Proposed Registration Decision PRD2022-15

# Pyrifluquinazon and Pyrifluquinazon 20SC Insecticide

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# Overview

## Proposed registration decision for Pyrifluquinazon and Pyrifluquinazon 20SC Insecticide

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 Pyrifluquinazon Technical and Pyrifluquinazon 20SC Insecticide, containing the technical grade active ingredient pyrifluquinazon, for the control of aphids and whiteflies in greenhouse vegetables and greenhouse herbaceous and woody deciduous ornamentals.

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 section provides detailed technical information on the human health, environmental and value assessments of pyrifluquinazon and Pyrifluquinazon 20SC Insecticide.

## What does Health Canada consider when making a registration decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered 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 and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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

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

Before making a final registration decision on pyrifluquinazon and Pyrifluquinazon 20SC Insecticide, 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 pyrifluquinazon and Pyrifluquinazon 20SC Insecticide, 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 section of this consultation document.

## What is Pyrifluquinazon?

**Pyrifluquinazon is an insecticide that acts on the insect nervous system. Pyrifluquinazon controls insects by acting as a feeding blocker that disrupts feeding in plant-sucking insects. This leads to starvation and death as the insects can no longer penetrate plants with their mouthparts.**

Pyrifluquinazon displays translaminar (local systemic) movement by entering one side of a leaf and moving to the other leaf surface when applied to foliage. Pyrifluquinazon is the active ingredient in Pyrifluquinazon 20SC Insecticide, which controls aphids and whiteflies in greenhouse lettuce, cucumber, tomato, eggplant and pepper and greenhouse herbaceous and woody deciduous ornamentals.

## Health considerations

### Can approved uses of Pyrifluquinazon affect human health?

**Pyrifluquinazon 20SC Insecticide, containing pyrifluquinazon, is unlikely to affect your health when used according to proposed label directions.**

Potential exposure to pyrifluquinazon may occur through the diet (food), 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 selected 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

[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*.

effects noted in animals occur at dose levels 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, the technical grade active ingredient pyrifluquinazon was of moderate acute toxicity by the oral route; consequently, the signal word and hazard statement "WARNING – POISON" are required on the label. It was of low acute toxicity dermally and of slight acute toxicity following inhalation exposure. It was minimally irritating to the eyes and non-irritating to the skin, but caused an allergic skin reaction. Consequently, the hazard statement "POTENTIAL SKIN SENSITIZER" is required on the label.

The end-use product Pyrifluquinazon 20SC Insecticide, containing pyrifluquinazon, was of slight acute toxicity by the oral route; consequently, the signal word and hazard statement "CAUTION – POISON" are required on the label. It was of low acute toxicity through the dermal and inhalation routes of exposure. Pyrifluquinazon 20SC Insecticide was minimally 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 pyrifluquinazon to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on the nasal passages, altered fetal development, and mortality. There was no evidence to suggest that pyrifluquinazon has the potential to damage genetic material. Pyrifluquinazon did, however, cause testicular tumours in male rats and mice. An increase in benign mammary gland tumours observed in male rats could not be clearly attributed to treatment with pyrifluquinazon. There was an indication that the young were more sensitive than the adult animal. 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 food and drinking water**

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

Acute dietary (food alone) intake estimates indicated that the general population and all population subgroups including females 13 to 49 years old are exposed to less than 54% of the acute reference dose, and therefore are not of health concern.

Chronic (non-cancer and cancer) dietary (food alone) intake estimates indicated that the general population and all population subgroups are exposed to less than 15% of the acceptable daily intake, and therefore are not of health concern.

The *Food and Drugs Act (FDA)* 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 FDA purposes through the evaluation of scientific data under the *Pest Control Products Act (PCPA).* Given that dietary risks from the consumption of foods are shown to be acceptable when pyrifluquinazon is used according to the supported label directions, MRLs are being proposed as a result of this assessment.

MRLs for pyrifluquinazon were determined from the acceptable residue trials conducted throughout Canada on greenhouse tomatoes, peppers, lettuce and cucumbers, the United States on tuberous and corm vegetables, leafy vegetables, *Brassica* vegetables, fruiting vegetables, cucurbit vegetables, pome fruits, stone fruits, citrus fruits, small fruits vine climbing (except fuzzy kiwifruit), tree nuts, leaf petiole vegetables and cotton, and Japan on tea.

**Occupational risks from handling Pyrifluquinazon 20SC Insecticide**

**Occupational risks are not of health concern when Pyrifluquinazon 20SC Insecticide is used according to the label directions, which include protective measures.**

Workers mixing, loading or applying Pyrifluquinazon 20SC Insecticide, and workers entering recently treated greenhouses can be exposed to pyrifluquinazon residues through direct skin contact and through inhalation. Therefore, the label specifies that anyone mixing, loading and applying Pyrifluquinazon 20SC Insecticide must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. 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 Pyrifluquinazon 20SC Insecticide is used according to the proposed label directions.**

Applications of Pyrifluquinazon 20SC Insecticide will occur within commercial greenhouses only. Therefore, health risks in residential and other non-occupational environments are not of concern.

**Health risks to bystanders**

**Bystander risks are not of health concern when Pyrifluquinazon 20SC Insecticide is used according to the proposed label directions.**

Applications of Pyrifluquinazon 20SC Insecticide will occur within greenhouses only. Therefore, health risks to bystanders are not of concern.

## Environmental considerations

**What happens when Pyrifluquinazon is introduced into the environment?**

**When pyrifluquinazon is used according to label directions, the risks to the environment are acceptable.**

Pyrifluquinazon 20SC Insecticide, containing pyrifluquinazon, will not be released directly into the environment when used on greenhouse food crops and ornamentals. Should pyrifluquinazon enter the environment, it is expected to break down quickly in both soil and water. Pyrifluquinazon exhibits low mobility in soil and low potential to leach through the soil profile to enter ground water.

When pyrifluquinazon is used as a foliar spray for control of pests on greenhouse food crops and ornamentals, beneficial arthropods and bees, which may be used for greenhouse pest management and pollination, could be exposed to spray droplets or residues through contact or oral exposure. While pyrifluquinazon is non-toxic to beneficial arthropods, there is a potential risk to bees. As such, to avoid exposure to bees that may be used in greenhouse production, a label statement is required to avoid application when bees are in the treatment area.

Pyrifluquinazon is toxic to some species of aquatic invertebrates; therefore, label statements prohibiting release of greenhouse effluent into aquatic systems are required.

When pyrifluquinazon is used in accordance with the label directions and the required risk reduction measures are applied, the resulting environmental risk is acceptable.

## Value considerations

**What is the value of product Pyrifluquinazon 20SC Insecticide?**

**Pyrifluquinazon 20SC Insecticide is a new active ingredient that provides control of aphids and whitefly in greenhouse lettuce, tomato, eggplant, cucumber and pepper and greenhouse herbaceous and woody ornamentals. Aphids and whitefly are widespread and significant pests of greenhouse crops.**

Pyrifluquinazon 20SC Insecticide can aid in resistance management of aphids and whitefly when used in rotation with other insecticides in integrated pest management programs. As pyrifluquinazon stops feeding by insects, it may also aid in reducing the transmission of insect-vectored plant viruses.

## 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 Pyrifluquinazon Technical and Pyrifluquinazon 20SC Insecticide to address the potential risks identified in this assessment are as follows.

### Key risk-reduction measures

### Human health

To reduce the potential of workers to pyrifluquinazon through direct skin contact or inhalation of sprays, workers mixing, loading and applying Pyrifluquinazon 20SC Insecticide and performing cleaning and repair activities must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. The label also requires that workers do not enter or be allowed entry into treated greenhouses, during the REI of 12 hours. Furthermore, a statement preventing the use of handheld airblast, mistblowers and foggers is present on the label.

### Environment

With the following risk reduction measures on the label, the risks are considered acceptable:

- Label statements indicating application should be avoided when bees are in the treatment areas.
- Label statements prohibiting release of greenhouse effluent into aquatic systems.
- Label statement indicating toxicity to aquatic organisms.

## Next steps

Before making a final registration decision on pyrifluquinazon and Pyrifluquinazon 20SC Insecticide, 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.

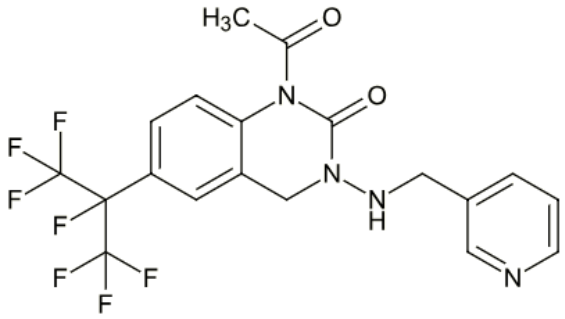
## Other information

When the Health Canada makes its registration decision, it will publish a Registration Decision on pyrifluquinazon and Pyrifluquinazon 20SC Insecticide (based on the Science Evaluation section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

# Science evaluation

## Pyrifluquinazon and Pyrifluquinazon 20SC Insecticide

### 1.1 Identity of the active ingredient

| | |
|---|---|
| **Active substance** | Pyrifluquinazon |
| **Function** | Insecticide |
| **Chemical name** | |
| **1. International Union of Pure and Applied Chemistry (IUPAC)** | 1-acetyl-1,2,3,4-tetrahydro-3-[(3-pyridylmethyl)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]quinazolin-2-one |
| **2. Chemical Abstracts Service (CAS)** | 1-acetyl-3,4-dihydro-3-[(3-pyridinylmethyl)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-2(1*H*)-quinazolinone |
| **3. French IUPAC Name** | 1-acétyl-1,2,3,4-tétrahydro-3-[(3-pyridylméthyl)amino]-6-[1,2,2,2-tétrafluoro-1-(trifluorométhyl)éthyl]quinazolin-2-one |
| **CAS number** | 337458-27-2 |
| **Molecular formula** | $C_{19}H_{15}F_7N_4O_2$ |
| **Molecular weight** | 464.34 |
| **Structural formula** |  |
| **Purity of the active ingredient** | 98.4% |

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

**Technical product—Pyrifluquinazon Technical**

| Property | Result | | |
|---|---|---|---|
| Colour and physical state | Off-white powder | | |
| Odour | No discernible odour | | |
| Melting range | 138-139°C | | |
| Boiling point or range | N/A | | |
| Specific gravity | 1.50-1.53 at 20.0°C | | |
| Vapour pressure at 20°C | $5 \times 10^{-8}$ Pa | | |
| Ultraviolet (UV)-visible spectrum | Medium | $\lambda_{max}$ (nm) | $\varepsilon$ ($L_{*}mol^{-1}{}_{*}cm^{-1}$) |
| | Neutral | 206.4 | 23297 |
| | | 241.0 | 11021 |
| | Acidic | 205.8 | 24755 |
| | | 241.4 | 11483 |
| | Basic | 219.9 | 11259 |
| | | 261.0 | 13248 |
| Solubility in water at 20°C | 12.1 mg/L (pH 5.78-6.11) | | |
| Solubility in organic solvents at 20°C | Solvent | | Solubility (g/L) |
| | n-heptane | | 0.215 |
| | xylene | | 20.2 |
| | methanol | | 111 |
| | ethyl acetate | | 170 |
| | dichloromethane | | ≥343 |
| | acetone | | ≥272 |
| *n*-Octanol-water partition coefficient ($K_{ow}$) | log $K_{ow}$ = 3.12 | | |
| Dissociation constant (p$K_a$) | 5.8 (calculated using a computer model) | | |
| Stability (temperature, metal) | Stable in contact with aluminum, aluminum acetate, iron, zinc and zinc acetate, but unstable in contact with iron acetate, at 54°C for 14 days. | | |

**End-use product — Pyrifluquinazon 20SC Insecticide**

| Property | Result |
|---|---|
| Colour | Off-white |
| Odour | Odourless |
| Physical state | Liquid |
| Formulation type | Suspension |

| Property | Result |
|---|---|
| Label concentration | 224 g/L |
| Container material and description | HDPE bottle, jug or tote |
| Specific gravity | 1.12 at 20°C |
| pH of 1% dispersion in water | 6.5 |
| Oxidizing or reducing action | Compatible with monoammonium phosphate, zinc, potassium permanganate and water |
| Storage stability | The product is stable for 1 year when stored in the commercial warehouse conditions at ambient temperature. |
| Corrosion characteristics | No corrosion to the commercial packaging was observed when stored at ambient temperature for 1 year. |
| Explodability | Not explosive |

### 1.3 Directions for use

**Greenhouse lettuce and greenhouse herbaceous and deciduous woody ornamentals (not grown for cut flowers):** For control of whitefly, apply Pyrifluquinazon 20SC Insecticide as a foliar spray to full coverage at an application concentration of 125 to 250 mL product in 1000 L water. For control of aphids, apply Pyrifluquinazon 20SC Insecticide as a foliar spray to full coverage at an application concentration of 187 to 250 mL product per 1000 L water. Up to two applications, applied with a minimum re-application interval of 10 days, may be applied per crop cycle.

**Greenhouse cucumbers, peppers, tomatoes and eggplant:** For control of whitefly and aphids, apply Pyrifluquinazon 20SC Insecticide as a foliar spray to full coverage at an application concentration of 125 to 164 mL product per 1000 L water. Only one application may be applied per crop cycle.

### 1.4 Mode of action

Pyrifluquinazon is in the Insecticide Resistance Action Committee (IRAC) mode of action (MOA) group 9B (chordotonal organ TRPV channel modulators, pyridine azomethine derivatives). Pyrifluquinazon acts on insect nerves, targeting the transient receptor potential (TRP) ion channel complex found in insect stretch receptor cells. Pyrifluquinazon displays translaminar movement when applied to foliage. Pyrifluquinazon acts as a feeding blocker that disrupts feeding in plant-sucking insects, causing insects to halt feeding, leading to starvation and death as they can no longer penetrate plants with their mouthparts.

# 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. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis in environmental media are summarized in Appendix I, Table 1.

A high performance liquid chromatography method with tandem mass spectrometric detection (HPLC-MS/MS; Method Meth-188 in plant matrices) was developed and proposed for data generation and enforcement purposes. This method fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant 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 in plant commodities are summarized in Appendix I, Table 2.

# 3.0 Impact on human and animal health

## 3.1 Hazard assessment

### 3.1.1 Toxicology summary

Pyrifluquinazon, also known as NNI-0101, is a quinazoline insecticide. The pesticidal mode of action (MOA) of pyrifluquinazon involves modulation of the chordotonal organ transient receptor potential vanilloid (TRPV) channel resulting in reduced feeding behaviour in insects.

A detailed review of the toxicology database for pyrifluquinazon 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 MOA for testicular interstitial cell tumours that also assessed various endocrine-related endpoints, as well as studies assessing the effects of pyrifluquinazon exposure on thyroid function in rats, acute oral

and genotoxicity studies for several metabolites of pyrifluquinazon, and genotoxicity studies for several impurities of pyrifluquinazon. The required studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The human health risk assessment also considered any relevant information found in the published literature. The scientific quality of the data is acceptable and the database is considered to be adequate to characterize the potential health hazards associated with pyrifluquinazon.

The metabolism and toxicokinetics of pyrifluquinazon in the rat were investigated following the administration of a single oral dose of pyrifluquinazon radiolabelled at the quinazolinone-phenyl ring, or the pyridine ring. Studies in bile duct-cannulated and intact rats showed that pyrifluquinazon was quickly and extensively absorbed following the administration of a single low or high oral dose. The absorption of pyrifluquinazon 72 hours following oral dosing was estimated to be approximately 63% of the administered dose (AD) based on the sum of radioactivity quantified in bile, urine, tissues, and carcass. The time to peak plasma concentration was 1 to 3 hours post administration at the low dose and 9 to 12 hours at the high dose following the administration of pyrifluquinazon radiolabelled at the quinazolinone-phenyl ring. For pyrifluquinazon radiolabelled at the pyridine ring, the time to peak plasma concentration was 1 hour post administration at the low dose, and 3 to 9 hours post-exposure at the high dose. Pyrifluquinazon was widely distributed, with the highest residues found in the liver, kidney, gastrointestinal tract and adrenal glands. The pattern of tissue distribution was similar for both dose levels; however time to peak tissue levels varied, with maximum levels occurring 3 and 9 hours following the administration of the low- and high-dose levels, respectively. Elimination of orally-administered pyrifluquinazon was bi-phasic and approximately 80% complete at 48 hours post-dosing at the low dose, and approximately 90% complete at 144 hours post-exposure at the high dose. In intact rats, the major routes of excretion for the quinazolinone-phenyl ring at 168 hours post-dosing were the feces, representing up to 80% of the AD, followed by urine with 15% to 20% of the AD. For the pyridine ring, major routes of excretion were the urine (42% to 48% of the AD), feces (45% to 61% of the AD) and expired air (6% to 9% of the AD). In bile-duct cannulated rats administered pyrifluquinazon radiolabelled on the pyridine ring, bile was the major excretion pathway accounting for 35% of the AD, with 12% and 5% of the AD detected in urine and feces, respectively, at 72 hours post-dosing. Excretion patterns were similar between sexes.

Pyrifluquinazon was extensively metabolized in rats. No unchanged pyrifluquinazon was found in urine or bile, and only low levels of pyrifluquinazon were noted in the feces. The presence of metabolites in the gastrointestinal tract (GIT) of bile duct-cannulated rats suggested that pyrifluquinazon is unstable and easily degraded in the natural conditions of the GIT. The major metabolic reactions of pyrifluquinazon involve initial deacetylation of the nitrogen atom at the 1-position of the quinazoline ring, hydroxylation of the 4-position in the quinazoline ring followed by conjugation by glucuronic acid, oxidation of the 1-position of the pyridine ring, dehydrogenation of the amino group, hydroxylation of the 8-position in the quinazoline ring, cleavage of the nitrogen-carbon bond, cleavage of the quinazoline ring followed by conjugation by glucuronic acid, cleavage of the nitrogen-carbon bond followed by aqueous vitamin, and methylation of the nitrogen atom of the pyridine ring. In urine, the main metabolites were IV-04, IV-303 glucuronide, IV-211 glucuronide and IV-405. The main metabolites in bile were

identified as IV-27 glucuronide, IV-211-glucuronide, IV-208, and IV-303. The main metabolites in the feces and gastrointestinal contents were IV-01, IV-02, IV-211, and IV-203. The metabolites found in bile were similar to those detected in feces collected from intact rats. In the blood, liver, brain and heart, the major metabolites were IV-402, IV-404 and IV-403. The main metabolites identified in the plasma included IV-01, IV-02, IV-203 and IV-208.

A supplemental in vitro study was also available to assess potential species-related differences in the metabolism of pyrifluquinazon by liver microsomes obtained from rats, dogs, and humans, as well as the metabolism of pyrifluquinazon by nasal mucosa microsomes obtained from unexposed rats and dogs, and dogs orally dosed with pyrifluquinazon for one year. No major species-related differences were noted in the metabolism of pyrifluquinazon by hepatic or nasal microsomes. Minor differences were observed including a higher proportion of minor metabolites and lower levels of metabolite IV-01 derived from human liver microsomes compared to those of rats and dogs, and slightly higher levels of IV-01 derived from the nasal mucosal microsomes of treated dogs, compared to those from control dogs and rats.

In acute toxicity studies, the technical grade active ingredient pyrifluquinazon was of moderate toxicity via the oral route, low toxicity via the dermal route, and of slight toxicity via the inhalation route of exposure in rats. It was minimally irritating to the eyes and non-irritating to the skin of rabbits. Pyrifluquinazon was positive for skin sensitization in guinea pigs when tested using the guinea pig maximization test (GPMT).

The end-use product, Pyrifluquinazon 20SC Insecticide, was of slight acute toxicity via the oral route, and of low acute toxicity via the dermal and inhalation routes of exposure in rats. It was minimally irritating to the eyes and skin of rabbits, and was positive for skin sensitization in mice when tested using the local lymph node assay (LLNA).

Repeat-dose dietary toxicity studies with pyrifluquinazon were available in mice and rats, and pyrifluquinazon was administered via capsule in repeat-dose oral toxicity studies in dogs. The longer term oral studies in dogs consisted of two 1-year studies, one of which included a 6-month recovery phase. Throughout the pyrifluquinazon database, effects were observed in numerous organs and tissues in rodents and dogs, however, the liver, thyroid, adrenal glands, and hematopoietic system were identified as the targets of toxicity following repeated oral exposure to pyrifluquinazon. Liver effects observed among mice, rats and dogs included increased organ weight, hepatocellular hypertrophy, altered clinical chemistry parameters, elevated liver enzymes, dark liver, necrosis, cellular infiltration, fatty change, and vacuolation. Effects observed in the thyroid included increased organ weight, follicular cell hypertrophy, enlarged thyroid, and increased thyroid follicles. Thyroid hormone levels were also affected in multiple short-term oral mechanistic studies in rats. The most common effects on thyroid hormones were changes in triiodothyronine ($T_3$) levels, and increased thyroid stimulating hormone (TSH) and thyroxine ($T_4$) levels. Hypertrophy and histopathological changes were also evident in the adrenal glands and pituitary, and were accompanied by a change in organ weight.

In addition, effects in reproductive organs, primarily the epididymides, testes, prostate, and uterus, were noted in several studies and included organ weight changes and histopathological changes such as atrophy and, in some cases, hyperplasia. Nasal tract toxicity was observed following chronic oral dosing in rats, mice, and dogs, but was not reported in rats following 28-days of inhalation exposure to pyrifluquinazon.

With respect to species-related differences in sensitivity, only a limited number of tissues demonstrated toxicity in dogs as compared to the vast number of tissues, organs, and systems exhibiting effects in rats. However, the lowest points of departure were observed in the dog, with the nasal passages being the main target of toxicity, in which mononuclear cell infiltration of the olfactory region of the nasal cavity was evident in both sexes after one year of dosing. This critical effect was shown to be reversible after a 6-month recovery period. Additional immunological investigations in dogs indicated that pyrifluquinazon did not induce an immune-mediated response; therefore, the pathogenesis of these lesions is unclear. A guideline 28-day dietary immunotoxicity study in rats further demonstrated the absence of an effect of pyrifluquinazon on immune system dysregulation.

There was evidence of increased toxicity with increasing duration of dosing in the database. Nasal lesions were observed in dogs (mononuclear cellular infiltration of the olfactory epithelium of the nasal cavity), rats (nasal cavity rhinitis), and mice (intracytoplasmic eosinophilic bodies in olfactory cells) following longer term dosing only.

Following short-term repeated dermal exposure in rats to pyrifluquinazon for 28 days, no dermal effects or signs of systemic toxicity were observed at dose levels up to and including the limit dose of testing in males or females. Information was provided by the applicant to demonstrate that the criteria related to the conditional requirement for a 90-day dermal toxicity study were met. The applicant cited the acceptable 28-day dermal toxicity study with pyrifluquinazon, as well as the low acute dermal toxicity of the end-use product.

Short-term repeated inhalation exposure (nose only) in rats to pyrifluquinazon for 28 days resulted in portal of entry effects consisting of terminal airway inflammation in the lungs of males. This effect was observed in rats at an equivalent systemic dose level that was higher than the oral dose levels producing nasal olfactory lesions in dogs in the 1-year oral capsule studies, the most sensitive species for pyrifluquinazon-related toxicity. The systemic effects observed in one or both sexes of rats in the 28-day inhalation toxicity study consisted of clinical signs of toxicity that included palpebral closure, splayed gait, lethargy, hunched posture, ataxia, sluggishness, ocular effects and mortality. Information was provided by the applicant to demonstrate that the criteria related to the conditional requirement for a 90-day inhalation toxicity study were met. The applicant cited the acceptable 28-day inhalation toxicity study with pyrifluquinazon, the low acute inhalation toxicity of the end-use product, and the low volatility of pyrifluquinazon.

Overall, it was concluded that there was no evidence of genotoxicity for pyrifluquinazon. Negative results were obtained in a battery of in vitro and in vivo genotoxicity studies, which included a bacterial reverse mutation assay, a gene mutation assay in mouse lymphoma cells, an in vitro chromosome aberration assay in Chinese hamster lung cells, and an in vivo micronucleus test in mice.

In an 18-month dietary oncogenicity study in mice, an increased incidence of Leydig cell tumours was observed in the testis of males at the highest dose level tested. Leydig cell tumours were also observed in mid- and high-dose males in the 2-year rat dietary carcinogenicity study. In both species, the incidences of these tumours were statistically significantly increased by pair-wise comparison when compared to controls. An MOA related to androgen receptor antagonism was proposed for tumour induction. Several mechanistic studies were provided by the applicant to support the proposed MOA. A description of key events was presented, with evidence demonstrating both dose and temporal relationships for the key events. The proposed MOA suggests that anti-androgenic effects mediated through suppressed transcriptional activity and signaling (disruption of negative feedback regulation) in the rat androgen receptor (rAR) leads to a sustained increase in circulating luteinizing hormone (LH) resulting in overstimulation of Leydig cells. The provided mechanistic data included in vitro assays assessing: antagonism and agonism of an androgen reporter gene in a human breast cancer cell line; androgen receptor (AR) binding affinity in the castrated male rat; androgen-independent transactivation in human kidney cells; AR protein expression in human breast cancer cells; nuclear localization of AR on human kidney, breast cancer, and prostate cancer cell lines; forced expression of rAR in human kidney and breast cancer cell lines; and estrogen receptor binding in human blood. Additionally, the following in vivo studies were provided: a uterotrophic assay in female rats, two Hershberger assays in castrated male rats, an acute oral assay to assess prostatic AR in male rats, 90-day dietary studies to assess LH levels in the mouse and rat, and 14-day and 56-day dietary studies to assess thyroid hormones in male rats.

