Re-evaluation Decision RVD2018-16

Iprodione and Its Associated End-use Products

Final Decision Document

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Re-evaluation Decision

Under the authority of the *Pest Control Products Act,* all registered pesticides must be regularly re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental safety standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports and other regulatory agencies. PMRA applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Iprodione is a contact fungicide with protective and curative action. It is used to control a broad range of fungal pathogens on a wide variety of greenhouse, orchard and field crops, ornamentals and turf. Currently registered products containing iprodione are listed in Appendix I. Registered product labels containing iprodione in Canada can be accessed through PMRA's label transcription service.[1]

This document presents the final regulatory decision[2] for the re-evaluation of iprodione, including the required risk mitigation measures to protect human health and the environment. All products containing iprodione that are registered in Canada are subject to this re-evaluation decision.

This re-evaluation has undergone a 120-day consultation period on the Proposed Re-evaluation Decision PRVD2016-09, *Iprodione,*[3] which ended on 15 July 2016. PMRA received comments relating to health, environment and value. These comments are summarized in Appendix II along with responses by PMRA. These comments and new data/information resulted in revisions to the risk assessments (see Science Evaluation Update), and subsequently, in changes to the proposed regulatory decision as described in PRVD2016-09. A reference list of data used as the basis for the proposed re-evaluation decision is included in PRVD2016-09, and further data used in the re-evaluation decision is listed in Appendix VII.

Regulatory Decision for Iprodione

PMRA has completed the re-evaluation of iprodione. Under the authority of the *Pest Control Products Act*, PMRA has found the continued registration of some products containing iprodione to be acceptable for sale and use in Canada. An evaluation of available scientific information found that some uses of iprodione products meet current standards for the protection of human health or the environment, when used according to the conditions of registration which include required amendments to label directions. Certain uses of iprodione are cancelled to address potential risks of concern for human health. Label amendments, as summarized below and listed in Appendix VI, are required for all end-use products. No additional data are requested.

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1 PMRA's label transcription service is available online here: http://pr-rp.hc-sc.gc.ca/ls-re/index-eng.php. Pesticide labels can also be accessed on a mobile device using the pesticide label app available here: https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management/registrants-applicants/tools/pesticide-label-search.html.

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

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

Risk Mitigation Measures

Registered pesticide product labels include specific instructions for use. Directions include risk mitigation measures to protect human health and the environment. Following these directions is required by law. As a result of the re-evaluation of iprodione, the PMRA is requiring further risk mitigation measures in addition to those already identified on iprodione product labels.

Human Health

- Removal of the following uses from the labels of commercial class products:
  - Garlic seed dip.

- Cancellation of the following uses from the labels of commercial class products:
  - 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;
  - Foliar treatment of greenhouse and outdoor cut flowers;
  - Greenhouse tomato and cucumber;
  - Seed treatment of canola and mustard;
  - Potato seed treatment for seed potatoes.

- The following uses are acceptable for continued registration when required mitigation measures, as outlined below, are implemented:
  - Foliar application to outdoor and greenhouse potted ornamentals (non-cut flowers);
  - Soil drench application to outdoor and greenhouse ornamentals (including cut flowers);
  - Greenhouse lettuce;
  - Conifer seedlings;
  - Potato seed treatment for table and processing potatoes;
  - Imported treated carrot seed.

- Required mitigation measures:
  - Mixers/loaders and applicators: increased personal protective equipment (PPE) and prohibition of certain handheld application equipment (mist blower and fogger).
  - Postapplication workers: increased restricted-entry intervals (REIs) for some activities and limited number of applications for most crops.
  - For potato seed treatment (table and processing potatoes):
    - Increased PPE and limit to amount treated per day.
    - A plant back interval (PBI) of 30 days is required for all crops except root vegetables (crop group 1) and leafy brassica greens (crop group 5b). The PBI requirement for crop group 1 and 5b is 12 months.
  - To protect bystanders from spray drift: a statement to promote best management practices to minimize human exposure from spray drift or spray residues resulting from drift.

Environment

- Spray buffer zones to protect non-target habitats from pesticide spray drift (1 to 2 m for freshwater habitats).
- Standard runoff reduction labelling.
- Hazard statements on product labels warning of the potential to contaminate groundwater through leaching.
- Warnings on foliar use product labels regarding toxicity of iprodione to aquatic organisms, birds, and bees.
- Hazard statement on all seed treatment product labels stating that any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned-up from the soil surface.
- Warning on greenhouse product labels that use may harm bees and other beneficial insects used in greenhouse production.

International Context

Iprodione is currently acceptable for use in other Organization for Economic Co-operation and Development (OECD) member countries, including the United States, and Australia. In November 2017, the European Commission published a decision of non-renewal of iprodione as a plant protection product. Therefore, PMRA has initiated a special review under subsection 17(2) of the *Pest Control Products Act*. No other decision by an OECD member country to prohibit all uses of iprodione for health or environmental reasons has been identified.

Next Steps

To comply with this decision, the required mitigation measures must be implemented on all products labels sold by registrants no later than 24 months after the publication date of this decision document. Appendix I lists the products containing iprodione that are registered under the authority of the *Pest Control Products Act*.

Other Information

Any person may file a notice of objection[4] regarding this decision on iprodione within 60 days from the date of publication of this Re-evaluation 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 Health Canada's website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

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

Science Evaluation Update

1.0 Revised Health Risk Assessment

1.1 Toxicology Assessment for Iprodione

Comments and data were received with respect to PRVD2016-09, *Iprodione*, regarding a range of issues including the mode of action for mouse liver tumours, the use of para-chloroaniline data as a surrogate for 3,5-dichloroaniline and repeat-dose inhalation toxicity. Based on this information, some changes were made to the toxicology reference values outlined in PRVD2016-09 which included the following:

- updated inhalation reference values as a result of the submitted repeat-dose inhalation toxicity study, and
- replacement of the q_1* value for the mouse liver tumours used in PRVD2016-09 with the q_1* for the rat testicular tumours.

Detailed responses to the comments received are provided in Appendix II. Revised reference values are provided in Appendix III, Table 1.

1.2 Dietary Exposure and Risk Assessment

Based on comments received on PRVD2016-09, further refinements to the dietary exposure and risk assessment were made taking into account revised drinking water estimates, revised toxicological reference values, as well as import maximum residue limits (MRLs) and recent registrations for potato seed pieces.

Sufficient information was available to adequately assess the dietary exposure and risk to iprodione. Acute, chronic, and cancer dietary (food and drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™; Version 4.02) program. This program incorporates food consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) from 2005 to 2010 which is available through the Centers for Disease Control and Prevention (CDC)'s National Center for Health Statistics. For detailed information on dietary risk, refer to Appendix IV.

The acute and chronic exposure estimates are considered to be highly refined (more precise) as monitoring residues, percent crop treated, experimental processing factors and domestic/import data were used to the extent possible.

1.2.1 Exposure from Drinking Water

The assessment for drinking water exposure was conducted first as it was necessary to mitigate concerns from water sources prior to assessing risk from food sources. Modelled water estimates for the combined residues of iprodione and its transformation products, RP30228 and RP32490, were updated.

Furthermore, separate estimates were generated for 3,5-dichloroaniline (3,5-DCA), a terminal metabolite of iprodione that may be formed in water as a result of iprodione use, whereas 3,5-DCA could not be modelled previously. This metabolite is not expected to be formed in food commodities. The q_1* for 3,5-DCA is higher than that of iprodione and its other metabolites. Thus, a separate cancer assessment was conducted for 3,5-DCA exposure from drinking water.

Drinking water estimates were generated for several uses to examine different mitigation scenarios. The modelled use scenarios are summarized in Appendix IV. The highest daily (acute), yearly (chronic), and average (cancer) estimated environmental concentrations (EEC) were assessed for each scenario where required.

Greenhouse uses (USC5 and USC6) and outdoor ornamental uses (USC27) were not modelled. It is not expected that greenhouse effluent would contribute significantly to the overall exposure to iprodione. For outdoor ornamentals, the exposure to iprodione is low taking into consideration the scale of use.

Acute and chronic risks to iprodione in drinking water were below 18% of the acute reference dose (ARfD) and 20% of the acceptable daily intake (ADI) for all relevant population groups when using the highest EECs of all the use scenarios and thus, are not of concern.

For the cancer assessment, iprodione/RP30228/RP32490 and 3,5-DCA were assessed separately as discussed earlier. For iprodione/RP30228/RP32490, the cancer risk from exposure to drinking water exceeded one-in-a-million (that is 1×10^{-6}) threshold for the turf use scenario at both the high rate (cancer risk:1×10^{-5}) and the typical rate (cancer risk: 6×10^{-6}). Cancer risks were below 1×10^{-6} for all other use scenarios. For 3,5-DCA, the cancer risk from exposure to drinking water exceeded 1×10^{-6} threshold for all outdoor foliar application uses that were modelled (cancer risk: 2×10^{-6} to $8x10^{-5}$) and was of concern for potato seed piece treatment (potatoes used for seed) at the higher planting rate (cancer risk: 2×10^{-6}). For other seed treatment uses, the cancer risk was below 1×10^{-6} and is not of concern.

In summary, the uses below were not of concern with respect to potential drinking water exposure:

- Potato seed piece treatment for table and processing potatoes at the lower planting rate of 203.4 g a.i./ha;
- Mustard and canola seed treatments;
- Imported carrot seeds;
- Greenhouse uses on tomatoes, cucumbers, and lettuce;

- Outdoor and greenhouse ornamentals;
- Outdoor and greenhouse conifer seedlings.

1.2.2 Exposure from Food Sources

The revised food assessment considered a subset of registered domestic and imported commodities. The domestic commodities included those that did not pose risk concerns via the drinking water route. Residues from imported counterparts (that is imported cucumbers, tomatoes, and carrots) were also included. Exposure from imported almond, cotton seed, kiwifruit, raspberries, grapes, and blackberries/loganberries were included to retain established Canadian MRLs for import purposes.

Most outdoor registered foliar food uses were excluded from the assessment due to concerns from drinking water, as well as their imported counterparts. Other than the commodities identified in the paragraph above, all other commodities with no Canadian MRLs, but with established US tolerances and Codex MRLs, were also excluded from the assessment. In addition, commodities with detected residues found in monitoring data that have no known registrations or MRLs were also excluded from the assessment.

Residue estimates for food commodities were updated for the assessment and were mostly based on Canadian Food Inspection Agency (CFIA) monitoring data. When CFIA monitoring data were not available, the Canadian MRL or field trial data were used. Percent crop treated information, chemical specific processing factors, and food supply information were used when available. Food residue estimates were refined to the extent possible.

