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Re-evaluation Decision

RVD2019-11

Permethrin and Its Associated End-use Products

Final Decision

(publié aussi en français)

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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 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.

Permethrin is a broad-spectrum synthetic pyrethroid insecticide. It is registered for use on a wide range of crops including grains and oilseeds, legumes, horticultural crops, mushroom houses, ginseng, greenhouse and field-grown ornamentals as well as tobacco. It is also registered for use on livestock, companion animals, forestry and woodlots, feedlots, termite treatment, pet premises, kennels, indoors and outdoors of homes, agricultural, commercial and institutional buildings, military clothing, mosquito netting and soil around honeybee hives. In Canada, there are over 400 registered pesticides containing permethrin. Information on these products can be found through Health Canada's label transcription service.¹

The regulatory approach for the re-evaluation of permethrin was first presented in the Proposed Re-evaluation Decision PRVD2017-18, *Permethrin and its End-use Products*,² which underwent a 90-day consultation period ending on 18 January 2018. PRVD2017-18 proposed mitigation measures to further protect human health and the environment, including cancellation of use in mushroom houses and certain application types (fogger, handheld mist blower/airblast, indoor broadcast in residential areas, indoor solid fogger), as well as a mandatory 10-metre vegetative strip for agricultural products.

Health Canada received comments and new data/information relating to the health, value and environmental risk assessments. These comments are summarized in Appendix I along with the responses by Health Canada. These comments and new data/information resulted in revisions to the risk assessments (see Science Evaluation Update section), and subsequently, in changes to the proposed regulatory decision as described in PRVD2017-18. A reference list of information used as the basis for the proposed re-evaluation decision is included in PRVD2017-18, and further data used in the re-evaluation decision are listed in Appendix VI of this RVD.

This document presents the final regulatory decision³ for the re-evaluation of permethrin, including the required risk mitigation measures to protect human health and the environment. All products containing permethrin that are registered in Canada are subject to this re-evaluation decision.

¹ PMRA's pesticide label search database is available online in the Pesticides portion of Canada.ca. Pesticide labels can also be accessed on a mobile device using the pesticide label app available in the Pesticides portion of Canada.ca.

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

³ "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Outcome of Revised Science Evaluation

Following the consultation on the proposed re-evaluation decision, Health Canada revised the occupational risk assessment based on the comments and new data/information received. As a result, use of permethrin in mushroom houses is acceptable for continued registration with implementation of new mitigation measures and label amendments. Also, mechanically-pressurized handheld sprayer applications of permethrin for mists, aerosols, and fogs, indoor structural manually-pressurized handwand application as well as rod and sub-slab injector applications for termites are acceptable for continued registration provided that additional personal protective equipment (PPE) is worn, when necessary. Health risks have not been shown to be acceptable for electric mistblower applications to attic spaces when these products are used according to current label directions, or when additional mitigation measures are considered. The environmental risks associated with the use of permethrin and associated end-use products are acceptable when permethrin products are used according to the mitigation measures including the vegetative strip for agricultural products and revised label directions.

Regulatory Decision for Permethrin

Health Canada has completed the re-evaluation of permethrin. Under the authority of the *Pest Control Products Act*, Health Canada has determined that continued registration of products containing permethrin is acceptable. An evaluation of available scientific information found that most uses of permethrin products meet current standards for protection of human health and the environment when used according to revised label directions which include new mitigation measures. Certain uses and application methods for permethrin are being cancelled to address potential risks of concern to human health. Label amendments, as summarized below and listed in Appendix III, are required for all technical and end-use products. No additional data are requested at this time.

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. The key risk-reduction measures and label updates required, as a result of the re-evaluation of permethrin, are summarized below. Refer to Appendix III for details.

Human Health

To protect workers, homeowners, those entering treated areas etc. from occupational/residential exposure, the following risk-reduction measures are required for continued registration of permethrin in Canada:

- Cancellation of electric mistblower and total release fumigating fogger applications.
- Limiting application timing in mushroom houses.
- The rate for application to residential yards reduced to 0.123 g a.i./m².
- Increased PPE.
- Increased restricted entry-intervals (REIs).

- Additional label statements are required for domestic- and commercial-class products used in residential areas.

To protect consumers from dietary exposure, the following risk-reduction measures are required for continued registration of permethrin in Canada:

- A minimum rotational crop plant-back interval of 60 days must be observed for all food/feed crops not currently on the label.
- The number of applications on tomato per year to be reduced from 6 to 5.

Label improvements required to meet current standards:

- Additional improvements to the product labels are required to provide clarity in areas such as the use directions. For certain products registered for uses on livestock and livestock housing, label updates must include the supported use directions (application rate, maximum number of applications, minimum re-treat interval, and/or pre-slaughter interval) on product labels, where applicable.
- Additional improvements to the product labels are required for domestic- and commercial-class products used in residential areas.

Environment

To protect the environment, the following risk-reduction measures are required:

- Environmental hazard statements for bees, beneficial insects, birds and aquatic organisms
- To reduce risk to pollinators, application is restricted or prohibited during the crop blooming period for bee attractive crops.
- To reduce risk to beneficial insects living in habitats adjacent to the application site, spray drift should be minimized.
- Spray buffer zones for non-target aquatic habitats.
- To reduce the potential for run-off of permethrin to adjacent aquatic habitats; precautionary statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecasted.
- Addition of a vegetative filter strip between the treatment area and the edge of a down-gradient water body to reduce runoff of permethrin to aquatic environments.

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. The registered products containing permethrin that are subject to this decision can be found through Health Canada's online pesticide label search database. One registered product, Raid Fumigator Fumigating Fogger (Registration Number 25167) is cancelled by this decision. Raid Fumigator Fumigating Fogger will be phased out following the implementation timeline outlined below.

- One (1) year of sale by registrant from the publication date of this decision document, followed by;
- One (1) year of sale by retailer from the last date of sale by registrant, followed by;
- One (1) year of permitted use from the last date of sale by retailer.

Other Information

Any person may file a notice of objection⁴ regarding this decision on permethrin 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 the Canada.ca website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (hc.pmra.info-arla.sc@canada.ca)..

The relevant test data on which the decision is based (as referenced in PRVD2017-18) are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please 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 Summary

The toxicological assessment for permethrin was previously conducted and summarized in PRVD2017-18. Comments were received from a member of the public regarding various aspects of the assessment including the methods used by the Health Canada to establish reference values, the application of the PCPA factor and the availability of more recent studies in the published literature and their impact on the risk assessment. Overall, the review of these comments did not result in a change in the reference values established in the human health risk assessment of the PRVD for permethrin and the risk assessment is still considered protective of the health of all Canadians.

Detailed responses to the comments received are provided in Appendix I.

1.2 Dietary Exposure and Risk Assessment

The dietary assessment for permethrin was previously conducted and published in PRVD2017-18. Dietary risks were shown to be acceptable. No comments specific to the dietary risk assessment were received. One comment, by the Canadian Horticultural Council (CHC), however, was received on the proposed label requirement for a plant-back interval (PBI) of 60 days for non-registered food/feed crops. This comment did not have any impact on the dietary assessment. Appendix I summarizes the comment and provides Health Canada's response. In turn, the dietary risk assessment from the PRVD did not need to be updated.

1.3 Occupational and Non-Occupational Risk Assessment

The scenarios and crops considered for occupational exposure have not changed from the previous assessment (PRVD2017-18). Comments were received and considered in the updated health risk assessment (See Appendix V). The occupational exposure and risk assessments were updated to incorporate additional new data and use information.

1.3.1 Occupational Applicator Exposure Risk Estimates

The updated cancer and non-cancer occupational risks are acceptable for mechanically-pressurized handheld sprayer applications for mists, aerosols, and fogs to commercial woodlots, outdoor areas, mushroom houses, for agricultural premise space sprays, indoor space sprays, and mosquito abatement, provided that additional PPE is worn. This PPE consists of chemical-resistant coveralls with a chemical-resistant hood over long pants, long-sleeved shirt, chemical-resistant gloves, and a respirator.

The updated cancer and non-cancer occupational risks are acceptable for indoor manually pressurized handwand applications to structural surfaces in agricultural premises, indoor areas, and aircraft disinsection, as well as for rod and sub-slab injector applications for termites. For

electric mistblower applications to attic spaces indoors cancer risks were not acceptable and could not be mitigated.

For all other scenarios, the applicator risk assessments and conclusions have not changed from the previous assessment (PRVD2017-18).

1.3.2 Occupational Postapplication Exposure Risk Estimates

For mushroom house applications additional use information became available to Health Canada (see Appendix V). This information indicated that exposure to postapplication workers would be minimal, provided the application of permethrin is limited to when the crop is not present, or the crop is covered during application. Under these conditions, the risks to postapplication workers are acceptable.

For all other scenarios, the postapplication risk assessments and conclusions have not changed from the previous assessment (PRVD2017-18).

1.3.3 Non-Occupational Applicator and Postapplication Exposure Risk Estimates

The non-occupational applicator and post-application risk assessments and conclusions have not changed from the previous assessment (PRVD2017-18).

2.0 Environmental Risk Assessment

Comments were received regarding the requirement for a 10-m wide vegetative filter strip to mitigate risk to aquatic habitats, the use of water monitoring data and proposed label language. The comments received did not result in changes to the conclusions of the risk assessment. For the RVD, spray buffer zones have been recalculated from those reported in PRVD 2017-18 to reflect the current Health Canada buffer zone policy. Marine buffer zones were recalculated using a single application to take into consideration tidal dilution that would result in negligible accumulation of concentrations in the marine environment. This resulted in a decrease in the size of the required marine spray buffer zones. In PRVD 2017-18, aerial spray buffer zones were identified for each product formulation. As the aerial buffer zones were similar regardless of formulation, for consistency and clarity, the most conservative values are used for all formulations.

3.0 Value Assessment

Permethrin is valued as it can be used to control a broad spectrum of pests on a wide range of sites. Permethrin commercial products are an important component of pest management programs to control agricultural, structural and public health pests, and are used as a rotational insecticide for managing insect resistance in susceptible pests. Permethrin domestic products are of benefit for the general public to use along with other control methods, such as prevention and non-chemical treatments, in the management of pests, in and around the home.

4.0 Incident Reports

The incident report review summarized in PRVD2017-18 focussed on incidents involving permethrin-only products, rather than permethrin products that also contain other active ingredients. While no concerns pertaining to health were identified in these incident data, the submitted incident reports did support the improvement of product labels that were proposed in PRVD2017-18.

