Proposed Registration Decision PRD2022-18

Ipflufenoquin and Kinoprol 20 SC

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Table of Contents

Overview 1
Proposed registration decision for Ipflufenoquin 1
What does Health Canada consider when making a registration decision? 1
What is Ipflufenoquin? 2
Health considerations 2
Environmental considerations 5
Value considerations 5
Measures to minimize risk 5
Next steps 6
Other information 6
Science evaluation 7
1.0 The active ingredient, its properties and uses 7
1.1 Identity of the active ingredient 7
1.2 Physical and chemical properties of the active ingredients and end-use product 7
1.3 Directions for use 9
1.4 Mode of action 9
2.0 Methods of analysis 9
2.1 Methods for analysis of the active ingredient 9
2.2 Method for formulation analysis 9
2.3 Methods for residue analysis 9
3.0 Impact on human and animal health 10
3.1 Hazard assessment 10
3.1.1 Toxicology summary 10
3.1.2 *Pest Control Products Act* hazard characterization 13
3.2 Toxicology reference values 14
3.2.1 Route and duration of exposure 14
3.2.2 Occupational and residential toxicology reference values 14
3.2.3 Acute reference dose (ARfD) 15
3.2.4 Acceptable daily intake (ADI) 15
3.2.5 Cancer assessment 15
3.2.6 Aggregate toxicology reference values 15
3.3 Dermal absorption 16
3.4 Occupational and residential exposure assessment 16
3.4.1 Acute hazards of the end-use product and mitigation measures 16
3.4.2 Occupational exposure and risk assessment 16
3.4.3 Residential exposure and risk assessment 17
3.4.4 Bystander exposure and risk assessment 18
3.5 Dietary exposure and risk assessment 19
3.5.1 Exposure from residues in food of plant origin 19
3.5.2 Residues in drinking water sources 19
3.5.3 Dietary risk assessment 20
3.6 Aggregate exposure and risk assessment 21

3.7 Cumulative assessment ... 21
3.8 Maximum residue limits ... 21
3.9 Health incident reports ... 22
3.10 Antimicrobial resistance assessment ... 22
4.0 Impact on the environment ... 23
4.1 Fate and behaviour in the environment ... 23
4.2 Environmental risk characterization ... 24
4.3 Environmental incident reports ... 26
5.0 Value ... 26
6.0 Pest control product policy considerations ... 27
6.1 Assessment of the active ingredient under the toxic substances management policy 27
6.2 Formulants and contaminants of health or environmental concern ... 27
7.0 Proposed regulatory decision ... 28
List of abbreviations ... 29
Appendix I Tables and figures ... 34
Table 1A Residue analysis in plants ... 34
Table 1B Residue Analysis in Environmental Media ... 35
Table 2 Identification of Select Mammalian Metabolites and Environmental Transformation Products of Ipflufenoquin ... 35
Table 3 Toxicity profile of technical Ipflufenoquin ... 35
Table 4 Toxicity profile of Kinoprol 20 SC ... 45
Table 5 Toxicology reference values for use in health risk assessment for Ipflufenoquin ... 46
Table 6 AHETF/PHED unit exposure estimates for mixer/loaders and applicators handling Kinoprol 20 SC (µg/kg a.i. handled) ... 47
Table 7 Mixer/Loader/Applicator risk assessment for workers handing Kinoprol 20 SC 47
Table 8 Postapplication worker exposure and risk estimate for Ipflufenoquin on day 0 after the last application to apples and pears ... 49
Table 9 Postapplication dermal exposure and risk estimates to residents on Day 0 from orchard trees treated commercially with Ipflufenoquin ... 49
Table 10 Integrated food residue chemistry summary ... 50
Table 11 Food residue chemistry overview of metabolism studies and risk assessment ... 58
Table 12 Ipflufenoquin and its environmental transformation products identified in laboratory and field dissipation studies ... 59
Table 13 Summary of fate and behaviour of ipflufenoquin in the environment ... 63
Table 14 Summary of toxicity effects of Ipflufenoquin and Ipflufenoquin SC 200 g/L formulation on terrestrial organisms ... 67
Table 15 Summary of toxicity effects of Ipflufenoquin technical on aquatic organisms ... 70
Table 16 Study endpoints, uncertainty factors and levels of concern relevant for risk assessment ... 74
Table 17 Estimated environmental exposures ... 76
Table 18 Screening level risk ipflufenoquin and its end-use product to terrestrial organisms: Earthworms, Honey bees, Non-target arthropods and Vascular plants ... 78

Table 19 Screening level risk assessment for birds and mammals from consumption of contaminated food sources based on maximum nomogram residues 79
Table 20 Screening level risk of ipflufenoquin to aquatic organisms 80
Table 21 List of supported uses 81
Table 22 Toxic substances management policy considerations - comparison to TSMP track 1 criteria for ipflufenoquin 82
Appendix II Supplemental maximum residue limit information—International situation and trade implications 84
References 85

Overview

Proposed registration decision for Ipflufenoquin

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 Kinoprol Technical and Kinoprol 20 SC, containing the technical grade active ingredient ipflufenoquin, for control or suppression of pome fruit diseases.

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

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of ipflufenoquin and Kinoprol 20 SC.

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 portion of the Canada.ca website.

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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 ipflufenoquin and Kinoprol 20 SC, 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 ipflufenoquin and Kinoprol 20 SC, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

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

What is Ipflufenoquin?

Ipflufenoquin is new fungicide with a unique mode of action for control or suppression of pome fruit diseases. Ipflufenoquin is quickly absorbed into plant tissue and has the ability to move within the plant between the upper and lower leaf surfaces.

Health considerations

Can approved uses of Ipflufenoquin affect human health?

Kinoprol 20 SC, containing ipflufenoquin, is unlikely to affect your health when used according to proposed label directions.

Potential exposure to ipflufenoquin may occur through the diet (food and drinking water), when handling and applying the end-use products, or when entering an area that has been treated with the product. 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 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 ipflufenoquin was of low acute toxicity by the oral, dermal, and inhalation routes. It was non-irritating to the eyes and skin. It did not cause an allergic skin reaction.

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

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

The acute toxicity of the end-use product Kinoprol 20 SC, containing ipflufenoquin, was low via the oral and dermal routes of exposure. Kinoprol 20 SC was of slight toxicity via the inhalation route of exposure; consequently, the signal word and hazard statement "CAUTION – POISON" are required on the label. It was non-irritating to the eyes and skin and did not cause an allergic skin reaction.

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

Residues in water and food

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

Aggregate acute dietary (food plus drinking water) intake estimates indicated that the general population and all population subgroups are exposed to less than 1% of the acute reference dose, and therefore are not of health concern.

Aggregate chronic dietary (food plus drinking water) intake estimates indicated that the general population and all population subgroups are exposed to less than 1% of the acceptable daily intake, and therefore are not of health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Given that dietary risks from the consumption of foods are shown to be acceptable when ipflufenoquin is used according to the supported label directions, MRLs are being proposed as a result of this assessment (refer to PMRL2022-24, *Ipflufenoquin*).

MRLs for ipflufenoquin determined from the acceptable residue trials conducted throughout Canada and the United States on various crops can be found in the Science Evaluation of this consultation document.

Occupational risks from handling Kinoprol 20 SC herbicide

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

Workers mixing, loading or applying Kinoprol 20 SC, and workers entering recently treated pome fruit orchards can be exposed to ipflufenoquin residues through direct skin contact or through inhalation. Therefore, the label specifies that anyone mixing, loading and applying Kinoprol 20 SC must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and

shoes. Chemical-resistant gloves are not required during application within a closed cab. The label also requires that workers do not enter or allowed into treated areas during the restricted-entry interval (REI) of 12 hours. Taking into consideration the label statements, the application rate, the number of applications and the duration of exposure for handlers and postapplication workers, the risks to these individuals are not of health concern when the end-use product is used according to the proposed label directions.

Health risks in residential and other non-occupational environments

Risks in residential and other non-occupational environments are not of health concern when Kinoprol 20 SC is used according to the proposed label directions and restricted-entry intervals (REIs) are observed.

Adults, youth and children involved in postapplication activities, such as pruning and hand harvesting, may come in direct contact with ipflufenoquin residues on the skin when pome fruit trees in residential areas are treated with Kinoprol 20 SC by commercial applicators. Taking into consideration the label statements, the application rate, the number of applications and the duration of exposure, the risks to homeowners and their family are not of health concern once the sprays have dried when the end-use product is used according to the proposed label directions.

Non-occupational exposure during pick-your-own fruit activities in treated orchards and residential areas are also not of health concern when the end-use product is used according to the proposed label directions.

Aggregate health risks

When pome fruit trees in residential settings or pick-your-own facilities are treated with Kinoprol 20 SC, there is potential for individuals to be exposed to ipflufenoquin via the dermal and oral routes of exposure concurrently. Based on the toxicological assessment, aggregation of dermal and dietary exposure is not required. For ipflufenoquin, the aggregate assessment consisted of combining food and drinking water exposure only.

Health risks to bystanders

Bystander risks are not of health concern when Kinoprol 20 SC is used according to the proposed label directions and spray drift restrictions are observed.

A standard label statement to protect against drift during application is on the label. Therefore, health risks to bystanders are not of concern when the end-use product is used according to the proposed label directions.

Environmental considerations

What happens when Ipflufenoquin is introduced into the environment?

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

When ipflufenoquin is applied as a foliar spray to control powdery mildew and scab on pome fruit (for example, apples and pears), it will bind to the soil where up to half of the applied amount may remain for more than 2 years depending on soil type and environmental conditions.

Ipflufenoquin will not move from the treatment area into the air and therefore is not expected to move to non-treated sites via air. Ipflufenoquin may move downward in the soil, and, therefore, may reach groundwater. It has low potential to move from the treatment area to surface waters such as ponds, streams and rivers. If it does enter water, ipflufenoquin will move to the sediment where up to half of it may remain for more than a year and a half, depending on sediment type and conditions. Ipflufenoquin is not expected to accumulate in plant or animal tissues.

When ipflufenoquin is used in accordance with the label directions and the required precautions, the risk to terrestrial invertebrates, birds, wild mammals, bees, beneficial arthropods, terrestrial plants, aquatic invertebrates (including sediment-dwelling invertebrates), amphibians, fish, algae and vascular aquatic plants from the use of ipflufenoquin were determined to be acceptable without the requirement of additional risk mitigation measures.

Value considerations

What is the value of Kinoprol 20 SC fungicide?

Kinoprol 20 SC fungicide offers pome fruit growers a new mode of action fungicide to manage economically important diseases.

Kinoprol 20 SC Fungicide will contribute to disease management in pome fruit orchards with effective reduction of powdery mildew and scab. The new mode of action will help manage the development of resistance to fungicides currently registered for use against these diseases.

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

Key risk-reduction measures - Human health

To reduce the potential exposure of workers to ipflufenoquin through direct skin contact or inhalation of sprays, workers mixing, loading and applying Kinoprol 20 SC and performing cleaning and repair activities must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Additionally, a standard label statement to protect against drift during application is on the label. The label also requires that workers do not enter or be allowed entry into treated agricultural fields during the REI of 12 hours. Furthermore, standard label statements to restrict the use of handheld airblast, misters and foggers is present on the label.

Key risk-reduction measures - Environment

Precautionary statements are required to inform users of the potential of ipflufenoquin to reach groundwater.

Next steps

Before making a final registration decision on ipflufenoquin and Kinoprol 20 SC, 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

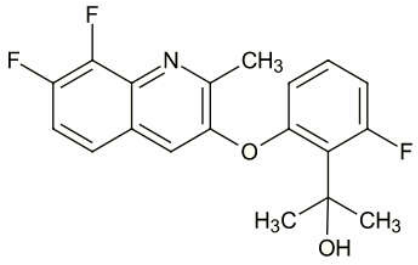
When the Health Canada makes its registration decision, it will publish a Registration Decision on ipflufenoquin and Kinoprol 20 SC (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection,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

Science evaluation

Ipflufenoquin and Kinoprol 20 SC

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active substance	Ipflufenoquin
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	2-{2-[(7,8-difluoro-2-methyl-3-quinolyl)oxy]-6-fluorophenyl}propan-2-ol
2. Chemical Abstracts Service (CAS)	2-[(7,8-difluoro-2-methyl-3-quinolinyl)oxy]-6-fluoro-α,α-dimethylbenzenemethanol
CAS number	1314008-27-9
Molecular formula	$C_{19}H_{16}F_3NO_2$
Molecular weight	347.3
Structural formula	
Purity of the active ingredient	99.2%

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

Technical product—Kinoprol technical

Property	Result
Colour and physical state	Pale yellow powder
Odour	Odourless
Melting range	114.4-115.5°C
Boiling point or range	450°C

Property	Result
Density	1.3904 g/cm^3
Vapour pressure at 20°C	7.26 × 10^{-3} mPa at 20°C
Ultraviolet (UV)-visible spectrum	No absorption above 400 nm
Solubility in water at 20°C	10.3 mg/L (pH 7.0)
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) Hexane — 2.83 Heptane — 2.76 Xylene — 118 Toluene — 182 Dichloromethane — > 250 Methanol — > 250 Ethanol — 187 Octanol — 65.5 Acetone — > 250 Ethyl Acetate — > 250
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 3.89
Dissociation constant (pK_a)	pK_a = 2.18
Stability (temperature, metal)	Stable at 54°C for at least 14 days, 40°C for at least 6 months. Stable in the presence of zinc. Unstable when exposed to potassium permanganate (the active is a reducing agent).

End-use product—Kinoprol 20 SC

Property	Result
Colour	Off-white
Odour	Paint-like
Physical state	Liquid
Formulation type	Suspension
Label concentration	200 g/L
Container material and description	0.25-1050 L plastic bottle, jug, or tote
Density	1.0845 g/cm^3
pH of 1% dispersion in water	6.75 (1% w/v)
Oxidizing or reducing action	No oxidizing or reducing action
Storage stability	Stable at 54°C for 14 days in polyethylene bottles
Corrosion characteristics	Corrosion of the PE bottle after storage for 2 weeks at 54°C was not observed
Explodability	Not explosive

1.3 Directions for use

For control or suppression of powdery mildew and control of scab on Crop Group 11-09 (Pome Fruit), Kinoprol 20 SC Fungicide is applied at 165–220 mL/ha (33–44 g a.i./ha). For powdery mildew, the 165 mL/ha rate provides suppression. If disease pressure is moderate to high, or if control is required, use the 220 mL/ha rate.

The first application should be made at the green tip stage (BBCH 9 to BBCH 76). Use the higher rate under heavier pest pressure. The retreatment interval is 7–10 days. Do not make more than three (3) applications per year. Do not exceed 660 mL product (120 g a.i.) per ha per year. The recommended spray volume for ground application is 187 L water/ha. A non-ionic surfactant may be added to the Kinoprol 20 SC spray solution at 0.125–0.5% v/v or the recommended rate under conditions conducive to high disease pressure (for example, Agral 90 at 0.125% v/v).

1.4 Mode of action

Ipflufenoquin belongs to Fungicide Resistance Action Committee (FRAC) mode of action Group 52, dihydroorotate dehydrogenase inhibitors (DHODHI fungicides). This fungicide moves locally within the plant between the upper and lower leaf surfaces. Research has shown that ipflufenoquin is not cross-resistant with other fungicides registered to control scab and powdery mildew on pome fruits.

2.0 Methods of analysis

2.1 Methods for analysis of the active ingredient

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

2.2 Method for formulation analysis

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

2.3 Methods for residue analysis

High-performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; Method P 3996 G, GPL-MTH-104, and GPL-MTH-095 in plant matrices) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant matrices. The proposed enforcement method was successfully validated in plant matrices by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled samples of apple and grape analyzed with the enforcement method.

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 plant matrices and environmental media are summarized in Appendix I, Tables 1A and 1B.

3.0 Impact on human and animal health

3.1 Hazard assessment

3.1.1 Toxicology summary

Ipflufenoquin is a broad-spectrum fungicide containing a quinoline group. Currently, there are no known quinoline fungicides with similar chemical structures to ipflufenoquin. The details of the pesticidal mode of action have not been fully elucidated.

A detailed review of the toxicology database for ipflufenoquin was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Several mechanistic studies were also submitted to support proposed modes of action. A limited number of studies on select transformation products as well as a manufacturing impurity were also available. The required studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to characterize the potential health hazards associated with ipflufenoquin.

Metabolism and toxicokinetics in the rat were investigated using ipflufenoquin radiolabelled at the quinoline or phenyl ring. Ipflufenoquin was well absorbed at low and high dose levels, with peak plasma concentrations occurring at 2 hours post-dosing. Absorption, as a percent of the administered dose (AD), was 90% following a single low dose but decreased to 60–79% following administration of a single high dose. The highest residues during the final sacrifices were found in the gut and gut contents, as well as the liver. Elimination of orally-administered ipflufenoquin was rapid and extensive. The majority of the AD was recovered in the excreta within 48 hours. The major route of excretion was via the feces, with urinary excretion also representing a significant portion of the AD; a biliary excretion study indicated high absorption and excretion of ipflufenoquin via the bile. Radioactivity in tissues 96 hours after single or repeat oral dose administration was low and there was no evidence of tissue retention. The distribution and excretion of radiolabel following pre-treatment with multiple non-radiolabelled doses were comparable to that following administration of a single radiolabelled dose. The toxicokinetic parameters measured were comparable between sexes. In an in vitro comparative metabolism study using human and rat liver cells, rat liver cells were far more effective at metabolizing ipflufenoquin than human liver cells.

Twenty-two metabolites were identified in excreta. Additionally, unchanged ipflufenoquin was not identified in urine or bile, indicating extensive metabolism. The main biotransformation reactions of ipflufenoquin in rats are as follows: biotransformation proceeds either via initial Phase I oxidation yielding single or multiple hydroxylation products which are then subsequently conjugated, or by the formation of an intermediate epoxide on the quinoline ring. The epoxide then either opens to give di-hydroxy products or is displaced by glutathione giving rise to intact glutathione conjugates and an array of metabolites produced by its subsequent metabolism via the mercapturic acid pathway. The sum total of identifiable metabolites as measured by percentage of the AD was higher in low dose males than in females. At the high-dose level, the metabolic profile was comparable between sexes. The identification of select metabolites is presented in Appendix I, Table 2.

In acute toxicity testing, the technical grade active ingredient ipflufenoquin was of low acute toxicity via the oral, dermal, and inhalation routes in rats. It was non-irritating to the eyes and skin of rabbits. Ipflufenoquin was negative for skin sensitization in mice when tested using a local lymph node assay.

The end-use product Kinoprol 20 SC was of low acute toxicity via the oral and dermal routes in rats. It was slightly acutely toxic to rats by the inhalation route. It was non-irritating to the eyes and skin of rabbits. Kinoprol 20 SC was negative for skin sensitization in guinea pigs when tested using the Buehler method.

The liver, thyroid, teeth, and bones were identified as targets of toxicity for ipflufenoquin following repeated dietary exposure in mice and rats. Liver effects observed among mice and rats included increased weight, hepatocyte enlargement, inflammatory cells, mitotic figures, single cell necrosis, and clinical chemistry effects, as well as elevated liver enzymes. Thyroid effects included increased weight, and follicular cell hypertrophy or hyperplasia observed in rats in short-term dietary toxicity studies. Other effects observed in mice and rats included tooth enamel hypoplasia and breakage of the teeth and whitening of the teeth and bones, as well as bone globules. A 14-day mechanistic study in rats explored the progression of dental effects. The available data suggest that the whitening was not due to fluorosis. In the absence of other effects, whitening was not considered toxicologically adverse. There was no evidence that a longer duration of dosing resulted in increased toxicity in mice or rats.

Decreased body weight was the primary sign of toxicity for ipflufenoquin following repeated oral capsule exposure in dogs. The high-dose level was decreased during the 28-day study due to severe body weight effects and was considered well above a maximum tolerated dose.

There was no evidence of genotoxicity in a battery of in vitro and in vivo genotoxicity studies conducted with ipflufenoquin, nor was there evidence of tumourigenicity in mice or rats after long-term dietary administration.

In the 18-month dietary carcinogenicity study in the mouse, an adverse effect on the teeth in the form of broken teeth was noted in females at the highest dose tested. Other findings at this dose level included pale teeth and bone globules, which were observed in both sexes. The pale teeth were not considered an adverse effect, and the bone globules were of uncertain toxicological

significance. However, given that the bone globules were minimal in severity, there was no other evidence of skeletal effects in the toxicology database, and they may have been an artefact of processing technique, they were not considered adverse. Although no adverse effects were noted in males up to the highest dose tested, it was determined that dosing in males in the 18-month study was considered adequate when comparing the dose levels selected for the study to those used in the 90-day dietary study in mice. In that 90-day study, significant toxicity was observed at the LOAEL and a similar high-dose level over 18 months may have resulted in excessive toxicity. Consideration was also given to the fact that there was no indication of tumourigenicity in rats, no pre-cancerous lesions in mice, and no evidence of genotoxicity with ipflufenoquin.

In a 2-year chronic toxicity/carcinogenicity study in rats, pale teeth and bone globules were also not considered adverse in the absence of other toxicity. At higher doses, body weight and body weight gain were reduced. There was no evidence of tumourigenicity.

In a 2-generation dietary reproductive toxicity study in rats, no reproductive toxicity was observed. Both parental animals and offspring had decreased body weights at the highest dose tested, while parents also had hyperplasia in the colon, incisor dysplasia and mild anemia at the same dose level. There was no evidence of sensitivity of the young. In a 1-generation dietary reproductive toxicity range-finding study in rats at higher dose levels, similar effects were observed in adult animals. Additionally, adults exhibited missing or broken incisors and ungroomed coat, while both adults and offspring showed mild dehydration in addition to dark and/or large spleens.

In the gavage developmental toxicity studies, there was no evidence of sensitivity of the young in rats or rabbits. Maternal rats were tested up to the limit dose resulting in transient body weight decreases at the start of dosing and no treatment-related developmental effects. In the rabbit developmental toxicity study, maternal body weight gain and food consumption were decreased at the highest dose level tested and there were no treatment-related developmental effects.

Ipflufenoquin showed no evidence of selective neurotoxicity in an oral acute neurotoxicity study in rats.

A variety of mechanistic studies were performed with ipflufenoquin to further define toxicology and metabolic pathways. In a 3-, 7-, or 14-day dietary study in rats, ipflufenoquin showed minimal to mild tooth enamel effects that progressed with increasing duration of dosing. In a dietary liver enzyme induction study in rats, toxicity consistent with other short-term studies was observed, along with increased liver enzyme activity and associated metabolic gene expression.