Acute and chronic exposure estimates to iprodione from food sources were below 5% of the ARfD and 1% of the ADI for all relevant population groups and are not of concern when excluding most uses from the assessment as discussed above. While the cancer risk from exposure to iprodione from food is at the risk threshold of 1×10^{-6} for the general population, therefore the cancer risk is not of concern only when most uses are excluded from the dietary assessment.

1.2.3 Exposure from Food and Drinking Water

Exposure from food sources were aggregated with exposure from water sources. The drinking water EECs used in this assessment were selected based on the highest modelled use that was not of risk concern from the water route.

Acute and chronic exposure estimates to iprodione from food and drinking water were below 5% of the ARfD and 1% of the ADI for all relevant populations group and are not of concern when excluding most uses from the assessment as discussed in Section 1.2.2. While the cancer risk from exposure to iprodione from food and drinking water is at the risk threshold of 1×10^{-6} for the general population, therefore the cancer risks from food and drinking water are not of concern only when most uses are excluded from the dietary assessment.

1.2.4 Registration Changes Based on the Food and Drinking Water Assessment

Garlic seed dip use is to be removed due to lack of data required to estimate exposure.

The following uses are to be removed in order to mitigate the health risk concerns to iprodione and its metabolites in food and drinking water:

> Alfalfa, apricot, beans (all varieties), cabbage, canola (ground and aerial applications), cauliflower, cherries, ginseng, grapes, leeks, lettuce (outdoor uses only), onions dry bulb, peachs, plums/prunes, raspberries, strawberries, and turf.

Plant Back Interval Restriction:

A plant back interval restriction (PBI) was identified in the initial re-evaluation review based on field crop rotation studies. The restriction was not proposed in PRVD2016-09 given that all uses were proposed for cancellation. As some uses can be retained as a result of the updated assessment, the restriction is required to applicable uses. Specifically, the restriction will be added to the potato seed piece treatment label where potential soil contamination can occur. The PBI restriction is not applicable to greenhouse, outdoor ornamental, and other seed treatment uses. The restriction is indicated below:

> A PBI of 30 days is required for all crops except root vegetables (crop group 1) and leafy brassica greens (crop group 5b). The PBI requirement for crop group 1 and 5b is 12 months.

1.2.5 Maximum Residue Limits (MRLs) for Iprodione in Food

As a next step in this re-evaluation decision, the PMRA intends to update Canadian MRLs and to remove MRLs that are no longer supported. MRLs for pesticides in/on food are specified by Health Canada's PMRA under the authority of the *Pest Control Products Act*.

Canadian MRLs for iprodione are currently specified for several commodities.

As a result of the iprodione re-evaluation, the PMRA will:

- maintain the current MRLs for almond nuts (0.3 ppm), blackberries (25 ppm), carrots (5 ppm), cucumbers (0.5 ppm), grapes (10 ppm), head lettuce (25 ppm), kiwifruit (0.5 ppm), leaf lettuce (25 ppm), loganberries (25 ppm), raisins (60 ppm), raspberries (25 ppm), tomatoes (0.5 ppm), underlinted cotton seed (0.1 ppm), and wild raspberries (25 ppm);
- establish MRLs for potatoes based on field trials for potato seed piece treatment;
- remove the MRL for wine (5 ppm) as the grape MRL of 10 ppm is sufficient to cover wine;
- replace the current Canadian MRLs for apricots (3 ppm), cherries (5 ppm), dry and succulent beans (2 ppm), dry bulb onions (0.2 ppm), ginseng root (4 ppm), leeks (13 ppm), loganberries (25 ppm), mustard greens (11 ppm), nectarines (10 ppm), peaches (10

ppm), plums and fresh prunes (2 ppm), rapeseed/canola (1 ppm), and strawberries (5 ppm) with risk-based MRLs at the LOQ of the CFIA enforcement method; and
- specify risk-based MRLs (i.e., at the limit of quantitation (LOQ) of the CFIA enforcement method) for all non-registered food crops.
- Change the enforcement residue definition from iprodione and the metabolites RP30228 and RP32490 to iprodione alone, and to specify the residue definition for all food crops instead of all food commodities. The proposed change is based on available metabolism data where iprodione was found to be a sufficient marker in different plant commodities. The residue definition is only required for plant based foods or food crops as there are no MRLs and no expectation of residues for animal commodities.

Any changes to the MRLs will be consulted on through a Proposed Maximum Residue Limit (PMRL2018-14) document. Refer to the PMRA MRL database for further information on MRLs.

1.3 Occupational and Non-Occupational Exposure and Risk Assessment

In PRVD2016-09, PMRA had identified many application and postapplication risks of concern. Calculated restricted-entry intervals (REIs) were not considered to be agronomically feasible for most crops. Since all uses were proposed for cancellation due to drinking water and food risks of concern, proposed mitigation measures were not outlined in PRVD2016-09 at that time.

Comments and use information were received with respect to PRVD2016-09 and considered in the revised risk assessment. PMRA responses to comments are provided in Appendix II. Details regarding the revised occupational risk assessment are presented in Appendix V.

The revised occupational risk assessment considered only those uses that did not pose risks of concern via the food and drinking water route (refer to Section 1.2.1). The revisions to the risk assessment included updates to the dislodgeable foliar residue (DFR) default for greenhouse ornamentals and updates to the toxicology reference values for inhalation risk and cancer risk.

As a result of the comments and additional information submitted, the outcome of the occupational risk assessment and mitigation measures proposed in PRVD2016-09 has changed for a few scenarios:

- Most of the agricultural uses previously proposed for cancellation are still of concern and will be removed from the product labels due to drinking water and food concerns (see Section 1.2.4), therefore the occupational assessments for these uses were not revised.
- Some uses are acceptable for continued registration provided the use pattern and mitigation measures outlined in Appendix VI are implemented for: greenhouse lettuce, greenhouse/outdoor conifer seedlings, greenhouse/outdoor foliar treated potted ornamentals (non-cut-flowers), greenhouse/outdoor soil drench treated ornamentals (including cut-flowers), planting imported carrot seed, and potato seed treatment and planting for table and processing potatoes.

Risks of concern continue to be identified for the following uses and these uses are required to be cancelled:

- Foliar treatment of greenhouse/outdoor cut flowers;
- Greenhouse tomatoes and cucumbers;
- Seed treatment for canola and alfalfa.

There were no data available to estimate exposure for garlic dip use. Furthermore, no data was available for handheld mist blower and handheld fogger equipment; therefore, this use and these application methods will be removed from labels.

The non-occupational and aggregate exposure and risk assessments were updated based on the revised use pattern and toxicology reference values. No risks of concern were identified for the relevant scenarios.

2.0 Revised Environmental Risk Assessment

In PRVD2016-09, PMRA had proposed risk mitigation measures to minimize exposure and potential risks to the environment. Since all uses were proposed for cancellation due to drinking water and food risks of concern, proposed mitigation measures were not specified in PRVD2016-09 at that time.

The environmental risk assessment has been updated to reflect the revised use pattern, as a result of the updated health risk assessments, as well as additional information and comments received regarding PRVD2016-09. Updates include:

- examination of ecotoxicity studies received during the comment period,
- environmental risk assessment revisions based on reduced use pattern, and
- recalculation of spray buffer zones for the protection of aquatic habitats.

The initial environmental risk assessment conducted for PRVD2016-09 considered the highest registered foliar application rates on raspberry (1000 g a.i./ha × 8 at 7 day intervals) and turf (9000 g a.i./ha × 3 at 14 day intervals). The revised use pattern includes outdoor foliar uses on conifer seedlings which are applied at a lower application rate of 1000 g/ha × 3 applications per season with a 21 day interval. As a result, the amount of iprodione released to the environment from these uses is much lower than what was considered in the initial risk assessment.

The revised environmental risk assessment shows that outdoor foliar uses of iprodione remain a potential risk of concern to bees, birds and aquatic organisms; however, the risk exceedances for these organisms are relatively low. The ingestion of treated carrot seed may pose a potential reproductive risk to birds and small mammals. The use of iprodione in greenhouses (lettuce) may also pose a risk to beneficial arthropods.

Additional environmental toxicity data for iprodione were submitted in regards to PRVD2016-09 and endpoints from these studies were compared to the toxicity endpoints considered in the initial risk assessment. The new information did not change the conclusions of the initial risk assessment; therefore, formal reviews of the submitted studies were not conducted.

Based on the risks identified, the following mitigation measures are required (refer to Appendix VI):

- Spray buffer zones to protect non-target habitats from pesticide spray drift:
- Standard runoff reduction labelling.
- Hazard statements on product labels warning of the potential to contaminate groundwater through leaching.
- Warnings on foliar use product labels regarding toxicity of iprodione to aquatic organisms, birds and bees.
- Warnings on seed treatment product labels regarding toxicity of iprodione to birds and mammals.
- Warnings on seed treatment product labels stating that any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned-up from the soil surface.
- Warning on greenhouse product labels that use may harm bees and other beneficial insects used in greenhouse production.

3.0 Value Assessment

3.1 What is the Value of Iprodione?

Iprodione is a contact fungicide that belongs to the Fungicide Resistance Management Group 2. It is valued by growers for its efficacy against certain plant diseases, as well as a rotational chemistry for resistance management purposes.

Based on the occupational, dietary and drinking water risk assessments, the following uses were acceptable for continued registration: greenhouse lettuce, greenhouse and outdoor conifer seedlings, greenhouse and outdoor foliar treated potted ornamentals (non-cut-flowers), greenhouse and outdoor soil drench treated ornamentals (including cut flowers), imported carrot seed treatment, and potato seed treatment for table and processing potatoes (not potatoes grown for seed).

Currently, there are several active ingredients registered for the majority of the iprodione uses that will be cancelled. There is one low-risk conventional fungicide, fluazinam, and two multisite fungicides, captan and chlorothalonil, that are registered or approved for continued registration for some of the iprodione uses that were identified as being important by growers. These uses include: control of Botrytis on strawberry, brown rot on peach, brown patch, snow moulds (only chlorothalonil) and leaf spot and melting-out on turf. In addition, there are other alternative active ingredients registered for these uses, although most of these alternatives are classified as having a medium to high risk for resistance development in susceptible fungal pathogens.

Of the remaining iprodione uses to be cancelled, the use to control of *Sclerotinia* on alfalfa grown for seed was indicated as important by this sector. There are two alternatives registered to manage this disease, however they are both from the same fungicide resistance management group (Group 7), which may limit grower’s ability to rotate fungicides for resistance management purposes.

