Re-evaluation Decision RVD2018-40

Pyridaben and Its Associated End-use Products

Final Decision

(publié aussi en français)

19 December 2018

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

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: canada.ca/pesticides
hc.pmra.publications-arla.sc@canada.ca
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
hc.pmra.info-arla.sc@canada.ca

Canada

ISSN: 1925-1017 (print)
1925-1025 (online)

Catalogue number: H113-28/2018-40E (print version)
H113-28/2018-40E-PDF (PDF version)

Table of Contents

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. The PMRA applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Pyridaben is an insecticide and acaricide registered for use on greenhouse and outdoor ornamentals, greenhouse food crops (peppers, cucumbers and tomatoes), orchard crops, grapes, raspberries and strawberries to control mites, whiteflies and pear psylla. Currently registered products containing pyridaben are listed in Appendix I.

This document presents the final regulatory decision[1] for the re-evaluation of pyridaben, including the required risk mitigation measures to protect human health and the environment. All products containing pyridaben that are registered in Canada are subject to this re-evaluation decision. This re-evaluation decision has undergone a 60-day consultation period on the Proposed Re-evaluation Decision PRVD2016-04, *Pyridaben,*[2] which ended on 5 April 2016.

The registrant provided Health Canada with an environmental toxicology study and comments on the health risk assessments. Additional information was also received from Ontario grape growers. Comments and information received are summarized in Appendix II along with the response by Health Canada. The risk assessments were revised in consideration of the information provided (see Science Evaluation Update), resulting in changes to the proposed regulatory decision as described in PRVD2016-04. A reference list of data used as the basis for the proposed re-evaluation decision is included in PRVD2016-04, and further data used in the re-evaluation decision is listed in Appendix V.

Outcome of Science Evaluation

Health risks have been shown to be acceptable when pyridaben is used according to the revised label directions, which include restricted-entry interval (REI) requirements for all crops.

Pyridaben enters the environment when used to control insects on food crops and outdoor ornamentals. Environmental risks of pyridaben continue to be acceptable when used according to the revised label directions.

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

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

Regulatory Decision for Pyridaben

Health Canada has completed the re-evaluation of pyridaben. Under the authority of the *Pest Control Products Act*, Health Canada has determined that continued registration of products containing pyridaben is acceptable. An evaluation of available scientific information found that health and environmental risks and the value of pyridaben continue to be acceptable when products are used according to the conditions of registration, which include required amendments to label directions. Label amendments, as summarized below and listed in Appendix IV, are required for all technical and end-use products. No additional data are requested.

Risk Mitigation Measures

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment and must be followed by law.

Human Health

The following risk-reduction measures are required for continued registration of pyridaben in Canada:

- Increased REIs for postapplication activities on grapes and a 12-hour REI on remaining crops to protect workers and those entering treated areas.
- Precautionary statement prohibiting use in residential areas to protect the public from non-occupational exposure.
- Precautionary statements to clarify protective equipment for workers.
- Precautionary statement to minimize human exposure from spray drift or spray residues resulting from drift.

Environment

- Precautionary statements to protect non-target terrestrial and aquatic organisms.
- Spray buffer zones to protect non-target terrestrial and aquatic habitats.
- To protect bees and other pollinators, restrictions to applications when crops are not blooming or when bees are not actively foraging.
- Precautionary statements to identify environmental hazards and prevent runoff from areas of application to aquatic habitats.

Next Steps

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

Other Information

Any person may file a notice of objection[3] regarding this decision on pyridaben 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 section of Canada.ca (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

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

Science Evaluation Update

1.0 Revised Health Risk Assessment

1.1 Toxicology Assessment

The toxicological assessment for pyridaben was previously described in PRVD2016-04. Comments were received from the registrant regarding the neurodegenerative potential of pyridaben and the associated additional threefold uncertainty factor applied by Health Canada in the risk assessment (Appendix II). However, after considering this information, no changes to the toxicology endpoints or uncertainty factors outlined in PRVD2016-04 were deemed warranted by Health Canada.

1.2 Occupational and Non-Occupational Exposure and Risk Assessment

PRVD2016-04 proposed the cancellation of the use on grapes as well as an increased REI for greenhouse cut flowers. Comments were received from the registrant regarding spray volumes, personal protective equipment (PPE) and REIs (Appendix II). Additional information on agricultural practices was also received from Ontario grape growers.

The occupational post-application risk assessments for grapes and greenhouse cut flowers were revisited based on the above information. The REIs calculated for grapes in PRVD2016-04 are now considered feasible since it was clarified that certain postapplication activities are either not performed by all growers (cane turning and girdling), can occur prior to pyridaben application (training and tying), or can be performed mechanically (leaf pulling). For greenhouse cut flowers, the REIs proposed in PRVD2016-04 for hand harvesting, hand pruning and disbudding was reduced from 6 days to 12 hours based on the spray volume provided by the registrant (Appendix III).