Pyrifluquinazon demonstrated anti-androgenic activity in the two Hershberger assays in rats. The in vitro studies also supported anti-androgenic potential, which was most likely to occur through disruption of the AR-mediated signaling pathway by decreasing the intracellular protein expression, rather than through the more common mechanism of competitive inhibition of androgen binding. Increases in LH, testosterone, and dihydrotestosterone (DHT), decreased absolute and relative epididymis weight, and testicular interstitial cell hypertrophy were observed in the 90-day dietary mechanistic study in male mice. In male rats, increased LH and testosterone, an increased incidence of testicular seminiferous tubular atrophy, vacuolation of tubular epithelial cells of the epididymis, germ cell debris in the epididymis and decreased weights of the prostate, seminal vesicles with coagulating gland, and epididymis were observed following 90 days of dietary administration of pyrifluquinazon. It should be noted that although the Leydig cell tumours in rats in the 2-year dietary carcinogenicity study appeared to have occurred at dose levels lower than those exhibiting an increase in LH, this discrepancy was determined to be likely related to the lack of hormone measurements following chronic dosing.

Additionally, in the 2-year dietary carcinogenicity study in rats, a slight increase in the incidence of benign mammary gland fibroadenomas was noted in males in the mid- and high-dose groups when compared to controls. This lesion was only observed in male rats, and although the dose-response relationship did reach statistical significance when using the Cochran-Armitage linear trend test, there were no statistically significant differences from controls at any dose level when using the Fisher exact test for pair-wise comparison, and no evidence of genotoxicity was observed in the database. Therefore, the slight increase in the incidence of mammary gland fibroadenomas in male rats at the mid- and high-dose levels was considered to provide equivocal evidence for tumourigenicity, and a threshold approach for mammary gland tumours was taken for risk assessment purposes as it was concluded that a linear low dose extrapolation ($q_1$*) approach to the cancer risk assessment would be overly conservative.

Pyrifluquinazon demonstrated signs of increased pre-natal sensitivity in rats. In the oral developmental toxicity study in rats, effects on the maternal animals, in the form of decreased body weights and mean gravid uterine weights, were observed at a dose level higher than that at which fetal effects, which included decreased anogenital distance (AGD) in males and increased incidences of supernumerary ribs in both sexes, were reported. There were no adverse effects observed in maternal animals or fetuses in the oral developmental toxicity study conducted in the rabbit up to the highest dose level tested, which was the same dose level that showed decreased body weight gain in maternal animals, and one dose lower than that at which abortions occurred in maternal animals in the rabbit oral dose range-finding study.

No evidence of increased sensitivity of the young was noted in the 2-generation dietary reproductive toxicity study in the rat. Effects in parental animals were consistent with those noted in rats throughout the database, and occurred at the same dose levels as those producing offspring and reproductive effects. Reproductive effects included increased duration of gestation, a reduction in the number of live offspring, reduced sperm motility and higher abnormal sperm counts, and increased organ weights (testes and uterus). Effects in the offspring consisted of decreased body weights and decreased spleen and thymus weights, and in males only, effects consistent with anti-androgenic activity including hypospadias, decreased AGD, nipple retention, and delayed preputial separation. In a supplemental 2-generation dietary dose range-finding reproductive toxicity study in rats, similar effects to those in the main study were noted in parents and offspring, while additional reproductive effects consisted of reductions in mating, gestation, and fertility indices at dose levels exceeding those tested in the main study.

In a supplemental study identified in the published scientific literature in which pregnant rats were administered pyrifluquinazon via gavage, developmental and offspring effects occurred at the same or lower oral dose levels than those resulting in decreased maternal body weight gain, and included nipple retention, hypospadias, decreased AGD, and genital and reproductive tract abnormalities.

The neurotoxic potential of pyrifluquinazon was investigated in rats following acute gavage dosing, and 90 days of dietary administration. Clinical signs of toxicity, loss of body weight, and mortality were evident shortly after dosing in the acute study; however, these effects were considered to be the result of generalized systemic toxicity and not evidence of selective

neurotoxicity as the signs resolved within a few days and there was no treatment-related neuropathology. Additionally, no signs of neurotoxicity were observed in the 90-day neurotoxicity study. Information was provided by the applicant to demonstrate that the criteria related to the conditional requirements for an acute delayed neurotoxicity study and a developmental neurotoxicity study were met. Pyrifluquinazon does not contain an organophosphate moiety and is not structurally related to other substances that may cause acute delayed neurotoxicity. The overall weight of evidence supported that testing for the potential for pyrifluquinazon to cause developmental neurotoxicity is not required given that evidence of selective neurotoxicity was not observed in other studies in the supporting database. Although hormonal perturbations were apparent in the database, the selected reference values are considered to be protective of these effects, and pyrifluquinazon is not expected to elicit other types of nervous system involvement at the developmental stage.

Additional, yet limited, toxicity studies were conducted with several metabolites and impurities of pyrifluquinazon. Metabolites IV-01, IV-02, IV-15, IV-27, IV-28, and IV-203 were determined to be of low acute toxicity to rats via the oral route. Metabolites IV-01, IV-02, IV-203, and IV-208 were tested in vitro for androgen reporter gene expression, AR binding affinity, and estrogen receptor (ER) binding affinity. Additionally, metabolite IV-01 was tested for the nuclear localization of AR on human cells. For metabolite IV-01, a concentration-dependent increase in luciferase activity in the presence of DHT, indicating slight agonism, was evident in the androgen reporter expression assay, and a weak binding affinity was observed in the AR binding affinity assay. At high concentrations, metabolite IV-208 was determined to have potential binding affinity to ER-α and ER-β. In genotoxicity testing, metabolite IV-203 and impurities 1 through 7 inclusive, were negative when tested using the bacterial reverse mutation assay.

The identification of select metabolites is presented in Table 3 of Appendix I. The toxicology reference values for use in the human health risk assessment are summarized in Table 4 of Appendix I. Results of the toxicology studies conducted on laboratory animals with pyrifluquinazon, with its associated end-use product, and with relevant metabolites and impurities are summarized in Tables 5, 6, and 7, respectively, of Appendix I.

### 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* (PCPA) 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].

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

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. Oral developmental toxicity dose range-finding studies in the rat and rabbit, a 2-generation reproductive toxicity dose range-finding study in the rat, as well as a published literature study that assessed developmental toxicity in the rat were also available.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the rabbit. In the main oral developmental toxicity study in the rabbit, there were no treatment-related effects in the maternal animals or fetuses at the highest dose level tested. This was the same dose level that showed decreased body weight gain in maternal animals in the oral developmental toxicity dose range-finding study in the rabbit. At the next higher dose tested in the dose range-finding study, abortions occurred and maternal animals additionally exhibited decreased food consumption. In the rat, evidence of sensitivity of the young was noted in the developmental toxicity study as indicated by an increased incidence of a developmental variation (supernumerary rib) and altered development of the reproductive tract (decreased AGD in males) in fetuses, in the absence of maternal toxicity. In the 2-generation reproductive toxicity study in rats, effects in offspring were observed in the presence of thyroid effects in maternal animals. Effects in offspring of both sexes in the reproduction study included decreased body weights and decreased spleen and thymus weights, while effects observed only in male offspring were generally consistent with anti-androgenic activity and included hypospadias, nipple retention, decreased AGD, and delayed preputial separation. Concern for these findings was tempered by the presence of maternal toxicity at the same dose level.

Overall, the database is adequate for determining the sensitivity of the young. There is a concern for prenatal toxicity and sensitivity of the young based on the seriousness of the endpoint (decreased AGD) observed in the absence of maternal toxicity in the rat developmental toxicity study. Therefore, the full 10-fold PCPA factor was retained for scenarios in which the endpoint of decreased AGD in rats was used to establish the point of departure for assessing risk to women of reproductive age. For exposure scenarios involving other sub-populations, including children, the risk was considered well-characterized and the PCPA factor was reduced to 1-fold.

## 3.2 Toxicology reference values

### 3.2.1 Route and duration of exposure

Potential exposure to pyrifluquinazon may occur via the diet (food). Workers are also expected to be exposed via the dermal route over short-, intermediate- and long-term exposure durations and the inhalation route over short and intermediate term exposure durations.

For mixers, loaders and applicators, occupational exposure to Pyrifluquinazon 20SC Insecticide is characterized as short-term in duration and is predominantly by the dermal and inhalation routes. For postapplication workers, occupational exposure to Pyrifluquinazon 20SC Insecticide is characterized as intermediate to long-term in duration and is predominantly by the dermal route.

### 3.2.2 Occupational toxicology reference values

**Short- and intermediate-term dermal and inhalation**

For short- and intermediate-term occupational exposures via the dermal and inhalation routes, the developmental NOAEL of 5 mg/kg bw/day from the oral developmental toxicity study in the rat was selected for risk assessment. At the developmental LOAEL of 10 mg/kg bw/day, toxicity was observed in this study in the form of altered development of the reproductive tract in males, and an increased incidence of a developmental variation (supernumerary ribs) in both sexes. These effects were observed in the absence of maternal toxicity. Worker populations could include pregnant women and therefore these endpoints were considered appropriate for the occupational risk assessment. The available 28-day dermal and inhalation toxicity studies did not assess the relevant endpoints of concern (that is, developmental effects following prenatal exposure), thus necessitating the use of an oral toxicity study for risk assessment purposes.

The target MOE for these scenarios is 1000, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a factor of 10-fold for the reasons outlined in the PCPA Hazard Characterization section. 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.

**Long-term dermal**

For long-term occupational exposures via the dermal route, the NOAEL of 0.5 mg/kg bw/day from the combined results of the two 1-year dog oral toxicity studies was selected for risk assessment purposes. At the LOAEL of 1.5 mg/kg bw/day, lesions in the nasal cavity were observed in the form of mononuclear cellular infiltration of the olfactory epithelium. The available 28-day dermal toxicity study did not assess the most sensitive species (the dog) and was of insufficient duration for the assessment of long-term dermal exposure scenarios, thus necessitating the use of the dog oral toxicity studies for risk assessment purposes.

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

### 3.2.3 Acute reference dose (ARfD)

**Females 13-49 years of age**

To estimate acute dietary risk to females 13 to 49 years of age, the developmental toxicity study in the rat with a developmental NOAEL of 5 mg/kg bw/day was selected for risk assessment purposes. At the developmental LOAEL of 10 mg/kg bw/day, an increased incidence of supernumerary ribs (a variation) and decreased AGD were observed in the absence of maternal toxicity.

These effects could result from 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. As discussed in the PCPA Hazard Characterization section, the PCPA factor of 10-fold was retained. The composite assessment factor (CAF) is thus 1000.

The ARfD is calculated according to the following formula:

$$\text{ARfD (females 13-49 years)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{5 mg/kg bw/day}}{1000} = 0.005 \text{ mg/kg bw of pyrifluquinazon}$$

**General population (excluding females 13-49 years of age)**

To estimate acute dietary risk for the general population, the NOAEL of 100 mg/kg bw from the acute oral neurotoxicity study in the rat was selected for risk assessment purposes. At the LOAEL of 300 mg/kg bw, mortality and clinical signs of toxicity 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. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. The CAF is thus 100.

The ARfD is calculated according to the following formula:

$$\text{ARfD (general population)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{100 mg/kg bw}}{100} = 1.0 \text{ mg/kg bw of pyrifluquinazon}$$

### 3.2.4 Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, the results of the two 1-year oral toxicity studies in the dog were considered and the combined NOAEL of 0.5 mg/kg bw/day was selected. At the LOAEL of 1.5 mg/kg bw/day, nasal lesions in the olfactory epithelium were observed. These studies provide 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 PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. The CAF is thus 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{0.5 mg/kg bw/day}}{100} = \text{0.005 mg/kg bw/day of pyrifluquinazon}$$

The ADI provides a margin of 700 to the NOAEL for the equivocal increase in mammary gland fibroadenomas and the testicular interstitial cell tumours in male rats, 5400 to the NOAEL for testicular interstitial cell tumours in the male mice, 1000 to the NOAEL for developmental effects in the rat, and 460 to the NOAEL for offspring effects in the rat.

### 3.2.5 Cancer assessment

An increased incidence of testicular interstitial cell tumours was observed in male mice and rats following chronic dietary dosing. An MOA for tumour induction was proposed related to that of androgen receptor antagonism. Despite some limitations, the MOA was deemed plausible and the overall weight of evidence was considered sufficient to conclude that a linear low-dose extrapolation ($q_1$*) approach to the cancer risk assessment may be overly conservative. For these reasons, a threshold approach for testicular interstitial cell tumours was applied for the cancer risk assessment. An increase in the incidence of benign mammary gland fibroadenomas was observed in male rats in the 2-year carcinogenicity study with pyrifluquinazon. The relationship to treatment for this tumour was considered equivocal based on the weight of evidence. Overall, the toxicology reference values selected for the non-cancer risk assessment are protective of any residual concerns regarding the carcinogenic potential of pyrifluquinazon.

### 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). For pyrifluquinazon, an aggregate assessment is not required since no exposure via drinking water or residential scenarios is expected as the proposed uses are limited to greenhouses.

## 3.3 Dermal absorption

A rat in vivo dermal absorption study was reviewed. Based on the data presented in the study, a dermal absorption value of 19% was selected for the risk assessment of pyrifluquinazon (Appendix I, Table 8).

## 3.4 Occupational and residential exposure assessment

### 3.4.1 Acute hazards of end-use product(s) and mitigation measures

#### 3.4.1.1 Pyrifluquinazon 20SC Insecticide

The acute hazard assessment indicated that Pyrifluquinazon 20SC Insecticide is of slight oral toxicity, and of low toxicity via the inhalation and dermal routes in rats; is minimally irritating to the eye and on the skin of rabbits, and is a dermal sensitizer in mice (Local Lymph Node Assay). 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.

### 3.4.2 Occupational exposure and risk assessment

#### 3.4.2.1 Mixer, loader and applicator exposure and risk assessment

Individuals have the potential for exposure to pyrifluquinazon during mixing, loading, application, clean-up and repair. Dermal and inhalation exposure estimates were generated from the Agricultural Handlers Exposure Task Force (AHETF) database, and the Pesticide Handlers Exposure Database (PHED, v1.1) for mixers, loaders and applicators applying Pyrifluquinazon 20SC Insecticide to greenhouse grown vegetables and ornamentals using automated, and handheld equipment. The unit exposure values in the risk assessment are based on handlers wearing long sleeved shirt, long pants, chemical resistant gloves, socks and shoes (Appendix I, Table 9).

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value of 19%. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the selected toxicological reference value to obtain the margin of exposure (MOE); the target MOE is 1000. Dermal and inhalation MOEs were combined, since the dermal and inhalation reference values are based on the same toxicological effects. Calculated MOEs are greater than the target MOE of 1000 for all chemical handler scenarios and are therefore not of health concern (Appendix I, Table 10).

#### 3.4.2.2 Postapplication exposure and risk assessment

There is potential for exposure to workers entering areas treated with Pyrifluquinazon 20SC Insecticide to complete tasks such as hand harvesting. 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 pyrifluquinazon is considered non-volatile with a vapour pressure of $5.0 \times 10^{-11}$ kPa (at 25°C), which is less than the North American Free Trade Agreement (NAFTA) criterion for a non-volatile product for indoor scenarios $1 \times 10^{-5}$ kPa at 20-30°C. As such, a quantitative postapplication inhalation risk assessment is not required. Inhalation risk is not of health concern for postapplication workers as pyrifluquinazon 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.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue (DFR) values with activity-specific transfer coefficients (TCs). Activity TCs are based on data from the Agricultural Re-entry Task Force (ARTF). As chemical-specific DFR data were not submitted, a standard DFR value of 25% of the application rate coupled with 2% daily dissipation of residues were used in the exposure assessment.

Exposure estimates were compared to the selected toxicological reference value to obtain the margin of exposure (MOE); the target MOE is 100. Only exposures and risks to the activities with the highest TCs are presented as MOEs for these activities exceed the target MOE of 100, and are thus, not of health concern (Appendix I, Table 11). For all postapplication activities, the REI of 12 hours is adequate.

### 3.4.3 Residential exposure and risk assessment

#### 3.4.3.1 Handler exposure and risk assessment

Pyrifluquinazon 20SC Insecticide is not a domestic class product and is not permitted for use in residential settings; therefore, a residential handler exposure assessment is not required.

#### 3.4.3.2 Postapplication exposure and risk assessment

Pyrifluquinazon 20SC Insecticide is not a domestic class product and is not permitted for use in residential settings; therefore, a residential postapplication exposure assessment is not required.

### 3.4.4 Bystander exposure and risk assessment

Bystander exposure is considered negligible as application is limited to greenhouses only, where there is low risk of drift beyond the area to be treated. 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 Exposure from residues in food of plant origin

The residue definition in plants for risk assessment is pyrifluquinazon and the metabolite IV-01 (expressed as parent equivalents) and for enforcement is pyrifluquinazon. The data-gathering and enforcement analytical method is valid for the quantitation of pyrifluquinazon and metabolite IV-01 residues in crop commodities. The residues of pyrifluquinazon are stable in high-starch content crops for 12 months, high-water content crops for 2-12 months, high-acid content crops for 5-6 months, and in high-oil content crops for 5-12 months when stored in a freezer at ~-20°C. The raw agricultural commodities apple, cotton, grape, orange, plum, potato and tomato were processed, pyrifluquinazon residues concentrated in the following processed commodities: citrus oil (94x) and prunes (1.4x). Crop field trials conducted throughout Canada, United States, and Japan using end-use products containing pyrifluquinazon at exaggerated rates in or on tuberous and corm vegetables, leafy vegetables, *Brassica* vegetables, fruiting vegetables, cucurbit vegetables, pome fruits, stone fruits, citrus fruits, small fruits vine climbing (except fuzzy kiwifruit), tree nuts, leaf petiole vegetables, cotton and tea are sufficient to support the proposed maximum residue limits.

### 3.5.2 Exposure from residues in drinking water

As the supported Canadian uses are greenhouse vegetables and ornamental plants only, there is no expectation of pyrifluquinazon residues in drinking water.

### 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 refined acute analysis for pyrifluquinazon: 100% crop treated, default and experimental processing factors (where available), and residues in/on crops based on highest average field trial (HAFT) values. The refined acute dietary exposure (food alone) for all supported pyrifluquinazon food uses including imported commodities is estimated to be 53.5% (0.003 mg/kg bw/day) of the ARfD for females 13–49 years old ($95^{th}$ percentile, deterministic) and less than 1% of the ARfD for all the other population subgroups.

#### 3.5.3.2 Chronic dietary exposure results and characterization

The following assumptions were applied to the refined chronic cancer and non-cancer analysis for pyrifluquinazon: 100% crop treated, default and experimental processing factors (where available), and residues in/on crops based on supervised trial median residue (STMdR) values. The refined chronic dietary exposure (food alone) from all supported pyrifluquinazon food uses including imported commodities for the total population, including infants and children, and all representative population subgroups is less than 15% of the acceptable daily intake (ADI). The PMRA estimates that chronic dietary exposure to pyrifluquinazon from food is 8.0% (0.0004 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children (1-2 years old) at 14.1% (0.0007 mg/kg bw/day) of the ADI.

## 3.6 Aggregate exposure and risk assessment

For pyrifluquinazon, no aggregate assessment was required since residential and drinking water exposures are not expected.

## 3.7 Cumulative assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for pyrifluquinazon. Pyrifluquinazon, along with the registered pesticide pymetrozine, is classified as a pyridine azomethine derivative with a pesticidal MOA that involves modulation of the chordotonal organ TRPV channel. A review of the available toxicity information did not reveal

any common mechanisms of toxicity between pyrifluquinazon and pymetrozine. Pyrifluquinazon is also classified, based on its structure, as a quinazoline insecticide. Currently no other quinazoline insecticides are registered for use in Canada. Pyrifluquinazon and other quinazoline insecticides to which Canadians may be exposed via imported food commodities (e.g., fenazaquin, fluquinconazole) demonstrate different pesticidal modes of action and toxicological profiles, and as such are not considered to have a common mechanism of toxicity with pyrifluquinazon. Therefore, a cumulative health risk assessment is not required at this time.

## 3.8 Maximum residue limits

Dietary risks from the consumption of food commodities listed in Table 3.8.1 were shown to be acceptable when pyrifluquinazon is used according to the supported label directions. Therefore, foods containing residues at these levels are safe to eat, and the PMRA recommends that the following MRLs be specified for residues of pyrifluquinazon.

**Table 3.8.1 Recommended maximum residue limits**

| MRL (ppm) | Food Commodity |
|---|---|
| 30 | Citrus oil |
| 20 | Tea (dried leaves) |
| 5.0 | Leafy vegetables (crop group 4-13) |
| 1.5 | Leaf petiole vegetables (crop subgroup 22B) |
| 0.70 | Citrus fruits (revised; crop group 10) |
| 0.60 | *Brassica* head and stem vegetables (crop group 5-13) |
| 0.30 | Fruiting vegetables (crop group 8-09); cherries (crop subgroup 12-09A); small fruits vine climbing, except fuzzy kiwifruit (crop subgroup 13-07F); undelinted cotton seeds |
| 0.07 | Cucurbit vegetables (crop group 9), pome fruits (crop group 11-09) |
| 0.04 | Peaches (crop subgroup 12-09B) |
| 0.02 | Tuberous and corm vegetables (crop subgroup 1C); plums (crop subgroup 12-09C); 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 and Pest Management section of Health Canada's website.

For additional information on Maximum Residue Limits (MRLs) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Tables 2, 12 and 13 in Appendix I.

### 3.9 Health incident reports

Pyrifluquinazon is a new active ingredient pending registration for use in Canada, and as of April 25, 2022, no incident reports had been submitted to the PMRA.

## 4.0 Impact on the environment

### 4.1 Fate and behaviour in the environment

Environmental fate data for pyrifluquinazon and its transformation products, in the terrestrial and aquatic environment, are summarized in Appendix I, Tables 14-15.

Pyrifluquinazon is soluble in water. It has a low vapor pressure ($5 \times 10^{-8}$ Pa) and a Henry's law constant of $1.894 \times 10^{-11}$ atm $m^3$/mol, suggesting volatility from moist soils and water surfaces is not expected. Pyrifluquinazon is not expected to undergo long-range transport in the atmosphere. Hydrolysis is rapid under basic conditions and slower under acidic conditions. Pyrifluquinazon hydrolyzed and formed the major transformation product IV-01 at all measured pHs.

In the terrestrial environment, pyrifluquinazon is non-persistent in soil under aerobic conditions. Major transformation products (IV-01, IV-02, IV-15, IV-27, IV-28 and IV- 203) were identified from laboratory aerobic soil biotransformation studies. These transformation products were estimated to be non-persistent to moderately persistent under aerobic soil conditions.

Pyrifluquinazon is expected to be moderately mobile to immobile in a variety of soil types according to the mobility classification scheme of McCall *et al*. (1981). Transformation products IV-01, IV-02 and IV-15 have potential to be immobile, while IV-27 has low mobility. When taking into consideration the criteria of Cohen *et al.* (1984) and the groundwater ubiquity score of Gustafson (1989), it was determined that pyrifluquinazon is unlikely to leach through soil into groundwater. When taking into consideration the groundwater ubiquity score, it was determined that transformation products IV-01, IV-02, IV-15 and IV-27 are unlikely to leach through soil into groundwater.

In aquatic environments, pyrifluquinazon is non-persistent in water-sediment systems under both aerobic and anaerobic conditions. Under aerobic conditions, pyrifluquinazon dissipated with a half-life of 1.72 - 2.38 days. Under anaerobic aquatic conditions, pyrifluquinazon transformed rapidly, with a half-life of less than three days and no pyrifluquinazon remaining after seven days. The major transformation product IV-01 appeared to be persistent under anaerobic aquatic conditions with half-lives of 233-305 days. Pyrifluquinazon is not expected to bioaccumulate in aquatic organisms.

### 4.2 Environmental risk characterization

Characterization of the environmental risk is applicable for use of Pyrifluquinazon 20SC Insecticide on greenhouse food crops and ornamentals. The environmental risk assessment integrates environmental exposure and ecotoxicology information to estimate the potential for adverse effects to non-target species. This integration is achieved by comparing estimated

environmental concentrations (EECs) in various environmental media (food, water, soil, and air) with the concentrations at which adverse effects occur. The EECs are estimated using standard models that take into consideration the application rate(s), and chemical and environmental fate properties, including the dissipation of the pesticide between applications.

Ecotoxicology information includes acute and chronic toxicity data for organisms (invertebrates, vertebrates, and plants) from both terrestrial and aquatic habitats. Effects metrics are the toxicity study endpoints that have been adjusted by an uncertainty factor to account for potential differences in species sensitivity as well as varying protection goals (i.e., protection at the community, population, or individual level). A summary of the terrestrial and aquatic endpoints available and the effects metrics used in the risk assessment are presented in Appendix I, Tables 16, and 17, respectively.

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 groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (e.g., direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the EEC by the appropriate effects metric and is then compared to the level of concern (LOC; Appendix I, Table 17). If the screening level risk quotient is below the LOC, the risk is considered negligible, and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, further characterization of the risk is conducted by taking into consideration more realistic exposure scenarios and effects metrics.

For Pyrifluquinazon 20SC Insecticide, the environmental exposure resulting from use on greenhouse food crops and ornamentals is expected for bees and beneficial arthropods used in greenhouse. A risk assessment involving the calculation of risk quotients based on exposure concentrations and toxicity endpoints has been conducted. The screening level risk assessment for pyrifluquinazon is summarized in Appendix I, Table 18.

**Risk to foliar-dwelling benefical arthropods**

The main route of exposure of pyrifluquinazon to foliar-dwelling beneficial arthropods is via contact to surface residues as a result of a spray application. For direct overspray to plant surfaces in greenhouse, the maximum application rate per crop cycle (56 x 2 = 112) g a.i./ha was considered.

Effects metrics were compared to the screening level foliar EEC of 112 g a.i./ha. The RQs did not exceed the LOC for the end-use product, Pyrifluquinazon 20SC Insecticide (RQs <0.112; Appendix I, Table 18), indicating that risks to foliar-dwelling arthropods are acceptable when pyrifluquinazon is used according to the label.