List of Abbreviations

ADI	acceptable daily intake
ARfD	acute reference dose
AUC	area under the curve
bw	body weight
CAF	composite assessment factor
CFIA	Canadian Food Inspection Agency
CR	Chemical resistant
CSAF	chemical-specific adjustment factor
cm^2	centimetres squared
d	day(s)
DA	dermal absorption
DIR	Directive
DFR	dislodgeable foliar residue
EEC	Environmental estimated concentrations
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
et al	and others
F1	first generation
F2	second generation
F3	third generation
ha	hectare
JMPR	Joint Meeting on Pesticide Residues
kg	kilogram(s)
L	litre(s)
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
LOAEC	lowest observed adverse effect concentration
mg	milligram(s)
M/L	mixer/loader
M/L/A	mixer/loader/applicator
mg	milligram(s)
MOE	margin of exposure
MRL	maximum residue limit
NOAEL	no observed adverse effect level
NOAEC	no observed adverse effect concentration
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
PRVD	proposed re-evaluation decision
REI	restricted-entry interval
SPN	Science Policy Note
SU	Suspension
TC	transfer coefficient
UF	uncertainty factor
USEPA	United States Environmental Protection Agency

WP	wettable powder formulation

Appendix I Registered Iprodione Products in Canada[1]

Regn No	Marketing Class	Registrant	Product Name	Formulation	Guarantee (iprodione)
29379	Technical	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	QUALI-PRO IPRODIONE TECHNICAL	SOLID	99%
20267		FMC CORPORATION	IPRODIONE TECHNICAL	Not Specified	98.6%
31892		BAYER CROPSCIENCE INC.	BES IPRODIONE TECHNICAL	SOLID	98.6%
32489		SHARDA CROPCHEM LIMITED	SHARDA IPRODIONE TECHNICAL FUNGICIDE	SOLID	98.3%
29410	Commercial	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	QUALI-PRO IPRODIONE 240 SE	SUSPENSION	240 g/L
30275			OVERALL 240 SC	SUSPENSION	240 g/L
32765			QUALI-PRO INTAGLIO FUNGICIDE	SUSPENSION	55 g/L
24379		BAYER CROPSCIENCE INC.	GREEN GT	SUSPENSION	240 g/L
29870			TRILOGY STRESSGARD	SUSPENSION	29.41%
30534			IPRODIONE TURF AND ORNAMENTAL FUNGICIDE	WETTABLE POWDER	500 g/kg
31906			INTERFACE STRESSGARD	SUSPENSION	256 g/L
15213		FMC CORPORATION	ROVRAL FUNGICIDE WETTABLE POWDER	WETTABLE POWDER	500 g/kg
24378			ROVRAL RX FUNGICIDE	SUSPENSION	240 g/L
24709			ROVRAL WDG FUNGICIDE WATER DISPERSABLE GRANULE	WETTABLE GRANULES	500 g/kg
29315			ROVRAL FLO FUNGICIDE	SUSPENSION	240 g/L
29866			ID FUNGICIDE	SUSPENSION	240 g/L
28525		NIPPON SODA COMPANY LTD.	NISSO FOUNDATION LITE	SUSPENSION	132 g/L
32490		SHARDA CROPCHEM LIMITED	PRODEX SC FUNGICIDE	SUSPENSION	240 g/L
32491			PRODEX TZ FUNGICIDE	SUSPENSION	500 g/L
32868			PRODEX T 240SC FUNGICIDE	SUSPENSION	240 g/L
32872			PRODEX T 500SC FUNGICIDE	SUSPENSION	500 g/L

[1]as of 24 January 2018, excluding discontinued products or products with a submission for discontinuation

Appendix II Comments and Responses

In response to the consultation for the iprodione proposed re-evaluation decision, the following comments were received:

1.0 Comments Related to the Health Risk Assessments

1.1 Comments Related to Toxicology

1.1.1 Comment relating to the liver tumour response observed in mouse carcinogenicity studies

One registrant submitted a position paper (PMRA #2661283) to address the mode of action (MOA) and human relevance of the liver tumours noted in the mouse carcinogenicity studies conducted with iprodione. The position paper provides a summary of relevant data, including mechanistic data generated to explain the MOA for iprodione-induced mouse liver tumours. The paper concludes that the activation of the nuclear receptor, constitutive androstane receptor (CAR), is responsible for the increased incidence of liver tumours in mice. Since this MOA is rodent-specific, the registrant believes that iprodione will not pose a carcinogenic risk to humans.

PMRA Response:
The PMRA conducted a re-analysis of the hepatocellular tumour response in light of the position paper and has included an additional registrant-supplied study (PMRA #2661282) in the analysis that was not previously considered in PRVD2016-09.

The PMRA takes the position that overall, the key events were clear and demonstrable to support a CAR/PXR-mediated MOA. In general there was dose and temporal concordance for the parameters that were observed; however, there was a lack of information to describe the onset of precursor events at non-tumourigenic dose levels.

Despite this shortcoming, the key events were consistently demonstrated within the database and were centered specifically on the liver effects that would be expected with a CAR/PXR-mediated pathway.

The MOA for this tumour response was biologically plausible and coherent; however, there were some uncertainties. These included the lack of direct measures of CAR/PXR activation and cell proliferation at non-tumourigenic dose levels, the lack of data addressing specificity, and the possibility of alternative MOAs at play. Given these limitations, the PMRA determined that it was prudent to not dismiss human relevance at this time.

The data were considered sufficient to support the proposed MOA and consequently, a threshold approach to cancer risk assessment for liver tumours, despite the remaining uncertainties. The point of departure (POD) (4.1 mg/kg bw/day) used in the iprodione risk assessment for repeat exposure scenarios is lower than the no observed adverse effect level (NOAEL) of 115 mg/kg bw/day for liver tumours and is thus, considered protective. Furthermore, adequate margins (>8000) are obtained when comparing NOAEL for liver tumours to the reference values such as the ADI established in the iprodione assessment.

It should be noted that although the q_1^* for the mouse liver tumours is no longer necessary the PMRA continues to have concerns regarding other tumour types. As such, a q_1^* of 3.48×10^{-2} $(mg/kg\ bw/day)^{-1}$ for rat Leydig cell tumours has been used for the cancer risk assessment (see response below for additional discussion).

1.1.2 Comment regarding use of para-chloroaniline (PCA) data as surrogate for 3,5-dichloroaniline (DCA)

One registrant submitted a position paper to refute the PMRA's use of PCA data as surrogate for DCA data. The paper discusses the significant differences between these two molecules in terms of structure, genotoxicity, reactivity towards hemoglobin and DNA binding (PMRA #2661284). To support the claims made several studies, either recently conducted by one of the registrants or previously published in peer reviewed journals, were cited and discussed in the position paper.

The position paper contends that DCA should not be considered equivalent to PCA. The paper states DCA is 40-fold weaker than PCA as a base, based on the calculation of relative pKa value, and its binding to rat blood hemoglobin is approximately 0.1% of the degree of binding by PCA. Due to the inductive effect, the paper indicates there is a much greater electron density around the C1 and N atoms in PCA, making it much more reactive than DCA. The paper purports that PCA should be much more readily activated by P450 isozymes than DCA, forming hydroxylamines and nitrenium ions that are highly reactive towards DNA, thus forming DNA adducts. The paper goes on to state that DCA is not mutagenic, while PCA is a known mutagen. It is, therefore, suggested that PCA not be used as a surrogate for DCA in estimating cancer risk from possible exposure to DCA in drinking water.

The registrant indicated that work is currently underway to gain access to DCA data consisting of in vivo micronucleus studies as well as 28 and 90-day oral toxicity studies in rats. Furthermore, the registrant proposed conducting a new rat metabolism study to investigate whether DCA is a rat metabolite. Although DCA was not identified in the existing rat metabolism studies, a significant percentage of the metabolites found in these studies were unidentified. It was the registrant's opinion that if one of these metabolites was indeed DCA, then the long-term toxicity studies with iprodione would have taken into account DCA-related toxicity.

PMRA Response:
Limited data were available to the PMRA to assess the hazard potential of DCA, a transformation product of iprodione found in soil and water. Consequently, the PMRA used data on the structural analog PCA as surrogate for DCA, for cancer risk assessment. A q_1^* of 6.38×10^{-2} $(mg/kg\ bw/day)^{-1}$ was generated by the PMRA for DCA based on the increased incidence of hemangiosarcomas (spleen and liver) in mice and rats treated with PCA.

Although DCA may bind less strongly to rat hemoglobin than PCA, the relationship between hemoglobin binding and cytotoxicity has not been adequately explained. The same reference (PMRA #2780063) that is cited in the position paper states that "hemoglobin binding may prove not to be a useful index of the genotoxic potency of arylamines and nitroarenes. Further work is needed to investigate the relationship between hemoglobin binding and cytotoxicity of these compounds."

The registrant's rebuttal was focused primarily on the differences between DCA and PCA with respect to physicochemical and biological properties; with the exception of a discussion of genotoxicity, no comparisons of biological effects were undertaken. The hematopoietic system has been shown to be a target of toxicity for DCA (PMRA #2780065) and PCA (PMRA #2780058). Results from these studies indicate that both can induce methemoglobin formation despite their physiochemical differences.

Many chemicals are known to produce hemangiosarcomas by non-genotoxic, proliferative mechanisms (PMRA #2780059). The assertion that the increased incidence of hemangiosarcomas following PCA exposure was the result of genotoxicity has not been validated. Accordingly, the difference in genotoxicity profiles between PCA and DCA may be of little consequence. It has been postulated in the literature that for PCA, the potential MOA for the hemangiosarcomas tumour response involves hemolysis leading to iron overload in macrophages and increased reactive oxygen species (ROS) (PMRA #2780220).

Overall, there are similarities in biological response between DCA and its structural analog PCA. Although there are uncertainties surrounding the etiology of hemangiosarcomas, formation can occur via a non-genotoxic mechanism. Until such time that more comprehensive toxicity data are available for DCA, the PMRA considers it prudent to utilize the PCA data as surrogate data for DCA and maintains use of the q_1* value of 6.38×10^{-2} $(mg/kg\ bw/day)^{-1}$ in risk assessment.

Although the registrant was unable to provide the 28 and 90-day studies rat with DCA during the consultation period, the PMRA notes that recent documentation from the European Food Safety Agency (EFSA) (PMRA #2780060) summarizes the results of DCA studies of similar duration. The EFSA summary of the NOAELs from these studies suggests that from a non-cancer perspective, DCA is of equal or greater toxicity than iprodione. This notwithstanding, the quantitative risk values resulting from both the DCA and iprodione cancer assessments conducted by the PMRA subsume any possible DCA non-cancer risk associated to the endpoints, (both the ADI and ARfD) established by the EFSA report. As such, it is assumed that any uses deemed acceptable following the cancer assessments would also be acceptable with the assessed DCA non-cancer risk.