The toxicity of select transformation products of ipflufenoquin was investigated. The soil transformation product QP-1-1 was of low acute oral toxicity in rats. The phototransformation product QP-2 was of low acute oral toxicity in rats, had a similar NOAEL as ipflufenoquin in a 28-day oral toxicity study in rats, and was negative in two bacterial reverse gene mutation assays, an in vitro chromosome aberration assay, an in vivo mouse bone marrow micronucleus assay, an in vitro forward gene mutation assay in mouse cells, and in vivo Comet assays in mice and rats.

A manufacturing impurity of ipflufenoquin was also demonstrated to be of low acute oral toxicity in rats and negative in a bacterial reverse mutation assay. Based on the available information, the manufacturing impurity and the transformation products QP-1-1 and QP-2 were considered of equivalent toxicity to ipflufenoquin.

The identification of select metabolites and transformation products of ipflufenoquin is presented in Appendix I, Table 2. Results of the toxicology studies conducted in laboratory animals with ipflufenoquin and relevant transformation products, and Kinoprol 20 SC are summarized in Appendix I, Tables 3 and 4. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 5.

3.1.2 *Pest Control Products Act* hazard characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account the completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data[5].

With respect to the completeness of the ipflufenoquin toxicity database as it pertains to the toxicity to infants and children, the database contains the full complement of required studies including oral gavage developmental toxicity studies in rats and rabbits, and a dietary 2-generation reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the available studies. In the rat dietary 2-generation reproductive toxicity study, pup body weights were reduced during the lactation phase at the highest dose level; however, this effect occurred in the presence of maternal toxicity. There were no treatment-related adverse developmental effects identified in the rat or rabbit developmental toxicity studies.

Overall, the database is adequate for determining the sensitivity of the young. The effects observed in the young were well-characterized, not considered serious in nature, and occurred in the presence of maternal toxicity. On the basis of this information, the *Pest Control Products Act* factor (PCPA factor) was reduced to 1-fold.

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

3.2 Toxicology reference values

3.2.1 Route and duration of exposure

For mixers, loaders and applicators, occupational exposure to Kinoprol 20 SC is characterized as short- to intermediate-term in duration and is predominantly by the dermal and inhalation routes. For postapplication workers and homeowners in residential areas, exposure to Kinoprol 20 SC is also characterized as short- to intermediate-term in duration, while for patrons in pick-your-own facilities, postapplication exposure is expected to be of short-term duration.

Postapplication exposure to all individuals is expected to be primarily by the dermal route. Exposure to ipflufenoquin is also expected to occur via the diet and drinking water.

3.2.2 Occupational and residential toxicology reference values

Short- and intermediate-term dermal

For the short- and intermediate-term dermal occupational and residential risk assessments, the NOAEL of 1000 mg/kg bw/day from the 28-day dermal toxicity study in rats was selected, which was the highest dose level tested in this study. This study was conducted via the relevant route and was of an appropriate duration of exposure. For occupational and residential scenarios, the target margin of exposure (MOE) is 100, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. For residential scenarios, the PCPA factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization Section. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed women.

Short- and intermediate-term inhalation

For short- and intermediate-term occupational inhalation risk assessment, the parental NOAEL of 58 mg/kg bw/day from the 2-generation dietary reproductive toxicity study in rats was selected. At a dose level of 237 mg/kg bw/day, decreases in body weights and body weight gains were observed along with microscopic effects in the colon and incisors. With regards to the selection of reference values for inhalation risk assessment, a short-term or repeat-dose inhalation toxicity study was not available and thus, the use of a NOAEL from an oral study was appropriate.

The target MOE for these inhalation scenarios 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)

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

To estimate acute dietary risk, the NOAEL of 125 mg/kg bw from the acute oral neurotoxicity study in the rat was selected for risk assessment. At the LOAEL of 500 mg/kg bw, decreases in motor activity and body temperature 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 composite assessment factor (CAF) is thus 100.**

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{125 \text{ mg/kg bw}}{100} = 1.3 \text{ mg/kg bw of ipflufenoquin}$$

3.2.4 Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, the NOAEL of 28 mg/kg bw/day from the 2-year dietary chronic toxicity/carcinogenicity study in the rat was selected. The LOAEL of 142 mg/kg bw/day was based on reductions in body weight and body weight gain. This study NOAEL is comparable to those of the short-term studies in rats and dogs. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization Section, the PCPA factor was reduced to 1-fold. **The CAF is thus 100.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{28 \text{ mg/kg bw/day}}{100} = 0.3 \text{ mg/kg bw/day of ipflufenoquin}$$

The selected ADI provides a margin of 350 to the NOAEL for male mice in the 18-month dietary toxicity study.

3.2.5 Cancer assessment

There was no evidence of tumourigenicity and therefore, a cancer risk assessment is not necessary.

3.2.6 Aggregate toxicology reference values

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). Short-term aggregate exposure to ipflufenoquin may be comprised of food, drinking water and residential exposure via the dermal route in pick-your-own scenarios. No reference values were selected for the short-term aggregate

risk assessment as there was an absence of effects at the limit dose in the repeat-dose dermal toxicity study. Acute and chronic oral aggregate assessments, consisting of combined food and drinking water exposure only, were undertaken. The most relevant toxicology endpoints and assessment factors for acute and chronic oral aggregate exposure are the same as those selected for the ARfD (see Section 3.2.3) and ADI (see Section 3.2.4), respectively.

3.3 Dermal absorption

A dermal absorption value is not required in the risk assessment since the dermal toxicology reference value for ipflufenoquin is based on a dermal toxicity study.

3.4 Occupational and residential exposure assessment

3.4.1 Acute hazards of the end-use product and mitigation measures

The acute toxicity of the end-use product Kinoprol 20 SC, containing ipflufenoquin, was low via the oral and dermal routes of exposure. Kinoprol 20 SC was of slight toxicity via the inhalation route of exposure; consequently, the signal word and hazard statement "CAUTION – POISON" are required on the label. It was non-irritating to the eyes and skin, and did not cause an allergic skin reaction. 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

Kinoprol 20 SC is a suspension concentrate commercial-class product for postemergence foliar application to pome fruit trees by ground equipment.

Individuals have potential for exposure to ipflufenoquin 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) for mixers, loaders and applicators applying Kinoprol 20 SC to pome fruit trees. The applicant is a member of AHETF and has full access to the data that were used to estimate worker exposure. The unit exposure values in the risk assessment are based on handlers wearing a single layer of clothing and chemical-resistant gloves (Appendix I, Table 6).

The applicant is not a member of the Non-Dietary Exposure Task Force and therefore does not have access to the associated data. A label statement restricting the use of handheld mistblower/airblast or handheld fogging equipment will be added to the label.

Dermal exposure was estimated using the unit exposure values with the amount of product handled per day. 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.

Calculated MOEs are greater than the target margin of exposure (MOE) of 100 for all chemical handler scenarios in pome fruit orchards, and are therefore not of health concern (Appendix I, Table 7).

Taking into account both the acute toxicity of the end-use product (EP) and the risk assessment for ipflufenoquin, workers are required to wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Chemical-resistant gloves are not required during application within a closed cab.

3.4.2.2 Postapplication exposure and risk assessment

There is potential for exposure to workers entering areas treated with Kinoprol 20 SC to complete tasks such as hand thinning, hand harvesting, scouting, hand pruning, training, hand weeding, propping and other pome fruit orchard maintenance activities. Given the nature of activities performed, exposure should be primarily via the dermal route based on dermal contact with treated foliage. Inhalation exposure is not expected as ipflufenoquin is considered non-volatile with a vapour pressure of approximately 7.26×10^{-9} kPa (at 20°C), which is less than the North American Free Trade Agreement (NAFTA) criterion for a non-volatile product for outdoor scenarios of 1×10^{-4} kPa (7.5×10^{-4} mmHg) at 20-30°C. As such, a quantitative inhalation risk assessment is not required. Inhalation risk is not of health concern for postapplication workers as ipflufenoquin 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 vineyards is estimated using 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), of which the applicant is a member and has full access to the data used to estimate the worker exposure. As chemical-specific DFR data were not submitted, an agency standard DFR value of 25% of the application rate coupled with 10% daily dissipation of residues were used in the exposure assessment.

Exposure estimates were compared to the toxicology 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 (Appendix I, Table 8). As such, there are no health risks of concern and the REI of 12 hours is adequate to protect workers entering treated pome fruit orchards to conduct postapplication activities.

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk assessment

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

3.4.3.2 Postapplication exposure and risk assessment

Kinoprol 20 SC is proposed for use on pome fruit trees, which includes residential areas such as pick-your-own (PYO) settings or homeowners' gardens. Therefore, a postapplication residential risk assessment is required.

3.4.3.2.1 Pick-your-own (PYO) activities

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

3.4.3.2.2 Orchard trees treated with Kinoprol 20 SC in residential areas

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

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

Dermal exposure was estimated using standard DFR values, the transfer coefficients, durations of exposure and body weights from the USEPA Residential SOPs (2012). Calculated MOEs were greater than the target dermal MOE of 100 in all residential postapplication exposure scenarios on Day 0 (Appendix I, Table 9). As such, health risks are not of concern and the individuals can enter the treated area once the sprays have dried.

3.4.4 Bystander exposure and risk assessment

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

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

3.5 Dietary exposure and risk assessment

3.5.1 Exposure from residues in food of plant origin

The residue definition for risk assessment and enforcement in plant commodities is ipflufenoquin. The data gathering and enforcement analytical methods are valid for the quantitation of ipflufenoquin residues in crop matrices. The residues of ipflufenoquin are stable in apples for up to 12 months when stored in a freezer at ≤-10°C. The raw agricultural commodities of apples were processed, and ipflufenoquin residues concentrated in the processed commodity of dried apples (2.5×). Crop field trials conducted throughout Canada and the United States using end-use products containing ipflufenoquin at approved rates in or on apples, pears, and almonds are sufficient to support the proposed maximum residue limits.

3.5.2 Residues in drinking water sources

From a drinking water exposure perspective, the residue of concern is ipflufenoquin. Environmental concentrations of ipflufenoquin in potential drinking water sources were estimated using numerical models for the human health risk assessment. Modelling was conducted using the Pesticides in Water Calculator (PWC) version 1.52, using standard PMRA scenarios which take into account regional weather and soil characteristics as well as relevant plant properties.

A subset of use patterns was considered for the modelling, which is intended to provide a conservative exposure estimate for all labelled uses. The use-pattern selected for the modelling was for three foliar treatments at a rate of 44 g a.i./ha with an interval of 7 days in between treatments, representing a cumulative yearly application rate of 132 g a.i./ha. Major fate input parameters for the drinking water modelling are presented in Table 1 below.

Table 1 Fate inputs for water modelling

Fate Parameter	Drinking Water Value
K_{OC}	757
Soil half-life	855 days
Water half-life[1]	510 days
Sediment half-life[2]	544 days
Phototransformation half-life	4.1 days
Hydrolysis half-life	Stable

[1] Aquatic whole system half-life

[2] Anaerobic soil half-life used to estimate sediment half-life

For the human health assessment, estimated environmental concentrations (EECs) in potential drinking water sources are calculated for both groundwater and surface water.

For surface water, PWC calculates the amount of pesticide entering the water body by runoff and drift, and the subsequent degradation of the pesticide in the water system. EECs are calculated by modelling a total land area of 173 ha draining into a 5.3 ha reservoir with a depth of 2.7 m. Groundwater EECs are calculated by simulating leaching through a layered soil profile and reporting the average concentration in the top 1 meter of a water table.

Estimated concentrations in drinking water sources are presented in Table 2 below.

Table 2 Level 1 estimated environmental concentrations of Ipflufenoquin in potential sources of drinking water

Use pattern	Groundwater (µg a.i./L)		Surface Water (µg a.i./L)		
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Overall[5]
3 applications of 44 g a.i./ha with a 7-day interval	8.9	8.9	5.8	1.1	0.75

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

3.5.3 Dietary risk assessment

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

3.5.3.1 Acute dietary exposure results and characterization

The following assumptions were applied in the basic acute analysis for ipflufenoquin: 100% crop treated, default processing factors (where available), residues in/on crops at MRL levels. The basic acute dietary exposure (food alone) for all supported ipflufenoquin food commodities and imported commodities is estimated to range from 0.0 to 0.5% of the ARfD (95th percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable: the highest estimate is 0.6% of the ARfD for children 1-2 years old.

3.5.3.2 Chronic dietary exposure results and characterization

The following assumptions were applied to the basic chronic analysis for ipflufenoquin: 100% crop treated, default processing factors (where available), residues in/on crops at MRL levels. The basic chronic dietary exposure (food alone) from all supported ipflufenoquin food commodities and imported commodities for the total population, including infants and children, and all representative population subgroups is less than 0.6% of the acceptable daily intake

(ADI). Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to ipflufenoquin from food and drinking water is 0.1% (0.0003 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 0.7% (0.0021 mg/kg bw/day) of the ADI.

3.6 Aggregate exposure and risk assessment

There is potential for individuals to be exposed to ipflufenoquin via different routes and sources of exposure concurrently. As such, the Pick-Your-Own (PYO) and orchard trees in residential settings scenarios were considered. Since both the acute and chronic dietary (food and drinking water) and the short- and intermediate term dermal toxicology reference values are based on different toxicological endpoints/effects (and no effects were seen at the highest dose in the dermal study), no aggregation of dermal and dietary exposure is required.

3.7 Cumulative assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for ipflufenoquin.

Ipflufenoquin has a quinoline group; however there are currently no known quinoline fungicides with similar chemical structures, and although the pesticidal mode of action is said to be novel, the details have not been fully elucidated. The only other currently registered quinoline fungicide in Canada is quinoxyfen. Ipflufenoquin and quinoxyfen do not have similar structures or toxicological profiles.

No cumulative health risk assessment is 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 ipflufenoquin 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 ipflufenoquin.

Table 3.8.1 Recommended maximum residue limits

MRL (ppm)	Food Commodity
0.15	Pome fruits (Crop Group 11-09)
0.01	Almond nuts

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 Appendix I, Tables 1A, 10 and 11.

3.9 Health incident reports

Ipflufenoquin is a new active ingredient pending registration for use in Canada, and as of 16 June 2021, no incidents involving ipflufenoquin were reported to the PMRA.

3.10 Antimicrobial resistance assessment

Ipflufenoquin is a member of the class of quinoline compounds. The pharmacophore of quinolines is similar to that of quinolones, a number of which are used as antibacterial drugs in human medicine. A compound isolated from the commercial preparation of a quinoline was modified to produce the first marketed quinolone, nalidixic acid. Fluorine was subsequently added to produce the clinically important fluoroquinolone class of antibiotics (for example, ciprofloxacin and levofloxacin).

A search of the published scientific literature yielded two reports of quinolone resistance development in bacteria as a result of exposure to a quinoline. Given the structural similarity between ipflufenoquin and fluoroquinolones and these reports, the applicant was required to address the potential for antimicrobial resistance (AMR).

Fluoroquinolone resistance in *Pseudomonas aeruginosa* and many other bacterial pathogens is mediated primarily through mutations in the antibiotic's target, topoisomerase II (GyrA) and topoisomerase IV (ParC), as well as drug efflux regulatory genes.

Ipflufenoquin does not exhibit appreciable antibacterial activity against common bacterial plant pathogens, or Gram-positive and Gram-negative human pathogens. Ipflufenoquin has a different mode of action and different target enzyme from those of fluoroquinolones. The proposed use is also not expected to result in the overexpression of drug efflux pumps (to contribute to AMR) or to increase exposure of microorganisms to quinolone or quinolone-like compounds through impurities in the EP or through metabolism in plants or the environment. Although metabolism studies in rats indicated that there is the potential for metabolites to be formed that can undergo further reactions to be quinolone-like in structure, these metabolites are transient in nature, rapidly excreted and any quinolone-like compounds, if produced, are likely present at very small quantities. Taken together, ipflufenoquin is not expected to result in the development of AMR in bacterial species against fluoroquinolones.

The label for Kinoprol SC includes statements to limit the development of AMR in non-target fungi including instructions to rotate ipflufenoquin with other active ingredients with different modes of action and standard statements to limit occupational exposure to ipflufenoquin. Such statements will also serve to minimize any potential for the development of AMR in bacteria.

The risk of bacterial species developing AMR against fluoroquinolones when Kinoprol 20 SC is used according to the label instructions is, therefore, considered to be low.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

Physicochemical chemical properties of ipflufenoquin are summarized in Section 1.2. Environmental fate properties of ipflufenoquin are summarized in Appendix I, Tables 12 and 13.

Terrestrial environment: Ipflufenoquin is persistent in soil. No major transformation products were observed in aerobic, anaerobic or irradiated laboratory soil studies. Due to the persistence of ipflufenoquin, no major routes of terrestrial dissipation were identified. Ipflufenoquin is persistent under aerobic and anaerobic soil condition and persistent on soil in the presence of light.

Observations from the terrestrial field dissipation study indicated that ipflufenoquin is non-persistent to slightly persistent under field conditions on bare ground plots with no major transformation products observed. Although the observed DT_{50s} were less than 1 month, due to the biphasic dissipation of ipflufenoquin, maximum carry-over observed during field trials on bare ground 12 months after application ranged from 33.8 to 35.9% of applied. Based on these percentages, ipflufenoquin is expected to be present in the soil the following year under field conditions. However, a label statement pertaining to the carry-over potential is not required as the risks to non-target terrestrial and aquatic organisms associated with the use of ipflufenoquin were found to be acceptable.

Laboratory experiments show that ipflufenoquin has slight to low mobility depending on soil type. Observations from the field dissipation study indicate that ipflufenoquin was confined to the top 30 cm layer. Based on the groundwater ubiquity score (GUS) classification scheme, ipflufenoquin is classified as a borderline-leacher to leacher, mainly due to its persistence in soil. Considering all the information available in a leaching assessment, the PMRA concludes that ipflufenoquin can leach and therefore a leaching statement is required on the product label.

Aquatic environment: Ipflufenoquin is persistent in water and water-sediment systems. No major transformation products were observed in aerobic and anaerobic aquatic laboratory studies. Ipflufenoquin is stable to hydrolysis at pH 4, 7 and 9, however, non-persistent in water in the presence of light, with carbon dioxide being the only major transformation product observed in irradiated water studies. In aerobic and anaerobic water/sediment systems, ipflufenoquin partitions to the sediment, and is persistent.

Air: Ipflufenoquin is soluble in water, has low vapour pressure and a low Henry's law constant. The intrinsic physio-chemical properties suggest that ipflufenoquin is not likely to volatilize from moist soil or water surfaces under field conditions.

Bioaccumulation: The logKow for ipflufenoquin suggests a potential for bioaccumulation. However, results from a bioconcentration study conducted with bluegill sunfish showed a growth corrected, lipid-normalized kinetic bioconcentration factor for whole fish that indicated the potential for bioaccumulation is low. The depuration half-life of ipflufenoquin from bluegill sunfish was less than one day. Ipflufenoquin is therefore not expected to bioaccumulate.

4.2 Environmental risk characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing estimated environmental exposures (EEEs) in various media (food, water, soil and air) with the concentrations, rates, doses or daily doses at which adverse effects occur.

The EEEs are determined using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. For ipflufenoquin and its end-use product Kinoprol 20 SC, the rates considered in this risk assessment included the maximum proposed single foliar application rate of 44.0 g a.i./ha and the maximum cumulative application rate of 132 g a.i./ha taking into consideration the maximum proposed number of applications (3) per year (growing season) and the minimum proposed reapplication interval of 7 days. A summary of the EEEs used in the risk assessment is presented in Appendix I, Table 17.

Ecotoxicology information includes acute and chronic toxicity data for organisms (invertebrates, vertebrates and plants) from both terrestrial and aquatic habitats. Effects metrics are established for all organism groups that represent the estimated level at which exposure could result in adverse effects. These metrics can include unaltered laboratory or higher tiered endpoints, laboratory or higher tiered endpoints to which an uncertainty factor is applied, geomeans of laboratory or higher tiered endpoints and species sensitivity distributions. A summary of effects metrics used in the risk assessment is presented in Appendix I, Table 16.

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (e.g., direct application at a maximum cumulative application rate) and the relevant effects metric. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate effects metric, and the risk quotient is then compared to the level of concern (LOC; Appendix 1, Table 16). If the screening level RQ is below the LOC, the risk is considered acceptable and no further risk characterization is necessary.

The screening level risk assessment for ipflufenoquin is summarized in Appendix I, Tables 18 and 19 for terrestrial organisms and Table 20 for aquatic organisms.

4.2.1 Risks to terrestrial organisms

Terrestrial organisms, such as earthworms, pollinators, beneficial arthropods, birds, small mammals, and terrestrial non-target vascular plants can be exposed to ipflufenoquin through direct contact with spray, spray drift, run-off, contact with sprayed surfaces, or from ingestion of contaminated food. A risk assessment of ipflufenoquin and the associated end-use product, Kinoprol 20 SC, was undertaken based on available toxicity data for earthworms, honeybees, other beneficial arthropods, birds, small wild mammals, and terrestrial plants.

The RQs resulting from the foliar application screening level risk assessment for earthworms, beneficial arthropods, pollinators, birds, terrestrial plants vegetative vigour and wild mammals did not exceed any of the LOCs. The RQs for seedling emergence of terrestrial plants slightly exceeded the LOC (RQ < 1.3). At the highest rate tested (100 g a.i./ha), the greatest effect observed for all test species for seedling emergence was a reduction of 13.5% in dry weight for onion. The rate tested during the seedling emergence study was 227% higher than the single proposed application rate of 44 g a.i./ha and 32% lower than the maximum cumulative soil application rate of 131.3 g/ha. As the greatest effect observed during the seedling emergence study was a reduction of 13.5%, it is very unlikely that adverse effects greater than 25% will be observed under the proposed use pattern. Further characterization of risk for terrestrial organisms was therefore not required.

The available terrestrial toxicity data for ipflufenoquin and its formulated end-use product are presented in Appendix I, Table 14. The screening level terrestrial EEEs from the use of ipflufenoquin were determined using the single maximum foliar application rate of 44 g a.i./ha for bees and the maximum cumulative foliar application rate of 132 g a.i./ha for all other terrestrial organisms and accounting for degradation between applications. Screening level terrestrial EEEs are presented in Appendix I, Table 17. The effects metrics used in the risk assessment are presented in Appendix I, Table 16. The screening level risk assessment for non-target terrestrial organisms is presented in Appendix I, Tables 18 and 19.

In summary, when used according to the proposed label directions, risks associated with the use of ipflufenoquin are acceptable for the following terrestrial organisms:

- Earthworms
- Beneficial arthropods
- Pollinators
- Birds and mammals
- Terrestrial plants

4.2.2 Risks to aquatic organisms

Aquatic organisms, such as invertebrates, fish, plants and algae can be exposed to ipflufenoquin through spray drift or run-off. A risk assessment of ipflufenoquin and the associated end-use product, Kinoprol 20 SC, was undertaken based on available toxicity data for freshwater and marine invertebrates, fish, plants and algae.

