Proposed Registration Decision PRD2025-09

Isofetamid 400SC Fungicide, containing Isofetamid

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Overview

Proposed registration decision for isofetamid

Health Canada's Pest Management Regulatory Agency (PMRA), pursuant to subsection 28(1) of the *Pest Control Products Act*, is proposing registration for the sale and use of Isofetamid 400SC Fungicide, containing the technical grade active ingredient isofetamid, to control botrytis grey mould (*Botrytis cinerea*) on greenhouse ornamentals. This evaluation was completed under the User Requested Minor Use Label Expansion program, which is a cooperative program between Agriculture and Agri-Food Canada and Health Canada's Pest Management Regulatory Agency and includes participation by sponsors group, manufacturers, and both provincial and federal governments.

Isofetamid 400SC Fungicide is currently registered to control various fungal diseases on a wide variety of crops under use-site category numbers 13, 14 and 30. For details, see Proposed Registration Decision PRD2014-19, *Isofetamid*, and Registration Decision RD2016-19, *Isofetamid*.

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 Isofetamid 400SC Fungicide, containing isofetamid.

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 individuals 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 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). They also consider the unique characteristics of organisms in the environment.

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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."

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

Before making a final registration decision on Isofetamid 400SC Fungicide, containing isofetamid, Health Canada's PMRA will consider any written comments received from the public directly related to the proposed decision in this consultation document.[3] Health Canada will then publish a Registration Decision[4] on Isofetamid 400SC Fungicide, containing isofetamid, 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 isofetamid?

Isofetamid is a member of the succinate-dehydrogenase inhibitor group of fungicides which affect fungal respiration. Isofetamid 400SC is applied via foliar applications to control or suppress various pathogens on certain crops.

Health considerations

Can approved uses of isofetamid affect human health?

Isofetamid 400SC Fungicide, containing isofetamid, is unlikely to affect your health when used according to label directions.

Potential exposure to isofetamid may occur through the diet (food and drinking water), when handling and applying the product or when in contact with treated surfaces. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

[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*.

In laboratory animals, the technical grade active ingredient isofetamid was of low acute toxicity by the oral, dermal and inhalation routes. It was non-irritating to skin, minimally irritating to eyes and did not cause an allergic skin reaction.

The acute toxicity of the end-use product Isofetamid 400SC Fungicide was low via the oral, dermal and inhalation routes of exposure. It was non-irritating to eyes and skin and did not cause an allergic skin reaction.

Prior to the initial registration of isofetamid, 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 isofetamid to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. As described in PRD2014-19, the most sensitive endpoints for risk assessment were effects on the liver and on the developing cardiovascular system. 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.

Risks in residential and other non-occupational environments

Non-occupational risks are not of concern when used according to label directions.

There are no risks in residential and other non-occupational environments as Isofetamid 400SC will only be applied in commercial greenhouses. Furthermore, exposure to treated ornamental plants that are subsequently purchased at retail locations is considered negligible.

Occupational risks from handling Isofetamid 400SC Fungicide

Occupational risks are not of concern when Isofetamid 400SC Fungicide is used according to the proposed label directions, which include protective measures.

Workers mixing, loading or applying Isofetamid 400SC Fungicide, and workers entering recently treated areas can come in direct contact with isofetamid residues on the skin and through inhalation. Therefore, the label specifies that anyone mixing, loading and applying Isofetamid 400SC Fungicide must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair. The label also requires that workers do not enter or be allowed into treated areas during the restricted-entry interval (REI) of 12 hours. Taking into consideration the label statements, the number of applications and the duration of exposure for handlers and postapplication workers, the health risks to these individuals from exposure to Isofetamid 400SC Fungicide are not of health concern.

Bystander exposure is considered negligible since the potential for drift is expected to be minimal. Application is limited to a greenhouse environment where there is no potential for drift. Therefore, bystander exposure and risk are not of health concern.

Environmental considerations

What happens when isofetamid is introduced into the environment?