1.1.3 Comment relating to ovarian and uterine histopathology evaluation in a two-year rat study

One registrant indicated that work was proceeding with another registrant, who submitted the two-year rat study to determine if tissue samples remain available for analysis and submission to the PMRA.

PMRA Comment:
No data were provided during the consultation period; thus, no changes were warranted to the PMRA assessment.

1.1.4 Comment relating to the Leydig cell testicular tumours observed in rat carcinogenicity studies

One registrant noted that a study had been commissioned to support a proposed non-genotoxic threshold MOA for the testicular tumours seen in the rat carcinogenicity studies conducted with iprodione. The study was intended to fully characterize the point of departure for the precursor effects leading to Leydig cell tumour development to support a MOA. The registrant indicated that the study has taken longer than predicted to complete due to unforeseen scientific questions. The registrant states that the preliminary data collected from this study indicates that there is a clear threshold mode of action for all measured endpoints which may relate to Leydig cell tumour formation in male rats, with a NOAEL of 24 mg/kg/day.

PMRA Response:
As the final report of the aforementioned study was not provided to the PMRA during the consultation period, the PMRA maintains that the currently available information is insufficient to conclusively support a MOA for the Leydig cell tumours. Although the proposed MOA involving hormonal perturbation is biologically plausible, uncertainty remains with respect to the dose level corresponding to the onset of effects on the testosterone and luteinizing hormone. In the absence of this key information to support the MOA, the PMRA will use the q_1^* of 3.48×10^{-2} $(mg/kg\ bw/day)^{-1}$ for rat Leydig cell tumours for the cancer risk assessment.

It should also be noted that the aforementioned study was intended to address a data gap with regards to effects of iprodione on sperm measurements (namely sperm count, motility and morphology). The PMRA continues to lack robust information on these parameters, which was taken into consideration in terms of providing the toxicology endpoints for risk assessment purposes.

1.1.5 Comment relating to the two-generation reproduction study

One registrant indicated that work was underway to gain access to a two-generation reproduction study completed by another registrant.

PMRA Response:
No study was provided during the consultation period. Consequently, the PMRA continues to lack information regarding the potential effects of iprodione on sexual differentiation and onset of puberty. Accordingly, the PMRA is maintaining use of the threefold PCPA factor for dietary and residential risk assessment and the additional threefold uncertainty factor for occupational risk assessment.

1.1.6 Comment regarding the availability of a repeat-dose inhalation toxicity study

One registrant provided two inhalation toxicity studies in rats: a seven-day range-finding study (PMRA #2661279) and a 28-day study (PMRA #2661280). The purpose of the 28-day study was to determine the potential toxicity of iprodione and its effect on serum and testicular testosterone

levels when rats were exposed via the inhalation route. The toxicity of iprodione was determined by examining the endpoints of mortality, clinical observations, body weight, food consumption, serum and testicular fluid testosterone analysis, clinical pathology and anatomic pathology. The NOAEL for the 28-day study was stated to be an inhaled dose of up to 250 mg/kg bw/day (1.07 mg/L) for both male and female rats.

PMRA Response:
The PMRA has reviewed the data and identified iprodione-related effects following both the 28-day exposure period and the 28-day post-exposure recovery period:

Exposure period

- **≥ 0.043 mg/L (7.3/9 mg/kg bw/day):** Squamous metaplasia of the epiglottis in the larynx (considered non-adverse)
- **≥ 0.21 mg/L (36/41 mg/kg bw/day):** ↑ ovarian weights, ↑ liver weights (♀)
- **≥ 1.07 mg/L (196/226 mg/kg bw/day):** ↑ adrenal weights, ↑ cholesterol, minimal grade hypertrophy in the adrenal glands, hyperplasia in the epithelium of the epiglottis of the larynx ; ↑ thyroid weights, ↑ liver weights, hyperplasia and metaplasia of the respiratory epithelium in the nose/turbinates (1), erosion of the olfactory epithelium (1), ↑ minimal grade nephropathy in the kidneys, ↑ histiocytic cellular infiltrate in the lungs, minimal grade degeneration in the testes (1) (♂); degeneration in the epithelium of the trachea (♀).

Recovery period

- **≥ 0.21 mg/L (36/41 mg/kg bw/day):** ↓ body weight (~5–9%) and body weight gain during study days 26–54 (~19-–50%) (♂/♀) ; ↓ food consumption during study days 33–54 (♂)

The PMRA established a LOAEC of 0.21 mg/L for this study, based on decreased body weight, body weight gain (both sexes) and food consumption (males) during the recovery period as well as increased ovarian and liver weights in females recorded at the end of the exposure period. The NOAEC was determined to be 0.043 mg/L.

The short and intermediate-term inhalation reference values were revised in view of the submission of this study and are lower than those established in PRVD2016-09. The endpoints are based on the NOAEC from the 28-day inhalation toxicity study; 0.043 mg/L (7.3 mg/kg bw/day). The target MOE established by the PMRA was 300; this includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a threefold factor for uncertainty regarding potential effects on onset of puberty and sexual differentiation resulting from in utero or lactational exposure to iprodione. Although the oral toxicity studies in the iprodione database showed evidence of increasing toxicity with increasing duration of exposure, an additional uncertainty factor for the use of a short-term inhalation toxicity study for the intermediate-term exposure scenario was deemed unnecessary. The PMRA determined that the use of the threefold PCPA factor would encompass potential durational effects, including progression of respiratory tract pathology. Progression of the respiratory tract changes to neoplasia in humans was considered unlikely (PMRA #2780061). No changes were made to the reference values for long-term inhalation exposure scenarios.

The PMRA also revised the short-term aggregate reference value. The critical effect for short-term aggregate risk assessment was increased adrenal weight. For the inhalation route, the NOAEC from the 28-day inhalation study in rats of 0.21 mg/L (36/41 mg/kg bw/day) was selected on the basis of this endpoint. For the oral route, the selection of the oral NOAEL (15 mg/kg bw/day) from the 13-week rat study remains in place as per PRVD2016-09. As the existing 3-week dermal rabbit study did not assess the adrenal gland, the NOAEL of 15 mg/kg bw/day from the oral study was used as the endpoint for the dermal route as well. The target MOE for all routes is 300 which reflects the use of the threefold PCPA factor in addition to the standard 10-fold factors each for interspecies extrapolation and intraspecies variability.

1.2 Comments Related to Dietary Exposure

1.2.1 Registrant Comments

Registrants submitted comments regarding drinking water and percent crop treated (PCT) estimates. There were no comments regarding residue estimates for food commodities or for the residue chemistry review.

PMRA Response:
The information was reviewed by the PMRA and considered in the revised assessment. The information provided did not have a significant impact on the results of the dietary assessment.

1.2.2 Grower and User Comments

Comment:
A number of comments were submitted that indicated the importance of iprodione as a pest management tool.

PMRA Response:
The PMRA recognizes the importance of iprodione in agriculture and commercial sectors. A revised dietary exposure and risk assessment was conducted to examine whether important registered uses could be retained. Drinking water estimates were determined for specific use scenarios including turf, orchards, canola, greenhouse crops, outdoor ornamentals, and seed treatment. The results of the dietary assessment indicate no concerns for some greenhouse uses, outdoor ornamental uses, and seed treatment uses. However, all other outdoor uses remain of concern.

Comment:
The inclusion of turf use in the food and drinking water exposure and risk assessment was questioned.

PMRA Response:
Turf use was considered in the dietary exposure and risk assessment because of the potential for iprodione and its metabolite to enter drinking water sources following turf application. There is no expectation of exposure and risk from food sources as a result of turf use.

1.2.3 Comments from Grower Associations and Registrants Related to MRLs

Comments were submitted on the proposed revocation of MRLs for grapes, raspberries, almonds, and kiwifruit. The registrants also indicated concerns over the potential trade impact of revoking MRLs on these commodities and petitioned to keep the existing Canadian MRLs. No other comments regarding MRL changes were submitted.

PMRA Response:
A revised dietary exposure and risk assessment was conducted that considered exposure from imported grapes, raspberries, almonds, and kiwis, as well as exposure from a subset of registered Canadian uses and other commodities with import MRLs. The updated dietary exposure assessment indicates no risk concerns from the imported commodities and the MRLs can remain.

1.3 Comments Related to Occupational Exposure

1.3.1 Use Pattern Information

Grower associations and registrants submitted important use information and grower practices for several crops and turf.

PMRA Response:
PMRA acknowledges receipt of this information and has considered it to be very useful. However, many outdoor foliar applications to agricultural crops and turf pose a cancer risk of concern through drinking water and/or food exposure and are to be removed from labels. Therefore, the uses were not considered in the occupational risk assessment.

1.3.2 Protective Equipment for Postapplication Workers

Grower groups commented that PMRA should consider personal protective equipment (PPE) for postapplication workers.

PMRA Response:
Studies that are used currently to estimate postapplication worker exposure are based on workers wearing long-sleeved shirts, long pants, socks and footwear. It is also understood that many postapplication workers may wear gloves for their own personal comfort or for food safety purposes (to reduce food contamination). However, currently there are no reliable studies to indicate the degree of protection gloves may provide to postapplication workers, or conversely, the extent that gloves may enhance exposure under certain conditions.

Before PMRA can estimate risk for postapplication workers wearing gloves or other PPE, worker exposure studies comparable to those currently used by PMRA are required. Studies that are currently used are discussed further in the Regulatory Proposal PRO2014-14, *Updated Agricultural Transfer Coefficients for Assessing Occupational Post-application Exposure to Pesticides*. Most, if not all, studies conducted by the Agricultural Re-entry Task Force (ARTF), submitted by registrants, or available in the scientific literature and used to determine the transfer coefficients used in PMRA's occupational risk assessments did not include gloves as personal protective equipment. Gloves may be worn, but they function as dosimeters to measure hand

exposure, rather than for the purpose of reducing exposure as a result of protection from the glove. Some available studies suggest that exposure actually increases when wearing gloves (Brouwer, 2000; Boman et al., 2005; Garrigou et al., 2011; Graves et al., 1995; Keifer, 2000; Rawson et al., 2005).

