Proposed Special Review Decision PSRD2021-01

Special Review for Iprodione and Its Associated End-use Products

Consultation Document

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1.0 Introduction

Pursuant to subsection 17(2) of the *Pest Control Products Act*, Health Canada's Pest Management Regulatory Agency (PMRA) has initiated a special review of iprodione (Canada, 2018a). This special review was based on the decision taken by the European Union to prohibit the use of iprodione due to human health and environmental concerns (European Commission, 2017a; Rotterdam Convention, 2019).

Pursuant to subsection 18(4) of the *Pest Control Products Act*, Health Canada has evaluated the aspects of concern that prompted the special review of pest control products containing iprodione. The aspects of concern for this special review are relevant to human health and the environment.

2.0 Uses of iprodione in Canada

Iprodione is a contact fungicide used on greenhouse lettuce, certain greenhouse and outdoor ornamentals, conifer seedlings, potato seed treatment for table and processing potatoes, and imported treated carrot seed. Following a re-evaluation of iprodione in 2018 (Canada, 2018b), Health Canada cancelled the following uses to address unacceptable health risks:

- Foliar treatment of canola, alfalfa, strawberries, raspberries, peaches, plums, prunes, cherries, apricots, grapes, lettuce, cauliflower, cabbage, snap beans, kidney beans, white beans, onions, leeks, and ginseng; turf; garlic seed dip; foliar treatment of greenhouse and outdoor cut flowers; greenhouse tomato and cucumber; seed treatment of canola and mustard; potato seed treatment for seed potatoes.

3.0 Aspects of the pest control product that prompted the special review

Based on a review of the European Commission's decision on iprodione (European Commission, 2017a), Health Canada identified the aspects of concern that prompted the special review of iprodione as:

Human Health

- Potential carcinogenicity of iprodione;
- Potential genotoxicity of metabolite RP30228;
- Potential reproductive toxicity of iprodione;
- Potential acute dietary risk of iprodione;

Environment

- Exposure to metabolites (RP35606, RP30181 and RP30228) from groundwater;
- Potential risk to aquatic organisms from iprodione.

4.0 Evaluation of the aspect of concern that prompted the special review

In order to evaluate the identified aspects of concern, Health Canada has considered currently available relevant scientific information. This includes the comprehensive human health and environmental risk assessments conducted as part of the 2018 re-evaluation of iprodione in Canada outlined in the Re-evaluation Decision RVD2018-16, *Iprodione and Its Associated End-use Products* (Canada, 2018b) and the Proposed Re-evaluation Decision PRVD2016-09, *Iprodione,* consultation document (Canada, 2016), incident reports, and information from the European Union (EFSA, 2016; European Commission, 2017a, b).

Following the initiation of the special review, Health Canada requested information related to the aspects of concern from provinces and other relevant federal government departments and agencies in accordance with the subsection 18(2) of the *Pest Control Products Act*. In response, water monitoring information was received and considered for the special review.

4.1 Assessment of aspects of concern related to human health potential

Carcinogenicity of iprodione: As part of Health Canada's recent comprehensive human health assessment of iprodione, four dietary carcinogenicity studies conducted in rodents (two in mice, two in rats) were assessed (Canada, 2016; Canada, 2018b). There was an increase in four tumour types, namely liver and ovarian tumours in mice, and testicular and uterine tumours in rats. A standard battery of genotoxicity studies was also reviewed, the results of which did not suggest that iprodione was genotoxic. Data supported a threshold mode of action approach to cancer risk assessment for the liver tumours (Canada, 2018b). Although a linear low-dose extrapolation (non-threshold) approach was deemed appropriate for the rat uterine tumours, it could not be undertaken due to a lack of uterine histopathology in all animals in the low- and mid-dose groups. A linear low-dose extrapolation was conducted for the remaining tumour types. The rat testicular tumours yielded the most potent unit risk (q_1*) of 3.48×10^{-2} $(mg/kg\ bw/day)^{-1}$ and was thus selected for the cancer risk assessment (Canada, 2018b).

