Proposed Registration Decision PRD2023-08

Pyriofenone 300 SC Fungicide, containing pyriofenone

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Publications
Pest Management Regulatory Agency
Health Canada
2 Constellation Drive
8th floor, A.L. 2608 A
Ottawa, Ontario K1A 0K9

Internet: canada.ca/pesticides
pmra.publications-arla@hc-sc.gc.ca

Information Service:
1-800-267-6315
pmra.info-arla@hc-sc.gc.ca

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Overview

Proposed registration decision for Pyriofenone 300 SC Fungicide

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 Pyriofenone 300 SC Fungicide, containing the technical grade active ingredient pyriofenone, to suppress/control powdery mildew on greenhouse ornamentals, greenhouse pepper, greenhouse eggplant, greenhouse cucumber and greenhouse tomato. 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 sponsor groups, manufacturers, and both provincial and federal governments.

The end use product, Pyriofenone 300 SC Fungicide, and the active ingredient, pyriofenone, are currently registered for the control of powdery mildew on field grown food crops and outdoor ornamentals. For details, see Proposed Registration Decision PRD2016-23, *Pyriofenone*, and Registration Decision RD2016-33, *Pyriofenone*.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of Pyriofenone 300 SC, containing pyriofenone, 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 Pyriofenone 300 SC Fungicide, containing pyriofenone, when applied to greenhouse ornamentals and greenhouse cucumber, pepper, eggplant and tomato.

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.

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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

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 Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of the Canada.ca website.

Before making a final registration decision on Pyriofenone 300 SC Fungicide, containing pyriofenone, 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 Pyriofenone 300 SC Fungicide, containing pyriofenone, 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 pyriofenone?

Pyriofenone disrupts cellular activity, leading to reduced growth and reproduction of the fungus. This active ingredient is effective against powdery mildew on agricultural and ornamental crops.

Health considerations

Can approved uses of pyriofenone affect human health?

Pyriofenone 300 SC Fungicide, containing pyriofenone, is unlikely to affect your health when used according to label directions.

Potential exposure to pyriofenone may occur through the diet (food and drinking water) or when coming into contact with treated surfaces or when handling and applying Pyriofenone 300 SC Fungicide. 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.

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contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

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

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

The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose level where 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 pyriofenone and the associated end-use product Pyriofenone 300 SC Fungicide were both of low acute toxicity by the oral, dermal, and inhalation routes of exposure. They were both 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 pyriofenone to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were abortions and adverse effects noted in the kidneys. 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.

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

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and children 1–2 years olds, the subpopulation which would ingest the most pyriofenone residues relative to body weight, are expected to be exposed to less than 9% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from pyriofenone is not of health concern for all population subgroups.

Pyriofenone is not carcinogenic; therefore, a cancer dietary risk assessment is not required.

Animal studies revealed no acute health effects. Consequently, a single dose of pyriofenone is not likely to cause acute health effects in the general population (including infants and children).

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using pyriofenone on greenhouse tomatoes, greenhouse peppers and greenhouse cucumbers are acceptable. The MRLs for this active ingredient can be found in the Science evaluation section of this Consultation/Evaluation Document.

Occupational risks are not of health concern when Pyriofenone 300 SC Fungicide is used according to the proposed label directions, which include protective measures.

Workers mixing, loading or applying Pyriofenone 300 SC Fungicide, and workers entering recently treated greenhouses can come in direct contact with pyriofenone residues on the skin and through inhalation. Therefore, the label specifies that anyone mixing, loading and applying Pyriofenone 300 SC Fungicide must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. The label also requires that workers do not enter or be allowed into treated areas during the restricted-entry interval (REI) of 12 hours. Taking into consideration the label statements, the number of applications and the duration of exposure for handlers and postapplication workers, the risks to these individuals are not of health concern.

Health risks to bystanders

Bystander risks are not of health concern when Pyriofenone 300SC Fungicide is used according to the proposed label directions and spray drift restrictions are observed.

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

Environmental considerations

Environmental risks associated with the use of pyriofenone are acceptable when Pyriofenone 300SC Fungicide is used according to label directions.

The new uses of pyriofenone on greenhouse ornamentals and greenhouse food crops may result in exposure to beneficial arthropods and pollinators used for greenhouse pest management and pollination. Considering the application rates and patterns for the greenhouse uses, and the ecotoxicity data available in PRD2016-23, risks from pyriofenone were found to be acceptable for beneficial arthropods and pollinators in greenhouses. A label statement is required to prevent greenhouse effluent containing pyriofenone from entering aquatic systems.

Value considerations

What is the value of Pyriofenone 300 SC Fungicide?

Pyriofenone is a fungicide for use against powdery mildew on ornamental crops and certain vegetable crops grown in the greenhouse.

Powdery mildew affects the aesthetic quality and marketability of ornamental plants and can negatively affect the yield and quality of vegetable crops. Canadian growers identified management of powdery mildew on greenhouse ornamental crops as a national priority at the Canadian Minor Use Priority Setting Workshop in 2014. Pyriofenone will contribute to protection against powdery mildew and the management of pathogen resistance.