In addition to the lack of scientific studies to estimate postapplication exposures while using specific PPE, the feasibility of postapplication workers wearing PPE must also be considered. As such, compliance, enforcement, training, regulatory jurisdiction, labelling, and communication are all aspects that need to be in place. PMRA is actively exploring these issues, including the feasibility of obtaining postapplication exposure studies for workers wearing certain PPE, for the purpose of estimating risk under these types of conditions.

1.3.3 Imported Treated Carrot Seeds

Grower associations provided specific use information for imported carrot seeds including the low potential for occupational exposure.

PMRA Response:
This information was considered in the revised risk assessment. Imported carrot seeds may be planted in Canada provided label statements are in place according to Appendix VI.

2.0 Comments Related to the Environmental Risk Assessment

2.1 Comments Relating to the Drinking Water Assessment

Registrants recommended that estimated environmental concentrations (EECs) of iprodione in potential sources of drinking water be generated using the Pesticide in Water Calculator (PWC v1.52) model, as this model is more recent than the Leaching Estimation and Chemistry Model (LEACHM) used for PRVD2016-09.

In addition, registrants submitted their own modelling results based on PWC and/or PRZM-GW (a groundwater modelling component of PWC). Several refinement options were discussed by the registrants, including the consideration of the percent cropped area (PCA) to refine the surface water modelling.

PMRA Response:
PMRA updated the drinking water modelling for most use patterns using PWC v1.52 and recent calculation tools for selecting the modelling input parameters. The updated EECs in potential surface water and groundwater drinking water sources include those for the combined residue of iprodione, RP30228 and RP32490, as well as for 3,5-DCA (RP32596). These EECs were used in the updated dietary assessment, as presented in this document.

The modelling approaches and refinements used by registrants were examined. With respect to the percent cropped area (PCA), the registrant compared USEPA water resource regions and Canada crop growing areas to select the most appropriate PCA adjustment factor from the range of PCAs considered by the USEPA when refining surface water modelling. As a general comment, it is noted that the PCAs used at the PMRA are different than those used at the

USEPA, as PMRA PCAs are based on Census of Agriculture data at the consolidated census subdivision level, and thus are specific to Canada. More importantly, for iprodione, a refinement based on the PCA was not applied given that the groundwater EEC is the dietary risk driver for most use patterns and the use of a PCA factor is only appropriate for surface water.

Other differences were noted when comparing the approaches used by registrants with the PMRA approach. For example, in the ground modelling, PMRA considered the dynamic transformation of iprodione to RP30228 through both aerobic soil transformation and hydrolysis, and the transformation of iprodione to 3,5-DCA by biotransformation in soil, as well as the degradation of all the compounds. By this way, PMRA modelled iprodione, RP30228 and 3,5-DCA separately and simultaneously. In the surface water modelling, PMRA included the transformation product RP32490. Overall, the revised modelling approach used by PMRA for iprodione is considered realistic based on available environmental fate data.

3.0 Comments Related to the Value Assessment

3.1 Comments relating to the Importance of Iprodione for Resistance Management

Comments received from grower associations and other stakeholders indicated that iprodione is effective as a protective and curative fungicide. Because of these properties, it can be used as a tank-mix partner or as a rotational fungicide with fungicides from other chemical groups in an integrated pest management (IPM) program to manage development of resistance in pathogens.

PMRA Response:
The PMRA agrees that iprodione is important for resistance management in a disease management program, both as a tank-mix partner and as a rotational fungicide. For the uses that will be retained, iprodione will continue to be available to growers to use in their plant protection programs. For the iprodione uses that will be cancelled, there are a number of other active ingredients registered that growers can use, including those uses identified by growers as being important to their production practices. These alternatives include multi-site fungicides such as captan and chlorothalonil, as well as other fungicides with a low resistance risk, such as fluazinam, in addition to several other fungicides that have a higher risk for resistance development. Growers may use these fungicides in rotation with, or as a tank-mix partner with fungicides from different mode of action groups for resistance management.

3.2 Comments relating to Canola Production

Comments received from grower associations, registrants and other stakeholders indicated that iprodione is valued by canola farmers since it is an effective solution for managing *Sclerotinia* stem rot and *Alternaria* black spot. It remains the best control strategy farmers have available and ensures the profitability of their crop. As a generic, it also provides a lower price option. Cancellation of iprodione use will negatively impact canola yields and quality due to the lack of fungicides for rotation to treat the most important disease, *Sclerotinia*.

PMRA Response:
The PMRA acknowledges the value of iprodione use on canola; however, despite updates to the health risk assessments, risks of concern remain and this use will be cancelled.

There are multiple active ingredients registered for the management of *Sclerotinia* stem rot and *Alternaria* black spot on canola, including co-formulated products, multi-site fungicides and fungicides from other mode of action groups. In addition there are several azoxystrobin generic products registered that are more cost-effective options for growers.

3.3 Comments relating to Grapes

Comments received from grower associations and registrants indicated that maintaining the use of iprodione is of critical importance so that the production system can include rotation to this active ingredient as a measure to limit the development of pathogen resistance.

PMRA Response:
The PMRA acknowledges the value of iprodione for *Botrytis* bunch rot control on grapes; however, despite updates to the health risk assessments, risks of concern remain and this use will be cancelled.

Active ingredients from eight single-site fungicide mode of action groups, co-formulated products and one multi-site biofungicide (BLAD polypeptide) are currently registered to manage this disease on grapes. They can be alternated as part of good resistance management practices in grape production.

3.4 Comments relating to Ginseng

Comments received from grower associations and registrants indicated that iprodione is an important tool in the management of *Alternaria* leaf and stem blight of ginseng, especially for protection of seed crops. Many new tools are available to control *Alternaria* in most situations. However, growers rely on cheaper options in their rotations that also provide resistance management.

PMRA Response:
The PMRA acknowledges the value of iprodione for *Alternaria* blight control on ginseng; however, despite updates to the health risk assessments, risks of concern remain and this use will be cancelled.

A number of alternative active ingredients from five different fungicide mode of action groups, including multi-site fungicides such as chlorothalonil, are currently registered. Growers may use these fungicides and in rotation as part of their resistance management program.

3.5 Comments relating to Strawberries

Comments received from grower associations indicated that iprodione is one of the most effective fungicides to control multi-fungicide resistant isolates of *Botrytis cinerea* (the causal agent of fruit rot) as it has been reported that strains of *Botrytis cinerea* are developing resistance to some conventional fungicides.

PMRA Response:
The PMRA acknowledges the value of iprodione for *Botrytis* fruit rot control on strawberries and that some of the single-site mode of action fungicides have developed some level of resistance to the fruit rot pathogen. However, despite updates to the health risk assessments, risks of concern remain and this use will be cancelled.

A number of alternative active ingredients from 11 fungicide mode of action groups including the multi-site fungicides captan, folpet, BLAD polypeptide and chlorothalonil are registered for this use. Growers may use these fungicides for Botrytis fruit rot control and resistance management.

3.6 Comments relating to Alfalfa Grown for Seed

Comments received from stakeholders indicated that cancellation of this use will negatively impact alfalfa yields and quality due to the lack of proper fungicide rotation to treat the most economically important disease, *Sclerotinia*. This will result significant financial implications to alfalfa seed industries in Saskatchewan.

PMRA Response:
The PMRA acknowledges the importance of iprodione for *Sclerotinia* control on alfalfa grown for seed; however, despite updates to the health risk assessments, risks of concern remain and this use will be cancelled.

In terms of alternative active ingredients, fluxapyroxad and pyraclostrobin are registered for suppression of *Sclerotinia*. In addition, boscalid and penthiopyrad are registered for the control of *Sclerotinia*. The PMRA acknowledges that these alternative active ingredients are from a single site fungicide mode of action, and that resistance management of *Sclerotinia* on alfalfa is a growing concern.

3.7 Comments relating to Carrot Seed Treatment

Comments were received from grower associations regarding the importance of iprodione for carrot seed treatment for the control of seed-borne *Alternaria.* It is the only chemical seed treatment option that effectively controls seed-borne *Alternaria* in carrots. Carrot seeds are not commercially produced in Canada and the growers depend on imported seeds which are typically treated with a fungicide.

PMRA Response:
The PMRA acknowledges the value of iprodione for imported carrot seed treatment for the control of seed-borne *Alternaria*. The PMRA has refined the risk assessments associated with the use of imported iprodione treated carrot seeds and as a result this use is acceptable for continued registration with respect to importation of iprodione treated carrot seeds into Canada.

3.8 Comments relating to Dry Beans

Comments received from grower associations indicated that one of the major uses of iprodione is the control of *Sclerotinia* white mould on dry beans.

PMRA Response:
The PMRA acknowledges the value of iprodione for Sclerotinia white mould control on dry beans; however, despite updates to the health risk assessments, risks of concern remain and this use will be cancelled.

Several other active ingredients including co-formulated products belonging to five fungicide mode of action groups are currently registered for control of Sclerotinia white mould on dry beans. Growers may use these fungicides for rotation as a part of resistance management programs.

3.9 Comments relating to the Management of Turf Diseases

Comments received from grower associations and other stakeholders indicated that for golf course turf, iprodione is an affordable and key component in the management of pink and grey snow mould, Fusarium patch, brown patch and dollar spot. It is the only active ingredient registered for turf in Canada with protective and curative mode of action which makes it very important for disease resistance management. Iprodione is particularly effective against the two most devastating diseases in Canada, snow mould and dollar spot, which make up approximately 90% of the disease pressure faced in Canada. Removing this product on turf would have a large negative impact on this industry and a safe and reliable product will be removed from our toolkit. Options for quality snow mould control products are very limited and removing iprodione would be a major blow to golf courses all over Canada that need to protect their turf over the winter.

PMRA Response:
The PMRA acknowledges the value of iprodione for turf disease management especially for snow moulds and dollar spot control; however, despite updates to the health risk assessments, risks of concern remain and this use will be cancelled.

Other active ingredients from several different fungicide mode of action groups are currently registered for turf disease management of brown patch, dollar spot, Fusarium patch, grey and pink snow moulds. In addition, the multi-site fungicide chlorothalonil is also registered for control of brown patch, dollar spot and snow moulds. Golf course superintendents and managers may use these fungicides for turf disease control and for resistance management.

3.10 Comments relating to the Management of *Monolinia* Brown Rot on Stone Fruit

The PMRA received comments from grower associations regarding the value of iprodione for the control of *Monolinia* brown rot as this pathogen is at medium risk of developing resistance to fungicides.

PMRA Response:
The PMRA acknowledges the value of iprodione for the control of *Monolinia* brown rot/ blossom blight on apricot, cherry, peach and plum/prune. However, despite updates to the health risk assessments, risks of concern remain and this use will be cancelled.