The available aquatic toxicity data for ipflufenoquin is presented in Appendix I, Table 15. The screening level aquatic EECs from the use of ipflufenoquin were determined using the maximum cumulative foliar application rate of 132 g a.i./ha, assuming direct overspray and instantaneous complete mixing in the water body and accounting for degradation between applications. The effects metrics used in the risk assessment are presented in Appendix I, Table 16. Screening level aquatic EECs are presented in Appendix I, Table 17. The screening level risk assessment for aquatic organisms is presented in Appendix I, Table 20.

The RQs resulting from the foliar application screening level risk assessment for freshwater vascular plants and algae, marine algae, freshwater and marine invertebrates, freshwater and marine fish and amphibians did not exceed the LOC.

In summary, when used according to the proposed label directions, risks associated with ipflufenoquin are acceptable for the following aquatic organisms:

- Freshwater vascular plants and algae, and marine algae
- Freshwater and marine invertebrates
- Freshwater and marine fish
- Amphibians

4.3 Environmental incident reports

Ipflufenoquin is pending registration for use in Canada. There are no incident reports in the PMRA database.

5.0 Value

Twenty-one trials conducted on pear and apple in Canada and the United States between 2012 and 2019 were reviewed to support the claims of control of powdery mildew and scab on pome fruit (Crop Group 11-09). Trials conducted on powdery mildew showed that the lower rate suppresses powdery mildew and the higher rate is required for control; however, the use of a non-ionic surfactant improved efficacy in most cases. Trials reviewed on scab demonstrated control at the proposed rates. The addition of a non-ionic surfactant improved efficacy under higher levels of disease pressure. The results of the efficacy trials supported the registration of the disease claims on apple and pear. A scientific rationale supported extrapolation of the claims to all crops in Crop Group 11-09 Pome Fruit.

Cultural methods are used by growers to reduce the incidence of scab and powdery mildew in orchards. Scab and secondary powdery mildew infections are often treated simultaneously because the phenological stages for both diseases often overlap. Frequent fungicide applications protect developing leaves and flowers.

Ipflufenoquin is a new mode of action fungicide that offers growers a rotational tool for use with currently registered products to manage resistance development. Although the mode of action has not been fully characterized, testing indicates that ipflufenoquin is not cross-resistant with

other modes of action registered to control powdery mildew and scab on pome fruit. Fungicides currently registered for these uses belong to FRAC mode of action groups 3, 7, 11, and BM02 (formerly 44), plus co-formulations of fungicides from these groups. Additional modes of action are registered on apple and/or pear.

6.0 Pest control product policy considerations

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

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

During the review process, ipflufenoquin 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 ipflufenoquin and its transformation products do not meet all of the TSMP Track 1 criteria. Please refer to Appendix I, Table 22 **Error! Reference source not found.**for further information on the TSMP assessment.

6.2 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the active ingredient as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.[7] The list is used as described in the PMRA Science Policy Note SPN2020-01[8] and is based on existing policies and regulations, including the Toxic Substances Management Policy and Formulants Policy[9], and taking into consideration the Ozone-depleting Substances and Halocarbon Alternatives Regulations, under the *Canadian Environmental Protection Act, 1999*, (substances designated under the Montreal Protocol).

Health Canada has reached the following conclusions:

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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 4, 2020. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*

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

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

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

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

7.0 Proposed regulatory decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Kinoprol Technical and Kinoprol 20 SC, containing the technical grade active ingredient ipflufenoquin, for control or suppression of pome fruit diseases.

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
°C	degree(s) Celsius
µg	micrograms
♀	female
♂	male
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
A:G ratio	ratio of albumin to globulin
abs	absolute
ACN	acetonitrile
AD	administered dose
ADI	acceptable daily intake
AHETF	Agricultural Handler Exposure Task Force
ALP	alkaline phosphatase
ALS	acetolactate synthase
ALT	alanine aminotransferase
AMR	antimicrobial resistance
APTT	activated partial thromboplastin time
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
ASAE	American Society of Agricultural and Biological Engineers
AST	aspartate animotransferase
atm	atmosphere
ATPD	Area Treated Per Day
AUC	area under the curve
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BCF	bioconcentration factor
BAF	bioaccumulation factor
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	Canadian Environmental Protection Act
CFIA	Canadian Food Inspection Agency
cm	centimetres
Cmax	maximum concentration
CR	Chemical-Resistant
CYP	cytochrome P

DACO	data code
DER	data evaluation record
DF	dry flowable
DFR	Dislodgeable Foliar Residue
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the time required to observe a 90% decline in concentration)
d	day(s)
dpm	disintegrations per minute
dw	dry weight
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EEC	Environmental Exposure Concentrations
EEE	Estimated Environmental Exposure
EP	End-use Product
eq	equivalent
ER_{25}	effective rate for 25% of the population
ER_{50}	effective rate for 50% of the population
ERC	evaluation report conditional
EROD	7-ethoxyresorufin O-dealkylase
F0	initial parental generation
F1	first offspring generation
F2	second offspring generation
fc	food consumption
FOB	functional observational battery
FQPA	Food Quality Protection Act
FRAC	Fungicide Resistance Action Committee
g	gram(s)
GD	gestation day
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
h	hour(s)
ha	hectare(s)
HAFT	highest average field trial
HCl	hydrochloric acid
HDT	highest dose tested
HED	Health Effects Division
Hg	mercury

HPLC	high-performance liquid chromatography
hr	Hour
ILV	independent laboratory validation
IUPAC	International Union of Pure and Applied Chemistry
iv	intravenous
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
kg	kilogram
km	kilometre
km/h	kilometers per hour
K_{oc}	organic-carbon partition coefficient
KOH	potassium hydroxide
K_{ow}	*n*–octanol-water partition coefficient
kPa	Kilopascal
L	litre(s)
LAFT	lowest average field trial
LC_{50}	concentration lethal to 50% of the test population
LD_{50}	dose lethal to 50% of the test population
LOAEL	lowest observed adverse effect level
LOEC	low observed effect concentration
LOC	level of concern
LOD	limit of detection
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
m	metre
M/L	Mixer/Loader
M/L/A	Mixer/Loader/Applicator
MAS	maximum average score
max	maximum
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
min	minimum
MIS	maximum irritation score
mL	millilitre
mmHg	millimetre of mercury
MOE	margin of exposure
mol	mole

mPa	millipascal
MRL	maximum residue limit
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MTD	maximum tolerated dose
N/A	not applicable
N/R	not required
NAFTA	North American Free Trade Agreement
ng	nanogram
nm	nanometre
NOAEC	no observed adverse effects concentration
NOAED	no observed adverse effect dose
no observed adverse effect daily dose	
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
NZW	New Zealand white
OC	organic carbon content
OECD	Organisation for Economic Co-operation and Development
OM	organic matter content
Pa	Pascal
PBI	plantback interval
PDP	Pesticide Data Program
PHED	Pesticide Handler Exposure Database
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	post-natal day
p-NPH	p-nitrophenol hydroxylase
PPE	Personal Protective Equipment
ppm	parts per million
PRD	proposed registration decision
PRDD	proposed regulatory decision document
PROD	pentoxyresorufin o-dealkylase
PWC	pesticides water calculator
PYO	pick-your-own
RAC	raw agricultural commodity
REI	restricted-entry interval
rel	relative
RQ	risk quotient

RSD	relative standard deviation
RTI	Retreatment Interval
S9	mammalian metabolic activation system
SC	soluble concentrate
SDEV	standard deviation
SOP	standard operating procedure
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TC	Transfer coefficient
TGAI	technical grade active ingredient
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
UAN	urea ammonium nitrate
uridine diphosphate glucuronyltransferase	
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution
w/w	weight by weight
w/v	weight per volume
WG	water dispersible granules
wt	weight
yrs	years

Appendix I Tables and figures

Table 1A Residue analysis in plants

Analytical Methods	Matrices	Analyte	Method ID/ Type	LOQ (ppm)	Reference (PMRA#)
Plant Commodities					
Enforcement and Data-Gathering Method	Apple, Grape, Wheat Grain, Almond and Dry Bean	Ipflufenoquin	# P 3996 G, Modified QuEChERS/ HPLC-MS/MS	0.01	3073041
Data-Gathering Method	Almond Nutmeat and Hulls	Ipflufenoquin	# GPL-MTH-104/ HPLC-MS/MS	0.01	3073040
	Apple fruit	Ipflufenoquin	# GPL-MTH-095/ HPLC-MS/MS	0.01	3073042
ILV of Enforcement Method	Apple, Grape, Wheat Grain, Almond and Dry Bean	Ipflufenoquin	Modified QuEChERS/HPLC-MS/MS	0.01	3073044
Radiovalidation	Apple and Grape	Ipflufenoquin	HPLC-MS/MS Method No.1: Enforcement Method Validated in P 3996 G (adapting QuEChERS Method) Method No.2: Extraction as used in the Metabolism Studies	0.01	3073047

Table 1B Residue Analysis in Environmental Media

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Soil	GPL-MTH-099	Ipflufenoquin	HPLC-MS/MS	0.002 ppm	3070092
		QP-1-1		0.002 ppm	
		QP-1-7		0.002 ppm	
Water	N/A	Ipflufenoquin	HPLC-MS/MS	0.05 µg/L	3070095
		QP-1-7		0.05 µg/L	3070097

Table 2 Identification of Select Mammalian Metabolites and Environmental Transformation Products of Ipflufenoquin

Code	Chemical Name	Source
QP-1-23	Exact structure not provided, described as NF-180 -2H +2O +SO_2CH_3 ($C_{20}H_{16}F_3NO_6S$)	Rat metabolite
QP-1-8	2-[2-(7,8-difluoro-2-methylquinolin-3-yloxy)-6-flurophenyl]propane-1,2-diol	Rat metabolite
QP-1-1	7,8-difluoro-3-(3-fluoro-2-isopropenylphenoxy)-2-methylquinoline	Soil transformation product
QP-2	5,7',8'-trifluoro-2',4,4-trimethyl-4*H*,4'*H*-spiro[1,3-benzodioxin-2,3'-quinoline]	Phototransformation product

Table 3 Toxicity profile of technical Ipflufenoquin

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, toxicokinetics, metabolism and excretion study following single gavage doses (low and high) Wistar rats PMRA No. 3070062, 3070064	Absorption, distribution, metabolism and excretion were investigated with [quinoline-U-^{14}C] (A-ring) or [phenyl-U-^{14}C] (C-ring) labelled ipflufenoquin. Single doses of A-ring-labelled ipflufenoquin were administered by gavage at 3 or 300 mg/kg bw, or following 14 days of dosing with 3 mg/kg bw/day of non-radiolabelled ipflufenoquin. Some rats were bile duct-cannulated to assess biliary excretion. Additionally, a single dose of C-ring-labelled ipflufenoquin was administered at 3 mg/kg bw. **Absorption:** Absorption was higher at 3 mg/kg bw than at 300 mg/kg bw and bile was an important route of excretion. The total absorbed radiolabel was approximately 90% of the administered dose (AD) at 3 mg/kg bw and 60-79% of the AD at 300 mg/kg bw.

Study Type / Animal / PMRA #	Study Results
	Kinetic Parameters: Systemic exposure at 300 mg/kg bw was 56-72 times higher than the 3 mg/kg bw group measured by AUC. Half-life values in plasma were estimated to be 15-27 hours. **Distribution:** In general, concentrations of radioactivity in the tissues were similar in males and females. Concentrations of radioactivity in tissues were frequently highest in the liver for both sexes and dose levels. Overall, tissue retention was low with low detectable levels of the radioactivity retained in tissues at 96 hours post-dosing. In the 3 (single and repeat dosing) and 300 mg/kg bw groups, peak tissue concentrations generally occurred at 2 hours post-dosing and were generally higher in females than males. At 2 hours, the highest concentrations of radioactivity (excluding gastrointestinal tract) were in the liver. Concentrations of radioactivity in tissues declined over time in all dosing scenarios; elimination from liver and kidney appeared slightly slower following repeat dosing. **Excretion:** Most of the radioactivity (>87%) was eliminated in urine and feces within 72 hours post-dosing. Excretion was mainly via the feces. Urinary excretion was slightly higher at 3 mg/kg bw than at 300 mg/kg bw. At 96 hours, urinary excretion in the 3 mg/kg bw group accounted for 6% and 12% of the AD and fecal excretion accounted for approximately 86% and 80% of the AD in males and females, respectively. At 300 mg/kg bw, in both sexes, the 96 hour radiolabel recovery in urine and feces was approximately 6% and 85%, respectively. Recovered radiolabel in bile accounted for 83-84% of the AD for low dose and 54-70% of the AD for high dose. Overall excretion of radioactivity was rapid with > 91% of the AD excreted during the first 48 hours for both sexes and both dose levels. Following 14 consecutive daily oral administrations to male and female rats, rates and routes of excretion were similar to that observed following single administration at the low dose level. There was low potential for tissue retention. **Metabolites:** Ipflufenoquin is extensively metabolized giving rise to an extensive array of metabolites resulting from transformations at multiple positions in the molecule. Biotransformation proceeds either via initial Phase I oxidation yielding single or multiple hydroxylation products which are then subsequently conjugated, or by the formation of an intermediate epoxide on the quinoline ring. The epoxide then either opens to give di-hydroxy products or is displaced by glutathione giving rise to intact glutathione conjugates and an array of metabolites produced by its subsequent metabolism via the mercapturic acid pathway. There were some minor differences in the profile of radioactive components between sexes. Unchanged ipflufenoquin was not identified in the urine of

Study Type / Animal / PMRA #	Study Results
	either sex. In the excreta, unchanged ipflufenoquin accounted for a maximum of 6.4% of the 3 mg/kg bw dose and 73% of the 300 mg/kg bw dose. Fifteen metabolites were identified, but only two metabolites (M17 (QP-1-23) and QP-1-8) were identified at slightly more than 10% of AD, and that was only in males dosed at 3 mg/kg bw with A-ring labelled ipflufenoquin.
Absorption, distribution, and excretion study following single gavage doses or single intravenous injections Wistar rats PMRA No. 3070063	Absorption, distribution, and elimination were investigated with [quinoline-U-^{14}C] (A-ring) labelled ipflufenoquin. Single doses of A-ring-labelled ipflufenoquin were administered by gavage at 3 mg/kg bw or by intravenous injection at 1 mg/kg bw. Following a single oral dose, maximum systemic concentration was reached at 0.25-2 hours. The concentration of radioactivity declined with half-life values of 21-22 hours in whole blood and 15-16 hours in plasma. Comparison of systemic exposure following oral and intravenous dosing showed oral bioavailability was 75-99% depending on the compartment evaluated. Following a single intravenous dose of 1 mg/kg bw the concentration of radioactivity in blood and plasma was below the limit of reliable detection by 96 hours after dosing. Half-life values were 21-22 hours in whole blood and 16 hours in plasma. The Cmax in ng eq/g was 612/682 in ♂/♀ in blood and 1130/974 in ♂/♀ in plasma following oral administration and 1160/1290 in ♂/♀ in blood and 1810/2030 in ♂/♀ in plasma following intravenous administration.
Comparative in vitro metabolism study Human and rat liver S9 PMRA No. 3070071	Supplemental - non-guideline Rat liver S9 metabolized approximately 90% of the test substance, producing 9 identified metabolites and 2 unidentified metabolites. Human liver S9 metabolized approximately 5% of the test substance, producing two identified metabolites There were no novel metabolites produced by the human liver S9
Acute Toxicity Studies	
Acute Oral Toxicity (gavage) Sprague Dawley rats PMRA No. 3070023	LD_{50} > 2000 mg/kg bw (♂/♀) No clinical signs of toxicity Low acute toxicity
Acute Dermal Toxicity Sprague Dawley rats PMRA No. 3070025	LD_{50} > 2000 mg/kg bw (♂/♀) No clinical signs of toxicity Low acute toxicity

Study Type / Animal / PMRA #	Study Results
Acute Inhalation Toxicity Han Wistar rats PMRA No. 3070026	LC_{50} > 5.06 mg/L (♂/♀) Clinical signs at 5.06 mg/L included hunched posture, piloerection, wet fur, and decreased respiratory rate at one hour post-dosing Low acute toxicity
Eye Irritation New Zealand White rabbits PMRA No. 3070027	MAS = 0/110, MIS = 3/110 at 1 hour Minimally irritating
Dermal Irritation New Zealand White rabbits PMRA No. 3070028	MAS = 0/8, MIS = 0/8 Non-irritating
Skin Sensitization, Local Lymph Node Assay CBA/J mice PMRA No. 3070029	Negative
Short-Term Toxicity Studies	
90-Day Oral Toxicity (diet) CD-1 mice PMRA No. 3070031	NOAEL = 164/185 mg/kg bw/day (♂/♀) LOAEL = 443/607 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw, ↓ bwg, ↓ fc, ↑ liver wt, ↑ dark livers, ↑ liver single cell necrosis, ↑ bile duct hyperplasia, ↑ hepatocellular hypertrophy, ↑ pale teeth, ↑ ALP, ↑ ALT, ↑ AST (♂/♀); ↑ pale areas of liver, ↑ mitotic figures in liver, ↑ triglycerides (♂); ↑ A:G ratio, ↑ dysplasia of the ameloblast of the teeth, ↑ A:G ratio (♀)
28-Day Oral Toxicity (gavage) Wistar rats PMRA No. 3070037	NOAEL = 50 mg/kg bw/day (♂/♀) LOAEL = 250 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ epithelial hyperplasia and epithelial regeneration of the colon, ↑ dark urine, ↑ black contents in GI tract (♂/♀)
90-Day Oral Toxicity (diet) Han Wistar rats PMRA No. 3070030	Supplemental – dose range-finding NOAEL and LOAEL not established Effects at 175/199 mg/kg bw/day (♂/♀): ↑ liver wt, ↑ centrilobular hepatocellular hypertrophy, ↑ thyroid follicular cell hypertrophy, ↑ pale coloured teeth, ↑ dark feces, ↑ dark urine, ↑ dark contents of GI tract (♂/♀);

Study Type / Animal / PMRA #	Study Results
	↑ globules in the sternum, ↑ phosphorus (♂); ↓ bwg transiently (♀) Effects at 361/394 mg/kg bw/day (♂/♀): ↓ bw, ↓ bwg, ↓ hematocrit, ↓ hemoglobin, ↓ erythrocytes, ↑ reticulocytes, ↑ globules in the bone of the femur, ↑ ameloblast dysplasia, dentin/enamel globules, and basophilic pigment in the teeth, ↑ epithelial hyperplasia and mucosal cell inflammatory infiltrates in the colon (♂/♀); ↑ broken incisors, ↑ rel spleen wt, ↑ rel thyroid/parathyroid wt (♂); ↑ dark kidneys and/or livers, ↑ globules in the sternum, ↑ cholesterol (♀) Effects at 790/1098 mg/kg bw/day (♂/♀): ↑ rel brain wt, ↑ constriction or elongation of cecum, ↑ pale bone, ↑ tubular degeneration, dilatation, interstitial fibrosis, and granular casts in the kidneys ↓ ALT (♂/♀); ↑ rel kidney wt, ↑ broken teeth, ↑ basophilic pigment in the bone of the femur, ↑ cholesterol, ↑ GGT (♂); ↑ spleen wt, ↑ broken incisors, ↑ phosphorus, ↑ urine volume, ↓ specific gravity, ↑ urine protein (♀)
90-Day Oral Toxicity (diet) Wistar rats PMRA No. 3070035	NOAEL = 27/34 mg/kg bw/day (♂/♀) LOAEL = 137/171 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ liver wt, ↑ hepatocellular hypertrophy and deposition of basophilic substances in the femur, ↓ butyrylcholinesterase activity, blackish feces, black contents of the GI tract (♂/♀); ↑ APTT, ↑ platelets, ↑ calcium (♂) No treatment-related FOB findings
28-Day Dermal Toxicity Sprague Dawley rats PMRA No. 3070039	NOAEL = 1000 mg/kg bw/day (♂/♀) No adverse effects observed up to 1000 mg/kg bw/day
28-Day Oral Toxicity (capsule) Beagle dogs PMRA No. 3070034	Supplemental – dose range-finding NOAEL and LOAEL not established Effects at 100 mg/kg bw/day: ↑ vomiting Effects at 500 reduced to 250 mg/kg bw/day: MTD exceeded, bw loss and extreme ↓ fc
90-Day Oral Toxicity (capsule) Beagle dogs PMRA No. 3070032	NOAEL = 20/180 mg/kg bw/day (♂/♀) LOAEL = 60 mg/kg bw/day/not established (♂/♀) Effects at the LOAEL: ↓ bw, ↓ bwg (♂)
1-Year Oral Toxicity (diet)	NOAEL = 180/60 mg/kg bw/day (♂/♀) LOAEL = not established/360 mg/kg bw/day (♂/♀)

Study Type / Animal / PMRA #	Study Results
Beagle dogs PMRA No. 3070033	Effects at the LOAEL: ↓ bw, ↓ bwg (♀)
Chronic Toxicity/Carcinogenicity Studies	
18-Month Carcinogenicity (diet) CD-1 mice PMRA No. 3070042	NOAEL = 106/30 mg/kg bw/day (♂/♀) LOAEL = not established/117 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ pale teeth (non-adverse), ↑ bone globules (non-adverse) (♂/♀); broken teeth (♀) No evidence of tumourigenicity
2-Year Chronic Toxicity/Carcinogenicity (diet) Han Wistar rats PMRA No. 3070043	NOAEL = 28/40 mg/kg bw/day (♂/♀) LOAEL = 142/201 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw, ↓ bwg, ↑ pale teeth (non-adverse), ↑ bone globules (non-adverse) (♂/♀) No evidence of tumourigenicity
Developmental/Reproductive Toxicity Studies	
1-Generation Reproductive Toxicity (diet) Sprague Dawley rats PMRA No. 3070045	Supplemental – dose range-finding NOAEL and LOAEL not established Parental Effects at 601/730 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc, ↓ erythrocytes, ↓ hemoglobin, ↓ hematocrit, ↑ MCV, ↑ reticulocytes (♂/♀); ↑ spleen wt, ↑ dark and/or large spleen, ↑ hyperplasia of colon mucosa, ↓ MCHC, ↑ red cell distribution width, ↑ MCH (♂); ↑ missing or broken incisors, ↑ ungroomed coat, ↑ mild dehydration, ↑ segmented neutrophils (♀) Reproductive No treatment-related reproductive effects Offspring Effects at 730 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc, ↑ mild dehydration, ↑ spleen wt, ↑ altered hematological parameters (♂/♀); ↑ dark and/or large spleen (♂)
2-Generation Reproductive Toxicity (diet) Sprague Dawley rats PMRA No. 3070044	Parental NOAEL = 58/76 mg/kg bw/day (♂/♀) Parental LOAEL = 237/314 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw (F0 and F1), ↓ fc (F0 ♂; F0 and F1 ♀), hyperplasia of colon mucosa (F0 and F1), incisor dysplasia (F0 and F1) (♂/♀); mild anemia (F1) (♀) Reproductive NOAEL = 237/314 mg/kg bw/day (♂/♀) Reproductive LOAEL not established