When used according to label directions, the environmental risks associated with the major new use of isofetamid and its associated end-use product, Isofetamid 400SC Fungicide, on greenhouse ornamental plants are acceptable.

The environmental impact of the use of isofetamid as a foliar treatment against various *Botrytis* and *Sclerotinia* diseases on grape, lettuce (head and leaf), rapeseed (Crop Subgroup 20A), low growing berry (Crop Subgroup 13-07G), and turfgrass on golf courses and sod farm was evaluated in Proposed Registration Decision PRD2014-19, *Isofetamid,* and Registration Decision RD2016-19, *Isofetamid*. Isofetamid is toxic to aquatic organisms, birds and small wild mammals. Risk mitigation measures for these organisms are present on the registered label of Isofetamid 400SC Fungicide.

After a scientific review of the available information, the PMRA has concluded that the environmental risks associated with the major new use of isofetamid against *Botrytis cinerea* (Botrytis grey mould) on greenhouse ornamental plants are acceptable when Isofetamid 400SC Fungicide is used according to label directions.

Value considerations

What is the value of Isofetamid 400SC Fungicide?

Isofetamid is the active ingredient in Isofetamid 400SC Fungicide. Isofetamid 400SC Fungicide provides control of botrytis grey mould (*Botrytis cinerea*) on greenhouse ornamentals. The registration of Isofetamid 400SC Fungicide for this use will provide greenhouse ornamental growers with an alternative product for use to manage botrytis grey mould.

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 Isofetamid 400SC Fungicide to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human health

To reduce the potential of workers coming into direct contact with isofetamid on the skin or through inhalation, workers mixing, loading and applying Isofetamid 400SC Fungicide and performing cleaning and repair activities must wear long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. The label also requires that workers do not enter or be allowed entry into treated areas during the REI of 12 hours.

Environment

Label statement prohibiting the discharge of greenhouse releases, effluent or runoff to water.

Next steps

Before making a final registration decision on Isofetamid 400SC Fungicide, containing isofetamid, Health Canada's PMRA will consider any written comments received from the public that are directly related to this proposed decision, such as comments directed to the science evaluation, in response to this consultation document up to 45 days from the date of publication (26 September 2025) of this document. Please forward all comments to PMRA Publications, through the Public Engagement Portal (Public Engagement Forms – Consultation Comment). 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 Isofetamid 400SC Fungicide, containing isofetamid, (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 or if you have questions, please contact the PMRA's Pest Management Information Service.

Science evaluation

Isofetamid, Isofetamid 400SC Fungicide

1.0 The active ingredient, its properties and uses

1.1 Directions for use

Isofetamid 400SC Fungicide is applied as a foliar application to control botrytis grey mould on greenhouse ornamentals at 78–133 mL product per 100 L water. The product may be applied up to three times per crop cycle at the highest rate or up to six times per crop cycle at the lowest rate, with a 7–14 day re-application interval.

1.2 Mode of action

Isofetamid is a succinate-dehydrogenase inhibitor (FRAC Group 7) fungicide which affects fungal respiration. Isofetamid has both preventative and curative properties.

2.0 Impact on human and animal health

2.1 Hazard assessment

A detailed review of the toxicology database for isofetamid was conducted previously and is summarized in the Proposed Registration Decision, PRD2014-19 along with *Pest Control Products Act* Hazard Characterization. An extensive toxicology database is available for the assessment of human health effects of isofetamid and the data quality is considered adequate to define the majority of the toxic effects that may result from exposure to isofetamid. No new toxicology data were received for these proposed new uses. As the new uses for isofetamid are only for greenhouse ornamentals, the dietary risk assessment for isofetamid will not be impacted. Residential exposure to isofetamid resulting from these new uses will be limited. Given the limited scope of the new uses, the hazard assessment relied on the previous assessment and an updated review of the published literature was not conducted.