Since the publication of PRVD2017-18, a separate regulatory proposal entitled “Consultation on Proposed Regulatory Changes for Pesticide Products Used on Companion Animals” (PRO2018-01) has been published with proposed mitigation measures to address concerns identified with spot-on flea and tick control products used on pets (including those that contain permethrin). A review of the additional permethrin incident reports received since the publication of PRVD2017-18 (that is, human and domestic animal incidents that did not involve a spot-on product), indicated that the product types, exposure scenarios and adverse effects reported in incidents were consistent with those published in PRVD2017-18. Therefore, no further mitigation measures specific to health are required based on the additional incident reports received since the publication of the PRVD2017-18.

5.0 Conclusion of Science Evaluation

With respect to human health, risks associated with the use of permethrin and associated end-use products are acceptable when these products are used according to revised label directions with the risk mitigation measures that include cancellation of total release foggers, electric mistblower application into attic spaces, and indoor residential broadcast applications. These mitigation measures are the same as what were proposed in the PRVD2017-18, with the exception of the updated scenarios, as discussed above and presented in Appendix V.

The environmental risks associated with the use of permethrin and associated end-use products are acceptable when these products are used according to revised label directions with the risk mitigation measures discussed above and presented in Appendix III.

Use of permethrin as an insecticide is important for control of a broad spectrum of pests on a wide range of sites.

List of Abbreviations

AKT	protein kinase B
ALL	acute lymphoid leukemia
AML	acute myeloid leukemia
AMPK α	adenosine monophosphate-activated protein kinase α
aOR	adjusted odds ratio
ASR	acoustic startle response
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDL ₂₀	benchmark dose 95% lower confidence limit at the 20% effect level
bw	body weight
bwg	body weight gain
CAT	catalase
CI	confidence interval
DA	dopamine
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOPAC	3,4-dihydroxyphenylacetic acid
DPH	1,6-Diphenyl-1,3,5-hexatriene
DPPP	diphenyl-1-pyrenylphosphine
E ₂	estradiol
ER α	estrogen receptor alpha
ER β	estrogen receptor beta
GPx	glutathione peroxidase
GSH	glutathione
GST	glutathione transferase
hER	human estrogen receptor
5-HIAA	5-hydroxyindoleacetic acid
HMGCoA	3-hydroxy-3-methylglutaryl-CoA
hr(s)	hour(s)
5-HT	5-hydroxytryptamine (serotonin)
ht	height
HVA	homovanillic acid
kg	kilogram
L-DOPA	L-3,4-dihydroxyphenylalanine
LH	luteinizing hormone
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEL	lowest observed effect level
M	molar
mg	milligram
MHPG	plasma 3-methoxy-4-hydroxyphenolglycol
MOA	mode of action
mRNA	messenger ribonucleic acid
NE	norepinephrine
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B cells
NO	nitric oxide

NOAEL	no observed adverse effect level
NOEL	no observed effect level
Nrf2	transcription factor
Nurr1	nuclear receptor related 1 protein
OR	odds ratio
3-PBA	3-phenoxybenzoic acid
PBR	peripheral benzodiazepine receptor
PCPA	Pest Control Products Act
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPAR α	peroxisome proliferator-activated receptor α
pPDK	phosphorylated phosphoinositide-dependent kinase
PRVD	Proposed Re-evaluation Decision Document
rER	rat estrogen receptor
RQ	risk quotient
RR	relative risk
RTI	retreatment interval
SER	smooth endoplasmic reticulum
SOD	superoxide dismutase
StAR	steroidogenic acute regulatory protein
TBARS	thiobarbituric acid reactive substances
TH	tyrosine hydroxylase
wk(s)	week(s)
wt	weight
μ g	microgram
μ M	micromolar

Appendix I Comments and Responses

In response to the consultation for the permethrin proposed re-evaluation decision, 43 written comments were received (respondents' affiliations listed in Appendix II). These comments were considered during the final decision phase of this re-evaluation. Summarized comments and Health Canada's responses to them, are provided below.

1.0 Comments Related to the Health Risk Assessment

1.1 Comments Related to Toxicology

Comment

One commenter from the general public expressed concern that Health Canada is not determining human health risk parameters based on No Observed Effect Levels (NOEL) from animal studies. Instead, for acute exposure, Health Canada used a 'Benchmark Dose' and for chronic exposure (acceptable daily intake), Health Canada used a No Observed Adverse Effect Level (NOAEL) based on experimental animal studies. The commenter stated that this approach serves to increase rather than reduce risk. It was indicated that the re-evaluation document needs to be revised replacing NOAELs or Benchmark Dose Lower Confidence Limit (BMDLs) with NOELs.

Health Canada Response

All pesticides used, sold or imported into Canada go through rigorous science-based assessments before being approved. During the conduct of these science-based assessments, Health Canada applies internationally accepted hazard and risk assessment methods along with modern risk management approaches and existing policy to ensure the safety of each pesticide. It is internationally accepted practise to use NOAELs and Lowest Observed Adverse Effect Level (LOAELs) rather than NOELs and Lowest Observed Effect Level (LOELs) in human health risk assessment. The establishment of NOELs and LOELs do not necessarily imply toxic or harmful effects and can be used to describe the adaptive effects of substances. In the case of permethrin, NOAELs were selected from acceptable, well conducted studies to establish the toxicology endpoints for the acceptable daily intake. At the NOAELs, there were no toxicologically significant alterations in the frequency or severity of adverse effects noted between the exposed and control animals. Thus, these NOAELs were set at dose levels that did not demonstrate any effects that could be considered adverse to the health of the human population.

When the available data allow for it, a benchmark dose analysis can be undertaken to help further refine the risk assessment. By using a benchmark dose analysis, the risk is not increased as indicated in the detailed response of the commenter, but instead gives it a more realistic estimate for the actual dose level that could result in an adverse effect. The use of a benchmark dose value is a well-accepted risk assessment approach and addresses many of the limitations of a NOAEL method through incorporation of all available dose-response information.

In the case of the acute reference dose for permethrin, Health Canada utilized the data for the motor activity parameter from the study by Wolansky *et al.* (PMRA# 2078450) to calculate a benchmark dose value. This endpoint was considered relevant for this exposure scenario since reduced motor activity is a sensitive neurobehavioural endpoint relevant to pyrethroid toxicity and was derived from a relevant route and duration of exposure. Individual animal data were

obtained from the study author and the BMDL₂₀ (benchmark dose 95% lower confidence limit at the 20% effect level) was calculated by Health Canada using benchmark dose modelling software (Proast). As explained in the PRVD, the BMDL₂₀ was specifically selected based on the reported variability of motor activity in control rats from the literature, with the twenty percent response level considered to be the point at which the observed effects would be considered distinguishable from normal variability and thus, considered adverse.

Since the NOAELs and BMDLs were derived from acceptable, well conducted toxicity studies following internationally approved methods for conducting the human health risk assessment, no changes are warranted to the reference values that were presented in the PRVD.

Comment

One commenter from the general public was critical of Health Canada's reduction of the Pest Control Products Act factor (PCPA factor) to onefold indicating that the scientific data to justify this approach was not reliable.

Health Canada Response

Health Canada's *Science Policy Note: The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides* (SPN2008-01)⁵ describes how Health Canada addresses uncertainty and variability in the mammalian toxicity database in the human health risk assessment of pesticides as well as the application of the PCPA factor.

As presented in the PRVD, extensive data were available that examined the exposure of and toxicity to infants and children for permethrin. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and three multi-generation reproductive toxicity studies in rats, including a supplemental study. A non-guideline study examining behavioural endpoints in the offspring of mice exposed to permethrin only during pre-mating was available from the scientific literature. There was no evidence of increased susceptibility of rat or rabbit fetuses following in utero permethrin exposure in oral developmental toxicity studies. Fetal effects occurred at maternally toxic levels. In the multi-generation reproductive toxicity studies in rats, there was no evidence of sensitivity of the young with the exception of a slightly increased incidence of buphthalmos which was noted in the offspring in one study at a dose level that did not result in maternal toxicity. Since this effect could not be definitively linked to permethrin treatment, it was deemed insufficient for assessment of susceptibility of the young. In a non-guideline neurotoxicity study, permethrin was administered to female mice by gavage, five days a week for four weeks prior to mating (PMRA # 2045466).⁶ Behavioural endpoints, including motor reflexes, motor coordination and activity, were evaluated in the F1 progeny from the exposed parents. The results of this study revealed an effect on the behavioural endpoints in the offspring but only at dose levels that caused signs of neurotoxicity in the parents. In short, there was no evidence of sensitivity of the young in studies conducted with non-lethal dose levels. Included in the PRVD were two studies from the

⁵ Health Canada's Pest Management Regulatory Agency. SPN2008-01, Science Policy Note: The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides. 2008.

⁶ PMRA# 2045466: Effects of permethrin given before mating on the behavior of F₁-generation in mice. *NeuroToxicology* (2006), 27(3): 421-428.

literature that addressed age-related sensitivity by comparing lethality in young and adult rats. These include the study by Sheets *et al.* (PMRA Nos. 2078469 and 2078470) and, contrary to the assertion of the commenter, the study by Cantalamessa (PMRA# 2045468). Both of these studies led Health Canada to conclude that young rats were found to be at least 2-fold more sensitive than adults to the lethal effects of permethrin. It is known that young animals have incomplete maturation of enzyme systems which detoxify pyrethroids and, thus, may be more susceptible due to higher and prolonged brain concentrations, compared to adults. Consequently, it is scientifically plausible that sensitivity of the young is only manifested at high doses that overwhelm the young animals' ability to detoxify pyrethroids. The data to prove this hypothesis was lacking at the time of the PRVD and consequently residual uncertainty remained concerning susceptibility of the young to potential neurotoxic effects. Consistent with SPN2008-01, a 3-fold database uncertainty factor was applied as the lines of evidence from non-lethal studies showed a low degree of concern for sensitivity of the young. The PCPA factor was reduced to 1-fold for permethrin because the residual concerns were addressed through the application of a database uncertainty factor. Based on Health Canada's policy for establishing uncertainty and PCPA factors, no changes are warranted to the factors that were presented in the PRVD.

Comment

One commenter from the general public expressed concern with the age of many of the studies in the database and indicated that there were more recent toxicity studies in the literature that had not been included in the PRVD. The latter included studies by Abou-Donia (2001a, 2001b), Abdel-Rahman *et al.* (2001, 2004), Bloomquist *et al.* (2002), Nasuti *et al.* (2007), Gabbianelli *et al.* (2013), Carloni *et al.* (2012), Imanishi *et al.* (2013) and a 2017 PhD thesis by Xiao Xiao. The commenter noted that the more recent studies showed adverse effects at the cellular level at concentrations up to three orders of magnitude lower than those used in the studies cited in the Health Canada review in which decreased motor activity was observed.