Study Type / Animal / PMRA #	Study Results
	No treatment-related reproductive effects Offspring NOAEL = 76 mg/kg bw/day Offspring LOAEL = 314 mg/kg bw/day Effects at the LOAEL: ↓ bw PND 4-21 (F1 and F2) No evidence of sensitivity of the young
Developmental Toxicity (gavage) Sprague-Dawley rats PMRA No. 3070049	Supplemental – range-finding NOAEL and LOAEL not established Maternal effects at 1000 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc No adverse developmental effects observed up to 1000 mg/kg bw/day; fetuses were not examined for visceral or skeletal effects in this range-finding study
Developmental Toxicity (gavage) Sprague Dawley rats PMRA No. 3070048	Maternal NOAEL = 1000 mg/kg bw/day Maternal LOAEL not established No adverse maternal effects observed Developmental NOAEL = 1000 mg/kg bw/day Developmental LOAEL not established No adverse developmental effects observed No evidence of sensitivity of the young No treatment-related malformations
Developmental Toxicity (gavage) New Zealand White rabbits PMRA No. 3070051	Supplemental – range-finding NOAEL and LOAEL not established Maternal Effects at 50 mg/kg bw/day: ↓ bwg Effects at 100 mg/kg bw/day: ↓ fc Developmental Effects at 100 mg/kg bw/day: ↓ fetal wt, but ↑ fetuses/dam
Developmental Toxicity (gavage) New Zealand White rabbits	Maternal NOAEL = 150 mg/kg bw/day Maternal LOAEL = 300 mg/kg bw/day Effects at the LOAEL: ↓ bwg and fc Developmental NOAEL = 300 mg/kg bw/day

Study Type / Animal / PMRA #	Study Results
PMRA No. 3070050	Developmental LOAEL not established No adverse developmental effects observed No evidence of sensitivity of the young No treatment-related malformations
Genotoxicity Studies	
Bacterial reverse mutation assay S typhimurium strains TA1535, TA1537, TA98 and TA100, and E coli strain WP2uvrA PMRA No. 3070053	Negative ± metabolic activation Tested up to a limit concentration
Chromosome aberration assay Human lymphocytes in vitro PMRA No. 3070058	Negative ± metabolic activation Tested up to a cytotoxic concentration
Micronucleus assay CD-1 mice in vivo, bone marrow PMRA No. 3070055	Negative Tested up to a limit dose
Forward gene mutation assay in mammalian cells Mouse lymphoma L5178Y cells in vitro PMRA No. 3070057	Negative ± metabolic activation Tested up to a cytotoxic concentration
Comet assay CD-1 mice in vivo, sections of colon, duodenum, and liver PMRA No. 3070060	Negative No mortality or clinical signs of toxicity Tested up to a limit dose

Study Type / Animal / PMRA #	Study Results
Comet assay Sprague Dawley in vivo, sections of cecum, colon, duodenum, and liver PMRA No. 3070061	Negative No mortality or clinical signs of toxicity Tested up to a limit dose
Neurotoxicity Studies	
Acute Neurotoxicity (gavage) Sprague Dawley rats PMRA No. 3070046	NOAEL = 125 mg/kg bw (♂/♀) LOAEL = 500 mg/kg bw (♂/♀) Effects at the LOAEL: ↓ body temperature and ↓ motor activity on the day of dosing No evidence of selective neurotoxicity
Mechanistic Studies	
Tooth enamel hypoplasia mechanism of action study (diet) Wistar rats (♀) Groups were 3, 7, or 14 days PMRA No. 3070041	Supplemental - non-guideline NOAEL and LOAEL not established 3 days of treatment (16000 ppm, equivalent to 1311 mg/kg bw/day) No treatment-related effects on teeth 7 days of treatment (16000 ppm, equivalent to 1967 mg/kg bw/day) Minimal enamel hypoplasia in maxillary incisors 14 days of treatment (16000 ppm, equivalent to 1365 mg/kg bw/day) Mild enamel hypoplasia in maxillary and submaxillary incisors
Liver Enzyme Induction Dietary, 14 days Han Wistar rats (♂) PMRA No. 3070068	Supplemental - non-guideline NOAEL and LOAEL not established Effects at 244 mg/kg bw/day: ↓ bwg, ↑ soft stools, ↑ black feces, ↑ black contents of GI tract, ↑ dilated cecum, ↑ hepatocellular hypertrophy, ↑ thyroid follicular cell hypertrophy, ↑ CYP2B6, ↑ CYP3A1, ↑ UGT1A6, ↑ mRNA expression of *Cyp2b15*, *Cyp2e1*, *Cyp3a1*, and *Ugt1a6*, ↑ PROD, ↑ UDP-GT Effects at 729 mg/kg bw/day: ↓ bw, ↓ fc, ↑ large mesenteric lymph nodes, ↑ liver wt, ↑ TSH, ↓ T4, ↑ CYP2E1, ↑ mRNA expression of *Cyp1a1*, *Ugt1a1, and Ugt1a7*, ↑ EROD and *p*-NPH

Study Type / Animal / PMRA #	Study Results
Manufacturing Impurity	
Acute Oral Toxicity (gavage) Sprague Dawley rats PMRA No. 3070024	LD_{50} > 2000 mg/kg bw (♀) Brown urine and blackish feces were observed at 2000 mg/kg bw Low toxicity
Bacterial reverse mutation assay S typhimurium strains TA1535, TA1537, TA98 and TA100, and E coli strain WP2uvrA PMRA No. 3070054	Negative ± metabolic activation Tested up to a limit concentration
QP-1-1 Soil Metabolite	
Acute Oral Toxicity (gavage) Sprague Dawley rats PMRA No. 3070022	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity Low toxicity
QP-2 Phototransformation Product	
Acute Oral Toxicity (gavage) Sprague Dawley rats PMRA No. 3070021	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity Low toxicity
28-Day Oral Toxicity (gavage) Wistar rats PMRA No. 3070036	NOAEL = 50/250 mg/kg bw/day (♂/♀) LOAEL = 250/900 mg/kg bw/day (♂/♀) Effects at 250 mg/kg bw/day: ↓ bw, bwg, fc (♂) Effects at 900 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc, ↑ liver wt, hepatocellular hypertrophy, ↑ GGT, ↑ deposition of basophilic substance in the femur (♂/♀); ↑ ALP, ↑ platelets, ↑ APTT (♂); ↓ ALT, AST, ↑ calcium (♀) No treatment-related FOB findings
Bacterial reverse mutation assay S typhimurium strains TA1535, TA1537, TA98	Negative ± metabolic activation Tested up to a limit concentration

Study Type / Animal / PMRA #	Study Results
and TA100, and E coli strain WP2uvrA PMRA No. 3070052	
Forward gene mutation assay in mammalian cells Mouse lymphoma L5178Y cells in vitro PMRA No. 3070056	Negative ± metabolic activation Tested up to a cytotoxic concentration
Chromosome aberration assay Human lymphocytes in vitro PMRA No. 3070059	Negative ± metabolic activation Tested up to a cytotoxic concentration

Table 4 Toxicity profile of Kinoprol 20 SC

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons.

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity (gavage) Sprague Dawley rats PMRA No. 3073031	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity Low acute toxicity
Acute Dermal Toxicity Sprague Dawley rats PMRA No. 3073032	LD_{50} > 2000 mg/kg bw (♂/♀) No clinical signs of toxicity Low acute toxicity
Acute Inhalation Toxicity Sprague Dawley rats PMRA No. 3073033	LC_{50} > 1.6 mg/L (♂/♀) No clinical signs of toxicity Slight acute toxicity

Study Type/Animal/PMRA #	Study Results
Eye Irritation New Zealand White rabbits PMRA No. 3073034	MAS = 0/110, MIS = 0/110 Non-irritating
Dermal Irritation New Zealand White rabbits PMRA No. 3073035	MAS = 0/8, MIS = 0/8 Non-irritating
Skin Sensitization, Buehler Method Hartley guinea pigs PMRA No. 3073036	Negative

Table 5 Toxicology reference values for use in health risk assessment for Ipflufenoquin

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Acute oral neurotoxicity study in rats	NOAEL = 125 mg/kg bw Based on decreased motor activity and decreased body temperature	100
ARfD = 1.3 mg/kg bw			
Repeated (chronic) dietary	2-year dietary chronic toxicity/carcinogenicity study in rats	NOAEL = 28 mg/kg bw/day Based on decreased bw and bwg	100
ADI = 0.3 mg/kg bw/day			
Short and intermediate-term dermal	28-day dermal toxicity study in rats	NOAEL = 1000 mg/kg bw/day No adverse effects up to the highest dose tested	100
Short and intermediate-term inhalation[2]	2-generation dietary reproductive toxicity study in rats	Parental NOAEL = 58 mg/kg bw/day Based on decreased bw and bwg, and increased incidence of hyperplasia of colon mucosa and mild anemia	100
Short-term Aggregate	Pick your own residential exposure is possible, however aggregation for residential exposure is not required as no effects were observed in the 28-day dermal toxicity study.		
Cancer	No treatment-related tumours were observed; therefore, a cancer risk assessment is not required		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary

assessments; MOE refers to a target MOE for occupational and residential assessments.
[1] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 6 AHETF/PHED unit exposure estimates for mixer/loaders and applicators handling Kinoprol 20 SC (µg/kg a.i. handled)

Exposure Scenario and PPE		Dermal[1]	Inhalation[2]
PPE for all scenarios: Single layer and chemical-resistant gloves			
Mixer/loader AHETF estimates			
A	Open Mix/Load Liquid	58.5	0.63
Applicator AHETF estimates			
B	Open cab airblast application - without CR hat	3769.3	9.08
Mixer/loader + applicator AHETF/PHED estimates			
A+B	Open Mix/Load Liquids & Open Cab Airblast Application – Without CR Hat (AHETF)	3827.8	9.71
C	Open Mix/Load Liquid, Low Pressure Handwand (for manually-pressurized handwand) (PHED)	943.4	45.2
D	Open Mix/Load Liquid Backpack (PHED)	5445.9	62.1
E	Open Mix/Load Liquid, High Pressure Handwand (for mechanically-pressurized handheld sprayers) (PHED)	5585.5	151

[1] No adjustment since the dermal reference value is based on a dermal study.
[2] Light inhalation rate (except for backpack= moderate inhalation rate)

Table 7 Mixer/Loader/Applicator risk assessment for workers handing Kinoprol 20 SC

Exposure Scenario	Unit Exposure (µg/kg a.i. handled)[1]		ATPD (ha/day)[2]	Rate (kg a.i./ha)	Daily Exposure (mg/kg bw/day)[3]		MOE[4]	
	Dermal	Inhalation			Dermal	Inhalation	Dermal	Inhalation
PPE for all scenarios: Single layer and chemical-resistant gloves								
Open Mix/Load Liquids & Open Cab Airblast Application –	3827.8	9.71	20	0.044	0.042	1.1×10^{-4}	2.4×10^{4}	5.4×10^{5}

Exposure Scenario	Unit Exposure (µg/kg a.i. handled)[1]		ATPD (ha/day)[2]	Rate (kg a.i./ha)	Daily Exposure (mg/kg bw/day)[3]		MOE[4]	
	Dermal	Inhalation			Dermal	Inhalation	Dermal	Inhalation
Without CR Hat								
Open Mix/Load Liquid (AHETF), Low Pressure Handwand (for manually-pressurized handwand) (PHED)	943.4	45.2	0.802	0.044	4.2×10^{-4}	2.0×10^{-6}	2.4×10^{6}	2.9×10^{6}
Open Mix/Load Liquid (AHETF) Backpack (PHED)	5445.9	62.1	0.802	0.044	2.4×10^{-3}	2.7×10^{-5}	4.2×10^{5}	2.1×10^{6}
Open Mix/Load Liquid (AHETF), High Pressure Handwand (for mechanically pressurized handheld sprayers) (PHED)	5585.5	151	20.3	0.044	0.062	1.7×10^{-3}	1.6×10^{3}	3.4×10^{4}

ATPD = Area treated per day; MOE = Margin of exposure

[1] Unit exposure based on AHETF/PHED

[2] Area Treated per Day table (2017-09-20), ATPDs for handheld equipment were calculated using the formula ATPD (ha/day) = Litres applied per day (3800 L/day for mechanically-pressurized handheld sprayers and 150 L/day for manually-pressurized handwand and backpack sprayer) ÷ Labelled spray volume (187 L/ha)

[3] Exposure = (Unit exposure × ATPD × Rate) / (80 kg bw × 1000 µg/mg)

[4] Based on dermal NOAEL = 1000 mg/kg bw/day; inhalation NOAEL = 58 mg/kg bw/day; and target MOE = 100 for all exposure scenarios.

Table 8 Postapplication worker exposure and risk estimate for Ipflufenoquin on day 0 after the last application to apples and pears

Postapplication Activity	Peak DFR (µg/cm^2)[1]	Transfer Coefficient (TC) (cm^2/hr)[2]	Dermal Exposure (mg/kg bw/day)[3]	MOE[4]	REI[5]
Thinning fruit (hand)	0.1878	3000	0.0563	1.8×10^4	12 hrs
Harvesting (hand)	0.1878	1400	0.0263	3.8×10^4	12 hrs
Scouting, pruning (hand)	0.1878	580	0.0109	9.2×10^4	12 hrs
Transplanting	0.1878	230	0.0043	2.3×10^5	12 hrs
Orchard maintenance, weeding (hand), propping	0.1878	100	0.0019	5.3×10^5	12 hrs

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 10% dissipation per day (outdoor scenario)
[2] Transfer coefficients obtained from PMRA Agricultural TCs Table (last updated on 02-24-2021)
[3] Exposure = (Peak DFR [µg/cm^2] × TC [cm^2/hr] × 8 hours) / (80 kg bw × 1000 µg/mg)
[4] Based on a NOAEL of 1000 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 9 Postapplication dermal exposure and risk estimates to residents on Day 0 from orchard trees treated commercially with Ipflufenoquin

Crop (Max Rate; # App; RTI)	Life Stage	Peak DFR (µg/cm^2)[1]	TC (cm^2/hr)[2]	Exposure Duration (hr/day)	Dermal Exposure (mg/kg bw/day)[3]	Dermal MOE[4]	Re-entry Interval
Pome fruit (44 g a.i./ha; 3/season; 7-day RTI)	Adults (16+ yrs)	0.188	1700	1	3.99×10^{-3}	2.5×10^5	Until sprays have dried
	Children (6 < 11 yrs)		930	0.5	2.73×10^{-3}	3.7×10^5	Until sprays have dried

DFR = Dislodgeable foliar residue; TC = Transfer Coefficient; MOE = Margin of Exposure; REI = Restricted-entry interval
[1] Calculated using the standard value of 25% of the application rate on Day 0 after the last application and 10% dissipation per day. The DFR value was calculated based on 3 applications of the highest rate of all fruit trees and an RTI of 7 days.
[2] A single TC is representative of all activities in residential fruit trees. TCs were obtained from the PMRA memo entitled "Review of U.S. EPA Residential SOPs (2012) Section 4: Gardens and Trees" (Sept. 6, 2019) and the 2012 U.S. EPA SOP for Residential Pesticide Exposure Assessment.
[3] Dermal Exposure = (Peak DFR [µg/cm^2] × TC [cm^2/hr] × Exposure duration [hours/day]) / (Body weight [80 kg for adults; 32 kg for children] × 1000 µg/mg)
[4] Based on a NOAEL of 1000 mg/kg bw/day; Target MOE of 100

Table 10 Integrated food residue chemistry summary

NATURE OF THE RESIDUE IN GRAPES			**PMRA # 3070080**
Radiolabel Position	[^{14}C-A Ring]-ipflufenoquin (specific activity: 150,000,000 dpm/mg) [^{14}C-C Ring]-ipflufenoquin (specific activity: 150,000,000 dpm/mg)		
Treatment			
Test Site	Test plots located outside in enclosures.		
Treatment	Two applications performed at the beginning of grape bunch closure and 21 days later at the beginning of ripening.		
Total Rate	[^{14}C-A Ring]-ipflufenoquin: 2 x 120 g a.i./ha; Total of 240 g a.i./ha [^{14}C-C Ring]-ipflufenoquin: 2 x 120 g a.i./ha; Total of 240 g a.i./ha		
Formulation	Suspension concentrate (SC) (guarantee: 20%)		
Harvest	Leaves and fruit harvested at three stages: (1) just before the second application at BBCH 81, (2) 14 days after the second application at BBCH 85 (14-day PHI), and (3) at maturity 28 days after the second application at BBCH 89 (28-day PHI). Leaves were not further analyzed.		
Extraction solvents	Rinses: fruits were rinsed 2x with acetonitrile Homogenized samples: 2 x acetonitrile and water (1/1, v/v) and 1 x acetonitrile PES: Sequential extractions with weak base (0.1M KOH) followed by a strong base (24% KOH)		
Matrices	**PHI (days)**	**^{14}C-A Ring TRR (ppm)**	**^{14}C-C Ring TRR (ppm)**
Rinse	21 days after 1st of 2 applications	0.010	0.007
Rinsed immature grapes		0.021	0.018
Rinse	14	0.015	0.020
Rinsed immature grapes		0.032	0.019
Rinse	28	0.013	0.007
Rinsed mature grapes		0.045	0.029
NATURE OF THE RESIDUE IN APPLES			**PMRA # 3070081**
Radiolabel Position	[^{14}C-A Ring]-ipflufenoquin (specific activity: 151,000,000 dpm/mg) [^{14}C-C Ring]-ipflufenoquin (specific activity: 150,000,000 dpm/mg)		

Treatment			
Test Site	Trees grown outside in contained areas.		
Treatment	Three applications performed after most flowers with petals forming a hollow ball were present (BBCH 59), 10 days after the first application (BBCH 65), and when fruit diameter was approximately 40 mm (BBCH 74).		
Total Rate	[^{14}C-A Ring]-ipflufenoquin: 3 x 45 g a.i./ha; Total of 135 g a.i./ha [^{14}C-C Ring]-ipflufenoquin: 3 x 45 g a.i./ha; Total of 135 g a.i./ha		
Formulation	Suspension concentrate (SC) (guarantee: 20%)		
Harvest	Apple leaves and fruit were harvested at BBCH 75 (7-day PHI) and BBCH 89 (81-day PHI). Leaves were not further analyzed.		
Extraction solvents	Rinses: Apples were rinsed by submersion in acetonitrile twice. Homogenized samples: 2 x acetonitrile/water (1:1, v/v) and 1 x acetonitrile PES: Sequential extraction with a weak base (0.1M KOH) followed by a strong base (24% KOH).		
Matrices	**PHI (days)**	**^{14}C-A Ring TRR (ppm)**	**^{14}C-C Ring TRR (ppm)**
Rinse	7	0.016	0.012
Rinsed immature apples		0.035	0.033
Rinse	81	<0.001	<0.001
Rinsed mature apples		0.007	0.002
NATURE OF THE RESIDUE IN ALMONDS			**PMRA #3070082**
Radiolabel Position	[^{14}C-A Ring]-ipflufenoquin (Specific activity: 139,000,000 dpm/mg) [^{14}C-C Ring]-ipflufenoquin (Specific activity: 133,000,000 dpm/mg)		
Treatment			
Test Site	Test plots located outside in enclosures.		
Treatment	Three applications performed at full flowering (BBCH 65); 35 days after petal fall (BBCH 77); and 50 percent hull split (BBCH 85).		
Total Rate	[^{14}C-A Ring]-ipflufenoquin: 3 x 75 g a.i./ha; Total of 225 g a.i./ha [^{14}C-C Ring]-ipflufenoquin: 3 x 75 g a.i./ha; Total of 225 g a.i./ha 3 x 375 g a.i./ha; Total of 1125 g a.i./ha		
Formulation	Suspension concentrate (SC) (guarantee: 20%)		

Harvest	Leaves and nuts harvested at three stages: (1) 1-2 days prior to the 3rd application at BBCH 85 (96 and 104 days after the 2nd application), (2) at BBCH 87 (14-day PHI), and (3) at maturity BBCH 89 (28-day PHI). Immature almond hulls and leaves were not analyzed.
Extraction solvents	Rinses: Nuts and hulls rinsed by submersion in acetonitrile twice. Homogenized samples: 2 x acetonitrile/water (1:1, v/v) and 1 x acetonitrile PES: Sequential extractions with weak base (0.1M KOH) followed by a strong base (24% KOH). Some PES residues after extraction with base had residues >10% TRR unextracted which were further extracted with 6M HCl.

Matrices	**PHI (days)**	**^{14}C-A Ring (225 g a.i./ha)**	**^{14}C-C Ring (225 g a.i./ha)**	**^{14}C-C Ring (1125 g a.i./ha)**
		TRR (ppm)	**TRR (ppm)**	**TRR (ppm)**
Rinse	96 / 104 days after the 2nd of 3 applications[1]	0.001	0.001	0.019
Rinsed immature almond fruit		0.025	0.012	0.070
Rinse	14	0.015	0.030	0.185
Rinsed immature almond fruit		0.118	0.071	0.236
Rinse	28	0.060	0.070	0.286
Rinsed mature almond hull		0.219	0.209	1.023
Mature almond nutmeat	28	0.002	0.001	0.008

[1]Samples taken 96 days (C Ring (1X)) or 104 days (A Ring (1X); C Ring (5X)) after the 2nd of 3 applications.