Label amendments (Appendix IV) include a revised statement that limits the use of pyridaben products to certified pesticide applicators, thereby preventing the use by a homeowner or other uncertified users, as indicated in PRVD2016-04.

2.0 Revised Environmental Risk Assessment

2.1 Environmental Risk Characterization

2.1.1 Risks to Aquatic Organisms

In PRVD2016-04, the environmental risk assessment concluded that uses of pyridaben posed potential risks of concern for some non-target species such as bees and pollinators, beneficial insects, birds, terrestrial mammals, terrestrial plants and aquatic organisms. Mitigation measures were proposed to reduce potential exposure of non-target organisms and reduce environmental risks. Environmental data on bioaccumulation in sediment-dwelling invertebrates were required

and received from the registrant. The study confirmed that although bioaccumulation may occur, significant accumulation in the food web is not expected.

No other comments or information were received with respect to the environment. Consequently, Health Canada did not revise the environmental risk assessment, with the exception of spray buffer zones, which were further refined by restricting wind speed and droplet size.

3.0 Conclusion of Science Evaluation

With respect to human health, comments from the registrant did not result in changes to the toxicology assessment. However, the REIs calculated for grapes in PRVD2016-04 are now considered to be feasible due to recent clarifications on agricultural practices in grapes production in Canada. The occupational postapplication risk assessment for greenhouse cut flowers was revised based on the spray volume information provided by the registrant, resulting in a reduction of the proposed REI to 12 hours. Exposure to pyridaben is unlikely to affect human health when used according to the revised label directions.

Pyridaben enters the environment when used to control insects on food crops and outdoor ornamentals. Environmental risks of pyridaben continue to be acceptable when used according to the revised label directions. The submitted bioaccumulation study confirmed that significant accumulation in the food web is not expected.

List of Abbreviations

µg	microgram(s)
a.i.	active ingredient
ASAE	American Society of Agricultural Engineers
$BSAF_K$	kinetic biota sediment accumulation factor
$BSAF_{KL}$	lipid corrected kinetic biota sediment accumulation factor
$BSAF_{SS}$	steady state biota sediment accumulation factor
$BSAF_{SSL}$	lipid/organic carbon corrected steady state biota sediment accumulation factor
bw	body weight
CI	confidence interval
cm^2	centimetres squared
DFR	dislodgeable foliar residue
dw	dry weight
ha	hectare
hr	hour
kg	kilogram(s)
L	litre(s)
mg	milligram(s)
MOE	margin of exposure
NOAEL	no observed adverse effect level
OR	odds ratio
PCPA	*Pest Control Products Act*
PD	Parkinson's disease
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

Appendix I Registered Pyridaben Products in Canada [1]

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee (% a.i.)
25133	Technical	Nissan Chemical Industries Ltd.	Pyridaben Technical Miticide/Insecticide	Wettable powder	99.4
25134	Commercial	Canyon Group, LLC	Sanmite Miticide/Insecticide	Wettable powder	75
25135	Commercial	Canyon Group, LLC	Nexter WP Miticide/Insecticide	Wettable powder	75
25229	Commercial	Plant Products Co. Ltd.	Dyno-mite Miticide/Insectide Wettable Powder Formulation	Wettable powder	75

[1]As of 1 November 2018, excluding discontinued products or products with a submission for discontinuation.

Appendix II Comments and Responses

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

1.0 Comments Related to the Health Risk Assessment

1.1 Toxicology

In summary, the registrant had no issue with the points of departure selected for risk assessment or with the application of the standard uncertainty factors. The registrant indicated that the weight of evidence supported a finding of no concern for pyridaben and Parkinson's disease (PD). Accordingly, the registrant disagreed with the additional threefold uncertainty factor applied by Health Canada for the lack of data addressing the potential for specific neuronal damage via the route of expected exposure. After analyzing the comments, Health Canada has determined that the registrant has not provided any substantive new information to refute the concern. Although the registrant provided some valid points in their rebuttal, the available data still raise some concern about the neurodegenerative potential of pyridaben. There continues to be a lack of data addressing the potential for pyridaben to cause neuronal damage by a relevant route of exposure (that is, using sensitive staining techniques). In light of this, Health Canada will continue to apply the additional threefold uncertainty factor for all toxicology endpoints except the acute reference dose. As a result, the toxicology endpoints and composite assessment factors/margins of exposure remain unchanged from those outlined in PRVD2016-04.

Comment 1.1.1

The registrant concluded that the in vitro toxicology studies were not relevant to any pathway or route of human exposure. Further, they contended that any dose-response differences in the in vitro studies could not be reliably extrapolated to in vivo models with relevant routes of human exposure.

