a more conservative exposure scenario, demonstrates that there are no health risks of concern associated with dermal exposure to the patrons in a pick-your-own facility and therefore, a quantitative risk assessment is not required.

3.4.3.2.2 Orchard trees treated with parade fungicide in residential areas

When a commercial applicator is hired to treat apple trees in a residential area or a farmer treats apple trees adjacent to residential areas, there is potential for residential postapplication dermal exposure to homeowners and their family.

The residential postapplication dermal risk assessment was conducted for adults (16 years old and over) and children (6 to less than 11 years old) when contacting treated fruit trees to perform activities such as hand harvesting, thinning, pruning, or other related activities. Exposure to older children (from 11 to 15 years old) is covered by the exposure of younger children based on a higher body weight, and thus, a lower absorbed dose. Therefore, a quantitative risk assessment was not required for this population subgroup.

Dermal exposure was estimated using the chemical-specific DFR values derived from the reviewed apple DFR study along with TC, durations of exposure and body weights from the 2012 United States Environmental Protection Agency Residential Standard Operating Procedures. Using the default dermal absorption value of 100% for adults only, as the dermal endpoint for children is based on a dermal study and toxicological reference values, calculated MOEs were greater than the target dermal MOEs of 300 for adults and 100 for children in all residential postapplication exposure scenarios on Day 0 (Appendix I, Table 10). As such, health risks are not of concerns and the individuals can enter the treated area once the sprays have dried.

3.4.4 Bystander exposure and risk assessment

Bystander exposure is considered negligible, as application is limited when there is low risk of drift beyond the area to be treated, taking into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings.

Therefore, bystander exposure and risk are not of health concern since the potential for drift is expected to be minimal.

3.5 Dietary exposure and risk assessment

3.5.1 Residues in plant matrices

The residue definition for risk assessment and enforcement in plant products is pyraziflumid. The data gathering/enforcement analytical method is valid for the quantitation of pyraziflumid residues in crop matrices. The residues of pyraziflumid are stable in representative matrices from five crop categories (high water, high oil, high protein, high starch and high acid content) for up to 12 months when stored at ≤-10°C. Therefore, pyraziflumid residues are considered stable in all frozen crop matrices and processed crop fractions for up to 12 months. The raw agricultural commodities of apples, grapes, and plums were processed; and pyraziflumid residues concentrated in the following processed commodities: raisins (2.0×) and dried prunes (1.3×). Crop field trials conducted throughout the United States, including growing regions representative of Canada, using end-use products containing pyraziflumid at supported rates in or on the representative crops of pome fruits (crop group 11-09), stone fruits (crop group 12-09), caneberries (crop subgroup 13-07A), bushberries (crop subgroup 13-07B), small fruits vines climbing, except fuzzy kiwifruit (crop subgroup 13-07F), and tree nuts (crop group 14-11) are sufficient to support the proposed MRLs.

3.5.2 Exposure from residues in drinking water

3.5.2.1 Concentrations in drinking water

For the human health assessment, the residue definition for drinking water is pyraziflumid alone. Estimated environmental concentrations (EECs) in potential drinking water sources are calculated for both groundwater and surface water using the Pesticide in Water Calculator (PWC). The calculation of EECs 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.

For surface water, PWC calculates the amount of pesticide entering the waterbody 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 pyraziflumid was performed at Level 1. Model input parameters are presented in Appendix I, Table 13. 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; only the highest EECs from across these scenarios are reported. All scenarios were run for 50 years. The 90th percentile of the highest daily or yearly EECs from across these scenarios over the 50-year simulation are reported.

Level 1 EECs of pyraziflumid are reported as follows:

Level 1 Estimated environmental concentrations of pyraziflumid in potential sources of drinking water

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)		
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Overall[5]
3 applications of 75 g a.i./ha at 7-day intervals	69	69	11	2.2	1.6

[1] 90th percentile of daily concentrations
[2] 90th percentile of 365-day moving average concentrations
[3] 90th percentile of the highest 1-day average concentration from each year
[4] 90th percentile of yearly average concentrations
[5] Average of all yearly average concentrations

3.5.3 Dietary risk assessment

Acute and chronic (cancer and non-cancer) 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.

3.5.3.1 Acute dietary exposure results and characterization

The following assumptions were applied in the basic acute analysis for pyraziflumid: 100% crop treated, default processing factors, residues in/on crops commodities at MRL levels. The acute dietary exposure (food alone) for all supported pyraziflumid domestic and imported commodities is estimated to range from 0.6% to 2.8% of the ARfD (95th percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable: the highest being 3.0% (0.05 mg/kg bw/day) of the ARfD for children 1-2 years old.

3.5.3.2 Chronic dietary exposure results and characterization

The following criteria were applied to the refined (intermediate level) chronic (cancer and non-cancer) analysis for pyraziflumid: 100% crop treated, default and experimental processing factors (where available), and residues of pyraziflumid based on supervised trial median residue (STMdR) values for all crops. The chronic dietary exposure from all supported pyraziflumid food uses and imported commodities (alone) for the total population is 1.5 % of the ADI, and is less than 7 % of the ADI for all representative population subgroups including infants and children. Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to pyraziflumid from food and drinking water is less than 9% (0.002 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants (< 1 year) at less than 30% (0.006 mg/kg bw/day) of the ADI.

3.6 Aggregate exposure and risk assessment

There is potential for individuals to be exposed to pyraziflumid via different routes of exposure concurrently. As such, the following scenarios were considered.

Aggregation of acute dietary (food and drinking water) and dermal exposure to pyraziflumid from pick-your-own activities was not conducted, as the risk estimated for each individual route of exposure is well below the LOC and therefore, protective of this scenario.

Aggregation of chronic dietary (food and drinking water) and dermal exposure to pyraziflumid from harvesting, pruning, thinning of apple trees in residential settings (Appendix I, Table 11) was conducted. When combining dermal and dietary exposure values and comparing the total exposure to the aggregate toxicological reference values, calculated MOEs were greater than the target MOE of 100 for all life stages (Appendix I, Table 12). As such, aggregate health risks are not of concern.

3.7 Cumulative assessment

The *Pest Control Products Act* requires that the PMRA consider 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 pyraziflumid. Based on its chemical structure, pyraziflumid has been classified into the Fungicide Resistance Action Committee's Group 7: SDHI (succinate dehydrogenase inhibitors). Currently, pyraziflumid is one of 23 SDHI pesticides and 14 are registered in Canada. Pyraziflumid contains the 3-(trifluoromethyl) pyrazine-2-carboxamide group. Other structurally similar SDHI fungicides include oxycarboxin (oxathiin-carboxamides), benzovindiflupyr, bixafen, fluxapyroxad, inpyrfluxam, isopyrazam, penflufen, penthiopyrad, sedaxane (pyrazole-carboxamides), pydiflumetofen (N-methoxy-(phenyl-ethyl)-pyrazole-carboxamides), and boscalid (pyridine-carboxamides). The liver and thyroid toxicity linked to hepatic enzyme induction appears to be a common MOA for several SDHI fungicides. This will be further explored to determine whether a cumulative assessment is necessary, and if so, it will be performed with all relevant chemicals as a separate exercise.

3.8 Maximum residue limits

Table 3.8.1 Recommended maximum residue limits

MRL (ppm)	Food commodity
6	Bushberries (crop subgroup 13-07B)
4	Caneberries (crop subgroup 13-07A)
2	Stone Fruits (crop group 12-09), raisins
1.5	Small fruits vine climbing, except fuzzy kiwifruit (crop subgroup 13-07F)
0.4	Pome Fruits (crop group 11-09)
0.03	Tree Nuts (crop group 14-11)

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 Canada.ca.

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 plant matrices, analytical methodologies, field trial data, processing data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1b, 14 and 15.

3.9 Health incident reports

Pyraziflumid is a new active ingredient pending registration for use in Canada, and as of 12 April 2021, no human or domestic animal incident reports had been submitted to the PMRA.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

Pyraziflumid is persistent under laboratory and field conditions. It has low water solubility and does not volatilize from water and moist soil surfaces. Pyraziflumid is stable to hydrolysis and direct phototransformation. In the presence of certain photosensitizers such as nitrate, it has a potential to undergo indirect phototransformation in water. Biotransformation in soil and aquatic systems occurs very slowly under either aerobic or anaerobic conditions, forming minor transformation products, including carbon dioxide. The organic-carbon-normalized adsorption coefficients suggest low mobility. Due to its persistence, however, there is a potential for pyraziflumid to move through soil and reach groundwater at locations vulnerable to leaching, as evidenced in the field dissipation studies.

Pyraziflumid is systemic; when applied as a broadcast spray, pyraziflumid can be absorbed and transported inside the plant. Pyraziflumid is not expected to be found in air or travel long distances in the atmosphere from where it is applied. Pyraziflumid does not bioaccumulate in fish.

A summary of environmental fate data for pyraziflumid is presented in Appendix I, Table 16.

4.2 Environmental risk characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing estimated environmental concentrations (EECs) in various media (food, water, soil and air) with concentrations at which adverse effects occur. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including dissipation of the pesticide between applications. For Parade Fungicide, the proposed maximum use pattern considered in this risk assessment is: 3 applications of 75 g a.i./ha, the highest single application rate, at 7-day intervals per growing season. The resulting EECs in various media are summarized in Appendix I, Table 17.

Ecotoxicology information includes acute and chronic toxicity data for organisms (invertebrates, vertebrates and plants) from both terrestrial and aquatic habitats. The toxicity endpoints obtained from studies are adjusted by an uncertainty factor 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) and are termed effects metrics.

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and the relevant effects metrics. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate effect metric, and the RQ is then compared to the LOC. If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, further characteriation of the risk is conducted by taking into consideration more realistic exposure scenarios and effects metrics. These considerations may include additional exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods.

4.2.1 Risks to terrestrial organisms

Terrestrial organisms, such as earthworms, pollinators, beneficial arthropods, birds, small mammals, and terrestrial non-target vascular plants can be exposed to pyraziflumid through direct contact with spray, spray drift, run-off, contact with sprayed surfaces, or from ingestion of contaminated food. A risk assessment of pyraziflumid and the associated end-use product, Parade Fungicide, was undertaken based on toxicity data obtained from available studies.

A summary of the effects on terrestrial organisms considered in the selection of toxicity endpoints is provided in Appendix I, Table 18. The most sensitive endpoints for each taxon selected as surrogates for the screening level assessment, with the respective uncertainty factors, effect metrics and the LOCs are presented in Appendix I, Table 19. The screening level risk assessment for pyraziflumid is presented in Appendix I, Tables 20 and 21.

Terrestrial invertebrates: Screening level exposure for terrestrial invertebrates, excluding bees, considers direct spray application on soil or plant surfaces at the maximum cumulative application rates, which are 224.4 g a.i./ha and 149.6 g a.i./ha, respectively (Appendix I, Table 17). The RQ for earthworms resulting from chronic exposure to pyraziflumid in soil did not exceed the LOC at the screening level. The RQs for predatory mites and parasitic wasp resulting from exposure to pyraziflumid, either on soil surface or on plant surface, did not exceed the LOC at the screening level.

For honey bees representing pollinators, the exposure at the screening level is based on a single maximum application rate of 75 g a.i./ha. The RQs for adult honey bees exposed to pyraziflumid either through oral or contact routes did not exceed the LOC on acute and chronic exposure bases. The RQ for larvae exposed to pyraziflumid through diet did not exceed LOC on an acute exposure basis, but was just above LOC (1.07) on a chronic exposure basis. At the screening level, however, the exposure estimate is conservative, based on high estimates of nectar and pollen concentrations following spray application and the highest larvae food consumption rates. Therefore, the risk to larvae is acceptable.

The risks associated with the use of pyraziflumid are acceptable for terrestrial invertebrates.

Terrestrial plants: For non-target vascular plants, the screening level risk assessment was conducted using direct spray at the maximum cumulative application rates on surfaces of plant for vegetative vigour (149.6 g a.i./ha) or on soil for seedling emergence (224.4 g a.i./ha). The screening level RQ did not exceed the LOCs for vegetative vigour for in-field exposure. The screening level RQ, however, may have exceeded for seedling emergence for in-field exposure (RQ of <1.9). The refined risk assessment for seedling emergence considers the maximum spray drift deposition (fine droplets) at one metre downwind from the point of application on soil surface. The off-field exposure on soil was estimated by applying a drift factor, 74% for early season airblast and 59% for late season airblast application, resulting in refined EECs of 166.1 g a.i./ha and 132.4 g a.i./ha, respectively. The corresponding RQs are < 1.4 and < 1.1, respectively, which may still exceed the LOC. The highest rate tested in the seedling emergence study was below the maximum cumulative application rate, but there were no effects at the highest rate tested. Overall, there is some uncertainty in whether or not the LOC is exceeded. As a precautionary measure, buffer zones of 2 and 1 metres for early and late season airblast applications, respectively, will be added to the label. A statement of "Toxic to non-target terrestrial plants" will also appear on the label.

Terrestrial vertebrates: For birds and mammals, the screening level risk was assessed considering direct over spray application at the maximum cumulative rate of 149.6 g a.i./ha. The RQs for birds resulting from acute oral exposure to pyraziflumid did not exceed the LOC at the screening level. For chronic exposure, the RQ is > 0.6 as the reproductive endpoint was a non-definitive NOAEC, resulting in some uncertainty. However, when considering LOAEC, the RQ

was 0.6, and did not exceed the LOC. In addition, the screening level assessment assumes that birds only consume food items contaminated with pyraziflumid at the maximum cumulative amount throughout the reproduction period to cause chronic reproductive effects. The assumption is conservative. Therefore, together with the consideration of the magnitude of effects observed in the available studies, and no acute oral and dietary risk with the conservative exposure scenarios, risks associated with foliar application of pyraziflumid is acceptable for birds.

For mammals, the LOC was not exceeded for any mammal size or endpoints with direct foliar application as the exposure scenario. The risk associated with the use of pyraziflumid is acceptable for small wild mammals.

4.2.2 Risks to aquatic organisms

Aquatic organisms, such as invertebrates, fish, plants and algae can be exposed to pyraziflumid through spray drift or runoff. A risk assessment of pyraziflumid and the associated end-use product, Parade Fungicide, was undertaken based on available toxicity data for freshwater and marine invertebrates, fish, plants and algae.

For pelagic aquatic organisms, the exposure to pyraziflumid at the screening level considers direct application on water surface at the maximum cumulative application rate of 224.4 g a.i./ha and assuming instantaneous and complete mixing in the water body. The resulting EECs in water bodies 80 cm and 15 cm deep are 0.028 mg a.i./L and 0.15 mg a.i./L, respectively (Appendix I, Table 17).

For benthic invertebrates, a refined exposure estimate in pore water was considered because it is a relevant exposure route resulting from runoff entering surface waters. The surface water EECs, including pore water EECs, are calculated using the Pesticide in Water Calculator (PWC) model 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 (3 applications of 75 g a.i./ha at 7-day intervals) on apple by ground sprayer are modelled over a 50-year period. The parameters used for the modelling are presented in Appendix I, Table 13 and the resulting EECs are presented in Appendix I, Table 22. The EEC for pyraziflumid in water columns over a 21-day period and in pore water is 0.018 mg a.i./L.

A summary of available aquatic toxicity data for pyraziflumid and its formulated end-use product is presented in Appendix I, Table 18. The effects metrics used in the risk assessment and LOCs are presented in Appendix I, Table 19. Resulting RQs for aquatic organisms are presented in Appendix I, Table 23.

Aquatic invertebrates: For freshwater pelagic invertebrates, the RQs for acute and chronic exposure to pyraziflumid did not exceed the LOC at the screening level. The risk associated with the use of pyraziflumid is acceptable for freshwater invertebrates.

For marine pelagic invertebrates, the RQ for acute exposure to pyraziflumid did not exceed the LOC. The RQ for chronic exposure, however, exceeded the LOC (RQ of 2.3). The screening level EEC is conservative (direct application at level of cumulative maximum annual applications) and does not consider tidal dilution. It is highly unlikely that the maximum EEC could be maintained to cause chronic effects. Tides and dilution are expected to make concentrations in the coastal environment negligible at the time of subsequent applications. If considering the single maximum application rate of 75 g a.i./ha, the RQ for chronic exposure did not exceed the LOC (RQ of 0.78). Therefore, the risk associated with the use of pyraziflumid is acceptable for marine invertebrates.

For freshwater and marine benthic invertebrates, the toxicity endpoints were derived from tests in which pyraziflumid was introduced to the system by spiking the sediment directly and allowing the system to equilibrate with overlying water. This type of test is designed to simulate exposure to accumulated pesticide in sediment from runoff. Therefore, pore water is considered a relevant exposure medium for benthic invertebrates.

The RQs for exposure of pyraziflumid to freshwater and marine benthic invertebrates did not exceed the LOC through runoff. The risk associated with the use of pyraziflumid is acceptable for benthic invertebrates.

Fish: The RQs for freshwater and marine fish resulting from acute and early-life stage exposure to pyraziflumid did not exceed the LOC at the screening level. The risk associated with the use of pyraziflumid is acceptable for freshwater and marine fish.

Amphibians: Using the endpoints from acute and early-life stage studies with fish as a surrogate, along with an EEC for pyraziflumid in a 15-cm deep body of water, the RQs for amphibians resulting from acute and early-life stage exposure to pyraziflumid did not exceed the LOC at the screening level. The risk associated with the use of pyraziflumid is acceptable for amphibians.

Algae: The RQs for freshwater and marine algae resulting from acute exposure to pyraziflumid did not exceed the LOC at the screening level. The risk associated with the use of pyraziflumid is acceptable for freshwater or marine algae.

Aquatic vascular plants: The RQ for aquatic vascular plants resulting from exposure to pyraziflumid did not exceed the LOC at the screening level. The risk associated with the use of pyraziflumid is acceptable for aquatic vascular plants.

4.2.3 Environmental incident reports

Pyraziflumid is a new active ingredient pending registration for use in Canada and the United States. As of 5 May 2021, no environmental incident reports had been submitted to the PMRA.

5.0 Value

Scab and powdery mildew are serious and common fungal diseases of apple. Serious scab infections can result in significant defoliation and both diseases can substantially reduce yield by

reducing the number and size of fruit. Furthermore, marketability of fruit is reduced due to smaller fruit size, scab-caused lesions and/or powdery mildew-caused russeting. The registration of Parade Fungicide will provide Canadian growers with a new FRAC group 7 fungicide to manage these two economically important diseases while mitigating the risk of resistance development.

Field studies were conducted on apple to assess the efficacy of Parade Fungicide in controlling powdery mildew and scab. In five field trials, it was demonstrated that Parade Fungicide applied preventatively at 227-340 g a.i./ha can be expected to control scab on leaves and fruit and that the level of scab reduction was generally similar to that observed in treatments of other fungicides registered for control of this disease. Similarly, in six field trials, Parade Fungicide applied prior to disease onset at 227-340 mL/ha was shown to control powdery mildew to a similar extent as that observed in treatments of other fungicide products registered for control of this disease. As a rate response to Parade Fungicide was observed in some trials, the higher rate of 340 mL/ha is more appropriate for use under conditions that favour development of high scab and powdery mildew disease pressure. No visually detectable injury to foliage and fruit was evident following application of Parade Fungicide at up to 340 mL/ha.

Details of the supported uses are summarized in Appendix I, Table 25.

6.0 Pest control product policy considerations

6.1 Assessment of the active ingredient under the toxic substances management policy

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, pyraziflumid was assessed in accordance with the PMRA Regulatory Directive DIR99-03[6] and evaluated against the Track 1 criteria. The PMRA has reached the conclusion that pyraziflumid and its transformation products do not meet all of the TSMP Track 1 criteria. Please refer to Appendix I, Table 24 for further information on the TSMP assessment.