2.2 Toxicology reference values

Toxicology reference values for use in the human health risk assessment were established previously and are reported in PRD2014-19. At that time, however, reference values for use in assessing risks from long-term dermal and inhalation exposure were not established. For long-term dermal and inhalation occupational risk assessment, the no observed adverse effects levels (NOAEL) of 5.3 mg/kg bw/day from the 1-year oral study in the dog was selected. Effects on the liver were observed in this study. Long-term dermal and inhalation studies were not available and thus, the use of a NOAEL from an oral study was appropriate.

For this scenario, the target margin of exposure (MOE) is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this NOAEL and target MOE provides a margin of 2000 to the NOAEL for malformations in the rat developmental toxicity study, and is therefore considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 1.

2.3 Route and duration of exposure

For mixers, loaders and applicators, occupational exposure to Isofetamid 400SC Fungicide is characterized as short-term in duration and is predominantly by the dermal and inhalation routes. For postapplication workers, occupational exposure to isofetamid is characterized as long-term in duration for greenhouse uses, and is predominantly by the dermal route.

2.4 Dermal absorption

A dermal absorption value of 13% was selected for the risk assessment of isofetamid. Please refer to PRD2014-19 for further details regarding the dermal absorption of isofetamid.

2.5 Occupational and residential risk assessment

2.5.1 Acute hazards of Isofetamid 400SC Fungicide product and mitigation measures

The results of acute toxicity studies conducted with Isofetamid 400SC Fungicide are summarized in Appendix I, Table 2 of PRD2014-19. Isofetamid 400SC Fungicide is of low acute oral, dermal and inhalation toxicity in rats. It is non-irritating to the eyes and the skin of rabbits. It is not a skin sensitizer in mice by the local lymph node assay method. Based on these acute hazards, a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes are required during mixing, loading, application, clean-up and repair.

2.5.2 Occupational exposure and risk

2.5.2.1 Mixer/Loader/Applicator exposure and risk assessment

Individuals have the potential for exposure to isofetamid during mixing, loading, application, clean-up and repair activities.

Exposure estimates were derived for workers mixing and loading a liquid with an open-transfer system. Dermal and inhalation exposure estimates were generated from the Agricultural Handlers Exposure Task Force (AHETF) database and/or the Pesticide Handlers Database (PHED, v1.1) for mixers, loaders and applicators applying Isofetamid 400SC Fungicide to greenhouse ornamentals using conventional handheld application equipment. The unit exposure values in the risk assessment are based on handlers wearing a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes (Appendix I, Table 2).

Dermal exposure was estimated using the unit exposure values, the amount of product handled per day (derived from the maximum application rate and the default area treated per day), and the dermal absorption value of 13%.

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

Exposure estimates were compared to the selected toxicology reference value to obtain the MOE; the target MOE is 300 for short- to intermediate-term durations of dermal and inhalation exposure. Dermal and inhalation MOEs were combined, since the dermal and inhalation endpoints are based on the same toxicological effects. Calculated MOEs are greater than the target MOEs for all chemical handler scenarios for greenhouse ornamentals and are therefore not of health concern (Appendix I, Table 3).

Taking into account both the acute toxicity of the end-use product and the risk assessment of isofetamid, workers are required to wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes while mixing, loading, and applying Isofetamid 400SC Fungicide.

2.5.2.2 Postapplication exposure and risk assessment for workers entering treated areas

There is potential for long-term exposure to workers entering greenhouses treated with Isofetamid 400SC Fungicide to complete tasks such as scouting, transplanting, and hand weeding. Given the nature of activities performed, exposure should be primarily via the dermal route based on dermal contact with treated foliage.

Postapplication inhalation exposure is not considered to be a significant route of exposure as isofetamid is relatively non-volatile with a low vapour pressure of 4.2×10^{-10} kPa at 20°C, which is less than the North American Free Trade Agreement (NAFTA) criterion for a non-volatile product for greenhouse scenarios (1×10^{-5} kPa at 20–30°C) and the specified restricted-entry interval (REI) will allow residues to dry and suspended particles to settle.