As further explained below, the cancer risks from exposure to iprodione and its metabolites in food and drinking water, as well as occupational and non-occupational cancer risk from exposure to iprodione, were considered to be acceptable when the mitigation measures specified in RVD2018-06 (Canada 2018b) are implemented.

Potential genotoxicity of metabolite RP30228: The European Commission concluded that the genotoxic potential of metabolite RP30228 could not be excluded based on the results of a positive in vitro micronucleus test and equivocal results in an in vivo micronucleus test (EFSA, 2016). Although these particular studies were not available for review as part of Health Canada's recent iprodione assessment, metabolite RP30228 was accounted for in the risk assessment. Specifically, RP30228 was included in the residue definition for cereal grains, and drinking water modelling was undertaken to estimate the combined residues of iprodione and its transformation products, which included RP30228.

As further explained below, the cancer risks from exposure to iprodione and its metabolites (including RP30228) in food and drinking water were not considered to be of concern when the mitigation measures specified in RVD2018-06 (Canada 2018b) are implemented. Given that metabolite RP30228 has been included in Health Canada's cancer risk assessment for iprodione, there are no further concerns regarding the potential genotoxicity of this metabolite at this time.

Potential reproductive toxicity of iprodione: The potential for reproductive toxicity was addressed by Health Canada in the 2018 comprehensive health risk assessment for iprodione (Canada, 2018b), which included consideration of two reproductive toxicity studies, as well as several mechanistic studies. Some of the reproductive toxicity effects considered to be of concern by the European Commission (EFSA, 2016) were reported in an additional 2-generation reproductive toxicity study that was not available for review as part of the Health Canada assessment. These concerns included sperm effects, delayed onset of male puberty, and persistence of areolas in male offspring. When establishing toxicology reference values, Health Canada identified critical endpoints with lower points of departure than the dose levels used in the reproductive toxicity studies conducted with iprodione. As such, the toxicology reference values established for iprodione (Canada, 2018b) are considered protective of the reproductive effects reported in the toxicity studies with iprodione that were reviewed in both the Health Canada and European assessments.

For additional details on Health Canada's hazard assessment and toxicology reference values, refer to RVD2018-16 and PRVD2016-09 (Canada 2018b; Canada, 2016).

Non-cancer and cancer risk assessment for iprodione: The toxicology assessment conducted by Health Canada in RVD2018-16 (Canada, 2016) considered the carcinogenic, genotoxic, and reproductive hazard potential of iprodione and established reference values that are protective of these effects.

Potential exposure to iprodione and its metabolites may occur through the diet (food and water), when handling and applying products containing iprodione or by entering treated sites. There is also a potential for non-occupational exposure from spray drift during commercial applications. As such, Health Canada assessed potential dietary, occupational and non-occupational risks resulting from exposure to iprodione and its metabolites.

Dietary exposure and risk assessment: Acute, chronic, and cancer dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model – Food Commodity Intake Database™ (DEEM-FCID™; Version 4.02) program which incorporates food consumption data from the National Health and Nutrition Examination Survey (NHANES) 2005-2010 (Canada, 2018b). The residue definition for the risk assessment in plant commodities (except cereals) is the parent alone. The residue definition for cereal grains includes both iprodione and RP30228. Health Canada considered modelled drinking water estimates for the combined residues of iprodione and its transformation products, RP30228 and RP32490.

As noted in RVD2018-16 (Canada, 2018b), exposures from food sources were aggregated with exposures from water sources. Following the implementation of mitigation measures specified in RVD2018-16 (Canada, 2018b), acute and chronic exposures to iprodione in food and drinking water were below 5% of the Acute Reference Dose (ARfD of 0.067 mg/kg bw for females 13–49

years; no ARfD is required for any other population subgroup) and 1% of the Acceptable Daily Intake (ADI of 0.014 mg/kg bw/day for all population groups) for all relevant population groups and are not of concern. The cancer risk from exposure to iprodione in food and drinking water is at the threshold of 1×10^{-6} for the general population and is not considered to be of concern (Canada, 2018b).