Health Canada Response:

The in vitro data includes pyridaben-affected endpoints such as dose dependent cell death, depletion of adenosine triphosphate and oxidative cell damage in neuroblastoma cells, competition with ^{3}H-dihydrorotenone binding to Complex I in isolated rat brain mitochondria and dendritic pruning in cultured rat pup mid-brain slices. Health Canada concurs that the data are insufficient to allow in vitro to in vivo extrapolation in the absence of physiologically-based pharmacokinetic modelling. Nonetheless, the studies are still useful for understanding mechanisms of action and for identifying areas of concern for in vivo follow-up. In the case of pyridaben, the in vitro studies lend support to the characterization of the brain as a sensitive tissue.

Two new papers published since the re-evaluation assessment provided further in vitro evidence of the brain as a target tissue. In rat dopaminergic neuronal cells, pyridaben caused dose-dependent cell death (similar to rotenone), induced oxidative damage and structural impairment to mitochondria, impaired mitochondrial respiration and depleted intracellular bioenergy levels (PMRA #2656032). In a second study in mouse cortical cells, gene expression placed pyridaben

in a cluster of compounds that transcriptionally mimicked brain disorders (PMRA #2656037). While the PMRA acknowledges that this latter study uses novel approaches and that the regulatory translation of this gene expression data has yet to be ascertained, the new data do not diminish the concern for potential neurological effects.

Comment 1.1.2

The registrant indicated that no PD-like signs were observed in the typical in vivo toxicology studies required for registration with the exception of the acute oral neurotoxicity study. In this study, signs were seen in rats on days 1 through 5 after single gavage dosing at 80 mg/kg bw and above. They noted that the effects were not uncommon for other chemistries in this type of study and that chemical-induced PD is considered to be a continuous effect, not transient.

Health Canada Response:

Health Canada concurs with these points.

Comment 1.1.3

The registrant concluded that the non-guideline neurotoxicity study in mice with subcutaneous dosing of pyridaben for 7 days was not relevant to human health hazard or risk assessment. Firstly, they indicated that study route of exposure was not a pathway or route of exposure for humans. Secondly, the registrant indicated that the delivery vehicle (ethanol:oil) substantially increases the solubility of pyridaben compared to water, thus increasing crossing of the lipophilic blood-brain barrier.

Health Canada Response:

While Health Canada concurs that the subcutaneous route of exposure is not a relevant route of exposure, Health Canada considers this study to be important in that it is the only study conducted with pyridaben that used immunostaining to detect neuron loss. Mice demonstrated significant neurodegeneration in the substantia nigra as well as a significant increase in α-synuclein aggregates, both considered pathological hall marks of PD. Given the concordance between the oral and subcutaneous routes of exposure for the similar-acting rotenone (that is, both routes produced neuronal degeneration), there is some concern that the neurodegeneration may not be a route-specific finding for pyridaben.

The choice of vehicle in a toxicity study should ensure absorption of the test compound. As pyridaben has poor solubility in water, it is appropriate that alternate vehicles are used to facilitate absorption. The registrant's choice of vehicle (carboxymethyl cellulose) in their gavage studies conducted with pyridaben underscores this principle. Oil vehicles are also suitable for lipophilic substances such as pyridaben. The lipophilicity of pyridaben is characterized by its octanol water partition coefficient (log K_{ow}) of 6.37. These lipophilic properties contribute to the ability of pyridaben to cross the blood-brain barrier.

Comment 1.1.4

The registrant noted the results of several rotenone studies that have relevance to pyridaben. They referenced the 56-day oral study in mice with rotenone and concluded that although rotenone was frankly toxic at all doses and durations, there was a clear dose/duration effect of decreased motor activity. Because of the frank toxicity at doses humans will never legally encounter, the registrant refuted the relevance to human exposures and risks to rotenone or pyridaben. Furthermore, the registrant cited an additional reference concerning a 28-day oral range-finding study in mice with rotenone with doses up to and including 30 mg/kg bw/day (PMRA #2656034). They indicated that 5 mg/kg bw/day was a no observed adverse effect level (NOAEL) for histopathological changes and no PD-like clinical signs were reported. They also indicated that no mortalities were mentioned (presence or lack) in this study.

Health Canada Response:

Health Canada concurs that frank toxicity was evident in the 56-day study. Health Canada notes that the purpose of this study was to evaluate rotenone as a PD model for assessing the relationship between mitochondrial dysfunction and dopaminergic injury and not to establish a NOAEL for rotenone. As nigrostriatal dopamine neurodegeneration, α-synuclein immunoreactivity and behavioural impairment were observed at the lowest dose tested of 30 mg/kg bw/day, there remains some uncertainty as to effects that would occur at a lower dose.

In the additional reference cited by the registrant, it is again noted that the purpose of the study was to investigate the usefulness of the rotenone mouse model for understanding the mechanism of dopamine neurodegeneration in PD and not to establish a NOAEL. Nigrostriatal dopamine neurodegeneration was observed at 10 and 30 mg/kg bw/day whereas no pathological change was noted at 5 mg/kg bw/day. There is no indication in the publication that clinical signs were assessed. Contrary to the registrant's finding, the publication reported that two mice in the rotenone group at 10 or 30 mg/kg died within 3 days after treatment. Effects on motor co-ordination only appear to have been measured in the 30 mg/kg bw/day group; motor deficits were apparent at this level.