Health Canada Response

During the conduct of the human health risk assessment, all of the available toxicity studies and published journal articles were carefully reviewed for their relevance to the re-evaluation of permethrin. Health Canada utilized scientifically robust studies, regardless of the year of publication that focussed on the most sensitive indicators of toxicity in the most sensitive populations for the appropriate exposure scenarios. All of the more recent toxicity studies that were not available to Health Canada prior to the publication of the PRVD for permethrin, that contained information relevant to the risk assessment, have been reviewed and included in a follow-up review in Appendix IV. These include the studies conducted by Nasuti *et al.* (PMRA# 2916596), Carloni *et al.* (PMRA# 2879065) and Gabbianelli *et al.* (PMRA# 2916632).

The repeat-dose dermal studies from the literature conducted by Abou-Donia (2001a, 2001b) and Abdel-Rahman *et al.* (2001, 2004) were previously reviewed by Health Canada and were not considered acceptable for risk assessment purposes. These studies had significant deficiencies that affected their acceptability, including missing identification of the cis:trans isomer ratio, small group size, testing in only one sex and in the majority of these studies, the use of only a single dose level of permethrin, thus prohibiting the assessment of any dose-response relationship to add to the weight of evidence of the findings. Furthermore, the individual animal data were not available, rarely were the mean values for the investigated parameters presented and the results of almost all of these studies were only displayed in graphical format. Given these deficiencies, Health Canada was unable to analyze the data and as a result, the authors' reported

findings and conclusions could not be confirmed. It should be noted that the USEPA also came to the conclusion that these studies do not contribute high quality scientific information useful for human risk assessment (PMRA# 2884169). As a result, these studies were considered unacceptable for the human health risk assessment of permethrin and were not included in the PRVD.

The study conducted by Bloomquist *et al.* (2002) was considered unacceptable for risk assessment purposes by Health Canada. In this study, permethrin, of unspecified purity and unknown cis:trans isomer ratio, was administered to an unknown number of mice by three intraperitoneal injections during a two week period. Injection by the intraperitoneal route is considered to be unrepresentative of how humans would be exposed to permethrin in Canada and can result in differences in metabolism from the oral, dermal or inhalation routes of exposure. Thus, results from intraperitoneal studies would not be used to establish any effect levels or points of departure in the human health risk assessment. Notwithstanding this unrepresentative route of exposure, the presented results were limited, only available in visual format (bar graphs) and lacked any individual animal data. Given all of these limitations, this study was not suitable for risk assessment purposes and as such was not presented in the PRVD for permethrin.

The study by Imanishi *et al.* (2013) was also not considered acceptable for risk assessment. This study had numerous deficiencies including missing identification of the purity and of the cis:trans isomer ratio, and inconsistencies such as differing numbers of treated dams reported in the methods versus the results section. Furthermore, for some parameters, only the results from one of the four permethrin-treated groups were reported, while for other parameters, the data were only provided in graphical format.

Concerning the PhD thesis by X. Xiao, this study has recently been presented in two published journal articles (PMRA Nos. 2878511 and 2878512). These studies have been examined and high level results are presented in Appendix IV. The data were considered supplemental for risk assessment purposes due to the lack of study details, concerns regarding the number of animals examined, unclear statistical analysis and numerous parameters were reported only as bar graphs. While the data suggest an effect of low doses of permethrin on lipid and glucose metabolism in mice fed high-fat diets, at best, the data could only be considered qualitatively due to the limitations.

There were two studies not mentioned by the commenter but these are included as part of this update. One of these studies involved a discussion concerning the mode of action (MOA) for the development of lung tumors in female mice and liver tumors in male mice following long-term dietary exposure to permethrin (PMRA# 2884193)⁷. As part of the process to establish a MOA for a tumor type, dose-response concordance should be demonstrated for each key event in the proposed MOA. In female mice, the MOA studies examined morphological changes in Clara cells and Clara cell hyperplasia to determine whether a dose-response concordance was established. Clara cells were only examined at dose levels higher than those that resulted in the formation of lung tumors, thus prohibiting the demonstration of dose-response concordance. For liver tumors in male mice, the activation of PPAR- α and the number and size of peroxisomes were also only evaluated at dose levels above the tumorigenic dose. Therefore, Health Canada concluded that the mechanistic data were inadequate to support a mode of action assessment for

⁷ PMRA# 2884193: An evaluation of the human relevance of the lung tumors observed in female mice treated with permethrin based on mode of action. *Toxicological Sciences* (2017), 157(2): 465-486.

the permethrin-induced tumors since clear dose-response concordance between the key events and the development of tumors was not demonstrated in either male or female mice.

The second noteworthy article involved six experiments assessing the effect of a single exposure of higher doses of permethrin on the acoustic startle response in adult and postnatal day (PND) 15 Sprague-Dawley rats (PMRA# 2905889). These experiments demonstrated that under the conditions of these studies, PND 15 rats had slightly greater concentrations of cis- and trans-permethrin in the brain and plasma compared to the levels noted in adult animals. However, the same dose levels of permethrin induced a greater acoustic startle response in adult rats as compared to the younger animals. Although the individual animal data were not available, the mean values for the investigated parameters were not presented and the results of all of these experiments were only displayed in a graphical format, this study contained sufficient information to be considered supplemental to the human health risk assessment.

None of the additional published studies included in Appendix IV were deemed to have an impact on the reference values established for permethrin in PRVD2017-18.

Comment

One commenter from the general public indicated that there were many studies listed for which no publication date was provided and thus, the reader could not know whether these studies were recent or from 30-50 years ago when the technical grade of permethrin used was different.

Health Canada Response

All of the toxicity studies included in the assessment of the toxicity profile of permethrin (Table 1 of PRVD 2017-18) listed a PMRA number that corresponded to a full citation presented in the reference list section of the PRVD. This reference list included all of the toxicology studies which were determined to be of sufficient quality and relevance to the risk assessment of permethrin. Additional toxicity studies which were reviewed but were not considered scientifically robust or relevant to the hazard characterization or dose-response analysis of permethrin were not included in this reference list.

Comment

One commenter from the general public indicated that the PMRA omitted important epidemiological studies that suggest relationships to cardiac disease, type 2 diabetes, effects on sexual differentiation, Parkinson's disease and fertility issues. These include studies by Oulhote and Bouchard (2013), Shelton *et al.* (2014), Hicks *et al.* (2017), Furlong *et al.* (2017), Saillenfait *et al.* (2015) and Jianjun *et al.* (2017). Furthermore, the commenter indicated that Health Canada omitted information on piperonyl butoxide in the reporting of results from an epidemiological study by Horton *et al.* (2011) which was important as piperonyl butoxide measures could reflect exposure to permethrin.

Health Canada Response

During the conduct of the human health risk assessment, all available toxicity studies and published journal articles were carefully reviewed for their relevance to the re-evaluation of permethrin. Since the completion of the human health risk assessment, performed well in advance of the publication date of the PRVD, additional epidemiological studies have become available for permethrin and were considered by Health Canada.

These more recent epidemiological studies examined the potential association of exposure to pyrethroid pesticides and the development of parentally reported behavioral problems in children (Oulhote and Bouchard, PMRA# 2916627), pyrethroid exposure during pregnancy and behavioral alterations (Furlong *et al.*, PMRA# 2916629) or neurodevelopmental delays (Shelton *et al.*, PMRA# 2916626) in children. Non-occupational exposure to pyrethroid pesticides and the risk of developing coronary heart disease was also examined (Jianjun *et al.*, PMRA# 2916631). These studies all contained significant limitations. A critical limitation was the lack of permethrin-specific data. These studies all examined pyrethroids as a class of pesticides and often used information on the presence of urinary metabolites to form their conclusions. The metabolites that were investigated in these studies, 3-phenoxybenzoic acid and the cis- and trans-isomers of 2,2-dichlorovinyl-2,2-dimethylcyclo-propane-1-carboxylic acid, are common to many pyrethroid pesticides and did not add any permethrin-specific information to the re-evaluation. Other critical limitations were noted with each of these studies and included self-reporting of behavioral problems in children, which can be very subjective, and the recall of pesticides used in and around the homes, which introduces significant recall bias. The pyrethroid metabolites that were measured from individuals were determined from a single urine sample and did not take into account the relatively short-half lives of these compounds. In all of these studies, it was unclear whether the individuals investigated were exposed to the parent compounds or to the metabolites themselves. Many potential confounding factors including genetics, dietary habits, and the other environmental pollutants were not adjusted for and the number of cases examined was small which could lead to high variability and significant confounding bias.

An ecological cross-sectional study was conducted to investigate the prevalence of neurodevelopmental delays (developmental delay and autism spectrum disorder) in children from central New York that were exposed to yearly aerial permethrin applications (Hicks *et al.*, PMRA# 2916628). A retrospective review of pediatric charts was performed from outpatient medical records from March 15, 2010 to March 15, 2015. The average pesticide exposure over a 3-year period (2007 to 2009) was determined for each zip code using available data from a state database. Comparisons were made between the 19,073 children residing in the 8 aerially-exposed zip codes and the 44,697 children residing in the 16 control zip codes for the prevalence of neurodevelopmental delay. While the study authors stated that “a significant relationship between aerial pesticide use and developmental delay and autism spectrum disorder rates (adjusted RR = 1.37, 95% CI = 1.06-1.78)” was noted, due to the design of this study, no conclusions as to the potential association of neurodevelopmental delays and pyrethroid exposure can be made. There was no attempt to collect biomonitoring data to demonstrate that these children were ever exposed to permethrin. Without this information, this study is of limited value to the risk assessment of permethrin.

A review of the literature available since 2005 pertaining to potential hazards associated with pyrethroid pesticides in humans was presented by Saillenfait *et al.* in PMRA# 2916630. The majority of the studies discussed in this review article were conducted with pyrethroid pesticides other than permethrin; however, the acceptable studies that examined permethrin have been included in the PRVD or are summarized in Appendix IV.