In addition to the modeling, Health Canada considered the water monitoring information received following the initiation of this special review. Although water monitoring data is available for iprodione indicating it is not detected in groundwater in Canada or the United States, no data is available for the transformation products RP30228 and RP32490.

Following the implementation of mitigation measures (for example, cancellation of most outdoor foliar use) specified in RVD2018-16 (Canada, 2018b), the acute, chronic, cancer and aggregate dietary risks from exposure to iprodione residues are considered to be acceptable for all populations. No further risk mitigation measures are proposed as a result of this Special Review. For additional information on the dietary exposure and risk assessments, refer to RVD2018-16 (Canada, 2018b).

Occupational and non-occupational exposure and risk assessment: As part of the 2018 human health assessment (Canada, 2018b), Health Canada conducted scientifically-based risk assessments to determine the potential risks to workers mixing/loading/applying iprodione, and workers entering the treated field to conduct post application activities. Toxicology reference values for occupational dermal and inhalation risks were outlined in the RVD2018-16 (Canada, 2018b). Several risk mitigation measures to minimize exposure to workers are currently included on the label such as personal protective equipment (PPE), prohibition of certain handheld application equipment, restricted-entry intervals, and decreasing the amount of potato seed treated per day.

Following the implementation of mitigation measures specified in RVD2018-16 (Canada, 2018b), occupational cancer and non-cancer risk from exposure to iprodione is considered to be acceptable. No further risk mitigation measures are proposed as a result of this special review.

There is potential for residential exposure to iprodione applied in agricultural areas through spray drift. The non-occupational and aggregate exposure and risks were considered acceptable. A statement promoting best management practices to minimize human exposure from spray drift or spray residues resulting from drift is currently included on the labels. For additional information on the occupational exposure and risk estimates, refer to RVD2018-16 and PRVD2016-09 (Canada, 2018b; Canada, 2016).

4.2 Assessment of the aspects of concern related to the environment

Exposure to metabolites (RP35606, RP30181 and RP30228) from groundwater: Iprodione is soluble in water and has a low potential to volatilize from moist soil or water surfaces. RP35606 and RP30228 are identified as major hydrolysis products. Iprodione is shown to photolyze in soil. Biotransformation is a route of transformation for iprodione in soil under aerobic and anaerobic conditions. In the terrestrial environment, iprodione is expected to be slightly to moderately persistent under aerobic conditions depending on the soil type. The major

transformation products identified under aerobic laboratory conditions are RP30228 and RP36221 (Canada, 2016). Under anaerobic soil conditions, iprodione biotransforms more readily and is considered slightly persistent; only one major transformation product, RP30228, was identified under anaerobic soil conditions. In aquatic environments, iprodione is expected to be non-persistent under aerobic and anaerobic conditions. The major transformation products identified under aerobic aquatic conditions were RP30228 and RP32490; RP30228 partitions mainly into the sediment phase whereas RP32490 predominantly remains in the water phase. RP30228 was the only major transformation product identified under anaerobic aquatic conditions.

Adsorption data indicate that iprodione has low to medium mobility in soils. The transformation product RP30228 is shown to be immobile (Canada, 2016). Soil column leaching experiments revealed that the majority of iprodione applied to soil does not leach beyond 20 cm soil depth, with the exception of sandy soil that is low in organic matter. On this basis, iprodione is not expected to leach into groundwater with the possible exception of sandy soil conditions (Canada, 2016). RP30181 was not identified as a major or minor transformation product in hydrolysis and photolysis studies and other biotransformation studies. Water monitoring data is not available for RP35606, RP30181 and RP30228. Water modelling was used to determine potential risk from iprodione and its metabolites in Section 4.1.