Notwithstanding the toxicity seen in these studies, Health Canada is of the opinion that these studies are still relevant in highlighting an area of concern. The studies clearly demonstrate a pattern of neurodegeneration with oral exposure to rotenone at sufficiently high dose levels.

Comment 1.1.5

The registrant cited the repeat-dose subcutaneous rat study with rotenone as support for the statement that when dopaminergic lesions occur, PD-like signs are observed. They conclude that no dopaminergic lesions occurred with pyridaben in repeated dosing studies given the absence of clinical signs.

Health Canada Response:

Health Canada concurs that the dopaminergic lesions are a precursor to PD-like signs. As indicated in the PRVD, in humans, clinical features are apparent when 40–60% of the nigrostriatal dopaminergic neurons are lost. This does not lessen concern for subthreshold effects on neuron loss. In other words, neuron depletion could occur in the absence of clinical signs and accordingly, the absence of lesions cannot be predicted on the basis of the lack of clinical signs.

Comment 1.1.6

The registrant indicates there is a large body of information that distinguishes pyridaben from rotenone. They provide two examples. The first example is structural dissimilarity. The second example is a difference in clearance from the brain following a single oral dose with pyridaben clearing faster than rotenone.

Health Canada Response:

Health Canada concurs that rotenone and pyridaben are structurally dissimilar; however, structural similarity is not a prerequisite for common mechanism of toxicity.

Health Canada concurs that pyridaben clears rapidly from the brain after a single dose (by 72 hours). That said, the high brain levels at 2 hours post-exposure (115–131 ng/g) suggests that pyridaben has easy access to this tissue. It should be noted that in a repeat dose study, no detects of pyridaben were found in brain tissue, however, sampling was performed at 168 hours after dosing and the lack of pyridaben in the brain likely reflects the rapid clearance of this chemical.

Health Canada is of the opinion that insufficient information has been provided to indicate that the rotenone findings are irrelevant to considerations regarding pyridaben.

Comment 1.1.7

The registrant pointed to the lack of published studies of oral, dermal or inhalation dosing with pyridaben for the purpose of eliciting PD-associated neuropathologies and clinical signs. They suggested that “among other things, that the academic community had no interest in pyridaben and these routes of exposure; that funding for such studies could not be justified or obtained; or, that the preliminary tests did not produce results worth publishing or further pursuing which indicates pyridaben doesn’t produce PD.”

Health Canada Response:

The absence of studies does not negate the possibility of an association.

Comment 1.1.8

The registrant cited three epidemiological studies concerning rotenone and PD that were summarized in the literature paper reported by Health Canada. One study reported a weak association that was not confirmed in a supplement to the study.

The second study found no association. The third study found an association with "use of organic pesticides such as rotenone". The registrant contended that these studies do not support a conclusion of association of rotenone exposure to PD.

Health Canada Response:

Health Canada found the three epidemiological studies cited by the registrant to be limited or insufficient to draw conclusions.

The first study examined pesticide use and PD in licensed private pesticide applicators in the Agricultural Health Study (AHS) (PMRA #2656035). Although rotenone use was not queried in the enrolment questionnaire, it was queried in a supplemental applicator questionnaire. The study reported an odds ratio (OR) of 1.7 with a 95% confidence interval (CI) of 0.6–4.7) for rotenone use and prevalent PD; the result was based on four exposed cases. No association could be determined for incident PD as only one incident case had used rotenone. The registrant did not provide a reference to the study supplement that purportedly failed to confirm the association. The study authors did report further on the cohort (PMRA #2656036), examining the role of dietary fat intake as a risk modifier. The odds ratio (OR) for rotenone was reported to be 5.8 (CI 2.3–15) in those with saturated fat intake above the median but 1.5 (CI 0.5–4.2) in those with lower intake. One of the major limitations of this study was that PD was self-reported.

The second study cited by the registrant was a clinic-based case-control study distinct from the AHS in which participants were questioned on occupational rotenone use (PMRA #2656038). The study reported an OR of 0.82 (CI 0.05–13.34) however only two individual were exposed to rotenone (one of which had PD). No conclusion can be drawn from a study with such small numbers of exposed individuals.

The third study involved PD clinic attendees who were asked about "use of organic pesticides such as rotenone" in the previous year (PMRA #2656033). An OR of 10.0 (CI 2.9–34.3) was reported. In addition to the lack of clarity regarding the metric of exposure, the study evaluated association of PD with rotenone use after diagnosis.

Health Canada maintains that the study noted in PRVD2016-04 is the most robust epidemiological study with rotenone. This study was nested in the AHS but diagnosis was based on in-person exams. An OR of 2.5 (CI 1.3–4.7) was reported. The numbers of exposed individuals (19/110 cases, 32/358 controls) were more robust than in previous studies and the nested case control design reduced the likelihood of bias or confounding.