Chemical-specific dislodgeable foliar residue (DFR) data for assessing human exposures during postapplication activities specific to greenhouse ornamentals were reviewed. The study was conducted at a research greenhouse in Agassiz, British Columbia. In the submitted DFR study, isofetamid was applied six times on a 6–8 day retreatment interval to greenhouse chrysanthemums at a nominal application rate of 533 g a.i./ha, which corresponds to the upper range of the proposed application rate, and is therefore not expected to underestimate exposure. Data were not corrected for recovery as all field fortification samples were above 95%.

For the purpose of this risk assessment, the actual DFR values were used instead of the predicted values, as the residues did not follow a linear decline model ($R^2<0.85$), and therefore the regression equation could not be used to estimate a dissipation rate. Therefore, the DFR values of 0.9893 µg/cm^2 (measured after the third application) and 1.0826 µg/cm^2 (measured after the sixth application) were deemed most appropriate for estimating postapplication exposure (Appendix I, Table 4). These values were chosen given the proposed use pattern and label restrictions, where three applications can be made at the higher rate of 533 g a.i./ha (used in the DFR study), while six applications can be made at the lower rate of 312 g a.i./ha.

Dermal exposure to workers entering treated areas is estimated by combining chemical-specific DFR values and a 13% dermal absorption factor with activity-specific transfer coefficients (TCs). Activity TCs are based on data from the Agricultural Re-entry Task Force (ARTF).

Exposure estimates were compared to the toxicology reference value (NOAEL = 5.3 mg/kg bw/day) 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. Although the calculated MOE of 94 for cut flowers (6 applications at 312 g a.i./ha) does not quite meet the target MOE of 100, the DFR value used in the risk assessment was derived from a higher application rate (~1.7× higher than the proposed rate for this use) and is therefore conservative and considered adequate to address the proposed use. The remaining calculated MOEs all exceed the target MOE of 100 and are thus, not of health concern (Appendix I, Table 5).

2.5.3 Residential exposure and risk assessment

2.5.3.1 Handler exposure and risk

Isofetamid 400SC Fungicide is not a domestic class product; therefore, a residential handler exposure assessment is not required.

2.5.3.2 Postapplication exposure and risk

Isofetamid 400SC Fungicide is not a domestic class product and is not for use in residential settings. Furthermore, exposure to treated ornamental plants that are subsequently purchased at retail locations is considered negligible. Residues are anticipated to decline from the time of application to the time of consumer purchase. In addition, the postapplication occupational exposure risk mitigation measures would also protect the consumer purchasing treated retail plants from dermal exposure. Therefore, a quantitative residential postapplication exposure assessment is not required.

2.5.3.3 Bystander exposure and risk

Bystander exposure is considered negligible as application is limited to within greenhouses only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas. Therefore, health risks to bystanders are not of concern when the end-use product is used according to the proposed label directions.

2.6 Aggregate exposure and risk assessment

For the proposed use of isofetamid on greenhouse ornamentals, no food or drinking water exposure is expected, and residential exposure is expected to be negligible; therefore, there is no impact on the aggregate risk assessment for isofetamid from the proposed use. The aggregate exposure to isofetamid from food, drinking water and residential exposure for the registered uses of isofetamid is covered by the risk assessments previously conducted (see PRD2014-19).

2.7 Cumulative assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative non-occupational exposure to pesticides with a common mechanism of toxicity, based on the likelihood that people may be exposed to more than one of these pesticides at the same time. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for the active ingredient isofetamid.