NATURE OF THE RESIDUE IN CUCUMBER	**PMRA # 3070090**
Radiolabel Position	[^{14}C-A Ring]-ipflufenoquin (specific activity: 136,000,000 dpm/mg)
Treatment	
Test Site	Test plants grown in pots in greenhouses.
Treatment	Applications were performed at the flowering stage (one application at BBCH 61-69) and at the fruit development stage (two applications at BBCH 71, at a 7-day retreatment interval). Two treatment scenarios were used: normal and partially covered applications to assess translocation.
Total Rate	[^{14}C-A Ring]-ipflufenoquin: 3 x 200 g a.i./ha; Total of 600 g a.i./ha
Formulation	Suspension concentrate (SC) (guarantee: 20%)
Harvest	Fruit, leaf, and stem collected from the plants from the normal application plot at PHIs of 0, 7, 14, and 28 days. Treated and non-treated fruits, treated and non-treated leaves, and stem were collected from the plant from the partial application plot at PHIs of 0, 14, 19, and 28 days.
Extraction solvents	Rinses: Surface washed with methanol. Homogenized samples: 80% methanol aqueous solution PES: None

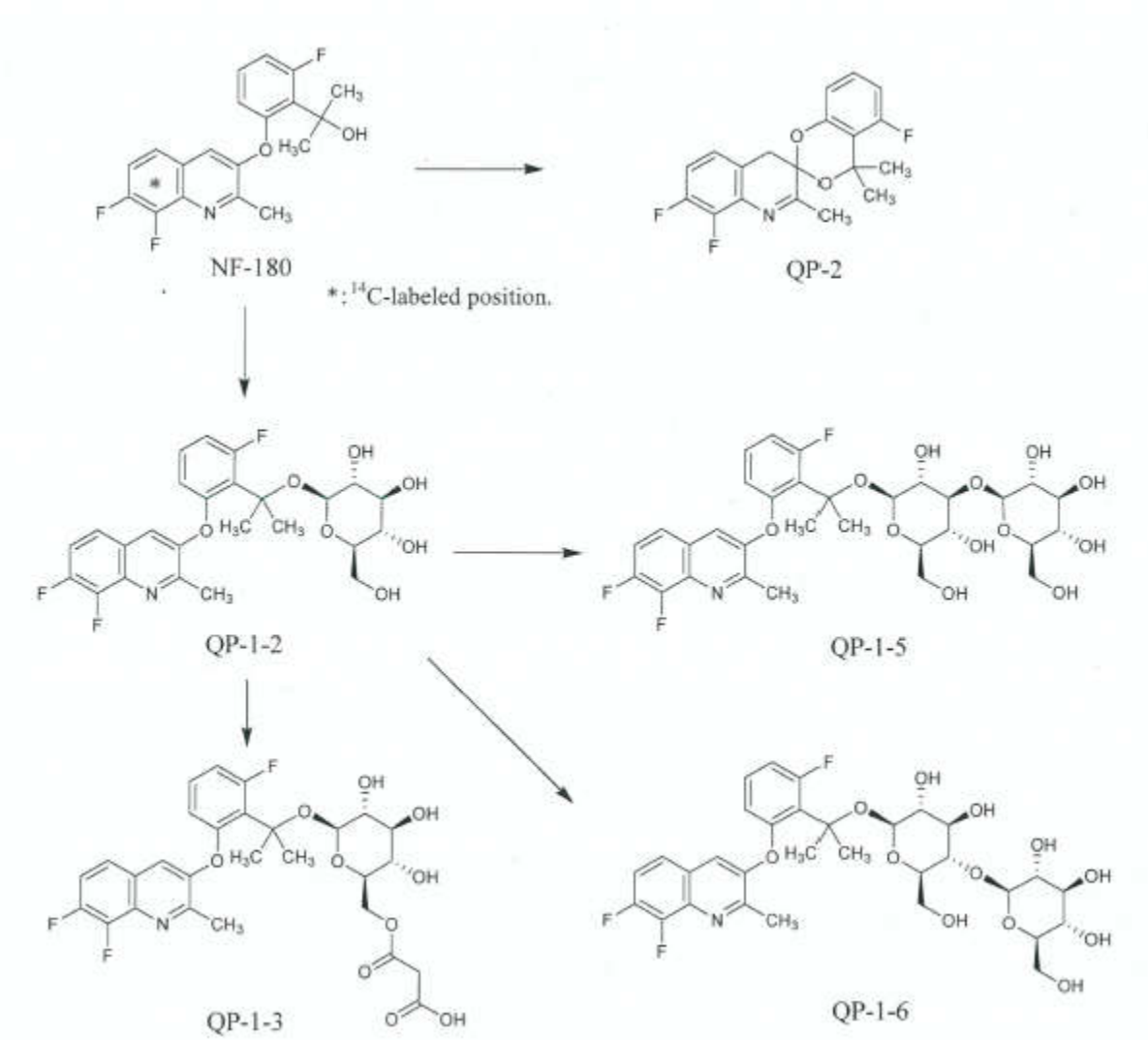
Matrices	PHI (days)	^{14}C-A Ring TRR (ppm)
Normal Application		
Fruit		
Surface wash	0	**0.078**
Extract		0.022
PES		0.002
Rinsed fruit		**0.023**
Surface wash	7	**0.002**
Extract		0.013
PES		0.001
Rinsed fruit		**0.014**
Surface wash	14	**0.001**
Extract		0.012
PES		0.001
Rinsed fruit		**0.014**
Surface wash	28	**0.000**
Extract		0.006
PES		0.000
Rinsed fruit		**0.006**
Leaf		
Surface wash	0	**9.161**
Extract		3.478
PES		0.111
Rinsed leaf		**3.589**
Surface wash	7	**3.142**
Extract		2.297
PES		0.093
Rinsed leaf		**2.390**
Surface wash	14	**8.797**
Extract		5.613
PES		0.357
Rinsed leaf		**5.970**
Surface wash	28	**2.278**
Extract		4.493
PES		0.300
Rinsed leaf		**4.793**
Stem		
Surface wash	28	**-**
Extract		0.450
PES		0.021
Rinsed stem		**0.471**
Partial Application		
Non-Treated Fruit		

Surface wash	0	0.000
Rinsed fruit		0.002
Surface wash	19	0.000
Rinsed fruit		0.001
Surface wash	28	0.000
Rinsed fruit		0.001
Non-Treated Leaf		
Surface wash	0	**0.004**
Extract		0.037
PES		0.002
Rinsed leaf		**0.039**
Surface wash	14	**0.003**
Extract		0.054
PES		0.005
Rinsed leaf		**0.059**
Surface wash	28	**0.003**
Extract		0.065
PES		0.006
Rinsed leaf		**0.071**
Treated Fruit		
Surface wash	0	0.002
Rinsed fruit		0.005
Surface wash	28	0.000
Rinsed fruit		0.004
Treated Leaf		
Surface wash	0	**2.701**
Extract		1.253
PES		0.036
Rinsed leaf		**1.289**
Surface wash	14	**4.385**
Extract		3.908
PES		0.296
Rinsed leaf		**4.204**
Surface wash	28	**1.561**
Extract		2.751
PES		0.140
Rinsed leaf		**2.891**
Stem		
Surface wash	28	**-**
Extract		0.065
PES		0.004
Rinsed stem		**0.069**
Summary of Major Identified Metabolites in Plant Matrices		
Radiolabel Position		^{14}C-A Ring and ^{14}C-C Ring Ipflufenoquin

Metabolites Identified	Major Metabolites
Grapes	
Immature Grape (21 days after 1st of 2 applications)	Ipflufenoquin
Immature Grape (14-day PHI)	
Mature Grape (28-day PHI)	
Apples	
Immature Apple (7-day PHI)	Ipflufenoquin
Mature Apple (81-day PHI)	None
Almonds	
Immature almond fruit (96 / 104 days after the 2nd of 3 applications)	225 g a.i./ha: None 1125 g a.i./ha: Ipflufenoquin
Immature almond fruit (14-day PHI)	225 g a.i./ha: Ipflufenoquin 1125 g a.i./ha: Ipflufenoquin, QP-2
Mature almond hull (28-day PHI)	225 g a.i./ha: Ipflufenoquin 1125 g a.i./ha: Ipflufenoquin
Mature almond nutmeat (28-day PHI)	225 g a.i./ha: Not analyzed 1125 g a.i./ha: None
Cucumber (Normal application)	
Cucumber Fruit	
0-day PHI	Ipflufenoquin
7-day PHI	
14-day PHI	
28-day PHI	
Cucumber Leaves	
0-day PHI	Ipflufenoquin
7-day PHI	
14-day PHI	Ipflufenoquin, QP-2
28-day PHI	Ipflufenoquin
Cucumber Stems	
28-day PHI	Ipflufenoquin
Cucumber (Partial application)	
Non-Treated Cucumber Fruit	
0-day PHI	None
19-day PHI	
28-day PHI	
Non-Treated Cucumber Leaves	
0-day PHI	Ipflufenoquin, QP-1-3
14-day PHI	Ipflufenoquin, QP-1-3, QP-1-5
28-day PHI	
Treated Cucumber Fruit	

0-day PHI	Ipflufenoquin
28-day PHI	None
Treated Cucumber Leaves	
0-day PHI	Ipflufenoquin
14-day PHI	Ipflufenoquin, QP-1-3
28-day PHI	Ipflufenoquin, QP-1-3, QP-1-5
Cucumber Stems	
28-day PHI	Ipflufenoquin, QP-1-3

Proposed Metabolic Scheme in Plants



NF-180: Ipflufenoquin
QP-1-2, QP-1-3, QP-1-5, QP-1-6: Glycoconjugates

FREEZER STORAGE STABILITY IN PLANT MATRICES	**PMRA # 3073048**

Tested Matrices	Analyte(s)	Tested Intervals (months)	Temperature (°C)	Category
Apple fruit	Ipflufenoquin	0, 1, 3, 6, and 12 months	≤-10	High-water

CROP FIELD TRIALS & RESIDUE DECLINE ON APPLES AND PEARS **PMRA # 3073038**

Crop field trials were conducted in 2016 in Canada and the United States. Trials were conducted in North American growing regions 1 (5 trials), 2 (1 trial), 5 (7 trials), 9 (1 trial), 10 (1 trial), and 11 (5 trials) for apples and growing regions 1 (1 trial), 5 (3 trials), 10 (2 trials), and 11 (4 trials) for pears for a total of 30 trials. A suspension concentrate containing ipflufenoquin was applied three times as foliar broadcast sprays at a rate of 42.9-47.3 g a.i./ha/application at 21 (17-23), 14 (10-16), and 7 (4-8) days before harvest for a seasonal application rate of 131.5-139.1 g a.i./ha. The applications were made at 5- to 10-day intervals.

Adjuvants were used in/on apples and pears at all field trial sites. The number and geographic distribution of trials were generally in accordance with Health Canada's DIR2010-05. Independence of trials was assessed for apples and pears. At one pair of test sites for apples (Zone 5), trials were determined to be replicates, residues were averaged. Residue decline data show that residues of ipflufenoquin decreased in apples and pears with increasing preharvest intervals (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 a.i./ha)	PHI (days)	Analyte	Residue Levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
Apple fruit	133.0-139.1	6-8 with one trial at 4	Ipflufenoquin	20	<0.01	0.04	<0.02	<0.02	0.01
Pear fruit	131.5-138.6	6-7	Ipflufenoquin	10	<0.01	0.08	<0.03	<0.04	0.02

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

CROP FIELD TRIALS & RESIDUE DECLINE ON ALMONDS **PMRA # 3073039**

Crop field trials were conducted in 2017 in the United States. Trials were conducted in North American growing region 10 (5 trials) for a total of 5 trials. A suspension concentrate containing ipflufenoquin was applied three times as foliar broadcast sprays at a rate of 74.22-76.35 g a.i./ha/application at 28 (27-28), 21 (20-21), and 14 (13-14) days before harvest for a seasonal application rate of 223.12-225.85 g a.i./ha. The applications were made at 6- to 7-day intervals.

Adjuvants were used in/on almonds at all field trial sites. The number and geographic distribution of trials were in accordance with the US requirements, and acceptable for the imported commodity. Independence of trials was assessed for almonds. Residue decline data show that residues of ipflufenoquin decreased in almonds with increasing preharvest intervals (PHIs). Freezer storage stability data were not required since samples were analysed within 30 days. Samples were analyzed using a validated analytical method.

Crop	Total Application Rate (g a.i./ha)	PHI (days)	Analyte	Residue Levels (ppm)					
				n	LAFT	HAFT	Median	Mean	SDEV
Nutmeat	223.12-225.85	13-14	Ipflufenoquin	5	<0.01	<0.01	<0.01	<0.01	0
Hulls				5	0.464	1.055	0.648	0.725	0.262

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

PROCESSED FOOD AND FEED - APPLES **PMRA # 3073049**

The processing study was conducted in France using a suspension concentrate containing ipflufenoquin at 651-706 g a.i./ha (5-fold of maximum single seasonal use rate) in/on pome fruits. Adequate storage stability data are available to support the storage intervals of the processed commodities. Samples were analyzed using a validated analytical method.

RAC	Processed Fractions	$HAFT_{[RAC]}$ (ppm)	Median Processing Factor of Ipflufenoquin	Anticipated Residues of Ipflufenoquin (ppm)
Apples	Canned applesauce	0.04	0.14x	0.006
	Pasteurized apple juice	0.04	0.13x	0.005
	Dried apples	0.04	2.5x	0.10

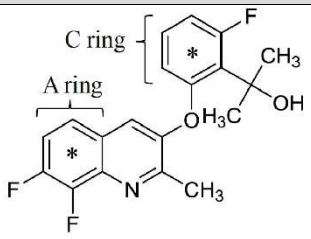
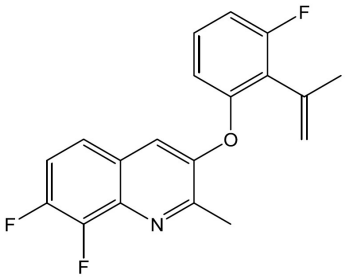
Table 11 Food residue chemistry overview of metabolism studies and risk assessment

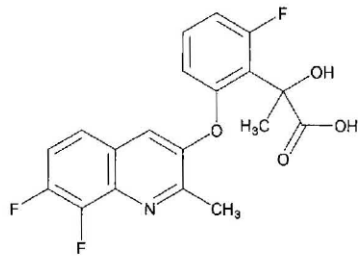
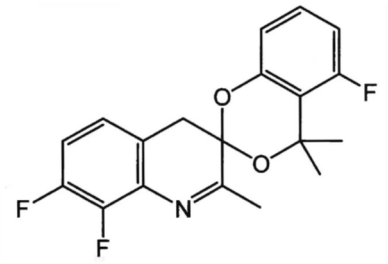
PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT Primary crops	Ipflufenoquin		
RESIDUE DEFINITION FOR RISK ASSESSMENT Primary crops			
METABOLIC PROFILE IN DIVERSE CROPS	Similar in fruit commodities (grapes, apples, almonds, and cucumbers).		
DIETARY RISK FROM FOOD AND DRINKING WATER			
Basic acute dietary exposure analysis, 95th percentile	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Alone	**Food and Drinking Water**
ARfD = 1.3 mg/kg bw	All infants <1 year	0.4	0.4
Estimated acute drinking water concentration = 0.0089 ppm	Children 1–2 years	0.5	0.6
	Children 3–5 years	0.3	0.3
	Children 6–12 years	0.1	0.2

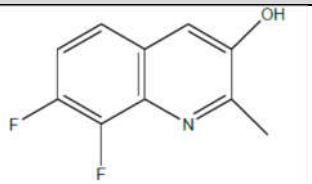
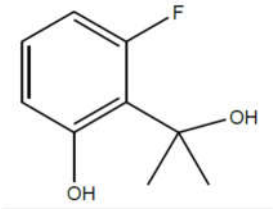
	Youth 13–19 years	0.1	0.1
	Adults 20–49 years	0.0	0.1
	Adults 50+ years	0.0	0.1
	Females 13-49 years	0.0	0.1
	Total population	0.1	0.1
Basic chronic dietary exposure analysis **ADI = 0.3 mg/kg bw/day** **Estimated chronic drinking water concentration = 0.0089 ppm**	**POPULATION**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Drinking Water**
	All infants <1 year	0.4	0.6
	Children 1–2 years	0.6	0.7
	Children 3–5 years	0.3	0.4
	Children 6–12 years	0.1	0.2
	Youth 13–19 years	0	0.1
	Adults 20–49 years	0	0.1
	Adults 50+ years	0	0.1
	Females 13-49 years	0	0.1
	Total population	0.1	0.1

Table 12 Ipflufenoquin and its environmental transformation products identified in laboratory and field dissipation studies

Code and Chemical Name and Chemical structure	Study (PMRA#)		Max %AR (d)	%AR at Study End (study length, days)
	Hydrolysis (3070100)		98.5% AR (5)	98.5 AR (5)
	Soil Phototransformation (3070103)		103.2% (0)	88.9% (32 OECD summer days)
	Aqueous Phototransformation	Deionised water with pH 7 buffer A ring (3070102)	100.0% (0)	10.0% (11.9 OECD summer days)

Code and Chemical Name and Chemical structure	Study (PMRA#)		Max %AR (d)	%AR at Study End (study length, days)
 * Labeled position Ipflufenoquin (Parent) CAS#: 1314008-27-9 CAS name: benzenemethanol, 2-[(7,8-difluoro-2-methyl-3-quinolinyl)oxy]-6-fluoro-a, a-dimethyl- IUPAC Name: 2-[2-(7,8-difluoro-2-methylquinolin-3-yloxy)-6-fluorophenyl]propan-2-ol Common name: Ipflufenoquin Synonyms: NF-180		Deionised water with pH 7 buffer C ring (3070101)	104.7% (0) OECD summer days)	5.7% (13.8 OECD summer days)
	Aerobic soil (3140464)		99.9% (0)	73.9(120)
	Anaerobic soil (3070105)		99.3% (0)	77.4 (122)
	Aerobic aquatic with sediment (3140465)		97.2 (1)	70.1 (100)
	Anaerobic aquatic with sediment (3140466)		99.1 (3)	85.7 (100)
	Terrestrial Field Study (3070114)	Iowa: Idaho: New York:	315.5% (0) 104.8% (7) 166.9% (0)	31.3% (120) 24.9% (450) 32.9% (730)
	Koc: 944.8 (Mean based on 5 soils) Koc Range: 735.2 to 1290)			
Major (> 10%) TRANSFORMATION PRODUCTS				
No Major Transformation products were observed in any of the environmental fate studies submitted during the review of Ipflufenoquin.				
Minor (< 10%) TRANSFORMATION PRODUCTS				
 QP-1-1 CAS#: Not assigned/Unknown CAS or chemical name: 7,8-difluoro-3-(3-fluoro-2-isopropenylphenoxy)-2-methylquinoline	Hydrolysis		Not Measured	Not Measured
	Soil Phototransformation		Not Measured	Not Measured
	Aqueous Phototransformation	Deionised water with pH 7 buffer A ring	Not Measured	Not Measured
		Deionised water with pH 7 buffer C ring	Not Measured	Not Measured
	Aerobic soil		Not Measured	Not Measured
	Anaerobic soil		Not Measured	Not Measured
	Aerobic aquatic without sediment		< LOD	< LOD
	Aerobic aquatic with sediment		Not Measured	Not Measured
	Anaerobic aquatic		Not Measured	Not Measured
	Field studies		< LOQ	< LOQ

Code and Chemical Name and Chemical structure	Study (PMRA#)		Max %AR (d)	%AR at Study End (study length, days)
Common name: Unknown Synonyms: Unknown	Koc: No data.			
 QP-1-7 CAS#: Not assigned/Unknown CAS or chemical name: Not reported nor determined Common name: Unknown Synonyms: Unknown	Hydrolysis		Not Measured	Not Measured
	Soil Phototransformation		Not Measured	Not Measured
	Aqueous Phototransformation	Deionised water with pH 7 buffer A ring	Not Measured	Not Measured
		Deionised water with pH 7 buffer C ring	Not Measured	Not Measured
	Aerobic soil		4.0% (120)	4.0% (120)
	Anaerobic soil		1.0% (122)	1.0% (122)
	Aerobic aquatic without sediment		Not Measured	Not Measured
	Aerobic aquatic with sediment		Not Measured	Not Measured
	Anaerobic aquatic		Not Measured	Not Measured
	Field studies		Not Measured	Not Measured
	Koc: No data.			
 QP-2 CAS#: Not assigned/Unknown CAS or chemical name: Not reported nor determined Common name: Unknown Synonyms: Unknown	Hydrolysis		Not Measured	Not Measured
	Soil Phototransformation		Not Measured	Not Measured
	Aqueous Phototransformation	Deionised water with pH 7 buffer A ring	Not Measured	Not Measured
		Deionised water with pH 7 buffer C ring	Not Measured	Not Measured
	Aerobic soil		Not Measured	Not Measured
	Anaerobic soil		Not Measured	Not Measured
	Aerobic aquatic without sediment		< LOD	< LOD
	Aerobic aquatic with sediment		Not Measured	Not Measured
	Anaerobic aquatic		Not Measured	Not Measured
	Field studies		Not Measured	Not Measured
	Koc: No data			
	Hydrolysis		Not Measured	Not Measured

Code and Chemical Name and Chemical structure	Study (PMRA#)		Max %AR (d)	%AR at Study End (study length, days)
 QN-1 CAS#: 6032-012 CAS or chemical name: 7,8-difluoro-2-methylquinolin-3-ol Common name: Unknown Synonyms: Unknown	Soil Phototransformation		1.2% (32 OECD summer days)	1.2% (32 OECD summer days)
	Aqueous Phototransformation	Deionised water with pH 7 buffer A ring	Not Measured	Not Measured
		Deionised water with pH 7 buffer C ring	Not Measured	Not Measured
	Aerobic soil		Not Measured	Not Measured
	Anaerobic soil		Not Measured	Not Measured
	Aerobic aquatic without sediment		< LOD	< LOD
	Aerobic aquatic with sediment		< LOD	< LOD
	Anaerobic aquatic		Not Measured	Not Measured
	Field studies		Not Measured	Not Measured
	Koc: No data			
 QH-1 CAS#: Not assigned/Unknown CAS or chemical name: 2-(2-fluoro-6-hydroxyphenyl) propan-2-ol Common name: Unknown Synonyms: Unknown	Hydrolysis		Not Measured	Not Measured
	Soil Phototransformation		0.9% (32 OECD summer days)	0.9% (32 OECD summer days)
	Aqueous Phototransformation	Deionised water with pH 7 buffer A ring	Not Measured	Not Measured
		Deionised water with pH 7 buffer C ring	8.7% (4.1 OECD summer days)	5.2% (13.8 OECD summer days)
	Aerobic soil		Not Measured	Not Measured
	Anaerobic soil		Not Measured	Not Measured
	Aerobic aquatic without sediment		Not Measured	Not Measured
	Aerobic aquatic with sediment		Not Measured	Not Measured
	Anaerobic aquatic		Not Measured	Not Measured
	Field studies		Not Measured	Not Measured
	Koc			
	Hydrolysis		Not Measured	Not Measured
	Soil Phototransformation		0.4% (32 OECD summer days)	0.4% (32 OECD summer days)
	Aqueous Phototransformation	Deionised water with pH 7 buffer A ring	Not Measured	Not Measured

