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Registration Decision RD2024-11

# Pyriofenone 300 SC Fungicide, containing pyriofenone

*(publié aussi en français)*

**19 November 2024**

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

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

Canada

ISSN: 1925-0932 (print)
1925-0940 (online)

Catalogue number: H113-25/2024-11E (print version)
H113-25/2024-11E-PDF (PDF version)

Under the authority of the *Pest Control Products Act*, pesticides must be assessed before they are sold or used in Canada in order to determine that they do not pose unacceptable risks to humans or the environment and have value when used according to the label instructions. The pre-market assessment considers available data and information[1] from pesticide registrants, published scientific reports, other governments, and international regulatory agencies, as well as written comments if received during public consultations. Health Canada applies internationally accepted current risk assessment methods as well as risk management approaches and policies. More details, on the legislative requirements, risk assessment and risk management approach, are provided under the section of Evaluation approach of this document.

## Registration Decision Statement[2] for Pyriofenone 300 SC Fungicide

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is granting registration for the sale and use of Pyriofenone 300 SC Fungicide, containing the technical grade active ingredient pyriofenone, to control suppress/control powdery mildew on greenhouse ornamentals, greenhouse pepper, greenhouse eggplant, greenhouse cucumber and greenhouse tomato.

The Proposed Registration Decision PRD2023-08, *Pyriofenone 300 SC Fungicide, containing pyriofenone,* containing the detailed evaluation of the information submitted in support of this registration, underwent a 45-day consultation period ending on 24 November 2023. The evaluation found that under the approved conditions of use, the health and environmental risks and the value of the pest control product(s) are acceptable. Health Canada received written comments relating to the health assessments during the public consultation period conducted in accordance with section 28 of the *Pest Control Products Act*.

## Comments and responses

### Comments on the cancer risk assessment

### General discussion

Most of the comments received focused on the cancer risk assessment of pyriofenone. The commenter expressed concerns that Health Canada did not conduct a cancer risk assessment for pyriofenone whereas the European Food Safety Authority (EFSA) classified pyriofenone as a category 2 carcinogen (H351 - suspected of causing cancer). The commenter also raised general questions surrounding Health Canada's data requirements for cancer hazard assessment and the decision process to determine the requirement for a cancer risk assessment.

To register a food-use pesticide in Canada such as pyriofenone, a large number of toxicology studies is required. The requirements include an assessment of carcinogenicity and a battery of in vitro and in vivo genotoxicity studies. These requirements are published in the Guidance for Developing Datasets for Conventional Pest Control Product Applications. Evaluation of cancer

[1] Information Note – *Determining Study Acceptability for use in Pesticide Risk Assessments*

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

risks is an integral part of Health Canada's framework for risk assessment. Health Canada's approach for cancer hazard assessment is similar to that of the United States Environmental Protection Agency (USEPA) approach and also considers available international guidance on cancer assessment. This approach typically incorporates the results of at least two separate long-term cancer studies in different species, other repeat-dose toxicity studies in multiple species that can provide further details about mechanisms of toxicity, and a battery of genotoxicity studies. When no cancer concerns are identified, as was the case for the pyriofenone evaluation, the documentation will state that a cancer risk assessment is not required. When a cancer concern is identified, there are generally two approaches used by the PMRA:

1) Cancer effects for which a dose threshold was established - Reference values (ARfD, ADI) are established for assessing dietary exposures that consider both the acute and the chronic nature of the toxic effects, including cancer threshold effects. The determination of whether dietary exposure is acceptable is made by comparing the estimated human exposure to the dietary reference value (ARfD and ADI);

2) Cancer effects for which a dose threshold was not established – The linearized multistage (LMS) model is used to calculate the likelihood or probability of developing cancer (lifetime cancer risk) from an average daily lifetime exposure.

These two hazard assessments are then applied against various human exposure models to assess risk to ensure that Canadians are protected from potential hazards. Please refer to the Framework for Risk Assessment and Risk Management of Pest Control Products for more details. The EU uses a hazard-based approach and may classify a compound as carcinogenic without taking into consideration the levels of possible human exposure and the potential risk to humans. If a pesticide is classified as carcinogenic by the EU, it is sometimes ineligible for registration in Europe.