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 Pyriofenone 300 SC Fungicide 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 pyriofenone through direct contact on the skin or through inhalation, workers mixing, loading and applying Pyriofenone 300 SC Fungicide and performing cleaning and repair activities must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. The label also requires that workers do not enter or be allowed entry into treated greenhouses during the REI of 12 hours. Furthermore, a standard label statement to protect against drift during application and to prevent the use of handheld airblast, misters and foggers are present on the label.

Environment

Label statement to prohibit greenhouse effluent containing pyriofenone from entering aquatic systems.

Next steps

Before making a final registration decision on Pyriofenone 300SC Fungicide, Health Canada's PMRA will consider any comments received from the public in response to this consultation document. Health Canada will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international

trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

Other information

When the Health Canada makes its registration decision, it will publish a Registration Decision on Pyriofenone 300 SC Fungicide, containing pyriofenone (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

1.0 The active ingredient, its properties and uses

There was no proposed change to the registered formulation of Pyriofenone 300 SC Fungicide. For information about pyriofenone and its properties, refer to Proposed Registration Decision PRD2016-23, *Pyriofenone* (referred to as PRD2016-23 in the rest of this consultation document).

1.1 Directions for use

Applications should be initiated prior to disease development at the following rates: Greenhouse ornamentals at 15–45 mL/100 L water; Greenhouse vegetable crops at 300–366 mL/ha. Repeat applications should be made at 7–10 day intervals up to a maximum of 900 mL/ha per year for greenhouse ornamentals or a maximum of 1.2 L/ha per crop cycle for greenhouse pepper, eggplant, tomato, and cucumber. The higher rate and shorter interval should be used under high disease pressure.

1.2 Mode of action

Pyriofenone interacts with the cytoskeleton and motor proteins of fungi, which disrupts cellular action, prevents the formation of haustoria, and inhibits fungal sporulation and mycelial growth. Pyriofenone is classified as a Group 50 fungicide by the Fungicide Resistance Action Committee (FRAC).

2.0 Methods of analysis

Please refer to PRD2016-23 for the detailed review of the methods of analysis.

3.0 Impact on human and animal health

3.1 Toxicology summary

Pyriofenone (5-chloro-2-methoxy-4-methylpyridin-3-yl)-(2,3,4-trimethoxy-6-methylphenyl) methanone is an aryl phenyl ketone developed for the control of powdery mildew in cereals, grapes, and vegetables. The fungicidal mode-of-action for this group of fungicides involves the disruption of the actin cytoskeleton.

A detailed review of the toxicological database for pyriofenone was previously conducted and published under PRD2016-23. The database was complete, consisting of the full array of toxicity studies required for hazard assessment purposes. The studies were carried out in accordance with accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database was considered adequate to characterize the potential health hazards associated with pyriofenone. For the toxicological summary, see PRD2016-23.

The results of acute toxicity studies conducted with the end-use product Pyriofenone 300SC Fungicide are summarized in Appendix I, Table 3 of PRD2016-23. Pyriofenone 300SC Fungicide was of low acute toxicity by the oral, dermal, and inhalation routes of exposure in rats. It was not an eye or skin irritant in rabbits and was negative for dermal sensitization when tested using the Buehler method in guinea pigs.

Exposure to pyriofenone, from the proposed uses of Pyriofenone 300SC, may occur via the diet and drinking water, as well as occupationally via the dermal route over the short- to the long-term and via inhalation over the short- to intermediate-term. Toxicology reference values for use in the human health risk assessment for most of these exposure scenarios were established previously and are reported in PRD2016-23. At that time, however, a reference value for use in assessing risk from long-term dermal exposure had not been established. For the current review, for long-term dermal risk assessment, a NOAEL of 9 mg/kg bw/day from the 2-year dietary toxicity study in the rat was selected. At the dose level of 46.5 mg/kg bw/day, chronic nephropathy was observed. The use of the 28-day dermal toxicity study in rats was not considered appropriate for the long-term dermal scenario as there was evidence of durational effects in the database.

For this long term dermal occupational scenario, the target MOE for this endpoint is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Cumulative assessment

The *Pest Control Products Act* requires that the PMRA 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 pyriofenone. One other pesticide from the same aryl phenyl ketone class, metrafenone, is registered in Canada; however, there is insufficient evidence to link the apical endpoints observed in the toxicology databases for these two pesticides to a specific mode of action. Furthermore, the toxicological effects following exposure to this class of fungicides are considered indicative of more generalized toxicity, and a common mechanism of toxicity has not been identified. Therefore, a cumulative health risk assessment is not required at this time.

3.2 Toxicology reference values

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

3.2.1 Route and duration of exposure

For mixers, loaders and applicators, occupational exposure to Pyriofenone 300SC Fungicide is characterized as short to intermediate-term in duration and is predominantly by the dermal and inhalation routes. For postapplication workers, occupational exposure to pyriofenone is characterized as long-term in duration and is predominantly by the dermal route.

3.3 Dermal absorption

A rat in vivo dermal absorption study was previously reviewed. Based on the data presented in the study, a dermal absorption value of 35% was selected for the risk assessment of pyriofenone.