Comment 1.1.9

The registrant critiqued the epidemiology study concerning rotenone and PD that was reported by Health Canada. They suggested that rotenone was unique since it was only one of six mitochondrial Complex I inhibitors in the study to have a statistically significant positive odds ratio. Furthermore, they indicated that the odds ratio was devoid of information on magnitude of use of rotenone, frequency of use or duration of use.

Health Canada Response:

It is noted that most of the other mitochondrial Complex I inhibitors in the epidemiology study had a small number of exposed cases and controls thereby impacting the robustness of the comparison. Notwithstanding this limitation, as with any chemical that shares a mechanism of action, a range of potencies is to be expected. Rotenone is of particular interest due to the observation that pyridaben has demonstrated similar or greater potency than rotenone is some mechanistic studies.

With regards to the limitations of the epidemiology study, Health Canada notes that the study did address duration of use (cumulative lifetime days of use). An OR of 4.9 (CI 1.9–13) was reported for rotenone cases less than or equal to the median duration of use whereas cases greater than the median duration of use had an OR of 1.8 (CI 0.59–5.4). These values, however, must be interpreted with caution as the sample size becomes limited with this analysis (for example, the number of rotenone-exposed cases for greater than the median duration of use is only five).

Health Canada does concur that robust quantitative exposure information is lacking from the epidemiology study; this limitation is broadly applicable to most epidemiological studies conducted with pesticides. For these reasons, Health Canada is not purporting there to be evidence of causation based on this study but rather that the study is sufficient to raise a level of concern. Accordingly, it has been taken into account in the weight of evidence.

1.2 Occupational Exposure

The registrant identified areas where there was scope to further refine the mixer/loader/ application and postapplication exposure estimates and risk assessments. Comments regarding PPE, spray volumes, REIs and limited label instructions were received and are addressed below. A revised risk assessment that takes into account additional use information is presented in Appendix III.

Comment 1.2.1

The registrant provided information to clarify the spray concentration and volume values that were used by Health Canada for assessment of use on greenhouse crops.

Health Canada Response:

Health Canada revised the occupational postapplication risk assessment for greenhouse cut flowers (Appendix III) based on the information provided by the registrant. As a result, the proposed REI of 6 days in PRVD2016-04 for hand harvesting, hand pruning and disbudding of greenhouse cut flowers was reduced to 12 hours. The postapplication risk assessments for the other greenhouse crops were not revised as risks were shown to be acceptable at the minimum 12-hour REI proposed in PRVD2016-04.

Comment 1.2.2

The registrant commented that no dermal protection factor was accorded to account for rubber boots, goggles, respirators or hats.

Health Canada Response:

Occupational mixer/loader/applicator exposure was estimated using the Pesticide Handlers Exposure Database (PHED) Version 1.1, which represents the best available data for assessing the exposure scenarios relevant to the registered uses of pyridaben (no chemical-specific exposure studies were submitted or identified in the literature). Standard protection factors were applied to the PHED exposure estimates to account for increased PPE where appropriate; a 90% protection factor was applied to dermal exposure estimates to account for waterproof rain gear when worn over a long-sleeved shirt and long pants, and a 90% protection factor was applied to inhalation exposure estimates to account for the use of a respirator.

Comment 1.2.3

The registrant commented that the increased PPE requirements for greenhouses could be cumbersome for handlers and should be left to the discretion of the handler or supervisor.

Health Canada Response:

The PPE required by Health Canada is in keeping with the current label directions on the end-use products containing pyridaben. No additional PPE will be required for workers mixing, loading or applying pyridaben beyond what is currently specified on the product labels. Label statements were updated to reflect current standards, which are that single layer work clothes would be worn under higher levels of PPE, such as rain gear. The results of the risk assessment detailed in PRVD2016-04 confirmed that PPE is necessary in order to mitigate exposure, since target margins of exposure (MOE) are not met unless PPE protection factors are applied.

Comment 1.2.4

The registrant indicated that the “DO NOT enter” statements may be unnecessary given the use pattern and chemical properties of pyridaben, and proposed a 12-hour REI for all crops except grapes.

Health Canada Response:

The “DO NOT enter” statements are to protect postapplication workers from entering treated areas during the restricted entry period. These restrictions are in keeping with the current label statements, and have been updated to current labelling standards. The activities associated with the registered uses of pyridaben require frequent postapplication activities and multiple applications are recommended, therefore postapplication exposure is anticipated.

As a result of revised risk assessment, the pyridaben end-use product labels will be harmonized such that a 12-hour REI is required for all remaining crops except grapes.

Comment 1.2.5

A postapplication risk assessment for grapes conducted by the registrant proposed REIs for girdling, turning, tying/training, hand harvesting and leaf pulling. The registrant conducted the risk assessment for the purpose of retaining the use of pyridaben on grapes as a tool in mite and insect resistance management.