**Risk to bees**

Foraging bees could be exposed directly to pyrifluquinazon via spray droplets during application, to residues on the surface of leaves (acute contact exposure), and through the ingestion of contaminated pollen and nectar (oral exposure). In addition, brood may be exposed to pyrifluquinazon as foraging bees bring contaminated pollen and nectar back to the hive. Proposed uses are for greenhouse only, and therefore environmental exposure to bees is not expected. Managed bees may be used in greenhouse production for pollination services; greenhouse producers do not typically maintain bee colonies following these services.

In laboratory tests, pyrifluquinazon was non-toxic to adult honey bees when applied directly on bees, or through diet consumption. Following chronic oral exposure, adult bee mortality was affected at doses ≥ 1.2 µg a.i./bee/day and sublethal effects occurred at early time points and at dose rates as low as 0.0039 µg a.i./bee/day.

Based on acute effects (mortality), there were no exceedances identified at the screening level for adult and larval bees. Based on sub-lethal effects, the LOC was exceeded for adult bees (RQ = 134.4 – 162.4), but not for larval bees (RQ = 0.048), (Appendix I, Table 18). The LOC was also exceeded for adult bees being exposed through foliar spray on a chronic basis (RQ = 1.35 - >416.4) (Appendix I, Table 18). In all acute and chronic tests, bees exhibited sublethal effects including hyperactivity, loss of equilibrium, lethargy and immobility, and bees did not recover from these effects during the test period. For this greenhouse use, broad environmental exposure is not expected, a label statement advising greenhouse growers to avoid application when bees are foraging in the treatment areas is required.

Overall, there is a potential risk to pollinators used in greenhouse production from foraging on crops treated with pyrifluquinazon. In order to alert the greenhouse growers to the risk to bees used in greenhouse production, label statements are required to indicate that bees may be harmed and application should be avoided when bees are in the treatment areas. With the proposed label statements, the risks are considered acceptable.

**Risk to aquatic organisms**

The toxicity endpoints for aquatic organisms are presented in Appendix I, Table 16. Pyrifluquinazon is classified as moderately to highly toxic to aquatic organisms. A quantitative risk assessment was not conducted as this compound is non-persistent in aquatic systems and environmental exposure from closed system greenhouse use is not expected. Label statements informing the user of the toxicity of pyrifluquinazon to aquatic organisms, and prohibiting releases of effluent from greenhouses to aquatic systems, will be required.

**Overall conclusion about potential risks to the environment**

The use of pyrifluquinazon on greenhouse food crops and ornamentals is not expected to result in pyrifluquinazon being released directly into the environment when used according to approved label directions. Risks associated with greenhouse uses of pyrifluquinazon are considered to be acceptable.

### 4.3 Environmental incident reports

Pyrifluquinazon is a new active ingredient pending registration for use in Canada, and as of April 25, 2022, no incident reports had been submitted to the PMRA.

## 5.0 Value

Value information reviewed in support of the claim for aphids consisted of ten efficacy trials. These trials included both greenhouse and field trials, and tested the efficacy of Pyrifluquinazon 20SC Insecticide against several different aphid species. Of these trials, two were on greenhouse pepper, three were on greenhouse ornamentals (chrysanthemum, climbing rose and Belgian chrysanthemum), seven were on field-grown romaine or head lettuce, and one was on field-grown pepper. Value information reviewed in support of the claim for whitefly consisted of five greenhouse efficacy trials. Of these trials, one was on lettuce, one was on tomato, one was on verbena, one was on ornamental kale and one was on poinsettia.

In addition to the efficacy trials, results from 127 crop safety trials on various herbaceous and deciduous ornamental crops were provided by the applicant. In both the efficacy trials and the crop safety trials, no adverse effects of concern were reported on treated crops.

Results from the efficacy trials support application of Pyrifluquinazon 20SC Insecticide to greenhouse lettuce and greenhouse herbaceous and woody deciduous ornamentals to control whitefly at an application concentration of 125 to 250 mL product in 1000 L water and control aphids at a concentration of 187 to 250 mL product per 1000 L water. The value information also supports two applications to these crops applied to full coverage, with a reapplication interval of 10 days for these crops. In addition, the value information supports the use of one application of Pyrifluquinazon 20SC Insecticide at a concentration of 125 to 164 mL product per 1000 L water to provide control of both aphids and whitefly on greenhouse cucumbers, peppers, tomatoes and eggplant.

Pyrifluquinazon 20SC Insecticide has value as a new active ingredient that provides control of aphids and whitefly in greenhouse lettuce, tomato, eggplant, cucumber and pepper and greenhouse herbaceous and woody ornamentals. Aphids and whitefly are widespread and significant pests of greenhouse crops. Pyrifluquinazon 20SC Insecticide can aid in resistance management of aphids and whitefly when used in rotation with other insecticides in integrated pest management programmes. As pyrifluquinazon stops feeding by insects, it may also aid in reducing the transmission of insect-vectored plant viruses.

# 6.0 Pest control product policy considerations

## 6.1 Toxic substances management policy considerations

The *Toxic Substances Management Policy* (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, i.e., 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 PCPA requires that the TSMP be given effect in evaluating the risks of a product.

During the review process, pyrifluquinazon and its transformation products were 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 pyrifluquinazon and its transformation products do not meet all of the TSMP Track 1 criteria. See Table 19 in Appendix I for comparison with Track 1 criteria.

## 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 product 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*[1] 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 Pyrifluquinazon Technical and its end-use product Pyrifluquinazon 20SC Insecticide, do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

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

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 New Pest Control Products Act.

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

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 Pyrifluquinazon Technical and Pyrifluquinazon 20SC Insecticide, containing the technical grade active ingredient pyrifluquinazon, ~~to control~~ for the control of aphids and whiteflies in greenhouse vegetables and greenhouse herbaceous and woody deciduous ornamentals.

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

## Additional information being requested

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

# List of abbreviations

| | |
|---|---|
| ↑ | increased |
| ↓ | decreased |
| ♂ | male |
| ♀ | female |
| 4-NP | 4-nitrophenol |
| ºC | degree Celsius |
| µg | microgram(s) |
| µM | microMolar |
| a.i. | active ingredient |
| abs | absolute |
| AD | administered dose |
| ADI | acceptable daily intake |
| AFC | antibody-forming cell |
| A/G | albumin/globulin ratio |
| AGD | anogenital distance |
| AHETF | Agricultural Handlers Exposure Task Force |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AR | androgen receptor |
| AR-LBD | androgen receptor ligand binding domain |
| ARfD | acute reference dose |
| ARTF | Agricultural Reentry Task Force |
| AST | aspartate aminotransferase |
| atm | atmosphere |
| ATPD | area treated per day |
| AUC | area under the curve |
| BAF | Bioaccumulation Factor |
| BCF | Bioconcentration Factor |
| BUN | blood urea nitrogen |
| bw | body weight |
| bwg | body weight gain |
| CA | California |
| CAF | composite assessment factor |
| CAS | Chemical Abstracts Service |
| CEPA | *Canadian Environmental Protection Act* |
| chAR | chimpanzee androgen receptor |
| cm | centimetres |
| $CO_2$ | carbon dioxide |
| d | day(s) |
| DFR | dislodgeable foliar residue |
| DIR | Regulatory Directive |
| DHT | dihydrotestosterone |
| DNA | deoxyribonucleic acid |

| | |
|---|---|
| $DT_{50}$ | dissipation time 50% (the dose required to observe a 50% decline in concentration) |
| $DT_{90}$ | dissipation time 90% (the dose required to observe a 90% decline in concentration) |
| $EC_3$ | concentration required to induce a threshold positive sensitization response (SI=3) |
| $EC_{50}$ | effective concentration on 50% of the population |
| $EDD_{50}$ | effective daily dose 50% |
| EEC | estimated environmental concentration |
| EP | end use product |
| ER | estrogen receptor |
| ER-α | estrogen receptor α |
| ER-β | estrogen receptor β |
| F1 | first filial generation |
| F2 | second filial generation |
| fc | food consumption |
| FDA | *Food and Drugs Act* |
| FOB | functional observational battery |
| g | gram(s) |
| GD | gestation day |
| GGTP | gamma-glutamyl transpeptidase |
| GIT | gastrointestinal tract |
| GPT | glutamate pyruvic transaminase |
| GPMT | guinea pig maximization test |
| GR | glucocorticoid receptor |
| h | hour(s) |
| ha | hectare(s) |
| HAFT | highest average field trial |
| hAR | human androgen receptor |
| Hb | hemoglobin |
| HC | historical control |
| Hct | hematocrit |
| HPLC-MS | high performance liquid chromatography – Mass spectrometry |
| HPLC-MS/MS | high performance liquid chromatography with tandem mass spectrometry |
| $IC_{50}$ | concentration of competitor required to displace 50% of the bound ligand |
| IgE | immunoglobulin E |
| IgG | immunoglobulin G |
| IgM | immunoglobulin M |
| ILV | independent laboratory validation |
| IORE | indeterminate order rate equation; $T_R$ = representative half-life |
| i.p. | intraperitoneal |
| IRAC | Insecticide Resistance Action Committee |
| IUPAC | International Union of Pure and Applied Chemistry |
| IV-01 | 1,2,3,4-tetrahydro-3-[(3-pyridylmethyl)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl) ethyl]quinazolin-2-one |

| | |
|---|---|
| IV-02 | 1,2,3,4-tetrahydro-3-[(3-pyridylmethylene)amino]-6-[1,2,2,2-tetrafluoro-1-trifluoromethyl)ethyl]quinazolin-2-one |
| IV-15 | 1,2,3,4-tetrahydro-3-[(3-pyridylmethyl)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl) ethyl]quinazolin-2,4-dione |
| IV-27 | 1,2,3,4-tetrahydro-4-hydroxy-3-[(3-pyridylmethyl)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]quinazolin-2-one |
| IV-28 | 4-hydroxy-3-[(pyridin-3-ylmethylene)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl) ethyl]-3,4-dihydro-1H-quinazolin-2-one |
| IV-203 | 1,2,3,4-tetrahydro-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl) ethyl]quinazolin-2,4-dione |
| $K_d$ | soil-water partition coefficient |
| kg | kilogram(s) |
| $K_i$ | inhibition constant |
| km | kilometre |
| $K_{oc}$ | organic-carbon partition coefficient |
| kPa | kilopascal(s) |
| $K_{ow}$ | *n*–octanol-water partition coefficient |
| L | litre(s) |
| LABC | levator ani muscle and bulbocavernous muscle |
| LAFT | lowest average field trial |
| $LC_{50}$ | concentration estimated to be lethal to 50% of the test population |
| $LD_{50}$ | dose estimated to be lethal to 50% of the test population |
| $LDD_{50}$ | lethal daily dose 50% |
| L(E)D50 | lethal (or effective) dose 50% |
| LH | luteinizing hormone |
| LLNA | local lymph node assay |
| LOAEC | lowest observed adverse effect concentration |
| LOAEL | lowest observed adverse effect level |
| LOC | level of concern |
| LOEDD | lowest observed effect dose |
| LOQ | limit of quantitation |
| $LR_{50}$ | lethal rate 50% |
| $m^3$ | cubic metre(s) |
| M/L/A | mixer/loader/applicator |
| mg | milligram(s) |
| mL | millilitre(s) |
| MAS | maximum average score |
| MCH | mean corpuscular hemoglobin |
| MCV | mean corpuscular volume |
| MIS | maximum irritation score |
| MMTV | murine mammary tumour virus |
| MOA | mode of action |
| MOE | margin of exposure |
| mol | mole(s) |
| MRL | maximum residue limit |
| mRNA | messenger ribonucleic acid |

| | |
|---|---|
| MS | mass spectrometry |
| MSL | Mutchler sandy loam |
| NA | not applicable |
| NAFTA | North American Free Trade Agreement |
| NOAEC | no observed adverse effect concentration |
| NOAEL | no observed adverse effect level |
| NOEC | no observed effect concentration |
| NOED | no observed effect dose |
| NOEDD | no observed effect daily dose |
| OC | organic carbon content |
| OE | Ostlie East |
| P | parental generation |
| Pa | Pascal(s) |
| PBI | plantback interval |
| PCPA | *Pest Control Products Act* |
| PHED | Pesticide Handlers Exposure Database |
| PHI | preharvest interval |
| p*K*a | dissociation constant |
| PMRA | Pest Management Regulatory Agency |
| PND | postnatal day |
| PPE | personal protective equipment |
| ppm | parts per million |
| PPS | preputial separation |
| PRO | Regulatory Proposal |
| Py | pyridine |
| $q_1$* | cancer potency factor |
| Qn | Quinazolinone-phenyl |
| RQ | risk quotient |
| RAC | raw agricultural commodity |
| rAR | rat androgen receptor |
| REI | restricted-entry interval |
| rel | relative |
| RNA | ribonucleic acid |
| SC | suspension concentrate |
| SFO | Single First Order |
| SI | stimulation index |
| SPN | Science Policy Note |
| STMdR | supervised trial median residue |
| $t_{1/2}$ | half-life |
| T | testosterone |
| $T_3$ | triiodothyronine |
| $T_4$ | thyroxine |
| TAR | total applied radioactivity |
| TC | transfer coefficient |
| TGAI | technical grade active ingredient |
| TLC | thin-layer chromatography |

| | |
|---|---|
| $T_{max}$ | time to reach maximum concentration |
| TRP | transient receptor potential |
| TRPV | transient receptor potential (vanilloid) |
| TRR | total radioactive residue |
| TSH | thyroid stimulating hormone |
| TSMP | Toxic Substances Management Policy |
| UDP-GT | uridine diphosphate glucuronyl transferase |
| UF | uncertainty factor |
| UR | unextracted residue |
| US | United States |
| USEPA | United States Environmental Protection Agency |
| UV | ultraviolet |
| v/v | volume per volume dilution |
| WBC | white blood cells |
| wt | weight |
| w/w | weight by weight |

# Appendix I Tables and figures

**Table 1 Residue analysis (environmental media)**

| Matrix | Analyte | Method Type | LOQ | Reference |
|---|---|---|---|---|
| | | | | |
| Soil / Sediment | active | HPLC-MS | 0.01 ppm | PMRA # 3042129, 3042127 |
| | Metabolites (IV-01, IV-02, IV-15, IV-27, IV-28, IV-203) | | 0.01 ppm | PMRA # 3042129, 3042127 |
| Water | active | | 0.50 ppb | PMRA # 3042128 |
| | Metabolites (IV-01, IV-02, IV-15, IV-27, IV-28, IV-203) | | 0.50 ppb | PMRA # 3042128 |

**Table 2 Residue analysis (plant commodities)**

| Analytical Methods | Matrix | Analytes | Method ID/ Type | LOQ | Reference |
|---|---|---|---|---|---|
| **Plant Commodities** | | | | | |
| Enforcement Method | Raw and processed commodities | Pyrifluquinazon | Meth-188, Revision # 4 / LC-MS/MS | 0.01 ppm | PMRA# 3333822 |
| Data-Gathering Method | | Pyrifluquinazon and IV-01 | Meth-188, Revision #s 2, 3, and 4 / LC-MS/MS | 0.01 ppm per analyte in all matrices | PMRA # 3043973, 3333822 |
| ILV of Enforcement Method | Undelinted cottonseed | Pyrifluquinazon | Meth-188, Revision # 4 / LC-MS/MS | 0.01 ppm | PMRA # 3333823 |
| Radiovalidation | The extraction solvents used in the metabolism studies are very similar to those used in the proposed enforcement method, hence the extraction efficiency of the method is considered to be adequately demonstrated. | | | | |

**Table 3 Identification of select metabolites of Pyrifluquinazon**

| Code | Synonyms; Chemical Name (IUPAC) | Matrices |
|---|---|---|
| IV-01 | NNI-0101-1H; 3-[(pyridin-3-ylmethyl)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-3,4-dihydro-*1H*-quinazolin-2-one | Rat, goat, soil, water, plants |
| IV-02 | NNI-0101-1H-imino; 3-[(pyridin-3-ylmethylene)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-3,4-dihydro-*1H*-quinazolin-2-one | Rat, soil, water |
| IV-03 | NNI-0101-1H-oxide; 3-[(1-oxo-pyridin-3-ylmethyl)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-3,4-dihydro-*1H*-quinazolin-2-one | Rat, dog, goat, poultry |
| IV-04 | NNI-0101-1H-imino-oxide; 3-[(1-oxo-pyridin-3-ylmethylene)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-3,4-dihydro-*1H*-quinazolin-2-one | Rat, goat |
| IV-15 | NNI-0101-1H-4-oxo; 3-[(pyridin-3-ylmethyl)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-*1H*-quinazolin-2,4-dione | Goat, poultry, soil, water |
| IV-27 | NNI-0101-1H-4-OH; 4-hydroxy-3-[(pyridin-3-ylmethyl)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-3,4-dihydro-*1H*-quinazolin-2-one | Rat, soil, water |
| IV-28 | NNI-0101-1H-imino-4-OH; 4-hydroxy-3-[(pyridin-3-ylmethylene)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-3,4-dihydro-*1H*-quinazolin-2-one | Soil, water |
| IV-203 | NNI-0101-quinazolinedione; 6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-*1H*-quinazolin-2,4-dione | Rat, goat, poultry, soil, water, plants |
| IV-206 | NNI-0101-quinazolinone; 6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-3,4-dihydro-*1H*-quinazolin-2-one | Rat, dog, plants |
| IV-208 | NNI-0101-aminoquinazolinone-N-Ac; N-[2-oxo-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-1,4-dihydro-2*H*-quinazolin-3-yl]acetamide | Rat, goat, poultry |
| IV-211 | NNI-0101-8-OH-quinazolindione, Biliary polar metabolite B2; 8-hydroxy-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-*1H*-quinazolin-2,4-dione | Rat, goat |
| IV-212 | NNI-0101-aminoquinazolinone-N-Ac-4-OH; N-[4-hydroxy-2-oxo-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-1,4-dihydro-2*H*-quinazolin-3-yl]acetamide | Rat |

| Code | Synonyms; Chemical Name (IUPAC) | Matrices |
|---|---|---|
| IV-303 | NNI-0101-anthranilic acid; 2-amino-5-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]benzoic acid | Rat, goat, poultry, water |
| IV-402 | NNI-0101-nicotinaldehyde; pyridin-3-aldehyde | Rat |
| IV-403 | Nicotinic acid; pyridine-3-carboxylic acid | Rat, goat, poultry |
| IV-404 | Nicotinamide; pyridine-3-carboxamide | Rat, goat, poultry |
| IV-405 | NNI-0101-methylnicotinamide; 3-carbamoyl-1-methylpyridinium chloride | Rat, goat |

**Table 4 Toxicology reference values for use in health risk assessment for Pyrifluquinazon**

| Exposure Scenario | Study | Point of Departure and Endpoint | CAF[1] or Target MOE |
|---|---|---|---|
| Acute dietary general population | Acute oral neurotoxicity study in the rat | NOAEL = 100 mg/kg bw<br>Clinical signs of toxicity, mortality | 100 |
| ARfD (general population) = 1.0 mg/kg bw | | | |
| Acute dietary females 13-49 years of age | Oral developmental toxicity study in the rat | NOAEL = 5 mg/kg bw/day<br>Increased incidence of supernumerary ribs (variation) and decreased AGD in the absence of maternal toxicity | 1000 |
| ARfD (females 13-49 years of age) = 0.005 mg/kg bw | | | |
| Repeated (chronic) dietary | Combined results of the two 1-year oral toxicity studies in the dog | NOAEL = 0.5 mg/kg bw/day<br>Nasal lesions in olfactory epithelium | 100 |
| ADI = 0.005 mg/kg bw/day | | | |
| Short- to intermediate-term dermal[2] and inhalation[3] | Oral developmental toxicity study in the rat | NOAEL = 5 mg/kg bw/day<br>Increased incidence of supernumerary ribs (variation) and decreased AGD in the absence of maternal toxicity | 1000 |
| Long-term dermal[2] | Combined results of the two 1-year oral toxicity studies in the dog | NOAEL = 0.5 mg/kg bw/day<br>Nasal lesions in olfactory epithelium | 100 |
| Cancer | Testicular interstitial cell tumours observed in male rats and mice, and equivocal evidence of mammary gland tumours in male rats; a threshold approach to cancer risk assessment was deemed appropriate and the endpoints selected for the non-cancer risk assessment are protective of these findings for all tumour types. | | |

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

[2] Since an oral NOAEL was selected, a dermal absorption factor of 19% was used in 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 5 Toxicity profile of Technical Pyrifluquinazon**

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

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| **Toxicokinetic Studies** | |
| Absorption, distribution, metabolism, elimination, and pharmacokinetics studies following single gavage doses (low and high)<br><br>Fischer rat<br><br>PMRA 3042114, 3042115, 3042116 | Single gavage dose administration of 1 or 100 mg/kg bw ([Quinazolinone-phenyl ring-$^{14}$C(U)]pyrifluquinazon) or ([Pyridine ring-2,6-$^{14}$C]pyrifluquinazon) to intact rats to assess absorption, distribution, metabolism, elimination, and pharmacokinetics.<br><br>Single gavage dose administered to bile duct-cannulated rats at 1 mg/kg bw [Quinazolinone-phenyl ring-$^{14}$C(U)]pyrifluquinazon (♂ only).<br><br>**Absorption:** For the biliary excretion study, the absorption of pyrifluquinazon, as a sum of radioactivity in the bile, urine and carcass, was 63% of the AD.<br><br>**Pharmacokinetics:** In the blood and plasma of animals that received a single dose of the [Quinazolinone-phenyl ring-$^{14}$C(U)] radiolabel, $T_{max}$ was 1-3 hours at the low-dose level and 9-12 hours at the high-dose level. In the blood and plasma of animals that received a single dose of the [Pyridine ring-2,6-$^{14}$C] radiolabel, $T_{max}$ was determined to be 1 hour at the low-dose level, and 3-9 hours at the high-dose level.<br><br>In the blood of animals that received a single dose of the [Quinazolinone-phenyl ring-$^{14}$C(U)] radiolabel, the elimination half-lives were 0.6-4.8 hours at the low-dose level and 0.8-1.7 hours at the high-dose level. In the plasma of animals that received a single dose of the [Quinazolinone-phenyl ring-$^{14}$C(U)] radiolabel, the elimination half-lives were 0.6-2.9 hours at the low-dose level and 0.9-1.4 hours at the high-dose level.<br><br>In the blood of animals that received a single dose of the [Pyridine ring-2,6-$^{14}$C] radiolabel, the elimination half-lives were 2.6-6.6 |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| | hours at the low-dose level and 1.9-11.5 hours at the high-dose level. In the plasma of animals that received a single dose of the [Pyridine ring-2,6-$^{14}$C] radiolabel, the elimination half-lives were 1.0-4.4 hours at the low-dose level and 0.9-3.7 hours at the high-dose level.<br><br>For both radiolabels in both sexes, the AUCs for the high-dose group were almost 100 times higher than those for the low-dose group, suggesting the bioavailability of pyrifluquinazon was approximately the same for both dose levels.<br><br>**Distribution:** In single-dose experiments using the [Quinazolinone-phenyl ring-$^{14}$C(U)] radiolabel, the concentration of radioactivity was highest in the GIT at 3 hours post-dosing at the low dose and at 9 hours at the high dose in both sexes. By 168 hours post-dosing, levels of radioactivity decreased significantly in all tissues, with highest levels retained in the liver, kidney and adrenal gland for both sexes. In single-dose experiments using the [Pyridine ring-2,6-$^{14}$C] radiolabel, the concentration of total radioactivity was highest in the liver 3 hours post-dosing at the low dose and at 9 hours at the high dose. In both sexes, significant radioactivity in the brain, heart and liver was still identified at 168 hours post-dosing, as well as in the kidney and adrenal gland.<br><br>**Excretion:** In rats dosed with the [Quinazolinone-phenyl ring-$^{14}$C(U)] radiolabel, excretion was higher in feces (75-80% of the AD) than in urine (14-20% of the AD) at 168 hours post-dosing. Following administration of the [Pyridine ring-2,6-$^{14}$C] radiolabel, excretion was fairly rapid within 24 hours post-dosing in the urine (16% of the AD), feces (22% of the AD) and expired air (2% of the AD). Excretion occurred more slowly at 24 through 168 hours in the urine (26-32% of the AD), feces (23-39% of the AD) and expired air (4-7% of the AD). Radioactivity remaining in the carcass in low and high dose ♂ and low dose ♀ reached 27, 18 and 31% of the AD, respectively at 168 hours.<br><br>In bile duct-cannulated ♂ rats, biliary excretion was the major excretion pathway accounting for 35% of the AD by 72 hours. Urinary and fecal excretion also reached 12% and 4.7% of the AD, respectively by 72 hours.<br><br>**Metabolism:** The main metabolites found in feces following a single low dose of [Quinazolinone-phenyl ring-$^{14}$C(U)] were IV-02, IV-211, IV-27 glucuronide and IV-212 conjugate. In the high-dose group, unchanged pyrifluquinazon (11% of the AD) was the main |