With regards to the Horton *et al.* study (PMRA# 2078458), the authors reported that prenatal exposure to piperonyl butoxide, measured via 48-hour maternal air samples in the third trimester of pregnancy, was associated with altered cognitive development in 36-month-old children; no association was found for motor development. It should be noted that mothers with piperonyl

butoxide exposure in the highest quartile were less likely to have a high school diploma and scored lower on a home inventory test used to assess the physical and interactive aspects of the home environment. It is expected that both covariates (or more importantly, what they are intended to measure) are highly related to study outcomes and as such, very careful analysis is required to remove their confounding effect. Although adjustment for the covariates was undertaken, the impact of this adjustment was not reported and it could not be determined if the adjustment was adequately performed. As noted in the PRVD, no significant associations were noted between permethrin measures in either prenatal personal air or maternal/cord plasma and neurodevelopment. The study authors note that the low volatility and rapid metabolism of permethrin may have been factors to explain this lack of association. The lack of internal measures of piperonyl butoxide represents a significant limitation of this study and it is noted that the authors consider the findings to be preliminary. Furthermore, as piperonyl butoxide can be formulated with other pyrethroids, it is inappropriate to conclusively link the results to permethrin.

Two additional epidemiological studies, further to those mentioned by the commenter, were identified from the scientific literature. A hospital-based case-control study (PMRA# 2879068)⁸ was carried out in 13 Brazilian states. Controls (423 children less than 24 months of age) were frequency-matched with 252 cases of children with a conclusive diagnosis of acute lymphoid or myeloid leukemia according to age, and enrolled from the same geographic areas where cases were diagnosed. In-person interviews were carried out from 1999 through 2007 with mothers of newly diagnosed patients with a standardized questionnaire. Pesticide exposure was evaluated based on the mother's report of any contact with pesticides (at least once) during the three months before pregnancy, throughout pregnancy or during the three months after birth. Based on reported maternal exposure to permethrin, the authors describe positive associations for both acute lymphoid leukemia (adjusted odds ratio (aOR) = 2.47; 95% CI: 1.17, 5.25) and for acute myeloid leukemia (aOR = 7.28; 95% CI: 2.60, 20.38) for infants 0 to 11 months of age. Significant limitations were noted with the study including differing sociodemographic characteristics between the cases and controls, imprecise estimates of associations with exposure to individual pyrethroids during pregnancy due to small numbers of reported exposures, self-reporting of exposure to permethrin and missing information on permethrin use in both control and case groups.

Male farmers from North Carolina and Iowa that participated in the 2005-2010 interviews of the Agricultural Health Study were studied to determine if there was an association between allergic and non-allergic wheeze and self-reported use of pesticides (PMRA# 2878516).⁹ Of the 22 134 pesticide applicators, 1310 (6%) had allergic wheeze (wheeze and doctor-diagnosed hay fever) and 3939 (18%) had non-allergic wheeze (wheeze but no hay fever). The use of permethrin was associated with an increase in allergic (OR 1.38, 95% CI: 1.09, 1.75) and non-allergic wheeze (OR: 1.35, 95% CI: 1.17, 1.55). The highest odds ratios were associated with the highest levels of permethrin use (13–365 days per year) with an increase in allergic (OR 1.70, 95% CI: 1.05, 3.04) and non-allergic wheeze (OR: 1.76, 95% CI: 1.30, 2.39). Limitations of this study included self-reporting of both symptoms and pesticide use. It was also unknown if the pesticide use actually preceded the respiratory symptoms.

⁸ PMRA# 2879068: In utero pesticide exposure and leukemia in Brazilian children < 2 years of age. *Environmental Health Perspectives* (2013), 121(2): 269-275.

⁹ PMRA# 2878516: Pesticides are associated with allergic and non-allergic wheeze among male farmers. *Environmental Health Perspectives* (2017), 125(4): 535-543.

Overall, these epidemiological studies were not considered sufficiently robust for risk assessment purposes.

Comment

One commenter from the general public, expressed concern regarding the synergistic interactions of permethrin with piperonyl butoxide.

Health Canada Response

Piperonyl butoxide is a pesticide synergist used to enhance the pesticidal properties of certain active ingredients such as permethrin. It works by directly binding to microsomal enzymes in insects which prevents the breakdown of other active ingredients. Although it has been shown to inhibit microsomal enzymes in mammalian systems in mice several hours following intraperitoneal exposure, microsomal enzyme induction was noted 24 hours post-dosing (PMRA# 2407829). The results of numerous studies in the published literature (for example, PMRA Nos. 2420879 and 2407825) suggest a similar induction of microsomal enzymes with repeated dietary exposure in rats and mice. Thus, piperonyl butoxide does not effectively act as a pyrethroid synergist in mammals and accordingly, does not alter the assessment of permethrin. The risks associated with piperonyl butoxide will be addressed in the forthcoming re-evaluation of piperonyl butoxide.

1.2 Comments Related to Dietary Exposure**Comment**

The Canadian Horticultural Council (CHC) commented that the extended plant-back interval of 60 days for non-registered food/feed crops on the permethrin label is not compatible with many integrated pest management (IPM) practices for vegetables; specifically for lettuce, radish, and green onion production in Quebec. The CHC stated that a 60 day plant-back interval for non-registered food crops on the permethrin label would limit a grower's ability to plant green onions following radish or lettuce and limit grower economic returns.

Health Canada Response

Based on the available residue chemistry data for confined crop rotational studies and field accumulation in rotational crops, a plant-back interval of 60 days for non-registered crops is required on all agricultural product labels of permethrin. This plant back interval is applied only to non-registered crops. Vegetables, such as radish, lettuce, onions (bulb and green onion) and peas (dry and succulent pea), are currently registered crops, and therefore, the plant back interval of 60 days would not apply to those crops.

1.3 Comments Related to Occupational and Residential Exposure

Comments were received related to the proposed decision to cancel mechanically-pressurized handheld sprayer application for mists, aerosols, and fogs. The registrants submitted a study to address the data gaps for mechanically-pressurized handheld sprayer application for mists, aerosols, and fogs (Thouvenin, 2015) along with their review of the study. The Canadian Pest Management Association submitted 3 comments referencing this study and offered to work with Health Canada to gather additional data required to conduct an applicator risk assessment for these uses; however, this additional information was not necessary as the study itself was sufficient to refine the risk assessment. Pesticide control operators submitted 16 comments opposing the proposed decision to cancel mechanically-pressurized handheld sprayer applications for mists, aerosols, and fogs, and provided recommendations on PPE options to reduce exposure. Others provided information regarding current industry standards and training that applicators receive. There were 13 comments submitted from the general public opposing the decision to cancel mechanically-pressurized handheld sprayer applications for mists, aerosols, and fogs to control pests, due to public health concerns for mosquito- and tick-borne diseases such as West Nile virus, Lyme disease, and Zika virus, mosquito allergy concerns, or nuisance issues with mosquitoes. There was one comment from academia offering to provide use information, if necessary, for the risk assessment. However, this information was not necessary as the study provided by the Registrants was sufficient to refine the risk assessment.

Health Canada Response

The study provided by the registrant (Thouvenin, 2015), as well as another study by Testman (2015) were reviewed and found acceptable for use in the applicator risk assessment for mechanically-pressurized handheld sprayer for mists, aerosols, and fogs. As such, the dermal and inhalation risk assessments for these scenarios were updated (see Appendix V). The calculated risks for commercial applicators using mechanically-pressurized handheld sprayer for mists, aerosols, and fogs outdoors were shown to be acceptable, provided that additional PPE is worn (in other words, chemical-resistant coveralls with a chemical-resistant hood over long pants, long-sleeved shirt, chemical-resistant gloves, and a respirator). As a result, this application method will be retained on product labels, together with the appropriate directions for use.

2.0 Comments Related to the Environmental Risk Assessment

Comment

Concerns were raised by the registrant and CropLife regarding the proposal to add the requirement of a 10-m vegetative filter strip (VFS) to all labels for products containing permethrin.

The commenters point out that the size of the proposed vegetative filter strip (10 m) is greater than that of the United States (10 feet, or 3 meters). The commenters feel that the vegetative filter strip size appears to be influenced not on a model or any formal quantified estimate but rather on the most conservative buffer requirement within all of the provinces.

In the PRVD, it is stated that Prince Edward Island has instituted a requirement for a 15-m VFS for all agricultural fields that border water courses. The commenter points out that VFS in Prince Edward Island are required for all agricultural operations – not just those applying pyrethroid insecticides. The commenters indicated that the main purpose of the 15-m VFS in Prince Edward

Island is to trap silt from the highly erodible land found in Prince Edward Island as well as other contaminants, such as nutrients, soluble pesticides or bacteria, before they enter into aquatic systems.

The commenters argue that the width of a VFS is dependent upon the purpose of the strip. For example, a VFS designed to trap sediment does not need to be as wide as one that is intended to remove soluble compounds, such as nitrates or certain pesticides (USDA-NRCS 2000). In Prince Edward Island, the VFS are intended to trap soil particles as well as soluble compounds, resulting in the requirement for a relatively wide VFS. Pyrethroid insecticides, such as permethrin, tend to bind strongly to soil particles; therefore, the main purpose of the VFS in fields treated with permethrin will be to remove soil particles that may contain adsorbed pesticide. Thus, the VFS required for permethrin containing products can be significantly narrower than that required in Prince Edward Island to remove soluble compounds. In Robinson *et al.* (1996) a VFS as narrow as 3 m is shown to remove more than 70% of the sediment from run-off, indicating that a 3 m buffer should be sufficient to remove the majority of soil particles.

The commenters argue that under certain conditions, to protect areas where the risk from erosion is high, a 10 m VFS could be required, but not for all situations.

The commenters expressed that the PMRA had deferred to the most conservative provincial standard for VFS rather than conducting a scientific assessment of potential mitigation measures and that this was a deviation from the PMRA's normal practice. The commenter requests clarification on the nature of the assessment conducted on potential mitigation measures and assurance that deferral to the most conservative provincial standard will not become the Agency's standard approach.

Health Canada Response

A refined risk assessment for runoff of permethrin determined that there is a high risk to aquatic organisms. In order to reduce risks to aquatic organisms and maintain the registered uses of permethrin, Health Canada proposed the requirement for a 10 m VFS. The VFS is intended to reduce soil and bound permethrin carried in runoff water from entering aquatic habitats. A review of the available literature found that other jurisdictions use a variety of VFS widths (from 1 to 40 m). The rationale for the size of the VFS (infiltration vs. soil trapping) is not always clear in the available literature. A detailed analysis of the literature by Health Canada (see below) provides clear evidence that a 10 m VFS is expected to provide adequate risk mitigation for aquatic organisms from bound pesticides (such as permethrin) in runoff across Canada.

Robinson *et al.* (1996) examined 13 natural rainfall events that ranged from low to very high intensity. High levels of pesticide would be expected to be carried to aquatic habitats during very high rainfall events, categorized in this study as rainfall amounts of 18 to 72 mm within no set timeframe. The study determined that during these high intensity rainfall events, 3, 6 and 9 m VFSs retained approximately 50, 75 and >95%, respectively, of soil in the resulting runoff from a 7% slope. Assuming soil and pesticide (permethrin) losses are proportional, a 50 to 75% reduction (from 3 and 6 m VFSs) in the aquatic EECs from runoff would still result in exceedance of the level of concern for aquatic organisms; however, the level of concern would not be exceeded for aquatic organisms using a 9 m VFS.