[6] DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

6.2 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the active ingredient as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*[7]

The list is used as described in the PMRA Science Policy Note SPN2020-01[8] and is based on existing policies and regulations, including the *Toxic Substance Management Policy* and *Formulants Policy,*[9] 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 pyraziflumid and its end-use product Parade Fungicide do not contain any formulants or contaminants identified 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 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 Pyraziflumid Technical and Parade Fungicide, containing the technical grade active ingredient pyraziflumid, to control powdery mildew and scab on apple.

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.

---

7 SI/2005-114, last amended on June 24, 2020. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

8 PMRA's Science Policy Note SPN2020-01, Policy on the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under paragraph 43(5)(b) of the Pest Control Products Act

9 DIR2006-02, Formulants Policy and Implementation Guidance Document

List of abbreviations

↑	increased
↓	decreased
♂	male
♀	female
°C	Degree Celsius
µg	micrograms
µM	micromolar
a.i.	active ingredient
abs	absolute
ACN	acetonitrile
AD	administered dose
ADI	acceptable daily intake
AHETF	Agricultural Handler Exposure Task Force
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	Applied Radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
AST	aspartate aminotransferase
ATPD	Area treated per day
AUR	Amplex UltraRed
BAF	Bioaccumulation Factor
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BCF	BioConcentration Factor
BCF_K	Kinetic BioConcentration Factor
BCF_{SS}	Steady State BioConcentration Factor
BrdU	bromodeoxyuridine
BUN	blood urea nitrogen
bw	body weight
bwg	bodyweight gain
CA	California
CAF	composite assessment factor
CAR	constitutive androstane receptor
CAS	Chemical Abstracts Service
CEPA	Canadian Environmental Protection Act
chol	cholesterol
CL	Confidence Limit
cm	centimetre(s)
CR	Chemical-resistant
d	day(s)
DAFA	Days After First Application
DFOP	Double First-Order in Parallel rate model
DFR	Dislodgeable foliar residue
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)
dw	dry weight
EC_{25}	effective concentration on 25% of the population
ED	Estimated Dose
EDE	Estimated Daily Exposure
EEC	Estimated Environmental exposure Concentration
ELS	Early Life-Stage
ER_{25}	effective rate for 25% of the population
ER_{50}	Effective Rate on 50% of the population
EROD	7-ethoxyresorufin O-dealkylase
F1	first generation
F2	second generation
fc	food consumption
fe	food efficiency
FIR	Food Ingestion Rate
FRAC	Fungicides Resistance Action Committee
g	gram(s)
GA	Georgia
GD	gestation day
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
GLP	good laboratory practices
h	hour(s)
ha	hectare(s)
HAFT	highest average field trial
HC	historical control
HCl	hydrochloric acid
Hg	mercury
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
hr	hour(s)
IC_{50}	Inhibition Concentration 50%
ILV	independent laboratory validation
IORE	Indeterminate Order Rate Equation model
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
kPa	Kilopascal(s)
L	litre(s)
LAFT	lowest average field trial
LC_{50}	lethal concentration 50%
LD	lactation day
LD_{50}	lethal dose 50%
LLNA	local lymph node assay
LN	Natural log
LOAEC	Lowest Observed Adverse Effect Concentration

LOAEL	lowest observed adverse effect level
LOAER	Lowest Observed Adverse Effect Rate
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
MEA	Method efficiency adjustment
mg	milligram(s)
mL	millilitre(s)
MAS	maximum average score
MBq	Megabecquerel(s)
MI	Michigan
MIS	maximum irritation score
M/L	Mixing and loading
M/L/A	Mixer/loader/applicator
mmHg	Millimeter(s) of mercury
MOA	mode of action
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
MTD	maximum tolerated dose
n	number of independent trials
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NAFTA	North American Free Trade Agreement
ND	North Dakota
NER	Non-Extractible Residues
NOAEL	no observed adverse effect level
NY	New York
NZW	New Zealand white
OC	organic carbon content
OM	organic matter content
P	parental generation
PCPA	*Pest Control Product Act*
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	Personal protective equipment
ppm	parts per million
PROD	pentoxyresorufin o-dealkylase
PXR	pregnane X receptor
PW	pure water
PWN	pure water containing nitrate salt
PYO	Pick-your-own
R	Correlation coefficient
R^2	Coefficient of determination
RAC	raw agricultural commodity
RD	residue definition
REI	Restricted-entry interval

rel	relative
RTI	retreatment interval
SDEV	standard deviation
SDHI	succinate dehydrogenase inhibitor
SFO	Single First-Order rate model
SL	Single layer of clothing
SNW	stimulated natural water
STMdR	supervised trial median residue
T_{max}	time of peak effect
t_R	representative half-life
T3	tri-iodothyronine
T4	thyroxine
T.Bil	total bilirubin
TC	Transfer coefficient
TPO	thyroid peroxidase
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
UDP-GT	uridine diphosphate glucuronyltransferase
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution
WA	Washington
WBC	white blood cells
wt	weight

Appendix I Tables and figures

Table 1a Residue analysis in environmental media

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Soil and sediment	N/A	Parent	HPLC-MS/MS	1.0 ppb	PMRA# 3059491, 3059371
Water	N/A	Parent	HPLC-MS/MS	0.1 µg/L	PMRA# 3059492, 3059371

Table 1b Residue analysis in plant matrices

Analytical methods	Matrix	Analytes	Method ID/ type	LOQ (ppm)	Reference
Plant Commodities					
Enforcement and Data-Gathering Method	Apple, grape, lettuce, peanut, potato, rice, and tomato commodities	Pyraziflumid	GLP-MTH-096 / LC-MS/MS	0.01	PMRA# 3071050
ILV of Enforcement Method	Apple juice, grape, leaf lettuce, peanut nutmeat, potato tuber, rice straw, and tomato				PMRA# 3071048
Radiovalidation	Rice hull and straw		N/A	N/A	PMRA# 3059437

Table 2 Identification of select metabolites of pyraziflumid

Code	Chemical Name	Source
BC-01	N-(3',4'-difluoro-5-hydroxybiphenyl-2-yl)-3-(trifluoromethyl)pyrazine-2-carboxamide	Rat, livestock, plant, environmental
BC-03	N-(3',4'-difluoro-6-hydroxybiphenyl-2-yl)-3-(trifluoromethyl)pyrazine-2-carboxamide	Rat, environmental
BC-05	pyraziflumid-3',4'-OH	Rat
BC-06	N-(3',4'-difluorobiphenyl-2-yl)-5-hydroxy-3-(trifluoromethyl) pyrazine-2-carboxamide	Rat, livestock, plant, environmental
BC-08	3',4'-difluorobiphenyl-2-amine	Rat, environmental
BC-09	3-(trifluoromethyl)pyrazine-2-carboxylic acid	Rat, livestock, plant, environmental
BC-10	3-(trifluoromethyl)pyrazine-2-carboxamide	Rat, livestock, plant, environmental
BC-11	pyraziflumid-4',6'-OH	Rat
BC-12	pyraziflumid-oxamic acid	Rat, livestock
BC-01 glucuronide	pyraziflumid-4'-OH glucuronide	Rat, livestock, plant
BC-03 glucuronide	pyraziflumid-3'-OH glucuronide	Rat
BC-05 glucuronide	pyraziflumid-3',4'-OH glucuronide	Rat
BC-06 glucuronide	pyraziflumid-5-OH glucuronide	Rat

Table 3 Toxicity profile of technical pyraziflumid

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 bodyweights 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
Toxicokinetic studies	
Absorption, distribution, excretion and metabolism in the rat (gavage) Wistar Hannover rats PMRA# 3059416, 3059415, and 3059414	Absorption, distribution, metabolism and excretion were investigated with [pyrazinyl-5(6)- ^{14}C]-, [aniline-U-^{14}C]-, or [difluorophenyl-U-^{14}C]-pyraziflumid. Single doses were administered by gavage at 1 or 100 mg/kg bw. **Absorption:** Absorption was quick and extensive via the GI tract. T_{max} values were between 3-24 hours, and elimination half-lives in blood and plasma were 1-3.8 days in the low dose group and 3.1-5.1 days in the high dose group. There were no significant differences between sexes or dose levels. There was no evidence of saturation of the metabolic pathways in the high-dose groups, and the bioavailability was similar at both dose levels. **Distribution:** Tissue concentrations at 48 hours post-dosing were less than 1.5-3% of the AD. The majority of tissues had no or trace radioactivity by 168 hours post-dosing and the highest concentrations were in the GI tract or GI contents, followed by the fat, liver, kidney, and adrenal. **Elimination:** Rapid excretion occurred, mainly via feces (80-93% of the AD) with some excretion via the urine (6-16% of the AD). The majority of radioactivity was excreted by 96 hours post-dosing, regardless of dose group. Excretion via the urine and expired air was slightly higher in females. **Metabolism:** The proposed metabolic pathway was hydroxylation and subsequent conjugation with glucuronic acid. Absorbed pyraziflumid was extensively metabolized and the major metabolites in the feces were BC-01 and BC-03. BC-01 and BC-12 were the major metabolites in the plasma and liver. Metabolite profiles were qualitatively similar between males and females. Only minor metabolites (≤5% of the AD) were observed in the urine, including BC-12.
Biliary excretion in the rat (gavage) Wistar Hannover rats PMRA# 3059413	Bile duct-cannulated rats were administered a single oral gavage dose of [pyrazinyl-5(6)- ^{14}C]- or [aniline-U-^{14}C]-pyraziflumid at 1 mg/kg bw. **Absorption/Elimination:** Over 98% of the AD was eliminated by 72 hours post-dosing, largely into bile (83-85% of the AD) for both radiolabels. Urinary and fecal excretion each accounted for < 10% of the AD for each radiolabel. A very small portion was observed in GI contents, GI tract, liver, and cage wash (<5% of the AD). The absorption of pyraziflumid following oral dosing was estimated to be 90-93% of the AD. **Metabolism:** The major metabolites with both radiolabels in bile were BC-01-glucuronide, BC-03-glucuronide, and BC-01. The major metabolite with both radiolabels in urine was BC-01-glucuronide. Unchanged pyraziflumid was the major source of dosed radioactivity with both radiolabels in feces. Metabolite constituents in bile were generally consistent with those in feces obtained in toxicokinetic studies using intact rats.

Study type/ Animal/PMRA#	Study results
In vitro metabolism study liver microsomes Wistar/Sprague-Dawley rat, CD-1 mouse, NZW rabbit, goat, Beagle dog, and mixed pool human PMRA# 3059412	In an in vitro metabolism study, liver microsomes from rat, mouse, rabbit, goat, dog, and human were incubated with [pyrazinyl-5(6)- ^{14}C]- or [aniline-U-^{14}C]-pyraziflumid with and without NADPH at a concentration of 0.3 µM. No significant species- or sex-related qualitative differences in metabolic profile of pyraziflumid were noted. Quantitatively, preparation of liver microsomes from rats had more unchanged pyraziflumid and less BC-01 than those from the other species. The major metabolite in all of the liver microsome preparations with NADPH was BC-01, along with the minor metabolites of BC-03, BC-05, BC-06, and BC-10. BC-06 production by dog liver microsomes was higher than that by liver microsomes from other animals. Pyraziflumid was not metabolized in any of the reaction systems without NADPH. The results of in vitro metabolism are similar to those of phase I metabolism of in vivo toxicokinetic studies.
Acute toxicity studies (pyraziflumid technical)	
Acute oral Wistar rats PMRA# 3059378	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity Low toxicity
Acute dermal Sprague-Dawley rats PMRA# 3059379	LD_{50} > 2000 mg/kg bw (♂/♀) No clinical signs of toxicity Low toxicity
Acute inhalation Wistar rats PMRA# 3059380	LC_{50} > 2.10 mg/L (♂/♀) Clinical signs at 2.10 mg/L included ruffled fur Low toxicity
Eye irritation Japanese White rabbits PMRA# 3059381	MAS = 0/110 MIS = 0.67/110 at 1 hour Non-irritating
Dermal irritation Japanese White rabbits PMRA# 3059382	MAS = 0/8 MIS = 0/8 Non-irritating
Dermal sensitization (LLNA BrdU-ELISA) CBA/J mice PMRA# 3059383	Negative
Short-term toxicity studies	
28-Day oral (dietary) CD-1 mice PMRA# 3059388	NOAEL = 520/759 mg/kg bw/day (♂/♀) LOAEL = 1744/2475 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ albumin, ↑ hepatocyte hypertrophy (♂/♀); ↓ total protein (♂); ↓ bw, ↓ bwg (♀)

Study type/ Animal/PMRA#	Study results
90-Day oral (dietary) CD-1 mice PMRA# 3059384	NOAEL = 119/146 mg/kg bw/day (♂/♀) LOAEL = 433/514 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ total cholesterol, ↑ hepatocyte hypertrophy (♂/♀); ↑ WBC (♂); ↑ phosphorus (♀)
28-Day oral (dietary) Wistar rats PMRA# 3059389	NOAEL= 38/40 mg/kg bw/day (♂/♀) LOAEL= 181/186 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ GGT, ↓ ALT, ↑ hepatocellular hypertrophy, ↑ follicular cell hypertrophy (♂/♀); ↑ thyroid wt (♂); ↓ bw, ↓ bwg, ↓ fc, ↓ fe, ↑ BUN, ↓ organ wt (thymus, spleen, pituitary, kidney, adrenals, ovaries) (♀)
90-Day oral (dietary) Wistar rats PMRA# 3059385	NOAEL= 7.1/8.6 mg/kg bw/day (♂/♀) LOAEL= 36/42 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ liver wt, ↑ mid-zonal hepatocellular hypertrophy, ↑ thyroid follicular cell hypertrophy, ↑ brown pigment in kidney (lipofuscin) (♂/♀); ↓ triglycerides (♂);↑ brown pigment in hepatocytes (hemosiderin) (♀)
28-Day oral (dietary) Beagle dogs PMRA# 3059387 Pilot: PMRA# 3196188	Supplemental NOAEL and LOAEL not established 283/309 mg/kg bw/day: ↑ ALP, ↑ AST, ↑ ALT, ↑ GGT, ↑ T.Bil, ↑ hepatocellular degeneration and necrosis (♀) 721/761 mg/kg bw/day: dose level changed from 32,000 ppm to 20,000 ppm on Day 6; however, no signs of recovery therefore dosing stopped since Wk 2 (severe ↓ bw, clinical signs (vomiting, mucous stool, no feces), ↑ALP, ↑ AST, ↑ ALT, ↑ GGT, ↑ T.Bil, ↓ total cholesterol, ↑ hepatocellular degeneration (♂/♀);↓ BUN (♀)
90-Day oral (dietary) Beagle dogs PMRA# 3059386	NOAEL= 29/31 mg/kg bw/day (♂/♀) LOAEL= 167 /320 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ ALP, ↑ liver wt, ↑ liver cell necrosis (♂/♀); bw loss, ↑ AST, ↑GGT, ↑ T.Bil, ↑ albumin, ↑ triglycerides (♂)
1-year oral (dietary) Beagle dogs PMRA# 3059393	NOAEL= 28/28 mg/kg bw/day (♂/♀) LOAEL= 51/48 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ mortality (3 ♂, 2 ♀), ↓ bw, ↓ fc, ↑ liver degeneration, ↑ necrosis, and ↑ oval cell hyperplasia in dogs that died before end of study, ↑ ALP, ↑ AST, ↑ ALT, ↑ T.Bil, ↑ BUN
5-Day dermal Sprague-Dawley rats PMRA# 3059392	Supplemental NOAEL and LOAEL not established 1000 mg/kg bw/day: No mortality, clinical signs, bw, fc, liver wt, or necropsy findings (♂/♀)
90-Day dermal Sprague-Dawley rats PMRA# 3059390	NOAEL= 200 mg/kg bw/day (♂/♀) LOAEL= 1000 mg/kg bw/day (♂/♀) ≥200 mg/kg bw/day: evidence of skin trauma during clinical examination, slight dorsal skin erosion and crust noted at histopathological examination (♀) Effects at the LOAEL: ↓ T.Bil (♂); ↑ GGT, ↑ thyroid wt (♀)
Chronic toxicity/Carcinogenicity studies	
78-week carcinogenicity (dietary)	NOAEL= 21/251 mg/kg bw/day (♂/♀) LOAEL= 227/1030 mg/kg bw/day (♂/♀)

Study type/ Animal/PMRA#	Study results
CD-1 mice PMRA# 3059394, 3059395	Effects at the LOAEL: ↑ hepatocellular hypertrophy (♂/♀); ↓bw, ↓ bwg, ↑ marked enlargement in liver (♂); ↑ hepatocellular vacuolation,↑ liver wt (♀) 905 mg/kg bw/day: equivocal ↑ bronchioloalveolar adenomas (♂) – incidences of (16, 24, 20, 33%) (HC 17.6-48%) Equivocal evidence of tumourigenicity
104-week combined chronic toxicity/carcinogenicity (dietary) Wistar rats PMRA# 3059396 PMRA#3059397	NOAEL= 2.2/2.9 mg/kg bw/day (♂/♀) LOAEL= 4.3/5.7 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ glucose (♂/♀); ↓ reticulocytes, ↓ WBC, ↓ lymphocytes, ↑ liver wt, ↑ hepatocellular vacuolation (♂);↑ follicular cell hypertrophy (♀) 45.7/66.3 mg/kg bw/day: At 52 weeks: Follicular cell adenoma in thyroid in two (♂); hepatocellular adenoma in one (♀) at high dose. At 104 weeks: Thyroid follicular cell adenoma incidence (4, 10, 14, 12, 35%) (HC 0-11%) and carcinoma (0, 0, 0, 0, 4%) (HC 0-3.6%) (♂); hepatocellular adenoma (0, 2, 2, 0, 12%) (HC 0-2%) (♀) at high dose. Evidence of tumourigenicity
Developmental/Reproductive toxicity studies	
Two-generation reproductive toxicity (dietary) (range-finding) Sprague-Dawley rats PMRA# 3059403	Supplemental NOAEL and LOAEL not established Parental toxicity ≥25/31 mg/kg bw/day: ↑ P and F1 liver wt, ↑ P incidence of hepatocyte hypertrophy (♂/♀); ↓ bwg P (pre-mating) (♀) 96/115 mg/kg bw/day: ↑ P incidences of thyroid follicular cell hypertrophy (♂); ↓ bwg P (gestation), ↓ bw, ↓ bwg F1(pre-mating), ↑ P and F1 incidence of liver coloration, ↑ F1 incidence of kidney coloration (♀) Offspring toxicity ≥3.1 mg/kg bw/day: ↑ F1 organ wt (liver, testes, uterus) (♂/♀) ≥31 mg/kg bw/day: ↓ F1 spleen wt (♂/♀) 115 mg/kg bw/day: ↓ F1 (PND 7-21) and F2 (PND 7-21) pup bw, ↑ F1 incidences of hepatocyte hypertrophy and fatty degeneration in liver, ↑ F2 liver wt, ↑ F2 rel brain wt, ↓ F2 spleen wt, ↓ F2 thymus wt, ↓ F2 abs brain wt (♂/♀) Reproductive toxicity ≥2.5/3.1 mg/kg bw/day: ↑ F1 prostate wt (♂); ↓ F1 animals with normal estrus cycle (5-15%) (♀) ≥25/31 mg/kg bw/day: ↓ P and F1 ovary and uterus wt (♀)