| Study Type/Animal/PMRA # | Study Results |
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| | metabolite identified in feces. In both the low- and high-dose groups, IV-04, IV-303 glucuronide, and IV-211 glucuronide were the main metabolites found in urine. The main metabolites identified in the plasma 9 hours post-dosing at 100 mg/kg bw were IV-01, IV-02, IV-203, and IV-208.<br><br>Following a single low or high dose of [Pyridine ring-2,6-$^{14}$C], IV-405 was the sole metabolite found in urine (18-21% of the AD). The most abundant metabolites in feces were IV-02 and IV-27. In high dose ♂, unchanged pyrifluquinazon (2% of the AD) was identified in the feces. In the blood, liver, brain and heart, the major metabolites were IV-402, IV-403, and IV-404.<br><br>The major metabolites identified in bile following a single low dose of [Quinazolinone-phenyl ring-$^{14}$C(U)] were IV-212, IV-27 glucuronide and IV-211 glucuronide. The major metabolites found in the urine were identified as IV-04 and a polar metabolite (TLC origin). The main metabolites in the feces and gastrointestinal contents were IV-01, IV-02, and IV-203. Unchanged pyrifluquinazon was also identified in the GIT contents. The metabolites found in bile were similar to those detected in feces collected from intact rats. The metabolites in the feces and GIT of bile duct-cannulated rats suggest that pyrifluquinazon is unstable and easily deacetylated in natural conditions of the GIT.<br><br>The major metabolic reactions of pyrifluquinazon included: deacetylation of the nitrogen atom (position 1) of the quinazolinone ring, hydroxylation of the 4-position carbon atom in the quinazolinone ring followed by conjugation by glucuronic acid, oxidation of 1-position of the pyridine ring, dehydrogenation of the amino group, hydroxylation of the 8-position carbon atom in the quinazolinone ring, cleavage of the nitrogen-carbon bond, cleavage of the quinazolinone ring followed by conjugation by glucuronic acid, cleavage of the nitrogen-carbon bond followed by aqueous vitamin, and methylation of the nitrogen atom of the pyridine ring. |
| In Vitro Metabolism<br><br>Fischer rat (♂) liver microsomes<br><br>Sprague-Dawley rat (♂) nasal mucosa microsomes | Supplemental – non-guideline and limited reporting.<br><br>Liver and nasal mucosa microsomes were exposed to ([Quinazolinone-phenyl ring-$^{14}$C(U)]pyrifluquinazon) as a 1.0% v/v mixture in acetonitrile.<br><br>No major differences related to species, sex or microsome source were observed, except that a higher proportion of minor metabolites and lower levels of metabolite IV-01 were derived from human liver |

| Study Type/Animal/PMRA # | Study Results |
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| Beagle dog (♂) liver and nasal mucosa microsomes<br><br>Human (♀) liver microsomes<br><br>Beagle dog nasal mucosa microsomes prepared from dogs (both sexes) from the control and high-dose groups from a 1-year oral toxicity study (PMRA 3042070)<br><br>PMRA 3042097 | microsomes compared to those of rats and dogs.<br><br>NNI-0101 was completely and rapidly metabolized to IV-01, IV-02, IV-03, IV-04, and IV-27 in both the liver and nasal microsomes. Additional metabolites such as IV-206 and IV-303 were also identified as minor metabolites.<br><br>Major qualitative differences were not observed in the metabolites in dog nasal mucosa microsomes between the high-dose and control groups, suggesting administration of pyrifluquinazon to the dog has no significant effect on the metabolism. Slightly higher levels of IV-01 were derived from nasal microsomes of previously treated dogs compared to those from control dogs and rats. |
| **Acute Toxicity Studies** | |
| Acute Oral Toxicity (Toxic Class)<br><br>Fischer rat<br><br>PMRA 3042049 | 300 mg/kg bw < $LD_{50}$ < 2000 mg/kg bw (♀)<br><br>Clinical signs of toxicity included moribundity, prone/lateral/crouching position, decreased or lost locomotor activity, abnormal gait, bradypnea, hypothermia, piloerection and lacrimation.<br><br>Moderate acute oral toxicity |
| Acute Oral Toxicity (Up and Down)<br><br>Sprague-Dawley rat<br><br>PMRA 3042056 | $LD_{50}$ = 2000 mg/kg bw (♀)<br><br>Clinical signs of toxicity included decreased or lost locomotor activity, stained fur, tremor, prone/lateral/crouching position, abnormal (staggering) gait, decreased body temperature, lacrimation, stained urine.<br><br>Slight acute oral toxicity |
| Acute Dermal Toxicity<br><br>Sprague-Dawley rat<br><br>PMRA 3042057 | $LD_{50}$ > 2000 mg/kg bw (♂/♀)<br><br>No clinical signs of toxicity or dermal effects noted.<br><br>Low acute dermal toxicity |
| Acute Inhalation Toxicity (nose-only)<br><br>Fischer rat<br><br>PMRA 3042058 | 1.2 mg/L < $LC_{50}$ < 2.4 mg/L (♂/♀)<br><br>Clinical signs of toxicity included flat or hunched posture, lean bodies, slow or laboured respiration, lethargy, pale skin, piloerection, hypothermia, recumbency, ptosis, uncoordinated movement, clinic spasms. |

| Study Type/Animal/PMRA # | Study Results |
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| | Slight acute inhalation toxicity |
| Eye Irritation<br><br>Japanese white rabbit<br><br>PMRA 3042059 | Unwashed eyes<br>MIS = 2.7/110 (1 hour)<br>MAS = 0.4/110<br><br>Washed eyes<br>MIS = 2.0/110 (1 hour)<br>MAS = 0.2/110<br><br>Minimally irritating to eyes |
| Dermal Irritation<br><br>Japanese white rabbit<br><br>PMRA 3042060 | MIS = 0/8 (all time points)<br>MAS = 0/8<br><br>Non-irritating to skin |
| Sensitization (Maximization)<br><br>Hartley guinea pig<br><br>PMRA 3042061 | Positive reaction in 20% of test animals after challenge<br><br>Potential dermal sensitizer |
| **Short-term Toxicity Studies** | |
| 90-Day Oral Toxicity (diet)<br><br>CD-1 mouse<br><br>PMRA 3042064 | NOAEL = 7.6/9.1 mg/kg bw/day (♂/♀)<br>LOAEL = 102/119 mg/kg bw/day (♂/♀)<br><br>Effects at LOAEL: ↑ liver wt, centrilobular hepatocellular hypertrophy, thyroid follicular cell hypertrophy (♂/♀); ↓ WBC, ↓ lymphocytes, ↑ AST, ↑ ALT, ↓ total protein, ↓ albumin, ↓ globulin, ↓ calcium, ↑ thyroid wt, ↓ epididymides wt, dark liver (♂); ↓ Hct, ↓ Hb (♀) |
| 28-Day Oral Toxicity (diet)<br><br>Sprague-Dawley rat<br><br>PMRA 3316795 | NOAEL = 50/50 mg/kg bw/day (♂/♀)<br>LOAEL = 247/234 mg/kg bw/day (♂/♀)<br><br>Effects at LOAEL: ↓ spontaneous activity, red eye discharge, ↓ bw, ↓ bwg, ↓ fc, ↑ reticulocyte count, ↓ Hct, ↓ Hb, ↓ eosinophil count/ratio, ↑ bilirubin, enlarged thyroid, ↑ thyroid wt, ↑ liver wt, ↓ abs. thymus wt, ↓ abs. brain wt, diffuse hepatocellular hypertrophy, thyroid follicular epithelial cell hypertrophy, ↑ thyroid follicles (♂/♀); urine-soiled lower belly, ↓ leukocytes, ↓ MCV, ↓ MCH, ↓ lymphocyte count/ratio, ↑ ALP, ↓ cholesterol, ↓ triglycerides, ↓ epididymis wt, ↑ rel. adrenal wt, ↑ rel. testes wt, ↑ periportal hepatocellular vacuolation (♂); lacrimation, ↓ erythrocytes, ↓ platelets, ↑ AST, ↑ ALT, ↑ GGTP, ↑ inorganic phosphorus, ↓ A/G, ↓ pituitary wt, ↓ ovary wt, ↓ abs. adrenal wt, hepatocyte mitosis, |

| Study Type/Animal/PMRA # | Study Results |
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| | single cell necrosis of hepatocytes, extramedullary hematopoiesis (spleen), ↓ fatty bone marrow, single cell necrosis of acinar cells (pancreas) (♀) |
| 90-Day Oral Toxicity (diet)<br><br>Fischer rat<br><br>PMRA 3042063 | NOAEL = 5.7/6.4 mg/kg bw/day (♂/♀)<br>LOAEL = 29/33 mg/kg bw/day (♂/♀)<br><br>Effects at LOAEL: ↑ liver wt (♂/♀); ↑ reticulocytes, ↓ BUN, ↑ rel. kidney wt (♂); ↑ cholesterol (♀) |
| 90-Day Oral Toxicity (capsule)<br><br>Beagle dog<br><br>PMRA 3042066 | NOAEL = 5 mg/kg bw/day (♂/♀)<br>LOAEL = 30 mg/kg bw/day (♂/♀)<br><br>Effects at LOAEL: ↑ ALP, ↑ GPT, ↓ albumin, ↓ A/G, ↑ liver wt, hepatocellular hypertrophy, thyroid follicular cell hypertrophy (♂/♀); ↓ serum calcium, prostate atrophy, ↓ prostate wt (♂); ↑ thyroid wt (♀) |
| 1-Year Oral Toxicity (capsule)<br><br>Beagle dog<br><br>PMRA 3042067 | NOAEL not established<br>LOAEL = 1.5 mg/kg bw/day (♂/♀)<br><br>Effects at LOAEL: mononuclear cell infiltration of the nasal cavity (olfactory region) (♂/♀) |
| 1-Year Oral Toxicity with 6-Month Recovery (capsule)<br><br>Beagle dog<br><br>PMRA 3042070, 3042078 | NOAEL = 0.5 mg/kg bw/day (♂/♀)<br>LOAEL = 5 mg/kg bw/day (♂/♀)<br><br>Effects at LOAEL: mononuclear cellular infiltration of the olfactory epithelium of the nasal cavity, ↑ ALP (♂/♀); ↓ bwg, ↓ total cholesterol, ↓ phospholipids, ↑ creatine phosphokinase, ↓ total protein (♂); ↓ triglycerides, ↓ calcium (♀)<br><br>Recovery group: no treatment-related effects.<br><br>Immunological assessment: There were no treatment-related effects observed in the analysis of lymphocyte subsets in peripheral blood or the submandibular lymph nodes, or on the IgE, IgM, and IgG levels in peripheral blood in this study. |
| 28-Day Dermal Toxicity<br><br>Sprague-Dawley rat<br><br>PMRA 3042072 | NOAEL = 1000 mg/kg bw/day (♂/♀)<br>LOAEL not established<br><br>No treatment-related adverse findings. |
| 90-Day Dermal Toxicity – waiver request<br><br>PMRA 3042071 | The request to waive the conditional requirement for a 90-day dermal toxicity study is approved on the basis that an acceptable 28-day dermal toxicity study has been submitted to address the short-term repeat-dose dermal data requirement for greenhouse uses in |

| Study Type/Animal/PMRA # | Study Results |
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| | Canada. In addition, the available 28-day dermal toxicity study provided a NOAEL of 1000 mg/kg bw/day and the acute dermal toxicity of the end-use formulation is low. |
| 28-Day Inhalation Toxicity (nose-only)<br><br>Sprague-Dawley rat<br><br>PMRA 3042074 | NOAEC = 0.042/0.16 mg/L (equivalent to 11/41 mg/kg bw/day) (♂/♀)<br>LOAEC = 0.16/0.56 mg/L (equivalent to 41/147 mg/kg bw/day) (♂/♀)<br><br>Effects at LOAEC: piloerection, ↓ bwg, ↑ centrilobular hypertrophy (♂/♀); ↑ abs. lung wt, terminal airway inflammation (♂) |
| 90-Day Inhalation Toxicity – waiver request<br><br>PMRA 3042073 | The request to waive the conditional requirement for a 90-day inhalation toxicity study is approved on the basis that an acceptable 28-day inhalation toxicity study has been submitted to address the short-term repeat-dose inhalation data requirement for greenhouse uses in Canada. In addition, the available 28-day inhalation toxicity study provided a NOAEC of 0.042 mg/L (approximately 11 mg/kg bw/day) in male rats, the acute inhalation toxicity of the end-use formulation is low, and pyrifluquinazon meets the PMRA's definition of a non-volatile compound (that is, vapour pressure less than $1x10^{-5}$ kPa at 20-30°C). |
| **Chronic Toxicity/Oncogenicity Studies** | |
| 18-Month Oral Oncogenicity (78-week) (diet)<br><br>CD-1 mouse<br><br>PMRA 3042077 | NOAEL = 6.3/5.8 mg/kg bw/day (♂/♀)<br>LOAEL = 27/25 mg/kg bw/day (♂/♀)<br><br>Effects at LOAEL: ↓ bw, tactile hair loss, thyroid follicular cell hypertrophy, adrenal subcapsular cell hyperplasia (♂); uterine horn endometrial hyperplasia (♀)<br><br>Incidence of testicular interstitial cell tumours (in %): 0, 0, 0, 23<br><br>Evidence of tumourigenicity. |
| 1-Year Oral Toxicity (diet)<br><br>Fischer rat<br><br>PMRA 3042075 | NOAEL = 4.1/5.0 mg/kg bw/day (♂/♀)<br>LOAEL = 14/18 mg/kg bw/day (♂/♀)<br><br>Effects at LOAEL: ↑ rel. liver wt, ↑ rel. kidney wt (♂/♀); ↑ nucleated cell counts in bone marrow, ↑ basophilic cells with hydropic degeneration (pituitary gland)(♂); ↑ abs. liver wt, ↑ abs. kidney wt, ↑ rel. heart wt, ↑ thyroid wt, ↑ urinary pH, bile duct hyperplasia (♀) |
| 2-Year Oral Carcinogenicity (diet)<br><br>Fischer rat | NOAEL = 3.5/4.5 mg/kg bw/day (♂/♀)<br>LOAEL = 12/16 mg/kg bw/day (♂/♀)<br><br>Effects at LOAEL: ↓ bw, ↓ bwg, ↑ retinal atrophy (♂/♀); ↑ eye |

| Study Type/Animal/PMRA # | Study Results |
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| PMRA 3042076 | opacity, ↑ cataracts, ↓ testes softening, ↑ epididymis softening, ↑ masses in testes, ↑ epididymis atrophy, ↑ testicular atrophy, ↑ seminal vesicle atrophy, ↑ coagulating gland atrophy, ↑ prostate atrophy, ↓ epididymis wt, ↑ rel. kidney wt, ↑ rel. liver wt (♂); ↓ abs. adrenal wt, ↓ abs. spleen wt, ↑ hematopoiesis in the spleen, ↑ bile duct hyperplasia, ↑ renal tubular basophilic change, ↑ decrease in zymogen granules in the pancreas, ↑ focal acinar cell atrophy in the pancreas, ↑ luminal dilatation of endometrial gland of uterine horn (♀)<br><br>Tumour incidences (in %)<br>Testicular interstitial cell tumours: 82, 76, 98, 96 (HC range 68-86%)<br>Mammary gland fibroadenomas (♂): 2.1, 4, 6.3, 10 (HC range 0-4%)<br><br>Evidence of tumourigenicity (testicular interstitial cell tumours).<br>Equivocal evidence of tumourigenicity (mammary gland fibroadenomas in ♂). |
| **Developmental/Reproductive Toxicity Studies** | |
| 2-Generation Reproductive Toxicity (diet) (Dose range-finding)<br><br>Sprague-Dawley rat<br><br>PMRA 3042098 | Supplemental – dose range-finding study<br><br>Parental NOAEL and LOAEL not established<br><br>Effects at ≥ 7.6 mg/kg bw/day: ↑ thyroid wt (P) (♀)<br><br>Effects at ≥ 37 mg/kg bw/day: ↑ rel. liver wt (P), ↑ rel. kidney wt (P), hepatocellular centrilobular hypertrophy (P) (♀)<br><br>Effects at ≥ 84/81 mg/kg bw/day: ↓ bw (P), ↓ bwg (P), ↓ fc (P) (♂/♀); hepatocellular centrilobular hypertrophy (P) (♂); hypertrophy of thyroid follicular cells (P) (♀)<br><br>Effects at 128 mg/kg bw/day: soiled fur in the nasorostral region (P) (♀)<br><br>Offspring NOAEL and LOAEL not established<br><br>Effects at ≥ 37 mg/kg bw/day: delayed PPS (F1), ↓ bw (F1), ↑ liver wt (F1), ↓ spleen wt (F1), nipple retention (F1; PND 8-14), ↓ AGD (F2) (♂)<br><br>Effects at ≥ 84/81 mg/kg bw/day: hepatocellular centrilobular hypertrophy (F1) (♂/♀); hypospadias (F1) (PND 15-21) (♂) |

| Study Type/Animal/PMRA # | Study Results |
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| | Reproductive NOAEL and LOAEL not established<br><br>Effects at ≥ 7.0/7.6 mg/kg bw/day: ↓ number of F2 pups delivered, ↓ number of implantation sites (F1)<br><br>Effects at 84/81 mg/kg bw/day: ↓ gestation index, half of litters not delivered (P)<br><br>Effects at 145/128 mg/kg bw/day: ↓ mating index (P; 4/8 ♀ mated successfully), ↓ fertility index (P; 0/4 mated ♀ became pregnant) |
| 2-Generation Reproductive Toxicity (diet)<br><br>Sprague-Dawley rat<br><br>PMRA 3042099 | Parental NOAEL = 10/2.3 mg/kg bw/day (♂/♀)<br>Parental LOAEL = 52/12 mg/kg bw/day (♂/♀)<br><br>Effects at the LOAEL: hepatocellular centrilobular hypertrophy (P, F1), ↑ rel. adrenal gland (F1), ↑ rel. liver wt (P), ↑ rel. kidney wt (P), ↑ rel. thyroid wt (P), ↓ abs. brain wt (♂); thyroid follicular cell hypertrophy (F1; slight), ↑ thyroid wt (F1) (♀)<br><br>Offspring NOAEL = 2.3 mg/kg bw/day<br>Offspring LOAEL = 12 mg/kg bw/day<br><br>Effects at LOAEL: slightly delayed PPS (F1; 1.4 days), ↑ bw at PPS completion (F1) (♂); ↓ bw PND 7-21 (F2) (♀)<br><br>Reproductive NOAEL = 10/12 mg/kg bw/day (♂/♀)<br>Reproductive LOAEL = 52/59 mg/kg bw/day (♂/♀)<br><br>Effects at LOAEL: ↓ number of pups delivered (P, F1) (♂/♀); ↑ abnormal sperm (P, F1), ↓ sperm motility (P, F1), ↑ abs. testes wt (P), ↑ rel. testes wt (P, F1) (♂); ↑ duration of gestation (P, F1), ↑ uterus wt (F1) (♀)<br><br>No evidence of sensitivity of the young. |
| Developmental Toxicity (gavage) (Dose range-finding)<br><br>Sprague-Dawley rat<br><br>PMRA 3042105 | Supplemental – dose range-finding study<br><br>Maternal NOAEL not established<br><br>Effects at ≥ 50 mg/kg bw/day: ↓ bw, ↓ bwg GD 6-9 and 6-18, ↓ fc<br><br>Effects at 100 mg/kg bw/day: soiled fur, eye discharge, ↓ locomotor activity, prone/side position, 2 maternal rats found dead, remaining 5 litters showed only embryonic resorptions and fetal deaths (no live fetuses were produced) |

| Study Type/Animal/PMRA # | Study Results |
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| | Developmental NOAEL not established<br><br>Effects at ≥ 50 mg/kg bw/day: ↓ mean fetal wt, ↓ placental wt<br><br>Effects at 100 mg/kg bw/day: resorptions, fetal deaths |
| Developmental Toxicity (gavage)<br><br>Sprague-Dawley rat<br><br>PMRA 3042106 | Maternal NOAEL = 10 mg/kg bw/day<br>Maternal LOAEL = 50 mg/kg bw/day<br><br>Effects at LOAEL: ↓ bw, ↓ bwg, bw loss GD 6-9 and 6-12, ↓ fc GD 6-12, ↓ gravid uterine wt<br><br>Developmental NOAEL = 5 mg/kg bw/day<br>Developmental LOAEL = 10 mg/kg bw/day<br><br>Effects at LOAEL: ↑ supernumerary rib, ↓ AGD (♂ only; abs. and rel. to $bw^{1/3}$)<br><br>Evidence of increased sensitivity of the young.<br>No treatment-related malformations. |
| Developmental Toxicity (gavage) (Dose range-finding)<br><br>Japanese white rabbits<br><br>PMRA 3042107 | Supplemental – dose range-finding study<br><br>Maternal NOAEL not established<br><br>Effects at ≥ 20 mg/kg bw/day: ↓ bwg GD 21 and thereafter<br><br>Effects at ≥ 50 mg/kg bw/day: ↓ fc GD 18-21, 3/8 ♀ aborted GD 18-24<br><br>Effects at 100 mg/kg bw/day: ↓ bw GD 15 and thereafter, clinical signs (soiled fur, scleral congestion, nasal discharge, salivation, no-feces, red/brown discharge on the tray, emaciation and/or prone/side position), 6/8 ♀ found dead GD 15-23, 2/8 ♀ aborted on GD 17 (no live fetuses), ↑ incidences of gross pathological findings (hardened contents in the cecum, subcutaneous hemorrhage in the abdominal region, hair bolus in the stomach, distended with diet in the stomach, mucosal hemorrhage in the cecum, distention in the cecum, yellow color of liver, spots in the liver, pale color of kidney, luminal distention of the uterus and vagina)<br><br>Developmental NOAEL not established (assessments did not include visceral or skeletal examinations)<br><br>Effects at ≥50 mg/kg bw/day: abortions |

| Study Type/Animal/PMRA # | Study Results |
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| Developmental Toxicity (gavage)<br><br>Japanese white rabbits<br><br>PMRA 3042108 | Maternal NOAEL = 20 mg/kg bw/day<br>Maternal LOAEL not established<br><br>No treatment-related findings.<br><br>Developmental NOAEL = 20 mg/kg bw/day<br>Developmental LOAEL not established<br><br>No treatment-related findings.<br><br>No evidence of increased sensitivity of the young.<br>No treatment-related malformations. |
| **Genotoxicity Studies** | |
| Bacterial Reverse Mutation Assay<br><br>*S.* Typhimurium strains TA1535, TA1537, TA98, TA100 and<br>*E. coli* strain WP2 uvrA<br><br>PMRA 3042109 | Negative ± metabolic activation<br><br>Tested up to cytotoxic concentrations. |
| Forward Gene Mutation in Mammalian Cells<br><br>Mouse lymphoma L5178Y cells<br><br>PMRA 3042112 | Negative ± metabolic activation<br><br>Tested up to cytotoxic concentrations. |
| Chromosome Aberrations in vitro<br><br>CHL/IU cells<br><br>PMRA 3042110 | Negative ± metabolic activation<br><br>No induction of structural chromosome aberrations, potential for formation of numerical chromosome aberration without metabolic activation.<br><br>For the 6-hour exposure only: significant increase in numerical aberrations (polyploidy cells) compared to negative control cultures without activation.<br><br>Tested up to cytotoxic concentrations. |
| Micronucleus Test (gavage)<br><br>CD-1 mouse | Negative<br><br>Tested up to dose levels causing slight bone marrow cell toxicity. |

| Study Type/Animal/PMRA # | Study Results |
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| PMRA 3042113 | Clinical signs included irregular respiration, unresponsiveness, flat and hunched posture, over- and under-activity, abnormal gait, piloerection, prostrate posture, and partially closed eyes. |
| **Neurotoxicity Studies** | |
| Acute Delayed Neurotoxicity – waiver request<br><br>PMRA 3042100 | The request to waive the conditional requirement for an acute delayed neurotoxicity study is approved on the basis that pyrifluquinazon does not contain organophosphate moieties, is not a carbamate, and is not structurally related to other substances that may cause delayed neurotoxicity. |
| Acute Neurotoxicity (gavage)<br><br>Sprague-Dawley rat<br><br>PMRA 3042101, 3042102 | NOAEL = 100 mg/kg bw (♂/♀)<br>LOAEL = 300 mg/kg bw (♂/♀)<br><br>Effects at LOAEL: unscheduled sacrifice (1-2 days post-dosing), moribundity, dehydration, decreased motor activity, prostration, ataxia, hyporeactivity, scant or no feces, hunched posture, loss of righting reflex, cold to the touch, lacrimation, bradypnea, ptosis, piloerection, bw loss (days 1-3), ↓ fc (days 1-4), FOB findings (unusual posture, abnormal gait, abnormal respiration, lower body temperature), ↓ motor activity (total movement, time spent in movement) (♂/♀); FOB findings (lacrimation, ↓ visual reaction) (♂); FOB findings (↓ forelimb grip strength) (♀)<br><br>No evidence of selective neurotoxicity |
| 90-Day Neurotoxicity (diet)<br><br>Sprague-Dawley rat<br><br>PMRA 3042103 | NOAEL = 47/2.2 mg/kg bw/day (♂/♀)<br>LOAEL = not established/11 mg/kg bw/day (♂/♀)<br><br>Effects at LOAEL: ↓ bw, ↓ bwg (♀)<br><br>No evidence of neurotoxicity |
| Developmental Neurotoxicity – waiver request<br><br>PMRA 3042104 | The request to waive the conditional requirement for a developmental neurotoxicity study is approved on the basis that pyrifluquinazon does not affect cholinesterase activity and effects of selective neurotoxicity were not observed in other studies in the supporting database. In addition, there were no signs of neuropathology in adult animals reported in any study and pyrifluquinazon is not expected to elicit other types of nervous system involvement at a developmental stage. Although hormonal perturbations were apparent in the database, the selected reference values are protective of these effects. |
| **Other Studies** | |
| 28-Day Immunotoxicity (diet)<br><br>Sprague-Dawley rat | NOAEL = 12/13 mg/kg bw/day (♂/♀)<br>LOAEL = 62/63 mg/kg bw/day (♂/♀)<br><br>Effects at the LOAEL: ↓ bw, ↓ bwg, ↓ fc (♂/♀) |