The dermal absorption of pyriofenone was determined in vivo in male Sprague Dawley rats. Rats were dermally administered doses of either 0.0045 mg a.i./cm^2 (low dose) or 3 mg a.i./cm^2 (high dose) and monitored up to 168 hours post-dosing. Exposure periods were 6, 10, or 24 hours before skin was washed, and the termination period ranged from 10 hours to 168 hours depending on the group. Excreta (feces and urine) were collected at multiple time points from the time of dosing to the time of sacrifice for all exposure groups. Analyzed matrices included excreta, cage wash, blood and plasma, carcass, the O-ring and protective cover, skin wash, skin at the application site, tape strips, and hair. Overall mean group recoveries of the applied dose of ^{14}C-IKF-309 (radiolabelled active ingredient) ranged from 95 to 101%.

The total absorbed dose was calculated as the sum of the amounts in the tape strips, skin at the application site, cage wash, urine, feces, carcass, blood and plasma. Maximum mean percent absorption values for the low and high dose groups were estimated for rats exposed for and sacrificed at 24 hours (39% and 1.3%, respectively). Minimum mean percent absorption values for the low and high dose groups were estimated for rats exposed for 6 hours and sacrificed 24 hours post-dosing (24% and 0.6%, respectively). The observed pattern of dermal absorption suggests that pyriofenone might reach a threshold of absorption with increasing dose as the percent of the applied dose that was absorbed was substantially lower in the high dose group compared to the low dose group at all combinations of exposure duration and sacrifice time tested.

The low dose group represents the dose group most closely related to handling the diluted end-use product in the field. The dermal absorption value for the 168 hours post-dosing measurement is considered the most appropriate for estimating the dermal absorption of IKF-309. Therefore, a dermal absorption value of 35% was selected for risk assessment purposes.

3.4 Occupational and residential exposure assessment

3.4.1 Acute hazards of Pyriofenone 300SC Fungicide product and mitigation measures

The acute hazard assessment indicated that Pyriofenone 300SC is of low acute toxicity by the oral, dermal and inhalation routes in rats. It is minimally irritating to the rabbit eye and non-irritating to the rabbit skin. The formulation is not a skin sensitizer in guinea pigs. Based on these acute hazards, a long-sleeved shirt, long pants, socks, and chemical-resistant gloves are required for workers during mixing, loading, application, clean-up and repair.

3.4.2 Occupational exposure and risk assessment

3.4.2.1 Mixer, loader and applicator exposure and risk assessment

Individuals have potential for exposure to pyriofenone 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 Database (PHED, v1.1) for mixers, loaders and applicators applying Pyriofenone 300SC Fungicide to greenhouse grown ornamentals, and greenhouse cucumbers, peppers, eggplants, and tomatoes using handheld application equipment and automated 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 by coupling the unit exposure values with the amount of product handled per day with a dermal absorption value of 35%. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the selected toxicology reference value to obtain the margin of exposure (MOE); the target MOE is 300. Dermal and inhalation MOEs were combined, since the dermal and inhalation reference values are based on the same toxicological effects. Calculated MOEs are greater than the target MOE of 300 for all chemical handler scenarios for greenhouse grown crops 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 pyriofenone, workers are required to wear long sleeved shirt, long pants, chemical resistant gloves, socks and shoes.

3.4.2.2 Exposure and risk assessment for workers entering treated areas

There is potential for exposure to workers entering areas treated with Pyriofenone 300SC Fungicide to complete tasks such as harvesting, disbudding, and pruning. Given the nature of activities performed, exposure should be primarily via the dermal route based on contact with treated foliage. Inhalation exposure is not expected as pyriofenone is considered non-volatile

with a vapour pressure of 1.9×10^{-6} Pa (at 25°C), which is less than the North American Free Trade Agreement (NAFTA) criterion for a non-volatile product for outdoor scenarios [1×10^{-4} kPa (7.5×10^{-4} mm Hg) at 20-30°C]. As such, a quantitative postapplication inhalation risk assessment is not required. Inhalation risk is not of health concern for postapplication workers as pyriofenone is considered to be non-volatile and the restricted-entry interval of 12 hours will allow residues to dry, suspended particles to settle and vapours to dissipate.

Dermal exposure to workers entering treated areas is estimated 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). As chemical-specific DFR data were not submitted, a default DFR value of 25% of the application rate coupled with 2% daily dissipation of residues were used in the exposure assessment.

Exposure estimates were compared to the 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, and are thus, not of health concern (Appendix I, Table 4). The REI of 12 hours is adequate to protect workers entering treated greenhouses to conduct postapplication activities.

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk assessment

Pyriofenone 300SC Fungicide is not a domestic class product; therefore, a residential handler exposure assessment is not required.

3.4.3.2 Postapplication exposure and risk assessment

Pyriofenone 300SC Fungicide is not a domestic class product and is not for use in residential settings; therefore, a residential postapplication exposure assessment is not required.

3.4.4 Bystander exposure and risk assessment

Bystander exposure is considered negligible as application is limited to 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, bystander exposure and risk are not of health concern since the potential for drift is expected to be minimal.

3.5 Food residues exposure assessment

3.5.1 Residues in plant and animal foodstuffs

Please refer to PRD2016-23 for the complete review of residues of pyriofenone in plants and animal foodstuffs.