Isofetamid belongs to a class of fungicides known as the succinate dehydrogenase inhibitors (SDHI). Other SDHI fungicides registered in Canada and have maximum residue limit for imported commodities include benzovindiflupyr, bixafen, boscalid, carbathiin, cyclobutrifluram, fluopyram, flutolanil, fluxapyroxad, inpyrfluxam, isopyrazam, penflufen, penthiopyrad, pydiflumetofen, pyraziflumid, and sedaxane. Liver and thyroid toxicity linked to hepatic enzyme induction appears to be a common mechanism of action for several SDHI fungicides. A semi-quantitative cumulative risk assessment was conducted for the SDHI fungicides under the Proposed Registration Decision for cyclobutrifluram (PRD2025-06), which concluded that the cumulative risks from potential co-exposure to SDHIs through food, drinking water and residential exposure, where relevant, are acceptable.

The proposed expansion of use for isofetamid is for the control of botrytis grey mould (*B. cinerea*) on greenhouse ornamentals. No food or drinking water exposure is expected, and residential exposure is expected to be negligible from the proposed use. Therefore, the contribution of exposure to cumulative risk of the SDHI fungicides will not be impacted from the new use of isofetamid.

3.0 Impact on the environment

3.1 Fate and behaviour in the environment

Refer to Proposed Registration Decision PRD2014-19, *Isofetamid,* and Registration Decision RD2016-19, *Isofetamid*, for details on the environmental fate of isofetamid.

3.2 Environmental risk characterization

Refer to Proposed Registration Decision PRD2014-19, *Isofetamid,* and Registration Decision RD2016-19, *Isofetamid*, for the environmental risk assessment.

The risks to non-target organisms were evaluated using the maximum cumulative application rate for the proposed major new use on greenhouse ornamental plants.

The maximum cumulative application rate is 1599 g a.i./ha, with a maximum single rate of 533 g a.i./ha with 3 applications while the maximum cumulative registered rate of isofetamid is 5088 g a.i./ha, with a maximum single rate of 636 g a.i./ha with 8 applications. The proposed application rate is lower than the registered application rate. As such, the proposed major new use is not expected to increase the environmental exposure of non-target organisms to isofetamid.

4.0 Incident reports

Health incident reports

As of 17 April 2025, no human or domestic animal incidents involving isofetamid have been submitted to the PMRA.

Environment incident reports

As of 17 April 2025, no environment incidents involving isofetamid have been submitted to the PMRA.

5.0 Value

Isofetamid 400SC Fungicide will provide Canadian growers with an additional product to manage botrytis grey mould on greenhouse ornamental plants as part of an integrated disease management program. The value of this use is in part supported by the selection of botrytis grey mould on greenhouse ornamentals as an "A" priority at the 2017 Minor Use Priority Setting Workshop. The results of seven efficacy trials further support the value by providing evidence that Isofetamid 400SC Fungicide will control botrytis grey mould on greenhouse ornamentals when applied according to the use directions on the label.

6.0 Pest control product policy considerations

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

Refer to Proposed Registration Decision PRD2014-19, *Isofetamid,* and Registration Decision RD2016-19, *Isofetamid*, for further information on the Toxic Substances Management Policy 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*.[5] The list is used as described in the PMRA Science Policy Note SPN2020-01[6] and is based on existing policies and regulations, including the *Toxic Substance Management Policy* and *Formulants Policy*,[7] 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).*

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

6 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*

7 DIR2006-02, *Formulants Policy and Implementation Guidance Document*

The PMRA has reached the conclusion that isofetamid and its end use product, Isofetamid 400SC Fungicide, do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

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

7.0 Proposed regulatory decision

Health Canada's PMRA, pursuant to subsection 28(1) of the *Pest Control Products Act*, is proposing registration for the sale and use of Isofetamid 400SC Fungicide, containing the technical grade active ingredient isofetamid, to control botrytis grey mould (*Botrytis cinerea*) on greenhouse ornamental plants.

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.