The toxicology database for pyriofenone is considered complete since it fulfills all the data requirements in support of the registration (Guidance for developing datasets for conventional pest control applications). Health Canada conducted a detailed review of the toxicology database, including an assessment of two carcinogenicity studies submitted, namely a 2-year rat study (2010) and 78-week mouse study (2010). These studies were also reviewed by EFSA, USEPA, and the Joint Meeting on Pesticide Residues (JMPR). In addition, Health Canada assessed a battery of genotoxicity studies with an adequate range of in vitro and in vivo assays.

Health Canada concluded that there was no evidence of carcinogenicity for pyriofenone. In other words, there was no treatment-related increase in tumour incidence of any kind in rats and mice following a lifetime daily oral exposure to pyriofenone. Because a cancer hazard was not identified in the available toxicology database, a cancer risk assessment was not necessary (as stated in page 18 of Proposed Registration Decision PRD2016-23, *Pyriofenone*). This conclusion is consistent with that of the USEPA. JMPR stated that there was limited evidence of carcinogenicity in the livers of male mice and that pyriofenone was not carcinogenic in female mice or rats. JMPR established a carcinogenicity LOAEL in mice at 716 mg/kg bw/day. They concluded that pyriofenone is unlikely to pose a carcinogenic risk to humans from the diet.

**Comment 1:**

The commenter indicated that the EFSA determined that pyriofenone is a category 2 carcinogen (H351 – suspected of causing cancer), based on combined incidences of hepatocellular adenomas and carcinomas in male rats at 197 mg/kg bw/day with a NOAEL of 36.4 mg/kg bw/day in a 2-year dietary rat study (2010). The commenter raised a concern that Health Canada based their cancer assessment on a 2-year rat study and 78-week mouse study that are more than ten years old.

**Health Canada's response:**

Health Canada reviewed the same carcinogenicity studies as EFSA, JMPR, and the USEPA to assess the carcinogenic potential of pyriofenone. These studies satisfy the most recent guideline requirements for scientific studies that have been conducted according to internationally-approved study protocols and Good Laboratory Practices (GLP) for carcinogenicity studies in rodents (OPPTS 870.4200, 1998 and OECD 451, 2018). Health Canada did not consider the increase in hepatocellular adenomas and carcinomas in males to be treatment related in the 2-year dietary rat study (2010). The increase in adenomas, carcinomas, and the increase in combined adenoma/carcinoma incidence was not statistically significant and no dose-related increasing trend was observed in the combined incidence of adenomas/carcinomas. The increase in hepatocellular adenomas at the high dose was marginal (six animals with adenomas at 197 mg/kg bw compared to four animals with adenomas in the control group) and the adenomas were not considered to progress to carcinomas (only two animals with carcinomas at the high dose). Based on the lack of treatment related increase in tumour incidence of any kind in rats and mice, Health Canada concluded that pyriofenone was not carcinogenic. This conclusion is consistent with the USEPA and JMPR decisions.

**Comment 2:**

The commenter acknowledged that the European Chemicals Agency Committee for Risk Assessment (ECHA RAC) was of the opinion that pyriofenone was a "borderline case for classification as a carcinogen". However, the commenter also indicated that a rat study that shows increases in hepatocellular adenomas and carcinomas accompanied by reduced survival is concerning. The commenter indicated that they disagreed with Health Canada's decision to waive the requirement for a cancer study, stating that the regulatory question under s.2(2) of the *Pest Control Products Act* is whether there is a compelling scientific basis to exclude carcinogenicity - not whether there is proof of carcinogenicity, particularly at the stage where Health Canada is just determining whether or not to require a cancer assessment. The commenter also stated that it is not clear how Health Canada can determine that no harm will occur, with reasonable certainty, without requiring some follow up information on pyriofenone carcinogenicity from the registrant in light of the conclusions of EFSA scientific experts.

**Health Canada's response:**

EFSA classifies carcinogens in accordance with Regulation (EC) No 1272/2008. Cancer classification under Regulation (EC) No 1272/2008 is a hazard-based classification based on intrinsic properties and does not provide information on the level of the human cancer risk which the use of the substance or mixture may represent. Therefore, anticipated exposure modelling is not applied in a similar manner as in Canada and the US. As stated in the comment, ECHA RAC was of the opinion that pyriofenone was a "borderline case for classification as a carcinogen". Nonetheless, RAC agreed with EFSA's conclusion and reached a consensus to classify pyriofenone as a category 2 carcinogen (H351 - suspected of causing cancer).