| Study Type/Animal/PMRA # | Study Results |
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| PMRA 3042119 | No effect on the immunologic response (AFC assay).<br>No evidence of immune system dysregulation. |
| In vitro Androgen Reporter Gene Assay<br><br>Human breast cancer cell line (MDA-MB-453-kb2) stably transfected with the luciferase reporter gene construct<br><br>PMRA 3042079 | Cells were exposed to pyrifluquinazon and metabolites IV-01, IV-02, IV-203, and IV-208.<br><br>A concentration-dependent increase in luciferase activity was observed with metabolite IV-01, reaching 138% and 150% of control at 10 and 30 µM in the presence of DHT, indicating slight agonism. Undetermined if this increase is AR- or GR-mediated. No biologically relevant increases in luciferase activity were observed with pyrifluquinazon or the remaining metabolites at any test concentration. Cytotoxicity at 100 µM for pyrifluquinazon and metabolite IV-01 undetermined. |
| Androgen Receptor Binding Affinity<br><br>Recombinant AR ligand binding domain (AR-LBD)<br><br>Castrated rat prostate (Sprague-Dawley rat)<br><br>PMRA 3042080 | Supplemental – limited reporting<br><br>Competitive binding with $^{3}$H-methyltrienolone assessed relative to hydroxyflutamide and DHT for pyrifluquinazon and metabolites IV-01, IV-02, IV-203, and IV-208.<br><br>The competitive binding assay using AR-LBD and rat prostate AR showed pyrifluquinazon and IV-01 have weak affinities to AR. Affinities of pyrifluquinazon and IV-01 were lower to the rat prostate AR than to AR-LBD. A comparison of $K_d$ values for binding of $^{3}$H-methyltrienolone in the presence and absence of IV-01 also indicated that it was a weak competitive binder to the rat prostate AR.<br><br>Metabolites IV-02, IV-203, and IV-208 showed no affinity to AR-LBD or rat prostate AR. |
| In vivo Uterotrophic Assay (gavage)<br><br>♀ Sprague-Dawley rat<br><br>PMRA 3042089 | Weak anti-estrogenic activity.<br><br>Decrease in absolute wet uterine weight at 200 mg/kg bw/day pyrifluquinazon when co-exposed to 17 α-ethynyl estradiol supports weak anti-estrogenic activity. |
| Hershberger Assay (gavage)<br><br>Castrated ♂ Sprague-Dawley rat<br><br>PMRA 3316794 | Positive for anti-androgenic activity.<br><br>Experiment 1 (rats dosed with pyrifluquinazon and testosterone propionate):<br><br>Effects at ≥ 50 mg/kg bw/day: ↓ LABC wt<br><br>Effects at ≥ 100 mg/kg bw/day: ↓ ventral prostate wt, ↓ seminal |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| | vesicles with coagulating glands wt<br><br>Effects at 200 mg/kg bw/day: ↓ bw<br><br>Experiment 2 (rats dosed with pyrifluquinazon and DHT):<br><br>Effects at ≥ 100 mg/kg bw/day: ↓ ventral prostate wt, ↓ LABC wt, ↓ seminal vesicles with coagulating glands wt |
| Hershberger Assay<br>(gavage)<br><br>Castrated ♂ Sprague-Dawley rat<br><br>PMRA 3042082 | Positive for anti-androgenic activity.<br><br>Rats dosed with pyrifluquinazon and testosterone propionate.<br><br>Effects at 200 mg/kg bw/day: ↓ ventral prostate wt, ↓ seminal vesicles with coagulating glands wt, ↓ LABC wt, ↓ AR protein |
| Effects of Acute Oral Administration on Prostatic AR<br>(gavage)<br><br>♂ Sprague-Dawley rat<br><br>PMRA 3042087 | Rats were sacrificed 6, 12, or 24 hours following the administration of a single dose of pyrifluquinazon for processing of ventral prostate for protein and RNA extraction to measure AR levels.<br><br>Treatment-related decrease in AR protein in ventral prostate following single dose of 100 or 200 mg/kg bw. Decrease recorded for both doses at 6 hours, observable up to 12 hours at 100 mg/kg bw and ≥ 24 hours at 200 mg/kg bw. Decrease confirmed by immunohistostaining after 12 hours of treatment. No effects observed on AR mRNA levels suggesting a post-transcriptional effect.<br><br>No treatment-related effects on ventral prostate weights were seen in any dose group suggesting that the effects on AR levels precede the decrease in prostate weight observed in other mechanistic studies with pyrifluquinazon. |
| Androgen-Independent Transactivation<br><br>Human kidney cells (HEK293)<br><br>PMRA 3042083 | Cells transfected with rAR expression vector or mutated rAR (missing ligand binding domain) and luciferase reporter vector (pGL4.14-ARE2-TATA-Luc) exposed to pyrifluquinazon or DHT.<br><br>Pyrifluquinazon inhibited mutated (missing ligand binding domain) rAR-mediated transactivation at a comparable level to non-mutated rAR. |
| Human AR Protein Assay<br><br>Human breast cancer cell line (MDA-kb2)<br><br>PMRA 3042084 | Supplemental – limited data and reporting<br><br>Human AR protein levels were highly variable across concentration levels. Levels were ↑ to approximately 130 % of controls at 10 µM then ↓ to approximately 65% of controls at 30 µM. No changes reached statistical significance. No raw data were provided, and no |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| | confirmatory independent experiment was conducted. Findings were inconclusive. |
| Nuclear Localization of AR on Cells<br><br>Human kidney cells (HEK293)<br><br>Human breast cancer cell (MDA-MC-453-kb2)<br><br>Human prostate cancer cell (LNCaP)<br><br>PMRA 3042085 | Cells exposed to pyrifluquinazon or metabolite IV-01<br><br><u>Before treatment</u><br><br>Without DHT, rAR and hAR found distributed in both the cytoplasm and nucleus.<br><br>With DHT, rAR and hAR had nuclear localization.<br><br><u>After treatment</u><br><br>Selective inhibition of rAR nuclear translocation, but no inhibition of hAR.<br><br>Effects at 25 µM: rAR partially in cytoplasm (+DHT), no cytoplasmic localization effect on hAR<br><br>With Emodin (AR nuclear transport inhibitor), ↑ cytoplasmic localization for both hAR and rAR<br><br>Implied species-specific effects on the inhibition of nuclear localization |
| Forced Expression of Rat AR<br><br>Human kidney cells (HEK293) cells co-transfected with rAR expression vector and luciferase reporter vector (pGL4.14-ARE2-TATA-Luc)<br><br>Human breast cancer cell (MDA-kb2)<br><br>PMRA 3042086 | Cells exposed to pyrifluquinazon evaluated for rAR and hAR protein levels by western blot analysis. Microscopic examination of morphological cell abnormalities 24 hours after exposure.<br><br>For forcibly expressed rAR, dose-dependent suppression of luciferase activity ($IC_{50}$ = 7.2 µM) in the presence of DHT.<br><br>↓ protein levels in rAR, but not hAR after treatment.<br><br>No morphological cell abnormalities at any concentration.<br><br>Implied species-specific effects on luciferase activity suppression, mediated by decreased AR protein, dependent on DHT. |
| Estrogen Receptor Binding Assay<br><br>Purified human recombinant ER | Supplemental<br><br>Cells exposed to pyrifluquinazon or metabolites IV-01, IV-02, IV-203, and IV-208. Competitive binding with estrogen ligand assessed. |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| PMRA 3042088 | Based on $IC_{50}$ values, only metabolite IV-208 at a high concentration may have a binding affinity to ER-α ($1.4 \times 10^{-4}$ M) and ER-β ($8.8 \times 10^{-5}$ M). |
| 90-Day Study - Luteinizing Hormone Assay (diet)<br><br>♂ CD-1 mouse<br><br>PMRA 3302149 | Supplemental<br><br>Effects at ≥33 mg/kg bw/day: ↑ liver wt, ↑ LH (week 8)<br><br>Effects at ≥71 mg/kg bw/day: ↑ LH (weeks 4 and 13)<br><br>Effects at 136 mg/kg bw/day: ↓ epididymis wt, ↑ DHT, testicular interstitial cell hypertrophy<br><br>Data for testosterone were highly variable and not dose-responsive, but elevated over controls at all dose levels.<br><br>The results of this study support the conclusion that treatment with pyrifluquinazon impairs AR function or signaling in ♂ CD-1 mice as evidenced by changes in LH, T, and DHT, decreased epididymis weights (absolute and relative), and increased interstitial cell hypertrophy in the testis. The study results suggest that repeated administration of pyrifluquinazon at 71 mg/kg bw/day and above caused an increase in LH that may stimulate proliferation of interstitial cells in the testes of mice. |
| 90-Day Study - Luteinizing Hormone Assay (diet)<br><br>♂ Fischer rat<br><br>PMRA 3042081 | Positive for anti-androgenic activity.<br><br>Clear anti-androgenic effects in response to treatment at 77 mg/kg bw/day and greater. Effects include elevated LH (sustained at high dose only), total T, free T, and DHT, and decrease in androgen-responsive organ weights.<br><br>Effects at ≥ 77 mg/kg bw/day: ↑ rel. testes wt, ↓ ventral prostate wt, ↓ epididymal wt, ↑ incidence and severity of atrophy of prostate and seminiferous tubules, degenerative change (germ cell debris) in epididymis, ↑ LH (week 8), ↑ total T, ↑ free T, ↑ DHT<br><br>Effects at 145 mg/kg bw/day: stained fur, lacrimation, ↓ bw, ↓ fc, ↓ seminal vesicle wt, ↑ rel. testes wt, ↑ rel. pituitary wt |
| 14-Day Thyroid Hormone Assay (diet)<br><br>♂ Fischer rat<br><br>PMRA 3334520 | Supplemental<br><br>Effects at ≥ 32 mg/kg bw/day: slightly ↓ bw, ↓ serum $T_3$ (day 7), ↑ serum $T_3$ (day 14)<br><br>Effects at 117 mg/kg bw/day: ↓ fc (week 1), ↑ rel. thyroid wt, ↑ rel. liver wt, follicular cell hypertrophy, centrilobular hepatocyte |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| | hypertrophy, ↑ UDP-GT activity toward p-nitrophenol and androsterone, ↑ $T_4$ (day 14), ↑ TSH (day 14) |
| 56-Day Thyroid Hormone Assay (diet)<br><br>♂ Fischer rat<br><br>PMRA 3334519 | Supplemental<br><br>Effects at ≥ 28 mg/kg bw/day: ↑ UDP-GT activity toward 4-NP (substrate for $T_4$) , ↓ $T_4$ after week 2<br><br>Effects at ≥ 103 mg/kg bw/day: ↓ bw, ↓ fc, stained fur, ↑ liver wt, ↑ thyroid wt, centrilobular hepatocellular hypertrophy, thyroid follicular cell hypertrophy, small sized thyroid follicles, ↑ TSH after week 2, ↑ free $T_3$ (♂)<br><br>Effects at 179 mg/kg bw/day: lacrimation, discolored eyeball, ↓ abs. pituitary wt, ↑ rel. pituitary wt, diffuse centrilobular hepatocellular hypertrophy, periportal hepatocellular vacuolative change, ↑ total $T_3$ after week 2, enlarged liver, seminal vesicle atrophy, coagulative gland atrophy, prostate atrophy (♂) |
| Acute Pharmacology Study<br><br>♀ Fischer rat<br>♀ CD-1 mouse<br><br>PMRA 3333814 | Supplemental – non-guideline study<br><br><u>General Conditions (FOB)</u><br><br>Effects at ≥ 50 mg/kg bw: piloerection, ↓ mobility (spontaneous motor activity), ↓ muscle tone in the abdomen and limbs<br><br>Effects at 500 mg/kg bw: prone or lateral position, hunched posture, respiratory failure, easy handling and ↓ reactivity, palpebral closure, lacrimation, low body temperature, abnormal gait, ↓ movements, ↓ arousal, loss of responses (approach, touch, sound, pain), loss of pinna reflex, abnormal righting reflex, ↓ mean forelimb and hindlimb grip strength, incontinent urination, pale red urine, cyanosis, ↓ bw (24 hours to day 3), 2 rats found dead (day 3 and 4)<br><br><u>Effects on Central Nervous System</u><br><br>Effects at ≥ 50 mg/kg bw: ↓ motor activity<br><br><u>Effects on Hexobarbital-Induced Sleep</u> (mice; hexobarbital administered by i.p. injection 1 hour post-dosing)<br><br>Effects at ≥ 50 mg/kg bw: ↑ mean sleep time<br><br><u>Effects on Cardiovascular System</u><br><br>Effects at 500 mg/kg bw: ↓ blood pressure, ↓ heart rate |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| | <u>Effects on Renal Function</u><br><br>No treatment-related findings |
| Developmental Toxicity (gavage)<br><br>Sprague-Dawley rat<br><br>PMRA 3379388 | Supplemental – study from the published literature in which 5 pregnant ♀/group were dosed GD 14-18 and allowed to give birth naturally. Offspring were assessed for AGD (PND 2), nipple retention and genital malformations (PND 13), and sexual maturation (♂ only). Offspring sacrificed at 6 months (♀) or 9 months (♂) and assessed for the following: reproductive organ weights, gubernacular ligament measurements, retained nipples, hydronephrosis, bladder stones, and reproductive malformations in ♂; ovary weight, external abnormalities, and reproductive malformations in ♀.<br><br><u>Maternal Toxicity</u><br><br>100 mg/kg bw/day: ↓ maternal bwg<br><br><u>Developmental / Offspring Toxicity</u><br><br>≥ 12.5 mg/kg bw/day: ↑ nipple retention (♂)<br><br>≥ 25 mg/kg bw/day: ↓ AGD, ↑ total reproductive tract abnormalities (variations or malformations) (♂)<br><br>≥ 50 mg/kg bw/day: genital abnormalities, major reproductive malformations (agenesis or aplasia of any reproductive tissue), ↓ ventral prostrate wt, ↓ cowpers gland wt, ↑ number of ♂ with permanent nipples, ↑ percentage of ♂ with nipples, hypospadias, retained nipples (♂)<br><br>100 mg/kg bw/day: ↓ pup wt until PND 13 (♂/♀); ↓ seminal vesicle wt, ↓ paired testes wt, ↓ paired epididymis wt, ↓ cauda epididymis wt, undescended testes, malformed epididymis, malformed ventral prostate, ectopic testes, malformed testis, vaginal pouch (♂)<br><br>Study reported no effect on PPS; data not shown |
| In vitro Assays to Assess AR Agonism<br><br>Monkey kidney cells (CV-1) | Supplemental - study from the published literature to assess the anti-androgenic activity of pyrifluquinazon in chimpanzee CV-1 cells. Four separate in vitro experiments were conducted to assess: 1) the ability of pyrifluquinazon to act as an AR ligand in a competitive binding assay with chimpanzee AR (chAR), 2) pyrifluquinazon as an androgen receptor transcriptional activation agonist using CV-1 cells |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| PMRA 3379388 | transfected with rAR or hAR and the MMTV-luciferase reporter-promoter construct, 3) anti-androgenic activity of pyrifluquinazon in CV-1 cells that were adenovirus transduced with chAR and the MMTV-luciferase reporter-promoter construct, 4) pyrifluquinazon and 3 additional compounds as AR transcriptional activation antagonists in CV-1 cells that were adenovirus transduced with chAR and the MMTV-luciferase reporter-promoter construct.<br><br>Pyrifluquinazon demonstrated androgen antagonist activity at high, cytotoxic concentrations, near the limit of solubility.<br><br>Pyrifluquinazon demonstrated AR-binding and inhibited androgen-induced luciferase expression in hAR, chAR, and rAR cells.<br><br>The $EC_{50}$ for pyrifluquinazon shifted downwards when DHT concentration was reduced, reflective of an AR antagonist.<br><br>Pyrifluquinazon did not interact differently with rAR compared to hAR and did not display androgenic activity in chAR cells.<br><br>The log $K_i$ value of pyrifluquinazon-bound chAR was approximately 6-fold greater than that of the positive control, metribolone.<br><br>Pyrifluquinazon was the weakest AR antagonist of the 4 compounds evaluated, with a log 10 $K_i$ value from the chAR antagonist assay of -5.0. |

**Table 6 Toxicity profile of Pyrifluquinazon 20SC Insecticide containing Pyrifluquinazon**

Effects are known or assumed to occur in both sexes unless otherwise noted.

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| **Acute Toxicity Studies** | |
| Acute Oral Toxicity (Up and Down)<br><br>Sprague-Dawley rat<br><br>PMRA 3045552 | $LD_{50}$ = 2000 mg/kg bw (♀)<br><br>Clinical signs of toxicity included abnormal posture, piloerection, hypoactivity, abnormal gait, reduced fecal volume, irregular respiration.<br><br>Slight acute oral toxicity |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Acute Dermal Toxicity<br><br>Sprague-Dawley rat<br><br>PMRA 3045553 | $LD_{50}$ >2000 mg/kg bw (♂/♀)<br><br>No clinical signs of toxicity noted.<br><br>Low acute dermal toxicity |
| Acute Inhalation Toxicity (nose-only)<br><br>Sprague-Dawley rat<br><br>PMRA 3045554 | $LC_{50}$ > 2.1 mg/L (♂/♀)<br><br>Clinical signs of toxicity included abnormal respiration.<br><br>Low acute inhalation toxicity |
| Eye Irritation<br><br>New Zealand white rabbit<br><br>PMRA 3045555 | MIS = 7.3/110 (1 hour)<br>MAS = 1.1/110<br><br>Minimally irritating to eyes |
| Dermal Irritation<br><br>New Zealand white rabbit<br><br>PMRA 3045556 | MIS = 1.7/8 (1 hour)<br>MAS = 0.1/8<br><br>Minimally irritating to the skin |
| Sensitization (LLNA)<br><br>CBA/J mouse<br><br>PMRA 3045557 | Positive<br>SI = 1.45, 2.17, 3.77 at 50%, 75%, 100%, respectively<br><br>$EC_3$ = 88.0%<br><br>Potential dermal sensitizer |

**Table 7 Toxicity profile of metabolites and impurities of Pyrifluquinazon**

Effects are known or assumed to occur in both sexes unless otherwise noted.

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| **Impurity 1** | |
| Bacterial Reverse Mutation Assay<br><br>S. Typhimurium strains TA1535, TA1537, TA98, TA100 and<br>*E. coli* strain WP2 uvrA<br><br>PMRA 3042090 | Negative ± metabolic activation<br><br>Tested up to cytotoxic or precipitating concentrations. |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| **Impurity 2** | |
| Bacterial Reverse Mutation Assay<br><br>S. Typhimurium strains TA1535, TA1537, TA98, TA100 and<br>*E. coli* strain WP2 uvrA<br><br>PMRA 3042091 | Negative ± metabolic activation<br><br>Tested up to cytotoxic or precipitating concentrations. |
| **Impurity 3** | |
| Bacterial Reverse Mutation Assay<br><br>*S*. Typhimurium strains TA1535, TA1537, TA98, TA100 and<br>*E. coli* strain WP2 uvrA<br><br>PMRA 3042092 | Negative ± metabolic activation<br><br>Tested up to cytotoxic or precipitating concentrations. |
| **Impurity 4** | |
| Bacterial Reverse Mutation Assay<br><br>*S*. Typhimurium strains TA1535, TA1537, TA98, TA100 and<br>*E. coli* strain WP2 uvrA<br><br>PMRA 3042093 | Negative ± metabolic activation<br><br>Tested up to cytotoxic or precipitating concentrations. |
| **Impurity 5** | |
| Bacterial Reverse Mutation Assay<br><br>*S*. Typhimurium strains TA1535, TA1537, TA98, TA100 and<br>*E. coli* strain WP2 uvrA<br><br>PMRA 3042094 | Negative ± metabolic activation<br><br>Tested up to cytotoxic or precipitating concentrations. |
| **Impurity 6** | |
| Bacterial Reverse Mutation Assay | Negative ± metabolic activation<br><br>Tested up to cytotoxic or precipitating concentrations. |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| *S.* Typhimurium strains TA1535, TA1537, TA98, TA100 and *E. coli* strain WP2 uvrA<br><br>PMRA 3042095 | |
| **Impurity 7** | |
| Bacterial Reverse Mutation Assay<br><br>*S.* Typhimurium strains TA1535, TA1537, TA98, TA100 and *E. coli* strain WP2 uvrA<br><br>PMRA 3042096 | Negative ± metabolic activation<br><br>Tested up to precipitating concentrations. |
| **Metabolite IV-01** | |
| Acute Oral Toxicity (Up and Down)<br><br>Sprague-Dawley rat<br><br>PMRA 3042051 | $LD_{50}$ > 2000 mg/kg bw (♀)<br><br>No clinical signs of toxicity were noted.<br><br>Low acute oral toxicity |
| **Metabolite IV-02** | |
| Acute Oral Toxicity (Up and Down)<br><br>Sprague-Dawley rat<br><br>PMRA 3042052 | $LD_{50}$ > 2000 mg/kg bw (♀)<br><br>No clinical signs of toxicity were noted.<br><br>Low acute oral toxicity |
| **Metabolite IV-15** | |
| Acute Oral Toxicity (Up and Down)<br><br>Sprague-Dawley rat<br><br>PMRA 3042053 | $LD_{50}$ > 2000 mg/kg bw (♀)<br><br>No clinical signs of toxicity were noted.<br><br>Low acute oral toxicity |
| **Metabolite IV-27** | |
| Acute Oral Toxicity (Up and Down)<br><br>Sprague-Dawley rat<br><br>PMRA 3042054 | $LD_{50}$ > 2000 mg/kg bw (♀)<br><br>No clinical signs of toxicity were noted.<br><br>Low acute oral toxicity |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| **Metabolite IV-28** | |
| Acute Oral Toxicity (Up and Down)<br><br>Sprague-Dawley rat<br><br>PMRA 3042055 | $LD_{50}$ > 2000 mg/kg bw (♀)<br><br>No clinical signs of toxicity were noted.<br><br>Low acute oral toxicity |
| **Metabolite IV-203** | |
| Acute Oral Toxicity (Toxic Class)<br><br>Wistar rat<br><br>PMRA 3042050 | $LD_{50}$ > 2000 mg/kg bw (♀)<br><br>No clinical signs of toxicity were noted.<br><br>Low acute oral toxicity |
| Bacterial Reverse Mutation Assay<br><br>*S.* Typhimurium strains TA1535, TA1537, TA98, TA100 and<br>*E. coli* strain WP2 uvrA<br><br>PMRA 3042111 | Negative ± metabolic activation<br><br>Tested up to cytotoxic or precipitating concentrations. |

**Table 8 Dermal absorption study in the rat (in vivo): Amount of $^{14}$C-NNI-0101 (radiolabeled pyrifluquinazon) in each matrix at specified hours post-application for rats dermally administered 0.001 mg/cm$^2$**

| Matrix analyzed | Residues in Matrix (% of applied dose)[a] | | | | | |
|---|---|---|---|---|---|---|
| | 0.5 h | 1.0 h | 2.0 h | 4 h | 10 h | 24 hr |
| Urine | 0 | 0.01±0.01 | 0 | 0.03±0.02 | 0.18±0.04 | 0.70±0.27 |
| Feces | 0 | 0 | 0 | 0 | 0.06±0.11 | 2.62±0.47 |
| Cage Wash (ACN) | 0 | 0 | 0 | 0 | 0 | 0.19±0.14 |
| Enclosure | 0.09±0.18 | 0.19±0.22 | 0.28±0.28 | 0.19±0.13 | 0.34±0.33 | 0.21±0.14 |
| Non-occlusive Cover | 0.08±0.09 | 0.17±0.08 | 0.15±0.05 | 0.11±0.08 | 0.10±0.07 | 0.08±0.09 |
| Skin Wash | 83.70±4.15 | 82.60±2.52 | 76.20±8.11 | 75.10±6.29 | 79.20±2.49 | 74.30±1.93 |

| Matrix analyzed | Residues in Matrix (% of applied dose)[a] | | | | | |
|---|---|---|---|---|---|---|
| | 0.5 h | 1.0 h | 2.0 h | 4 h | 10 h | 24 hr |
| Brain | 0 | 0 | 0 | 0 | 0.02±0.01 | 0 |
| Carcass (residual) | 0 | 0 | 0 | 0 | 4.23±0.81 | 2.84±0.59 |
| Fat (reproductive) | 0 | 0 | 0 | 0 | 0.00±0.01 | 0 |
| Heart | 0 | 0 | 0 | 0 | 0.01±0.01 | 0.01±0.01 |
| Kidney(s) | 0 | 0 | 0.01±0.01 | 0.01±0.02 | 0.07±0.02 | 0.04±0.01 |
| Liver | 0 | 0.05±0.09 | 0.26±0.l1 | 0.13±0.15 | 0.59±0.16 | 0.32±0.08 |
| Lungs | 0 | 0 | 0 | 0 | 0.03±0.01 | 0.01±0.01 |
| Pancreas | 0 | 0 | 0 | 0 | 0.01±0.02 | 0 |
| Skin (test site) | 6.45±2.27 | 7.91±1.64 | 11.20±5.37 | 14.40±7.12 | 7.64±0.91 | 12.00±0.69 |
| Testis(es) | 0 | 0 | 0 | 0 | 0.03±0.02 | 0 |
| Subtotal | 6.45±2.27 | 7.95±1.65 | 1l.50±5.37 | 14.50±7.07 | 12.70±1.27 | 15.20±1.29 |
| Total Recovered (%) | 90.30±3.51 | 90.90±1.60 | 88.10±4.43 | 89.90±0.66 | 92.50±3.84 | 93.20±3.61 |
| Total Absorbed [b] (%) | 6.45±2.27 | 7.96±1.65 | 1l.50±5.37 | 14.50±7.04 | 12.90±1.19 | 18.70±1.94 |

ACN = acetonitrile

[a] Mean % ± SD based on 4 rats/group.

[b] Total percent absorbed includes urine, feces, all cage washes, all cage wipes, and all tissues, including test site.