List of abbreviations

µg	microgram(s)
ADI	Acceptable Daily Intake
AHETF	Agricultural Handler Exposure Task Force
a.i.	active ingredient
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
ATPD	Area Treated Per Day
bw	Bodyweight
CAF	Composite Assessment Factor
cm	Centimeter
DFR	Dislodgeable Foliar Residue
DIR	Regulatory Directive
FRAC	Fungicide Resistance Action Committee
g	Gram
ha	Hectare
hr	Hour
kg	Kilogram(s)
kPa	Kilopascal
L	litre(s)
mL	millilitre(s)
mg	Milligram(s)
MOE	margin of exposure
NAFTA	North American Free Trade Agreement
NOAEL	No Observed Adverse Effects Levels
PCPA	*Pest Control Products Act*
PMRA	Pest Management Regulatory Agency
PHED	Pesticide Handler Exposure Database
PPE	Personal Protective Equipment
PRD	Proposed Registration Decision
R^2	Coefficient of Determination
RD	Registration Decision
REI	restricted-entry interval
SPN	Science Policy Note
TC	Transfer Coefficient

Appendix I Tables

Table 1 Toxicology reference values for use in health risk assessment for isofetamid

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or Target MOE
Acute dietary (females 13–49)	Rat developmental toxicity study	NOAEL = 100 mg/kg bw/day Increased cardiovascular malformations	300
	ARfD = 0.3 mg/kg bw		
Acute dietary (general population)	Not required as no endpoint of concern attributable to a single exposure was identified.		
Repeated dietary (all populations)	1-year dog toxicity study	NOAEL = 5.3 mg/kg bw/day Increased liver weight, hepatocellular hypertrophy and clinical chemistry changes	100
	ADI = 0.05 mg/kg bw/day		
Short- and intermediate-dermal (Adults)[2]	Rat developmental toxicity study	NOAEL = 100 mg/kg bw/day Increased cardiovascular malformations	300
Short- and intermediate-dermal (Youth 6–11 years of age)	28-day dermal toxicity study in the rat	NOAEL = 1000 mg/kg bw/day No effects	100
Short- and intermediate-term inhalation (Adults)[3]	Rat developmental toxicity study	NOAEL = 100 mg/kg bw/day Increased cardiovascular malformations	300
Short- and intermediate-term inhalation (Youth 6–11 years of age)[3]	90-day oral toxicity study in the rat	NOAEL = 7 mg/kg bw/day Liver toxicity and clinical chemistry alterations	100
Long-term dermal[2] and inhalation[3] (All populations)	1-year oral toxicity study in the dog	NOAEL = 5.3 mg/kg bw/d Increased liver weight, hypertrophy and clinical chemistry changes	100
Aggregation of Short and Intermediate Oral and Inhalation Exposure (Youth 6–11 years of age)	90-day oral toxicity study in the rat	NOAEL = 7 mg/kg bw/day Liver toxicity and clinical chemistry alterations	100
Cancer	Not required since there was no evidence of oncogenicity		

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

[2] Since an oral NOAEL was selected, a dermal absorption factor of 13% was used for route-to-route extrapolation

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

Table 2 AHETF/PHED unit exposure estimates for mixers, loaders and applicators handling Isofetamid 400SC Fungicide (µg/kg a.i. handled)

Exposure scenario and PPE		Dermal	Dermal Absorbed[1]	Inhalation[2]	Total Unit Exposure[3]
PPE: Single layer and chemical-resistant gloves					
Mixer/loader AHETF estimates					
A	Open Mix/Load Liquids	58.50	7.61	0.63	8.24
Mixer/loader/applicator PHED estimates					
B	Manually Pressurized Handwand (MPHW)	943.37	122.64	45.20	167.84
C	Backpack sprayer	5445.85	707.96	62.10	770.06
D	Mechanically Pressurized Handgun (MPHG)	5585.49	726.11	151	877.11

[1] DAF of 13% was applied to the dermal exposure estimates

[2] Light inhalation rate except for backpack, which has a moderate inhalation rate