Health Canada assesses pesticide health risks, including cancer risks, using a risk-based approach (refer to the general discussion). Health Canada concluded there was no treatment-related increase in tumour incidence in rats (refer to the previous comment for more information) or in mice. Because a cancer hazard was not identified in the available toxicology database, a cancer risk assessment was not necessary. In contrast, EFSA established a NOAEL for carcinogenic effects of 36.4 mg/kg bw/day. EFSA employed a threshold-based approach to the human health risk assessment that was considered protective against both tumours and other health effects. EFSA established an ADI for pyriofenone of 0.07 mg/kg bw/day based on the study NOAEL from the rat carcinogenicity study. Health Canada used the same long-term rat study to establish an ADI, though the dose level for females was selected, which resulted in a similar ADI of 0.09 mg/kg bw/day. Health Canada's assessment is protective of the adverse effects of pyriofenone resulting from chronic exposure by ensuring that the level of human exposure is well below the lowest dose at which toxicological effects occurred in animal tests.

Health Canada did not waive a requirement for cancer studies. As mentioned in the general discussion, Health Canada reviewed the same carcinogenicity studies as EFSA, namely the 2-year rat study and 78-week mouse study. In addition, Health Canada assessed a battery of genotoxicity studies. Based on a thorough review of these studies, and considering the weight of evidence as discussed above, Health Canada concluded that there was no cancer hazard associated with pyriofenone. Therefore, a cancer risk assessment was not conducted.

S2(2) of the *Pest Control Products Act* states:
"For the purposes of this Act, the health or environmental risks of a pest control product are acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the product, taking into account its conditions or proposed conditions of registration."

As mentioned above, Health Canada concluded there was no treatment-related increase in tumour incidence of any kind in rats or in mice following a lifetime daily oral exposure to pyriofenone. Because there was no evidence of carcinogenicity for pyriofenone, a cancer risk assessment was not necessary. The risk assessment of pyriofenone demonstrated that the level of human exposure to pyriofenone is well below the lowest dose at which health effects occurred in animal tests and hence protective against its effects (refer to PRD2016-23 and PRD2023-08). Therefore, Health Canada's assessment of pyriofenone is considered protective of potential human health effects as per S2(2) of the *Pest Control Products Act*.

**Comment 3:**

The commenter stated that the data relied on to support the decision to "decline to conduct a cancer risk assessment" does not appear to meet the USEPA Cancer Guidelines. The commenter also stated that the PMRA lacks transparency around data requirements for carcinogenicity assessments.

**Health Canada response:**

Health Canada provides clear guidance on the toxicology data requirements to support pesticide registrations in Guidance for Developing Datasets for Conventional Pest Control Product Applications. This document contains detailed information on Health Canada's data requirements for toxicology evaluations, including potential cancer hazards.

Health Canada also provides detailed information on data requirements per Use-Site Category (USC). In this case, the relevant USC categories are USC 6 (Data Requirements for Use Site Category (USC # 6): Greenhouse Non-Food Crops -TGAI), USC 14 (Data Requirements for Use Site Category (USC # 14): Terrestrial Food Crops - TGAI), and USC 27 (Ornamentals Outdoor - Technical Grade Active Ingredients: Data Requirements for Use Site Category (USC # 27): Ornamentals Outdoor - TGAI). A cancer hazard assessment is performed for all food-use conventional pesticides. If a pesticide is not considered carcinogenic or if the observed carcinogenicity is considered to occur via a threshold mode of action (as EFSA determined for pyriofenone), then a separate human health cancer risk assessment is not conducted, as the established chronic toxicology reference value (in other words, ADI) is considered protective of the threshold effect.

As stated in the general discussion, Health Canada reviewed the same carcinogenicity studies as the USEPA and EFSA to assess the carcinogenic potential of pyriofenone. Both Health Canada and the USEPA concluded that there was no evidence of carcinogenicity. Based on the PMRA conclusion, it was determined that a separate cancer risk assessment was not required in the absence of evidence of carcinogenicity.

Please refer to the General Discussion section of this document as well as Health Canada's Guidance Document: A Framework for Risk Assessment and Risk Management of Pest Control Products for information on the cancer hazard characterization and cancer risk assessment at Health Canada.

**Comment on the cumulative risk assessment**

The commenter stated that published literature (EFSA, 2018) on cumulative risk assessment includes suggestions that pyriofenone is part of a subgroup of pesticides including bitertanol, bromuconazole, clethodim, dithianon, fenarimol, flazasulfuron, phoxim, pyridate, quinmerac, spirodiclofen, vinclozolin and others which cause liver enzyme induction. These pesticide active ingredients were not included in the cumulative assessment for pyriofenone. The commenter suggested that the PMRA should conduct a cumulative risk assessment of these active ingredients.