Study type/ Animal/PMRA#	Study results
	115 mg/kg bw/day: ↓ F1 implantation sites (♀)
Two-generation reproductive toxicity (dietary) Sprague-Dawley rats PMRA# 3059398	Parental toxicity NOAEL= 5.6/7.0 mg/kg bw/day in (♂/♀) LOAEL= 17/21 mg/kg bw/day in (♂/♀) Effects at the LOAEL: ↑ P and F1 incidence of hepatocyte hypertrophy (♂/♀); ↑ P and F1 incidence of liver fatty degeneration (♂) Offspring toxicity NOAEL= 7.0 mg/kg bw/day LOAEL= 21 mg/kg bw/day Effects at the LOAEL: ↑ F2 liver wt, ↑ F1 and F2 incidence of hepatocyte hypertrophy (♂/♀) Reproductive toxicity NOAEL= 57/70 mg/kg bw/day in ♂/♀ LOAEL= not established No treatment-related effects were observed on reproductive parameters. No evidence of sensitivity of the young
Developmental toxicity (gavage) Range-finding Sprague-Dawley rats PMRA# 3059427	Supplemental NOAEL and LOAEL not established Maternal toxicity ≥ 300 mg/kg bw/day: ↓ bwg (GD 6-20), ↓ fc (Day 9-20) Developmental toxicity No effects observed but the assessment was limited
Developmental toxicity (gavage) Sprague-Dawley rats PMRA# 3059404	Maternal toxicity NOAEL= 20 mg/kg bw/day LOAEL= 100 mg/kg bw/day Effects at the LOAEL: ↓ bwg (GD 6-20), ↓ fc (GD 6-20) Developmental toxicity NOAEL= 500 mg/kg bw/day LOAEL= not established No evidence of treatment-related malformations. No evidence of sensitivity of the young
Developmental toxicity (gavage) Range-finding Japanese White rabbits PMRA# 3059428	Supplemental NOAEL and LOAEL not established Maternal toxicity ≥100 mg/kg bw/day: ↓ bwg (GD 6-27), ↓ fc (GD 12-24) ≥300 mg/kg bw/day: mortality (1♀ on GD18) and the rest euthanized due to significant ↓ bw and ↓ fc Developmental toxicity

Study type/ Animal/PMRA#	Study results
	No effects observed but the assessment was limited
Developmental toxicity (gavage) Japanese White rabbits PMRA# 3059405	Maternal toxicity NOAEL= 30 mg/kg bw/day LOAEL= 100 mg/kg bw/day Effects at the LOAEL: ↓ bwg (GD 6-27) ↓ fc (GD 12-21 and 24-28), 2 abortions Developmental toxicity NOAEL= 30 mg/kg bw/day LOAEL= 100 mg/kg bw/day Effects at the LOAEL: 2 abortions No evidence of treatment-related malformations No evidence of sensitivity of the young
Genotoxicity studies	
In vitro bacterial assay *S.* Typhimurium (TA 1535, TA 1537, TA 98, TA 100); *E. coli* (WP2uvrA) PMRA# 3059406	Negative ± metabolic activation Tested up to a precipitating concentration
In vitro mammalian cell assay Mouse Lymphoma L5178Y cells PMRA# 3059407	Negative ± metabolic activation Tested up to a cytotoxic concentration
In vitro chromosome aberration test Chinese hamster lung (CHL/IU) cells PMRA# 3059408	Negative ± metabolic activation, with an increased incidence of polyploidy Tested up to a precipitating concentration
Micronucleus test Slc/ICR mice PMRA# 3059410	Negative No mortality or clinical signs of toxicity Tested up to a limit dose
In vivo genotoxicity (somatic cells) alkaline comet assay in rats (gavage) Wistar rats PMRA# 3059429	Negative No mortality or clinical signs of toxicity Tested up to a limit dose
Neurotoxicity studies	
Acute neurotoxicity (gavage) Range-finding Crl:CD (SD) rats	Supplemental NOAEL and LOAEL not established 2000 mg/kg bw: hunched posture, low arousal at 8 hours (~ T_{max}) (♀)

Study type/ Animal/PMRA#	Study results
PMRA# 3059400	
Acute neurotoxicity (gavage) Crl:CD (SD) rats PMRA# 3059399	NOAEL= 1000 mg/kg bw/not established (♂/♀) LOAEL= 2000/500 mg/kg bw (♂/♀) Effects at the LOAEL: ↑ defecation on Day 0 (♂); ↓ motor activity (total and ambulatory) on Day 0 (~ T_{max}) (♀) No evidence of selective neurotoxicity
Immunotoxicity studies	
Immunotoxicity (Waiver request) PMRA# 3059424	Request to waive the conditional requirement for immunotoxicity testing accepted based on the absence of immunotoxic effects in the database.
Special studies (non-guideline)	
Effects on general activity and behavior in rats in accordance with the modified Irwin's Multidimensional Observation Method (single gavage dose) Crl:CD (SD) rats PMRA# 3059430	Supplemental – non-guideline NOAEL and LOAEL not established No effects on mortality, clinical signs of toxicity, or body weight. No findings were noted in behavioral, neurological, or autonomic profile in either sex up to a dose level of 2000 mg/kg bw.
Mechanistic in vitro study (effect on rat thyroid peroxidase (TPO) activity) Thyroid microsomes Wistar rats (♂) PMRA# 3059426	Supplemental – non-guideline Negative for thyroid peroxidase (TPO) inhibition in rat thyroid microsome preparations in TPO-catalyzed AUR oxidation assay at up to 50 µM.
Mechanistic 7-day oral (dietary) study in the rat (effect on thyroid hormone and liver enzyme activity) Wistar rats (♂) PMRA # 3059425	Supplemental – non-guideline NOAEL and LOAEL not established ≥24 mg/kg bw/day: ↑ TSH levels on Day 3 and 7, ↑ T4-UDP-GT, ↑ liver wt, ↑ P-450, ↑ hepatocellular hypertrophy, ↑ thyroid follicular cell hypertrophy on Day 7 ≥78 mg/kg bw/day: ↑ thyroid wt 158 mg/kg bw/day: ↑ microsomal protein Conclusion: Based on the study findings, which demonstrated ↑ hepatic enzyme activity and ↑ thyroid hormone concentrations, pyraziflumid affects liver and thyroid via hepatic enzyme induction in rats.
Mechanistic oral (dietary) study in the rat (supplemental data of thyroid hormone and liver enzyme activity – 28-day oral study in rats PMRA# 3059389)	Supplemental – non-guideline NOAEL and LOAEL not established ≥38/40 mg/kg bw/day: ↑ microsomal protein, ↑ EROD, ↑ PROD, ↑ T4-UDP-GT (♂/♀); ↑ TSH (♂);↑ TSH (♀) ≥181/186 mg/kg bw/day: ↑ microsomal protein (♀)

Study type/ Animal/PMRA#	Study results
Wistar rats Dosed for 14 or 28 days PMRA# 3196193	727/696 mg/kg bw/day: ↑ T3, ↓ T4 (♂/♀) The findings were significant and more apparent following the 14-day treatment than the 28-day treatment, except T3 in females, for which the increase was larger following the 28-day treatment. Conclusion: Pyraziflumid affects the liver and thyroid via increased hepatic enzyme activity and increased thyroid hormone concentrations following the 28-day treatment.
Mechanistic oral (dietary) study in the rat (effect on thyroid hormone and liver enzyme activity) Wistar rats (♂) PMRA# 3059432	Supplemental – non-guideline NOAEL and LOAEL not established ≥17 mg/kg bw/day: ↑ liver wt, ↑ thyroid wt, ↑ hepatocellular hypertrophy, ↑ hepatocellular vacuolation, ↑ P-450, ↑ T4-UDP-GT ≥55 mg/kg bw/day: ↑ liver wt, ↑ thyroid wt, ↑ TSH, ↑ microsomal protein 113 mg/kg bw/day: dark abnormal colour in liver, kidneys and thyroids, ↑ follicular cell hypertrophy, ↑ colloid alteration Conclusion: Based on the study findings, which demonstrated increased hepatic enzyme activity and increased thyroid hormone concentrations, pyraziflumid affects liver and thyroid via the hepatic enzyme induction in rats.
Mechanistic oral (dietary) study in the rat (effect on hepatocellular proliferation and liver enzyme activity) Wistar rats (♀) Dosed for 1, 2, or 4 weeks PMRA# 3059431	Supplemental – non-guideline NOAEL and LOAEL not established ≥ ~70 mg/kg bw/day: ↑ liver wt, ↑ hepatocellular hypertrophy, ↑ hepatocellular vacuolation, ↑ P-450, ↑ EROD, ↑ PROD ~140 mg/kg bw/day: ↓ bw, ↓fc, ↑ rel liver wt, ↑ liver wt, dark abnormal liver colour, ↑ hepatocellular hypertrophy, ↑ hepatocellular vacuolation, ↑ microsomal protein Conclusion: Pyraziflumid exposure results in liver weight increase and hepatic enzyme induction in female rats.
Metabolite Study (pyraziflumid-amine)	
Micronucleus test Slc/ICR mice PMRA# 3059409	Negative No mortality or clinical signs of toxicity Tested up to a limit dose

Table 4 Toxicity profile of parade fungicide containing pyraziflumid

Study type/Animal/PMRA#	Study results
Acute oral Wistar rats PMRA# 3071040	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity Low acute toxicity
Acute dermal Sprague-Dawley rats PMRA# 3071041	LD_{50} > 2000 mg/kg bw (♂/♀) No clinical signs of toxicity Low acute toxicity
Acute inhalation Sprague-Dawley rats PMRA# 3071042	LC_{50} > 5.31 mg/L (♂/♀) Clinical signs at 5.31 mg/L included irregular respiration Low acute toxicity
Eye irritation Japanese White rabbits PMRA# 3071043	MAS = 0/110 MIS = 0/110 (no reaction) Non-irritating
Eye irritation NZW rabbits PMRA# 3071044	MAS = 0/110 MIS = 3.33/110 at 1 hour Non-irritating
Dermal irritation Japanese White rabbits PMRA# 3071045	MAS = 0/8 MIS = 0/8 (no reaction) Non-irritating
Dermal sensitization (Buehler test) Hartley guinea pigs PMRA# 3071046	Positive Potential dermal sensitizer

Table 5 Toxicology reference values for use in the human health risk assessment for pyraziflumid

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or Target MOE
Acute dietary general population	Acute neurotoxicity study in rats	LOAEL = 500 mg/kg bw Decreased motor activity in females	300
ARfD = 1.7 mg/kg bw			
Repeated dietary	2-year dietary chronic toxicity/carcinogenicity study in rats	NOAEL = 2.2 mg/kg bw/day Increased incidence of hepatocellular vacuolation in males and increased thyroid follicular cell hypertrophy in females	100

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or Target MOE
ADI = 0.02 mg/kg bw/day			
Short- and intermediate-term dermal[2]	Developmental toxicity study in rabbits	NOAEL = 30 mg/kg bw/day Increased incidence of abortions	300
Short- and intermediate-term inhalation[3]	2-generation reproductive toxicity study in rats	Parental NOAEL = 5.6 mg/kg bw/day Increased incidence of hepatocellular hypertrophy in males and females and increased incidence of liver fatty degeneration in males	100
Aggregate short- and intermediate-term (oral, dermal) (all populations)	Oral: 2-year dietary chronic toxicity/carcinogenicity study in rats Dermal: 90-day dermal study in rats	Common endpoint: hepatotoxicity Decreased total bilirubin, increased gamma-glutamyl transpeptidase, increased incidence of hepatocellular vacuolation Oral NOAEL 2.2 mg/kg bw/day Dermal NOAEL = 200 mg/kg bw/day	100
Cancer	Evidence of thyroid tumours in male rats and an equivocal increase in lung adenomas in male mice. Cancer risk (threshold) was addressed through the selected toxicology reference values.		

[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 and residential assessments.
[2] Since an oral NOAEL was selected, a dermal absorption factor of 100% (default value) was used in a route-to-route extrapolation.
[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 6 AHETF unit exposure estimates for mixer/loaders and applicators handling parade fungicide (µg/kg a.i. handled)

Exposure scenario & PPE[1]		Dermal[2]	Inhalation[3]
Mixer/loader AHETF estimates			
A	Open mixing/loading a liquid (SL + CR gloves)	58.5	0.63
Applicator AHETF estimates			
B	Open-cab airblast application (SL + CR gloves)	3 769.3	9.08
Mixer/loader + applicator AHETF estimates			
A+B	Open mixing/loading + open-cab airblast (SL + CR gloves for M/L/A)	3 827.8	9.71

[1] SL: single layer of clothing; CR: chemical-resistant; M/L/A: mixer/loader/applicator
[2] No dermal absorption factor (i.e., 100% default); no MEA adjustment of the AHETF unit exposure values.
[3] Light inhalation rate

Table 7 Mixer/Loader/Applicator exposure and risk assessment for chemical handlers of parade fungicide

Exposure scenario and PPE[1]		ATPD[2] (ha/day)	App. rate (kg a.i./ ha)	Exposure route	Unit exposure[3] (µg/kg a.i. handled)	Daily exposure[4] (mg/kg bw/day)	MOE[5]
A+B	Open mixing/loading + open-cab airblast (SL + CR gloves for M/L/A)	20	0.075	Dermal	3 827.8	0.071771	4.18×10^2
				Inhalation	9.71	0.000182	3.30×10^4

[1] SL: single layer of clothing; CR: chemical-resistant; M/L/A: mixer/loader/applicator
[2] Default Area Treated per Day (ATPD) tables (updated 2017-09-20)
[3] Unit exposure estimates are based on AHETF (see Table 6).
[4] Daily exposure = (Total unit exposure × ATPD × Rate) / (80 kg bw × 1000 µg/mg)
[5] Margin of exposure (MOE) = NOAEL/Daily exposure; based on a dermal NOAEL of 30 mg/kg bw/day with a target MOE of 300 and an inhalation NOAEL of 6 mg/kg bw/day with a target MOE of 100 (see Table 5).

Table 8 Summary of dislodgeable foliar residue (DFR) values for combined residues of pyraziflumid and metabolite BC-01 from three trial sites

Location	New York	Michigan	Washington
Actual Peak DFR	**0.1512 µg/cm^2** on Day 0 after the 3rd application	**0.1187 µg/cm^2** on Day 0 after the 3rd application	**0.1433 µg/cm^2** on Day 0 after the 1st application
% DFR on Day 0 based on the rates of each application	App 1: 15.8% App 2: 13.9% **App 3: 18.2%**	App 1: 12.4% App 2: 14.0% **App 3: 16.0%**	**App 1: 19.3%** App 2: 11.0% App 3: 17.8%
Equation of the linear regression	y = -0.0641x – 1.6491	y = -0.0770x – 1.8349	y = -0.0472x – 1.8138
Coefficient of Determination (R^2)	0.9582	0.9205	0.9167
Correlation coefficient (R)	- 0.9789	- 0.9594	- 0.9574
Slope	-0.0641	-0.0770	-0.0472
% dissipation per day[1]	6.2%	7.4%	4.6%
Half-life[2]	10.8 days	9.0 days	14.7 days

[1] % dissipation per day = $(1 - e^{slope}) \times 100$
[2] Half-life = - LN 2 ÷ slope

Table 9 Occupational postapplication exposure and risk estimate for pyraziflumid on day 0 after the last application

Crop (Max. rate; No. of App.; RTI[1])	**Peak DFR[2] ($\mu g/cm^2$)**	**Postapplication activity**	**Transfer coefficient[3] (cm^2/hr)**	**Dermal exposure[4] (mg/kg bw/day)**	**MOE[5]**	**REI[6]**
Apples (75 g a.i./ha; 3 app./season; 7-day RTI)	0.3235	Hand thinning fruit	3000	0.0971	3.09×10^2	12 hours
		Hand harvesting	1400	0.0453	6.62×10^2	
		Scouting, hand pruning, training	580	0.0188	1.60×10^3	
		Hand weeding, propping, orchard maintenance	100	0.0032	9.27×10^3	

[1] RTI: Retreatment interval
[2] Calculated using the chemical- and crop-specific DFR values of 19.3% of the application rate dislodgeable on the day of the last application (Day 0) and 4.6% dissipation per day.
[3] Transfer coefficients (TCs) obtained from the ARTF Transfer Coefficients Table (last updated: 02-24-2021).
[4] Dermal Exposure = (Peak DFR [$\mu g/cm^2$] × TC [cm^2/hr] × 8 hours × 100% dermal absorption) / (80 kg bw × 1000 µg/mg)
[5] MOE = NOAEL / Dermal Exposure; based on a dermal NOAEL of 30 mg/kg bw/day and a target MOE of 300 (Table 5).
[6] REI: Restricted-entry interval; minimum REI is 12 hours to allow residues to dry, suspended particles to settle and vapours to dissipate.

Table 10 Residential postapplication exposure and risk estimates for pyraziflumid on day 0 after the last application

Crop (Max. Rate; No. of App.; RTI[1])	**Life stage**	**Postapplication activities**	**Peak DFR[2] ($\mu g/cm^2$)**	**Transfer coefficient[3] (cm^2/hr)**	**Dermal exposure[4] (mg/kg bw/day)**	**MOE[5]**	**REI[6]**
Apples (75 g a.i./ha; 3/season; 7-day RTI)	Adults (16+ yrs)	Hand harvesting, pruning and/or other related activities	0.3235	1700	6.88×10^{-3}	4.36×10^3	Until sprays have dried
	Children (6 < 11 yrs)			930	4.70×10^{-3}	4.25×10^4	

[1] RTI = Retreatment interval
[2] Calculated using the chemical- and crop-specific values of 19.3% dislodgeable on the day of the last application (Day 0) and 4.6% dissipation per day.
[3] Transfer coefficients (TCs) obtained from the PMRA memo entitled 'Review of USEPA Residential SOPS (2012) Section 4: Gardens and Trees" (6 Sept. 2019) and the 2012 USEPA SOP for Residential Pesticide Exposure Assessment (PMRA# 2409268).
[4] Dermal exposure = (Peak DFR [$\mu g/cm^2$] × TC [cm^2/hr] × Exposure duration [1 hour for adults; 0.5 hour for children] × 100% dermal absorption for adults only) / (Body weight [80 kg for adults; 32 kg for children] × 1000 µg/mg)
[5] MOE = NOAEL / Dermal Exposure; based on a dermal NOAEL of 30 mg/kg bw/day with a target MOE of 300 for adults and a dermal NOAEL of 200 mg/kg bw/day with a target MOE of 100 for children (Table 5).
[6] REI: Restricted-entry interval

Table 11 Residential postapplication exposure and risk estimates for pyraziflumid on day 0 after the last application – exposure values used in the aggregate risk assessment

Crop (Max. Rate; No. of App.; RTI[1])	Life Stage	Postapplication Activities	Peak DFR[2] (µg/cm^2)	Transfer Coefficient[3] (cm^2/hr)	Dermal Exposure[4] (mg/kg bw/day)	MOE[5]	REI[6]
Apples (75 g a.i./ha; 3/season; 7-day RTI)	Adults (16+ yrs)	Hand harvesting, pruning and/or other related activities	0.3235	1700	6.88×10^{-3}	2.91×10^4	Until sprays have dried
	Children (6 < 11 yrs)			930	4.70×10^{-3}	4.25×10^4	

[1] RTI = Retreatment interval
[2] Calculated using the chemical- and crop-specific values of 19.3% dislodgeable on the day of the last application (Day 0) and 4.6% dissipation per day.
[3] Transfer coefficients (TCs) obtained from the PMRA memo entitled 'Review of USEPA Residential SOPS (2012) Section 4: Gardens and Trees" (6 Sept. 2019) and the 2012 USEPA SOP for Residential Pesticide Exposure Assessment (PMRA# 2409268).
[4] Dermal exposure = (Peak DFR [µg/cm^2] × TC [cm^2/hr] × Exposure duration [1 hour for adults; 0.5 hour for children]) / (Body weight [80 kg for adults; 32 kg for children] × 1000 µg/mg)
[5] MOE = NOAEL / Dermal Exposure; based on a dermal NOAEL of 200 mg/kg bw/day and a target MOE of 100 for both adults and children (Table 5).
[6] REI: Restricted-entry interval

Table 12 Residential postapplication aggregate exposure and risk estimates for pyraziflumid

Crop	Life Stage	Exposure Source	Exposure [1,2] (mg/kg bw/day)	Calculated MOEs[3]	Aggregate MOE[4]
Apples	Adult (16+ yrs)	Oral	3.97×10^{-3}	5.04×10^2	495
		Dermal	6.88×10^{-3}	2.91×10^4	
	Children (6<11 yrs)	Oral	4.40×10^{-3}	4.55×10^2	450
		Dermal	4.70×10^{-3}	4.25×10^4	

[1] Dermal exposure values from Table 11.
[2] Oral exposure values from the chronic dietary exposure assessment (PMRA# 3212501).
[3] MOE = NOAEL ÷ Exposure; based on a dermal NOAEL of 200 mg/kg bw/day and a chronic dietary NOAEL of 2.0 mg/kg for both adults and children (Table 5).
[4] Aggregate (total) margin of exposure = $MOE_{Aggregate} = 1/(1/MOE_{Oral} + 1/MOE_{Dermal})$; the target MOE is 100 (Table 5).