A number of active ingredients are registered from several fungicide mode of action groups including multi-site fungicides for control of *Monolinia* brown rot/ blossom blight on these crops. Growers may rotate these fungicides for resistance management.

Appendix III Revised Toxicological Reference Values

Table 1 Toxicology Endpoints for Use in Health Risk Assessment for Iprodione

Exposure Scenario	Endpoint	Study/Point of Departure	CAF or MOE[a]
Acute Dietary (females 13–49 years of age)	Decreased anogenital distance in fetuses	Rat gavage developmental toxicity study NOAEL: 20 mg/kg bw	300
	ARfD = 0.067 mg/kg bw		
Chronic Dietary	Increased adrenal weights and decreased in prostate weights.	Dog 1-yr oral study LOAEL: 4.1 mg/kg bw/day	300
	ADI = 0.014 mg/kg bw/day		
Dermal[b] (Short-term)	Decreased testes and prostate weights. Increased adrenal weights.	Rat 13-wk oral study NOAEL: 15 mg/kg bw/day	300
Dermal[b] (Intermediate-term/Long-term)	Increased adrenal weights and decreased prostate weights.	Dog 1-yr oral study LOAEL: 4.1 mg/kg bw/day	300
Inhalation (Short-term/Intermediate-term)	Decreased body weight, body weight gain (both sexes) and food consumption (♂) and increased ovarian and liver weights (♀)	Rat 28-day inhalation toxicity study NOAEC = 0.043 mg/L (7.3/9 mg/kg bw/day)	300
Inhalation[b] (Long-term)	Increased adrenal weights and decreased prostate weights.	Dog 1-yr oral study LOAEL: 4.1 mg/kg bw/day	300
Aggregate[b] Short-term (Oral/Dermal/ Inhalation)	Increased adrenal weight.	Oral/ Dermal Rat 13-wk oral study NOAEL: 15 mg/kg bw/day Inhalation Rat 28-day inhalation toxicity study NOAEC = 0.043 mg/L (7.3/9 mg/kg bw/day)	300
Cancer	q_1* value = 3.48×10^{-2} (mg/kg bw/day)-1 for rat Leydig cell tumours (♂)		

[a] - CAF (composite assessment factor) refers to the total of uncertainty and PCPA factors for dietary risk assessments, MOE refers to target MOE for occupational assessments.
[b] Since an oral point of departure was selected, a dermal absorption value of 16% or inhalation absorption value of 100% (default value) was used in route-to-route extrapolation.

Appendix IV Dietary Exposure and Risk Estimates for Iprodione

Table IV-1 Use Patterns Considered in Drinking Water Modelling

Use Pattern	Rate (g a.i./ha)
Seed treatment for carrot	1 × 18.24
Seed treatment for seed potato	1 × 406.7
Seed treatment for table and processing potatoes	1 × 203.4
Seed treatment for mustard	1 × 33.26
Typical rate for turf	1 × 5760 + 2 × 1440 at 14-day intervals
Typical rate for orchard	1 × 750
Minimum rate for canola	1 × 374
Maximum rate for turf	3 × 9000 at 14-day intervals

Table IV-2 Estimated Environmental Concentrations for Iprodione, RP30228, and RP30249

Use Scenarios	Ground Water (µg/L)			Surface Water (µg/L)		
	Daily[1]	Yearly[2]	Average[5]	Daily[3]	Yearly[4]	Average[5]
Outdoor Foliar Uses						
Turf High Rate	6.1	6.1	2.8	**98**	**35**	**18**
Turf Typical Rate	2.1	2.1	0.94	50	15	**7.9**
Orchard	0.14	0.14	0.063	12	3.6	**2.0**
Canola	0.12	0.12	0.054	9.1	2.6	**1.7**
Seed Treatment Uses						
Potato for Seed Only[6]	0.37	0.37	**0.17**	0	0	0
Potato for Consumption[6]	0.19	0.18	**0.084**	0	0	0
Mustard	0.009	0.009	0.004	**4.5**	**0.57**	**0.30**
Carrot	0.005	0.005	0.002	2.5	0.31	**0.16**

1 90th percentile of daily average concentrations.
2 90th percentile of 365-day moving average concentrations.
3 90th percentile of the peak concentrations from each year.
4 90th percentile of yearly average concentrations.
5 Overall mean of 50 years of daily average concentrations.
6 Surface water EECs are reported as zero for seed treatment on seed, table and processing potatoes because seeding depths are deeper than 2 cm and the model, PWC, assumes that the pesticide does not enter surface water bodies via runoff or eroded soil when the pesticide is applied at the depth.

Table IV-3 Estimated Environmental Concentrations for 3,5-DCA

Use Scenario	Ground Water (µg/L)			Surface Water (µg/L)		
	Daily[1]	Yearly[2]	Average[5]	Daily[3]	Yearly[4]	Average[5]
Foliar Uses						
Turf High Rate	87	87	**60**	< 98	< 35	< 18
Turf Typical Rate	28	28	**19**	< 50	< 15	< 7.9
Orchard	2.3	2.3	1.6	< 12	< 3.6	**< 2.0**
Canola	1.2	1.2	0.81	< 9.1	< 2.6	**< 1.7**
Seed Treatment Uses						
Potato for Seed Only[6]	1.7	1.7	**1.2**	0	0	0
Potato for Consumption[6]	0.84	0.83	**0.59**	0	0	0

Use Scenario	Ground Water (µg/L)			Surface Water (µg/L)		
	Daily[1]	Yearly[2]	Average[5]	Daily[3]	Yearly[4]	Average[5]
Mustard	0.11	0.11	0.077	< 4.5	< 0.57	< **0.30**
Carrot	0.061	0.061	0.042	< 2.5	< 0.31	< **0.16**

1 90th percentile of daily average concentrations.
2 90th percentile of 365-day moving average concentrations.
3 90th percentile of the peak concentrations from each year.
4 90th percentile of yearly average concentrations.
5 Overall mean of 50 years of daily average concentrations.
6 Surface water EECs are reported as zero for seed treatment on seed, table and processing potatoes because seeding depths are deeper than 2 cm and the model, PWC, assumes that the pesticide does not enter surface water bodies via runoff or eroded soil when the pesticide is applied at the depth.

Table IV-4 Iprodione Drinking Water Acute Exposure and Risk Assessment

Population Group	Exposure (mg/kg bw/day)[1]	% ARfD[2]
Female 13–49 years	0.011	17

1 Exposure estimate taken at the 99.9th percentile. Drinking water estimate at 98 µg/L was used based on the daily modelled EEC for surface water for turf use at the high rate.
2 Acute Reference Dose (ARfD) = 0.067 mg/kg bw for females 13–49 years. No ARfD is required for any other population subgroup.

Table IV-5 Iprodione Drinking Water Chronic Exposure and Risk Assessment

Population Group	Exposure (mg/kg bw/day)[1]	% ADI[2]
General Population	0.000707	5
All Infants	0.002642	19
Children 1–2 years	0.000973	7
Children 3–5 years	0.000791	6
Children 6–12 years	0.000588	4
Youth 13–19 years	0.000499	4
Adults 20–49 years	0.000703	5
Adults 50–99 years	0.000683	5
Female 13–49 years	0.000691	5

1 Drinking water estimate at 35 µg/L was based on the yearly modelled surface water EEC for turf at the high rate.
2 Acceptable Daily Intake (ADI) = 0.014 mg/kg bw/day for all population groups.

Table IV-6 Iprodione Drinking Water Cancer Exposure and Risk Assessment

Use	Exposure (mg/kg bw/day)[1]	Cancer Risk[2]
Foliar Uses		
Turf High Rate	0.000364	1×10^{-5}
Turf Typical Rate	0.000160	6×10^{-6}
Orchard	0.000040	1×10^{-6}
Canola	0.000034	1×10^{-6}
Seed Treatment Uses		
Potato for Seed Only	0.000003	1×10^{-7}
Potato	0.000002	6×10^{-8}
Mustard	0.000006	2×10^{-7}
Carrot	0.000003	1×10^{-7}

1 Exposure estimate for the general population. The highest modelled average EEC was used for each use scenario. Iprodione, RP30228, and RP30249 are included in the EEC.
2 Cancer risk = exposure × q_1*. The q_1* = 0.0348 $(mg/kg\ bw/day)^{-1}$.
Shaded cells represent scenarios with unacceptable risk.

Table IV-7 3,5-DCA Drinking Water Cancer Exposure and Cancer Risk Assessment

Use	Exposure (mg/kg bw/day)[1]	Cancer Risk[2]
Foliar Uses		
Turf High Rate	0.001212	8×10^{-5}
Turf Typical Rate	0.000384	2×10^{-5}
Orchard	0.000040	3×10^{-6}
Canola	0.000034	2×10^{-6}
Seed Treatment Uses		
Potato for Seed Only	0.000024	2×10^{-6}
Potato	0.000012	8×10^{-7}
Mustard	0.000006	4×10^{-7}
Carrot	0.000003	2×10^{-7}

[1] Exposure estimate for the general population. The highest modelled average EEC was used for each use scenario.
[2] Cancer risk = exposure × q_1*. The q_1* = 0.0638 (mg/kg bw/day)$^{-1}$.
Shaded cells represent scenarios with unacceptable risk.

Table IV-8 Iprodione Food Acute Exposure and Risk Assessment

Population Group	Exposure (mg/kg bw/day)[1]	% ARfD[2]
Female 13–49 years	0.002750	4

[1] Exposure estimate taken at the 99.9th percentile.
[2] Acute Reference Dose (ARfD) = 0.067 mg/kg bw for females 13–49 years. No ARfD is required for any other population subgroup.

Table IV-9 Iprodione Food Chronic Exposure and Risk Assessment

Population Group	Exposure (mg/kg bw/day)	% ADI[1]
General Population	0.000031	< 1
All Infants	0.000028	< 1
Children 1–2 years	0.000101	< 1
Children 3–5 years	0.000072	< 1
Children 6–12 years	0.000035	< 1
Youth 13–19 years	0.000020	< 1
Adults 20–49 years	0.000026	< 1
Adults 50–99 years	0.000028	< 1
Female 13–49 years	0.000027	< 1

[1] Acceptable Daily Intake (ADI) = 0.014 mg/kg bw/day for all population groups.

Table IV-10 Iprodione Food Cancer Exposure and Risk Assessment

Population Group	Exposure (mg/kg bw/day)	Cancer Risk[1]
General Population	0.00031	1×10^{-6}

[1] Cancer risk = exposure × q_1*. The q_1* = 0.0348 (mg/kg bw/day)$^{-1}$.