In the context of the current applications, greenhouse trials conducted throughout Canada using an end-use product containing pyriofenone at approved rates in or on greenhouse tomatoes and greenhouse peppers are sufficient to support the proposed maximum residue limits. The greenhouse trials conducted in the United States using an end-use product containing pyriofenone at approved rates in or on greenhouse cucumbers are sufficient to support the proposed use. Residues are expected to be covered by the established MRL for this commodity.

3.5.2 Dietary risk assessment

A chronic (non-cancer) dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™).

3.5.2.1 Chronic dietary exposure results and characterization

The following criteria were applied to the basic chronic non-cancer analysis for pyriofenone: 100% crop treated, default processing factors, Canadian MRLs and American tolerances for imported commodities. The basic chronic dietary exposure from all supported pyriofenone food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 9% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to pyriofenone from food and drinking water is 2% (1.9×10^{-3} 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 9% (8.1×10^{-3} mg/kg bw/day) of the ADI.

3.5.2.2 Acute dietary exposure results and characterization

No appropriate toxicological reference value attributable to a single dose for the general population (including children and infants) was identified.

3.5.3 Maximum residue limits

Maximum residue limits (MRLs) are currently established for residues of pyriofenone on the commodities within crop group 8-09 (fruiting vegetables). Based on the greenhouse trials reviewed with the current application, MRLs are now being proposed for the crop subgroups of crop group 8-09, leading to a decrease for crop subgroup 8-09A (tomatoes) and an increase for crop subgroup 8-09B (peppers/eggplants). Dietary risks from the consumption of foods listed in Table 3.5.1 were shown to be acceptable when pyriofenone 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 MRLs in Table 3.5.1 be specified for residues of pyriofenone. Residues of pyriofenone from the use of Pyriofenone 300SC Fungicide on greenhouse cucumbers will be covered by the established MRL of 0.3 ppm on cucumbers. For specific details related to the increase and decrease in MRLs, refer to PMRL2023-44, *Pyriofenone*.

Table 3.5.1 Proposed maximum residue limits

Commodity	Recommended MRL (ppm)
Peppers/Eggplants (crop subgroup 8-09B)	2
Tomatoes (crop subgroup 8-09A)	0.2

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

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

The nature of the residues in plant matrices, analytical methodologies, and freezer storage stability data are summarized in PRD2016-23. Greenhouse trial data and chronic dietary risk estimates are summarized in Appendix I, Tables 5 and 6.

3.6 Aggregate exposure and risk assessment

For pyriofenone, the aggregate assessment consisted of combining food and drinking water exposure only, since residential exposure is not expected.

3.7 Health incident reports

As of 27 June 2023, no human or domestic animal incidents involving pyriofenone had been submitted to the PMRA.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

The environmental fate and behavior of pyriofenone is discussed in detail in PRD2016-23. Only major aspects relevant to the greenhouse environment are listed here. Briefly, when pyriofenone is sprayed on foliage, it may be distributed throughout the plant. In soil, pyriofenone is slightly persistent to persistent.

4.2 Environmental risk characterization

During the previous assessment of field uses, pyriofenone was found to be toxic to freshwater algae and marine invertebrates, and field uses were found to pose a slight risk to these organisms (see PRD2016-23 for details). Guidance is present on the label for Pyriofenone 300SC Fungicide to mitigate risk to aquatic organisms from field use. In addition, a standard label statement is required to prohibit the release of greenhouse effluent to aquatic habitats.

Greenhouse uses require consideration of risk to pollinators and beneficial arthropods that may be used in pest management and pollination programs. Regarding the new use on greenhouse food crops, the application rate and pattern for greenhouse peppers, eggplants, tomatoes, and cucumbers falls within what is registered for field uses of pyriofenone. Since the risk to pollinators and beneficial arthropods from registered field uses was found to be acceptable in PRD2016-23 and RD2016-33, the environmental risk from the use on greenhouse peppers, eggplants, tomatoes, and cucumbers is also acceptable. Environmental risk mitigation specific to pollinators and beneficial arthropods is not required for the greenhouse food crop uses.

Regarding the new use on greenhouse ornamentals, the application to greenhouse ornamentals results in greater estimated environmental concentrations (EECs) for both beneficial arthropods and pollinators, relative to what was assessed for registered field uses in PRD2016-23. As a result, an environmental risk assessment for greenhouse ornamental use was conducted for both of these groups of organisms. The environmental risk assessment approach was the same as that described in PRD2016-23. Briefly, risk quotients (RQs) were determined by dividing EECs by ecotoxicity effect metrics. Risk quotients were then compared to the relevant level of concern (LOC) to determine the potential for risk.

At the screening level, the application rates and patterns resulting in maximum EECs were used. Toxicity endpoints were taken from PRD2016-23. The resulting screening level risk quotients for use on greenhouse ornamentals were all below the respective levels of concern. Thus, environmental risk mitigation specific to pollinators and beneficial arthropods is not required for the use on greenhouse ornamentals. Risk quotients, toxicity endpoints, and EEC calculation details can be found in Appendix I, Table 7.

4.3 Environmental incident reports

As of 27 June 2023, no environment incident reports involving pyriofenone had been submitted to the PMRA.