Table 13 Major fate inputs for the modelling

Fate parameter	Drinking and ecological modelling	Comment
K_{oc} (L/kg)	635.1	20th percentile of 5 values
Water half-life (d)*	1654	Longer of 2 values at 20°C
Sediment half-life (d)**	2040	Longer of 2 values at 20°C
Photolysis half-life (d)	282	Single value
Hydrolysis half-life (d)	Stable	Single value at pH 7
Soil half-life (d)	1948	90th percentile upper confidence on the mean of 4 values at 20°C

*Aerobic aquatic whole system
** Anaerobic aquatic whole system

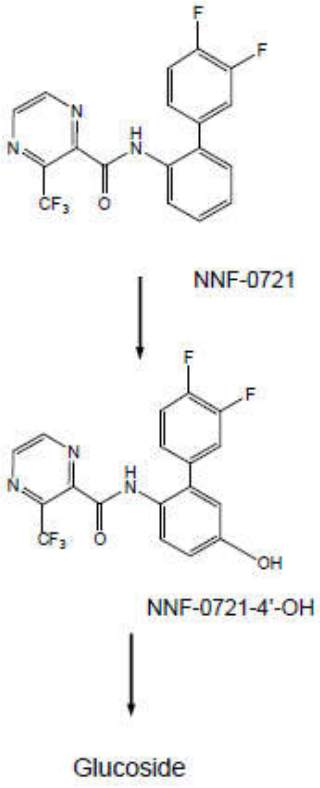
Table 14 Integrated food residue chemistry summary

Nature of the residue in lettuce			**PMRA# 3059438**
Radiolabel Position	[aniline-U-^{14}C]pyraziflumid (specific activity: 5.73 MBq/mg) and [pyrazinyl-5(6)-^{14}C]pyraziflumid (specific activity: 5.70 MBq/mg)		
Treatment			
Test Site	In individual pots in greenhouse		
Treatment	Postemergence foliar treatment made three times with a 7-day RTI, starting with immature plants and ending with mature lettuce heads.		
Total Rate	[aniline-U-^{14}C]pyraziflumid: 3 × ~330 g a.i./ha; Total actual rate of 978 g a.i./ha [pyrazinyl-5(6)-^{14}C]pyraziflumid: 3 × ~330 g a.i./ha; Total actual rate of 982 g a.i./ha		
Formulation	Suspension concentrate (SC; guarantee: 20%)		
Harvest	Samples of head and outer leaves were harvested at 0- and 7-day PHIs, and mature head and outer leaves, stems, and roots were harvested at a 14-day PHI.		
Extraction solvents	Sequential extractions of samples (rinsed once with ACN) were conducted as follows: 1 × ACN:water (4:1, v/v), ACN:0.1 N HCl (4:1, v/v), and ACN:1 N HCl (4:1, v/v).		
Lettuce matrices	**PHI (days)**	**Residues (ppm [^{14}C]pyraziflumid equivalents)**	
		Pyrazinyl 5(6)-^{14}C-label	**Aniline-U-^{14}C-label**
Heads	0	2.24	2.64
	7	0.57	1.23
	14	0.71	0.71
Outer leaves	0	33.42	41.59
	7	32.05	35.18
	14	29.04	43.11
Stems	14	2.90	4.05
Roots		23.00	26.32
Nature of the residue in tomato (cherry)			**PMRA # 3059436**
Radiolabel Position	[aniline-U-^{14}C]pyraziflumid (specific activity: 5.73 MBq/mg) and [pyrazinyl-5(6)-^{14}C]pyraziflumid (specific activity: 5.70 MBq/mg)		
Treatment			
Test Site	In individual pots in greenhouse		
Treatment	Postemergence foliar treatment (×3) beginning when plants bore immature fruit, at 7-day intervals. The last application was made to plants with mature fruit.		
Total Rate	[aniline-U-^{14}C]pyraziflumid: 3 × ~300 g a.i./ha; Total rate of ~900 g a.i./ha [pyrazinyl-5(6)-^{14}C]pyraziflumid: 3 × ~300 g a.i./ha; Total rate of ~900 g a.i./ha		
Formulation	Suspension concentrate (SC; guarantee: 20%)		
Harvest	Samples of fruit and leaves were obtained at 0-, 1-, and 7-day PHIs. Mature fruit, leaves, stems, and new leaves (pyrazinyl-5(6)-^{14}C-label only), and roots were obtained at a 14-day PHI.		
Extraction solvents	Sequential extractions of samples (rinsed once with ACN) were conducted as follows: 3 × ACN:water (4:1, v/v), and 3 × ACN:0.1 N HCl (4:1, v/v).		
Cherry tomato matrices	**PHI**	**Residues (ppm [^{14}C]pyraziflumid equivalents)**	

	(days)	Pyrazinyl 5(6)-^{14}C-label	Aniline-U-^{14}C-label
Fruit	0	1.39	1.50
	1	0.98	2.03
	7	1.08	1.02
	14	1.00	0.91
Leaves	0	21.02	22.13
	1	20.22	29.41
	7	16.69	22.24
	14	11.28	14.25
Stems	14	1.07	6.05
New leaves		0.09	Not collected
Roots		0.03	Not determined
Nature of the residue in paddy rice			**PMRA # 3059437**
Radiolabel Position	[aniline-U-^{14}C]pyraziflumid (specific activity: 5.73 MBq/mg) and [pyrazinyl-5(6)-^{14}C]pyraziflumid (specific activity: 5.70 MBq/mg)		
Treatment			
Test Site	In individual pots in greenhouse		
Treatment	Postemergence foliar treatment at BBCH 53-57, BBCH 57-59, and BBCH 73-77 (at intervals of 7 days). It is noted that although it was flooded, care was taken to ensure that radioactivity did not reach the soil surface by placing a paper cover to the base of each plant.		
Total Rate	[aniline-U-^{14}C]pyraziflumid: 3 × ~100 g a.i./ha; Total actual rates of 324-335 g a.i./ha [pyrazinyl-5(6)-^{14}C]pyraziflumid: 3 × ~100 g a.i./ha; Total actual rate of 313-326 g a.i./ha		
Formulation	Suspension concentrate (SC; guarantee: 5%)		
Harvest	Samples of foliage and panicle were taken from immature plants at 0-day PHI. Samples of straw, hulls, grain, and roots were taken from mature plants at a 28-day PHI. This was followed by dehydration in greenhouse for 14 days.		
Extraction solvents	Sequential extractions of samples (rinsed once ACN, except grain) were conducted as follows: 2 × ACN:water (4:4, v/v), ACN:0.1 N HCl (4:1, v/v), ACN:1 N HCl (4:1, v/v), ACN:0.1 N NaOH (4:1, v/v), and ACN:1 N NaOH (4:1, v/v).		
Paddy rice matrices	**PHI (days)**	**Residues (ppm [^{14}C]pyraziflumid equivalents)**	
Foliage	0	**Pyrazinyl 5(6)-^{14}C-label**	**Aniline-U-^{14}C-label**
		2.37	2.08
Panicle		1.97	1.90
Straw	28	4.09	3.09
Hulls		1.86	1.42
Grain		0.03	0.07
Roots		0.01	0.01
Summary of major identified metabolites in plant matrices			
Radiolabel Position		**Aniline-U-^{14}C-label and Pyrazinyl 5(6)-^{14}C-label**	
Metabolites Identified		**Major Metabolites**	

Lettuce Heads	Pyraziflumid
Lettuce Outer Leaves	
Lettuce Stems and Roots	
Tomato Fruit	
Tomato Leaves	
Rice Foliage and Panicle	
Rice Straw	Pyraziflumid and BC-01 glucoside
Rice Hulls and Grain	Pyraziflumid

Proposed metabolic scheme in plants



NNF-0721: Pyraziflumid
NNF-0721-4'-OH: BC-01

Freezer storage stability in plant matrices			**PMRA# 3071051**	
Tested Matrices	**Analyte**	**Tested Intervals (months)**	**Temperature (°C)**	**Category**
Apple, leaf lettuce, and tomato	Pyraziflumid	0, 2, 6, and 12	≤ -10	High-water
Navy bean				High-protein
Potato tuber, rice grain, and rice straw				High-starch
Peanut nutmeat				High-oil
Grape				High-acid

Crop field trials and residue decline on pome fruits	**PMRA# 3071055 (apples and pears)**

Crop field trials were conducted in 2016 in the United States including growing regions representative of Canada. For apples, a total of 16 trials were conducted in growing regions 1 (4 trials), 2 (1 trial), 5 (4 trials), 10 (1 trial), and 11 (6 trials). For pears, a total of 6 trials were conducted in growing regions 1 (1 trial), 10 (2 trials), and 11 (3 trials). An SC formulation containing pyraziflumid was applied three times as foliar broadcast sprays at rates of 79-86 g a.i./ha/application at growth stages BBCH 75-87 for total application rates of 246-257 g a.i./ha. The applications were made at 7-day intervals with the last application occurring approximately 6-7 days before harvest.

Adjuvants were used at all field trial sites. In selected trials, side-by-side tests were conducted with concentrated and dilute spray volumes. Residue decline data show that residues of pyraziflumid decreased in both apples and pears with increasing PHIs. Adequate storage stability data are available on diverse crop types 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)	Analyte	Residue Levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
Apples	246-257	6-7	Pyraziflumid	16	0.035	0.212	0.102	0.105	0.047
Pears	248-251			6	0.077	0.171	0.143	0.134	0.038

n = number of independent trials. LAFT = Lowest Average Field Trial; HAFT = Highest Average Field Trial; SDEV = Standard Deviation

Crop field trials and residue decline on stone fruits — **PMRA# 3071059 (cherries, peaches, and plums)**

Crop field trials were conducted in 2016 in the United States. For cherries, a total of 6 trials were conducted in growing regions 1 (1 trial, tart cherry), 5 (2 trials, tart cherry), 10 (1 trial, sweet cherry), and 11 (2 trials, sweet cherry). For peaches, a total of 9 trials were conducted in growing regions 1 (1 trial), 2 (3 trials), 5 (1 trial), 6 (1 trial), and 10 (3 trials). For plums, a total of 8 trials were conducted in growing regions 5 (2 trials), 10 (5 trials), and 12 (1 trial). An SC formulation containing pyraziflumid was applied three times as foliar broadcast sprays at rates of 108-112 g a.i./ha/application at growth stages BBCH 77-89 for total application rates of 327-335 g a.i./ha. The applications were made at 6 to 8-day intervals with the last application occurring on the day of harvest.

Adjuvants were used in all field trials. In selected trials, side-by-side tests were conducted using concentrated and dilute spray volumes. Residue decline data generally show that residues of pyraziflumid decreased in all three crops with increasing preharvest intervals (PHIs). Adequate storage stability data are available on diverse crop types 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)	Analyte	Residue Levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
Cherries	329-334	0	Pyraziflumid	6	0.329	0.799	0.666	0.597	0.187
Peaches	327-335			9	0.175	0.501	0.314	0.343	0.108
Plums	329-333			8	0.068	0.267	0.137	0.152	0.082

n = number of independent trials. LAFT = Lowest Average Field Trial; HAFT = Highest Average Field Trial; SDEV = Standard Deviation

Crop field trials and residue decline on caneberries	PMRA# 3071057 (raspberries)

Crop field trials were conducted in 2016 in the United States. For raspberries, a total of 6 trials were conducted in growing regions 1 (1 trial), 5 (1 trial), and 12 (4 trials). An SC formulation containing pyraziflumid was applied three times as foliar broadcast sprays at rates of 106-114 g a.i./ha/application at growth stages BBCH 65-89 for total seasonal application rates of 325-336 g a.i./ha. The applications were made at 6 to 7-day intervals with the last application occurring on the day of harvest.

Adjuvants were used in all field trials. In selected trials, side-by-side tests were conducted using concentrated and dilute spray volumes. Residue decline data generally show that residues of pyraziflumid decreased with increasing PHIs. Adequate storage stability data are available on diverse crop types 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)	Analyte	Residue Levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
Raspberries	325-336	0	Pyraziflumid	6	0.617	1.53	0.928	1.06	0.356

n = number of independent trials. LAFT = Lowest Average Field Trial; HAFT = Highest Average Field Trial; SDEV = Standard Deviation

Crop field trials and residue decline on bushberries	PMRA# 3071057 (highbush blueberries)

Crop field trials were conducted in 2016 in the United States. For blueberries, a total of 8 trials were conducted in growing regions 1 (1 trial), 2 (3 trials), 5 (3 trials), and 12 (1 trial). An SC formulation containing pyraziflumid was applied three times as foliar broadcast sprays at rates of 109-114 g a.i./ha/application at growth stages BBCH 65-89 for total seasonal application rates of 327-341 g a.i./ha. The applications were made at 6 to 8-day intervals with the last application occurring on the day of harvest.

Adjuvants were used in all field trials. In selected trials, side-by-side tests were conducted using concentrated and dilute spray volumes. Residue decline data generally show that residues of pyraziflumid decreased with increasing PHIs. Adequate storage stability data are available on diverse crop types 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)	Analyte	Residue Levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
Highbush Blueberries	327-341	0	Pyraziflumid	8	0.806	3.91	1.14	1.57	1.01

n = number of independent trials. LAFT = Lowest Average Field Trial; HAFT = Highest Average Field Trial; SDEV = Standard Deviation

Crop field trials and residue decline on small fruits vine climbing, except fuzzy kiwifruit	PMRA# 3071058 (grapes)

Crop field trials were conducted in 2016 in the United States. For grapes, a total of 12 trials were conducted in growing regions 1 (2 trials), 10 (8 trials), and 11 (2 trials). An SC formulation containing pyraziflumid was applied three times as foliar broadcast sprays at rates of 82-85 g a.i./ha/application at growth stages BBCH 75-89 for total application rates of 247-252 g a.i./ha. The applications were made at 12 to 15-day intervals, with the last application occurring 7 days before harvest.

Adjuvants were used in all field trials. In selected trials, side-by-side tests were conducted using concentrated and dilute spray volumes. Residue decline data generally show that residues of pyraziflumid decreased with increasing PHIs. Adequate storage stability data are available on diverse crop types 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)	Analyte	Residue Levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV

Grapes	247-252	7	Pyraziflumid	12	0.061	0.799	0.272	0.314	0.230

n = number of independent trials. LAFT = Lowest Average Field Trial; HAFT = Highest Average Field Trial; SDEV = Standard Deviation

Crop field trials and residue decline on tree nuts	**PMRA# 3071056 (almonds and pecans)**

Crop field trials were conducted in 2016 in the United States. For almonds, a total of 6 trials were conducted in growing region 10 (6 trials). For pecans, a total of 6 trials were conducted in growing regions 2 (2 trials), 4 (1 trial), 6 (2 trials), and 8 (1 trial). An SC formulation containing pyraziflumid was applied three times as foliar broadcast sprays at rates of 108-112 g a.i./ha/application at growth stages BBCH 77-89 for total application rates of 326-334 g a.i./ha. The applications were made at 6 to 9-day intervals with the last application occurring approximately 6 to 7-days before harvest.

Adjuvants were used in all field trials. In selected trials, side-by-side tests were conducted using concentrated and dilute spray volumes. Residue decline data were inconclusive since residues of pyraziflumid were <0.01 ppm (<LOQ) with increasing PHIs that were greater than 7 days. Adequate storage stability data are available on diverse crop types 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)**	**Analyte**	**Residue Levels (ppm)**					
				n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
Almonds	326-332	7	Pyraziflumid	6	<0.01	0.017	0.010	0.011	0.003
Pecans	328-334	6-7		6	<0.01	0.019	0.010	0.012	0.004

n = number of independent trials. LAFT = Lowest Average Field Trial; HAFT = Highest Average Field Trial; SDEV = Standard Deviation
For computation, values <LOQ are assumed to be at the LOQ.

Processed food and feed – apples, grapes, and plums	**PMRA# 3071055 (apples) PMRA# 3071058 (grapes) PMRA# 3071059 (plums)**

For apples, the processing study was conducted at 1237 g a.i./ha (5.5-fold the maximum seasonal rate). For grapes, the processing study was conducted at 1245 g a.i./ha (fivefold the maximum seasonal rate). For plums, the processing study was conducted at 1649 g a.i./ha (fivefold the maximum seasonal rate). All three processing studies were conducted using an SC formulation of pyraziflumid (220 g a.i./L). Adequate storage stability data are available on diverse crop types to support the storage intervals of the processed commodities. Samples were analyzed using a validated analytical method.