**Table 9 AHETF and PHED unit exposure estimates for mixers, loaders and applicators handling Pyrifluquinazon 20SC Insecticide (µg/kg a.i. handled)**

| Exposure Scenario & PPE | | Dermal | Dermal Absorbed[1] | Inhalation[2] | Total Unit Exposure[3] |
|---|---|---|---|---|---|
| **PPE:** single layer and chemical-resistant gloves | | | | | |
| **Mixer/loader AHETF estimates** | | | | | |
| A | AHETF: Open mix/load liquids | 58.5 | 11.115 | 0.63 | 11.75 |
| **Mixer/loader + applicator PHED estimates** | | | | | |

| Exposure Scenario & PPE | | Dermal | Dermal Absorbed[1] | Inhalation[2] | Total Unit Exposure[3] |
|---|---|---|---|---|---|
| B | PHED: Liquid open pour manually pressurized handwand (M/L/A) (scenario 21a) | 943.37 | 179.2403 | 45.2 | 224.44 |
| C | PHED: Liquid open pour backpack (M/L/A) (scenario 23a) | 5445.85 | 1034.7115 | 62.1 | 1096.81 |
| D | PHED: Liquid open pour mechanically pressurized handgun (M/L/A) (scenario 24a) | 5585.49 | 1061.2431 | 151 | 1212.24 |

[1] Adjusted with dermal absorption factor 19%
[2] Light inhalation rate for all scenarios except backpack, where a moderate inhalation rate is assumed.
[3] Total unit exposure = Dermal exposure + inhalation exposure

**Table 10 Mixer/loader/applicator exposure and risk assessment**

| Exposure Scenario | Unit Exposure (µg/kg a.i. handled)[1] | ATPD (ha/day or L/day)[2] | Rate (kg a.i./ha or kg a.i./L) | Daily Exposure (mg/kg bw/day)[3] | MOE[4] |
|---|---|---|---|---|---|
| **PPE:** single layer and chemical-resistant gloves | | | | | |
| A- Automated equipment | 11.75 | 3.6 | 0.114 | $6.03 \times 10^{-5}$ | 82985 |
| B- Manually pressurized handwand | 224.44 | 150 | $5.60 \times 10^{-5}$ | $2.36 \times 10^{-5}$ | 212168 |
| C- Backpack | 1096.81 | 150 | $5.60 \times 10^{-5}$ | $1.15 \times 10^{-4}$ | 43416 |
| D- Mechanically pressurized handgun | 1212.24 | 3800 | $5.60 \times 10^{-5}$ | $3.22 \times 10^{-3}$ | 1551 |

ATPD = Area treated per day; MOE = Margin of exposure
[1] Unit exposure based on AHETF and PHED.
[2] Default Area Treated per Day table (2021-09-14)
[3] Exposure = (Unit exposure × ATPD × Rate) / (80 kg bw × 1000 µg/mg)
[4] Based on NOAEL = 5 mg/kg bw/day; Target MOE = 1000

**Table 11 Postapplication exposure and risk estimates for Pyrifluqinazon on day 0 after the last application**

| Postapplication activity | Peak DFR (µg/cm$^2$)[1] | Transfer coefficient (cm$^2$/hr)[2] | Dermal exposure (mg/kg bw/day)[3] | MOE[4] | REI[5] (hours) |
|---|---|---|---|---|---|
| All activities in greenhouse lettuce | 0.5179 | 230 | 0.0023 | 221 | 12 |
| All activities in cucumbers, tomatoes, peppers and eggplant | 0.1875 | 1400 | 0.0050 | 100 | 12 |
| All activities in greenhouse herbaceous and deciduous woody ornamentals excluding cut flowers | 0.5179 | 230 | 0.0023 | 221 | 12 |

DFR = Dislodgeable foliar residue; TC = Transfer Coefficient; MOE = Margin of exposure; REI = Restricted-entry interval
[1] Calculated using the standard 25% dislodgeable on the day of application and 2% dissipation per day for greenhouse ornamentals and vegetables.
[2] Transfer coefficients obtained from PMRA Agricultural TCs Table (3.28.2022).
[3] Exposure = (Peak DFR [µg/cm$^2$] × TC [cm$^2$/hr] × 8 hours × 19% dermal absorption) / (80 kg bw × 1000 µg/mg)
[4] Based on a NOAEL of 0.5 mg/kg bw/day, Target MOE = 100
[5] Minimum REI is 12 hours to allow residues to dry, suspended particles to settle and vapours to dissipate.

**Table 12 Integrated food residue chemistry summary**

| **NATURE OF THE RESIDUE IN RADISH** | **PMRA # 3119297** |
|---|---|
| Radiolabel Position | [quinazolinonephenyl ring-U-$^{14}$C]pyrifluquinazon (specific activity 2.55-2.85 MBq/mg) and [pyridine-2,6-$^{14}$C]pyrifluquinazon (specific activity 2.79-2.86 MBq/mg) |
| **Treatment** | |
| Test Site | In individual pots in greenhouse |
| Treatment | Postemergence foliar treatment at 7-day RTIs. |
| Total Rate | Qn-label: 3 x 60.6-102.8 g ai/ha; Total rate of 262 g ai/ha<br>Pyr-label: 3 x 88.0-97.8 g ai/ha; Total rate of 274 g ai/ha |
| Formulation | Wettable granule (WG) formulation of pyrifluquinazon with an adjuvant called "My-Lino" (guarantee: 50 mg ai/L) |
| Harvest | Samples of immature and mature radish plants were harvested 0, 1, 7 and 14 days following the final application. |
| Extraction solvents | Radish tops were rinsed with ACN:water (4:1, v/v) prior to homogenization for extraction and analysis.<br><br>Homogenized samples were extracted 3 x ACN. |

| Matrices | PHI (days) | [quinazolinonephenyl ring-U-$^{14}$C]pyrifluquinazon | [pyridine-2,6-$^{14}$C]pyrifluquinazon |
|---|---|---|---|
| | | TRR (ppm) | |
| Roots | 0 | 0.113 | 0.158 |
| | 1 | 0.128 | 0.174 |
| | 7 | 0.094 | 0.128 |
| | 14 | 0.058 | 0.076 |
| Tops | 0 | 14.382 | 10.750 |
| | 1 | 14.798 | 10.896 |
| | 7 | 10.933 | 5.844 |
| | 14 | 5.856 | 3.641 |

| **Summary of Major Identified Metabolites in Plant Matrices** | |
|---|---|
| Radiolabel Position | [quinazolinonephenyl ring-U-$^{14}$C]pyrifluquinazon, [pyridine-2,6-$^{14}$C]pyrifluquinazon |
| Metabolites Identified | Major Metabolites |
| Radish tops (0- and 1-day PHIs) | Pyrifluquinazon<br>IV-01 |
| Radish tops (7- and 14-day PHIs) | Pyrifluquinazon |
| Radish roots (0- and 1-day PHIs) | Pyrifluquinazon<br>IV-01 |
| Radish roots (7- and 14-day PHIs) | Pyrifluquinazon |

| **NATURE OF THE RESIDUE IN LETTUCE** | **PMRA # 3119295** |
|---|---|
| Radiolabel Position | [quinazolinonephenyl ring-U-$^{14}$C]pyrifluquinazon (specific activity 0.48-0.53 MBq/mg) and [pyridine-2,6-$^{14}$C]pyrifluquinazon (specific activity 0.49-0.50 MBq/mg) |
| **Treatment** | |
| Test Site | In individual pots in greenhouse |
| Treatment | First application 12 days after seeding; second and third application at 7-day RTIs. |
| Total Rate | Qn-label: 3 x 190-248 g ai/ha; Total rate of 639 g ai/ha<br>Pyr-label: 3 x 172-187 g ai/ha; Total rate of 545 g ai/ha |
| Formulation | Wettable granule (WG) formulation of pyrifluquinazon with an adjuvant called “My-Lino” (guarantee: 67 mg ai/L) |
| Harvest | Mature plants (head and wrapper leaves) were harvested at 0, 1, 7 and 14-day PHIs following 3 applications. Stems and roots were sampled at 14-day PHI, also following 3 applications. |
| Extraction solvents | Lettuce plants and wrapper leaves were rinsed with ACN:water (4:1, v/v) prior to homogenization for extraction and analysis.<br><br>Rinsed heads and wrapper leaves were extracted 3x with ACN. |

| Matrices | PHI (days) | [quinazolinonephenyl ring-U-$^{14}$C]pyrifluquinazon | [pyridine-2,6-$^{14}$C]pyrifluquinazon |
|---|---|---|---|
| | | TRR (ppm) | |
| Heads | 0 | 2.927 | 1.821 |
| | 1 | 0.590 | 2.323 |
| | 7 | 0.555 | 0.867 |
| | 14 | 1.419 | 0.568 |
| Wrapper leaves | 0 | 21.372 | 19.167 |
| | 1 | 23.740 | 24.037 |
| | 7 | 24.910 | 17.216 |
| | 14 | 24.067 | 16.848 |
| Stems | 14 | 0.304 | 0.233 |
| Roots | | 0.103 | 0.063 |

| **Summary of Major Identified Metabolites in Plant Matrices** | |
|---|---|
| Radiolabel Position | [quinazolinonephenyl ring-U-$^{14}$C]pyrifluquinazon, [pyridine-2,6-$^{14}$C]pyrifluquinazon |
| Metabolites Identified | Major Metabolites |
| Lettuce heads (0- and 1-day PHIs) | Pyrifluquinazon<br>IV-01 |
| Lettuce heads (7-day PHI) | IV-01 |
| Lettuce heads (14-day PHI) | Pyrifluquinazon<br>IV-01 |
| Wrapper leaves (0- and 1-day PHIs) | Pyrifluquinazon |
| Wrapper leaves (7- and 14-day PHIs) | Pyrifluquinazon<br>IV-01 |
| Stems | Pyrifluquinazon<br>IV-01 |
| Roots | None |

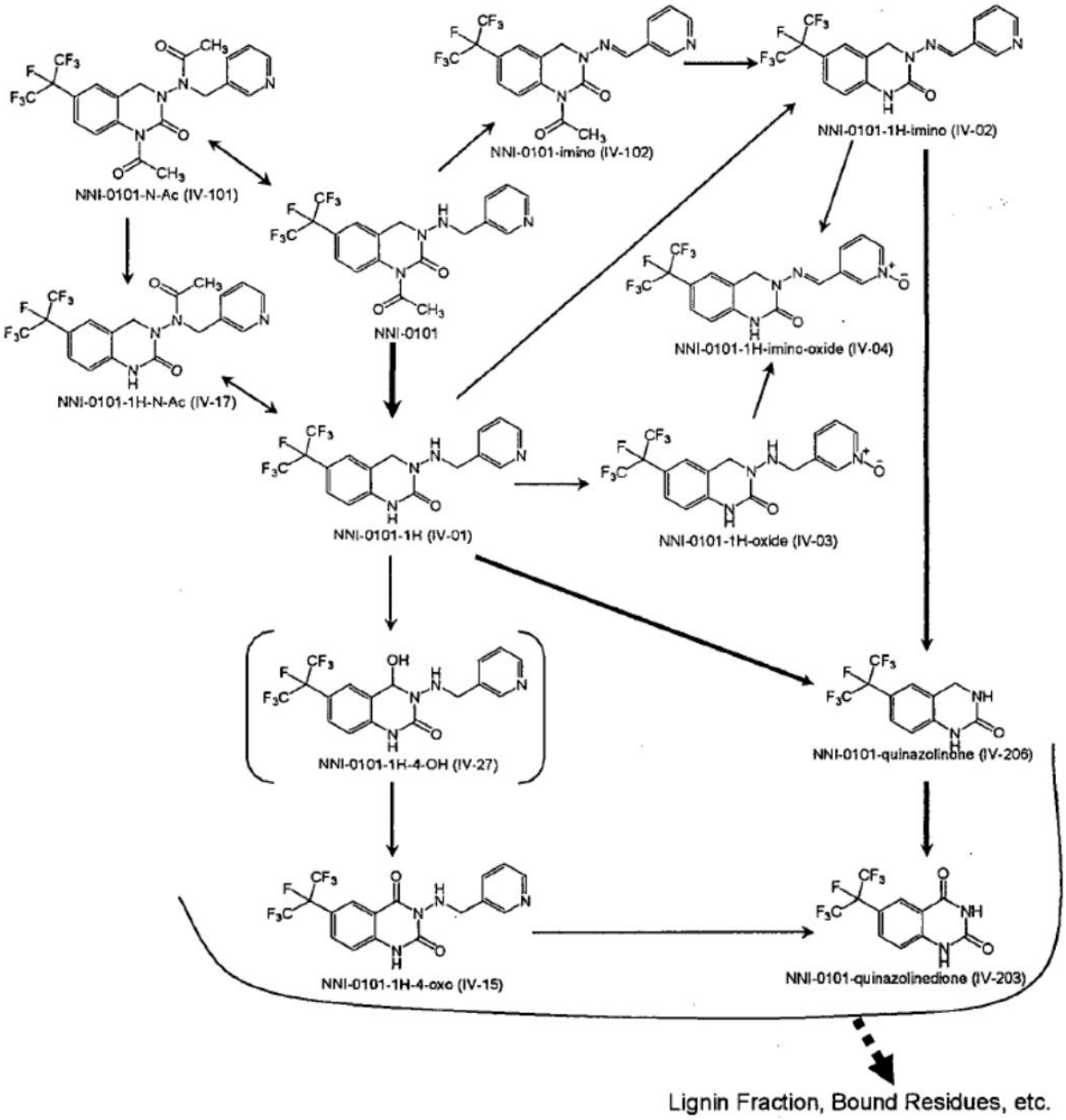
| **NATURE OF THE RESIDUE IN CHERRY TOMATO** | **PMRA # 3119296** |
|---|---|
| Radiolabel Position | [quinazolinonephenyl ring-U-$^{14}$C]pyrifluquinazon (specific activity 2.71-2.73 MBq/mg) and [pyridine-2,6-$^{14}$C]pyrifluquinazon (specific activity 2.02-2.04 MBq/mg) |
| **Treatment** | |
| Test Site | In individual pots in greenhouse |
| Treatment | First application 102 days after seeding. Second and third applications at 7-day RTIs. |
| Total Rate | Qn-label: 3 x 25.8-29.3 g ai/ha; Total rate of 81 g ai/ha<br>Pyr-label: 3 x 21.0-21.9 g ai/ha; Total rate of 64 g ai/ha |
| Formulation | Wettable granule (WG) formulation of pyrifluquinazon with an adjuvant called “My-Lino” (guarantee: 50 mg ai/L) |

| | |
|---|---|
| Harvest | Samples of tomato fruits and leaves were harvested at maturity (0, 1, 7 and 14-day PHIs) after the last application. Samples of stems and roots were collected at 14-day PHI. |
| Extraction solvents | Samples of tomatoes, leaves, and stems were rinsed with ACN:water (4:1, v/v) prior to homogenization for extraction and analysis.<br><br>Rinsed fruit and stems were extracted with ACN x3 |

| **Matrices** | **PHI (days)** | **[quinazolinonephenyl ring-U-$^{14}$C]pyrifluquinazon** | **[pyridine-2,6-$^{14}$C]pyrifluquinazon** |
|---|---|---|---|
| | | **TRR (ppm)** | |
| Tomatoes | 0 | 0.608 | 0.346 |
| | 1 | 0.763 | 0.628 |
| | 7 | 0.612 | 0.411 |
| | 14 | 0.514 | 0.650 |
| Leaves | 0 | 14.355 | 13.278 |
| | 1 | 17.144 | 17.944 |
| | 7 | 15.980 | 13.523 |
| | 14 | 20.665 | 13.060 |
| Stems | 14 | 1.295 | 0.670 |
| Roots | | 0.160 | 0.051 |

| **Summary of Major Identified Metabolites in Plant Matrices** | |
|---|---|
| Radiolabel Position | [quinazolinonephenyl ring-U-$^{14}$C]pyrifluquinazon, [pyridine-2,6-$^{14}$C]pyrifluquinazon |
| Metabolites Identified | Major Metabolites |
| Tomatoes | Pyrifluquinazon |
| Leaves | |
| Stems | |
| Roots | |

**Proposed Metabolic Scheme in Plants**




| **FREEZER STORAGE STABILITY IN PLANT MATRICES** | | | **PMRA # 3043980** | |
|---|---|---|---|---|
| **Tested Matrices** | **Analyte** | **Tested Intervals (days)** | **Temperature (°C)** | **Category** |
| Apples | Pyrifluquinazon | 0, 66, 157 | ≤ -20 | High-water |
| Cauliflower | | 0, 7, 14, 21, 31, 70, 102 | | |
| Cucumbers | | 0, 31, 62, 90 | | |
| Peaches | | 0, 64, 377 | | |
| Tomatoes | | 0, 30, 61, 93, 170, 223 | | |
| Head lettuce | | 0, 30, 61, 93, 170 | | |

| | | | | |
|---|---|---|---|---|
| Potato tubers | | 0,33,93,183,365 | ≤ -20 | High-starch |
| Almond nutmeat | | 0, 63, 163 | | High-oil |
| Cottonseed | | 0, 30, 93, 182, 366 | | |
| Grapes | | 0, 63, 194 | | High-acid |
| Oranges | | 0, 64, 158 | | |
| **Processed Commodities:** | | | | |
| Cotton gin byproducts | Pyrifluquinazon | 0, 14, 64, 393 | ≤ -20 | High-oil |
| Cottonseed refined oil | | 0, 35, 106, 182, 365 | | |
| Orange dried pulp | | 0, 35, 95, 184, 367 | | High-acid |
| Orange juice | | 0, 31, 94, 181, 365 | | |
| Tomato paste | | 0, 32, 94, 195, 368, 546 | | High-water |

**CROP FIELD TRIALS & RESIDUE DECLINE ON Tuberous and Corm Vegetables (Potatoes)** **PMRA # 3043995**

In support of a request for an MRL on imported tuberous and corm vegetables, crop field trials conducted in 2009 in the United States were assessed. Trials were conducted in North American growing regions 1 (2 trials), 2 (1 trial) 3 (1 trial), 5 (4 trials), 9 (1 trial), 10 (1 trial), and 11 (6 trials) for a total of 16 trials. A 20% SC pyrifluquinazon formulation was applied three times as foliar broadcast sprays at a nominal rate of 100 g a.i./ha/application at 14-day intervals for a seasonal application rate of 300 g a.i./ha. The last application occurred approximately 14 days before harvest.

Adjuvants were used in/on potatoes at all field trial sites. The number and geographic distribution of trials were generally in accordance with USEPA's OPPTS 860 1500. Independence of trials was assessed. Residue decline of pyrifluquinazon in/on potato tubers could not be assessed as residues were <LOQ in all samples. Adequate storage stability data are available to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Potato tubers | 299-310 | 13-14 | Pyrifluquinazon | 16 | <0.01 | <0.01 | 0.01 | 0.01 | 0 |

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

**CROP FIELD TRIALS & RESIDUE DECLINE ON Leafy Vegetables (Head lettuce, leaf lettuce, spinach, and mustard greens)** **PMRA # 3043981, 3043982**

In support of a request for an MRL on imported leafy vegetables, crop field trials conducted in 2008-2009 in the United States were assessed. Trials were conducted in North American growing regions 1 (2 trials), 3 (1 trial), and 10 (4 trials) for a total of 7 trials on head lettuce, regions 2 (1 trial), 3 (1 trial), and 10 (5 trials) for a total of 7 trials on leaf lettuce, regions 1 (1 trial), 2 (1 trial), 6 (1 trial), 9 (1 trial), and 10 (3 trials) for a total of 7 trials for spinach, regions 2 (1 trial), 4 (1 trial), 5 (1 trial), 6 (1 trial), and 10 (1 trial) for a total of 5 trials for mustard greens. A 20% SC pyrifluquinazon formulation was applied three times as foliar broadcast sprays at a nominal rate of 50 g a.i./ha/application at 7-day intervals for a seasonal application rate of 150 g a.i./ha. The last

application occurred approximately 1 day before harvest.

Adjuvants were used in/on all field trial sites. The number and geographic distribution of trials were generally in accordance with USEPA's OPPTS 860 1500. Independence of trials was assessed for each representative crop. Residue decline of pyrifluquinazon in/on head lettuce show that residues of pyrifluquinazon decrease with increasing PHIs. Adequate storage stability data are available to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Head lettuce | 148-165 | 1 | Pyrifluquinazon | 7 | <0.01 | 0.422 | 0.113 | 0.165 | 0.159 |
| Leaf lettuce | 148-152 | 1 | | 7 | 0.017 | 0.982 | 0.327 | 0.370 | 0.313 |
| Spinach | 148-156 | 1 | | 7 | <0.01 | 1.84 | 0.758 | 0.898 | 0.620 |
| Mustard greens | 149-155 | 1 | | 5 | 0.352 | 1.64 | 0.594 | 0.858 | 0.538 |

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

**CROP FIELD TRIALS & RESIDUE DECLINE ON Greenhouse Lettuce** **PMRA # 3043986**

In support of the domestic registration on greenhouse lettuce, two greenhouse trials were conducted in 2011 in Canada. A 20% SC pyrifluquinazon formulation was applied twice as foliar broadcast sprays at actual rates of 68-75 g a.i./ha/application at 10- to 11-day intervals for application rates of 139-143 g a.i./ha. The last application occurred approximately 1 day before harvest.

Adjuvants were used in/on all greenhouse trial sites. The number of trials were in accordance with DIR2010-05. Residue decline in/on leaf lettuce grown in greenhouses show that residues of pyrifluquinazon decrease with increasing PHIs. Adequate storage stability data are available to support the storage intervals of the crop trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Greenhouse leaf lettuce | 139-144 | 1 | Pyrifluquinazon | 2 | 0.213 | 0.969 | 0.591 | 0.591 | N/A |

n = number of independent trials, LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SDEV = Standard Deviation, N/A = not applicable

**CROP FIELD TRIALS & RESIDUE DECLINE ON *Brassica* Head and Stem Vegetables (Cauliflower and cabbage)** **PMRA # 3043981**

In support of a request for an MRL on imported *Brassica* vegetables, crop field trials conducted in 2008-2009 in the United States were assessed. Trials were conducted in North American growing regions 1 (1 trial), 5 (1 trial), 10 (3 trials), and 12 (1 trial) for a total of 6 trials on cauliflower and in regions 1 (2 trials), 2 (2 trials), 3 (1 trial), 5 (1 trial), 6 (1 trial), and 10 (1 trial) for a total of 8 trials on cabbage. A 20% SC pyrifluquinazon formulation was applied three times as foliar broadcast sprays at a nominal rate of 50 g a.i./ha/application at 7-day intervals for a seasonal application rate of

150 g a.i./ha. The last application occurred approximately 1 day before harvest.

Adjuvants were used in/on all field trial sites. The number and geographic distribution of trials were generally in accordance with USEPA's OPPTS 860 1500. Independence of trials was assessed for each representative crop. Residue decline in/on cauliflower show that residues of pyrifluquinazon decrease 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 ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Cabbage | 149-156 | 1 | Pyrifluquinazon | 8 | <0.01 | 0.153 | 0.072 | 0.075 | 0.056 |
| Cauliflower | 148-152 | 1 | | 6 | <0.01 | 0.041 | 0.011 | 0.018 | 0.013 |

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

**CROP FIELD TRIALS & RESIDUE DECLINE ON Fruiting Vegetables (Tomato, bell pepper, non-bell pepper)** **PMRA # 3043984, 3043989**

In support of a request for an MRL on imported fruiting vegetables, crop field trials conducted in 2008 in the United States were assessed. Trials were conducted in North American growing regions 2 (1 trial), 3 (2 trials), 5 (1 trial), 6 (1 trial), and 10 (3 trials) for a total of 8 trials on bell peppers, regions 8 (1 trial) and 10 (3 trials) for a total of 4 trials on non-bell peppers, and in regions 1 (1 trial), 2 (1 trial), 3 (3 trials), 5 (1 trial), and 10 (8 trials) for a total of 14 trials for tomatoes. A 20% SC pyrifluquinazon formulation was applied three times as foliar broadcast sprays at a nominal rate of 100 g a.i./ha/application at 7-day intervals for a seasonal application rate of 300 g a.i./ha. The last application occurred approximately 1 day before harvest.

Adjuvants were used in/on all field trial sites. The number and geographic distribution of trials were generally in accordance with USEPA's OPPTS 860 1500. Independence of trials was assessed for each representative crop. Residue decline in/on tomatoes show that residues of pyrifluquinazon decrease with increasing PHIs. In bell peppers, residue decline could not be assessed as residues of pyrifluquinazon were <LOQ in all samples. Adequate storage stability data are available to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Bell pepper | 299-306 | 1 | Pyrifluquinazon | 8 | <0.01 | 0.070 | 0.020 | 0.030 | 0.023 |
| Non-bell pepper | 300-305 | 1 | | 4 | <0.01 | 0.140 | 0.051 | 0.063 | 0.057 |
| Tomato | 300-312 | 1 | | 14 | <0.01 | 0.141 | 0.041 | 0.052 | 0.039 |

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

**CROP FIELD TRIALS & RESIDUE DECLINE ON Greenhouse Pepper** **PMRA # 3043987**

In support of the domestic registration on greenhouse peppers, four greenhouse trials were conducted in 2011-2012 in Canada and in the United States on bell and non-bell peppers. A 20% SC

pyrifluquinazon formulation was applied twice as foliar broadcast sprays at actual rates of 106-116 g a.i./ha/application at 6- to 7-day intervals for application rates of 213-227 g a.i./ha. The last application occurred approximately 1 day before harvest.

Adjuvants were used in/on all greenhouse trial sites. The number of trials were in accordance with DIR2010-05. Residue decline in/on peppers grown in greenhouses show that residues of pyrifluquinazon decrease with increasing PHIs. Adequate storage stability data are available to support the storage intervals of the crop trials. Samples were analyzed using a validated analytical method.

Data for greenhouse peppers were extended to support the domestic registration on greenhouse eggplants.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Greenhouse peppers (extended to greenhouse eggplants) | 213-227 | 1 | Pyrifluquinazon | 4 | 0.011 | 0.154 | 0.102 | 0.092 | 0.073 |

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

**CROP FIELD TRIALS & RESIDUE DECLINE ON Greenhouse Tomato** **PMRA # 3043988**

In support of the domestic registration on greenhouse tomatoes, four greenhouse trials were conducted in 2010 in Canada and in the United States. A 20% SC pyrifluquinazon formulation was applied twice as foliar broadcast sprays at actual rates of 50-51 g a.i./ha/application at 9- to 11-day intervals for application rates of 99-102 g a.i./ha. The last application occurred approximately 1 day before harvest.