5.0 Value

Powdery mildew in greenhouse vegetable production was identified as a key pest priority by the minor use grower community in both Canada and the United States. Cooperative data generated between Agriculture and Agri-Food Canada’s Pest Management Centre and the United States Interregional Research Project No. 4 (IR-4) on greenhouse pepper, cucumber and tomato resulted in simultaneous submission to PMRA and the United States Environmental Protection Agency (USEPA), who collaborated on the scientific evaluation of the data. Such collaborations endeavor to result in regulatory decisions within similar timeframes and harmonized MRLs, ensuring equal access to labelled uses for producers on both sides of the border and thereby avoidance of potential trade barriers.

A total of 17 efficacy trials were reviewed in support of the use claims. The trials demonstrated suppression of powdery mildew on greenhouse pepper and eggplant, as well as one causal pathogen that infects greenhouse tomato. The product controlled powdery mildew on greenhouse ornamentals, cucumber and two causal pathogens on greenhouse tomato.

The submitted evidence supports the following claims. The complete claims and use directions are presented in Appendix 1, Table 8.

- **Control** of powdery mildew (*Podosphaera* spp., *Golovinomyces cichoracearum* (syn. *Erysiphe cichoracearum***)**) on greenhouse ornamental plants
- **Suppression** of powdery mildew (*Leveillula taurica*) on greenhouse pepper
- **Suppression** of powdery mildew (*Leveillula taurica*) on greenhouse eggplant
- **Control** of powdery mildew (*Podosphaera xanthii, Golovinomyces cichoracearum*) on greenhouse cucumber
- **Control** of powdery mildew (*Oidium lycopersici, O. neolycopersici*), **Suppression** of powdery mildew (*Leveillula taurica*) on greenhouse tomato

Powdery mildew can negatively affect the quality of greenhouse crops resulting in reduced economic returns for growers. Pyriofenone 300SC was chosen as the potential solution to manage powdery mildew, providing a key alternative mode of action for resistance management.

6.0 Pest control product policy considerations

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

The PMRA has reached the conclusion that pyriofenone and its transformation products do not meet all of the Toxic Substances Management Policy (TSMP) Track 1 criteria. Please refer to PRD2016-23 for further information on the TSMP assessment.

6.2 Formulants and contaminants of health or environmental concern

The PMRA has reached the conclusion that Pyriofenone 300SC Fungicide contains the preservative 1,2-benzisothiazoline-3-one which contains low levels of dioxins and furans. These contaminants are being managed as outlined in the PMRA Regulatory Directive DIR99-03[5] for the implementation of the TSMP. Other formulants and contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*[6] are not expected to be present in Pyriofenone 300SC Fungicide or technical grade pyriofenone. Please refer to PRD2016-23 for further details on the assessment of formulants and contaminants.

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

6 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.*

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 Pyriofenone 300 SC Fungicide, containing the technical grade active ingredient pyriofenone, to suppress/control powdery mildew on greenhouse ornamentals, greenhouse pepper, greenhouse eggplant, greenhouse cucumber and greenhouse tomato.

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
a.i.	active ingredient
ADI	acceptable daily intake
AHETF	Agricultural Handler Exposure Task Force
ARTF	Agricultural Re-entry Task Force
ATPD	area treated per day
bw	body weight
CAF	composite assessment factor
cm	Centimeter
d	day
DFR	Dislodgeable Foliar Residue
DIR	Regulatory Directive
EEC	estimated environmental concentration
FRAC	Fungicide Resistance Action Committee
g	gram(s)
h	hour
ha	hectare
HAFT	highest average field trial
hr	Hour
kg	kilogram(s)
kPa	Kilopascal
L	liter
LAFT	lowest average field trial
LD_{50}	lethal dose causing 50% mortality
LOC	level of concern
LR_{50}	lethal rate causing 50% mortality
mg	milligram(s)
mL	milliliter
MOE	Margin of Exposure
MRL	maximum residue limit
NAFTA	North American Free Trade Agreement
NOAEL	No Observed Adverse Effects Levels
PHED	Pesticide Handler Exposure Database
PHI	preharvest interval
PMRA	Pest Management Regulatory Agency
PPE	Personal Protective Equipment
ppm	parts per million
PRD	Proposed Registration Decision
RAC	raw agricultural commodity
RD	residue definition
RD	Registration Decision
REI	Restricted-Entry Interval

RQ	risk quotient
RTI	Retreatment Interval
TC	Transfer Coefficient
TSMP	Toxic Substances Management Policy

Appendix I Tables and figures

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

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or target MOE
Acute dietary	Establishment of an acute reference dose is not required, as an endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies.		
Repeated dietary	2-year rat dietary	NOAEL = 9 mg/kg bw/day Chronic nephropathy	100
	ADI = 0.09 mg/kg bw/day		
Short- and intermediate-term dermal[2] and inhalation[3] exposure	Rabbit Developmental	NOAEL = 100 mg/kg bw/day Abortions at 300 mg/kg bw/day	300
Long-term dermal[2]	2-year rat dietary	NOAEL = 9 mg/kg bw/day Chronic nephropathy	100
Cancer	A cancer risk assessment was not required		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors (PCPA factors) for dietary assessments; MOE refers to a target MOE for occupational assessments.

[2] Since an oral NOAEL was selected, a dermal absorption factor (35%) was used in a route-to-route extrapolation.