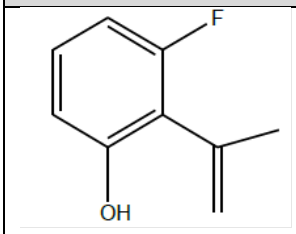
Code and Chemical Name and Chemical structure	Study (PMRA#)		Max %AR (d)	%AR at Study End (study length, days)
 QH-2 CAS#: 1375066-38-8 CAS or chemical name: 3-fluoro-2-(prop-1-en-2-yl)phenol Common name: Unknown Synonyms: Unknown		Deionised water with pH 7 buffer C ring	8.9% (4.1 OECD summer days)	2.6% (13.8 OECD summer days)
	Aerobic soil		Not Measured	Not Measured
	Anaerobic soil		Not Measured	Not Measured
	Aerobic aquatic without sediment		Not Measured	Not Measured
	Aerobic aquatic with sediment		Not Measured	Not Measured
	Anaerobic aquatic		Not Measured	Not Measured
	Field studies		Not Measured	Not Measured
	Koc			

Table 13 Summary of fate and behaviour of ipflufenoquin in the environment

Study type	Test material	DT_{50}/$t_{1/2\text{-}rep}$ (days)	Transformation products (Maximum % AR[1])	Comments/ classification	PMRA #
Abiotic transformation					
Hydrolysis	Ipflufenoquin	Half-life: Stable at pH 4, 7 and 9 Model: No model used	Major: None Minor: Unknowns (0.1%)	Stable to hydrolysis	3070100
Phototransformation on Soil	Ipflufenoquin [A ring-^{14}C] and [C ring-^{14}C]	Half-life: 219 days/219 days Model: SFO[2]	Major: None Minor: QN-1 (1.2%) QH-1 (0.9%) QH-2 (0.4%)	Not expected to be a route of dissipation in terrestrial environment	3070103
Phototransformation in Water with (pH 7 buffer)	Ipflufenoquin [C ring-^{14}C]	Half-life: 4.1 (mean of radio-labels) Model: SFO	Major: None Minor: QH-1 (8.7%) QH-2 (8.9%) CO_2 (8.8%) Unknowns (7.4%)	May be a route of dissipation in photic zone	3070101

Study type	Test material	DT_{50}/$t_{1/2\text{-}rep}$ (days)	Transformation products (Maximum % AR[1])	Comments/ classification	PMRA #
	Ipflufenoquin [A ring-^{14}C]		Major: CO2 (19%) Minor: Unknowns (< 4.9%)		3070102
Phototransformation in air	N/A	N/A	N/A	Not expected to be a route of dissipation	N/A
Volatilization	N/A	N/A	N/A	Not expected based on vapour pressure and Henry's law constant	N/A
Henry's law constant	Ipflufenoquin	$2.416 \cdot 10^{-09}$ atm m^3/mole			N/A
Biotransformation in soil					
Biotransformation in aerobic soil	Ipflufenoquin [A ring-^{14}C]	855/855 (DT_{50} & $t_{1/2,rep}$: 90th percentile of the upper bound on the mean: 855; n=4) DT_{50} & $t_{1/2,rep}$ range: 286 – 909 Model: SFO	Major: None Minor: QP-1-7 (Minor 4.0%) Unidentified (1.0%)	Persistent	3140464
Biotransformation in anaerobic Soil	Ipflufenoquin [A ring-^{14}C]	1711/1711 (DT_{50} & $t_{1/2,rep}$: 90th percentile of the upper bound on the mean: 1711 DT_{50} & $t_{1/2,rep}$ range: 551 –	Major: None Minor: QP-1-7 (1.0%) CO_2 (0.4%) Unknowns (1.2%)	Persistent	3070105

Study type		Test material	$DT_{50}/t_{1/2\text{-}rep}$ (days)	Transformation products (Maximum % AR[1])	Comments/ classification	PMRA #
			1902 Model: SFO			
Mobility						
Property		**Test substance**	**Mean K_d/K_{OC} (L/kg)**	**Comment**	**Mobility classification**	**PMRA #**
Adsorption in soil		Ipflufenoquin	Mean Kd: 21.98±12.48 Range (5.97-36.62) Mean Koc: 944.68±222.88 Range: (734.5 - 1290)	Linear adsorption, 6 soils	low to slight mobility	3070112
Soil leaching		Ipflufenoquin	Non-definitive according to criteria of Cohen *et al*. Borderline leacher to leacher according to the GUS index. (GUS value range: 2.18 to 3.36)			N/A
Field dissipation						
Test site		**Test item and rate**	**DT_{50} / DT_{90} (days)**	**Transformation products (Maximum % AR)**	**Classification/ comments**	**PMRA #**
Field dissipation	Iowa – Bareground	Ipflufenoquin applied as NF-180 SC 200 1 application of 255 g a.i./ha	3.15 / 138.3 Model: DFOP[3]	Major: None Minor: QP-1-1 (< LOQ of 0.002 mg/kg dry weight)	Non-persistent, max. depth < 30 cm, 31.3% carryover 6 months after treatment.	3070114
	Idaho - Bareground		23.2 / 1135 Model: DFOP		Slightly persistent, max. depth < 30 cm, 33.8% carryover	
	New York - Bareground		29.0 / 1127 Model: DFOP		Slightly persistent, max. depth < 30 cm, 35.9% carryover	

Study type	Test material	$DT_{50}/t_{1/2\text{-}rep}$ (days)	Transformation products (Maximum % AR[1])	Comments/ classification	PMRA #
Biotransformation in aquatic environment					
Aerobic Water/sediment	Ipflufenoquin [A ring-^{14}C]	Water layer: Half-life: 22 (longest of 2 values) Range: 12.6 – 22.0 Whole system: Half-life: 510 (longest of 2 values) Range: 231 – 510	Major: None Minor: Unknowns (1.4%)	Persistent (based on whole system) (98.7% AR found in the sediment at study termination)	3140465
Anaerobic Water/Sediment	Ipflufenoquin [A ring-^{14}C]	Water layer: Half-life: 40.7 (longest of 2 values) Range: 26.1 – 40.7 Whole System: Half-life: 544 (longest of 2 values) Range: 521 – 544	Major: None Minor: Unknowns (0.9%)	Persistent (based on whole system)	3140466
Partitioning					
Ipflufenoquin is anticipated to be primarily found in the sediment layer					N/A
Bioconcentration					
Not expected to bioaccumulate. BCF = 189 to 214 (Steady state, Normalized to 5% lipid content)					3070137
[1]Percent of applied radioactivity. [2]SFO = Single First-Order degradation kinetics model [3]DFOP = Double First-Order in Parallel degradation kinetics model					

Table 14 Summary of toxicity effects of Ipflufenoquin and Ipflufenoquin SC 200 g/L formulation on terrestrial organisms

Organism	Test substance	Exposure	Endpoint value	Effects/ Degree of toxicity[1]	PMRA #
Invertebrates					
Eisenia fetida (Earthworm)	Ipflufenoquin (TGAI Purity: 99.1%)	28 days	28-d LC_{50}: >1000 mg a.i./kg dry soil 28-d NOAEC: >1000 mg a.i./kg dry soil 28-d $NOAEC_{bw}$: 30 mg a.i./kg dry soil 0% mortality was observed up to the highest concentration tested.	N/A	3084751
		56 days, reproduction	56-d $NOAEC_{repro}$: 100 mg a.i./kg dry soil	N/A	
Apis mellifera (Honey bee)	Ipflufenoquin (TGAI Purity: 99.1%)	48-hour contact adult	48-h LD_{50}: > 100 µg a.i./bee (2% mortality was observed at the highest concentration tested)	Practically nontoxic	3070117
		48-hour oral adult	48-h LD_{50}: > 106.7 µg a.i./bee (5 µg a.i./mg diet) 2% mortality was observed at to the highest concentration tested	Practically nontoxic	
		10-day diet adult	10-d $NOAEDD_{mortality}$: > 12.3 µg a.i./bee/day (500 mg a.i./kg diet) (6.7% mortality was observed in the highest concentration tested)	N/A	3070120
		72-hour larvae	72-h LD_{50}: 83.9 µg a.i./larva (2542 mg a.i./kg diet)	Practically nontoxic	3070119

Organism	Test substance	Exposure	Endpoint value	Effects/ Degree of toxicity[1]	PMRA #
		22-day larvae	22-d $NOAEDD_{emergence}$: 12.5 µg a.i./larva/day (89 mg a.i./L diet)	N/A	3070118
Aphidius rhopalosiphi (parasitoid wasp)	Ipflufenoquin SC 200 g/L (Formulated product)	14-day glass plate	48-d LR_{50}: > 300 g a.i./ha 14-d $ER_{50\ reproduction}$: > 300 g a.i./ha No significant effects on mortality or reproduction were observed up to the highest concentration tested.	N/A	3070121
Predatory mite (*Typhlodromus pyri*)	Ipflufenoquin SC 200 g/L	14-day glass plate	48-d LR_{50}: > 300 g a.i./ha 14-d $ER_{50\ reproduction}$: > 300 g a.i./ha No significant effects on mortality or reproduction were observed up to the highest concentration tested.	N/A	3140462
Birds					
Colinus virginianus (Northern Bobwhite quail)	Ipflufenoquin (TGAI Purity: 99.1%)	Single dose oral	LD_{50}: > 2000 mg a.i./kg bw No mortality was observed up to the highest dose tested.	Practically non-toxic	3070138
		5-day Dietary	5-d LD_{50}: > 1286 mg a.i./kg bw/day (4960 mg a.i./kg feed) No mortality was observed up to the highest dose tested.	Practically non-toxic	3070141

Organism	Test substance	Exposure	Endpoint value	Effects/ Degree of toxicity[1]	PMRA #
		27 week Reproduction	27-week $NOAED_{reproduction}$: 49.7 mg a.i./kg bw/day (519 mg a.i./kg feed) No adverse effects were observed up to the highest dose tested.	N/A	3070145
Anas platyrhynchos (Mallard)	Ipflufenoquin (TGAI Purity: 99.1%)	Single dose oral	LD_{50}: > 1200 mg a.i./kg bw No mortality was observed up to the highest dose tested.	Practically non-toxic	3070139
		5-day Dietary	5-day LD_{50}: > 1275 mg a.i./kg bw/d) (LC_{50}: > 4960 mg a.i./kg diet) No mortality was observed up to the highest dose tested.	Practically non-toxic	3070143
		27 week Reproduction	27-week $NOAED_{reproduction}$: 54.5 mg a.i./kg bw/day ($NOAEC_{reproduction}$: 589 mg a.i./kg diet) An 18% reduction in number of eggs hatched of eggs set and a 17% reduction in 14-day hatchling survivors was observed at the highest dose tested.	N/A	3070148
Taeniopygia guttata (Zebra Finch)	Ipflufenoquin (TGAI Purity: 99.1%)	Single dose oral	LD_{50} > 2340 mg a.i./kg bw No mortality was observed up to the highest dose tested.	Practically non-toxic	3070140

Organism	Test substance	Exposure	Endpoint value	Effects/ Degree of toxicity[1]	PMRA #
Small wild mammals					
Sprague Dawley rat (*Rattus norvegicus domesticus*)	Ipflufenoquin (TGAI Purity: 99.1%)	Single dose oral (gavage)	LD_{50}: > 2000 mg a.i./kg bw	Practically non-toxic	3070023
		2 generation reproduction	NOAEL = 75.9 mg a.i./kg bw/day (decreased in pup weight)	N/A	3070044
Vascular plants					
Four monocot species: corn, onion, ryegrass, wheat and oat Six dicot species: cabbage, lettuce, oilseed rape, soybean, sugar beet, cucumber and tomato	Ipflufenoquin SC 200 g/L (Formulated product)	Vegetative vigour Single application of 100 g a.i./ha sprayed on planted seeds	ER_{25}: > 100 g a.i./ha (for all species tested) A maximum of 7.6% reduction for growth (plant height) was observed across all test species at the highest concentration tested.	N/A	3070154
Four monocot species: corn, onion, wheat and oat Six dicot species: oilseed rape, soybean, sugar beet, carrot, cucumber and tomato	Ipflufenoquin SC 200 g/L (Formulated product)	Seedling emergence Single application of 100 g a.i./ha sprayed on planted seeds	ER_{25}:> 100 g a.i./ha (for all species tested) A maximum of 13.5% reduction in dry weight was observed across all test species at the highest concentration tested.	N/A	3070155

[1]: USEPA classification (1985), where applicable.
N/A = not available

Table 15 Summary of toxicity effects of Ipflufenoquin technical on aquatic organisms

Test species	Test substance	Exposure	Endpoints	Degree of toxicity[1] / comments	PMRA #
Freshwater invertebrates					
Water Flea *(Daphnia magna)*	Ipflufenoquin (TGAI Purity: 99.1%)	48-hour Acute (static)	48-h EC_{50}: 2.4 mg a.i./L	Moderately toxic	3070122
		21-day	21-d NOAEC:	N/A	3070123

Test species	Test substance	Exposure	Endpoints	Degree of toxicity[1] / comments	PMRA #
		Chronic (static renewal)	1.1 mg a.i./L		
Midge *(Chironomus dilutus)*	Ipflufenoquin (TGAI Purity: 99.1%)	10-day sub-chronic (static renewal, spiked sediment)	10-d EC_{50}: > 2.5 mg a.i./L (pore water) A maximum of 20% mortality was observed at the highest concentration tested	N/A	3070124
Amphipod (*Hyalella azteca*)	Ipflufenoquin (TGAI Purity: 99.1%)	10-day sub-chronic (static renewal, spiked sediment)	10-d EC_{50}: > 2.5 mg a.i./L (pore water) A maximum of 27% mortality was observed at the highest concentration tested	N/A	3070126
Freshwater fish					
Rainbow Trout (*Oncorhynchus mykiss*)	Ipflufenoquin (TGAI Purity: 99.1%)	96-hour acute (static)	96-h LC_{50}: 3.6 mg a.i./L	Moderately toxic	3070131
Fathead minnow (*Pimephales promelas*)	Ipflufenoquin (TGAI Purity: 99.1%)	96-hour acute (static)	96-h LC_{50}: > 5.8 mg a.i./L 27% mortality was observed at the highest concentration tested	Moderately toxic	3070133
		34-day early life-stage (flow-through)	34-d $NOAEC_{growth}$: 0.086 mg a.i./L	N/A	3070136
Bluegill sunfish (*Lepomis macrochirus)*	Ipflufenoquin (TGAI Purity: 99.1%)	96-hour acute (static)	96-h LC_{50}: 5.6 mg a.i./L	Moderately toxic	3070132

Test species	Test substance	Exposure	Endpoints	Degree of toxicity[1] / comments	PMRA #
Amphibians					
Amphibians (using rainbow trout fish data as a surrogate)	Ipflufenoquin (TGAI Purity: 99.1%)	96-hour acute (static)	96-h LC_{50}: 3.6 mg a.i./L	N/A	3070131
Freshwater vascular plants					
Duckweed *(Lemna gibba)*	Ipflufenoquin (TGAI Purity: 99.1%)	7-day (static-renewal)	7-d EC_{50}: > 4.6 mg a.i./L A mean reduction of 15% for yield was observed at the highest concentration tested	N/A	3070156
Freshwater algae					
Green algae (*Pseudokirchneriella subcapitata)*	Ipflufenoquin (TGAI Purity: 99.1%)	96-hour Acute (static)	96-h EC_{50}: could not be statistically determined, however, 51% inhibition observed on area under the growth curve was observed at the highest concentration tested of 4.7 mg a.i./L.	N/A	3070150
Cyanobacteria (*Anabaena flos-aquae*)	Ipflufenoquin (TGAI Purity: 99.1%)	96-hour Acute (static)	96-h EC_{50}: > 4.7 mg a.i./L 13% reduction in yield was observed at the highest concentration tested	N/A	3070151
Diatom *(Navicula pelliculosa)*	Ipflufenoquin (TGAI Purity: 99.1%)	96-hour Acute (static)	96-h EC_{50}: 1.8 mg a.i./L	N/A	3070152

Test species	Test substance	Exposure	Endpoints	Degree of toxicity[1] / comments	PMRA #
Marine invertebrates					
Mysid shrimp (*Americamysis bahia)*	Ipflufenoquin (TGAI Purity: 99.1%)	96-hour Acute (static)	96-h LC_{50}: 4.0 mg/L	Moderately toxic	3070128
		28-day Chronic (flow-through)	28-d $NOAEC_{repro}$: 0.22 mg a.i./L	N/A	3070130
Eastern oyster (*Crassostrea virginica*)	Ipflufenoquin (TGAI Purity: 99.1%)	96-hour acute (flow-through)	96-h EC_{50}: > 0.78 mg a.i./L 7% reduction in shell deposition observed at the highest test concentration	Unable to be determined	3070129
Estuarine Amphipod (*Leptocheirus plumulosus*)	Ipflufenoquin (TGAI Purity: 99.1%)	10-day (spiked sediment)	10-d LC_{50}: > 2.2 mg a.i./L (Pore Water) A maximum of 24% mortality was observed up to the highest concentration tested.	N/A	3070127
Marine fish					
Sheepshead minnow (*Cyprinodon variegatus*)	Ipflufenoquin (TGAI Purity: 99.1%)	96-hour acute (static-renewal)	96-h LC_{50}: 4.0 mg a.i./L	Moderately toxic	3070134
		34 day early life-stage (flow-through)	34-d $NOAEC_{growth}$: 0.21 mg a.i./L	N/A	3070135
Marine algae					
Saltwater diatom *(Skeletonema costatum)*	Ipflufenoquin (TGAI Purity: 99.1%)	96-hour acute (static)	96-h EC_{50}: 1.5 mg a.i./L	N/A	3070153

[1]EPA classification; where applicable
N/A = not available

Table 16 Study endpoints, uncertainty factors and levels of concern relevant for risk assessment

Most sensitive Representitive species	Test Substance	Exposure	Endpoint Value	Uncertainty factor	Effects metric	Level of Concern (LOC)
Invertebrates						
Earthworm (*Eisenia fetida*)	Ipflufenoquin (TGAI Purity: 99.1%)	28-d LC_{50}	>1000 mg a.i./kg dry soil	2	> 500 mg a.i./kg soil dw	1
		56-d Reproduction NOAEC	100 mg a.i./kg soil dw	1	100 mg a.i./kg soil dw	1
Apis mellifera (Honey bee)	Ipflufenoquin (TGAI Purity: 99.1%)	48-h contact adult	100 µg a.i./bee	1	100 µg a.i./bee	0.4
		48-h acute oral adult	106.7 µg a.i./bee	1	106.7 µg a.i./bee	0.4
		10-d diet adult NOAEDD	12.3 µg a.i./bee/day	1	12.3 µg a.i./bee/day	1
		72-h larvae LD_{50}	83.9 µg a.i./larva	1	83.9 µg a.i./larva	0.4
		22-d larvae $NOAEDD_{emergence}$	12.5 µg a.i./larva/day	1	12.5 µg a.i./larva/day	1
Aphidius rhopalosiphi (parasitoid wasp)	Ipflufenoquin SC 200 g/L (Formulated product)	48-h LR_{50}	> 300 g a.i./ha	1	> 300 g a.i./ha	2
Predatory mite (*Typhlodromus pyri*)	Ipflufenoquin SC 200 g/L (Formulated product)	14-d $ER_{50reproduction}$	> 300 g a.i./ha	1	> 300 g a.i./ha	2
Birds						
Mallard (*Anas platyrhynchos*)	Ipflufenoquin (TGAI Purity: 99.1%)	Single dose Oral LD_{50}	> 1200 mg a.i./kg bw	10	> 120 mg a.i./kg bw	1
Northern Bobwhite quail (*Colinus virginianus)*	Ipflufenoquin (TGAI Purity: 99.1%)	27-w Reproduction NOAED	49.7 mg a.i./kg bw/day	1	49.7 mg a.i./kg bw/day	1
Mammals						
Sprague Dawley rat (*Rattus norvegicus domesticus*)	Ipflufenoquin (TGAI Purity: 99.1%)	Single dose Oral LD_{50}	> 2000 mg a.i./kg bw	10	> 200 mg a.i./kg bw	1
		2 Generation Reproductive NOAEL	75.9 mg a.i./kg bw/day	1	75.9 mg a.i./kg bw/day	1

Most sensitive Representitive species	Test Substance	Exposure	Endpoint Value	Uncertainty factor	Effects metric	Level of Concern (LOC)
Vascular plants						
All species tested	Ipflufenoquin SC 200 g/L (Formulated product)	Vegetative vigour ER_{25}	> 100 g a.i./ha	1	> 100 g a.i./ha	1
		Seedling emergence ER_{25}	> 100 g a.i./ha	1	> 100 g a.i./ha	1
Freshwater invertebrates						
Water flea (*Daphnia magna*)	Ipflufenoquin (TGAI Purity: 99.1%)	48-h EC_{50}	2.4 mg a.i./L	2	1.25 mg a.i./L	1
		21-d life-cycle	1.1 mg a.i./L	1	1.1 mg a.i./L	1
Midge *(Chironomus dilutus)*	Ipflufenoquin (TGAI Purity: 99.1%)	10-d EC_{50}	>2.5 mg a.i./L (pore water)	2	>1.25 mg a.i./L (pore water)	1
Freshwater Fish						
Rainbow Trout (*Oncorhynchus mykiss*)	Ipflufenoquin (TGAI Purity: 99.1%)	96-h LC_{50}	3.6 mg a.i./L	10	0.36 mg a.i./L	1
Fathead minnow (*Pimephales promelas*)	Ipflufenoquin (TGAI Purity: 99.1%)	32-d $NOAEC_{growth}$	0.086 mg a.i./L	1	0.086 mg a.i./L	1
Amphibians						
Amphibians (using rainbow trout fish data as a surrogate)	Ipflufenoquin (TGAI Purity: 99.1%)	96-h LC_{50}	3.6 mg a.i./L	10	0.36 mg a.i./L	1
Freshwater vascular plants						
Duckweed *(Lemna gibba)*	Ipflufenoquin (TGAI Purity: 99.1%)	7-d EC_{50}	> 4.6 mg a.i./L	2	> 2.3 mg a.i./L	1
Freshwater algae						
Diatom *(Navicula pelliculosa)*	Ipflufenoquin (TGAI Purity: 99.1%)	96-h EC_{50}	1.8 mg a.i./L	2	0.9 mg a.i./L	1
Marine invertebrates						
Eastern oyster (*Crassostrea virginica*)	Ipflufenoquin (TGAI Purity: 99.1%)	96-h EC_{50}	> 0.78 mg a.i./L	2	> 0.39 mg a.i./L	1
Mysid shrimp (*Americamysis bahia)*	Ipflufenoquin (TGAI Purity: 99.1%)	28-d $NOAEC_{repro}$	0.22 mg a.i./L	1	0.22 mg a.i./L	1