**Health Canada's response:**

Health Canada conducts cumulative health assessments based on the framework described in Science Policy Note Science Policy Note SPN2018-02 - Cumulative Health Risk Assessment Framework. In order to identify pesticides that might cause a common toxic effect by a common mechanism of toxicity, preliminary grouping is undertaken based on structural similarity, similar mechanism of action, or similarity of toxic effects. A weight-of-evidence approach is then used to refine the grouping. A cumulative health risk assessment is conducted if the pesticides with a common mechanism of toxicity have a potential for co-exposure.

None of the pesticides cited in the comment are in the same chemical class or in the same pesticidal mode of action group as pyriofenone.

Pyriofenone belongs to the aryl phenyl ketone class of pesticides. Only one other pesticide from this class, metrafenone, is registered in Canada. Metrafenone is also the only pesticide other than pyriofenone that is classified as a Group 50 fungicide by the Fungicide Resistance Action Committee (FRAC). As stated in PRD2023-08 for pyriofenone, there is insufficient evidence to link the apical endpoints observed in the toxicology databases for these two pesticides to a specific mode of action and therefore, a cumulative health risk assessment is not required at this time.

## Other information

The relevant confidential test data on which the decision is based (as referenced in PRD2023-08, *Pyriofenone 300 SC Fungicide, containing pyriofenone)* are available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

Any person may file a notice of objection[3] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and pest management portion of the Health Canada's website (Public Engagement Portal – Public Engagement Forms – Notice of Objection) or contact the PMRA's Pest Management Information Service.

[3] As per subsection 35(1) of the *Pest Control Products Act.*

## Evaluation approach

### Legislative framework

The Minister of Health's primary objective under the *Pest Control Products Act* subsection 4(1) is to prevent unacceptable risks to individuals and the environment from the use of pest control products.

As noted in the preamble of the Act, it is in the national interest that the attainment of the objectives of the federal regulatory system continue to be pursued through a scientifically-based national registration system that addresses risks to human health, the environment and value both before and after registration and applies to the regulation of pest control products throughout Canada; and that pest control products with acceptable risk and value be registered for use only if it is shown that their use would be efficacious and if there is acceptable risk to human health and the environment, taking into account the conditions of registration.

For the purposes of the Act, the health or environmental risks of a pest control product are acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the product, taking into account its conditions of registration as per subsection 2(2) of the *Pest Control Products Act*.

Risk for the human health and environment, and value are defined under the Act subsection 2(1) as follows:

> **Health risk**, in respect of a pest control product, means the possibility of harm to human health resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.
>
> **Environmental risk**, in respect of a pest control product, means the possibility of harm to the environment, including its biological diversity, resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.
>
> **Value**, in respect of a pest control product, means 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.

When evaluating the health and environmental risks of a pesticide and determining whether those risks are acceptable, subsection 19(2) of the *Pest Control Products Act* requires Health Canada to apply a scientifically-based approach. The science-based approach to assessing pesticides considers both the toxicity and the level of exposure of a pesticide in order to fully characterize risk.

Pre-market assessments are based on a required set of scientific data that must be provided by the applicants for pesticide registrations. Additional information from published scientific reports, other government departments and international regulatory agencies are also considered.[4]

**Risk and value assessment framework**

Health Canada uses a comprehensive body of modern scientific methods and evidence to determine the nature as well as the magnitude of potential risks posed by pesticides. This approach allows for the protection of human health and the environment through the application of appropriate and effective risk management strategies, consistent with the purpose described in the preambular text set out above.

Health Canada's approach to risk and value assessment is outlined in A Framework for Risk Assessment and Risk Management of Pest Control Products.[5] A high-level overview is provided below.

i) Assessing potential health risks

With respect to the evaluation and management of potential health risks, Health Canada's risk assessments follow a structured, predictable process that is consistent with international approaches and the Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks.[6]

The evaluation of potential health risks begins with a consideration of the toxicological profile of a pesticide to establish reference doses at which no adverse effect is expected and against which the expected exposure is assessed. This includes, where appropriate, the use of uncertainty (protection) factors to provide additional protection that accounts for the variation in sensitivity among members of human population and the uncertainty in extrapolating animal test data to humans. Under certain conditions, the *Pest Control Products Act* requires the use of another factor to provide additional protection to pregnant women, infants, and children. Other uncertainty factors, such as a database deficiency factor, are considered in specific cases. More details related to the application of the uncertainty factors are provided in SPN2008-01.[7]