Although there was >95% retention of soil in this study using a 9 m VFS, rainfall intensity and duration, soil characteristics and increased slope could result in decreased retention under the variety of Canadian conditions. Therefore, a 10-m VFS is expected to be protective of sensitive aquatic species.

Abu-Zreig *et al.* (2004) studied soil retention of various width VFS (2, 5, 10, and 15 m) and different slopes (2.3 and 5%) in Guelph, Ontario. The authors concluded that the width of the VFS was the predominant factor affecting soil deposition, at least up to 10 m. Syversen (2005) studied soil retention in 5 m and 10 m wide VFS in southern Norway and found that the 10 m wide VFS retained significantly more soil than the 5-m wide VFS. Both of these studies conclude that a VFS with a width of 10 m trapped significantly more soil than VFSs of smaller widths. Health Canada is aware of only two studies that studied the effects of VFS on permethrin concentrations in runoff. One of those studies (Moore *et al.* 2014) examined much larger VFS sizes (16 and 47 m). The other, Schmitt *et al.* (1999), found that permethrin concentrations were reduced in runoff by 36% using a 7.5 m wide VFS and by 66% using a 15 m wide VFS on slopes of 6 to 7%.

Given the available evidence, Health Canada has determined that a 10-m VFS is required to reduce permethrin concentrations entering aquatic environments in order to reduce risks to aquatic organisms. Building and maintaining a VFS will have positive impacts on the retention of other pesticides with similar properties (for example, high K_{oc} , low solubility, high toxicity to aquatic organisms).

Comment

CropLife Canada argues that the use of the LOD as an exposure concentration likely overestimates the risk to aquatic organisms; therefore, the use of label language that requires the user to avoid application to steep slopes, compacted soil or clay or when heavy rain is forecast should be sufficient to reduce the risk to an acceptable level. The commenter states that the requirement for a mandatory 10-m vegetative filter strip appears to be overly conservative in this situation considering water monitoring data showed that few samples had detectable residues of permethrin.

Health Canada Response

The low detection frequency of permethrin in water samples from Canadian waterbodies cannot be used to make a conclusion of acceptable risk. Of the 2600 samples analyzed for permethrin, 93% had limits of detection that were not sensitive enough to capture levels that could be a concern to aquatic invertebrates. Using the limit of detection as the EEC, therefore, estimates the magnitude of potential risk to aquatic invertebrates and is a more protective approach than making the potentially detrimental assumption that 93% of the samples contained absolutely no residues of permethrin. As described in the PRVD, the RQs using this approach reached a maximum of 26.3, again exceeding the level of concern. The calculation of acute risk quotients using actual detections resulted in risk quotients that exceeded the level of concern for aquatic invertebrates (maximum RQ = 265).

The requirement for mandatory 10 m VFS to help mitigate risks to aquatic organisms from runoff of permethrin is justified based on the collective evidence regarding the efficacy of VFSs from available scientific literature (see previous question and response), and the results of the aquatic risk assessment.

Computer modelling of EECs were used to derive risk quotients (RQ) for acute and chronic risk. The LOC was exceeded for all aquatic organisms at all permethrin application rates (RQ = 1.9-2300), with the exception of algae. Similarly, risk quotients derived for chronic exposure using EECs from computer models also exceeded the level of concern for all aquatic organisms (RQ = 1.8-113), except for freshwater fish and amphibians at the lowest application rate and marine/estuarine fish at all application rates. Peak exposure estimates generated using computer models are similar to, or in some cases less than, concentrations of permethrin measured in Canadian waterbodies. As such, modelled concentrations of permethrin are not considered to be overly conservative.

Since the implementation of VFS in the United States in 2008, no incidents of fish kills have been reported. The absence of further incidences in relation to adherence/implementation of the VFS is uncertain; however, VFS have been shown to reduce movement of contaminants, excess nutrients, soil and other detrimental components into aquatic systems.

Comment

Nailor Regulatory Consulting Inc. suggested wording changes to mitigation language:

Excerpt from PRVD: Page 184, Section V, # 2 and # 4: V. ALL END-USE PRODUCTS (DOMESTIC AND COMMERCIAL)

The following statements are proposed to be added to the Environmental Precautions section of all end-use product labels:

“TOXIC to aquatic organisms. Observe buffer zones specified under **DIRECTIONS FOR USE.**” “Toxic to birds.”

“TOXIC to bees.

The commenter suggests that the words “As necessary” be added because some of the products are for indoor use only, and, therefore, Environmental Precautions and protection of aquatic organisms, birds, bees, etc., are not relevant.

Health Canada Response:

The term “toxic” is used to identify a hazard or inherent toxicity to non-target organisms. The toxicity statements on product labels (in other words, aquatic organisms, birds and bees) provide a simple, clear message to users that the product is toxic to non-target organisms. These statements are independent of the product use (in other words, indoor or outdoor use) and are required on all product (commercial and domestic) and technical grade labels to inform users of the potential hazard or inherent toxicity to non-target organisms.

The spray buffer zones specified under **DIRECTIONS FOR USE** apply to commercial products with outdoor uses. The label statement under Environmental Precautions, “Observe buffer zones specified under **DIRECTIONS FOR USE**”, (Page 184 Section V of PRVD), therefore, is only applicable to commercial end-use products. The PRVD incorrectly implies that this statement applied to domestic products.

3.0 Comments Related to Incident Reports

Comment

A comment was received from a member of the public that questioned the exclusion of incidents related to pesticide spot-on products containing permethrin, indicating that no reason was given for the exclusion of this information in the re-evaluation of permethrin.

Health Canada Response

As indicated in-PRVD2017-18, while the focus of the incidents was permethrin-only products, a parallel initiative involving a broader examination of domestic animal incident data, for all registered spot-on products, was also underway. The underlying objective of this evaluation was to analyze the domestic animal incident reports collectively for all relevant active ingredients, based on the registered use patterns for spot-on products. In terms of the human incidents involving spot-on products containing permethrin, Health Canada had previously evaluated thirty human incidents involving spot-on products containing permethrin and other active ingredients. Most of these incidents involved products that contained both permethrin and imidacloprid, and thus the majority of these incidents were previously evaluated during the re-evaluation for imidacloprid (PRVD2016-20). The remaining incidents were evaluated through the review of the reports for pyrethrin and pyrethroid incidents, which is summarized in the “Annual Report on Pesticide Incidents for 2011”. In general, minor symptoms such as rash, itchy skin, headache and dizziness were reported. As the current labels for spot-on products containing permethrin already have precautionary statements to avoid contact with the product, to wear gloves during application, to wash hands after applying or handling the product, and to avoid contact with pets until the product has dried, no additional mitigation measures were recommended. The parallel evaluation of the broader animal incident data assessed all spot-on incident reports submitted to the PMRA from April 2007 until the end of 2015, and included an analysis of 5928 incident reports in dogs and cats. Following this in-depth analysis, the PMRA published the Regulatory Proposal *Consultation on Proposed Regulatory Changes for Pesticide Products Used on Companion Animals* (PRO2018-01) on 21 September 2018. This document proposed regulatory changes for pesticide products used on companion animals. The key outcome of this analysis is the addition of proposed label requirements for spot-on flea and tick control products used on pets (including those that contain permethrin) that will include a listing of potential side effects on the product label to better inform the consumer as to the possible effects that may be expected in pets following product use.

Comment

A comment was received from a member of the public that noted a discrepancy between the number of incidents involving permethrin alone (identified in PRVD2017-18) and the number of incidents for products containing permethrin and other active ingredients in the PMRA’s Public Registry.

Health Canada Response

As mentioned in the previous response, the review of incidents for PRVD2017-18 focused on permethrin-only incident reports, rather than permethrin products that also contain other active ingredients. Although the incidents involving permethrin as a single active ingredient did not identify any risks requiring additional mitigation, they did support the proposed best practice label amendments that are being required as a result of the re-evaluation of permethrin. These label amendments will be applied to all products containing permethrin, either alone or in

combination with other active ingredients. The improved label language will help ensure clarity, directness, specificity and consistency of label statements.

As noted in the response to Comment 1, the domestic animal incidents involving spot-on products containing permethrin were not considered in PRVD2017-18, but were reviewed separately as part of a broader examination of domestic animal incident data for all registered spot-on products. The results and proposed mitigation measures have since been published in PRO2018-01.

Comment

A comment was received from a member of the public that noted a discrepancy between the number of serious human incidents identified in PRVD2017-18 and the number of serious human incidents for products containing permethrin (alone or in combination with other active ingredients) in the PMRA's Public Registry.

Health Canada Response

The majority of incidents involving permethrin that have been received by the PMRA also involve other active ingredients. As noted in the responses to Comments 1 and 2, the review of incidents for PRVD2017-18 focused on permethrin-only incident reports. This explains, in part, the discrepancy in the number of serious incidents discussed in the Incident Report Section of PRVD2017-18 and the number of incidents classified as "Major" in the PMRA's Public Registry. In addition, this discrepancy is also influenced by both the severity level and causality level (the degree of association to the pesticide) assigned to serious incidents received by the PMRA. Some incidents that are reported as serious in their severity level by a registrant in the Public Registry do not meet the definition of a "Major" effect as outlined in the Incident Reporting Regulations. Upon assessment, if these incidents are re-classified to "Minor" or "Moderate" by the PMRA, they would not be reported as 'serious' incidents in the PRVD, but are still reflected as such in the Public Registry. Finally, when summarizing incidents for the re-evaluation of an active ingredient, the PMRA's Incident Reporting Program focuses on serious cases that were determined to have at least some association with the pesticide, which would also influence the total number of incidents reported in a proposed or final re-evaluation decision document.

4.0 Comment Related to the Value Assessment

Comment

One comment was received from the Canadian Horticulture Council (CHC). CHC required clarification on the 60-day plant-back interval (PBI) for field vegetables, specifically for the use on green onions. Green onions are often grown in rotation with lettuce or radish in the same growing season in Quebec, and a 60-day PBI is not compatible with current agronomic practices for these crops in Quebec.

Health Canada Response

Permethrin is registered for use on onions which includes green onions, and as such the 60-day PBI would not apply. Labels will be updated to more clearly identify the registered crops where the PBI restriction does not apply (for example onions include green and dry bulb onions).