Adjuvants were used in/on all greenhouse trial sites. The number of trials were in accordance with DIR2010-05. Residue decline in/on tomatoes grown in greenhouses show that residues of pyrifluquinazon decrease with increasing PHIs. Adequate storage stability data are available to support the storage intervals of the crop trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Greenhouse tomatoes (including small varieties) | 99-102 | 1 | Pyrifluquinazon | 4 | 0.012 | 0.095 | 0.050 | 0.052 | 0.038 |

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

| **CROP FIELD TRIALS & RESIDUE DECLINE ON Cucurbit Vegetables (Cucumber, muskmelon, and summer squash)** | **PMRA # 3043983** |
|---|---|

In support of a request for an MRL on imported cucurbit vegetables, crop field trials conducted in 2010 in the United States were assessed. Trials were conducted in North American growing regions 2 (2 trials), 3 (1 trial), 5 (2 trials), and 6 (1 trial) for a total of 6 trials on cucumbers, regions 2 (1 trial), 5 (1 trial), 6 (1 trial), and 10 (3 trials) for a total of 6 trials on muskmelon, and in regions 1 (1 trial), 2 (1 trial), 3 (1 trial), 5 (1 trial), and 10 (1 trial) for a total of 5 trials for summer squash. A 20% SC pyrifluquinazon formulation was applied three times as foliar broadcast sprays at a nominal rate of 100 g a.i./ha/application at 7-day intervals for a seasonal application rate of 300 g a.i./ha. The last application occurred approximately 1 day before harvest.

Adjuvants were used in/on all field trial sites. The number and geographic distribution of trials were generally in accordance with USEPA's OPPTS 860 1500. Independence of trials was assessed for each representative crop. Residue decline in/on cucumbers, muskmelon, and summer squash show that residues of pyrifluquinazon decrease with increasing PHIs. Adequate storage stability data are available to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Cucumber | 299-305 | 1 | Pyrifluquinazon | 6 | <0.01 | 0.049 | 0.024 | 0.024 | 0.014 |
| Muskmelon | 302-308 | 1 | | 6 | 0.011 | 0.053 | 0.025 | 0.029 | 0.016 |
| Summer squash | 302-306 | 1 | | 5 | <0.01 | 0.026 | 0.012 | 0.015 | 0.007 |

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

| **CROP FIELD TRIALS & RESIDUE DECLINE ON Greenhouse Cucumbers** | **PMRA # 3043985** |
|---|---|

In support of the domestic registration on greenhouse cucumbers, four greenhouse trials were conducted in 2012-2013 in Canada. A 20% SC pyrifluquinazon formulation was applied twice as foliar broadcast sprays at actual rates of 104-114 g a.i./ha/application at 9- to 11-day intervals for application rates of 212-223 g a.i./ha. The last application occurred approximately 1 day before harvest.

Adjuvants were used in/on all greenhouse trial sites. The number of trials were in accordance with DIR2010-05. Residue decline in/on cucumbers grown in greenhouses show that residues of pyrifluquinazon decrease with increasing PHIs. Adequate storage stability data are available to support the storage intervals of the crop trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Greenhouse cucumbers | 212-223 | 1 | Pyrifluquinazon | 4 | <0.01 | 0.044 | 0.019 | 0.023 | 0.015 |

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

| **CROP FIELD TRIALS & RESIDUE DECLINE ON Citrus Fruits (Grapefruit, lemon, and oranges)** | **PMRA # 3043993** |
|---|---|

In support of a request for an MRL on imported citrus fruits, crop field trials conducted in 2008-2009 in the United States were assessed. Trials were conducted in North American growing regions 3 (3 trials), 6 (1 trial), and 10 (2 trials) for a total of 6 trials on grapefruit, regions 3 (1 trial) and 10 (4 trials) for a total of 5 trials on lemon, and in regions 3 (7 trials), 6 (1 trial), and 10 (3 trials) for a total of 11 trials on oranges. A 20% SC pyrifluquinazon formulation was applied three times as foliar broadcast sprays at a nominal rate of 150 g a.i./ha/application at 7-day intervals for a seasonal application rate of 450 g a.i./ha. The last application occurred approximately 1 day before harvest.

Adjuvants were used in/on all field trial sites. The number and geographic distribution of trials were generally in accordance with USEPA's OPPTS 860 1500. Independence of trials was assessed for each representative crop. Residue decline in/on grapefruit, lemon, and oranges show that residues of pyrifluquinazon decrease with increasing PHIs. Adequate storage stability data are available to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Grapefruit | 453-460 | 1 | Pyrifluquinazon | 6 | 0.028 | 0.085 | 0.043 | 0.049 | 0.021 |
| Lemon | 451-455 | 1 | | 5 | 0.070 | 0.304 | 0.072 | 0.132 | 0.101 |
| Oranges | 447-457 | 1 | | 11 | 0.023 | 0.132 | 0.067 | 0.077 | 0.037 |

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

| **CROP FIELD TRIALS & RESIDUE DECLINE ON Pome Fruits (apples and pears)** | **PMRA # 3043991** |
|---|---|

In support of a request for an MRL on imported pome fruits, crop field trials conducted in 2009 in the United States were assessed. Trials were conducted in North American growing regions 1 (3 trials), 2 (1 trial), 5 (2 trials), 9 (1 trial), 10 (1 trial), and 11 (4 trials) for a total of 12 trials on apples and in regions 1 (1 trial), 10 (2 trials), and 11 (3 trials) for a total of 6 trials on pears. A 20% SC pyrifluquinazon formulation was applied three times as foliar broadcast sprays at a nominal rate of 100 g a.i./ha/application at 7-day intervals for a seasonal application rate of 300 g a.i./ha. The last application occurred approximately 14 days before harvest.

Adjuvants were used in/on all field trial sites. The number and geographic distribution of trials were generally in accordance with USEPA's OPPTS 860 1500. Independence of trials was assessed for each representative crop. Residue decline in/on apples and pears show that residues of pyrifluquinazon decrease with increasing PHIs. Adequate storage stability data are available to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Apples | 299-306 | 13-14 | Pyrifluquinazon | 12 | <0.01 | 0.074 | 0.010 | 0.019 | 0.019 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pears | 300-306 | 14 | | 6 | <0.01 | 0.066 | 0.015 | 0.024 | 0.022 |

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

**CROP FIELD TRIALS & RESIDUE DECLINE ON Stone Fruits (Cherries, peaches, and plums)** **PMRA # 3043996**

In support of a request for an MRL on imported stone fruits, crop field trials conducted in 2010 in the United States were assessed. Trials were conducted in North American growing regions 1 (1 trial), 5 (2 trials), 10 (1 trial), and 11 (2 trials) for a total of 6 trials on cherries (sweet and sour), regions 1 (1 trial), 2 (3 trials), 5 (1 trial), 6 (1 trial), and 10 (3 trials) for a total of 9 trials on peaches, and in regions 5 (1 trial), 10 (4 trials), and 11 (1 trial) for a total of 6 trials on plums. A 20% SC pyrifluquinazon formulation was applied three times as foliar broadcast sprays at a nominal rate of 50 g a.i./ha/application at 7-day intervals for a seasonal application rate of 150 g a.i./ha. The last application occurred approximately 7 days before harvest.

Adjuvants were used in/on all field trial sites. The number and geographic distribution of trials were generally in accordance with USEPA's OPPTS 860 1500. Independence of trials was assessed for each representative crop. Residue decline in/on cherries and peaches show that residues of pyrifluquinazon decrease with increasing PHIs. Residue decline of pyrifluquinazon on plums could not be assessed as residues were <LOQ in all samples. Adequate storage stability data are available to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Cherry | 149-154 | 7 | Pyrifluquinazon | 6 | <0.01 | <0.01 | 0.01 | 0.01 | 0 |
| Peach | 149-156 | 7 | | 9 | <0.01 | <0.01 | 0.01 | 0.01 | 0 |
| Plum | 150-154 | 7 | | 6 | <0.01 | <0.01 | 0.01 | 0.01 | 0 |

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

**CROP FIELD TRIALS & RESIDUE DECLINE ON Small fruits vine climbing, except fuzzy kiwifruit (Grapes)** **PMRA # 3043994**

In support of a request for an MRL on imported small fruits vine climbing (except fuzzy kiwifruit), crop field trials conducted in 2008 in the United States were assessed. Trials were conducted in North American growing regions 1 (2 trials), 10 (8 trials), and 11 (2 trials) for a total of 12 trials on grapes. A 20% SC pyrifluquinazon formulation was applied three times as foliar broadcast sprays at a nominal rate of 50 g a.i./ha/application at 7-day intervals for a seasonal application rate of 150 g a.i./ha. The last application occurred approximately 3 days before harvest.

Adjuvants were used in/on all field trial sites. The number and geographic distribution of trials were generally in accordance with USEPA's OPPTS 860 1500. Independence of trials was assessed for the representative crop. Residue decline in/on grapes show that residues of pyrifluquinazon decrease with increasing PHIs. Adequate storage stability data are available to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Grapes | 150-155 | 3 | Pyrifluquinazon | 12 | <0.01 | 0.164 | 0.024 | 0.044 | 0.049 |

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

**CROP FIELD TRIALS & RESIDUE DECLINE ON Tree Nuts (Almonds and pecans)** **PMRA # 3043997**

In support of a request for an MRL on imported tree nuts, crop field trials conducted in 2009 in the United were assessed. Trials were conducted in North American growing region 10 (5 trials) for a total of 5 trials on almonds and in regions 2 (2 trials), 4 (1 trial), 6 (1 trial), and 8 (1 trial) for a total of 5 trials in pecans. A 20% SC pyrifluquinazon formulation was applied three times as foliar broadcast sprays at a nominal rate of 100 g a.i./ha/application at 7-day intervals for a seasonal application rate of 300 g a.i./ha. The last application occurred approximately 7 days before harvest.

Adjuvants were used in/on all field trial sites. The number and geographic distribution of trials were generally in accordance with USEPA's OPPTS 860 1500. Independence of trials was assessed for the representative crops. Residue decline in/on could not be assessed since all residues were <LOQ. Adequate storage stability data are available to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Almonds | 302-304 | 7 | Pyrifluquinazon | 5 | <0.01 | <0.01 | 0.01 | 0.01 | 0 |
| Pecans | 302-308 | 7 | Pyrifluquinazon | 5 | <0.01 | <0.01 | 0.01 | 0.01 | 0 |

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

**CROP FIELD TRIALS & RESIDUE DECLINE ON Leaf petioles vegetables (Celery)** **PMRA # 3043982**

In support of a request for an MRL on imported leaf petioles vegetables, crop field trials conducted in 2008 and 2010 in the United States were assessed. Trials were conducted in North American growing regions 3 (1 trial), 5 (1 trial), and 10 (6 trials) for a total of 8 trials on celery. A 20% SC pyrifluquinazon formulation was applied three times as foliar broadcast sprays at a nominal rate of 50 g a.i./ha/application at 7-day intervals for a seasonal application rate of 150 g a.i./ha. The last application occurred approximately 1 day before harvest.

Adjuvants were used in/on all field trial sites. The number and geographic distribution of trials were generally in accordance with USEPA's OPPTS 860 1500. Independence of trials was assessed for the representative crop. Residue decline in/on celery was not assessed. Adequate storage stability data are available to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Celery | 148-151 | 1 | Pyrifluquinazon | 8 | <0.01 | 0.413 | 0.145 | 0.172 | 0.148 |

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

**CROP FIELD TRIALS & RESIDUE DECLINE ON Cottonseed** **PMRA # 3043992**

In support of a request for an MRL on imported cottonseed, crop field trials conducted in 2009 in the United States were assessed. Trials were conducted in North American growing regions 2 (1 trial), 4 (3 trials), 6 (1 trial), 8 (4 trials), and 10 (2 trials) for a total of 11 trials on cotton. A 20% SC pyrifluquinazon formulation was applied three times as foliar broadcast sprays at a nominal rate of 50 g a.i./ha/application at 7-day intervals for a seasonal application rate of 150 g a.i./ha. The last application occurred approximately 7 days before harvest.

Adjuvants were used in/on all field trial sites. The number and geographic distribution of trials were generally in accordance with USEPA's OPPTS 860 1500. Independence of trials was assessed for cotton. Residue decline in/on cotton seed show that residues of pyrifluquinazon decrease with increasing PHIs. Adequate storage stability data are available to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Undelinted cottonseed | 150-155 | 6-9 | Pyrifluquinazon | 11 | <0.01 | 0.178 | 0.01 | 0.037 | 0.050 |

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

**CROP FIELD TRIALS & RESIDUE DECLINE ON Tea** **PMRA #s 3044000, 3044001, 3044002, 3044003, 3044004**

In support of a request for an MRL on imported tea, crop field trials conducted in 2004-2006 in Japan were assessed. A 20% WDG pyrifluquinazon formulation was applied two times as foliar broadcast sprays at nominal rates of 134-1000 g a.i./ha/application at 6- to 9-day intervals for seasonal application rates of 804-1200 g a.i./ha. The last applications occurred approximately 7 and 14 days before harvest.

Adjuvants were not used at any of the field trial sites. Residue decline in/on tea show that residues of pyrifluquinazon decrease with increasing PHIs. Adequate storage stability data are available to support the storage intervals of the crop field trials. Samples were analyzed using a validated analytical method.

| Crop | Total Application Rate (g ai/ha) | PHI (days) | Analyte | Pyrifluquinazon Levels (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | LAFT | HAFT | Median | Mean | SDEV |
| Tea | 1200 | 7 | Pyrifluquinazon | 4 | 0.65 | 9.15 | 1.63 | 3.26 | 3.96 |

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

**PROCESSED FOOD AND FEED - Apple** **PMRA # 3043991**

Processing studies were conducted in one distinctive North American growing region using a 20% SC at 1540 g ai/ha (20-fold of maximum seasonal use rate) in/on pome fruits. Adequate storage stability data are available to support the storage intervals of the processed food. Samples were analyzed using a validated analytical method.

| RAC | Processed Fractions | $HAFT_{[RAC]}$ (ppm) | Median Processing Factor of Pyrifluquinazon | Anticipated Residues of Pyrifluquinazon (ppm) |
|---|---|---|---|---|
| Apples | Apple juice | 0.074 | 0.1x | 0.007 |

**PROCESSED FOOD AND FEED - Cotton** **PMRA # 3043992**

Processing studies were conducted in one distinctive North American growing region using a 20% SC at 769 g ai/ha (10-fold of maximum seasonal use rate) in/on cotton. Adequate storage stability data are available to support the storage intervals of the processed food. Samples were analyzed using a validated analytical method.

| RAC | Processed Fractions | $HAFT_{[RAC]}$ (ppm) | Median Processing Factor of Pyrifluquinazon | Anticipated Residues of Pyrifluquinazon (ppm) |
|---|---|---|---|---|
| Undelinted cottonseed | Refined oil | 0.178 | 0.4x | 0.07 |

**PROCESSED FOOD AND FEED - Grape** **PMRA # 3043994**

Processing studies were conducted in one distinctive North American growing region using a 20% SC at 768 g ai/ha (10-fold of maximum seasonal use rate) in/on grapes. Adequate storage stability data are available to support the storage intervals of the processed food. Samples were analyzed using a validated analytical method.

| RAC | Processed Fractions | $HAFT_{[RAC]}$ (ppm) | Median Processing Factor of Pyrifluquinazon | Anticipated Residues of Pyrifluquinazon (ppm) |
|---|---|---|---|---|
| Grapes | Juice | 0.164 | 0.7x | 0.12 |
| | Raisins | | 0.3x | 0.05 |

**PROCESSED FOOD AND FEED - Orange** **PMRA # 3043993**

Processing studies were conducted in one distinctive North American growing region using a 20% SC at 2290 g ai/ha (~10-fold of maximum seasonal use rate) in/on citrus fruits. Adequate storage stability data are available to support the storage intervals of the processed food. Samples were analyzed using a validated analytical method.

| RAC | Processed Fractions | $HAFT_{[RAC]}$ (ppm) | Median Processing Factor of Pyrifluquinazon | Anticipated Residues of Pyrifluquinazon (ppm) |
|---|---|---|---|---|
| Oranges | Juice | 0.304 (lemon) | 0.02x | 0.006 |

| | | | | |
|---|---|---|---|---|
| | Oil | | 94x | 28.58 |
| **PROCESSED FOOD AND FEED - Plum** | | | | **PMRA # 3043996** |
| Processing studies were conducted in one distinctive North American growing region using a 20% SC at 753 g ai/ha (10-fold of maximum seasonal use rate) in/on stone fruits. Adequate storage stability data are available to support the storage intervals of the processed food. Samples were analyzed using a validated analytical method. | | | | |
| **RAC** | **Processed Fractions** | **HAFT[RAC] (ppm)** | **Median Processing Factor of Pyrifluquinazon** | **Anticipated Residues of Pyrifluquinazon (ppm)** |
| Plum | Prune | <0.01 | 1.4x | <0.014 |
| **PROCESSED FOOD AND FEED - Potato** | | | | **PMRA # 3043995** |
| Processing studies were conducted in one distinctive North American growing region using a 20% SC at 1520 g ai/ha (15-fold of maximum seasonal use rate) in/on tuberous and corm vegetables. Adequate storage stability data are available to support the storage intervals of the processed food. Samples were analyzed using a validated analytical method.<br><br>Pyrifluquinazon residues were all <LOQ (<0.01 ppm) in potato tuber and all processed commodities (potato flakes, chips and wet peel). Processing factors could not be calculated for pyrifluquinazon in potato processed fractions. | | | | |
| **PROCESSED FOOD AND FEED - Tomato** | | | | **PMRA # 3043989** |
| Processing studies were conducted in one distinctive North American growing region using a 20% SC at 1510 g ai/ha (19-fold of maximum seasonal use rate) in/on tomatoes. Adequate storage stability data are available to support the storage intervals of the processed food. Samples were analyzed using a validated analytical method. | | | | |
| **RAC** | **Processed Fractions** | **HAFT[RAC] (ppm)** | **Median Processing Factor of Pyrifluquinazon** | **Anticipated Residues of Pyrifluquinazon (ppm)** |
| Tomato | Paste | 0.141 | 0.8x | 0.11 |
| | Puree | | 0.4x | 0.06 |

**Table 13 Food residue chemistry overview of metabolism studies and risk assessment**

| **PLANT STUDIES** | |
|---|---|
| **RESIDUE DEFINITION FOR ENFORCEMENT**<br>**Primary crops (Radish, lettuce, and cherry tomato)** | Pyrifluquinazon |
| **RESIDUE DEFINITION FOR RISK ASSESSMENT**<br>**Primary crops** | Pyrifluquinazon including the metabolite IV-01 (expressed as parent equivalents) |
| **METABOLIC PROFILE IN DIVERSE CROPS** | Similar in radish (root vegetable), lettuce (leafy vegetable) and cherry tomato (fruiting vegetable). |

| DIETARY RISK FROM FOOD | | |
|---|---|---|
| | **POPULATION** | **ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)** |
| | | **Food Alone** |
| **Refined acute dietary exposure analysis, 95th percentile**<br><br>**ARfD = 0.005 mg/kg bw (females 13-49 years)**<br><br>**ARfD = 1.0 mg/kg bw (general population, excluding females 13-49 years)** | All infants <1 year | 0.3 |
| | Children 1–2 years | 0.6 |
| | Children 3–5 years | 0.5 |
| | Children 6–12 years | 0.3 |
| | Males 13–19 years | 0.2 |
| | Males 20–49 years | 0.2 |
| | Adults 50+ years | 0.3 |
| | Females 13-49 years | 53.5 |

| | **POPULATION** | **ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)** |
|---|---|---|
| | | **Food Alone** |
| **Refined chronic non-cancer and cancer dietary exposure analysis**<br><br>**ADI = 0.005 mg/kg bw/day** | All infants <1 year | 6.5 |
| | Children 1–2 years | 14.1 |
| | Children 3–5 years | 10.9 |
| | Children 6–12 years | 7.0 |
| | Youth 13–19 years | 5.5 |
| | Adults 20–49 years | 7.5 |
| | Adults 50+ years | 8.9 |
| | Females 13-49 years | 7.8 |
| | Total population | 8.0 |

## Table 14 Fate and behaviour in the environment

| Property | Test substance | Value | Transformation products | Comments | PMRA# |
|---|---|---|---|---|---|
| **Abiotic transformation** | | | | | |
| Hydrolysis at 25 ± 1°C | [$^{14}$C]pyrifluquinazon | pH 5: $DT_{50}$: 89.3 d; $DT_{90}$: 297 d (SFO)<br><br>pH 7: $DT_{50}$: 25.2 d; $DT_{90}$: 83.6 d (SFO)<br><br>pH 9: $DT_{50}$:1 d; $DT_{90}$: 3.3 d (SFO)<br><br>pH 9: $DT_{50}$:0.63 d; $DT_{90}$:2.1 d (SFO) | <u>Major</u>:<br>IV-01<br><br><u>Minor (pH 9):</u><br>D-1, Unidentified | May be a route of dissipation under neutral to alkaline conditions, only. | 3042131<br><br>3042132 |
| Phototransformation on soil | Not required for greenhouse use | | | | |
| Phototransformation in water | Not required for greenhouse use | | | | |
| Phototransformation in air | Not required for greenhouse use | Pyrifluquinazon is not expected to be volatile under field conditions based on its low vapour pressure. | | | |
| **Biotransformation** | | | | | |
| Biotransformation in aerobic soil | [$^{14}$C]Pyrifluquinazon (Qn label)<br><br>[$^{14}$C]Pyrifluquinazon (Py label) | <u>North Dakota sandy loam soil</u> (pH 7.5, OC 1.57%, 25ºC): $DT_{50}$: 0.35 d; $DT_{90}$: 1.17 d (SFO)<br>(Combined label)<br><br>**IV-01** ($DT_{50}$: 2.6-3.2 d; $DT_{90}$: 8.7-10.7 d (SFO))<br>**IV-02** ($DT_{50}$: 21.4 d; $DT_{90}$: 71.2 d (SFO))<br>**IV-28** ($DT_{50}$: 16.5-20.1 d; $DT_{90}$: 79.8-90.7 d (SFO))<br>**IV-15** ($DT_{50}$: 108 d; $DT_{90}$: 361 d (SFO))<br>**IV-27** ($DT_{50}$: 8 d; $DT_{90}$: 30 d (SFO))<br>**IV-203** ($DT_{50}$: 119 d; $DT_{90}$: 5802 d (SFO)) | <u>Major</u>:<br>*Qn label*: IV-01, IV-02, IV-15, IV-28, IV-203 and UR.<br>*Py label*: IV-01, IV-02, IV-27, IV-28, DP-1, $CO_2$ and UR.<br><u>Minor:</u><br>*Qn label*: IV-27, IV-303, DQ-1, DQ-2, DQ-3 and $CO_2$.<br>*Py label*: IV-15, DP-2, DP-3 and DP-4. | Pyrifluquinazon is non persistent<br><br>Major transformation products are non-persistent to moderately persistent | 3042133<br><br>3042022 |

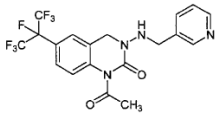
| Property | Test substance | Value | Transformation products | Comments | PMRA# |
|---|---|---|---|---|---|
| | Pyrifluquinazon (unlabeled) | California SL sandy loam (CA) soil (pH 7.6, OC 0.23%, 25ºC): $DT_{50}$: 0.62 d; $DT_{90}$: 2.1 d (SFO)<br><br>Mutchler sandy loam (MSL) soil (pH 6.7, OC 2%, 25ºC): $DT_{50}$: 1.9 d; $DT_{90}$: 6.2 d (SFO)<br><br>Ostlie East clay loam (OE) soil (pH 7.8, OC 3.2%, 25ºC): $DT_{50}$: 0.79 d; $DT_{90}$: 24 d (IORE) Slow $t_{1/2}$ = 7.3 d<br><br>**IV-01** ($DT_{50}$: 2.2-43.3 d; $DT_{90}$: 7.2-144 d (SFO))<br>**IV-02** ($DT_{50}$: 27.7 - 77 d; $DT_{90}$: 92-256 d (SFO))<br>**IV-27** ($DT_{50}$: 16.9 d; $DT_{90}$: 56.1 d (SFO))<br>**IV-28** ($DT_{50}$: 25.7 d; $DT_{90}$: 85 d (SFO)) | Major:<br>*CA soil*: IV-01, IV-02, IV-27, IV-28<br>*MSL soil*: IV-01, IV-02, IV-27, IV-28<br>OE soil: IV-01, IV-02, IV-27, IV-28<br>Minor:<br>IV-15 and IV-203 | Pyrifluquinazon is non persistent<br><br>Major transformation products are non-persistent to moderately persistent | 3042134<br><br>3042022 |
| | [$^{14}$C]Pyrifluquinazon (Qn label)<br><br>[$^{14}$C]Pyrifluquinazon (Py label) | Sandy loam soil (using non-polar and less polar solvents for extraction).<br>No radioactivity was detected in the *n*-hexane extracts, and only a slight amount of radioactivity (≤1.9%) of the total applied radioactivity (TAR) was detected in the ethyl acetate extracts. | Not determined | Confirms the level of radioactivity in the bound residue. | 3042135 |
| Biotransformation in aerobic water:sediment systems | [$^{14}$C]Pyrifluquinazon (Qn label)<br><br>[$^{14}$C]Pyrifluquinazon (Py label) | Georgia Pond Water:sand sediment<br>(water pH 6.4, 7.2 °C)<br>$DT_{50}$: 2.38 d; $DT_{90}$: 7.9 d (SFO)<br>(Combined label)<br><br>California Pond Water:loamy sand | Major:<br>IV-01, IV-27, $CO_2$, UR<br>Minor:<br>IV-02, IV-15, IV-28, IV-203, DQ-1, DP-1, DP-2, Other unidentified compounds<br><br>Major: | Pyrifluquinazon is non persistent | 3089078 |