Assessments estimate potential health risks to defined populations[8] under specific exposure conditions. They are conducted in the context of the proposed or registered conditions of use, such as the use of a pesticide on a particular field crop using specified application rates, methods and equipment. Potential exposure scenarios consider exposures during and after application of

4 Information Note – *Determining Study Acceptability for use in Pesticide Risk Assessments*

5 PMRA Guidance Document*, A Framework for Risk Assessment and Risk Management of Pest Control Products*

6 Health Canada Decision-*Making Framework for Identifying, Assessing, and Managing Health Risks - August 1, 2000*

7 Science Policy Note: *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*

8 Consideration of Sex and Gender in Pesticide Risk Assessment

the pesticide in occupational or residential settings, food and drinking water exposure, or exposure when interacting with treated pets. Also considered are the anticipated durations (short-, intermediate- or long-term) and routes of exposure (oral, inhalation, or skin contact). In addition, an assessment of health risks must consider available information on aggregate exposure and cumulative effects.

ii) Assessing risks to the environment

With respect to the evaluation of environmental risks, Health Canada's environmental risk assessments follow a structured, tiered approach to determine the likelihood that exposure to a pesticide can cause adverse effects on individual organisms, populations, or ecological systems. This involves screening assessments starting with simple methods, conservative exposure scenarios and sensitive toxicity effects metrics, then moving on, where required, to more refined assessments that can include exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods.

The environmental assessment considers both the exposure (environmental fate, chemistry, and behaviour, along with the application rates and methods) and hazard (toxic effects on organisms) of a pesticide. The exposure assessment examines the movement of the pesticide in soil, water, sediments and air, as well as the potential for uptake by plants or animals and transfer through the food web. The possibility for the pesticide to move into sensitive environmental compartments such as groundwater or lakes and rivers, as well as the potential for atmospheric transport, is also examined. The hazard assessment examines effects on a large number of internationally recognized indicator species of plants and animals (terrestrial organisms include invertebrates such as bees, beneficial arthropods, and earthworms, birds, mammals, plants; aquatic organisms include invertebrates, amphibians, fish, plants and algae), and includes considering effects on biodiversity and the food chain. Acute and chronic effects endpoints are derived from laboratory and field studies that characterize the toxic response and the dose–effect relationship of the pesticide.

The characterization of environmental risk requires the integration of information on environmental exposure and effects to identify which, if any, organisms or environmental compartments may be at risk, as well as any uncertainties in characterizing the risk.

iii) Value assessment

Value assessments consist of two components: an assessment of the performance of a pest control product and its benefits.

Assessing pesticide performance involves an evaluation of the pesticide’s efficacy in controlling the target pest and the potential for the pesticide to damage host crops or use-sites. Where the efficacy of a pesticide is acceptable, the assessment serves to establish appropriate label claims and directions and an application rate (or rate range) that is effective without being excessive, and with no unacceptable damage to the use-site or host organism/crop (and subsequent hosts or crops) under normal use conditions.

In many cases, proof of performance alone is sufficient to establish the value of the pesticide, so that an in-depth or extensive evaluation of benefits may not be required. However, a more thorough assessment of benefits may be undertaken in particular cases where performance alone does not sufficiently demonstrate value, or while developing risk management options.

**Risk management**

The outcomes of the assessments of risks to human health and the environment, and the assessment of value, form the basis for identifying risk management strategies. These include appropriate risk mitigation measures and are a key part of decision-making on whether health and environmental risks are acceptable. The development of risk management strategies take place within the context of the pesticide's conditions of registration. Conditions can relate to, among other things, the specific use (for example, application rates, timing and frequency of application, and method of application), personal protective equipment, pre-harvest intervals, restricted-entry intervals, buffer zones, spray drift and runoff mitigation measures, handling, manufacture, storage or distribution of a pesticide. If feasible conditions of use that have acceptable risk and value cannot be identified, the pesticide use will not be eligible for registration.

The selected risk management strategy is then implemented as part of the registration decision. The pesticide registration conditions include legally-binding use directions on the label. Any use in contravention of the label or other specified conditions is illegal under the *Pest Control Products Act*.

Following a decision, continuous oversight activities such as post-market assessments, monitoring and surveillance, including incident reporting, all play an essential role to help ensure the continued acceptability of risks and value of registered pesticides.