5.0 Other Comments Related to the Use of Permethrin

Comment

A comment was received from the general public that asked whether registrants were required to provide specific studies for the purpose of the re-evaluation and whether registrants were involved in writing the re-evaluation document.

Health Canada Response

As per the Regulatory Directive DIR2016-04, *Management of Pesticides Re-evaluation Policy*, upon initiation of a re-evaluation, the registrant(s) who support the re-evaluation (that is, indicate support for the registration of the active ingredient) are required to submit a list of existing studies and any studies that are underway along with the anticipated completion date. This re-evaluation considered data from registrants, published independent scientific studies, and information from other internationally recognized regulatory agencies. In certain cases, the PMRA will issue a data call-in for additional information and/or studies when considered necessary to conduct the review. Registrants are not involved in writing the re-evaluation documents (proposed and final decision).

Appendix II List of Respondents to PRVD2017-18

List of respondents' affiliations in terms of comments submitted in response to PRVD2018-17

Category	Respondent
Agricultural Organizations and Growers	Canadian Horticultural Council
	Canadian Pest Management Association
Pesticide Applicators	Target Specialty Products
	Gardex Inc.
	Independent, pest control operator
	Mosquito Buzz
Registrant	FMC Corporation
	Nailor Regulatory Consulting Inc.
Other Interest Groups	CropLife Canada
	University of Kentucky
General Public (in other words individuals)	15

Appendix III Label Amendments for Products Containing Permethrin

Information on labels of currently registered products should not be removed unless it contradicts the label statements provided below.

Use instructions for uses which are no longer supported (electric mistblower into attic spaces, application by total release fogger (formerly referred to as solid fogger), and broadcast applications in residential indoor environments) must be removed from the label.

I. Technical Grade Active Ingredients and Commercial Class Products

1. The following is required to be added to the labels of the technical grade active ingredients and all commercial end-use products under the section entitled **Toxicological Information**:

“Skin exposure may cause transient sensations (tingling, burning, itching, numbness). Treat symptomatically.”

II. Technical Grade Active Ingredients

1. The following statements are required to be added to the “**ENVIRONMENTAL HAZARDS/PRECAUTIONS**” section:

“TOXIC to aquatic organisms.”

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

2. The following statements are required under the “**Disposal**” Section of the Permethrin Technical Insecticide label:

“Canadian manufacturers should dispose of unwanted active ingredients and containers in accordance with municipal or provincial regulations. For additional details and clean up of spills, contact the manufacturer or the provincial regulatory agency.”

III. Commercial Class Products

1. The following label statements are required to be added on labels for agricultural food/feed crop uses, under “**DIRECTIONS FOR USE**”:

“A plant back interval of 60 days is required for all food/feed crops not currently listed on the label.”

“For use on field tomato, DO NOT apply more than five applications per year.”

-
2. The following label updates must be included for all products registered for uses on livestock and livestock housing, under “**DIRECTIONS FOR USE**”:

Poultry:

- Liquid application on poultry for control of northern fowl mites at a rate of 0.019 g a.i./animal/application with a maximum of 2 applications/year, a minimum re-treatment interval (RTI) of 14 days and a minimum pre-slaughter interval (PSI) of 7 days, using knapsack and handgun; and
- Poultry housing application at a rate of below 0.05 a.i./m² (for example, 0.0398 and 0.048 g a.i./m²) with a maximum of 12 applications/year, a minimum RTI of 14 days and a minimum PSI of 1 day, or at a rate of above 0.05 g a.i./m² but less or equal to 0.1 g a.i./m² (for example, 0.096 and 0.1 g a.i./m²) with a maximum of 12 applications/year, a minimum RTI of 14 days and a minimum PSI of 7 days.

Cattle:

- Ear tag for control of face flies and horn flies with a maximum of two ear tags/animal/year, each ear tag containing a maximum of 0.95 g permethrin, and a minimum PSI of 1 day;
- Self-oiler for control of black flies, face flies, horn flies and mosquitoes at a maximum rate of 0.125 g a.i./animal/day and a minimum PSI of 1 day;
- Pressurized product for control of face flies, horn flies, and mosquitoes at a rate of 0.045 g a.i./animal/application and a minimum PSI of 1 day;
- Pour-on, cloth for control of biting lice, sucking lice, horn flies, rocky mountain wood tick at a rate of 1.3 g a.i./animal/application with a maximum of 2 applications/year, a minimum RTI of 14 days and a minimum PSI of 1 day, as well as the existing statement of “For Dairy Cattle DO NOT use this product in combination with any other permethrin treatment.”;
- Liquid application on beef cattle and non-lactating dairy cattle for control of black flies, mosquitoes, face flies, horn flies and lice at a rate of 0.96 g a.i./animal/application with a maximum of 2 applications/year, a minimum RTI of 8 days and a minimum PSI of 7 days, using knapsack, handgun and low pressure sprayer;
- Liquid application on beef cattle only for control of rocky mountain wood tick at a rate of 1.5 g a.i./animal/application with a maximum of 2 applications/year, a minimum RTI of 14 days and a minimum PSI of 7 days, using high pressure sprayer; and
- Cattle housing application at a rate of below 0.05 a.i./m² (for example, 0.0398 and 0.048 g a.i./m²) with a maximum of 12 applications/year, a minimum RTI of 14 days and a minimum PSI of 1 day, or at a rate of above 0.05 g a.i./m² but less or equal to 0.1 g a.i./m² (for example, 0.096 and 0.1 g a.i./m²) with a maximum of 12 applications/year, a minimum RTI of 14 days and a minimum PSI of 7 days.

Sheep:

- Pressurized product for control of sheep ked at a rate of 0.045 g a.i./animal/application with a minimum PSI of 1 day;

- Liquid application for control of sheep ked at a rate of 0.144 g a.i./animal/application with a maximum of 1 application/year and a minimum PSI of 1 day using knapsack and handgun; and
- Sheep housing application at a rate of below 0.05 a.i./m² (for example, 0.0398 and 0.048 g a.i./m²) with a maximum of 12 applications/year, a minimum RTI of 14 days and a minimum PSI of 1 day, or at a rate of above 0.05 g a.i./m² but less or equal to 0.1 g a.i./m² (for example, 0.096 and 0.1 g a.i./m²) with a maximum of 12 applications/year, a minimum RTI of 14 days and a minimum PSI of 7 days.

Horse:

- Pressurized product for control of black flies, face flies, horn flies, horse flies, house flies and mosquitoes at a rate of 0.045 g a.i./animal/application with a minimum PSI of 1 day; and
- Horse housing application at a rate of below 0.05 a.i./m² (for example, 0.0398 and 0.048 g a.i./m²) with a maximum of 12 applications/year, a minimum RTI of 14 days and a minimum PSI of 1 day, or at a rate of above 0.05 g a.i./m² but less or equal to 0.1 g a.i./m² (for example, 0.096 and 0.1 g a.i./m²) with a maximum of 12 applications/year, a minimum RTI of 14 days and a minimum PSI of 7 days.

Swine housing:

- Swine housing application at a rate of below 0.05 a.i./m² (for example, 0.0398 and 0.048 g a.i./m²) with a maximum of 12 applications/year, a minimum RTI of 14 days and a minimum PSI of 1 day, or at a rate of above 0.05 g a.i./m² but less or equal to 0.1 g a.i./m² (for example, 0.096 and 0.1 g a.i./m²) with a maximum of 12 applications/year, a minimum RTI of 14 days and a minimum PSI of 7 days.

3. In order to promote best practices, and to minimize human exposure from spray drift or from spray residues resulting from drift due to the agricultural use of permethrin, the following label statement is required, under “**PRECAUTIONS**”:

“Apply only when the potential for drift to non-target areas of human habitation and human activity is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings.”

4. The following statements are required to be added to the labels for non-agricultural products, under “**DIRECTIONS FOR USE**”:

“DO NOT apply indoors in residential areas* as a broadcast application. ONLY indoor perimeter, spot or crack and crevice applications are permitted indoors in residential areas. Indoor perimeter application is less than 0.3 m wide along the edges of a room to baseboards, wall-floor and ceiling-wall joints, and around doorways or windows. Spot application is localized to a surface area not more than 0.2 m². Spots are not to be adjoining. The combined area of spots is not to exceed 10% of the total surface area of a room. Crack and crevice is an application directly into narrow openings on the surface of the structure. It does not include the treatment of exposed surfaces. Narrow openings typically occur at expansion joints, utility entry points and along baseboards and mouldings.”

“*Residential areas are defined as any use site where the general public, including children, could be exposed during or after application. For structural uses, in residential sites, this includes homes, schools, restaurants, public buildings, modes of transport in areas where passengers are present, or any other areas where the general public including children may potentially be exposed.”

“DO NOT apply to furniture, mattresses, linens, toys or clothing.” Any references to treating these objects must be removed from the label.

“DO NOT apply when people or pets [or livestock] are present.”

“DO NOT allow people or pets [or livestock] to enter treated areas until sprays have dried.”

“DO NOT allow spray to drip or allow drift onto non-target surfaces.”

“DO NOT apply to overhead areas or in confined spaces without appropriate respiratory and eye protection.”

“Ventilate treated areas after application either by opening windows and doors or using fans, where required, to aid in the circulation of air. Air exchange/ventilation systems confirmed to be operational may also be used.”

For broadcast, indoor perimeter and spot spray (liquid formulation) applications, add:

“Use a coarse droplet size and low pressure spray not exceeding 345 kPa (50 psi) to avoid splashing onto non-target surfaces.”

5. The following statements are required to be added to the labels not registered as a space spray application, under “**DIRECTIONS FOR USE**”:

“DO NOT apply as a space spray.”

6. The following statements must be added to space spray product labels, under “**DIRECTIONS FOR USE**”:

“DO NOT allow people or pets [or livestock] to enter treated areas until 15 minutes after a space spray application.”

“DO NOT remain in treated areas after a space spray application.”

7. Permethrin must not be applied in mushroom houses when there are mushrooms present, or crop must be covered, if hand harvesting is occurring. See required label statements under “Mushroom Houses” in section below, Revised Label Amendments for End-Use Products Containing Permethrin.
8. Permethrin must not be applied by electric mistblower into attic spaces. Remove from labels, the use of electrical mistblower application into attic spaces.

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9. The maximum application rate for residential yards is 0.123 g a.i./m². Labels must be changed to reflect this.
10. For treatment of wood using an enclosed linear system, the following statement regarding wood intended for export to Australia is required under “**DIRECTIONS FOR USE**”, as this was included in the original risk assessment and is no longer present on current labels. (Note: The statement was included in the original risk assessment (Submission# 2002-3773) and no explanation for the removal of this statement was provided.)