RAC	**Processed Fractions**	**$HAFT_{[RAC]}$ (ppm)**	**Individual Processing Factor of Pyraziflumid**	**Anticipated Residues of Pyraziflumid (ppm)**
Apples	Apple juice	0.212	0.1	0.02
Grapes	Grape juice	0.799	0.1	0.08
Grapes	Raisins	0.799	2.0	1.6 (rounded to 2)
Plums	Prunes	0.267	1.3	0.4

Table 15 Food residue chemistry overview of metabolism studies and risk assessment

Plant studies			
Residue definition for enforcement Primary crops		Pyraziflumid	
Residue definition for risk assessment Primary crops			
Metabolic profile in diverse crops		Similar in lettuce, cherry tomato, and paddy rice.	
Dietary risk from food and drinking water			
Basic acute dietary exposure analysis, 95th percentile **ARfD = 1.7 mg/kg bw** **Estimated acute drinking water concentration = 0.069 ppm**	**Population**	**Estimated risk % of acute reference dose (ARfD)**	
		Food Alone	**Food and Drinking Water**
	All infants <1 year	1.9	2.2
	Children 1–2 years	2.8	3.0
	Children 3–5 years	1.6	1.7
	Children 6–12 years	0.8	0.9
	Youth 13–19 years	0.3	0.4
	Adults 20–49 years	0.4	0.5
	Adults 50+ years	0.5	0.6
	Females 13–49 years	0.4	0.5
	Total population	0.6	0.8
Refined [at the intermediate level] chronic [non-cancer and cancer] dietary exposure analysis **ADI = 0.02 mg/kg bw/day** **Estimated chronic drinking water concentration = 0.069 ppm**	**Population**	**Estimated risk % of acceptable daily intake (ADI)**	
		Food alone	**Food and drinking water**
	All infants <1 year	3.8	29.8
	Children 1–2 years	6.3	15.9
	Children 3–5 years	4.3	12.1
	Children 6–12 years	2.0	7.8
	Youth 13–19 years	0.7	5.6
	Adults 20–49 years	1.0	7.9
	Adults 50+ years	1.4	8.2
	Females 13–49 years	1.1	7.9
	Total population	1.5	8.5

Table 16 Fate and behaviour of pyraziflumid in the environment

Study type	Test material/test system	Value[1]	Transformation products	Comments	References
Abiotic transformation					
Hydrolysis	Pyraziflumid [analine-^{14}C] and [pyrazinyl-^{14}C]-labelled pH 4, 7 and 9 at 50°C	Stable to hydrolysis at pH 4, 7 and 9 at 50°C	**Major:** none **Minor:** NNF-0721-acid (BC-09)	Hydrolysis is not expected to be an important route of dissipation for pyraziflumid in the environment.	Study: PMRA# 3059440
Phototransformation on soil	Pyraziflumid [pyrazinyl-^{14}C], [aniline-^{14}C], and [difluorophenyl-^{14}C]-labelled	Half-life for phototransformation: 250 days (SFO) Half-life equivalent under natural sunlight: 390 days (summer sunlight at 30-50ºN)	**Major:** none **Minor:** NNF-0721-4'-OH (BC-01), NNF-0721-6'-OH (BC-04), and NNF-0721-acid (BC-09) NER and CO_2 < 3% AR	Phototransformation on soil is not expected to be an important route of dissipation for pyraziflumid in the environment.	Study: PMRA# 3059442
Phototransformation in water	Pyraziflumid [analine-^{14}C] and [pyrazinyl-^{14}C]-labelled Phosphate buffered solution at pH 7 and 25ºC	Half-life for phototransformation: 141 days (SFO) Half-life equivalent under natural sunlight: 282 days (considered as double the half-life value from continuous artificial light source)	**Major:** none **Minor:** NNF-0721-amide (BC-10) CO_2 < 1% AR	Phototransformation in water is not expected to be an important route of dissipation for pyraziflumid in the environment; however, there is a potential for phototransformation via indirect photolysis when facilitated by certain photosensitizers. Indirect phototransformation is to be considered qualitatively.	Study: PMRA# 3059443
	Pyraziflumid [pyrazinyl-^{14}C], [aniline-^{14}C], and [difluorophenyl-^{14}C]-labelled 3 Test media: Buffered pure water (PW), buffered pure water containing	In the PWN test media, containing nitrate ion as a photosensitizer, degradation of pyraziflumid was observed; however in SNW, no degradation and no difference in results from those in PW was observed.	**Major:** NNF-0721-amide (BC-10) **Minor:** NNF-0721-acid (BC-09) and 3,4-difluorobenzoic acid CO_2 < 17% AR, unidentified minor phototransformation products were observed at		Study: PMRA# 3059441

Study type	Test material/test system	Value[1]	Transformation products	Comments	References
	nitrate salt (PWN) and simulated natural water containing humic acid (SNW). Buffer was phosphate buffered solution at pH 7 and 25ºC	PWN Half-life for phototransformation: 11.3 days (SFO) PWN Half-life equivalent under natural sunlight: 22.6 days (considered as double the half-life value from continuous artificial light source)	maximum individual concentrations < 6% AR, with total concentrations reaching 34% AR.		
Phototransformation in air	Pyraziflumid is not expected to be volatile under field conditions based on its vapour pressure and Henry's law constant. Transformation products of pyraziflumid are not expected to be volatile under field conditions based on low detection of volatile organics in soil biotransformation studies. A phototransformation study in air is not required.				
Biotransformation					
Biotransformation in aerobic soil	Pyraziflumid [analine-^{14}C] and [pyrazinyl-^{14}C]-labelled 4 soils: North Dakota (ND), Georgia (GA), New York (NY), and California (CA) at 20ºC Study duration: 160-161 days	**ND:** DT_{50} = 573 days, t_R = 673 days (DFOP) **GA:** DT_{50}/t_R = 2399 days (SFO) **NY:** DT_{50}/t_R = 1088 days (SFO) **CA:** DT_{50}/t_R = 1202 days (SFO)	**Major:** none **Minor:** NNF-0721-5-OH (BC-06), NNF-0721-6-OH (BC-07), NNF-0721-acid (BC-09) and CO_2 NER < 12% AR	Pyraziflumid is persistent. Biotransformation in aerobic soil is not an important route of dissipation for pyraziflumid.	Study: PMRA# 3059444
Biotransformation in anaerobic soil	Pyraziflumid [analine-^{14}C] and [pyrazinyl-^{14}C]-labelled 4 soils: North Dakota (ND), Georgia (GA), New York (NY), and California (CA) at 20ºC	**ND:** DT_{50}/t_R = 2009 days (SFO) **GA:** DT_{50}/t_R = 20152 days (SFO) **NY:** DT_{50}/t_R = 1371 days (SFO) **CA:** DT_{50}/t_R = 1330 days (SFO)	**Major:** none **Minor:** NNF-0721-5-OH (BC-06), NNF-0721-acid (BC-09), and CO_2 NER < 12% AR	Pyraziflumid is persistent. Biotransformation in anaerobic soil is not an important route of dissipation for pyraziflumid.	Study: PMRA# 3059445

Study type	Test material/test system	Value[1]	Transformation products	Comments	References
	Study duration: 122 days				
Biotransformation in aerobic water/sediment systems	Pyraziflumid [analine-^{14}C] and [pyrazinyl-^{14}C]-labelled 2 test systems: Goose River and Golden Lake at 20ºC Study duration: 160 days	Goose River: DT_{50}/t_R = 318 days (SFO) Golden Lake: DT_{50}/t_R = 1654 days (SFO) Note: All values are for the whole system	**Major:** none **Minor:** NNF-0721-4'-OH (BC-01), NNF-0721-6'-OH (BC-04), NNF-0721-5-OH (BC-06), NNF-0721-6-OH (BC-07), NNF-0721-acid (BC-09) and CO_2 NER < 20% AR	Pyraziflumid is persistent. Biotransformation in aerobic water/sediment systems is not an important route of dissipation for pyraziflumid.	Study: PMRA# 3059447
	Pyraziflumid, non-radiolabelled 4 test systems: Choptank River, Brandywine Creek, Joe Whaley Pond, and Abbey Lake at 20ºC Study duration: 160 days	Choptank River: DT_{50} and t_R > 10000 days (IORE) Brandywine Creek: DT_{50} = 1094 days, t_R > 10000 days (IORE) Joe Whaley Pond: DT_{50} = 358 days, t_R = 454 days (DFOP) Abbey Lake: DT_{50}/t_R = 452 days (SFO) Note: All values are for the whole system	As non-radiolabelled test substance was used, it was not possible to account for incorporation of non-extractable fragments into the sediment matrix, account for mineralization to CO_2, calculate mass balance, or track transformation products. Results are to be considered qualitatively.		Study: PMRA# 3059446
Biotransformation in anaerobic water/sediment systems	Pyraziflumid [analine-^{14}C] and [pyrazinyl-^{14}C]-labelled	Goose River: DT_{50} = 439 days, t_R = 581 days (DFOP) Golden Lake: DT_{50} = 1786 days,	**Major:** none **Minor:** NNF-0721-4'-OH (BC-01), NNF-0721-6'-OH (BC-04), NNF-0721-5-OH (BC-06), NNF-0721-6-OH	Pyraziflumid is persistent. Biotransformation in anaerobic water/sediment systems is not an important	Study: PMRA# 3059448

Study type	Test material/test system	Value[1]	Transformation products	Comments	References
	2 test systems: Goose River and Golden Lake at 20ºC Study duration: 161 days	t_R = 2040 days (DFOP) Note: All values are for the whole system	(BC-07), NNF-0721-acid (BC-09) and CO_2 NER < 11% AR	route of dissipation for pyraziflumid.	
Mobility					
Adsorption / desorption	Pyraziflumid [pyrazinyl-^{14}C]-labelled Values obtained in 5 German soils	K_{oc} ranging from 585.6 to 976.4	N/A	Pyraziflumid is classified as having a low potential for mobility in soil.	Study: PMRA# 3059449
Volatilization	Pyraziflumid is not expected to be volatile under field conditions based on its vapour pressure and Henry's law constant. Transformation products of pyraziflumid are not expected to be volatile under field conditions based on low detection of volatile organics in volatile traps in the laboratory studies.				
Field studies					
Terrestrial field dissipation	Pyraziflumid 20 SC formulation (20% w/w, 220 g a.i./L) Bare ground and turf grass sites in North Rose, New York Study duration: 812 days	Bare ground: DT_{50}/t_R = 575 days (SFO) Turf grass: DT_{50} = 274 days, t_R = 669 days (DFOP) Residues found in both bare soil and turf plots were mostly confined to the uppermost soil layers of 0-5 and 5-15 cm, and < 3% AR was detected below the 15-cm layer. There were very few detections above the LOQ in the lower soil depths (below 30 cm in turf plot). After 365 days (DAFA), approximately 42 and 31% of	As non-radiolabelled test substance was used, it was not possible to account for incorporation of non-extractable fragments into the soil matrix or to account for mineralization to CO_2. No mass balance could be calculated and transformation products were not tracked.	Pyraziflumid can accumulate in soil and carry over to the next growing season; however, carryover is reduced with vegetation present. At WA site, pyraziflumid was detected in soil depths deeper than 20 inches suggesting leaching potential at vulnerable locations.	Study: PMRA# 3059452

Study type	Test material/test system	Value[1]	Transformation products	Comments	References
		applied parent remained in bare soil and turf, respectively.			
	Pyraziflumid 20 SC formulation (20% w/w, 220 g a.i./L) Bare ground and turf grass sites in Ephrata, Washington Study duration: 818 days	Bare ground: DT_{50}/t_R = 360 days (SFO) Turf grass: DT_{50} = 125 days, t_R = 228 days (IORE) Residues found in both bare soil and turf plots were mostly confined to the uppermost soil layers of 0-5. 5-15 and 15-30 cm, and <11% AR was detected below the 30-cm layer, in both the bare soil plot and turf plot samples in the lower soil depths. After 365 days (DAFA), approximately 36 and 20% of applied parent remained in bare soil and turf, respectively.			Study: PMRA# 3059453
	Pyraziflumid 20 SC formulation (20% w/w, 220 g a.i./L) Bare ground and turf grass sites in Chula, Georgia Study duration: 806 days Note: Georgia does not represent Canadian	Bare ground: DT_{50} = 622 days, t_R = 860 days (DFOP) Turf grass: DT_{50} = 98.4 days, t_R = 250 days (IORE) Residues found in both bare soil and turf plots were mostly confined to the uppermost soil layers of 0-5 and 5-15 cm, and < 4% AR was detected below			Study: PMRA# 3059451

Study type	Test material/test system	Value[1]	Transformation products	Comments	References
	field use conditions; however, these results support the laboratory findings and demonstrate the potential persistence of pyraziflumid under field conditions.	the 15-cm layer. There were no detections above the LOQ in the lower soil depths (below 30 cm). After 365 days (DAFA), approximately 39 and 14% of applied parent remained in bare soil and turf, respectively.			
	Pyraziflumid 20 SC formulation (20% w/w, 220 g a.i./L) Bare ground and turf grass sites in Porterville, California Study duration: 822 days Note: California does not represent Canadian field use conditions; however, these results support the laboratory findings and demonstrate the potential persistence of pyraziflumid under field conditions.	Bare ground: DT_{50} = 250 days, t_R = 420 days (DFOP) Turf grass: DT_{50} = 30.2 days, t_R = 96.6 days (IORE) Residues found in both bare soil and turf plots were mostly confined to the uppermost soil layers of 0-5 and 5-15 cm, and < 5% AR was detected below the 15-cm layer. There were no detections above the LOQ in the lower soil depths in bare soil plots (below 30 cm). However, low levels were detected in the turf plots at depths below 30 cm. After 365 and 269 days (DAFA), approximately 37 and 10% of applied parent remained in bare soil and turf, respectively.			Study: PMRA# 3059450
Aquatic field dissipation	No aquatic field dissipation study with pyraziflumid was submitted and none is required.				

Study type	Test material/test system	Value[1]	Transformation products	Comments	References
Bioconcentration / bioaccumulation					
Bioconcentration in fish	Pyraziflumid Flow-through bioconcentration study Bluegill sunfish (*Lepomis macrochirus*) were exposed to [pyrazinyl-^{14}C]-labelled pyraziflumid at nominal concentrations of 1.5 and 15 µg/L for an uptake period of 21 days, followed by a depuration period of 14 days.	BCF_K parent = 50 and 41 $L \cdot Kg^{-1}$ BCF_K TRR = 77 and 64 $L \cdot Kg^{-1}$ (kinetic bioconcentration factor for whole fish, low does and high dose, respectively) BCF_{SS} parent = 62 and 54 $L \cdot Kg^{-1}$ BCF_{SS} TRR = 107 and 88 $L \cdot Kg^{-1}$ (steady-state bioconcentration factor for whole fish, low dose and high dose, respectively)	NNF-0721-4'-OH (BC-01)	Pyraziflumid does not readily bioconcentrate in fish tissue under the conditions of the study.	Study: PMRA# 3059471

[1] DT_{50} values for each fit are the times the fitted curve reaches 50% of the fitted initial concentration. These values are used for descriptive characterization and persistence classification for soil (Goring et al., 1975) and natural waters (McEwen and Stephenson, 1979). The representative half-life (t_R) is the half-life of an exponential curve that is considered to be a conservative approximation of the measured concentration decline, and is used for exposure estimation and modelling. The DT_{50} and t_R are the same if the SFO (single first-order) model is deemed acceptable.
The t_R value from DFOP (double first-order in parallel) rate model is a half-life determined from the slow degradation rate from the DFOP model. The t_R value from IORE (indeterminate order rate equation) model is the half-life of an exponential curve passing through the DT_{90} of the IORE model fit.
NER – Non-extractable Residues
AR – Applied Radioactivity

Table 17 Estimated environmental concentrations/Exposures for screening level assessment

Environmental exposure matrix	Application	Conversion considerations	Estimated environmental exposure (EEC[1]/EDE[2]/ ED[3])	Notes
Soil	3 × 75 g a.i./ha, 7-day interval	Aerobic soil half-life: 1948 days (90% of upper confidence bound on the mean)	Soil surface EEC: 224.4 g a.i./ha	Used for terrestrial plant seedling emergence risk assessment
			Soil EEC: 0.1 mg a.i./kg soil (assuming homogeneous mixing in 0-15 cm depth with a soil bulk density of 1.5 g/cm^3)	Used for soil invertebrates risk assessment
Plant	3 × 75 g a.i./ha, 7-day interval	Foliar half-life: 10 days	EEC: 149.6 g a.i./ha	Used for the terrestrial plant vegetative vigour and foliar dwelling beneficial arthropods risk assessment.
Spray droplets on surface of bees	1 × 75 g a.i./ha,	2.4 µg a.i./bee/day per kg a.i./ha	ED: 0.18 µg a.i./bee	Used for assessing adult bees contact exposure
Food source: pollen and nectar	1 × 75 g a.i./ha	28.6 µg a.i./bee/day per kg a.i./ha	ED: 2.15 µg a.i./bee/day	Used for assessing adult bees oral exposure
Food source: pollen and nectar	1 × 75 g a.i./ha	12 µg a.i./bee/day per kg a.i./ha	ED: 0.91 µg a.i./bee/day	Used for assessing larvae oral exposure
Food source: insects	3 × 75 g a.i./ha, 7-day interval	Foliar half-life: 10, FIR = 5.1 g dw diet/day	EDE: 12.2 mg a.i./kg bw/day	Used for small insectivorous bird (bw 20 g) risk assessment
Food source: insects	3 × 75 g a.i./ha, 7-day interval	Foliar half-life: 10, FIR = 19.9 g dw diet/day	EDE: 9.5 mg a.i./kg bw/day	Used for medium insectivorous bird (bw 100 g) risk assessment
Food source: short grass	3 × 75 g a.i./ha, 7-day interval	Foliar half-life: 10, FIR = 58.1 g dw diet/day	EDE: 6.1 mg a.i./kg bw/day	Used for large herbivorous bird (bw 1000 g) risk assessment
Food source: insects	3 × 75 g a.i./ha, 7-day interval	Foliar half-life: 10, FIR = 2.2 g dw diet/day	EDE: 7.0 mg a.i./kg bw/day	Used for small insectivorous mammal (bw 15 g) risk assessment
Food source: short grass	3 × 75 g a.i./ha, 7-day interval	Foliar half-life: 10, FIR = 4.5 g dw diet/day	EDE: 13.6 mg a.i./kg bw/day	Used for medium herbivorous mammal (bw 35 g) risk assessment
Food source: short grass	3 × 75 g a.i./ha, 7-day interval	Foliar half-life: 10, FIR = 68.7 g dw diet/day	EDE: 7.3 mg a.i./kg bw/day	Used for large herbivorous mammal (bw 1000 g) risk assessment
Fresh water	3 × 75 g a.i./ha,	Aerobic water/sediment	EEC (0-15 cm depth): 0.15 mg a.i./L	Used for amphibian risk assessment

Environmental exposure matrix	Application	Conversion considerations	Estimated environmental exposure (EEC[1]/EDE[2]/ ED[3])	Notes
	7-day interval	whole system half-life: 1654 days, assumeing instantaneous and homogeneous mixing in the specified depth	EEC (0-80 cm depth): 0.028 mg a.i./L	Used for all aquatic organism risk assessment
Estuary/marine water	3 × 75 g a.i./ha, 7-day interval	Aerobic water/sediment whole system half-life: 1654 days, assuming instantaneous and homogeneous mixing in 0-80 cm depth	EEC (0-80 cm depth): 0.028 mg a.i./L	Used for estuary/marine organism screening level risk assessment
	1 × 75 g a.i./ha	Assuming instantaneous and homogeneous mixing in 0-80 cm depth	EEC (0-80 cm depth): 0.009 mg a.i./L	Used for estuary/marine organism refined risk assessment

[1] EEC = Estimated environmental concentration (mg a.i./kg or mg a.i./L) in soil or water

[2] EDE = Estimated Daily Exposure (mg a.i./kg bw/day) for birds and mammals, specialized feeding guilds are considered for each category of animal weight to help determine exposure (herbivore, frugivore, insectivore and granivore). At the screening level, relevant food items representing the most conservative EDE for each feeding guild are used (in other words, insects and small grasses). The EDE is calculated using the following formula: (FIR/bw) × EEC, where: bw = body weight, FIR = Food ingestion rate: 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: FIR (g dry weight/day) = $0.398(\text{bw in g})^{0.850}$. All birds Equation: FIR (g dry weight/day) = $0.648(\text{bw in g})^{0.651}$. For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{bw in g})^{0.822}$

[3] ED = Estimated dose (µg a.i./bee) for bees, calculated by converting the maximum single application rate (75 g a.i./ha) by the conversion factor listed in the table.