Table IV-11 Food and Drinking Water Acute Exposure and Risk Assessment

Population Group	Exposure (mg/kg bw/day)[1]	% ARfD[2]
Female 13–49 years	0.002871	4

[1] Exposure estimate taken at the 99.9th percentile. The highest daily EEC for mustard seed treatment at 4.5 ug/L was used.
[2] Acute reference dose (ARfD) = be 0.067 mg/kg bw for females 13–49 years. No ARfD is required for any other Population subgroup.

Table IV-12 Food and Drinking Water Chronic Exposure and Risk Assessment

Population Group	Exposure (mg/kg bw/day)[1]	% ADI[2]
General Population	0.000042	< 1
All Infants	0.000071	< 1
Children 1–2 years	0.000117	< 1
Children 3–5 years	0.000085	< 1
Children 6–12 years	0.000044	< 1
Youth 13–19 years	0.000028	< 1
Adults 20–49 years	0.000037	< 1
Adults 50–99 years	0.000039	< 1
Female 13–49 years	0.000039	< 1

[1] The highest yearly EEC for mustard seed treatment at 0.57 ug/L was used.
[2] Acceptable Daily Intake (ADI) = be 0.014 mg/kg bw/day for all population groups

Table IV-13 Food and Drinking Water Cancer Exposure and Risk Assessment

Population Group	Exposure (mg/kg bw/day)	Cancer Risk[1]
General Population	0.000037	1×10^{-6}

[1] The highest average EEC for mustard seed treatment at 0.3 ug/L was used.
[2] Cancer risk = exposure x q_1*. The q_1* = 0.0348 $(mg/kg\ bw/day)^{-1}$.

Appendix V Occupational Mixer/Loader/Applicator (MLA) and Postapplication Exposure and Risk Estimates for Iprodione

Details for the revised risk assessment are included in this appendix and supporting documentation. Please refer to PRVD2016-09 for additional information.

Toxicological Reference Values
The toxicological reference values have been revised since the PRVD 2016-09 (Appendix II Table 1). The inhalation scenario was updated and the q_1* value for the mouse liver tumours was removed and replaced with a q_1* value for rat testicular tumours. All human health risk assessments have been updated as necessary using the revised values.

Dermal Absorption
The dermal absorption value described in the PRVD2016-09 was used in the human health risk assessments. No new studies were submitted during the PRVD comment period.

Use Pattern
The full use pattern was not revised for occupational exposure. Only uses determined to have acceptable food and drinking water risk were considered. Application rates are consistent with PRVD2016-09; however, the number of applications has been limited as a mitigation measure where required.

Seed Treatment
The surrogate seed treatment studies described in PRVD2016-09 were used to estimate worker exposure from commercial and on-farm canola and mustard seed treatment, potato seed piece treatment, as well as from planting treated seeds. Workers who perform planting duties were also reassessed using an additional in-house study available at PMRA.

Dislodgeable Foliar Residue (DFR)
Chemical-specific DFR studies and default values described in PRVD2016-09 were used in the outdoor postapplication risk assessment. No new DFR studies were submitted during the PRVD comment period. For greenhouse ornamental crops the default DFR values were updated; therefore, the current default values were used (peak DFR of 25% of the application rate, with a 2.3% dissipation rate per day).

Table 1 Wettable Powder/Wettable Granule Formulation:Occupational Exposure Risk Assessment Summary

Scenario		Mixer/Loader/Applicator	Postapplication Risk Assessment/Mitigation Required
USC	Crop		
5/6	Greenhouse Lettuce	Hand held equipment: Mid level PPE + respirator	Limitation: 1 application only REI: 0.5 days
	Greenhouse Cucumber	Hand held equipment: Mid level PPE + respirator	REI: unacceptable risk at 0.5 days. Data is required to extend beyond 0.5 days.
	Greenhouse Tomato	Hand held equipment: Mid level PPE + respirator	REI: unacceptable risk at 0.5 days. Data is required to extend beyond 0.5 days.
6/27	Conifer seedlings (spruce, fir, hemlock and	Airblast: Midlevel PPE + respirator + CR hat	Limitation: 3 applications, 21 days apart. Only 2 applications can occur in the

Scenario		Mixer/Loader/Applicator	Postapplication Risk Assessment/Mitigation Required
USC	Crop		
	cedar) - container or bareroot conifer seedlings in greenhouses and conifer nurseries	Groundboom: Mid level PPE	greenhouse Greenhouse REI (all tasks) : 1 day Outdoor REI (all tasks): 0.5 days
	Ornamentals Foliar treatment for control of *Botrytis*	Hand held equipment: Mid level PPE + respirator Airblast: Mid level PPE and CR hat Groundboom: Mid level PPE	Limitation: 3 applications, 21 days apart Greenhouse cut flower REI: 91 days (not feasible) Outdoor cut flower REI: 29 days (not feasible) Greenhouse potted ornamental REI (all tasks) : 0.5 days Outdoor potted ornamental REI (handline irrigation): 18 days Outdoor potted ornamental REI (all other tasks): 0.5 days
	Ornamentals – Soil drench for control of *Rhizoctonia*	Soil Drench: Mid level PPE + respirator	Soil drench only; no foliar contact Limitation: 2 applications, 21 days apart REI (all tasks): 0.5 days
10	Imported treated carrot seeds	Not applicable	Planting: Closed cab, baseline PPE + filtering face piece (dust mask) respirator

USC: Use site category; PPE: personal protective equipment; Mid level: baseline + coveralls; Baseline: single layer + gloves; CR: chemical resistant

Table 2 Suspension Formulation: Occupational Exposure Risk Assessment Summary

Scenario		Worker Risk Assessment / Mitigation Required
USC	Crop	
10	Canola and mustard commercial and on-farm seed treatment	Cancer and non-cancer risks of concern
	Potato Seed Piece Treatment	MLA: Baseline PPE Handlers: Mid level PPE Limitation: < 60400 kg planted per day Not for use on potatoes grown for seed

USC: Use site category; PPE: personal protective equipment; Baseline: single layer + gloves; Mid level: baseline + coverall

Appendix VI Label Amendments for Products Containing Iprodione

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the label statements provided below.

HUMAN HEALTH

1. Label Amendments for Commercial Class End-use Products Containing Iprodione

The following uses must be removed from all commercial class end-use labels:

- Foliar treatment of:
  - Canola
  - Alfalfa
  - Strawberries
  - Raspberries
  - Peaches
  - Plums
  - Prunes
  - Cherries
  - Apricots
  - Grapes
  - Lettuce
  - Cauliflower
  - Cabbage
  - Snap beans
  - Kidney beans
  - White beans
  - Onions
  - Leeks
  - Ginseng
  - Tomatoes (greenhouse)
  - Cucumbers (greenhouse)
  - Cut flowers (foliar treatment of *Botrytis* spp.) greenhouse and outdoors
- Turf
- Garlic seed dip
- Seed treatment of canola and mustard

1.1 PRECAUTIONS

1.1.1 General Label Improvements

Spray Drift Statement:

The following label statements are to be added to the **PRECAUTIONS** of all end-use product labels with the exception of seed treatment product labels:

> "Apply only when the potential for drift to areas of human habitation or areas of human activity (houses, cottages, schools and recreational areas) is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings."

1.1.2 Personal Protective Equipment

1.1.2.1 Wettable Powder Products

Add the following statements:

> "During mixing, loading, application, clean-up and repair, wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, chemical-resistant footwear and a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides or a NIOSH approved canister approved for pesticides."

> "When applying using open airblast equipment or for overhead spray, also wear chemical resistant headgear. Chemical resistant headgear includes Sou'Wester hat, chemical-resistant rain hat or large brimmed waterproof hat and hood with sufficient neck protection."

1.1.2.2 Water Dispersible Granule Products

Add the following statements:

> "During mixing, loading, application, clean-up and repair, wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, chemical-resistant footwear and a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides or a NIOSH approved canister approved for pesticides."

> "When applying using open airblast equipment or for overhead spray, also wear chemical resistant headgear. Chemical resistant headgear includes Sou'Wester hat, chemical-resistant rain hat or large brimmed waterproof hat and hood with sufficient neck protection."

1.1.2.3 Liquid Commercial-Class Seed Treatment Products

Potato Seed Piece Treatment

Add the following to the label under **PRECAUTIONS**:

"During mixing, loading, and application, wear:

- Long-sleeved shirt and long pants, chemical-resistant gloves and boots plus socks."

"When handling treated seed and/or riding at the back of the planter to monitor planting, workers must wear:

- Coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, boots and socks."

"DO NOT plant more than 60,400 kg of treated seed per day"

"Only for use on potato seed pieces to be grown for processing and table potatoes. DO NOT treat potato seed pieces grown for seed."

1.2 USE INSTRUCTIONS

a. Imported Treated Carrot Seed

Create a new section in the label titled 'For Importation of Treated Seed' under 'Directions for Use'. Then add the following statement:

"**DO NOT** treat carrot seeds in Canada"

"Treated seed bags must be labelled or tagged with the following instructions for workers planting treated seed. If seed is not bagged, then the following information must be provided in writing to the farmer through another means, such as a pamphlet:

For all activities involving handling of treated seeds (including planting), wear a long-sleeved shirt, long pants, chemical-resistant gloves, and a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit-tested. Closed cabs must be used for planting treated seeds. Respirators and chemical-resistant gloves are not required to be worn within the closed cab as long as the cab is equipped with equivalent respiratory protection (dust/mist filtering and/or vapour/gas purification system), but need to be available when exiting the cab for calibration, repair or cleaning of equipment."

b. Potato Seed Piece Treatment Restriction

The following restriction must be added to all labels as applicable:

"A minimum rotational crop plant back interval (PBI) of 30 days is required for all crops except root vegetables (crop group 1) and leafy brassica greens (crop group 5b). The PBI requirement for crop group 1 and 5b is 12 months."

c. Equipment Limitations

Add the following statement to all applicable labels:

"Do not apply using handheld mist blowers and handheld fogging equipment"

d. Ornamental Restrictions

Ornamentals – control of Botrytis spp.

Add the following statement:
"Not for foliar use on cut flowers."

Ornamentals – control of damping-off caused by Ryzoctonia

Add the following statement:
"Do not spray foliage when treating for Ryzoctonia."

e. Application Rates

Table 1 lists the maximum number of applications and minimum intervals to be updated on products labels as per applicable crop.