“For control of ambrosia and wood boring beetles in sawn lumber for export to Australia only”

11. The following statements, relating to engineering controls and personal protective equipment, must be added to the labels where the method is applicable, under “**PRECAUTIONS**”:

“For mechanically-pressurized handheld sprayer for mists, aerosols, and fogs applications, or entering treated areas before venting, wear chemical-resistant coveralls with a chemical-resistant hood over long pants, and long-sleeved shirt, chemical-resistant gloves, socks, 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 during mixing, loading, application, clean-up and repair.”

“For truck-mounted mistblower or airblast applications, wear a long-sleeved shirt, long pants, chemical-resistant gloves, and a chemical-resistant hat that covers the neck (e.g Sou’Wester) during mixing, loading, application, clean-up and repair, or use a closed cab (for example, tractor cab/truck with windows rolled up).”

“For mechanically pressurized handgun applications, wear cotton coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, socks, and shoes during mixing, loading, application, clean-up and repair.”

“For other application equipment wear long pants, long-sleeved shirt, chemical-resistant gloves, shoes, and socks during mixing, loading, application, clean-up and repair, unless otherwise specified.”

“Gloves are not required during application within a closed cab.”

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12. For wood treatment in an enclosed linear system, the following statements must be added, under “**PRECAUTIONS**”:

“Wear chemical-resistant coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, goggles or face shield, socks, and chemical-resistant footwear when handling the concentrate or during mixing/loading, application, clean-up, maintenance and repair activities.”

“Use a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH-approved canister approved for pesticides if the area is not well ventilated and during clean-up, maintenance, and repair activities.”

“When piling freshly treated lumber or if there is a potential for getting wet by the treating solution or by handling freshly treated lumber, wear chemical-resistant coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, socks and chemical-resistant footwear.”

“When working in the dip or spray area, wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks, and boots. Wear goggles or face shield if there is a possibility of splashing.”

“Once dry, the treated wood can be handled with cotton or leather gloves.”

“Wash hands and face before eating, drinking, smoking and using the toilet. Change clothes daily. Wash contaminated clothing separately from household laundry. Not for use or storage in or around the home. Clean contaminated equipment thoroughly prior to making welding repairs.”

13. For wood treatment in an enclosed linear system, references to aprons must be removed due to potential physical hazard concerns (for example, aprons being caught in machinery).
14. Consult the following table regarding REIs. Where deemed necessary, REIs are subdivided according to re-entry activities. Some of the activities in the REI table are not routinely conducted on every farm for every crop. The REIs specified for an activity must be followed only if that activity is being performed. If, for example, there is an REI for hand harvesting, but the crop is to be mechanically harvested, then the PHI should be followed if there is no contact with treated foliage or surfaces. Include a table on each label in this section that includes the crops, activities, and REIs from Appendix III, Table 1 for the crops registered on that label.

Table 1 **Restricted Entry Intervals**

Crop	Activity	REI^a
apple, nectarine, peach, pear, plum, asparagus, barley, canola, flax, oats, peanuts, peas, rape, rye, triticale, snap bean, sugar beet, wheat, lentils, beet, carrot, onion, potato, turnip, radish, wasabi, ginseng, horseradish, low/high bush blueberry, lettuce, bok choy, tomato, pepper, tobacco, commercial woodland, broccoli, Brussels sprouts, cabbage, cauliflower, Chinese broccoli, Chinese cabbage, conifer/tobacco seedlings, ornamentals, greenhouse tomato, greenhouse cucumber, fence rows, sunflowers, mushroom houses	all activities	12 hours
Grape	girdling, turning	15 days
	tying/training, hand harvesting, leaf pulling by hand	2 days
	all other activities	12 hours
corn, sweet corn	hand detasseling, hand harvest	8 days
	all other activities	12 hours

REI = restricted-entry intervals

^a Day at which the dermal exposure results in an MOE \geq 300. If the REI for hand harvesting and the PHI are different, follow the longer of the two intervals for both the REI and PHI. If the crop is harvested mechanically, with no contact with the treated foliage or crop, follow the PHI.

15. For all product labels, replace the entire “ENVIRONMENTAL HAZARDS” section with the following:

“ENVIRONMENTAL PRECAUTIONS”

“Toxic to aquatic organisms. Observe buffer zones specified under **DIRECTIONS FOR USE.**”

“Toxic to birds.”

“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, pears, nectarines, peaches, plums, canola, sunflowers) or when using managed bees for pollination services:

“Do not apply during the crop blooming period.”

For applications on all other crops:

“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.”

“Toxic to certain beneficial insects. Minimize spray drift to reduce harmful effects on beneficial insects in habitats next to the application site such as hedgerows and woodland. Permethrin may impact predatory and parasitic arthropod species used in IPM programs within the treatment area. Unsprayed refugia for beneficial species of at least 1 metre from treatment area will help maintain beneficial arthropod populations.”

“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.”

“To reduce risk to aquatic organisms from run-off, a vegetative filter strip of at least 10 metres wide between the field edge and adjacent, downhill aquatic habitats must be observed, as specified under **DIRECTIONS FOR USE**.”

For Greenhouse uses:

“Greenhouse use: Toxic to bees and other beneficial insects. May harm bees and other beneficial insects, including those used in greenhouse production. Do not apply when bees or other beneficial insects are foraging in the treatment area.”

16. The following statements are required under the “**DIRECTIONS FOR USE**” Section on all commercial-class product labels:

“To protect pollinators, follow the instructions regarding bees in the ENVIRONMENTAL PRECAUTIONS section.”

“For **apples, pears, nectarines, peaches, plums, canola, sunflowers** include:

- **Toxic to bees. DO NOT** apply during the crop blooming period.”

“For all other crops on label (excluding barley, oats, rye, wheat, triticale):

- 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.”

“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 runoff from greenhouses containing this product to enter lakes, streams, ponds or other waters.”

Replace the entire Buffer zone section starting at “Field Sprayer Application: DO NOT...” with the following:

“Vegetative Filter Strips”

“A Vegetative Filter Strip (VFS) of at least 10 metres wide must be observed. The VFS is required between the field edge and adjacent, downhill aquatic habitats to reduce risk to aquatic organisms from run-off. Aquatic habitats include, but are not limited to, lakes, reservoirs, rivers, permanent streams, marshes or natural ponds, estuaries, and commercial fish farm ponds.”

“The VFS is to be composed of grasses and may also include shrubs, trees, or other vegetation. The VFS must be maintained. Additional guidance can be found on the PMRA Environmental Risk Mitigation webpages. “

“Both VFS and spray drift buffer zones must be observed.”

“Spray Drift Buffer Zones”

“Spray drift buffer zones are to protect terrestrial and aquatic habitats from spray drift. Spray drift buffer zones are a separate requirement from VFS which are required to mitigate risks from run-off.”

“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.”

“Aerial 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 flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium-coarse classification. **DO NOT** apply under weather conditions of less than 50% relative humidity and temperatures greater than 20°C. Reduce drift caused by turbulent wingtip vortices. Nozzle distribution along the spray boom length **MUST NOT** exceed 65% of

the wing- or rotorspan.”

“Buffer zones:

Use of the following spray methods or equipment **DO NOT** require a buffer zone: hand-held or backpack sprayer and spot treatment.

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.

Application method	Crop		Buffer Zones (metres) Required for the Protection of:			
			Freshwater Habitat of Depths:		Estuarine/Marine Habitat of Depths:	
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
Field sprayer	Blueberry		5	3	15	5
	Canola, asparagus, barley, beet, field corn, flax, lettuce, oat, onion, pea, rye, sunflower, triticale, wheat, lentil		10	5	25	10
	Chinese broccoli, wasabi, horseradish, bok choy, peanut, radish, turnip		15	5	15	5
	Snap bean		15	5	20	10
	Ginseng, carrot, tobacco		20	10	25	10
	Broccoli, Brussel sprout, cabbage, cauliflower, pepper, potato, sweet corn		35	15	25	10
	Tomato		45	20	25	10
Airblast	Blueberry	Early growth stage	60	55	70	60
		Late growth stage	50	45	60	50
	Apple	Early growth stage	75	65	80	70
		Late growth stage	60	55	70	60
	Grape, nectarine, peach	Early growth stage	80	70	80	70
		Late growth stage	70	60	70	60
	Plum	Early growth stage	80	70	80	75
		Late growth stage	70	60	70	60
Pear	Early growth stage	80	70	90	80	
	Late growth stage	70	60	80	70	
Aerial	Broccoli, Cauliflower, cabbage, asparagus, barley, beets, carrots, field corn, flax, lettuce, oats, onions, peas, potato, rye, sunflower, triticale, wheat, Brussels sprouts, peppers, canola, legume vegetables: lentils	Fixed wing	800	800	800	800
		Rotary wing	700	475	800	675
	Sweet corn	Fixed wing	800	800	800	800
		Rotary wing	800	650	800	700
	Snap beans	Fixed wing	800	800	800	800
		Rotary wing	800	650	800	750

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 field sprayer or aerial application CANNOT be modified using the Buffer Zone Calculator.”

The following statements are required for greenhouse use:

Toxic to bees and other beneficial insects. May harm bees and other beneficial insects including those used in greenhouse production. Do not apply when bees or other beneficial insects are foraging in the treatment area.

IV. Domestic Class Products

1. The following statements must be added to the labels, under “**DIRECTIONS FOR USE**”:

“DO NOT apply indoors as a broadcast application. ONLY perimeter, spot or crack and crevice applications are permitted indoors in residential areas. Indoor perimeter application is less than 0.3 m wide along the edges of a room to baseboards, wall-floor and ceiling-wall joints, and around doorways or windows. Spot application is localized to a surface area not more than 0.2 m². Spots are not to be adjoining. The combined area of spots is not to exceed 10% of the total surface area of a room. Crack and crevice is an application directly into narrow openings on the surface of the structure. It does not include the treatment of exposed surfaces. Narrow openings typically occur at expansion joints, utility entry points and along baseboards and mouldings.”

“DO NOT apply to furniture, mattresses, linens, toys or clothing.” Any references to treating these objects must be deleted from the label.

“DO NOT apply to overhead areas or in confined spaces (for example, attics, crawlspaces, small storage rooms, closets).”

“Ventilate treated areas after application by opening windows and doors, or using fans where required to aid in the circulation of air.”

“DO NOT apply when people or pets [or livestock] are present.”

“DO NOT allow people or pets [or livestock] to enter treated areas until sprays have dried.” (except for space spray products, use below number 3).

“DO NOT allow spray to drip or allow drift onto non-target surfaces.”