Table 18 Toxicity of pyraziflumid to non-target organisms

Organism	Exposure	Test substance	Endpoint value[1]	Degree of toxicity[2]	PMRA#
Terrestrial species					
Earthworm, *Eisenia fetida*	56-d Chronic	Pyraziflumid (technical grade active ingredient, purity 94.8%)	NOAEC = **10.4** mg a.i./kg dw soil LOAEC = 18.8 mg a.i./kg dw soil For most sensitive endpoint of number of juveniles (reproduction). There were no statistically significant effects on survival or body weight at any of the treatment levels tested.	N/A	Study: PMRA# 3059455
Honey bee, *Apis mellifera*	48-h Oral, adults	Pyraziflumid (technical grade active ingredient, purity 94.8%)	LD_{50} > **80** µg a.i./bee	Practically non-toxic	Study: PMRA# 3059459
	48-h Contact, adults		LD_{50} > **100** µg a.i./bee	Practically non-toxic	
	72-h Oral, larva	Pyraziflumid (technical grade active ingredient, purity 94.8%)	LD_{50} > **110** µg a.i./larva Maximum mortality was 33% in the highest test level.	N/A	Study: PMRA# 3059458
	10-d Chronic, adults	End-use product, Pyraziflumid 20SC (20.1% a.i.)	LC_{50} > 4100 µg a.i./g diet NOAEC = 2100 µg a.i./g diet LOAEC = 4100 µg a.i./g diet LD_{50} > **78** µg a.i./bee/day LOAEL = 78 µg a.i./bee/day NOAEL = **55** µg a.i./bee/day For most sensitive endpoints of food consumption and weight.	N/A	Study: PMRA# 3059456
	22-d Chronic, larva	Pyraziflumid (technical grade active ingredient, purity 94.8%)	8d-LD_{50} = **2.71** µg a.i./larva/day (95% CL: 1.38-8.72%) 22d-NOAEL = **0.85** µg a.i./larva/day 8d LD_{50} for acute larval mortality;	N/A	Study: PMRA# 3059457

Organism	Exposure	Test substance	Endpoint value[1]	Degree of toxicity[2]	PMRA#
			22d-NOAEL for adult emergence		
Predatory arthropod (mite), *Typhlodromus pyri*	14-d Contact, glass plates	End-use product, Pyraziflumid 20SC (20.7% a.i.)	LR_{50} and ER_{50} **> 450** g a.i./ha LOAER = 150 g a.i./ha NOAER = 50 g a.i/ha For most sensitive endpoint of offspring/female (reproduction). There were no statistically significant effects on survival or escaping rate for any of the treatment levels tested.	N/A	Study: PMRA# 3072324
Parasitic arthropod (wasp), *Aphidius rhopalosiphi*	14-d Contact, glass plates	End-use product, Pyraziflumid 20SC (20.7% a.i.)	LR_{50} and ER_{50} **> 450** g a.i./ha NOAER = 450 g a.i/ha There were no statistically significant effects on survival or reproduction at any of the treatment levels tested.	N/A	Study: PMRA# 3059498
Bobwhite quail, *Colinus virginianus*	Acute Oral	Pyraziflumid (technical grade active ingredient, purity 96.8%)	LD_{50} > 2000 mg a.i./kg bw No treatment-related effects at highest dose tested.	Practically non-toxic	Study: PMRA# 3059472
	5-d Dietary	Pyraziflumid (technical grade active ingredient, purity 94.8%)	LC_{50} > 5000 mg a.i./kg diet LD_{50} > 820 mg a.i./kg bw/day No treatment-related effects at highest concentration tested.	Practically non-toxic	Study: PMRA# 3059474
	21-wk Reproduction	Pyraziflumid (technical grade active ingredient, purity 94.8%)	NOAEC < 412 mg a.i./kg diet NOAEL < 34.4 mg a.i./kg bw/day LOAEC = 412 mg a.i./kg diet LOAEC = 34.4 mg a.i./kg bw/day NOAEC/NOAEL is based on effects on most sensitive reproductive endpoints	N/A	Study: PMRA# 3059478

Organism	Exposure	Test substance	Endpoint value[1]	Degree of toxicity[2]	PMRA#
			(3% reduction in no. of hatchlings/eggs set and no. of hatchlings/live embryos) at the lowest treatment level.		
Mallard duck, *Anas platyrhynchos*	5-d Dietary	Pyraziflumid (technical grade active ingredient, purity 94.8%)	LC_{50} > 4805 mg a.i./kg diet LD_{50} > 1008 mg a.i./kg bw/day No mortality was observed; however, there were treatment-related effects on weight.	Practically non-toxic	Study: PMRA# 3059475
	22-wk Reproduction	Pyraziflumid (technical grade active ingredient, purity 94.8%)	NOAEC < 195 mg a.i./kg diet NOAEL **< 19.1** mg a.i./kg bw/day LOAEC = 195 mg a.i./kg diet LOAEC = 19.1 mg a.i./kg bw/day NOAEC/NOAEL is based on effects on no. of hatchlings per live embryos, 14-day survivors per eggs set, hatchling weight, 14-day survivor weight, and hatchlings per eggs at the lowest treatment level.	N/A	Study: PMRA# 3059479
Zebra finch, *Taeniopygia guttata*	5-d Dietary	Pyraziflumid (technical grade active ingredient, purity 94.8%)	LC_{50} = 3158 mg a.i./kg diet LD_{50} = **377** mg a.i./kg bw/day Treatment-related effects were observed at all concentrations, with mortality in the two highest treatment groups.	Slightly toxic	Study: PMRA# 3059477
Rat (Wistar)	Acute oral	Pyraziflumid (technical grade active ingredient, purity 94.8%)	LD_{50} **> 2000** mg a.i./kg bw No clinical signs of toxicity at highest tested dose.	Practically non-toxic	Study: PMRA# 3059378
		End-use product,	LD_{50} > 2000 mg/kg bw (> 402 mg a.i./kg bw)	Practically non-toxic	Study:

Organism	Exposure	Test substance	Endpoint value[1]	Degree of toxicity[2]	PMRA#
		Pyraziflumid 20SC (20.1% a.i.)	No clinical signs of toxicity at highest tested dose.		PMRA# 3071040
	2-Generation Reproduction	Pyraziflumid (technical grade active ingredient, purity 94.8%)	NOAEC = 300 mg a.i./kg diet NOAEL = **16.6** mg a.i./kg bw/day Based on toxicity in the F0, F1 and F2 rats (various endpoints) observed at the next higher dose.	N/A	Study: PMRA# 3059398
Monocot and dicot crop species (oat, onion, ryegrass, corn, bean, cabbage, cucumber, radish, soybean, and tomato)	14-d Seedling emergence	End-use product, Pyraziflumid 20SC (20.1% a.i.)	NOAEC = 118.5 g a.i./ha EC_{25} **> 118.5** g a.i./ha There were no significant inhibitions for any of the tested endpoints in any species.	N/A	Study: PMRA# 3059486
Monocot and dicot crop species (oat, onion, ryegrass, corn, bean, cabbage, cucumber, radish, soybean, and tomato)	21-d Vegetative vigour	End-use product, Pyraziflumid 20SC (20.1% a.i.)	NOAEC = 9.3 g a.i./ha (for the most sensitive endpoint, tomato dry weight) EC_{25} **> 150** g a.i./ha (for all tested species, including tomato) Potential solvent (non-ionic surfactant) effects noted.	N/A	Study: PMRA# 3059485
Freshwater species					
Daphnia magna	48-h Acute, static-renewal	Pyraziflumid (technical grade active ingredient, purity 94.8%)	LC_{50} **> 3.8** mg a.i./L (immobilization) Not toxic up to the limit of solubility under the conditions of the test.	N/A	Study: PMRA# 3059460
	48-h Acute, static	End-use product, Pyraziflumid 20SC (20.1% a.i.)	LC_{50} = 35.7 mg a.i./L (immobilization) Due to the lack of analytical verification of test concentrations and dose-response relationship, the endpoint is not reliable and will only be used qualitatively.	Slightly toxic	Study: PMRA# 3059497

Organism	Exposure	Test substance	Endpoint value[1]	Degree of toxicity[2]	PMRA#
	21-d Chronic, flow-through	Pyraziflumid (technical grade active ingredient, purity 94.8%)	NOAEC = **0.09** mg a.i./L LOAEC = 0.21 mg a.i./L For the most sensitive endpoint of number of live offspring. Potential solvent (DMF) effects noted.	N/A	Study: PMRA# 3059461
Amphipod, *Hyalella azteca*	10-d Acute, spiked sediment, intermittent flow-through	Pyraziflumid (technical grade active ingredient, purity 94.8%)	Pore water: LC_{50} **> 3.0** mg a.i./L NOAEC = 3.0 mg a.i./L Overlying water: LC_{50} > 0.37 mg a.i./L NOAEC = 0.37 mg a.i./L Endpoints based on lack of treatment-related effects on survival at highest tested concentration. Significant effects on dry weight were noted at all test concentrations.	N/A	Study: PMRA# 3059495
	42-d Chronic, spiked sediment, static-renewal	Pyraziflumid (technical grade active ingredient, purity 94.8%)	Pore water: NOAEC = **0.35** mg a.i./L LOAEC > 0.35 mg a.i./L Overlying water: NOAEC = 0.020 mg a.i./L LOAEC > 0.020 mg a.i./L No treatment-related effects on any endpoint (survival, length, reproduction) at highest concentration tested.	N/A	Study: PMRA# 3059494
Midge, *Chironomus dilutus*	10-d Acute, spiked sediment, intermittent flow-through	Pyraziflumid (technical grade active ingredient, purity 94.8%)	Pore water: LC_{50} > 3.4 mg a.i./L NOAEC = 3.4 mg a.i./L Overlying water: LC_{50} > 0.36 mg a.i./L NOAEC = 0.36 mg a.i./L	N/A	Study: PMRA# 3059496

Organism	Exposure	Test substance	Endpoint value[1]	Degree of toxicity[2]	PMRA#
			No treatment-related effects on survival or dry weight at highest concentration tested.		
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute, static-renewal	Pyraziflumid (technical grade active ingredient, purity 94.8%)	LC_{50} = 2.68 mg a.i./L NOAEC = 0.519 mg a.i./L (sublethal effects)	Moderately toxic	Study: PMRA# 3059465
Bluegill, *Lepomis macrochirus*	96-h Acute, static-renewal	Pyraziflumid (technical grade active ingredient, purity 94.8%)	LC_{50} = 3.0 mg a.i./L NOAEC = 1.1 mg a.i./L (mortality and sublethal effects)	Moderately toxic	Study: PMRA# 3059466
Fathead minnow, *Pimephales promelas*	96-h Acute, static-renewal	Pyraziflumid (technical grade active ingredient, purity 94.8%)	LC_{50} = 2.6 mg a.i./L NOAEC = 0.79 mg a.i./L (sublethal effects)	Moderately toxic	Study: PMRA# 3059468
	32-d ELS, flow-through	Pyraziflumid (technical grade active ingredient, purity 94.8%)	NOAEC = **0.39** mg a.i./L LOAEC = 0.78 mg a.i./L (weight) Potential solvent (DMF) effects noted.	N/A	Study: PMRA# 3059470
Carp, *Cyprinus carpio*	96-h Acute, static-renewal	Pyraziflumid (technical grade active ingredient, purity 94.8%)	LC_{50} = **1.7** mg a.i./L NOAEC = 0.44 mg a.i./L (sublethal effects)	Moderately toxic	Study: PMRA# 3059469
Diatom, *Navicula pelliculosa*	96-h Acute, static	Pyraziflumid (technical grade active ingredient, purity 94.8%)	IC_{50} **> 0.097** mg a.i./L NOAEC = 0.097 mg a.i./L No treatment-related effects at highest concentration tested. Potential solvent (DMF) effects noted.	N/A	Study: PMRA# 3059480
Blue-green algae, *Anabaena flos-aquae*	96-h Acute, static	Pyraziflumid (technical grade active ingredient, purity 94.8%)	IC_{50} > 0.099 mg a.i./L NOAEC = 0.099 mg a.i./L No treatment-related effects at highest concentration tested.	N/A	Study: PMRA# 3059481

Organism	Exposure	Test substance	Endpoint value[1]	Degree of toxicity[2]	PMRA#
Green algae, *Pseudokirchneriella subcapitata*	96-h Acute, static	Pyraziflumid (technical grade active ingredient, purity 94.8%)	IC_{50} = 2.98 mg a.i./L NOAEC = 0.371 mg a.i./L All endpoints were significantly affected by the test material (yield, growth rate, and area under the curve), with yield being the most sensitive endpoint.	N/A	Study: PMRA# 3059482
	72-h Acute, static	End-use product, Pyraziflumid 20SC (20.1% a.i.)	IC_{50} = 153 mg a.i./L NOAEC < 12.6 mg a.i./L All endpoints were significantly affected by the test material (yield, growth rate, and area under the curve), with yield being the most sensitive endpoint.	N/A	Study: PMRA# 3059483
Vascular plant, duckweed, *Lemna gibba*	7-d Static renewal	Pyraziflumid (technical grade active ingredient, purity 94.8%)	IC_{50} > **0.11** mg a.i./L NOAEC = 0.11 mg a.i./L No treatment-related effects at highest concentration tested.	N/A	Study: PMRA# 3059487
Marine species					
Amphipod, *Leptocheirus plumulosus*	10-d Acute, spiked sediment, static	Pyraziflumid (technical grade active ingredient, purity 94.8%)	Pore water: LC_{50} could not be calculated LOAEC = **1.95** mg a.i./L Overlying water: LC_{50} could not be calculated LOAEC = 1.01 mg a.i./L Significant treatment-related effects on survival and weight were observed. As an LC_{50} could not be calculated, the LOAEC for survival (38% mortality) is considered as a surrogate endpoint.	N/A	Study: PMRA# 3059493
	28-d Chronic, spiked sediment,	Pyraziflumid (technical grade active	Pore water: NOAEC = **0.17** mg a.i./L	N/A	Study: PMRA# 3059488

Organism	Exposure	Test substance	Endpoint value[1]	Degree of toxicity[2]	PMRA#
	intermittent flow-through	ingredient, purity 94.8%)	LOAEC > 0.17 mg a.i./L Overlying water: NOAEC = 0.011 mg a.i./L LOAEC > 0.011 mg a.i./L No treatment-related effects on any endpoint (survival, growth, reproduction) at highest concentration tested.		
Crustacean, mysid shrimp, *Americamysis bahia*	96-h Acute, static-renewal	Pyraziflumid (technical grade active ingredient, purity 94.8%)	LC_{50} = **2.6** mg a.i./L	Moderately toxic	Study: PMRA# 3059462
	28-d Chronic, flow-through	Pyraziflumid (technical grade active ingredient, purity 94.8%)	NOAEC = **0.012** mg a.i./L LOAEC = 0.019 mg a.i./L For the most sensitive endpoint of number of offspring per female. Potential solvent (DMF) effects noted.	N/A	Study: PMRA# 3059464
Mollusk, Eastern oyster, *Crassostrea virginica*	96-h Acute, flow-through	Pyraziflumid (technical grade active ingredient, purity 94.8%)	IC_{50} = **0.82** mg a.i./L (shell deposition)	Highly toxic	Study: PMRA# 3059463
Marine diatom, *Skeletonema costatum*	96-h Acute, static	Pyraziflumid (technical grade active ingredient, purity 94.8%)	IC_{50} **> 0.092** mg a.i./L NOAEC = 0.092 mg a.i./L No treatment-related effects at highest concentration tested.	N/A	Study: PMRA# 3059484
Sheepshead minnow, *Cyprinodon variegatus*	96-h Acute, flow-through	Pyraziflumid (technical grade active ingredient, purity 94.8%)	LC_{50} **> 2.6** mg a.i./L NOAEC = 1.4 mg a.i./L (sublethal effects)	Not toxic up to the limit of solubility under the conditions of the test.	Study: PMRA# 3059467

[1] The most sensitive values are bolded and will be used in the screening risk assessment.
[2] Atkins et al. (1981) for bees and USEPA classification for others, where applicable.

Table 19 Parameters used in the risk assessment for pyraziflumid

Organism	Exposure / Test substance	Endpoint	Value	Uncertainty factor	Effect metrics	Level of concern
Terrestrial species						
Earthworm, *Eisenia fetida*	Reproduction – a.i.	56-d NOAEC	10.4 mg a.i./kg dw soil	1	10.4 mg a.i./kg dw soil	1
Honey bee, *Apis mellifera*	Acute oral, adults – a.i.	96-h LD_{50}	> 80 µg a.i./bee	1	> 80 µg a.i./bee	0.4
	Acute contact, adults – a.i.	96-h LD_{50}	> 100 µg a.i./bee	1	> 100 µg a.i./bee	0.4
	Acute oral, larvae – a.i.	72-h LD_{50}	> 110 µg a.i./larva	1	> 110 µg a.i./larva	0.4
	Acute oral, larvae – a.i.	8-d LD_{50}	2.71 µg a.i./larva/day		2.71 µg a.i./larva/day	
	Chronic oral, adults – End-use product	10-d NOAEL	55 µg a.i./bee	1	55 µg a.i./bee	1
	Chronic oral, larvae – a.i.	22-d NOAEL	0.85 µg a.i./larva	1	0.85 µg a.i./larva	1
Predatory mite, *Typhlodromus pyri*	Contact, glass plates – End-use product	14-d LR_{50} / ER_{50}	> 450 g a.i./ha	1	> 450 g a.i./ha	2
Parasitoid wasp, *Aphidius rhopalosiphi*	Contact, glass plates – End-use product	14-d LR_{50} / ER_{50}	> 450 g a.i./ha	1	> 450 g a.i./ha	2
Mallard duck, *Anas platyrhynchos*	Reproduction – a.i.	22-wk NOAEL	< 19.1 mg a.i./kg bw/d	1	< 19.1 mg a.i./kg bw/d	1
Zebra finch, *Taeniopygia guttata*	Acute dietary – a.i.	5-d LD_{50}	377 mg a.i./kg bw/d	10	37.7 mg a.i./kg bw/d	1
Rat (Wistar)	Acute oral – a.i	LD_{50}	> 2000 mg a.i./kg bw	10	> 200 mg a.i./kg bw	1
	Reproduction – a.i.	NOAEL	16.6 mg a.i./kg bw/d	1	16.6 mg a.i./kg bw/d	1
Terrestrial vascular plants	Seedling emergence – End-use product	14-d ER_{25}	> 118.5 g a.i./ha	1	> 118.5 g a.i./ha	1
	Vegetative vigour – End-use product	21-d ER_{25}	> 150 g a.i./ha	1	> 150 g a.i./ha	1
Freshwater species						
Invertebrate, *Daphnia magna*	Acute – a.i.	48-h LC_{50}	> 3.8 mg a.i./L	2	> 1.9 mg a.i./L	1
	Chronic – a.i.	21-d NOAEC	0.09 mg a.i./L	1	0.09 mg a.i./L	1
Amphipod, *Hyalella azteca*	Acute – a.i. (spiked sediment)	10-d LC_{50}	> 3.0 mg a.i./L (pore water)	2	> 1.5 mg a.i./L (pore water)	1

Organism	Exposure / Test substance	Endpoint	Value	Uncertainty factor	Effect metrics	Level of concern
	Chronic – a.i. (spiked sediment)	42-d NOAEC	0.35 mg a.i./L (pore water)	1	0.35 mg a.i./L (pore water)	1
Fathead minnow, *Pimephales promelas*	ELS – a.i.	32-d NOAEC	0.39 mg a.i./L	1	0.39 mg a.i./L	1
Carp, *Cyprinus carpio*	Acute – a.i.	96-h LC_{50}	1.7 mg a.i./L	10	0.17 mg a.i./L	1
Amphibians (using fish data as a surrogate)	Acute – a.i.	96-h LC_{50}	1.7 mg a.i./L	10	0.17 mg a.i./L	1
	Chronic – a.i.	32-d NOAEC	0.39 mg a.i./L	1	0.39 mg a.i./L	1
Diatom, *Navicula pelliculosa*	Acute – a.i.	96-h IC_{50}	> 0.097 mg a.i./L	2	> 0.049 mg a.i./L	1
Aquatic vascular plant, *Lemna gibba*	Acute – a.i.	7-d IC_{50}	> 0.11 mg a.i./L	2	> 0.055 mg a.i./L	1
Marine species						
Amphipod, *Leptocheirus plumulosus*	Acute – a.i. (spiked sediment)	10-d LOAEC	1.95 mg a.i./L (pore water)	2	0.98 mg a.i./L (pore water)	1
	Chronic – a.i. (spiked sediment)	28-d NOAEC	0.17 mg a.i./L (pore water)	1	0.17 mg a.i./L (pore water)	1
Crustacean, mysid shrimp, *Americamysis bahia*	Acute – a.i.	96-h LC_{50}	2.6 mg a.i./L	2	1.3 mg a.i./L	1
	Chronic – a.i.	28-d NOAEC	0.012 mg a.i./L	1	0.012 mg a.i./L	1
Mollusk, Eastern oyster, *Crassostrea virginica*	Acute – a.i.	96-h IC_{50}	0.82 mg a.i./L	2	0.41 mg a.i./L	1
Sheepshead minnow, *Cyprinodon variegatus*	Acute – a.i.	96-h LC_{50}	> 2.6 mg a.i./L	10	> 0.26 mg a.i./L	1
Marine diatom, *Skeletonema costatum*	Acute – a.i.	96-h IC_{50}	> 0.092 mg a.i./L	2	> 0.046 mg a.i./L	1