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

Table 2 AHETF and PHED unit exposure estimates for mixers, loaders and applicators handling Pyriofenone 300SC 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 – Automated application (chemigation) AHETF estimates					
A	Open mixing/loading of a liquid	58.50	20.48	0.63	21.11
Mixer/loader + Applicator PHED estimates					
B	Liquid open pour low pressure handwand (scenario 21a)	943.37	330.18	45.20	375.38
C	Liquid open pour backpack (scenario 23a)	5445.85	1906.05	62.1	1968.15
D	Liquid open pour high pressure handwand (scenario 24a)	5585.49	1954.92	151	2105.92

[1] Adjusted with dermal absorption factor 35%

[2] Light inhalation rate (except for backpack - moderate inhalation rate)

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

Table 3 Mixer/loader/applicator risk assessment – Greenhouse vegetables and greenhouse ornamentals

Mixer/Loader/Applicator risk assessment – Greenhouse vegetables					
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- Vegetables	21.11	3.6	0.11	1.04E-04	957215
B- Vegetables	375.38	3.6	0.11	1.86E-03	53818
C- Vegetables	1968.15	3.6	0.11	9.74E-03	10264
D- Vegetables	2105.92	3.6	0.11	1.04E-02	9593
Mixer/Loader/Applicator risk assessment – Greenhouse ornamentals					
Exposure scenario	**Unit exposure (µg/kg a.i. handled)[1]**	**ATPD (L/day)[2]**	**Rate (kg a.i./L)**	**Daily exposure (mg/kg bw/day)[3]**	**MOE[4]**
PPE: Single layer and chemical-resistant gloves					
A- Ornamentals	21.11	1.3 ha/day	0.135 kg a.i./ha	4.63E-05	2159869
B- Ornamentals	375.38	150	0.000135	9.50E-05	1052433
C- Ornamentals	1968.15	150	0.000135	4.98E-04	200728
D- Ornamentals	2105.92	3800	0.000135	1.35E-02	7405

[1] Unit exposure based on AHETF and PHED
[2] Default Area Treated per Day table (updated on 2021-09-14)
[3] Daily exposure = (Unit exposure x ATPD × Rate) / (80 kg bw × 1000 µg/mg)
[4] Based on NOAEL = 100 mg/kg bw/day, target MOE = 300 (see Table 1)

Table 4 Postapplication exposure and risk estimates for pyriofenone on day 0 after the last application

Postapplication activity	**Peak DFR (µg/cm^2)[1]**	**Transfer coefficient (cm^2/hr)[2]**	**Dermal exposure (mg/kg bw/day)[3]**	**MOE[4]**	**REI[5]**
Greenhouse vegetables- all activities Use pattern: 4 applications at 90 g ai/ha; 7 day RTI	0.7371	1400	0.0361	249	12
Greenhouse ornamentals- cut flowers; Use pattern: 2 applications at 135 g ai/ha; 7 day RTI	0.6305	4000	0.0883	102	12

[1] Calculated using the default 25% dislodgeable on the day of application and 2% dissipation per day

[2] Transfer coefficients obtained from PMRA Agricultural TCs Table (09.14.2021)
[3] Exposure = (Peak DFR [µg/cm^2] × TC [cm^2/hr] × 8 hours × 35% dermal absorption) / (80 kg bw × 1000 µg/mg)
[4] Based on a NOAEL of 9 mg/kg bw/day, target MOE = 100 (see Table 1)
[5] Minimum REI is 12 hours to allow residues to dry suspended particles to settle and vapours to dissipate.

Table 5 Integrated food residue chemistry summary

Crop residue trials and residue decline on greenhouse peppers — **PMRA No. 3197233**

Greenhouse trials were conducted in 2017 in Canada. Trials were conducted in NAFTA Growing Regions 5 (2 trials) and 12 (2 trials) for a total of 4 trials. Of these, 2 trials were conducted on bell peppers and 2 trials on non-bell peppers. Pyriofenone 300SC Fungicide, a suspension concentrate formulation of pyriofenone, was applied four times as foliar directed application at a rate of 89.4–140 g a.i./ha/application for a seasonal application rate of 362–423 g a.i./ha. The applications were made at 6-8 day intervals with the last application occurring 0 days before harvest. No adjuvant was used.

Residue decline data show that residues of pyriofenone in greenhouse peppers increased between the 0- and 7-day preharvest intervals (PHIs) and decreased thereafter to levels similar to those at the 0-day PHI. Adequate storage stability data are available to support the storage intervals of the greenhouse trials. Samples were analyzed using a validated enforcement method.

Commodity	Total application rate (g a.i./ha)	PHI (days)	Residue levels (ppm)					
			n	LAFT	HAFT	Median	Mean	SD
Pyriofenone								
Bell peppers	365–382	0–7	2	0.058	0.333	0.195	0.195	N/A
Non-bell peppers	362–423	0	2	0.159	0.886	0.523	0.523	N/A

n = number of independent greenhouse trials.
LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation, N/A= Not applicable.
Values based on per-trial averages.