Health Canada Response:

The postapplication risk assessments for grapes, conducted by both Health Canada and the registrant, yielded REIs that ranged from 26 to 54 days (after a single application). In PRVD2016-04, it was noted that these REIs were not considered to be agronomically feasible. Consequently, the use was proposed for cancellation.

Since the publication of PRVD2016-04, PMRA has received additional information from Ontario grape growers on agricultural practices such as the use of machinery for leaf pulling, and the timing of training and tying activities. Based on these considerations, the abovementioned REIs are now agronomically feasible. It is expected that most grape growers will be able to conduct required postapplication activities while complying with the calculated REIs. The use of pyridaben on grapes will be supported for continued registration with the REIs outlined in Appendix IV.

Comment 1.2.6

The registrant commented that a refined interpretation of the greenhouse rose and chrysanthemum dislodgeable foliar residue (DFR) study values applied in the postapplication risk assessment of greenhouse cut flowers would reduce the proposed REI to 12 hours.

Health Canada Response:

The greenhouse DFR study was reviewed according to Health Canada's guidelines for DFR studies (Science Policy Note SPN2014-02, Estimating Dislodgeable Foliar Residue and Turf Transferrable Residues in Occupational and Residential Post-Application Exposure).

Using the rose DFR data and the updated application rates for greenhouse ornamentals, the calculated MOE is greater than the target MOE on day 0; therefore, the REI for greenhouse ornamentals has been reduced to 12 hours. Refer to the Science Evaluation Update Section for more information.

2.0 Comments Related to the Environmental Risk Assessment

2.1 Environmental Risk Characterization

Comment 2.1.1

The registrant submitted a study on the bioaccumulation of pyridaben in sediment-dwelling invertebrates. This study clarified the potential for bioaccumulation of pyridaben from the sediment where it is expected to be moderately persistent to persistent according to laboratory biotransformation studies.

Health Canada Response:

The submitted study was reviewed and found to be acceptable. The bioaccumulation and depuration of radiolabeled pyridaben in benthic oligochaetes was investigated in a static sediment system. Oligochaetes were continuously exposed at average measured concentrations in sediment of 0.00715 mg/kg dry weight for 28 days, followed by a 10-day depuration period.

Uptake was rapid with only a slight increase in average concentrations in oligochaetes after three days. Because a steady state was reached during the uptake phase of the study, Health Canada calculated a $BSAF_{SS}$ using the average concentrations in oligochaetes and sediment from days 14 to 28; the $BSAF_{SS}$ is 5.96. The lipid/organic carbon normalized $BSAF_{SSL}$ is 5.05.

Because a steady state was clearly reached in this study, Health Canada did not recalculate kinetic $BSAF_K$ values and reported the $BSAF_K$ as determined by the study authors; the $BSAF_K$ is 7.92; Health Canada calculated a lipid-corrected $BSAF_K$ ($BSAF_{KL}$) of 6.7 from that value and the percent lipid from the oligochaetes.

Depuration was initially rapid with a slower secondary loss to study termination. Using the depuration rate calculated by the study authors, Health Canada calculated a half-life of 13 days.

Oligochaetes appeared to metabolically transform pyridaben; on day 21, the transformation product PB-7 was formed at 11% total recovered radioactivity and an unknown compound was formed at 21% total recovered radioactivity. Pyridaben was found at 14.7% of total recovered radioactivity in oligochaetes.

The results indicated that pyridaben can be accumulated by sediment-dwelling, lower trophic organisms. Considering the half-life in oligochaetes is 13 days and that metabolic transformation occurs within the oligochaetes, as well as the low bioconcentration factor in fish, it is unlikely that significant bioaccumulation will occur in predatory organisms.

Appendix III Revised Occupational Postapplication Risk Assessment

Crop	Applications per Cycle		Rate[c] (kg a.i./ha)	Activity	Transfer Coefficient[d] (cm^2/hr)	Dermal Exposure[e] (µg/kg bw /day)	MOE[f]	REI[g] (days)
	Number[a]	Interval[b] (days)						
Greenhouse ornamentals (includes cut flowers)	2	28	0.315	Hand harvest, disbudding	4000	196.27	510	0.5
				All other activities	230	11.29	8861	0.5

[a] The maximum label listed number of applications per crop cycle.
[b] The minimum label listed application interval.
[c] Maximum listed label rates expressed in kg a.i./hectare using the spray volume of 1000L/hectare as indicated by the registrant during the comment period.
[d] Transfer coefficients are from Health Canada Agricultural Transfer Coefficients Memo, based on Agricultural Re-entry Task Force data.
[e] Dermal exposure = dislodgeable foliar residue (DFR) × transfer coefficients × 8 hr ÷ 80 kg. Greenhouse ornamental crops were assessed using the peak DFR and linear regression analysis of the available greenhouse rose DFR study.
[f] The resulting MOE on the determined REI day. Based on the dermal NOAEL (all durations) of 100 mg/kg/day and a dermal target MOE of 300.
[g] REI = restricted-entry interval. Day at which the dermal exposure results in an MOE ≥ 300.