Table 20 Screening level risk assessment of pyraziflumid for non-target terrestrial species other than birds and mammals

Organism	Exposure	Effect metric	EEC	RQ	Level of concern
Invertebrates					
Earthworm	Reproduction – a.i.	10.4 mg a.i./kg soil	0.1 mg a.i./kg soil	< 0.1	Not exceeded
Honey bee	Acute contact, adults – a.i.	> 100 µg a.i./bee	0.18 µg a.i./bee[1]	< 0.1	Not exceeded
	Acute oral, adults – a.i.	> 80 µg a.i./bee	2.15 µg a.i./bee[1]	< 0.1	Not exceeded

Organism	Exposure	Effect metric	EEC	RQ	Level of concern
	Acute oral, larvae – a.i.	2.71 µg a.i./larvae/day	0.91 µg a.i./bee[1]	0.3	Not exceeded
	Chronic oral, adults – End-use product	55 µg a.i./bee	2.14 µg a.i./bee[1]	< 0.1	Not exceeded
	Chronic oral, larvae – a.i.	0.85 µg a.i./larvae/day	0.91 µg a.i./bee[1]	**1.07**	**Exceeded**[2]
Predatory mite	Contact, glass plates – End-use product	> 450 g a.i./ha	plant surface: 149.6 g a.i./ha	< 0.3	Not exceeded
			Soil surface: 224.4 g a.i./ha	< 0.5	
Parasitoid wasp	Contact, glass plates – End-use product	> 450 g a.i./ha	plant surface: 149.6 g a.i./ha	< 0.3	Not exceeded
			Soil surface: 224.4 g a.i./ha	< 0.5	
Vascular plants					
Vascular plant	Seedling emergence	> 118.5 g a.i./ha	In-field: 224.4 g a.i./ha	**< 1.9**	**Exceeded**
			Off-field: 166.1 g a.i./ha	**< 1.4**	**Exceeded**
	Vegetative vigour	> 150 g a.i./ha	In-field: 149.6 g a.i./ha	< 1.0	Not exceeded
			Off-field: 110.7 g a.i./ha	< 0.7	Not exceeded

[1] The pollinator risk assessment followed a tiered framework developed jointly by the PMRA, USEPA (United States Environmental Protection Agency) and CDPR (California Department of Pesticide Regulation) in 2012 with guidance published in 2014 (Guidance for Assessing Pesticide Risks to Bees). The exposures to honey bees are estimated based on the maximum single application rate of 75 a.i./ha: 0.18 µg a.i./bee (0.075 kg a.i./ha × 2.4 µg a.i./bee/day per kg/ha) for adult acute contact exposure; 2.15 µg a.i./bee (0.075 kg a.i./ha × 28.6 µg a.i./bee/day per kg/ha) for adult acute and chronic oral exposure; and 0.91 µg a.i./larva (0.075 kg a.i./ha × 12.15 µg a.i./larva/day per kg/ha) for larvae acute and chronic oral exposure.
[2] RQ for chronic bee larvae slight exceeded the LOC based on conservative exposure estimates. The risk associated with the use of pyraziflumid is acceptable for pollinators.

Table 21 Screening level risk assessment of pyraziflumid for birds and mammals

	Effect metric (mg a.i./kg bw/day)	EDE (mg a.i./kg bw/day)[1]	RQ	Level of concern
Small sized bird (0.02 kg)				
Acute	> 201.0	12.2	< 0.1	Not exceeded
Dietary	37.7	12.2	0.3	Not exceeded
Reproduction	< 19.1	12.2	> 0.6	Not exceeded
Medium sized bird (0.10 kg)				
Acute	> 201.0	9.5	< 0.1	Not exceeded
Dietary	37.7	9.5	0.2	Not exceeded
Reproduction	< 19.1	9.5	> 0.5	Not exceeded
Large sized bird (1.00 kg)				
Acute	> 201.0	6.1	< 0.1	Not exceeded
Dietary	37.7	6.1	0.2	Not exceeded
Reproduction	< 19.1	6.1	> 0.3	Not exceeded
Small sized mammal (0.015 kg)				
Acute	> 200[2]	7.0	< 0.1	Not exceeded
Reproduction	16.6	7.0	0.4	Not exceeded
Medium sized mammal (0.035 kg)				
Acute	> 200[2]	13.6	< 0.1	Not exceeded

	Effect metric (mg a.i./kg bw/day)	EDE (mg a.i./kg bw/day)[1]	RQ	Level of concern
Reproduction	16.6	13.6	0.8	Not exceeded
Large sized mammal (1.00 kg)				
Acute	> 200[2]	7.3	< 0.1	Not exceeded
Reproduction	16.6	7.3	0.4	Not exceeded

[1] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987).
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 (body weight < 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(Bbw in g) $^{0.651}$.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(bw in g) $^{0.822}$
bw: Generic body weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.
[2] The acute LD_{50} value of > 2000 mg a.i./kg bw obtained from the study with the technical grade active ingredient was used in the screening level risk assessment. Technical grade pyraziflumid and its end-use product, Pyraziflumid 20SC, were practically non-toxic to rats on an acute oral basis, with oral LD_{50} values of > 2000 mg product/kg bw. There were no clinical signs of toxicity at the highest tested concentration for either of the acute oral studies. When accounting for the active ingredient content of the test substances, the endpoint from the acute oral study done with the end-use product is more conservative than the one from the study with technical pyraziflumid; however, this difference in endpoints is more a result of the test compound being a formulated product than an indication of higher toxicity.

Table 22 Modelled EECs (in µg a.i./L) in water bodies resulting from surface runoff for the ecological risk assessment of pyraziflumid

Use	Water depth	Water column				Pore water	
		Peak	24-hour	96-hour	21-day	Peak	21-day
3 × 75 g a.i./ha at 7-day intervals	80 cm	18	18	18	18	18	18
	15 cm	37	34	29	25	--	--

Table 23 Screening level risk assessment of pyraziflumid for aquatic organisms

Organism	Exposure	Effect metric (mg a.i./L)	EEC[1] (mg a.i./L)	RQ	Level of concern[2]
Freshwater species					
Pelagic invertebrate	Acute – a.i.	1.9	0.028	< 0.1	Not exceeded
	Chronic – a.i.	0.09	0.028	0.3	Not exceeded
Benthic amphipod	Acute – a.i.	1.5 (pore water)	0.018	< 0.01	Not exceeded
	Chronic – a.i.	0.35 (pore water)	0.018	0.05	Not exceeded
Fish	Acute – a.i.	0.17	0.028	0.2	Not exceeded
	ELS – a.i.	0.39	0.028	0.1	Not exceeded
Amphibians (using fish data as a surrogate)	Acute – a.i.	0.17	0.149	0.9	Not exceeded
	ELS – a.i.	0.39	0.149	0.4	Not exceeded
Algae	Acute – a.i.	> 0.049	0.028	< 0.6	Not exceeded
Aquatic vascular plant	Acute – a.i.	> 0.055	0.028	< 0.5	Not exceeded
Marine species					
Pelagic invertebrate	Acute – a.i.	0.41	0.028	< 0.1	Not exceeded
	Chronic – a.i.	0.012	0.028	**2.3**	**Exceeded**[3]

Organism	Exposure	Effect metric (mg a.i./L)	EEC[1] (mg a.i./L)	RQ	Level of concern[2]
Benthic amphipod	Acute – a.i.	0.975 (pore water)	0.018	0.02	Not exceeded
	Chronic – a.i.	0.17 (pore water)	0.018	0.1	Not exceeded
Fish	Acute – a.i.	> 0.26	0.028	< 0.1	Not exceeded
Algae	Acute – a.i.	> 0.046	0.028	< 0.6	Not exceeded

[1] The screening level EECs in water are based on direct application of a pesticide to a body of water, and is intended to be a simple, conservative, and reasonable worst-case estimate of pesticide concentrations in water. The maximum cumulative application rate for pyraziflumid on water is 224.4 g a.i./ha, based on the proposed use of Parade Fungicide. Based on this application rate, the EEC in water bodies 80 cm and 15 cm deep are 0.028 mg a.i./L and 0.15 mg a.i./L, respectively.

[2] Level of concern = 1

[3] RQ for pelagic invertebrates slight exceeded the LOC for chronic exposure when considering direct application of pyraziflumid at the cumulative maximum annual application rate of 224.4 g a.i/ha and did not consider tidal dilution. When considering the single maximum application rate of 75 g a.i./ha, the risk quotient did not exceed the level of concern (RQ of 0.78). Therefore, the risk associated with the use of pyraziflumid is acceptable for marine invertebrates

Table 24 Toxic substances management policy considerations-comparison to TSMP Track 1 criteria

TSMP Track 1 criteria	TSMP Track 1 criterion value		Pyraziflumid endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Yes: 573 to > 10,000 days (laboratory)
	Water	Half-life ≥ 182 days	Yes: 318 to > 10,000 days (laboratory, total system, aerobic systems)
	Sediment	Half-life ≥ 365 days	
	Air	Half-life ≥ 2 days or evidence of long range transport	No: Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (≤ 3.5×10^{-6} Pa, 20°C) and Henry's Law Constant (2.35×10^{-7}, dimensionless).
Bioaccumulation[4]	Log K_{OW} ≥ 5		No: 2.46 (pH 7.33) - 3.51 (pH 6.18)
	BCF ≥ 5000		No: 41-107
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet all 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 (in other words, all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3]If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) 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 25 Supported use claims for parade fungicide

Supported use claim
Crop: Apple
Diseases: Scab (*Venturia inaequalis*) and powdery mildew (*Podosphaera leucotricha*)
Claim: Control of both diseases at 227-340 mL/ha (50-75 g a.i./ha)
Adjuvant: Parade Fungicide is not to be applied with any type of adjuvant.
Application timing and methods: Prior to disease development using ground application equipment, specifically vertical boom and airblast sprayers
Spray volume: 375-2000 L water/ha
Maximum number of applications: three per year regardless of rate used
Application Interval: minimum of 7 days
Other Directions: In provinces other than British Columbia, Parade Fungicide must be applied in a tank mixture with another fungicide of a different mode of action that is registered for control of apple scab.

Appendix II Supplemental maximum residue limit information—International situation and trade implications

Pyraziflumid is an active ingredient that is concurrently being registered in Canada and the United States for use on apples. Canada is also establishing MRLs on plant commodities that may be imported into Canada from the United States. The MRLs proposed for pyraziflumid in Canada are the same as corresponding tolerances to be promulgated in the United States.

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

Currently, there are no Codex MRLs[10] listed for pyraziflumid in or on any commodity on the Codex Alimentarius Pesticide Index website.

[10] 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
3059357	2019, Content Analysis of Pyraziflumid Technical (PC-33046), DACO: 2.13.1,2.13.2,2.13.3 CBI
3059358	2019, Pyraziflumid Technical: Group A Product Properties (S-33004), DACO: 2.11.1,2.11.2,2.11.3,2.11.4,2.12.1,2.13.1,2.13.2 CBI
3059361	2018, Pyraziflumid (NNF-0721) Technical: Determination of the Physical/Chemical Properties (PC-33039), DACO: 2.14.1,2.14.2,2.14.3
3059362	2013, Determination of Physico-Chemical Properties of NNF-0721 (PC-33001), DACO: 2.14.1,2.14.13,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.9
3059363	2012, Measurement of Dissociation Constant in Water for NNF-0721 (PC-33005), DACO: 2.14.10
3059364	2013, n-Octanol/Water Partition Coefficient of NNF-0721 (PC-33010), DACO: 2.14.11
3059366	2013, Ultraviolet/visible Absorption Spectrum of NNF-0721 (PC-33012), DACO: 2.14.12
3059368	2013, Solubility of NNF-0721 in Distilled Water (PC-33011), DACO: 2.14.7
3059369	2012, Measurement of Solubility in Organic Solvents for NNF-0721 (PC-33004), DACO: 2.14.8
3059371	2019, Tier II Summary of the Analytical Methods and Validation for Pyraziflumid (NNF-0721), DACO: 2.16
3134980	2020, Structure Confirmation, Purity Analysis and Stability Study of NNF_0721 Analytical Standard (lot 9JB0002P), DACO: 2.13.2
3134981	2020, Structure Confirmation, Purity Analysis and Stability Study of NNF-0721 Related Compound [CBI Removed] Analytical Standard (Lot 9JB0802P), DACO: 2.13.2
3134982	2020, Structure confirmation, purity analysis and stability test of NNF-0721 related substance standards [CBI Removed], DACO: 2.13.2
3190600	2021, Discussion of Formation of Impurities [CBI Removed], DACO: 2.11.4 CBI
3059491	2018, "Determination of NNF-0721 in Soil, Sediment, Thatch, and Grass

	Clippings (E-33021) ", DACO: 9.9
3059492	2018, Development and Validation of a Method for the Determination of Pyraziflumid in Surface and Drinking Water (A-33022), DACO: 9.9
3071010	2019, Pyraziflumid End-use Product: Group A Product Properties (PC-TBD) S-33005, DACO: 3.1,3.2.1,3.2.2,3.2.3,3.3.1,3.5.4 CBI
3071012	2018, Pyraziflumid 20SC: Enforcement Analytical Method for the Determination of Pyraziflumid by High Performance Liquid Chromatography (A-33017), DACO: 3.4.1,3.5.10,3.5.14
3071013	2018, Pyraziflumid 20 SC: Physical and Chemical Characteristics: Color, Physical State, Odor, pH, and Viscosity (PC-33034) , DACO: 3.5.1,3.5.2,3.5.3,3.5.7,3.5.9
3071015	2019, "Pyraziflumid 20SC: Storage Stability and Corrosion Characteristics (PC-33043)", DACO: 3.5.10,3.5.14
3071018	2018, "Pyraziflumid (NNF-0721) Technical: Determination of Flammability (PC-33037)", DACO: 3.5.11
3071023	2018, Pyraziflumid 20SC (NNF-0721 20SC): Physical and Chemical Characteristics: Density/Relative Density (PC-33041), DACO: 3.5.6
3071027	2018, Pyraziflumid (NNF-0721) Technical: Determination of the Chemical Incompatibility (PC-33040), DACO: 3.5.8
3071028	2016, NNF-0721 (Pyraziflumid): Evaluation of Selected Physical Chemical Properties (PC-33027), DACO: 3.5.11,3.5.12,3.5.8

2.0 Human and animal health

PMRA Document Number	Reference
3059378	2014, Acute Oral Toxicity of NNF-0721 Technical in Rats (T-33008), DACO: 4.2.1
3059379	2013, Acute Dermal Toxicity Study of NNF-0721 Technical in Rats (T-33009), DACO: 4.2.2
3059380	2013, NNF-0721 Technical: 4-Hour Acute Inhalation Toxicity Study in the Rat (T-33010), DACO: 4.2.3
3059381	2013, Eye Irritation Study of NNF-0721 Technical in Rabbits (T-33012), DACO: 4.2.4
3059382	2013, Skin Irritation Study of NNF-0721 Technical in Rabbits (T-33011), DACO: 4.2.5
3059383	2015, Skin Sensitization Study of NNF-0721 Technical by Local Lymph Node Assay: BrdU-ELISA in Mice (T-33013), DACO: 4.2.6
3059384	2013, NNF-0721: Preliminary Carcinogenicity Study by Dietary Administration to CD-1 Mice for 13 Weeks (T-33019), DACO: 4.3.1

3059385	2010, NNF-0721: Toxicity Study by Dietary Administration to Han Wistar Rats for 13 Weeks (T-33015), DACO: 4.3.1
3059386	2013, NNF-0721: Repeated Dose 90-Day Oral Toxicity Study in Dogs (T-33023), DACO: 4.3.2
3059387	2012, NNF-0721: Repeated Dose 28-Day Oral Toxicity Study in Dogs (T-33022), DACO: 4.3.3
3059388	2015, 28-Day Repeated Oral Toxicity Study of NNF-0721 in Mice (T-33018), DACO: 4.3.3
3059389	2015, 28-Day Repeated Oral Toxicity Study of NNF-0721 in Rats (T-33014), DACO: 4.3.3
3059390	2017, Ninety-Day Repeated Dose Dermal Toxicity Study of NNF-0721 Technical Grade in Rats (T-33068), DACO: 4.3.4
3059391	2019, Weight of the Evidence Based Rationale for Waiving the 90-day Inhalation Study Requirement for Pyraziflumid (T-33075), DACO: 4.3.6
3059392	2017, Five-Day Repeated Dose Dermal Toxicity Study of NNF-0721 Technical Grade in Rats (T-33060), DACO: 4.3.8
3059393	2015, NNF-0721: Repeated Dose 1-Year Oral Toxicity Study in Dogs (IET 13-0016) (T-33024), DACO: 4.3.2
3059394	2015, NNF-0721: Carcinogenicity Study by Dietary Administration to CD-1 Mice for 78 Weeks - Additional Histology Investigations (T-33053), DACO: 4.4.2
3059395	2015, NNF-0721: Carcinogenicity Study by Dietary Administration to CD-1 Mice for 78 Weeks (T-33020), DACO: 4.4.2
3059396	2015, NNF-0721: Histopathology of the Thyroid Glands of 52 Weeks Satellite Group to: Combined Toxicity and Carcinogenicity Study by Dietary Administration to Han Wistar Rats for 104 Weeks (T-33039), DACO: 4.4.4
3059397	2015, NNF-0721: Combined Toxicity and Carcinogenicity Study by Dietary Administration to Han Wistar Rats for 104 Weeks (T-33017), DACO: 4.4.4
3059398	2014, NNF-0721: Two-Generation Reproduction Toxicity Study in Rats (T-33026), DACO: 4.5.1
3059399	2017, An Oral (Gavage) Acute Neurotoxicity Study of NNF-0721 in Rats (T-33067), DACO: 4.5.12
3059400	2017, An Oral (Gavage) Dose Range-Finding Acute Neurotoxicity Study of NNF-0721 in Rats (T-33066), DACO: 4.5.12
3059402	2019, Weight of the Evidence Based Rationale for Waiving the Subchronic Neurotoxicity Study Requirements for Pyraziflumid (T-33078), DACO: 4.8
3059403	2014, NNF-0721: Preliminary reproductive toxicity study in rats (T-33025), DACO: 4.5.1
3059404	2014, NNF-0721: Teratogenicity Study in Rats (T-33028), DACO: 4.5.2
3059405	2014, NNF-0721: Teratogenicity Study in Rabbits (T-33030), DACO: 4.5.3
3059406	2012, A Bacterial Reverse Mutation Test of NNF-0721 (T-33001), DACO: 4.5.4
3059407	2017, In Vitro Gene Mutation Study of Pyraziflumid Technical in Mouse Lymphoma L5178Y Cells (T-33069), DACO: 4.5.5
3059408	2014, In Vitro Chromosome Aberration Test of NNF-0721 in Cultured Chinese Hamster Cells (T-33032), DACO: 4.5.5