Potential risk to aquatic organisms: Aquatic organisms can be exposed to iprodione as a result of drift and run-off. Therefore, Health Canada characterized the potential risk to aquatic organisms from the use of iprodione through spray drift and runoff (Canada, 2018b). The level of concern was not exceeded for potential risks to fresh water organisms from spray drift; however, it did exceed for estuarine and marine species (risk quotient = 13). The level of concerns for aquatic organisms from runoff exceeded for certain species (risk quotient ranged from 0.1–8.6). For detailed environmental exposure and risk estimates, see RVD2018-16 (Canada, 2018b; Canada, 2016).

To mitigate potential risks to the environment, the following mitigation measures are currently implemented on the label (Canada, 2018b):

- Spray buffer zones to protect non-target habitats from pesticide spray drift:
- Standard runoff reduction labelling.
- Environmental hazard statements for foliar use (conifer seedlings) product labels regarding toxicity of iprodione to aquatic organisms
- Hazard statements on product labels warning of the potential to contaminate groundwater through leaching

No further mitigation measures are proposed at this time.

5.0 Incident reports

As of 29 October 2020, there were no Canadian incidents relating to the human health aspects of concern. One environmental incident involving iprodione, was related to aquatic organisms. The incident involved water used to douse a fire at a chemical distribution warehouse, which entered a stream and resulted in a large fish kill. Based on the concentration of iprodione in the water samples and its toxicity value, iprodione was unlikely to have caused the fish mortality.

6.0 Proposed special review decision for iprodione

Evaluation of available scientific information related to the aspects of concern indicates that the potential human health and environmental risks are considered to be acceptable under current conditions of use. No additional risk reduction measures are proposed.

On this basis, Health Canada's Pest Management Regulatory Agency, pursuant to subsection 21 (1) of the *Pest Control Products Act*, is proposing continued registration of iprodione products for sale and use in Canada. No additional mitigation measures are proposed

This proposed special review decision is a consultation document. Health Canada will accept written comments on this proposal up to 45 days from the date of publication of this document. All comments are to be directed to Publications (contact information on the cover page of this document).

7.0 Next steps

Before making a final decision on the special review of iprodione, Health Canada will consider all comments received from the public in response to this consultation document. Health Canada will then publish a special review decision document, which will include the decision, the reasons for it, a summary of the comments received on the proposed decision, and Health Canada's response to these comments.

List of abbreviations

µg	microgram(s)
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
DEEM-FCID	Dietary Exposure Evaluation Model - Food Commodity Intake Database
EFSA	European Food Safety Authority
kg	kilogram(s)
L	litre(s)
MRL	Maximum Residue Limit
mg	milligram(s)
NHANES	National Health and Nutrition Examination Survey
PPE	personal protective equipment
PRVD	proposed re-evaluation decision
q_1*	cancer potency factor
RVD	re-evaluation decision

Appendix I Registered products containing iprodione as of 23 December 2020

Table 1 Registered products containing iprodione as of 23 December 2020

Registration number	Marketing class	Registrant	Product name	Guarantee
20267	T	FMC CORPORATION	IPRODIONE TECHNICAL	98.6%
29379	T	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	QUALI-PRO IPRODIONE TECHNICAL	99%
31892	T	BAYER CROPSCIENCE INC.	BES IPRODIONE TECHNICAL	98.6%
32489	T	SHARDA CROPCHEM LIMITED	SHARDA IPRODIONE TECHNICAL FUNGICIDE	98.3%
15213	C	FMC CORPORATION	ROVRAL FUNGICIDE WETTABLE POWDER	500 g/KG
24378	C	FMC CORPORATION	ROVRAL RX FUNGICIDE	240 g/L
24379	C	BAYER CROPSCIENCE INC.	GREEN GT	240 g/L
24709	C	FMC CORPORATION	ROVRAL WDG FUNGICIDE WATER DISPERSABLE GRANULE	500 g/Kg
29315	C	FMC CORPORATION	ROVRAL FLO FUNGICIDE	240 g/L
29410	C	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	QUALI-PRO IPRODIONE 240 SE	240 g/L
29866	C	FMC CORPORATION	ID FUNGICIDE	240 g/L
29870	C	BAYER CROPSCIENCE INC.	TRILOGY STRESSGARD	29.41%
30275	C	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	OVERALL 240 SC	240 g/L