Appendix IV Label Amendments for Products Containing Pyridaben

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.

For Technical Grade Products:

On the **PRIMARY PANEL**:

Add the signal word "WARNING" and the accompanying hazard symbol (square set on point).

In a section entitled **ENVIRONMENTAL PRECAUTIONS**:

Add:

"TOXIC to aquatic organisms."

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

Under **DISPOSAL**:

Add:

"Canadian manufacturers must dispose of unwanted active ingredients and containers in accordance with municipal or provincial regulations. For additional details and cleanup of spills, contact the manufacturer and the provincial regulatory agency."

For Commercial Class Products:

Under **PRECAUTIONS**:

Add:

"This product is only to be used by individuals holding an appropriate pesticide applicator certificate or license recognized by the provincial/territorial pesticide regulatory agency where the pesticide application is to occur."

"**DO NOT** use in residential areas. Residential areas are defined as sites where bystanders including children may be potentially exposed during or after spraying. This includes around homes, school, parks, playgrounds, playing fields, public buildings or any other areas where the general public including children could be exposed."

"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."

"Hazardous to humans and domestic animals. Keep out of reach of children and pets."

For GREENHOUSE uses, under **PRECAUTIONS**:

Remove:

"Wear waterproof rain gear over long-sleeve shirt, long pants, rubber boots, goggles, gloves (rubber, PVC, neoprene or nitrile), hat and a vapour cartridge with dust/mist filter respirator during mixing, loading and application."

Add:

"Wear waterproof rain gear, rubber boots, socks, goggles, gloves (rubber, PVC, neoprene or nitrile), hat and a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides during mixing, loading application, clean-up and repair."

For GREENHOUSE and NURSERY uses, under **PRECAUTIONS**:

Remove:

"DO NOT re-enter treated areas within 12 hours. If required, individuals may re-enter treated areas within 12 hours for short-term tasks not involving hand labour if at least 4 hours has passed since application and long-sleeved shirt, long pants, gloves (rubber, PVC, neoprene or nitrile) and a vapour cartridge with dust/mist filter respirator are worn."

Add:

"**DO NOT** enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours. 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 waterproof rain gear over long-sleeved shirt and long pants, rubber boots, socks, goggles, gloves (rubber, PVC, neoprene or nitrile), hat and a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides are worn. Time spent in the treated area cannot exceed 1 hour in a 24 hour period or until the REI ends."

For OUTDOOR uses, under **PRECAUTIONS**:

Remove:

"Wear long-sleeved shirt, long pants, rubber boots, goggles, gloves (rubber, PVC, neoprene or nitrile), hat and a dust/mist filtering respirator during mixing, loading and application."

Add:

"Wear long-sleeved shirt, long pants, rubber boots, socks, goggles, gloves (rubber, PVC, neoprene or nitrile), hat and a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides during mixing, loading and application."

Remove:

"DO NOT re-enter treated areas within 24 hours. If required, individuals may re-enter treated areas within 24 hours for short-term tasks not involving hand labour if at least 4 hours has passed since application and long pants, long-sleeved shirt, hat and chemical-resistant gloves are worn."

Add:

"**DO NOT** enter or allow worker entry into treated areas during the restricted entry interval (REI). 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 (rubber, PVC, neoprene or nitrile), hat, 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 the REI ends."

Add:

"**DO NOT** allow entry or allow workers to enter treated areas during the restricted entry intervals REI(s) specified in the following table."

Crop	Postapplication Activity	Restricted Entry Interval
Grapes	Girdling, turning	54 days
	Tying (full foliage), training (full foliage), hand harvest, leaf pulling by hand	30 days
	All other activities (e.g. scouting, weeding, irrigation, bird control, propagating, trellis repair, pruning, transplanting)	12 hours
All other crops	All activities	12 hours

Under **DIRECTIONS FOR USE**:

Add:

"Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 8 km/h at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Air-induction nozzles must be used for the ground application of this product. Boom height must be 60 cm or less above the crop or ground."

"Airblast application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side."

"**DO NOT** apply by air."

"As this product 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."

"**DO NOT** allow effluent or run-off from greenhouses containing this product to enter lakes, streams, ponds or other waters".

Buffer zones:
"Spot treatments using hand-held 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 terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrub-lands), 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:		Estuarine/Marine Habitat of Depths:		Terrestrial habitat
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m	
Groundboom	Strawberry, raspberry		20	2	1	1	1
	Outdoor ornamental		10	1	1	1	0
Airblast	Pear, apple, raspberry	Late growth stage	65	40	30	20	1
	Cherry, peach, nectarine, grapes	Late growth stage	60	35	30	20	0
	Outdoor ornamental	Late growth stage	55	30	20	15	0

"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 airblast application of 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. Buffer zones for groundboom sprayer application CANNOT be modified using the Buffer Zone

Calculator."