Most sensitive Representitive species	Test Substance	Exposure	Endpoint Value	Uncertainty factor	Effects metric	Level of Concern (LOC)
Marine Amphipod (*Leptocheirus plumulosus*)	Ipflufenoquin (TGAI Purity: 99.1%)	10-d EC_{50}	> 2.2 mg a.i./L	2	> 1.1 mg a.i./L	1
Marine Fish						
Sheepshead minnow (*Cyprinodon variegatus*)	Ipflufenoquin (TGAI Purity: 99.1%)	96-h LC_{50}	4.0 mg a.i./L	10	0.4 mg a.i./L	1
		34-d $NOAEC_{growth}$	0.21 mg a.i./L	1	0.21 mg a.i./L	1
Marine algae						
Saltwater diatom *(Skeletonema costatum)*	Ipflufenoquin (TGAI Purity: 99.1%)	96-h EC_{50}	1.5 mg a.i./L	2	0.75 mg a.i./L	1

Table 17 Estimated environmental exposures

Environmental matrix	Application rate (g a.i./ha)[1]	Half-life (d)	Estimated environmental exposure (EEC[2] / EDE[3] / EER[4] / ED[5])	Notes
Soil	Maximum cumulative: 131.3	90th upper percentile of the mean of the aerobic soil representative half-life: 855	EEC: 0.058 g ai/kg soil	Assumes evenly distributed in the top 0 – 15 cm of soil with bulk density of 1.5 g/cm^3 Used in the earthworm risk assessment.
Soil surfaces	Maximum cumulative: 131.3	90th upper percentile of the mean of the aerobic soil representative half-life: 855	EER: 131.3 g a.i/ha	Used for the terrestrial plant seedling emergence risk assessment
Plant surfaces	Maximum cumulative: 87.8	Foliar half-life: 10	EER: 87.8 g a.i./ha	Used for the terrestrial plant vegetative vigour and foliar dwelling beneficial arthropods risk assessment.
Contact for bees	Single: 44	Not applicable	ED: 0.11 µg a.i./bee	Conversion factor of 2.4 µg a.i./bee/day per kg a.i./ha
Adult bee diet	Single: 44	Not applicable	ED: 1.26 µg a.i./bee/day	Conversion factor of 28.6 µg a.i./bee/day per kg a.i./ha

Environmental matrix	Application rate (g a.i./ha)[1]	Half-life (d)	Estimated environmental exposure (EEC[2] / EDE[3] / EER[4] / ED[5])	Notes
Bee larvae diet	Single: 44	Not applicable	EDE[6]: 0.528 µg a.i./bee/day	Conversion factor of 12 µg a.i./bee/day per kg a.i./ha
Diet of small birds: insects (BW = 20 g)	Maximum cumulative: 131.3	Foliar half-life: 10	EDE: 7.14 mg a.i./kg bw/day	FIR = 5.1 g dw diet/day
Diet of medium birds: insects (BW = 100 g)	Maximum cumulative: 131.3	Foliar half-life: 10	EDE: 5.57 mg a.i./kg bw/day	FIR = 19.9 g dw diet/day
Diet of large birds: short grass (BW = 1000 g)	Maximum cumulative: 131.3	Foliar half-life: 10	EDE: 3.6 mg a.i./kg bw/day	FIR = 58.1 g dw diet/day
Diet of small mammals: insects (BW = 15 g)	Maximum cumulative: 131.3	Foliar half-life: 10	EDE: 4.11 mg a.i./kg bw/day	FIR = 2.2 g dw diet/day
Diet of medium mammals: short grass (BW = 35 g)	Maximum cumulative: 131.3	Foliar half-life: 10	EDE: 7.97 mg a.i./kg bw/day	FIR = 4.5 g dw diet/day
Diet of large mammals: short grass (BW = 1000 g)	Maximum cumulative: 131.3	Foliar half-life: 10	EDE: 4.26 mg a.i./kg bw/day	FIR = 68.7 g dw diet/day
Water	Maximum cumulative: 131.3	Aerobic water/sediment whole system half-life: 510	EEC: 80 cm depth: 0.016 mg ai/L EEC: 15 cm depth: 0.088 mg a.i./L	Assumes instantaneous and homogeneous mixing. 15 cm EEC used for amphibians 80 cm EEC used for all other aquatic organisms

[1]Application rate used in the risk assessment was either the maximum cumulative rate (cumulative) or maximum single application rate (single), depending on the risk assessment methodology.
[2]EEC = Estimated environmental concentration (mg a.i./kg or mg a.i./L) in soil or water
[3]EDE = Estimated Daily Exposure (mg a.i./kg bw/day) for birds and mammals, specialized feeding guilds are considered for each category of animal weight to help determine exposure (herbivore, frugivore, insectivore and granivore). At the screening level, relevant food items representing the most conservative EDE for each feeding guild are used (i.e., insects and small grasses). The EDE is calculated using the following formula: (FIR/BW) × EEC, where: BW = Body weight, FIR = Food ingestion rate: For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used Passerine Equation: FIR (g dry weight/day) = $0.398(\text{BW in g})^{0.850}$. All birds Equation: FIR (g dry weight/day) = $0.648(\text{BW in g})^{0.651}$. For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{BW in g})^{0.822}$
[4]EER = Estimated environmental rate (g a.i./ha)
[5]ED = Estimated dose (µg a.i./bee) for bees is calculated by converting the maximum single application rate (44 g

Environmental matrix	Application rate (g a.i./ha)[1]	Half-life (d)	Estimated environmental exposure (EEC[2] / EDE[3] / EER[4] / ED[5])	Notes

a.i./ha) by the conversion factor listed in the table.
[6]EDE = Estimated Daily Exposure (µg a.i./larvae/day) for bee larvae is calculated by converting the maximum single application rate (44 g a.i./ha) by the conversion factor listed in the table

Table 18 Screening level risk ipflufenoquin and its end-use product to terrestrial organisms: Earthworms, Honey bees, Non-target arthropods and Vascular plants

Organism	Test Substance	Exposure	Effects metric	Estimated exposure	RQ[1]	Level of concern exceeded ?
Invertebrates						
Earthworm (*Eisenia fetida*)	Ipflufenoquin (TGAI Purity: 99.1%)	28 day, mortality	> 500 mg a.i./kg soil dw	0.058 mg a.i./kg soil	<0.0001	Not exceeded
		56 day, reproduction	100 mg a.i./kg soil dw	0.058 mg a.i./kg soil	0.001	Not exceeded
Honey Bee (*Apis mellifera*)	Ipflufenoquin (TGAI Purity: 99.1%)	48-h Contact adult	> 100 µg a.i./bee	0.11 µg a.i./bee/day	< 0.001	Not exceeded
		48-h Oral adult	> 106.7 µg a.i./bee	1.26 µg a.i./bee	< 0.01	Not exceeded
		10-d Dietary adult	> 12.3 µg a.i./bee/day	1.26 µg a.i./bee/day	< 0.1	Not exceeded
		72-h Oral larvae	83.9 µg a.i./larva	0.528 µg a.i./larva/day	0.01	Not exceeded
		22-d Dietary larvae	12.5 µg a.i./larva/day	0.528 µg a.i./larva/day	0.04	Not exceeded
Parasitoid wasp (*Aphidius rhopalosiphi*)	Ipflufenoquin SC 200 g/L	14-day glass plate	>300 g a.i./ha	87.8 g a.i./ha	< 0.3	Not exceeded

Organism	Test Substance	Exposure	Effects metric	Estimated exposure	RQ[1]	Level of concern exceeded ?
Predatory mite (*Typhlodromus pyri*)	Ipflufenoquin SC 200 g/L (EP)	14-day glass plate	> 300 g a.i./ha	87.8 g a.i./ha	< 0.3	Not exceeded
Vascular plants						
Vascular plant	Ipflufenoquin SC 200 g/L (200 g/L Ipflufenoquin)	Seedling emergence	> 100 g a.i./ha	131.3 g a.i./ha	< 1.3	Unlikely to be Exceeded
		Vegetative vigour	> 100 g a.i./ha	87.8 g a.i./ha[11]	< 0.9	Not exceeded

[1]RQ = Risk Quotient. The RQ is calculated by dividing the EEC, ED, EDE or ER by the effects metric value (RQ = exposure/effects metric)

Table 19 Screening level risk assessment for birds and mammals from consumption of contaminated food sources based on maximum nomogram residues

	Feeding Guild (food item)[1]	Effects metric (mg a.i./kg bw/day)	EDE[2] (mg a.i./kg bw/day)	RQ[3]	Level of Concern Exceeded?
Small Bird (0.02 kg)					
Acute	Insectivore	> 120.00	7.14	< 0.06	Not Exceeded
Reproduction	Insectivore	49.70	7.14	0.14	Not Exceeded
Medium Sized Bird (0.1 kg)					
Acute	Insectivore	> 120.00	5.57	< 0.05	Not Exceeded
Reproduction	Insectivore	49.70	5.57	0.11	Not Exceeded
Large Sized Bird (1 kg)					
Acute	Herbivore (short grass)	> 120.00	3.60	< 0.03	Not Exceeded
Reproduction	Herbivore (short grass)	49.70	3.60	0.07	Not Exceeded
Small Mammal (0.015 kg)					
Acute	Insectivore	> 200.00	4.11	< 0.02	Not Exceeded
Reproduction	Insectivore	75.9	4.11	0.05	Not Exceeded
Medium Sized Mammal (0.035 kg)					
Acute	Herbivore (short grass)	> 200.00	7.97	< 0.04	Not Exceeded
Reproduction	Herbivore (short grass)	75.9	7.97	0.11	Not Exceeded
Large Sized Mammal (1 kg)					
Acute	Herbivore (short grass)	> 200.00	4.26	< 0.02	Not Exceeded
Reproduction	Herbivore (short grass)	75.9	4.26	0.05	Not Exceeded

[1]Specialized feeding guilds are considered for each category of animal weights to help determine exposure (herbivore and insectivore).
[2]EDE = Estimated dietary exposure.
[3] RQ = Risk Quotient. The RQ for birds and mammals is calculated by dividing the EDE by the effects metric value (RQ = EDE/effects metric)

Table 20 Screening level risk of ipflufenoquin to aquatic organisms

Organism	Test Substance	Exposure	Effects metric (mg a.i./L)	Estimated Environmental Concentration (mg ai/L)	RQ[1]	Level of Concern
Freshwater Invertebrates						
Water flea (*Daphnia magna*)	Ipflufenoquin (TGAI Purity: 99.1%)	48-h flow through	1.2	0.016	0.01	Not Exceeded
		21 day life-cycle static renewal	1.1	0.016	0.01	Not Exceeded
Midge (*Chironomus dilutes*)	Ipflufenoquin (TGAI Purity: 99.1%)	10-d Static renewal spiked sediment	> 1.25	0.016	< 0.01	Not Exceeded
Freshwater Fish						
Rainbow Trout (*Oncorhynchus mykiss)*	Ipflufenoquin (TGAI Purity: 99.1%)	96-h Static	0.36	0.016	0.05	Not Exceeded
Fathead minnow (*Pimephales promelas*)	Ipflufenoquin (TGAI Purity: 99.1%)	32-d Early life-stage flow-through	0.0836	0.016	0.2	Not Exceeded
Amphibians (using rainbow trout fish data as a surrogate)	Ipflufenoquin (TGAI Purity: 99.1%)	96-h Static	0.36	0.088	0.2	Not Exceeded
Freshwater vascular plants						
Duck weed (*Lemna gibba*)	Ipflufenoquin (TGAI Purity: 99.1%)	7 day (static-renewal)	> 2.3	0.016	< 0.007	Not Exceeded
Freshwater Algae						
Freshwater diatom alga (*Navicula pelliculosa*)	Ipflufenoquin (TGAI Purity: 99.1%)	96-h Static	0.9	0.016	0.02	Not Exceeded

Organism	Test Substance	Exposure	Effects metric (mg a.i./L)	Estimated Environmental Concentration (mg ai/L)	RQ[1]	Level of Concern
Marine invertebrates						
Eastern oyster (*Crassostrea virginica*)	Ipflufenoquin (TGAI Purity: 99.1%)	96-h Flow-through	> 0.39	0.016	< 0.04	Not Exceeded
Mysid shrimp (*Americamysis bahia*)	Ipflufenoquin (TGAI Purity: 99.1%)	28-d Flow-through	0.22	0.016	0.1	Not Exceeded
Marine Amphipod (*Leptocheirus plumulosus*)	Ipflufenoquin (TGAI Purity: 99.1%)	10-d spiked sediment	> 1.1 pore water[2]	0.016	< 0.015	Not Exceeded
Marine Fish						
Sheepshead minnow (*Cyprinodon variegatus*)	Ipflufenoquin (TGAI Purity: 99.1%)	96-h Static-renewal	0.4	0.016	0.04	Not Exceeded
		34-d Early life-stage, Flow-through	0.21	0.016	0.1	Not Exceeded
Marine Alga						
Marine diatom (*Skeletonema costatum*)	Ipflufenoquin (TGAI Purity: 99.1%)	96-h static	0.75	0.016	0.02	Not Exceeded

[1]RQ = Risk Quotient. The RQ is calculated by dividing the EEC, by the effects metric value (RQ = exposure/effects metric)
[2]For the screening level risk assessment the pore water effects metric was conservatively compared to the screening level overlying water EEC.

Table 21 List of supported uses

Supported use claim	Use directions
Control or suppression of powdery mildew (*Podosphaera leucotricha, Phyllactinia mali*) on Crop Group 11-09 Pome fruit. The 165 mL/ha rate provides suppression. If disease pressure is moderate or high or if control is required, use the 220 mL/ha rate. Addition of a surfactant may improve efficacy.	Rates: 165 – 220 mL/ha (33 – 44 g a.i./ha). Make first application at green tip stage; BBCH 9 to BBCH 76. Use the higher rate under heavier pest pressure. The retreatment interval is 7 – 10 days. Do not make more than three (3) applications per crop cycle. Do not exceed 660 mL per ha per year. The recommended spray volume for ground

Supported use claim	Use directions
	application is 187 L water/ha.
Control of scab (*Venturia inaequalis, V. pyrina*) on Crop Group 11-09 Pome fruit.	Rates: 165 – 220 mL/ha (33 – 44 g a.i./ha). Make first application at green tip stage; BBCH 9 to BBCH 76. Use the higher rate under heavier pest pressure. The retreatment interval is 7 – 10 days. Do not make more than three (3) applications per crop cycle. Do not exceed 660 mL per ha per year. The recommended spray volume for ground application is 187 L water/ha.
Use of non-ionic surfactant	A non-ionic surfactant may be added to the KINOPROL 20 SC spray solution at 0.125 – 0.5% v/v or the recommended rate under conditions conducive to high disease pressure (e.g., Agral 90 at 0.125% v/v).

Table 22 Toxic substances management policy considerations - comparison to TSMP track 1 criteria for ipflufenoquin

Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria			
TSMP Track 1 Criteria	**TSMP Track 1 Criterion value**		**Active Ingredient[1]**
CEPA toxic or CEPA toxic equivalent[2]	Yes		Yes
Predominantly anthropogenic[3]	Yes		Yes
Persistence[4]:	Soil	Half-life ≥ 182 days	Yes Half-life: 286 - 1903 days
	Water/Sediment Whole System	Half-life ≥ 182 days (water) ≥ 365 days (sediment)	Yes Half-life: 545 days (longest water/sediment half-life value)
	Air	Half-life ≥ 2 days or evidence of long range transport	Not determined. The AOPWIN model is not suited for predicting the atmospheric half-life of ipflufenoquin given the large fraction expected to be sorbed to airborne particles.

Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria		
TSMP Track 1 Criteria	**TSMP Track 1 Criterion value**	**Active Ingredient[1]**
Bioaccumulation[5]	Log $K_{OW} \geq 5$	No log K_{ow} = 3.9 (at pH 6.17 to 6.3)
	BCF ≥ 5000	No 189 to 214 (Steady state, Normalized to 5% lipid content)
	BAF ≥ 5000	N/A
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No, does not meet all TSMP Track 1 criteria.

[1]No major transformation products were detected in lab or field studies.
[2]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).
[3]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.
[4]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.
[5]Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).

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

Ipflufenoquin is an active ingredient that is concurrently being registered in Canada and the United States for use on pome fruit. Canada is also establishing MRLs on plant commodities that may be imported into Canada from the United States. The MRLs proposed for ipflufenoquin in Canada are the same as corresponding tolerances in the United States.

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

Currently, there are no Codex MRLs[10] listed for ipflufenoquin 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
3069994	2019, Colour, Physical State, and Odour of NF-180 (Lot No.11426-[Privacy Removed]-2), DACO: 2.14.1,2.14.2,2.14.3
3069995	2016, Colour, Physical State and Odour of NF-180, DACO: 2.14.1,2.14.2,2.14.3
3070004	2016, Melting Point of NF-180, DACO: 2.14.4
3070005	2015, Boiling Point of NF-180, DACO: 2.14.5
3070006	2016, Density of NF-180, DACO: 2.14.6
3070008	2017, Water solubility of NF-180 at pH 4,7 and 9, DACO: 2.14.7
3070009	2016, Solubility of NF-180 in the organic solvents, DACO: 2.14.8
3070010	2019, Vapour Pressure of NF-180 (up to 1 X 10-10 Pa), DACO: 2.14.9
3069997	2015, Dissociation constant of NF-180, DACO: 2.14.10
3069999	2014, Partition Coefficient (n-octanol/water) of 72-9059, DACO: 2.14.11
3070000	2016, Spectra of NF-180, DACO: 2.14.12
3070001	2019, Storage Stability of NF-180 Technical Grade (54°C), DACO: 2.14.14
3070015	2017, NF-180: Determination of General Physico-Chemical Properties, DACO: 2.14.15,2.16,830.7000
3069978	2019, Ipflufenoquin (Code No. NF-180) TGAI Product Identity and Composition, DACO: 2.11.1,2.11.2,2.11.3,2.11.4,2.12.1 CBI
3244183	2021, Ipflufenoquin (Code No. NF-180) TGAI Product Identity and Composition, DACO: 2.11.1,2.11.2,2.11.3,2.11.4,2.12.1 CBI
3069983	2018, Analysis of representative 5 lots of NF-180 technical grade manufactured by [Privacy Removed], DACO: 2.13.1,2.13.2,2.13.3,2.13.4 CBI
3069984	2019, Analysis of Representative 5 Lots of Ipflufenoquin Technical Grade, DACO: 2.13.1,2.13.2,2.13.3,2.13.4 CBI
3069981	2018, Validation of analytical method for Active Ingredient in Technical Grade NF-180, DACO: 2.13.1
3069986	2019, Validation of Analytical Method for Residual Solvents [CBI Removed] in Technical Grade NF-180, DACO: 2.13.1,2.13.4 CBI
3069987	2018, Validation of analytical method for Residual Solvents [CBI Removed] in Technical Grade NF-180, DACO: 2.13.1,2.13.4 CBI

3069988 2019, Validation of analytical method for [CBI Removed] in NF-180 technical grade, DACO: 2.13.1,2.13.4 CBI

3069980 2018, Validation of Analytical Method for the active ingredient (NF-180) in NF-180 technical grade, DACO: 2.13.1

3069989 2019, Confirmatory analytical method validation of the [CBI Removed] in NF-180 technical grade, DACO: 2.13.1,2.13.4 CBI

3070092 2018, Validation of Method GPL-MTH-099 for the Determination of NF-180, [CBI Removed] in Soils and Spray Application Targets by LC-MS/MS, DACO: 8.2.2.1

3070093 2019, Independent Laboratory Validation of Residue Analytical Method for Determination of NF-180, [CBI Removed] in Soil and NF-180 in Sediment, DACO: 8.2.2.1,8.2.2.2

3070095 2018, NF-180 - Validation of the Analytical Method for the Determination of a Test Substance in Aqueous Solutions, DACO: 8.2.2.3

3070096 2019, Independent Laboratory Validation of Development and Validation of an Analytical Method for the Determination of NF-180 and its Metabolite [CBI Removed] in Surface and in Ground Water, DACO: 8.2.2.3

3070097 2018, Development and Validation of an Analytical Method for the Determination of NF-180 and its Metabolite [CBI Removed] in Surface and in Ground Water, DACO: 8.2.2.3

3073030 2018, Accelerated storage stability study and physico-chemical properties of NF-180 200 g/L SC – [Privacy Removed] 2017-, DACO: 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.2, 3.5.6, 3.5.7, 3.5.8, 3.5.9, 3.7

3073029 2019, Group B Product Chemistry and Waivers for Kinoprol 20 SC, DACO: 3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.14,3.5.15,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,3.5.9, 3.7

3073027 2019, Ipflufenoquin 20 SC Product Chemistry Part A, DACO: 3.1.1, 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.5.1, 3.5.11, 3.5.12, 3.5.2, 3.5.3, 3.5.6, 3.7 CBI

3073028 2019, Validation of Analytical Method for Active Ingredient in NF-180 200 g/L SC, DACO: 3.4.1

2.0 Human and animal health

PMRA Document Number	Reference

3070021 2018, Acute oral toxicity study of QP-2 in rats, DACO: 4.2.1

3070022 2016, Acute oral toxicity study of QP-1-1 in rats, DACO: 4.2.1

3070023 2017, Acute oral toxicity study of NF-180 in rats, DACO: 4.2.1

3070024 2018, Acute Oral Toxicity Study of [manufacturing impurity] in Rats, DACO: 4.2.1

3070025 2016, Acute Dermal Toxicity Study of NF-180 in Rats, DACO: 4.2.2

3070026 2017, NF-180: Acute Inhalation Toxicity (Nose only) Study in Rat, DACO: 4.2.3

3070027 2018, Eye irritation study of NF-180 in rabbits, DACO: 4.2.4

3070028 2018, Skin irritation study of NF-180 in Rabbits, DACO: 4.2.5

3070029 2018, NF-180 Local Lymph Node Assay in Mice: BrdU-ELISA, DACO: 4.2.6

3070030 2018, NF-180: Bridging Toxicity Study by Dietary Administration to Han Wistar Rats for 13 Weeks, DACO: 4.3.1

3070031 2018, NF-180: Preliminary Carcinogenicity Study by Dietary Administration to CD-1 Mice for 13 Weeks, DACO: 4.3.1,4.4.3

3070032 2016, A 90-Day Repeated Oral Dose Toxicity Study of NF-180 in Beagle Dogs, DACO: 4.3.2

3070033 2017, A 1-Year Repeated Oral Dose Toxicity Study of NF-180 in Beagle Dogs, DACO: 4.3.2

3070034 2014, A 28-Day Repeated Dose Oral Toxicity Study of 72-9059 in Beagle Dogs, DACO: 4.3.3

3070035 2014, 90-Day Repeated Dose Oral Toxicity Study of 72-9059 (Series 72-6032) in Rats, DACO: 4.3.3

3070036 2018, 28-Day Repeated Dose Oral Toxicity Study of QP-2 in Rats, DACO: 4.3.3

3070037 2018, 28-Day Repeated Dose Oral Toxicity Study of NF-180 in Rats, DACO: 4.3.3