3059409	2015, NNF-0721-amine: Micronucleus Test in the Bone Marrow of Mice (T-33054), DACO: 4.5.7
3059410	2014, NNF-0721: Micronucleus Test in the Bone Marrow of Mice (T-33033), DACO: 4.5.7
3059412	2015, In Vitro Metabolism Study of NNF-0721 (T-33049), DACO: 4.5.9
3059413	2014, Biliary Excretion Study of NNF-0721 Following a Single Oral Administration to Rats (T-33038), DACO: 4.5.9
3059414	2019, Absorption, Distribution, Metabolism and Excretion of [difluorophenyl -U-14C] NNF-0721 Following a Single Oral Administration to Male and Female Rats (T-33037), DACO: 4.5.9
3059415	2019, Absorption, Distribution, Metabolism and Excretion of [aniline -U-14C] NNF-0721 Following a Single Oral Administration to Male and Female Rats (T-33036), DACO: 4.5.9
3059416	2019, Absorption, Distribution, Metabolism and Excretion of [pyrazinyl -5(6)-14C] NNF-0721 Following a Single Oral Administration to Male and Female Rats (T-33035), DACO: 4.5.9
3059424	2019, Weight of the Evidence Based Rationale for Waiving the Immunotoxicity Study Requirement for Pyraziflumid (T-33076), DACO: 4.8
3059425	2019, NNF-0721: Effect on thyroid hormone and liver enzyme activity in rats by dietary administration for 7 days (T-33074), DACO: 4.8
3059426	2019, NNF-0721: Effect on rat thyroid peroxidase activity in vitro (T-33073), DACO: 4.8
3059427	2013, NNF-0721 technical: Dose range-finding teratogenicity study in SD rats (T-33027), DACO: 4.5.2
3059428	2013, NNF-0721: Teratogenicity Study in Rabbits Dose Range Finding Study (T-33029), DACO: 4.5.3
3059429	2015, NNF-0721 Technical Grade: Alkaline Comet Assay in Rats (T-33050), DACO: 4.8
3059430	2014, Effects of NNF-0721 Technical Grade on General Activity and Behavior in Rats in Accordance with the Modified Irwins Multidimensional Observation Method (T-33040), DACO: 4.8
3059431	2015, NNF-0721: Effect on Hepatocellular Proliferation and Liver Enzyme Activity in Rats by Dietary Administration (T-33034), DACO: 4.8
3059432	2015, NNF-0721: Effect on Thyroid Hormone and Liver Enzyme Activity in Rats by Dietary Administration (T-33016), DACO: 4.8
3071040	2014, Acute Oral Toxicity of NNF-0721 20SC in Rats (T-33044), DACO: 4.6.1
3071041	2014, Acute Dermal Toxicity of NNF-0721 20SC in Rats (T-33045), DACO: 4.6.2
3071042	2018, Pyraziflumid 20SC (NNF-0721 20SC): Acute Inhalation Toxicity in Rats (T-33072), DACO: 4.6.3
3071043	2014, Eye Irritation Study of NNF-0721 20SC in Rabbits (T-33047), DACO: 4.6.4
3071044	2018, Pyraziflumid 20SC: Primary Eye Irritation in Rabbits (T-33070), DACO: 4.6.4
3071045	2014, Skin Irritation Study of NNF-0721 20SC in Rabbits (T-33046), DACO: 4.6.5

3071046	2014, Skin Sensitization Study of NNF-0721 20SC in Guinea Pigs (Buehler Test) (T-33048), DACO: 4.6.6
3195932	2013, Historical Control Data - NNF-0721: Toxicity study by dietary administration to Han Wistar rats for 13 weeks, DACO: 4.3.1
3195933	2015, Historical Histopathology Data 104 week studies HAN Wistar Rats, DACO: 4.4.4
3195934	2021, Table(s) presenting the severity scores of histopathological findings in the liver and thyroid for both parental and offspring generations (reproductive study MRID 50876720), DACO: 4.5.1
3195935	2021, Historical control data for fertility index (male and female; %) for the P and F1 generation parental animals (reproductive study MRID 50876720), DACO: 4.5.1
3195936	2021, Historical control data for parental and offspring histopathology of the liver and thyroid (reproductive study MRID 50876720), DACO: 4.5.1
3195937	2021, NNF-0721: Historical Control Data on Rabbit Teratogenicity Studies in IET (IET 13-0055) Animal species: Specific pathogen-free (SPF) Kbl:JW rabbits, DACO: 4.5.3
3072323	2019, Dissipation of Dislodgeable Foliar Residues from Apple Foliage Following Treatment with Three Foliar Airblast Applications of Pyraziflumid 20SC (2016) (R-33083), DACO: 5.9
3059436	2014, Metabolism Study of NNF-0721 in Cherry Tomato (R-33055), DACO 6.3
3059437	2015, Metabolism Study of NNF-0721 in Paddy Rice (R-33052), DACO 6.3
3059438	2013, [^{14}C] NNF-0721: Metabolic Fate in Lettuce (R-33003), DACO 6.3
3071050	2018, Amended Report: Validation of Method GPL-MTH-096: Analytical Method for the Determination of Pyraziflumid and BC-01 in Raw Agricultural Commodities and Processed Commodities by LC-MS/MS (A-33013), DACO 7.2.1, 7.2.2
3071048	2017, Independent Laboratory Validation of an Analytical Method for the Determination of Pyraziflumid (NNF-0721) and BC-01 in Crop Matrices (A-33025)", DACO 7.2.1, 7.2.2, 7.2.3A
3071051	2019, Freezer Storage Stability of Pyraziflumid and BC-01 in Raw Agricultural Commodities and Processed Commodities (R-33090), DACO 7.3
3071055	2016, Magnitude and Decline of Pyraziflumid and Metabolite BC-01 Residues in/on The Pome Fruits Crop Group (11-10) Raw Agricultural and Processed Commodities Following Three Foliar Airblast Applications of Pyraziflumid 20SC Fungicide (R-33070), DACO 7.4.1, 7.4.2, 7.4.5
3071056	2016, Magnitude and Decline of Pyraziflumid and Metabolite BC-01 Residues in/on The Tree Nut Crop Group (14-12) Raw Agricultural Commodities Following Three Foliar Airblast Applications of Pyraziflumid 20SC Fungicide (R-33081), DACO 7.4.1, 7.4.2
3071057	2016, Magnitude and Decline of Pyraziflumid and Metabolite BC-01 Residues in/on the Caneberry Crop Subgroup (13-07A) and the Bushberry Crop Subgroup (13-07B) Raw Agricultural Commodities Following Three Foliar Applications of Pyraziflumid 20SC Fungicide (R-33076), DACO 7.4.1, 7.4.2

3071058	2016, Magnitude and Decline of Pyraziflumid and Metabolite BC-01 Residues in/on The Small Fruit Vine Climbing Except Fuzzy Kiwifruit Crop Subgroup 13-07F Raw Agricultural and Processed Commodities Following Three Foliar Airblast Applications of Pyraziflumid 20SC Fungicide (R-33091), DACO 7.4.1, 7.4.2, 7.4.5
3071059	2016, Magnitude and Decline of Pyraziflumid and Metabolite BC-01 Residues in/on The Stone Fruits Crop Group (12-12) Raw Agricultural and Processed Commodities Following Three Foliar Airblast Applications of Pyraziflumid 20SC Fungicide (R-33074), DACO 7.4.1, 7.4.2, 7.4.5

3.0 Environment

PMRA Number	Reference
3059454	2019, Tier II Summary of the Ecotoxicological Studies on the Active Substance for Pyraziflumid, DACO: 9.1
3059455	2019, Pyraziflumid technical grade: Effects on the Reproduction of the Earthworm *Eisenia fetida* (Annelida, Lumbricidae) in Artificial Soil with 5 % Peat (N-33026) , DACO: 9.2.3
3059456	2018, Pyraziflumid: 10-Day Oral Toxicity Test with the Adult Honey Bee (*Apis mellifera*) (N-33023), DACO: 9.2.4.4
3059457	2018, Pyraziflumid: Honey Bee (*Apis mellifera*) Larval Toxicity Test, Repeated Exposure (N-33020), DACO: 9.2.4.3
3059458	2017, Pyraziflumid: Honey Bee (*Apis mellifera*) Larval Toxicity Test, Single Exposure (N-33015), DACO: 9.2.4.3
3059459	2012, NNF-0721 Acute Toxicity to Honey Bees (N-33001), DACO: 9.2.4.1,9.2.4.2
3059460	2014, Acute Immobilization Test of NNF-0721 on *Daphnia magna* (W-33004), DACO: 9.3.2
3059461	2017, Pyraziflumid: Full Life-Cycle Toxicity Test with Water Fleas, *Daphnia magna*, Under Flow-Through Conditions (W-33016), DACO: 9.3.3
3059462	2018, Pyraziflumid - Acute Toxicity to Mysids (*Americamysis bahia*) Under Daily Static-Renewal Conditions (W-33025), DACO: 9.4.2
3059463	2018, Pyraziflumid: A 96-Hour Shell Deposition Test with the Eastern Oyster (*Crassostrea virginica*) (W-33024), DACO: 9.4.4
3059464	2018, Pyraziflumid: Life-Cycle Toxicity Test with Mysids (*Americamysis bahia*) (W-33023), DACO: 9.4.5
3059465	2016, Pyraziflumid - Acute Toxicity to *Oncorhynchus mykiss* (W-33014), DACO: 9.5.2.1
3059466	2018, Pyraziflumid - Acute Toxicity to Bluegill Sunfish (*Lepomis macrochirus*) Under Daily Static-Renewal Conditions (W-33028), DACO: 9.5.2.2
3059467	2017, Pyraziflumid: A 96-Hour Flow-Through Acute Toxicity Test with the Sheepshead Minnow (*Cyprinodon variegatus*) (W-33021), DACO: 9.5.2.3
3059468	2017, Pyraziflumid: Acute Toxicity to Fathead Minnow (*Pimephales promelas*) Under Daily Static-Renewal Conditions (W-33015), DACO: 9.5.2.3

3059469	2014, Acute Toxicity Test of NNF-0721 with Common Carp (*Cyprinus carpio*) (W-33003), DACO: 9.5.2.3
3059470	2017, Pyraziflumid: Early Life-Stage Toxicity Test with Fathead Minnow (*Pimephales promelas*) (W-33020), DACO: 9.5.3.1
3059471	2015, NNF-0721: Bioconcentration in Bluegill Sunfish (W-33002), DACO: 9.5.6
3059472	2010, NNF-0721: Acute Oral Toxicity (LD50) to the Bobwhite Quail (W-33001), DACO: 9.6.2.1
3059473	2018, Sample Analysis - Pyraziflumid: Zebra Finch (*Taeniopygia guttata*) Dietary Acute Toxicity Test (A-33020), DACO: 9.6.2.6
3059474	2016, NNF-0721: Dietary Toxicity (LD50) to the Bobwhite Quail (W-33009), DACO: 9.6.2.4
3059475	2017, Mallard Duck (*Anas platyrhynchos*) Dietary Toxicity Test (LC50) with Pyraziflumid (W-33019), DACO: 9.6.2.5
3059476	2017, Sample Analysis - Mallard Duck (*Anas platrhynchos*) Dietary Toxicity Test (LC50) with Pyraziflumid (A-33016), DACO: 9.6.2.5
3059477	2018, Pyraziflumid: Zebra Finch (*Taeniopygia guttata*) Dietary Acute Toxicity Test (W-33027), DACO: 9.6.2.6
3059478	2019, Pyraziflumid: Reproductive Toxicity Test with the Northern Bobwhite (*Colinus virginianus*) (W-33029), DACO: 9.6.3.1
3059479	2019, Pyraziflumid: Reproductive Toxicity Test with the Mallard (*Anas platyrhynchos*) (W-33030), DACO: 9.6.3.2
3059480	2018, Pyraziflumid: 96-Hour Toxicity Test with the Freshwater Diatom, *Navicula pelliculosa* (N-33019), DACO: 9.8.2
3059481	2018, Pyraziflumid: 96-Hour Toxicity Test with the Freshwater Cyanobacterium, *Anabaena flos-aquae* (N-33017), DACO: 9.8.2
3059482	2014, Algal Growth Inhibition Test of NNF-0721 (N-33006), DACO: 9.8.2
3059483	2014, Algal Growth Inhibition Test of NNF-0721 20SC (N-33005), DACO: 9.8.2
3059484	2018, Pyraziflumid: 96-Hour Toxicity Test with the Marine Diatom, *Skeletonema costatum* (N-33016), DACO: 9.8.3
3059485	2018, Pyraziflumid 20SC: Vegetative Vigor Test (N-33022), DACO: 9.8.4
3059486	2018, Pyraziflumid 20SC: Seedling Emergence Test (N-33021), DACO: 9.8.4
3059487	2018, Pyraziflumid: 7-Day Toxicity Test with Duckweed (*Lemna gibba*) (N-33018), DACO: 9.8.5
3059488	2019, Pyraziflumid - 28-Day Toxicity Test Exposing Estuarine Amphipods (*Leptocheirus plumulosus*) to a Test Substance Applied to Sediment Under Static-Renewal Conditions Following EPA Test Methods (W-33031), DACO: 9.4.5
3059489	2019, Pyraziflumid: Screening Level Ecological Risk Assessment for Proposed Uses on Pome Fruits (Crop Group 11-10), Stone Fruits (Crop Group 12-12), Tree Nuts (Crop Group 14-12), Caneberry (Crop Subgroup 13-07A), Bushberry (Crop Subgroup 13-07B), and Small Fruit Vine Climbing Subgroup, except Fuzzy Kiwifruit (Crop Subgroup 13-07F), and Turf, DACO: 9.9
3059490	2019, Independent Laboratory Validation of a Method for the Determination of Pyraziflumid in Aqueous Matrices by LC-MS/MS (A-33026), DACO: 9.9
3059491	2018, Determination of NNF-0721 in Soil, Sediment, Thatch, and Grass Clippings (E-33021), DACO: 9.9

3059492	2018, Development and Validation of a Method for the Determination of Pyraziflumid in Surface and Drinking Water (A-33022), DACO: 9.9
3059493	2018, Pyraziflumid: A 10-Day Toxicity Test with the Marine Amphipod (*Leptocheirus plumulosus*) Using Spiked Sediment (W-33026), DACO: 9.4.5
3059494	2017, 42-Day Toxicity Test Exposing Freshwater Amphipods (*Hyalella azteca*) to Pyraziflumid Applied to Sediment Under Static Renewal Conditions Following EPA Test Methods (W-33022), DACO: 9.3.4
3059495	2017, Pyraziflumid: 10-Day Toxicity Test Exposing Freshwater Amphipods (*Hyalella azteca*) to a Test Substance Applied to Sediment Under Intermittent-Renewal Conditions (W-33018), DACO: 9.3.4
3059496	2017, Pyraziflumid: 10-Day Toxicity Test Exposing Midge (*Chironomus dilutus*) to a Test Substance Applied to Sediment Under Intermittent-Renewal Conditions (W-33017), DACO: 9.3.4
3059497	2014, Acute Immobilization Test of NNF-0721 20SC on *Daphnia magna* (W-33008), DACO: 9.3.2
3059498	2018, Toxicity to the Aphid Parasitoid *Aphidius rhopalosiphi* De Stefani-Perez (Hymenoptera, Braconidae) under Laboratory Conditions (N-33024), DACO: 9.2.6
3059499	2018, Independent Laboratory Validation of for the Determination of Pyraziflumid in Soil, Sediment, and Grass Clippings (A-33023), DACO: 9.9
3059500	2017, Pyraziflumid Technical Grade: Validation of the Analytical Method for the Determination of a Test Substance in Avian Feed by LC-MS/MS Method (A-33014), DACO: 9.9
3072324	2018, Toxicity to the Predatory Mite, *Typhlodromus pyri* Scheuten (Acari, Phytoseiidae) under Laboratory Conditions (N-33025), DACO: 9.2.5
3134985	2012, NNF-0721 Acute Toxicity to Honey Bees (N-33001), DACO: 9.2.4.2
3134986	2020, Response from Smithers regarding the evaluation of the following study by the Pest Management Regulatory Agency: Pyraziflumid: 10-Day Oral Toxicity Test with the Adult Honey Bee (*Apis mellifera*) Smithers Study No. 13657.6191, DACO: 9.2.4.4
3134987	2017, Pyraziflumid - Full Life-Cycle Toxicity Test with Water Fleas, *Daphnia magna*, Under Flow-Through Conditions, DACO: 9.3.3
3134988	2020, Pyraziflumid: Request for a Waiver from the Fish Early Life Stage (Saltwater) Study with the Technical Grade Active Ingredient, DACO: 9.5.3,9.5.3.1
3134989	2020, Pyraziflumid: Rationale for Waiving the Requirement for an Avian Oral Acute Toxicity Test with the Mallard Duck, DACO: 9.6.2.2
3059354	2019, Pyraziflumid: Foreign Soil Comparability Analysis to Support Adsorption-Desorption Study No. E-33005, DACO: 8.2.4.2
3059439	2019, Tier II Summary of Fate and Behavior in the Environment for Pyraziflumid (NNF-0721), DACO: 8.1
3059440	2015, Hydrolysis Study of NNF-0721 (Parent) (E-33008), DACO: 8.2.3.2
3059441	2019, Indirect Photolysis Study of NNF-0721 (E-33027), DACO: 8.2.3.3.2
3059442	2016, Photodegradation of NNF-0721 on The Soil Surface (E-33015), DACO: 8.2.3.3.1

3059443	2015, Photodegradation of NNF-0721 in Buffer Solution (E-33009), DACO: 8.2.3.3.2
3059444	2017, Aerobic Soil Metabolism of [^{14}C] Pyraziflumid in Four Soils (E-33019) , DACO: 8.2.3.4.2
3059445	2017, Anaerobic Soil Metabolism of [^{14}C] Pyraziflumid in Four Soils (E-33020), DACO: 8.2.3.4.4
3059446	2018, Aerobic Aquatic Dissipation Study to determine DT50 of Non-radiolabeled Pyraziflumid (NNF-0721) in Four Sediment/Water Test Systems (E-33022), DACO: 8.2.3.5.4
3059447	2017, Aerobic Aquatic Metabolism of [^{14}C] Pyraziflumid in Two Sediment/Water Systems (E-33018), DACO: 8.2.3.5.4
3059448	2017, Anaerobic Aquatic Metabolism of [^{14}C] Pyraziflumid in Two Sediment/Water Systems (E-33017), DACO: 8.2.3.5.6
3059449	2014, Adsorption/desorption of NNF-0721 on Soil (E-33005), DACO: 8.2.4.2
3059450	2019, Terrestrial Field Dissipation (TFD) Study for Pyraziflumid in California, USA, 2019 (E-33032), DACO: 8.3.2
3059451	2019, Terrestrial Field Dissipation (TFD) Study for Pyraziflumid in Georgia, USA, 2018 (E-33031), DACO: 8.3.2
3059452	2019, Terrestrial Field Dissipation (TFD) Study for Pyraziflumid in New York, USA, 2017 (E-33030), DACO: 8.3.2
3059453	2019, Terrestrial Field Dissipation (TFD) Study for Pyraziflumid in Washington State, USA, 2016 (E-33029), DACO: 8.3.2

4.0 Value

PMRA Number	Reference
3072315	2019, 018 Nichino Apple Phyto mildew trial, DACO: 10.2.3.3
3072316	2019, Michigan State University Apple Scab Trial 2017 Nichino, DACO: 10.2.3.3
3072320	2019, Evaluate efficacy of anticipated commercial use rates of pyraziflumid against Apple Scab, DACO: 10.2.3.3
3072321	2019, Evaluation of fungicides for management of apple scab and powdery mildew on Rome, 2017, DACO: 10.2.3.3
3134998	2019, Gatten EC and Pyraziflumid 20SC Efficacy on Apple Powdery Mildew in Washington, DACO: 10.2.3.3
3150188	2020, Trial Report - Corrected - 2018-0085 Efficacy of Pyraziflumid 20SC for Control of Apple Scab with and without Non-ionic Surfactant, DACO: 10.2.3.3(D)
3150190	2020, Trial Report - Corrected - 2018-0127 Efficacy of Pyraziflumid 20SC for Control of Powdery Mildew on Apple with and without Non-ionic Surfactant, DACO: 10.2.3.3(D)
3150192	2020, Trial Report - Corrected - 2018-0138 Efficacy of Pyraziflumid 20SC for Control of Powdery Mildew on Jonathan Apple with and without Non-ionic Surfactant, DACO: 10.2.3.3(D)
3188796	2021, 2020-0325 Efficacy of Parade fungicide for control of apple scab, DACO: 10.2.3.3(D)