"To reduce run-off 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 filter strip between the treated area and the edge of the water body."

As applicable, add the following statements for pollinator protection under **DIRECTIONS FOR USE**:

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

"For apples, raspberries, cherries, nectarines, peaches, pears and outdoor ornamentals: TOXIC to bees. DO NOT apply during the crop blooming period."

"For grapes and strawberries: TOXIC to bees. Avoid application during the crop blooming period. If applications must be made during the crop blooming period, restrict applications to evening when most bees are not foraging. When using managed bees for pollination services, DO NOT apply during the crop blooming period.

For greenhouse use: TOXIC to bees and other beneficial insects. May harm bees and other beneficial insects used in greenhouse production. Avoid application when bees or other beneficial insects are foraging in the treatment area."

For GREENHOUSE uses, under **DIRECTIONS FOR USE**:

Add:

"**DO NOT** apply by hand-held mistblower."

"**DO NOT** use more than 1000 litres of spray solution per hectare."

For OUTDOOR uses, under **DIRECTIONS FOR USE**:

Add:

"**DO NOT** apply by hand-held mistblower or hand-held fogger."

Remove:

"Apply to raspberries after harvest when mites appear."

Add:

"Apply to raspberry plants after harvest when mites appear."

Under **ENVIRONMENTAL PRECAUTIONS**:

Add:

"TOXIC to bees. Bees may be exposed through direct spray, spray drift, and residues on leaves, pollen and nectar in flowering crops and weeds. Minimize spray drift to reduce harmful effects on bees in habitats close to the application site. 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 (www.healthcanada.gc.ca/pollinators). Follow crop specific directions for application timing."

"For applications on crops that are highly attractive to pollinators (apples, raspberries, cherries, nectarines, peaches, pears, and outdoor ornamentals), and crops where managed bees are present: DO NOT apply during the crop blooming period."

"For applications to grapes and strawberries: Avoid application during the crop blooming period. If applications must be made during the crop blooming period, restrict applications to evening when most bees are not foraging."

"For greenhouse use: Toxic to bees and other beneficial insects. May harm bees and other beneficial insects used in greenhouse production. Avoid application when bees or other beneficial insects are foraging in the treatment area."

"TOXIC to beneficial arthropods. Minimize spray drift to reduce harmful effects on beneficial arthropods in habitats next to the application site such as hedgerows and woodland."

"TOXIC to birds."

"TOXIC to small wild mammals."

"TOXIC to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE."

"TOXIC to non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE."

Under **STORAGE**:

Add:

"To prevent contamination store this product away from food or feed."

Under **DISPOSAL**:

Add:

"For information on disposal of unused, unwanted product, contact the manufacturer or the provincial regulatory agency. Contact the manufacturer and the provincial regulatory agency in case of a spill, and for clean-up of spills."

Appendix V References Considered Following Publication of PRVD2016-04

A. Information Considered in the Toxicological Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2656033	Dhillon, A. S. et al., 2008. Pesticide/Environmental Exposures and Parkinson's Disease in East Texas, Journal of Agromedicine, Volume 13, Number 1, Pages 37 to 48, DACO: 4.8
2656034	Inden, M. et al., 2007. Neurodegeneration of Mouse Nigrostriatal Dopaminergic System Induced by Repeated Oral Administration of Rotenone Is Prevented by 4-Phenylbutyrate, a Chemical Chaperone, Journal of Neurochemistry, Volume 101, Pages 1491 to 1504, DACO: 4.8
2656035	Kamel, F. et al., 2006. Pesticide Exposure and Self-reported Parkinson's Disease in the Agricultural Health Study, American Journal of Epidemiology, Volume 165, Number 4, Pages 364 to 374, DACO: 4.8
2656038	Tanner, C. M. et al., 2009. Occupation and Risk of Parkinsonism: A Multicenter Case-Control Study, Archives of Neurology, Volume 66, Number 9, Pages 1106 to 1113, DACO: 4.8

Published Information

PMRA Document Number	Reference
2656032	Charli, A. et al., 2015. Alterations in Mitochondrial Dynamics Induced by Tebufenpyrad and Pyridaben in a Dopaminergic Neuronal Cell Culture Model - Neurotoxicology, Volume 53, Pages 302 to 313, DACO: 4.8
2656036	Kamel, F. et al., 2014. Dietary Fat Intake, Pesticide Use, and Parkinson's Disease, Parkinsonism and Related Disorder, Volume 20, Number 1, Page 82 to 87, DACO: 4.8
2656037	Pearson, B. L. et al., 2016. Identification of Chemicals that Mimic Transcriptional Changes Associated with Autism, Brain Aging and Neurodegeneration, Nature Communications, DACO: 4.8

B. Information Considered in the Environmental Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2612072	Thomas, S.T. et al, 2015. ^{14}C-Pyridaben: A Bioaccumulation Test With *Lumbriculus variegatus* Using Spiked Sediment, DACO: 9.4.8