Registration number	Marketing class	Registrant	Product name	Guarantee
31906	C	BAYER CROPSCIENCE INC.	INTERFACE STRESSGARD	256 g/L
32490	C	SHARDA CROPCHEM LIMITED	PRODEX SC FUNGICIDE	240 g/L
32491	C	SHARDA CROPCHEM LIMITED	PRODEX TZ FUNGICIDE	500/L
32765	C	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	QUALI-PRO INTAGLIO FUNGICIDE	55 g/L
32868	C	SHARDA CROPCHEM LIMITED	PRODEX T 240SC FUNGICIDE	240 g/L
32872	C	SHARDA CROPCHEM LIMITED	PRODEX T 500SC FUNGICIDE	500 g/L

References

I) Information considered in the special review not supplied by registrant

Published

PMRA Document Number	Reference
1719718	US Geological Survey, 2009, USGS NAWAQ groundwater monitoring for Iprodione (R61593) 2005-2007 downloaded 2009, DACO: 8.6
2149078	Elliot J et al., 2011, Groundwater Vulnerability to Pesticide Contamination in the Assiniboine Delta Aquifer, DACO: 8.6
2397190	Nova Scotia Environment, 2012, Nova Scotia Groundwater Observation Well Network, DACO: 8.6
2634013 2397195	California Department of Pesticide Regulation, 2014, Sampling for Pesticide Residues in California Well Water, DACO: 8.6
2988086	California Department of Pesticide Regulation, 2013, Sampling for Pesticide Residues in California Well Water, DACO: 8.6
	Reilly, T.J. et al., 2012, Occurrence of boscalid and other selected fungicides in surface water and groundwater in three targeted use areas in the United States Chemosphere: 89: 228-234, DACO: 8.6
	Canada, 2016. Pest Management Regulatory Agency. Proposed Re-evaluation Decision PRVD2016-09, *Iprodione*, Consultation Document. 17 March 2016.
	Canada, 2018a. Announcement of Initiation of Special Review. Iprodione. 2018-1895. 13 June 2018.
	Canada, 2018b. Pest Management Regulatory Agency. Re-evaluation Decision Document RVD2018-16, *Iprodione and Its Associated End-use Products*. 21 June 2018.
3097823	European Commission, 2017a. Commission Implementing Regulation (EU) 2017/2091 of 14 November 2017 concerning the non-renewal of approval of the active substance iprodione, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending Commission Implementing Regulation (EU) No 540/2011.

3097824 European Commission, 2017b. Final Renewal report for the active substance iprodione finalised in the Standing Committee on Plants, Animals, Food and Feed at its meeting on 6 October 2017 in view of the non-renewal of the approval of XXX as active substance in accordance with Regulation (EC) No 1107/2009.

2780060 EFSA, 2016. Peer review of the pesticide risk assessment of the active substance iprodione. European Food Safety Authority. 14 October 2016.

3097825 Rotterdam Convention, 2019. Database of Notifications of Final Regulatory Action. European Union Final Regulatory Action, *Iprodione*. 12 December 2019.

Unpublished information

PMRA Document Number	Reference
3072199	Ministère de l'Environnement et de la Lutte contre les changements climatiques (MELCC), Pesticides 2005-2018: Eau Souterraine, received 2019 from Banque de données sur la qualité du milieu aquatique (BQMA), Québec, Direction générale du suivi de l'état de l'environnement, DACO: 8.6
3072201	Pesticide Water Monitoring Data from Alberta: 2003-2019, received 2019 from Alberta Environment and Parks, DACO: 8.6