[3] Total unit exposure = Dermal exposure + inhalation exposure

Table 3 Mixer/Loader/Applicator risk assessment

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]
PPE: Single layer and chemical-resistant gloves						
A	Open Mix/Load Liquids (Chemigation/automated sprayer)	8.24	1.6	0.533	8.78×10^{-5}	1138454
B	Manually Pressurized Handwand (MPHW)	167.84	1.6	0.533	1.79×10^{-3}	55892
C	Backpack sprayer	770.06	1.6	0.533	8.21×10^{-3}	12182
D	Mechanically Pressurized Handgun (MPHG)	877.11	1.6	0.533	9.35×10^{-3}	10695

[1] Unit exposure based on AHETF/PHED

[2] Area treated per day (ATPD) based on 95th percentile "greenhouse cut flowers" area of 1.6 from Statistics Canada 2021 Agricultural Census data

[3] Daily exposure = (AHETF/PHED Unit exposure × ATPD x Rate) / (80 kg bw × 1000 µg/mg)

[4] Target MOE = 300; based on NOAEL of 100 mg/kg bw/day for short-term dermal and inhalation exposure

Table 4 Isofetamid dislodgeable foliar residue results on greenhouse ornamentals

Location	Greenhouse in Agassiz, British Columbia
Peak DFR	1.4105 ug/cm^2 on Day 2 after the 6th application
DFR on Day 0 after the 3rd application	0.9893 ug/cm^2
DFR on Day 0 after the 6th application	1.0826 ug/cm^2
Equation of linear regression	y = -0.0183 – 0.2265
Coefficient of determination (R^2)	0.83
Correlation coefficient (R)	-0.91
Slope	-0.0183

Table 5 Postapplication exposure and risk estimates to workers for isofetamid

Postapplication activity	Application rate	TC[1] (cm^2/hr)	DFR value[2] (µg/cm^2)	Dermal Exposure[3] (mg/kg bw/day)	MOE[4]	REI[5]
Greenhouse ornamentals (not for cut flower production)	3 at higher rate (533 g IFM/ha)	230	0.9893	0.0030	1792	12 hours
	6 at lower rate (312 g IFM/ha)	230	1.0826	0.0032	1637	12 hours
Cut flowers (hand harvesting, disbudding, hand pruning)	3 at higher rate (533 g IFM/ha)	4000	0.9893	0.0514	103	12 hours
	6 at lower rate (312 g IFM/ha)	4000	1.0826	0.0563	94	12 hours

DFR = Dislodgeable foliar residue; TC = Transfer Coefficient; MOE = Margin of Exposure; REI = Restricted-Entry Interval

[1] Transfer coefficients obtained from PMRA Agricultural TCs Table (01.19.2023)

[2] DFR values from DFR study data (Review PMRA# 3500563, Calculations PMRA# 3557265). The use pattern requiring 3 applications at the higher rate used the DFR value of 0.9893 µg/cm^2, measured after Application #3 in the DFR study; the use pattern requiring 6 applications at the lower rate used the DFR value of 1.0826 µg/cm^2, measured after Application #6 in the DFR study.

[3] Exposure = (Peak DFR [µg/cm^2] × TC [cm^2/hr] × 8 hours/day × 13% dermal absorption) / (80 kg bw × 1000 µg/mg)

[4] Based on a NOAEL of 5.3 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.

References

List of studies/Information submitted by registrant

1.0 Human and Animal Health

PMRA document number	Reference
3463436	2023, Final DFR Report "Isofetamid: Dislodgeable Foliar Residue Dissipation from Greenhouse Ornamentals – Chrysanthemum", DACO 5.9

2.0 Value

PMRA document number	Reference
2913187	2018, Value Rationale and Trial Summaries - Isofetamid 400SC (isofetamid) for the control of Botrytis grey mold on greenhouse ornamentals, DACO: 10.1,10.2.3.1
2913188	2018, References Cited - Isofetamid 400SC (isofetamid) for the control of Botrytis grey mold on greenhouse ornamentals, DACO: 10.6