Table 1 Maximum Rate and Number of Applications for Iprodione

Crop	Maximum Application Rate(s)	Maximum number of applications, minimum retreatment interval
Lettuce (greenhouse)	1 kg a.i./ha	1 application
Conifer seedlings (greenhouse and outdoors)	1 kg a.i./ha	3 applications, 21 days apart. Only 2 of the applications can occur while in the greenhouse
Soil drench ornamentals (control of damping-off caused by *Rhizoctonia*) (potted ornamentals and cut flowers) (greenhouse and outdoors)	10 kg a.i./ha	2 applications, 21 days apart.
Ornamental foliar use (control of *Botrytis* spp.) (non-cut flowers) (greenhouse and outdoors)	5 g a.i./10 L (0.5-0.7 kg a.i./ha)	3 applications, 21 days apart.

1.3 Restricted-entry Interval (REI)

Add the following to the label under **PRECAUTIONS**:

a. For products that have label directions discussing entry into treated areas prior to expiry of the REI (specifically Registration #15213):

Replace the following, or similar wording:

> "If required, individuals may re-enter treated areas within 12 hours for short-term tasks not involving hand labour if at least 4 hours have passed since application and long pants, long-sleeved shirt, hat, protective eyewear and chemical resistant gloves are worn. "

With:

> "**DO NOT** enter or allow worker entry into treated areas during the restricted-entry interval (REI) on the label. Employers should make every effort to schedule pesticide applications and worker tasks in order to avoid early entry of workers into treated areas. Under exceptional circumstances, certified pesticide applicators may enter treated areas for short-term tasks not involving hand labour if at least 4 hours have passed since application and a long-sleeved shirt, long pants, rubber boots, socks, goggles, gloves and a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH-approved canister approved for pesticides is worn. Time spent in the treated area cannot exceed 1 hour in a 24 hour period or until restricted-entry interval is over."

b. For all products that include any of the following crops, add the following statement and the applicable REI:

"DO NOT enter or allow worker entry into treated areas during the restricted-entry interval REI(s) specified in the following table."

REIs for Iprodione

Crop	Re-entry Activity	Restricted-entry Interval
Greenhouse lettuce	All tasks	12 hours
Conifer seedlings (greenhouse)	All tasks	1 day
Conifer seedlings (outdoors)	All tasks	12 hours
Soil drench ornamentals (control of damping-off caused by *Rhizoctonia*) (potted ornamentals and cut flowers) (greenhouse and outdoors)	All tasks	12 hours
Ornamental foliar use (control of *Botrytis* spp.) (non-cut flowers) (greenhouse and outdoors)	All tasks (except handline irrigation)	12 hours
	Handline irrigation	18 days

ENVIRONMENT

1. Label Amendments for Iprodione Technical Insecticide

The following statements are to be added to the "Environmental Hazards" section of the Iprodione Technical Insecticide label:

> TOXIC to aquatic organisms.

The following statements are required under the "Precautions" section of the Iprodione Technical Insecticide label:

> DO NOT discharge effluent containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters.

2. Label Amendments for Commercial Class End-use Products Containing Iprodione

Add to ENVIRONMENTAL HAZARDS:

> TOXIC to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE.
>
> TOXIC to birds.
>
> TOXIC to bees. Minimize spray drift to reduce harmful effects on bees in habitats close to the application site. Avoid application during the crop blooming period. If applications must be made during the crop blooming period, restrict applications to the early morning or the evening when most bees are not foraging. Avoid applications when bees are foraging in the treatment area in ground cover containing blooming weeds. To further minimize exposure to pollinators, refer to the complete guidance "Protecting Pollinators during Pesticide Spraying – Best Management Practices" on the Health Canada website (https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management/growers-commercial-users/pollinator-protection.html).
>
> To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil, or clay.
>
> Avoid application when heavy rain is forecast.
>
> Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.
>
> The use of this chemical may result in contamination of groundwater particularly in areas where soils are permeable (e.g. sandy soil) and/or the depth to the water table is shallow.

Add the GENERAL DIRECTIONS FOR USE after the MIXING INSTRUCTIONS:

As this pesticide is not registered for the control of pests in aquatic systems, **DO NOT** use to control aquatic pests.

DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

To protect pollinators, follow the instructions regarding bees in the Environmental Hazards section.

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

Buffer zones:
Spot treatments using handheld equipment **DO NOT** require a buffer zone.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop	Buffer Zones (metres) Required for the Protection of Freshwater Habitat of Depths:	
		Less than 1 m	Greater than 1 m
Field sprayer	Outdoor ornamentals, conifer seedlings	2	1

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

For products with seed treatment uses:

Add the following statement to ENVIRONMENTAL HAZARDS section:

Treated seed is toxic to birds and small wild mammals. Any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned-up from the soil surface.

For products with greenhouse uses:

Add the following statement to the ENVIRONMENTAL HAZARDS section:

> Toxic to certain beneficial insects. May harm certain beneficial insects, including those used in greenhouse production.
>
> DO NOT allow effluent or runoff from greenhouses containing this product to enter lakes, streams, ponds or other waters.

The following statements is required under the DIRECTIONS FOR USE section:

> To protect pollinators, follow the instructions regarding bees in the Environmental Precautions section.

Appendix VII Additional References

Toxicology

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2661283	Iprodione: Mode of action and human relevance analysis of rodent-specific liver tumors found in the carcinogenicity mouse study"
2661280	Iprodione Technical: A 4-WEEK REPEAT-DOSE INHALATION TOXICITY STUDY OF IPRODIONE TECHNICAL IN SPRAGUE DAWLEY RATS, WITH TESTOSTERONE MEASUREMENTS (GLP). BATTELLE STUDY NUMBER: 49770B. Study report date: APRIL 26, 2016. DACO 4.3.7.

B. Published Information

PMRA Document Number	Reference
2780058	Chhabra, R.S. et al. Toxicity of p-chloroanaline in rats and mice. Fd Chem. Toxic. Vol. 28, No. 10, pp. 717-722 (1990)
2780063	G. Sabbioni and O. Sepai. Comparison of hemoglobin binding, mutagenicity, and carcinogenicity of arylamines and nitroarenes. Chimia, 49, 374-380 (1995)
2780065	MA Valentovic et al. Comparison of the in Vitro Toxicity of Dichloroaniline Structural Isomers Toxicol In Vitro 9 (1), 75-81. 2 (1995)
2780064	MA Valentovic et al. Characterization of methemoglobin formation induced by 3,5-dichloroaniline, 4-amino-2,6-dichlorophenol and 3,5-dichlorophenylhydroxylamine. Toxicology 118, 23-36 (1997)
2780220	Nyska et al. Association of Liver Hemangiosarcoma and Secondary Iron Overload in B6C3Fl Mice-The National Toxicology Program Experience. Toxicologic Pathology, 32:222-228, (2004)
2780059	Cohen et al. Hemangiosarcoma in Rodents Mode-of-Action Evaluation and Human Relevance. Toxicological Sciences 111(1), 4–18 (2009)
2780062	CR Racine et al. The Role of Biotransformation and Oxidative Stress in 3,5-Dichloroaniline (3,5-Dca) Induced Nephrotoxicity in Isolated Renal Cortical Cells From Male Fischer 344 Rats. Toxicology 341-343, 47-55. (2016)
2780061	W. Kaufmann et al., 1st International ESTP Expert Workshop: "Larynx squamous metaplasia". A re-consideration of morphology and diagnostic approaches in rodent studies and its relevance for human risk assessment. Experimental and Toxicologic Pathology 61 (2009) 591-603
2780060	European Food Safety Authority (EFSA). Peer review of the pesticide risk assessment of the active substance iprodione. (2016)
2841393	Lake BG et al., 2014. Mode of action analysis for pesticide-induced rodent liver tumours involving activation of the constitutive androstane receptor: relevance to human cancer risk. Pest Manag Sci 2015; 71: 829-834
2841386	Elcombe CR. et al., 2014. Mode of action and human relevance analysis for nuclear receptor-mediated liver toxicity: A case study with phenobarbital as a model constitutive androstane receptor (CAR) activator. Crit Rev Toxicol. 2014 January ; 44(1): 64–82
1927317	Nesnow S et al., 2009. Discrimination of Tumorigenic Triazole Conazoles from Phenobarbital by Transcriptional Analyses of Mouse Liver Gene Expression. Toxicological Sciences. 2009 110(1), 68–83

Dietary Assessment

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1626331	Vaughn, F.C. 2008. Magnitude of Residues in/on Potatoes Treated with Seed Piece Treatment of the Fungicide Rovral Flo.2008-03.

Occupational and Residential Assessment

A. List of Studies/Information Submitted by Registrant

None.

B. Published Information

PMRA Document Number	Reference
	Boman, A., Estlander,T.,Wahlburg J.E., Maibach, H.I. 2005. Protective Gloves for Occupational Use Second edition. CRC Press LLC.
	Brouwer, D.H., de Vreede, S.A.F., Meuling.,W.J.A., van Hemmen, J.J. 2000. Determination of the efficiency for pesticide exposure reduction with protective clothing: a field study using biological monitoring. Chapter 5 In: Assessment of Occupational Exposure to Pesticides in Dutch Bulb Culture and Glasshouse Horticulture. Doctoral Thesis of D.H. Brouwer. pp.158-179.
	Garrigou, A., Baldi I.,Le Frious P., Anselm R., Vallier M. 2011. Ergonomic contribution to chemical risks prevention: an ergotoxicologcial investigation of the effectiveness of coverall against plant pest risk in viticulture. 42: 321-330.
	Graves, CJ., Edwards, C., Marks R. 1995. The effects of protective occlusive gloves on stratum corneum barrier properties. Contact Derm 33: 183-187.
	Keifer, M.C., 2000. Effectiveness of Interventions in Reducing Pesticide Overexposure and Poisonings. American Journal of Preventive Medicine. 18 (4S); 80-89.
	Rawson, B.V., Cocker, J., Evans, P.G. Wheeler, J.P. and Akrill, P.M. 2005. Internal contamination of Gloves: routes and Consequences. Am. Occup. Hyg. 49 (6): 535-541.

C. Unpublished Information

PMRA Document Number	Reference
2557310	Lange, B. 2015. Observational Study to Determine Dermal and Inhalation Post-Application Exposure of Workers to Difenoconazole during Handling and Planting of Treated Potato Seed Pieces. Eurofins Agrosciences Services, Inc. (East Brunswick, NJ). Laboratory report no. S13-04252. Sponsor Study no. TK017267. Unpublished.
2313627	Krainz, A. 2013. Determination of Dermal and Inhalation Exposure to Operators During Loading and Sowing Seed Treated with Austral Plus Net Using Conventional or Pneumatic Sowing Machines. AHETF, AH823. Macon, Missouri. Unpublished. April 30, 2013