Crop residue trials and residue decline on greenhouse cucumbers — **PMRA No. 3197854**

Greenhouse trials were conducted in 2015 and 2016 in the United States. Trials were conducted in NAFTA Growing Regions 3 (2 trials), 5 (1 trial) and 10 (1 trial) for a total of 4 trials. Pyriofenone 300SC Fungicide, a suspension concentrate formulation of pyriofenone, was applied four or five times as foliar directed application at a rate of 85–93 g a.i./ha/application for a seasonal application rate of 342–440 g a.i./ha. The applications were made at 6–8 day intervals with the last application occurring 0 days before harvest. No adjuvant was used.

Residue decline data show that residues of pyriofenone decreased in greenhouse cucumbers with increasing preharvest intervals (PHIs). Adequate storage stability data are available to support the storage intervals of the greenhouse trials. Samples were analyzed using a validated enforcement method.

Commodity	Total application rate (g a.i./ha)	PHI (days)	Residue levels (ppm)					
			n	LAFT	HAFT	Median	Mean	SD
Pyriofenone								
Cucumbers	342-440	0	4	0.031	0.087	0.064	0.062	0.023

n = number of independent greenhouse trials.
LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation.
Values based on per-trial averages.

Crop residue trials and residue decline on greenhouse tomatoes	PMRA No. 3197894

Greenhouse trials were conducted in 2017 and 2018 in Canada. Trials were conducted in NAFTA Growing Regions 5 (4 trials) and 12 (1 trial) for a total of 5 trials. Pyriofenone 300SC Fungicide, a suspension concentrate formulation of pyriofenone, was applied four times as foliar directed application at a rate of 87.3–97.3 g a.i./ha/application for a seasonal application rate of 354–372 g a.i./ha. The applications were made at 6-8 day intervals with the last application occurring 0 days before harvest. No adjuvant was used.

Residue decline data show that residues of pyriofenone in greenhouse tomatoes increased between the 0- and 3-day preharvest intervals (PHIs) and decreased with increasing PHI. Adequate storage stability data are available to support the storage intervals of the greenhouse trials. Samples were analyzed using a validated enforcement method.

Commodity	Total application rate (g a.i./ha)	PHI (days)	Residue levels (ppm)					
			n	LAFT	HAFT	Median	Mean	SD
Pyriofenone								
Tomatoes	354–372	0-3	5	0.040	0.079	0.047	0.052	0.016

n = number of independent greenhouse trials.
LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation.
Values based on per-trial averages.

Table 6 Food residue chemistry overview of risk assessment

Dietary risk from food and water			
	Population	Estimated risk % of acceptable daily intake (ADI)	
		Food alone	Food and water
Basic chronic non-cancer dietary exposure analysis **ADI = 0.09 mg/kg bw/day** **Estimated chronic drinking water concentration = 1.17 µg/L (Level 1, surface water)**	**All infants < 1 year**	2.7	2.8
	Children 1–2 years	9.0	9.0
	Children 3 to 5 years	5.8	5.8
	Children 6–12 years	2.6	2.6
	Youth 13–19 years	1.3	1.3
	Adults 20–49 years	1.5	1.6

	Adults 50+ years	1.7	1.7
	Females 13-49 years	1.6	1.6
	Total population	2.0	2.1

Table 7 Screening level risk assessment for pollinators and beneficial arthropods from use on greenhouse ornamentals

Organism	Effect metric[a]	EEC[b]	RQ	LOC exceeded?[c]
Parasitoid wasp (*Aphidius rhopalosiphi*)	48-h LR_{50}: >1000 g a.i./ha	218 g a.i./ha	<0.22	No
Predatory mite (*Typhlodromus pyri*)	7-d LR_{50}: >1035 g a.i./ha	218 g a.i./ha	<0.21	No
Adult honeybee (*Apis mellifera*)	48-h LD_{50} (acute, contact): >100 µg a.i./bee	0.324 µg a.i./bee	<0.01	No
	48-h LD_{50} (acute, oral): >100 µg a.i./bee	3.92 µg a.i./bee	<0.04	No
	10-d NOAEL (chronic, oral): 27 µg a.i./bee	3.92 µg a.i./bee	0.15	No
Larval honeybee (*Apis mellifera*)	72-h LD_{50} (acute, oral): >100 µg a.i./bee	1.62 µg a.i./bee	<0.02	No

[a] Taken from PRD2016-23.

[b] EEC: Estimated Environmental Concentration. Beneficial arthropods: based on the maximum single application rate (135 g a.i./ha) × 2 applications at a 7-day interval, assuming a default 10-day foliar half-life. Bees: maximum single application rate × adjustment factor of 2.4 µg a.i./bee per kg a.i./ha (adult, contact), 29 µg a.i./bee per kg a.i./ha (adult, oral), or 12 µg a.i./bee per kg a.i./ha (larva, oral).

[c] LOC: Level of Concern = 2 for glass plate studies with beneficial arthropod indicator species *T. pyri* and *A. rhopalosiphi*, 0.4 for acute risk to pollinators, and 1 for chronic risk to pollinators.

Table 8 List of supported uses

Supported use claims
Control of powdery mildew (*Podosphaera* spp., *Golovinomyces cichoracearum* (syn. *Erysiphe cichoracearum*)) on greenhouse ornamental plants at a rate of 15–45 mL product/100 L water. Initiate applications prior to disease development and continue on a 7 to 10 day interval beginning with initial flowering or when disease conditions are favourable for disease development, but prior to disease development. Within the stated ranges, use the lowest rate and the longest interval as disease preventative sprays or when disease conditions are low.