3070039 2019, NF-180: Twenty-Eight Day Repeated Dose (Dermal) Toxicity Study In The Rat, DACO: 4.3.5

3070041 2018, 3, 7, and 14-Day Repeated Dose Oral Toxicity Study of 72-9059 (Series 72-6032) in Female Rats, DACO: 4.3.8

3070042 2018, NF-180: Carcinogenicity Study by Dietary Administration to CD-1 Mice for 78 Weeks, DACO: 4.4.3

3070043 2019, NF-180: Combined Carcinogenicity and Toxicity Study by Dietary Administration to Han Wistar Rats for 104 Weeks, DACO: 4.4.4

3070044 2018, Two-Generation (One Litter per Generation) Reproduction Study of NF-180 Diet in Rats, DACO: 4.5.1

3070045 2017, A Dosage-Range One-Generation Reproduction Study of NF-180 Diet in Rats, DACO: 4.5.1

3070046 2017, An Acute Neurotoxicity Study of NF-180 by Oral Gavage in Rats, DACO: 4.5.12

3070048 2016, An Embryo-Fetal Development Study of NF-180 by Oral Gavage in Rats, DACO: 4.5.2

3070049 2015, A Dose Range-finding Embryo-Fetal Development Study of NF-180 by Oral Gavage in Rats, DACO: 4.5.2

3070050 2018, An Embryo-Fetal Development Study of NF-180 by Oral Gavage in Rabbits, DACO: 4.5.3

3070051 2016, A Dose Range-finding Embryo-Fetal Development Study of NF-180 by Oral Gavage in Rabbits, DACO: 4.5.3

3070052 2017, QP-2 Bacterial Reverse Mutation Test, DACO: 4.5.4

3070053 2017, NF-180 Bacterial Reverse Mutation Test, DACO: 4.5.4

3070054 2018, A Bacterial Reverse Mutation Test of [manufacturing impurity], DACO: 4.5.4

3070055 2018, NF-180: CD1 Mouse In Vivo Micronucleus Test, DACO: 4.5.7

3070056 2018, Mouse Lymphoma Assay (MLA) of QP-2, DACO: 4.5.5

3070057 2013, 72-9059: In Vitro Mutation Test using Mouse Lymphoma L5178Y Cells, DACO: 4.5.5

3070058 2017, NF-180: In Vitro Mammalian Chromosome Aberration Test in Human Lymphocytes, DACO: 4.5.6

3070059 2018, Chromosomal Aberration Test with QP-2 in Cultured Human Lymphocytes, DACO: 4.5.6

3070060 2013, 72-9059: CD1 Mouse In Vivo Comet Assay, DACO: 4.5.8

3070061 2014, 72-9059 Crl:CD(SD) Rat In Vivo Comet Assay, DACO: 4.5.8

3070062 2018, Metabolism Study of 14C-NF-180 in Rats, DACO: 4.5.9

3070063 2019, A Pharmacokinetic Study of [14C]NF-180 following Single Oral (Gavage) and Intravenous Administration to Male and Female Wistar Han Rat, DACO: 4.5.9

3070064 2019, [A ring-14C]NF-180: Analysis of Representative Samples of Urine and Feces from Repeated Administration Rats for 14 Days, DACO: 4.5.9

3070068 2018, NF-180 Hepatic Drug-Metabolizing Enzyme Induction Study in Rats, DACO: 4.8

3070070 2019, Ipflufenoquin: Assessment to Determine the Need for a Comparative Thyroid Assay, DACO: 4.8

3070071 2019, In Vitro Comparative Metabolism Study of [^{14}C]NF-180 with Human and Rat Liver S9s, DACO: 4.8

3070020 2019, Ipflufenoquin: Dietary Exposure and Risk Assessment for Use on Pome Fruit (Crop Group 11-10) and Almond, DACO: 4.1,7.1

3073501 2019, Ipflufenoquin: Occupational Exposure and Risk Assessment for Use on Pome Fruit (Crop Group 11-09) in Canada, DACO: 5.1,5.2,5.3,5.6(A)

3073507 2019, Ipflufenoquin: Dietary Exposure and Risk Assessment for Use on Pome Fruit (Crop Group 11-09) and a Proposed Canadian Import Maximum Residue Limit on Almond, DACO: 4.1,7.1

3264173 2021, Data to Address Outstanding Data Reporting Requirements Kinoprol Technical (Ipflufenoquin; NF-180) Notice of Deficiencies Response to PMRA: Other Toxicological Studies – Antimicrobial Resistance, DACO: 4.8

3264174 2021, Data to Address Outstanding Data Reporting Requirements Kinoprol Technical (Ipflufenoquin; NF-180) Notice of Deficiencies Response to PMRA: Other Toxicological Studies – Antimicrobial Resistance, DACO: 4.8 CBI

3298662 2021, Outstanding data reporting requirements for the new active ingredient fungicide ipflufenoquin (Kinoprol Technical, containing ipflufenoquin, TGAI Submission Number: 2019-6970) Other Studies/Data/Reports (Antimicrobial Resistance), DACO: 4.8

3311098 Davidson, R.J., Davis, I., Willey, B.M., Rizg, K., Bolotin, S., Porter, V., Polskym J,, Daneman, N., McGeer, A., Yang, P., Scolnik, D., Rowsell, R., Imas, O., Silverman,M.S., 2008, Antimalarial therapy selection for quinolone resistance among *Escherichia coli* in the absence of quinolone exposure, in tropical South America., PLoS ONE 3(7): e2727. doi:10.1371/journal.pone.0002727 DACO: 4.8

3311101 Higgins, P.G., Fluit A.C., Milatovic, D., Verhoef, J., Schmitz, F.J., 2003, Mutations in GyrA, ParC, MexR and NfxB in clinical isolates of *Pseudomonas aeruginosa*., International Journal of Antimicrobial Agents 21 (2003) 409-413 DACO: 4.8

3311102 Konieczna, I., Lechowicz, L., Chrzanowska, M., et al., 2018, AB1319 Drug resistance in bacteria isolated from urine of rheumatoid arthritis patients and induction of resistance by chloroquine., Ann. Rheum.Dis. 10.1136/annrheumdis-2018-eular.5607 DACO: 4.8

3337436 2022, Assays of Topoisomerase inhibitory activity of ipflufenoquin, DACO: 4.8

3337437 2022, Ipflufenoquin: Toxicity Screening for Minimum Inhibitory Concentration, DACO: 4.8

3070080 2017, Metabolism of [14C]NF-180 by Grape, DACO: 6.3

3070081 2017, Metabolism of [14C]NF-180 by Apples (*Malus domestica*), DACO: 6.3

3070082 2018, Metabolism of [14C]NF-180 by Almonds, DACO: 6.3

3070090 2018, [A ring- 14C]72-9059 - Metabolism Study in Cucumber, DACO: 6.3

3073038	2017, Magnitude of The Residue of NF-180 Fungicide in Pome Fruit (Apples and Pears), DACO: 7.2.1,7.2.2,7.4,7.4.1
3073041	2016, Assessment and Validation of an Analytical Method for the Determination of Residues of NF-180 and its Photoproduct QP-2 in Apple, Grape, Wheat Grain, Almond and Dry Bean, Adapting the QuEChERS Multi-Residue Enforcement Method, DACO: 7.2.3A
3073042	2017, Validation of Method GPL-MTH-095 for the Determination of NF-180, QP-2, and Glycoconjugates in Pome Fruit by LC-MS/MS, DACO: 7.2.3A, 7.2.2
3073044	2019, Independent Laboratory Validation of Assessment and Validation of an Analytical Method for the Determination of Residues of NF-180 and its Photoproduct QP-2 in Apple, Grape, Wheat Grain, Almond, and Dry Bean, Adapting the QuEChERS Multi-Residue Enforcement Method, DACO: 7.2.3A
3073047	2019, Extraction Efficiency of Residues of NF-180 (Including Metabolites) from Apple and Grapes Crops, DACO: 7.2.3B
3073048	2018, Freezer Storage Stability of NF-180, QP-2, and Glycoconjugates in Apple Fruit, DACO: 7.3
3073049	2019, Determination of residues of NF-180, its Photoproduct QP-2 and its Glycoconjugates (represented by QP-1-2) analysed after hydrolysis as QP-1-1 in Apple processed fractions following three applications with NF-180 200SC at 4 sites 2 in Northern Europe and 2 in Southern Europe 2018, DACO: 7.4.5
3073039	2018, Magnitude of the Residue of NF-180 Fungicide in Almonds, DACO: 7.2.1, 7.4.1,7.4.2
3073040	2019, Validation of Method GPL-MTH-104 for the Determination of NF-180, QP-2, and Glycoconjugates in Almond Nutmeat and Almond Hulls by LC-MS/MS, DACO: 7.2.3A

3.0 Environment

PMRA Document Number	Reference
3070092	2018, Validation of Method GPL-MTH-099 for the Determination of NF-180, [CBI Removed] in Soils and Spray Application Targets by LC-MS/MS, DACO: 8.2.2.1
3070093	2019, Independent Laboratory Validation of Residue Analytical Method for Determination of NF-180, in Soil and NF-180 in Sediment, DACO: 8.2.2.1,8.2.2.2
3070094	2018, NF-180 - Validation of the Analytical Method for the Determination of a Test Substance in Sediment, DACO: 8.2.2.2
3070095	2018, NF-180 - Validation of the Analytical Method for the Determination of a Test Substance in Aqueous Solutions, DACO: 8.2.2.3

3070096	2019, Independent Laboratory Validation of Development and Validation of an Analytical Method for the Determination of NF-180 and its Metabolite in Surface and in Ground Water, DACO: 8.2.2.3
3070097	2018, Development and Validation of an Analytical Method for the Determination of NF-180 and its Metabolite in Surface and in Ground Water, DACO: 8.2.2.3
3070098	2017, [14C]NF-180 Validation of the Analytical Method for [Quinoline (benzene ring)-U-14C] NF-180 in Water, DACO: 8.2.2.3
3070099	2017, [14C]NF-180 Validation of the Analytical Method for [Quinoline (benzene ring)-U-14C] NF-180 in Fish Tissue, DACO: 8.2.2.4
3070100	2019, Hydrolysis of [14C]NF-180 in Aqueous Solutions at pH 4, 7, and 9, DACO: 8.2.3.2
3070101	2017, Photodegradation Study of [C ring-14C]NF-180 in a pH 7 Buffer , DACO: 8.2.3.3
3070102	2018, Photodegradation Study of [A ring-14C]NF-180 in a pH 7 Buffer , DACO: 8.2.3.3
3070103	2016, Photodegradation of [14C]NF-180 in/on Soil by Artificial Sunlight., DACO: 8.2.3.3
3070105	2017, Anaerobic soil metabolism of [14C]NF-180 in four US soils, DACO: 8.2.3.4.4
3070106	2017, Aerobic Soil Mineralization of [14C] NF-180 in Four US Soils, DACO: 8.2.3.4.2
3070107	2017, Aerobic soil metabolism of [14C]NF-180 in two US sediment/water test systems, DACO: 8.2.3.5.4
3070109	2017, Aerobic Mineralization of [14C] NF-180 in Surface Water, DACO: 8.2.3.5.4
3070110	2017, Anaerobic aquatic metabolism of [14C]NF-180 in two US test systems, DACO: 8.2.3.5.5
3070112	2018, [14C] NF-180: Adsorption/Desorption on soil , DACO: 8.2.4.2
3070113	2019, NF-180: Taxonomic Classification of Foreign Soils to Support Existing Adsorption-Desorption and Soil Photolysis Studies, DACO: 8.2.4.2,8.2.4.6
3070114	2019, Terrestrial field dissipation of NF-180 fungicide in bareground soil, DACO: 8.3.2.2,8.3.2.3
3070115	2018, Frozen Storage Stability of NF-180, QP-1-1, and QP-1-7 in Soil, DACO: 8.6
3140463	2017, Aerobic Mineralization of [14C]NF-180 in Surface Water, DACO: 8.2.3.5.4
3140464	2017, Aerobic Soil Metabolism of [14C]NF-180 in Four US Soils, DACO: 8.2.3.4.2
3140465	2017, Aerobic aquatic metabolism of [14C]NF-180 in two US sediment/water test systems, DACO: 8.2.3.5.4
3140466	2017, Anaerobic aquatic metabolism of [14C]NF-180 in two US test systems, DACO: 8.2.3.5.5
3070117	2018, NF-180: Effects (Acute Contact and Oral) on Honey Bees (*Apis mellifera* L.) in the Laboratory, DACO: 9.2.4.1,9.2.4.2

3070118 2018, NF-180: Toxicity to Honey Bee (*Apis mellifera* L.) Larvae after Repeated Exposure for 22 days under In Vitro Laboratory Conditions, DACO: 9.2.4.3

3070119 2019, NF-180: Honey Bee (*Apis mellifera* L.) Larval Toxicity Test, Single Exposure, DACO: 9.2.4.3

3070120 2017, NF-180: Chronic Oral Toxicity Test on the Honey Bee (*Apis mellifera* L.) in the Laboratory, DACO: 9.2.4.4

3070121 2016, NF-180 SC 200 g/L: Effects on the Parasitoid *Aphidius rhopalosiphi* in the Laboratory - Dose Response Test , DACO: 9.2.6

3070122 2017, NF-180: Acute Immobilization Study in *Daphnia magna*, DACO: 9.3.2

3070123 2018, NF-180 - Full Life-Cycle Toxicity Test with Water Fleas, Daphnia magna, Under Static-Renewal Conditions, DACO: 9.3.3

3070124 2018, NF-180: 10-Day Toxicity Test Exposing Midge (*Chironomus dilutus*) to a Spiked Sediment Under Static-Renewal Conditions, DACO: 9.3.4

3070126 2018, NF-180: A 10-Day Toxicity Test Exposing Freshwater Amphipods (*Hyalella azteca*) to a Spiked Sediment under Static-Renewal Conditions, DACO: 9.4.2

3070127 2018, NF-180: A 10-Day Toxicity Test Exposing Estuarine Amphipods (*Leptocheirus plumulosus*) to a Spiked Sediment under Static Conditions, DACO: 9.4.2

3070128 2019, NF-180 - Acute Toxicity to Mysids (*Americamysis bahia*) Under Static Conditions, Following OCSPP Draft Guideline 850.1035, DACO: 9.4.2

3070129 2017, NF-180 - Acute Toxicity to Eastern Oyster (*Crassostrea virginica*) Under Flow-Through Conditions, Following OCSPP Guideline 850.1025, DACO: 9.4.4

3070130 2018, NF-180 - Life-Cycle Toxicity Test with Mysids (*Americamysis bahia*), DACO: 9.4.5

3070131 2018, NF-180 - Acute Toxicity Test with Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions Following OECD Guideline 203 and OCSPP Guideline 850.1075, DACO: 9.5.2.1

3070132 2016, NF-180 - Acute Toxicity Test with Bluegill Sunfish (*Lepomis macrochirus*) Under Static Conditions Following OECD Guideline 203 and OCSPP Guideline 850.1075 , DACO: 9.5.2.2

3070133 2018, NF-180 - Acute Toxicity Test with Fathead Minnow (*Pimephales promelas*) Under Static Conditions Following OECD Guideline 203 and OCSPP Guideline 850.1075, DACO: 9.5.2.3

3070134 2017, NF-180 - Acute Toxicity to Sheepshead Minnow (*Cyprinodon variegatus*) Under Static-Renewal Conditions, Following OECD Guideline 203 and OCSPP Guideline 850.1075, DACO: 9.5.2.4

3070135 2018, NF-180 - Early Life-Stage Toxicity Test with Sheepshead Minnow, *Cyprinodon variegatus*, DACO: 9.5.3.1

3070136 2018, NF-180 - Early Life-Stage Toxicity Test with Fathead Minnow (*Pimephales promelas*), DACO: 9.5.3.1

3070137 2018, [14C]NF-180 - Flow-Through Bioconcentration and Metabolism Study with Bluegill Sunfish (*Lepomis macrochirus*), DACO: 9.5.6

3070138 2018, Northern Bobwhite (*Colinus virginianus*) Acute Oral Toxicity Test (LD_{50}) with NF-180, DACO: 9.6.2.1

3070139 2016, Mallard Duck (*Anas platyrhynchos*) Acute Oral Toxicity Test (LD_{50}) with NF-180, DACO: 9.6.2.2

3070140 2016, NF-180: Zebra Finch (*Taeniopygia guttata*) Oral Acute Toxicity Test, DACO: 9.6.2.3

3070141 2018, NF-180: Northern Bobwhite (*Colinus virginianus*) Dietary Toxicity Test (LC_{50}), DACO: 9.6.2.4

3070143 2018, NF-180: Mallard Duck (*Anas platyrhynchos*) Dietary Toxicity Test (LC_{50}), DACO: 9.6.2.5

3070145 2019, NF-180: Reproductive Toxicity Test with the Northern Bobwhite (*Colinus virginianus*), DACO: 9.6.3.1

3070146 2019, Ipflufenoquin: Weight of the Evidence Based Rationale for Setting the No Effect Level in Bean (2019b), A Bobwhite Quail Reproduction Study, DACO: 9.6.3.1

3070147 2019, Sample Analysis - NF-180: Reproductive Toxicity Test with the Mallard (*Anas platyrhynchos*), DACO: 9.6.3.2

3070148 2019, NF-180: Reproductive Toxicity Test with the Mallard (*Anas platyrhynchos*), DACO: 9.6.3.2

3070150 2017, NF-180: 96-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, DACO: 9.8.2

3070151 2017, NF-180: 96-Hour Toxicity Test with the Freshwater Cyanobacterium, *Anabaena flos-aquae*, DACO: 9.8.2

3070152 2017, NF-180 - 96-Hour Toxicity Test with the Freshwater Diatom, *Navicula pelliculosa*, DACO: 9.8.2

3070153 2017, NF-180 - 96-Hour Toxicity Test with the Marine Diatom, *Skeletonema costatum*, DACO: 9.8.3

3070154 2017, NF-180 SC 200 g/L: Effects on Terrestrial (Non-Target) Plants: Vegetative Vigour Test, DACO: 9.8.4

3070155 2017, NF-180 SC 200 g/L: Effects on Terrestrial (Non-Target) Plants: Seedling Emergence and Seedling Growth Test, DACO: 9.8.4

3070156 2017, NF-180 - 7-Day Toxicity Test with Duckweed (*Lemna gibba*), DACO: 9.8.5

3084751 2018, NF-180 Effects on Reproduction and Growth of Earthworms *Eisenia fetida* in Artificial Soil-signed, DACO: 9.2.3.2

3140462 2016, NF-180 SC 200 g/L: Effects on the Predatory Mite *Typhlodromus pyri* in the Laboratory - Dose Response Test -, DACO: 9.2.5

4.0 Value PMRA Document Number	Reference
3072016	2019, Summary of Value for Kinoprol 20 SC Fungicide, containing Ipflufenoquin, for Control of Apple Scab and Powdery Mildew on Pome Fruit (Crop Group 11-09), DACO: 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.3.1, 10.4, 10.5.1, 10.5.2, 10.5.3, 10.5.4
3072018	2014, Evaluation of SR-9059 for the Control of Powdery Mildew in Apples, DACO: 10.2.3.3(D)
3072019	2014, Evaluation of SR-9059 for the Control of Powdery Mildew in Apples, DACO: 10.2.3.3(D)
3072020	2014, Control of Apple Scab with New and Registered Fungicides on McIntosh Apples, 2014, DACO: 10.2.3.3(D)
3072021	2014, Evaluation of SR-9059 for the Control of Apple Scab and, if possible, Powdery Mildew in Apples, DACO: 10.2.3.3(D)
3072022	2014, Evaluation of SR-9059 for the Control of Apple Scab and other Diseases in Apples with Airblast Application, DACO: 10.2.3.3(D)
3072023	2014, Evaluation of SR-9059 for Control of Powdery Mildew in Apples, DACO: 10.2.3.3(D)
3072024	2016, Powdery Mildew Control on Apple, DACO: 10.2.3.3(D)
3072026	2016, Evaluate NF-180 for Disease Control on Apple, DACO: 10.2.3.3(D)
3072028	2016, Evaluate NF-180 for Disease Control on Apple (FINAL), DACO: 10.2.3.3(D)
3072029	2016, Evaluate NF-180 for Disease Control on Apple, DACO: 10.2.3.3(D)
3072030	2017, Evaluation of NF-180 for the control of powdery mildew and/or scab on apple, DACO: 10.2.3.3(D)
3072031	2017, Evaluation of NF-180 for the Control of Powdery mildew and/or Scab on Pear, DACO: 10.2.3.3(D)
3072032	2017, Evaluate NF-180 for Disease Control on Pear (FINAL), DACO: 10.2.3.3(D)
3072033	2017, Evaluation of NF-180 for the Control of Powdery mildew and/or Scab on Apple (FINAL), DACO: 10.2.3.3(D)
3072034	2017, Evaluate NF-180 for Disease Control on Pear (FINAL), DACO: 10.2.3.3(D)
3072035	2018, Non-GLP Field Efficacy of NF-180 on Pome Fruit Diseases, DACO: 10.2.3.3(D)
3072036	2018, Field Efficacy of NF-180 on Pome Diseases, DACO: 10.2.3.3(D)
3072037	2018, Field Efficacy of NF-180 on Pome Diseases, DACO: 10.2.3.3(D)
3072038	2018, Field Efficacy of NF-180 on Pome Diseases, DACO: 10.2.3.3(D)
3072039	2018, Field Efficacy of NF-180 on Pome Diseases, DACO: 10.2.3.3(D)
3072040	2018, Field Efficacy of NF-180, DACO: 10.2.3.3(D)
3072041	2018, Field Efficacy of NF-180 on Pome Diseases, DACO: 10.2.3.3(D)
3072042	2019, Field Efficacy of NF-180 on Pear Powdery Mildew, DACO: 10.2.3.3(D)
3072043	2019, Field Efficacy of NF-180 on Pear Powdery Mildew, DACO: 10.2.3.3(D)
3072044	2019, Non-GLP Field Efficacy of NF-180 on Pear Diseases, DACO:10.2.3.3(D)

B. Additional information considered

i) Published information

1.0 Human and animal health

PMRA Document Number	Reference
3385625	2015, Li XZ, Plésiat P, Nikaido H. The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. Clin Microbiol Rev 28(2):337-418. doi: 10.1128/CMR.00117-14., DACO: 4.8
3385626	2000, Marcinkeviciene J, Rogers MJ, Kopcho L, Jiang W, Wang K, Murphy DJ, Lippy J, Link S, Chung TD, Hobbs F, Haque T, Trainor GL, Slee A, Stern AM, Copeland RA. Selective inhibition of bacterial dihydroorotate dehydrogenases by thiadiazolidinediones. Biochem Pharmacol 60(3):339-342. doi: 10.1016/s0006-2952(00)00348-8., DACO: 4.8