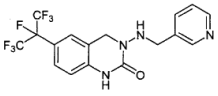
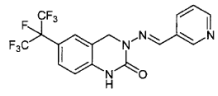
| Property | Test substance | Value | Transformation products | Comments | PMRA# |
|---|---|---|---|---|---|
| | | sediment (water pH 7.8, 7.2 °C)<br>$DT_{50}$: 1.72 d; $DT_{90}$: 5.72 d (SFO)<br><br>(Combined label) | IV-01, IV-02, $CO_2$, UR<br>Minor:<br>IV-15, IV-27, IV-28, IV-203, DQ-1, DP-1, DP-2, Other unidentified compounds | | |
| Biotransformation in anaerobic water:sediment systems | [$^{14}$C]Pyrifluquinazon (Qn label)<br><br>[$^{14}$C]Pyrifluquinazon (Py label) | Georgia Pond Water:sand sediment (pH 6.4, 7.2 °C)<br>$DT_{50}$ < 3 d; $DT_{90}$ < 7d (qualitative)<br>(Combined label)<br><br>**IV-01** ($DT_{50}$: 305 d; $DT_{90}$: 1014 d (SFO))<br><br>California Pond Water:loamy sand sediment (pH 7.8, 7.2 °C)<br>$DT_{50}$ < 3 d; $DT_{90}$ < 7d (qualitative)<br>(Combined label)<br><br>**IV-01** ($DT_{50}$: 233 d; $DT_{90}$: 773 d (SFO)) | Major:<br>IV-01<br>Minor:<br>IV-02, IV-203, $CO_2$, UR, Other unidentified compounds<br><br>Major:<br>IV-01, UR<br>Minor:<br>IV-02, IV-203, $CO_2$, Other unidentified compounds | Pyrifluquinazon is non persistent<br><br>IV-1 is persistent | 3089079 |
| **Mobility** | | | | | |
| Adsorption / desorption in soil (5 soils) | [$^{14}$C]Pyrifluquinazon (Qn label) | $K_d$ = 34.54 mL/g (average)<br>$K_{OC}$ = 1320 mL/g (average) | | Low mobility* | 3042136 |
| Adsorption / desorption in soil (5 soils) | Pyrifluquinazon transformation products:<br>**IV-01** | $K_d$ = 213.7 mL/g (average)<br>$K_{OC}$ = 8126.8 mL/g (average) | | Immobile | 3042137 |
| | **IV-15** | $K_d$ = 109.6 mL/g (average)<br>$K_{OC}$ = 4020 mL/g (average) | | Immobile | |
| | **IV-27** | $K_d$ = 35.6 mL/g (average)<br>$K_{OC}$ = 1500.4 mL/g (average) | | Low mobility | |
| | **IV-28** | $K_d$ = 2318.9 mL/g (average)<br>$K_{OC}$ = 68445 mL/g (average) | | Immobile<br>(Not reliable) | |

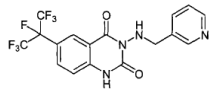
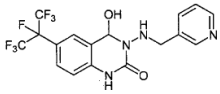
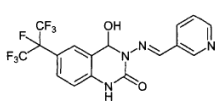
| Property | Test substance | Value | Transformation products | Comments | PMRA# |
|---|---|---|---|---|---|
| | **IV-203** | $K_d$ = 7.14 mL/g (average)<br>$K_{OC}$ = 491.6 mL/g (average) | | Moderate mobility (Not reliable) | |
| Adsorption / desorption in soil (4 soils + 1 sediment) | **IV-02** (Py label) | $K_d$ = 230.5 mL/g (average)<br>$K_{OC}$ = 8232 mL/g (average) | | Immobile | 3042138 |
| Volatilization | Not required. Pyrifluquinazon is not expected to be volatile under field conditions based on its low vapour pressure. | | | | |

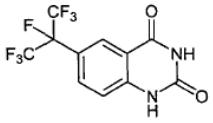
*Based on adsorption $K_{oc}$ and according to the classification scheme of McCall *et al.* (1981); UR: unextracted residues

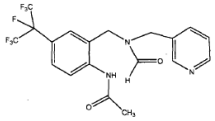
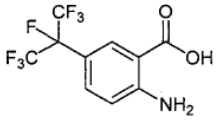
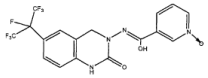
## Table 15 Transformation products formed in the environment

| Code Name/ Synonym | Chemical name | Chemical structure | Study | max %AR (day) | Final %AR (study length, day) | References (PMRA#) |
|---|---|---|---|---|---|---|
| **PARENT** | | | | | | |
| **Pyrifluquinazon** | IUPAC Name: 1-acetyl-1,2,3,4-tetrahydro-3-[(3-pyridylmethyl)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]quinazolin-2-one<br>CAS Name: 1-acetyl-3,4-dihydro-3-[(3-pyridinylmethyl)-amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-2-(1H)-quinazolinone<br>CAS Number: 337458-27-2<br>Formula: $C_{19}H_{15}F_7N_4O_2$<br>MW: 464.3 g/mol<br>SMILES: c1ccncc1CNN1Cc2cc(ccc2N(C1=O)C(=O)C)C(C(F)(F)F)(F)C(F)(F)F |  | Hydrolysis pH 5 | 103 (3) | 84.3 (31) | 3042131 |
| | | | Hydrolysis pH 7 | 103.8 (0) | 41.6 (31) | 3042131 |
| | | | Hydrolysis pH 9 | 91.4 (0)<br>98.4 (0) | 40.6 (1.04)<br>6.2 (2.6) | 3042131<br>3042132 |
| | | | Aerobic aquatic | 92.2 (0)<br>92.3 (0) | 3.9 (106)<br>0.7 (106) | 3089078 |
| | | | Anaerobic aquatic | 87.11 (0)<br>91.24 (0) | 0 (112)<br>0 (112) | 3089079 |
| | | | Aerobic soil | 95.0 (0) | 0 (84) | 3042133 |
| | | | Aerobic soil | 89 (0)<br>104.1 (0)<br>112.8 (0) | 0 (56)<br>1.66 (83)<br>0 (83) | 3042134 |

| Code Name/ Synonym | Chemical name | Chemical structure | Study | max %AR (day) | Final %AR (study length, day) | References (PMRA#) |
|---|---|---|---|---|---|---|
| **MAJOR (>10%) TRANSFORMATION PRODUCTS** | | | | | | |
| NNI-0101-IH (IV-01) | IUPAC Name: 1,2,3,4-tetrahydro-3-[(3-pyridylmethyl)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]quinazolin-2-one<br>Formula: $C_{17}H_{13}F_7N_4O$<br>MW: 422.3 g/mol<br>SMILES: C1=CC(=CN=C1)CNN3CC2=CC(=CC=C2NC3=O)C(C(F)(F)F)(C(F)(F)F)F |  | Hydrolysis pH 5 | 18.7(31) | 18.71 (31) | 3042131 |
| | | | Hydrolysis pH 7 | 57.5 (31) | 57.5(31) | 3042131 |
| | | | Hydrolysis pH 9 | 48.4 (1.04)<br>88.3 (2.6) | 48.4 (1.04)<br>88.3 (2.6) | 3042131<br>3042132 |
| | | | Aerobic aquatic | 65.2 (7)<br>83.5 (7) | 8.8 (106)<br>22.4 (106) | 3089078 |
| | | | Anaerobic aquatic | 83.23 (3)<br>86.28 (14) | 74.81 (101)<br>71.33 (101) | 3089079 |
| | | | Aerobic soil | 72.2 (1) | 0.7(84) | 3042133 |
| | | | Aerobic soil | 56.7 (3)<br>24.2 (3)<br>55.3 (1) | 0 (56)<br>0 (83)<br>10.0 (83) | 3042134 |
| NNI-0101-1H-imino (IV-02) | IUPAC Name: 1,2,3,4-tetrahydro-3-[(3-pyridylmethylene)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]quinazolin-2-one<br>Formula: $C_{17}H_{11}F_7N_4O$<br>MW: 420.3 g/mol<br>SMILES: C(F)(F)(F)C(F)(c1cc2c(cc1)NC(=O)N(N=Cc1cccnc1)C2)C(F)(F)F |  | Aerobic aquatic | 8.8 (14)<br>11.6 (30) | 5.0 (106)<br>11.1 (106) | 3089078 |
| | | | Anaerobic aquatic | 4.28 (112)<br>4.11 (60) | 4.281 (112)<br>3.35 (101) | 3089079 |
| | | | Aerobic soil | 18.7 (7) | 2.1 (84) | 3042133 |
| | | | Aerobic soil | 14.7 (7)<br>14.9 (27)<br>13.0 (55) | 3.2 (56)<br>1 (83)<br>9.9 (83) | 3042134 |

| Code Name/ Synonym | Chemical name | Chemical structure | Study | max %AR (day) | Final %AR (study length, day) | References (PMRA#) |
|---|---|---|---|---|---|---|
| NNI-0101-1H-4-oxo (IV-15) | IUPAC Name: 1,2,3,4-tetrahydro-3-[(3-pyridylmethyl)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]quinazolin-2,4-dione<br>Formula: $C_{17}H_{11}F_7N_4O_2$<br>MW: 436.3 g/mol<br>SMILES: C(F)(F)(F)C(F)(c1cc2C(=O)N(NCc3cccnc3)C(=O)Nc2cc1)C(F)(F)F |  | Aerobic aquatic | 6.8 (106)<br>2.8 (106) | 6.8 (106)<br>2.8 (106) | 3089078 |
| | | | Aerobic soil | 13.4 (3) | 7.6 (84) | 3042133 |
| | | | Aerobic soil | 2.4 (14)<br>1.9 (7)<br>1.4 (83) | 0 (56)<br>1.0 (83)<br>1.4 (83) | 3042134 |
| NNI-0101-1H-4-OH (IV-27) | IUPAC Name: 1,2,3,4-tetrahydro-4-hydroxy-3-[(3-pyridylmethyl)amino]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]quinazolin-2-one<br>Formula: $C_{17}H_{13}F_7N_4O_2$<br>MW: 438.3 g/mol<br>SMILES: C(F)(F)(F)C(F)(c1cc2c(cc1)NC(=O)N(NCc1cccnc1)C2O)C(F)(F)F |  | Aerobic aquatic | 13.7 (14)<br>7.6 (14) | 1 (106)<br>2.3 (106) | 3089078 |
| | | | Aerobic soil | 13.3 (7) | 0.4 (84) | 3042133 |
| | | | Aerobic soil | 16.8 (3)<br>20.6 (3)<br>8.3 (55) | 0 (56)<br>0 (83)<br>6.0 (83) | 3042134 |
| NNI-0101-1H-imino- | IUPAC Name: 4-hydroxy-3-[(pyridine-3-ylmethylene)amin |  | Aerobic aquatic | 6.1 (30)<br>2.6 (14) | 5.3 (106)<br>0.7 (106) | 3089078 |
| | | | Aerobic soil | 19.8 (14) | 4.8 (84) | 3042133 |

| Code Name/ Synonym | Chemical name | Chemical structure | Study | max %AR (day) | Final %AR (study length, day) | References (PMRA#) |
|---|---|---|---|---|---|---|
| 4-OH (IV-28) | o]-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-3,4-dihydro-1H-quinazolin-2-one<br>Formula: $C_{17}H_{11}F_7N_4O_2$<br>MW: 436.3 g/mol<br>SMILES: C(F)(F)(F)C(F)(c1cc2c(cc1)NC(=O)N(N=Cc1cccnc1)C2O)C(F)(F)F | | Aerobic soil | 16.0 (14)<br>16.8 (14)<br>14.2 (83) | 0 (56)<br>1.5 (83)<br>14.2 (83) | 3042134 |
| NNI-0101-quinazolindione (IV-203) | IUPAC Name: 1,2,3,4-tetrahydro-6-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]qunazolin-2,4-dione<br>Formula: $C_{11}H_5F_7N_2O_2$<br>MW: 330.2 g/mol<br>SMILES: C(F)(F)(F)C(F)(c1cc2C(=O)NC(=O)Nc2cc1)C(F)(F)F |  | Aerobic aquatic | 5.0 (106)<br>2.4 (106) | 5.0 (106)<br>2.4 (106) | 3089078 |
| | | | Anaerobic aquatic | 2.11 (28)<br>0.52 (101) | 0 (101)<br>0.52 (101) | 3089079 |
| | | | Aerobic soil | 10.3 (28) | 7.9 (84) | 3042133 |
| | | | Aerobic soil | 4.9 (28)<br>1.1 (55)<br>4.4 (7) | 3.5 (56)<br>0 (83)<br>1.7 (83) | 3042134 |
| Unidentified degradate DP-1 | NA | NA | Aerobic aquatic | 5.6 (106)<br>3.5 (106) | 5.6 (106)<br>3.5 (106) | 3089078 |
| | | | Aerobic soil | 36.1 (42) | 5.2 (84) | 3042133 |
| Unextracted residues | NA | NA | Aerobic aquatic | 38.2 (106)<br>51.8 (106) | 38.2 (106)<br>51.8 (106) | 3089078 |
| | | | Aerobic soil | 40.8 (84) | 40.8 (84) | 3042133 |

| Code Name/ Synonym | Chemical name | Chemical structure | Study | max %AR (day) | Final %AR (study length, day) | References (PMRA#) |
|---|---|---|---|---|---|---|
| **MINOR (<10%) TRANSFORMATION PRODUCTS** | | | | | | |
| Unidentified degradate D-1 | MW: 451 g/mol | Proposed structure  | Hydrolysis pH 9 | 7.7 (0.63) | 7.7 (1.04) | 3042131 |
| NNI-0101-anthranilic acid (IV-303) | Formula: $C_{10}H_6F_7NO_2$<br>MW: 305.15 g/mol |  | Aerobic soil | 1.8 (28) | 0 (84) | 3042133 |
| Unidentified degradate DQ-1 | NA | NA | Aerobic aquatic | 1.5 (14)<br>1.6 (30) | 0.4 (106)<br>0.9 (106) | 3089078 |
| | | | Aerobic soil | 8.6 (3) | 0 (84) | 3042133 |
| Unidentified degradate DQ-2 / DP-3 | MW: 452 g/mol | Proposed structure  | Aerobic soil | 7.9 (14) | 1.2 (84) | 3042133 |
| Unidentified degradate DQ-3 | NA | NA | Aerobic soil | 5.9 (84) | 5.9 (84) | 3042133 |
| Unidentified degradate DP-2 | NA | NA | Aerobic soil | 6.5 (3) | 0 (84) | 3042133 |

NA, not available

## Table 16 Effects of Pyrifluquinazon on non-target species

| Organism | Exposure | | Endpoint value | Degree of toxicity[a] | PMRA# |
|---|---|---|---|---|---|
| **Invertebrates** | | | | | |
| Bee<br>Honeybee, *Apis mellifera* | 96-h Acute Oral | | 48-h $LD_{50}$: 34.2 µg a.i./bee<br>48-h NOED = 0.01 µg a.i./bee (sublethal effects) | Practically non-toxic | 3089080 |
| | 96-h Acute Contact | | 48-h $LD_{50}$: >100 µg a.i./bee<br>48-h NOEC = 0.01 µg a.i./bee (sublethal effects) | Practically non-toxic | |
| | 48-h Acute Oral | | 48-h $LD_{50}$: >100 µg a.i./bee<br>48-h NOED = 0.01 µg a.i./bee (sublethal effects) | Practically non-toxic | 3089081 |
| | 48-h Acute Contact | | 48-h $LD_{50}$: >100 µg a.i./bee<br>48-h NOED = 0.01 µg a.i./bee (sublethal effects) | Practically non-toxic | |
| | 72-h Acute larva | | 72-h $LD_{50}$: 21 µg a.i./larva<br>72-h NOED: 14 µg a.i./larva (sublethal effects) | Practically non-toxic | 3089082 |
| | Chronic larva | 3-8 day larval survival | NOED / L(E)$D_{50}$ : 13 / 23 µg a.i./larva | NA | 3089083 |
| | | 8-22 day pupal survival | NOED / L(E)$D_{50}$ : 13 / 16 µg a.i./larva | | |
| | | 3-22 day adult emergence | NOED / L(E)$D_{50}$ : 6.7 / 14 µg a.i./larva | | |
| | | Adult weight at emergence | NOED / L(E)$D_{50}$ : 6.7 / >25 µg a.i./larva | | |
| | 10-d Chronic oral | Percent Survival | NOEDD / LOEDD / $LDD_{50}$: 1.2 / 3.1/ 3.6 µg a.i./bee/day | NA | 3089084 |
| | 10-d Chronic oral | Sublethal effects | NOEDD / $EDD_{50}$: <0.0039/ 0.0033µg a.i./bee/day | | |
| Honeybee, *Apis mellifera* | 96-h Contact | | 96-h $LD_{50}$>100 µg a.i./bee<br>NOED: 0.001 µg a.i./bee (sublethal effects) | Practically non-toxic | 3042140 |
| Silkworm, *Bombyx mori* | 8-d Contact | | $LR_{50}$>1000 g a.i./ha | NA | |
| Predatory mite, *Amblyseius californicus* | 3-d Contact | | $LR_{50}$>1000 g a.i./ha | NA | |
| Seven spotted lady beetle, *Coccinella septempunctata bruckii* | 3-d Contact | | $LR_{50}$>1000 g a.i./ha | NA | |
| Predatory mite *Phytoseiulus persimilis* | 3-d Contact | | $LR_{50}$>1000 g a.i./ha | NA | |

[a]Atkins et al.(1981) for bees and USEPA classification for others, where applicable; NA, not applicable.

**Table 17 Endpoints and uncertainty factors used to establish effects metrics for the risk assessment**

| Organism | Exposure | Test substance | Endpoint Value | UF applied[1] | Effect metric | LOC[2] |
|---|---|---|---|---|---|---|
| **Terrestrial Invertebrates** | | | | | | |
| Silkworm, *Bombyx mori* | 8-d Contact | Pyrifluquinazon technical | $LR_{50}$>1000 g a.i./ha | 1 | >1000 g a.i./ha | 1.0 |
| Predatory mite, *Amblyseius californicus* | 3-d Contact | Pyrifluquinazon technical | $LR_{50}$>1000 g a.i./ha | 1 | >1000 g a.i./ha | 1.0 |
| Seven spotted lady beetle, *Coccinella septempunctata bruckii* | 3-d Contact | Pyrifluquinazon technical | $LR_{50}$>1000 g a.i./ha | 1 | >1000 g a.i./ha | 1.0 |
| Bee adult *Apis mellifera* | 48-h contact | Pyrifluquinazon (TGAI; purity: 99.24% w/w) | $LD_{50}$ >100 µg a.i./bee | 1 | >100 µg a.i./bee | 0.4 |
| | 96-h oral | NNI-0101 SC (purity: 20% w/w) | 48-h $LD_{50}$: 34.2 µg a.i./bee | 1 | 34.2 µg a.i./bee | 0.4 |
| | | | 48-h NOED = 0.01 µg a.i./bee (sublethal effects) | 1 | 0.01 µg a.i./bee | 1.0 |
| | 96-h contact | Pyrifluquinazon technical | NOED: 0.001 µg a.i./bee (sublethal effect) | 1 | 0.001 µg a.i./bee | 1.0 |
| | 10-d chronic oral | Pyrifluquinazon (TGAI; purity: 97.45% w/w) | NOEDD = 1.2 µg a.i./bee/day (survival) | 1 | 1.2 µg a.i./bee/day | 1.0 |
| | | | NOEDD <0.0039 µg a.i./bee/day (sublethal effects) | 1 | <0.0039 µg a.i./bee/day | 1.0 |
| Bee larva *Apis mellifera* | 72-h acute larva | Pyrifluquinazon (TGAI; purity: 97.45% w/w) | $LD_{50}$ = 21 µg a.i./larva | 1 | 21 µg a.i./larva | 0.4 |
| | | | NOED: 14 µg a.i./larva (sublethal effects) | 1 | 14 µg a.i./larva | 1.0 |

| Organism | Exposure | Test substance | Endpoint Value | UF applied[1] | Effect metric | LOC[2] |
|---|---|---|---|---|---|---|
| | 8-d chronic (survival) | | NOED = 13 µg a.i./bee/day | 1 | 13 µg a.i./bee/day | 1.0 |
| | 22-d chronic (pupal survival) | | NOED = 13 µg a.i./bee/day | 1 | 13 µg a.i./bee/day | 1.0 |
| | 22-d chronic (adult emergence) | | NOED = 6.7 µg a.i./bee/day | 1 | 6.7 µg a.i./bee/day | 1.0 |

[1] UF = uncertainty factor; as per the Guidance Manual; [2]LOC = Level of Concern

**Table 18 Screening level risk to bees and other beneficial arthropods**

| Organism | Exposure | Endpoint Value | Effect metric | EEC[a] | RQ | LOC exceeded? |
|---|---|---|---|---|---|---|
| | **Invertebrates** | | | | | |
| Bee adult *Apis mellifera* | 48-h contact | $LD_{50}$ >100 µg a.i./bee | >100 µg a.i./bee | 0.1344 µg a.i./bee | □0.001 | No |
| | 96-h oral | 48-h $LD_{50}$: 34.2 µg a.i./bee<br>48-h NOED: 0.01 µg a.i./bee (sublethal effect) | 34.2 µg a.i./bee<br>0.01 µg a.i./bee | 1.624 µg a.i./bee | 0.04<br>162.4 | No<br>Yes |
| | 96-h contact | NOED: 0.001 µg a.i./bee (sublethal effects) | 0.001 µg a.i./bee | 0.1344 µg a.i./bee | 134.4 | Yes |
| | 10-d chronic oral | NOEDD = 1.2 µg a.i./bee/day (survival) | 1.2 µg a.i./bee/day | 1.624 µg a.i./bee | 1.35 | Yes |
| | | NOEDD □0.0039 µg a.i./bee/day (sublethal effects) | □0.0039 µg a.i./bee/day | 1.624 µg a.i./bee | >416.4 | Yes |
| Bee larva *Apis mellifera* | 72-h acute larva | $LD_{50}$ = 21 µg a.i./larva<br>NOED: 14 µg a.i./larva (sublethal effects) | 21 µg a.i./larva<br>14 µg a.i./larva | 0.672 µg a.i./bee | 0.03<br>0.048 | No |
| | 8-d chronic (survival) | NOED = 13 µg a.i./bee/day | 13 µg a.i./bee/day | 0.672 µg a.i./bee | 0.05 | No |
| | 22-d chronic (pupal survival) | NOED = 13 µg a.i./bee/day | 13 µg a.i./bee/day | 0.672 µg a.i./bee | 0.05 | No |
| | 22-d chronic (adult emergence) | NOED = 6.7 µg a.i./bee/day | 6.7 µg a.i./bee/day | 0.672 µg a.i./bee | 0.10 | No |

| Organism | Exposure | Endpoint Value | Effect metric | EEC[a] | RQ | LOC exceeded? |
|---|---|---|---|---|---|---|

[a]The pollinator EECs were calculated using the single maximum application rate of 56 g a.i./ha as follows:
Estimated contact exposure = 2.4 µg a.i./bee x 0.056 kg a.i./ha;
Estimated dietary exposure = 29 $\mu$g a.i./bee x 0.056 kg a.i./ha; and
Estimated brood exposure = 12 $\mu$g a.i./bee x 0.056 kg a.i./ha.

**Table 19 *Toxic substances management policy* considerations-comparison to TSMP track 1 criteria**

| TSMP Track 1 Criteria | TSMP Track 1 Criterion Value | | Active Ingredient Endpoints | Transformation Products Endpoints |
|---|---|---|---|---|
| CEPA toxic or CEPA toxic equivalent[1] | Yes | | Yes | Yes |
| Predominantly anthropogenic[2] | Yes | | Yes | Yes |
| Persistence[3]: | Soil | Half-life ≥ 182 days | Laboratory studies: $DT_{50}$ of 0.35 to 1.9 days in aerobic soil | IV-01, IV-02, IV-15, IV-27, IV-28 and IV-203: 0.1 – 119 days |
| | Water | Half-life ≥ 182 days | The $DT_{50}$ values range from 1.9 to 2.6 days in aerobic water layers. | Not available |
| | Whole system (water + sediment) | Half-life ≥ 365 days | Total system $DT_{50}$ values range from 1.72 to 2.38 days in aerobic and less than 3 days in anaerobic water-sediment systems. | Total system $DT_{50}$ values range from 233 to 305 days for IV-01 in anaerobic water-sediment systems. |
| | Air | Half-life ≥ 2 days or evidence of long range transport | Volatilization is not an important route of dissipation and thus long-range atmospheric transport is unlikely to occur based on the vapour pressure and Henry's Law Constant ($5 \times 10^{-8}$ Pa and $1.894 \times 10^{-11}$ atm $m^3$/mol at 20°C, respectively). | Not available |
| Bioaccumulation[4] | Log $K_{OW} \geq 5$ | | No: 3.12 | IV-01, IV-02, IV-15, IV-27, IV-28 and IV-203: 3.3 – 4.17 |
| | BCF ≥ 5000 | | No: 195- 198 | Not available |
| | BAF ≥ 5000 | | Not available | 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 (i.e., all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (e.g., BAFs) are preferred over laboratory data (e.g., BCFs) which, in turn, are preferred over chemical properties (e.g., log $K_{OW}$).

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

The MRLs proposed for pyrifluquinazon in Canada are the same as the corresponding American tolerances.

The established American tolerances for pyrifluquinazon are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[10] listed for pyrifluquinazon 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 |
|---|---|
| 3042023 | 2019, Product Chemistry for Pyrifluquinazon Technical, DACO: 2.1, 2.2, 2.3, 2.3.1 |
| 3042024 | 2019, Product Chemistry for Pyrifluquinazon Technical, DACO: 2.1, 2.2, 2.3, 2.3.1 CBI |
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## 4.0 Value

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## B. Additional information considered

### i) Published information

#### 1.0 Human and animal health

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