Increase to the highest rate and the shortest interval under moderate to heavy disease pressure. The maximum spray volume is 1000 L/ha. Do not apply more than 900 mL product (270 g a.i.)/ha/year (for example, 2 at 135 g a.i./ha or 3 at 90 g a.i./ha or 6 at 45 g a.i./ha).
Suppression of powdery mildew (*Leveillula taurica*) on greenhouse pepper and greenhouse eggplant at a rate of 0.3–0.366 L product/ha. Initiate applications prior to disease development and continue on a 7 to 10 day interval beginning with initial flowering or when disease conditions are favourable for disease development, but prior to disease development. Within the stated ranges, use the lowest rate and the longest interval as disease preventative sprays or when disease conditions are low. Increase to the highest rate and the shortest interval under moderate to heavy disease pressure. Normal spray volumes range from 500 to 2000 litres per hectare. Do not apply more than 1.2 L product (360 g a.i.)/ha/crop cycle.
Control of powdery mildew (*Podosphaera xanthii, Golovinomyces cichoracearum*) on greenhouse cucumber at a rate of 0.3–0.366 L product/ha. Initiate applications prior to disease development and continue on a 7 to 10 day interval beginning with initial flowering or when disease conditions are favourable for disease development, but prior to disease development. Within the stated ranges, use the lowest rate and the longest interval as disease preventative sprays or when disease conditions are low. Increase to the highest rate and the shortest interval under moderate to heavy disease pressure. Normal spray volumes range from 500 to 2500 litres per hectare. Do not apply more than 1.2 L product (360 g a.i.)/ha/crop cycle.
Control of powdery mildew (*Oidium lycopersici, O. neolycopersici*), **Suppression** of powdery mildew (*Leveillula taurica*) on greenhouse tomato at a rate of 0.3–0.366 L product/ha. Initiate applications prior to disease development and continue on a 7 to 10 day interval beginning with initial flowering or when disease conditions are favourable for disease development, but prior to disease development. Within the stated ranges, use the low rate and the longest interval as disease preventative sprays or when disease conditions are low. Increase to the highest rate and the shortest interval under moderate to heavy disease pressure. Normal spray volumes range from 300 to 1500 litres per hectare. Do not apply more than 1.2 L product (360 g a.i.)/ha/crop cycle.

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

The MRLs proposed for pyriofenone in Canada are the same as corresponding tolerances established in the United States.

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

Currently, there are no Codex MRLs[7] listed for pyriofenone in or on fruiting vegetables on the Codex Alimentarius Pesticide Index webpage.

[7] 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 Human and animal health

PMRA No.	Reference
3197233	2020, Pyriofenone: Magnitude of the Residue on Pepper, Greenhouse, DACO: 7.4.1,7.4.2
3197854	2018, Pyriofenone: Magnitude of the Residue on Cucumber (Greenhouse (GH)), DACO: 7.4.1,7.4.2
3197894	2020, Pyriofenone: Magnitude of the Residue on GH Tomato, DACO: 7.4.1,7.4.2
2933151	Thomas, J. 2018. *In Vivo* Percutaneous Absorption of [^{14}C]-IKF-309 in the Rat. Charles River Laboratories Ashland, LLC (1407 George Road, Ashland OH, United States). Laboratory Project ID 00282041, October 2, 2018. Unpublished.

2.0 Value

PMRA No.	Reference
3196883	2020, Value Report, DACO: 10.1
3196885	2020, Field Trial Reports, DACO: 10.2.3.3
3196886	2020, references cited, DACO: 10.6
3197234	2020, Value Report, DACO: 10.1
3197236	2020, a field trial report, DACO: 10.2.3.3
3197237	2020, references cited, DACO: 10.6
3197855	2020, Value Report, DACO: 10.1
3197857	2014, a field trial report, DACO: 10.2.3.3
3197858	2020, references cited, DACO: 10.6
3197895	2020, Value Report, DACO: 10.1
3197897	2017, a field trial report, DACO: 10.2.3.3
3197898	2020, references cited, DACO: 10.6

B. Additional information considered

i) Published information

1.0 Human and animal health

PMRA Document Number	Reference
3323965	Kunova, A., Pizzatti, C., Saracchi, M., Pasquali, M., & Cortesi, P. (2021). Grapevine Powdery Mildew: Fungicides for Its Management and Advances in Molecular Detection of Markers Associated with Resistance. Microorganisms, 9(7), 1541.
3323966	Liu, X., Xiao, Y., Li, J. Q., Fu, B., & Qin, Z. (2019). 1, 1-Diaryl compounds as important bioactive module in pesticides. Molecular Diversity, 23(3), 809-820. https://doi.org/10.1007/s11030-018-9895-3
3323967	Opalski, K. S., Tresch, S., Kogel, K. H., Grossmann, K., Köhle, H., & Hückelhoven, R. (2006). Metrafenone: studies on the mode of action of a novel cereal powdery mildew fungicide. Pest Management Science: formerly Pesticide Science, 62(5), 393-401. https://doi.org/10.1002/ps.1176