2. The following statements must be added to the labels that are not registered as a space spray application, under “**DIRECTIONS FOR USE**”:

“DO NOT apply as a space spray.”

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3. The following statements must be added to space spray product labels, under **“DIRECTIONS FOR USE”**:
- “DO NOT allow people or pets [or livestock] to enter treated areas until 15 minutes after a space spray application.”
- “DO NOT remain in treated areas after a space spray application.”
4. The following statement must be added to pet product labels, under **“PRECAUTIONS”**:
- “Avoid contact with treated animals until dried.”
5. The maximum application rate for residential yards is 0.123 g a.i./m².
6. The following statements are to be added to the **“ENVIRONMENTAL PRECAUTIONS”** section;
- “Toxic to aquatic organisms.”
- “Toxic to birds.”
- “Toxic to bees.”
- “Toxic to beneficial insects.”
- “To minimize possible contamination of groundwater, the use of spot treatment applications is recommended in areas where soils are permeable (e.g., sandy soil) and/or the depth to the water table is shallow.”
- “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.”
7. The following statements are required under the **“DIRECTIONS FOR USE”**
- “DO NOT apply to any body of water.”
- “DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.”
- “Avoid application of this product when winds are gusty.”

Revised Label Amendments for End-Use Products Containing Permethrin

Label improvements will be specified for products of all uses including structural use (as per PRO2018-04, *Structural Pest Control Products: Label Updates*) and use on companion animals (as per PRO2018-01, *Consultation on Proposed Regulatory Changes to Pesticide Products on Companion Animals*). These label improvements will be communicated to the respective registrants to provide instructions on how to clarify their product labels. A summary of the label improvements is found below.

Label amendments must be made to improve the clarity of the label instructions. This includes but is not limited to:

- Remove any instructions and/or references from the label for all uses being cancelled, and update the directions for use instructions for any uses with mitigation requirements, as outlined in this re-evaluation decision.
- Pest claims must be specific, accurate and consistently described throughout the label. As such, any vague statements must be deleted or amended to be clear on the specific pest claim. Replace the following vague references: “gnats”, “flies” (repellent claims only), “biting flies/midges” (repellent claims only), “crawling/flying/wood-infesting/nuisance/stored/household product/garden/edible plant insects/pests” and “insects such as...” with a specific list of pests. General terms may be used in a statement that clearly identifies specific pests. For example: “For control of the following insect pests: *Specific pests listed*”.
- The level of control (for example, kills versus controls) must be consistent throughout a label.
- Locations of use must clearly be identified on a label and reflect the registered use site category. Vague statements must be deleted or amended. This includes but is not limited to: “structures”, “hiding places such as...”, “other places where insects may alight, congregate, hide or are seen”, and “moist areas”. General terms may be used in a statement that clearly identifies specific locations. For example: “For use indoors on the following structures: *Specific structures listed*”.
- The primary display panel and general information section must reflect all of the uses stated in the DIRECTIONS FOR USE. Update these two sections of the label if they are incomplete.
- Headers within the DIRECTIONS FOR USE section of the label must be revised to clearly reflect where the product can be applied, rather than identify the pests. For example, “Indoor Plant Pests” must be amended to “For Use on Indoor Ornamental Plants (to control *list pests*)”.
- Use directions must be clear for each site/pest combination and contain all information regarding the use of the product (for example, pest claims, location of use, product application rates, timing and frequency of application and any limitations on its use). For example,

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- For products with multiple uses, use directions must clearly indicate which instructions belong to each use with similar uses being grouped together (e.g., indoor structural uses, outdoor structural uses and crop uses).
 - For concentrate products, all information regarding the use of the product must be placed in a table with headers. Note: Tables are encouraged but not required for Ready-to-Use products because of the limited spacing on most labels.
 - For concentrate products that must be diluted before use, add the following statement in the DIRECTIONS FOR USE: **DO NOT** apply undiluted.
 - For products with a specific re-treatment interval, vague statements indicating “reapply as necessary” or equivalent must be deleted from the label or replaced with the re-treatment interval statement followed by “Treatment must only be repeated if pest problem persist or reoccurs.”
 - For products with both Commercial and Restricted Uses on the label, instructions for all Restricted Uses must be located together after the Commercial uses and be surrounded by a text box. For further information, please refer to the PMRA publication [Checklist of Labelling Requirements for Pest Control Products](#).
 - As per section 3.10 of regulatory directive DIR2016-02, *Notifications/Non-notifications*, remove any vague or non-specific claims that the product can be tank mixed with another pesticide (fungicide, insecticide or herbicide).
 - Labels are to state the product rates. Any label changes that are required to convert active ingredient rates to product rates must be made by the registrants, and must factor in any formulation-specific calculations, such as specific gravity
 - Additional amendments to specific labels may be provided directly to registrants.

RESISTANCE MANAGEMENT RECOMMENDATIONS:

The following applies to Commercial and Restricted Class Products only:

- The Resistant Management Recommendations must have their own section and ensure that the statements located within this section are up to date with Regulatory Directive *DIR2013-04, Pesticide Resistance Management Labelling Based on Target Site/Mode of Action*. For non-plant protection products, it is acceptable to change the plant protection terminology (for example, field) to terminology reflective of the use (for example, location).

PRODUCTS FOR USE ON ANIMALS:

Products for use on cats and dogs:

- With the exception of spot-on products which are being examined separately under PRO2018-01, *Consultation on Proposed Regulatory Changes for Pesticide Products Used on Companion Animals*, labels of products used on cats and dogs must reflect the label requirements outlined in Regulatory Directive *DIR2002-01: Canadian Label Improvement Program for Pesticides Used on Companion Animals*.
- On the primary panel, add:
 - i. **DO NOT USE ON (TYPE OF ANIMAL; E.G., PUPPIES OR KITTENS) LESS THAN (add age) WEEKS OLD.**
 - ii. When products cannot be applied to animals of a certain weight range, add: “**DO NOT USE ON TYPE (TYPE OF ANIMAL; E.G., PUPPIES OR KITTENS) WEIGHING (add weight range) KG.**”
 - iii. If the product is only registered for use on dogs, add: “**DO NOT USE ON CATS, KITTENS OR ANY OTHER ANIMAL**”
 - iv. If the product is registered for use on dogs and cats, add “**DO NOT USE ON ANY OTHER ANIMAL**”
- In the **DIRECTIONS FOR USE** Section:
 - i. The following statements must appear immediately after the **DIRECTIONS FOR USE** header: “For use only on dogs or puppies over (add age) weeks old and weighing (add weight range) kg. **DO NOT** use on puppies under (add age) weeks of age. **DO NOT** use on dogs or puppies weighing less than (add weight) kg. Consult a veterinarian before using on sick, aged, pregnant or nursing animals or animals receiving drug or other pesticide treatment. This product contains permethrin. **DO NOT** apply another pest control product such as a spot on, collar or powder which contains permethrin to the treated animal when using [name of product].”
 - ii. Delete: “If pest problems persist, an insecticidal premise treatment may be required.” And replace with: “If pest problems persist, a premise treatment with an insecticide labelled for that use may be required.”

Products for use on animals other than cats and dogs (for example, horses, cattle, sheep, poultry):

- In the **DIRECTIONS FOR USE** section, add any specific information on the type (e.g., breed or use such as show, race, work, pleasure, slaughter) or age (e.g., not for use on newborn or nursing foals) of animal that can be treated with the product, and any precautions (e.g., **DO NOT** use on sick animals or animals under drug or pesticide treatment) must appear before the instructions on how to apply the product. This information must also be added to the primary display panel of the label.
- When the product is applied by two different methods (e.g., wipe on and spray), the instructions for the two methods must be clearly separated.

- For all cattle eartag products:
 - i. At the beginning of the DIRECTIONS FOR USE section, add: Controls Horn Flies and Face Flies on Beef and Dairy Cattle (Lactating and Non-Lactating).
 - ii. For GardStar Insecticide Ear Tags (Reg. No. 18686), move Steps 1 to 3 on page 1 into the DIRECTIONS FOR USE.

Registered Commercial and/or Domestic Class Products registered for use on animals:

From the table below, ensure that only the animal(s) for which permethrin is registered for use on is included in your particular product label. Retain product application rate ranges. Registrants are responsible for converting the active ingredient rate to product rate, based on individual product considerations such as specific gravity.

Sites	Formulation type ¹	Minimum and Maximum Application rate (g a.i./ha)	Maximum Cumulative Application rate (g a.i./ha)	Maximum Number of Applications Per Year
Cattle – beef to target Rocky mountain tick	EC	1.5 g a.i./animal	3 g a.i./animal/year	2
Cattle – beef and dairy (non-lactating)	EC	0.12 to 0.96 g a.i./animal	1.92 g a.i./animal/year	2
Cattle – beef and dairy (lactating and non-lactating)	EC, SN	0.125 g a.i./animal per day	Self-treatment oilers available for fly season. Treatment must only be repeated if pest problem persist or reoccurs.	
Cattle – dairy (lactating and non-lactating)	PP	0.045 g a.i./animal/application ²	Treatment must only be repeated if pest problem persist or reoccurs.	
Cattle – beef and dairy (lactating and non-lactating)	SN	cloth or pour-on: 1.17 to 1.3 g a.i./animal	2.6 g a.i./animal/year	2
Cattle – beef and dairy (lactating and non-lactating)	SR	Ear tag: 0.95 to 1.9 g a.i./animal	1.9 g a.i./animal/year	1
Poultry	EC	0.0192 g a.i./animal	0.0384 g a.i./animal/year	2
Sheep	EC	0.144 g a.i./animal	0.144 g a.i./animal/year	1
	PP	0.045 g a.i./animal/application ²	Treatment must only be repeated if pest problem persist or reoccurs.	

Sites	Formulation type ¹	Minimum and Maximum Application rate (g a.i./ha)	Maximum Cumulative Application rate (g a.i./ha)	Maximum Number of Applications Per Year
Horses	PP	0.045 g a.i./animal/application ²	Treatment must only be repeated if pest problem persist or reoccurs.	
Horses	SN	0.0398	Treatment must only be repeated if pest problem persist or reoccurs. DO NOT use on horses intended for slaughter.	

¹EC = Emulsifiable Concentrate or Emulsion, PP = Pressurized Product, SN = Solution, SR = slow release

²Application rate stated on labels is 3 seconds of spray per side of animal. Using USEPA SOP for Residential Pesticide Exposure Assessment rate of 1.5 g of product released per second the calculated rate of active ingredient per application is 0.045 g a.i.

PLANT PROTECTION USES:

Indoor/Outdoor Ornamental Plant Uses on Labels of Domestic Class Products:

- In the DIRECTIONS FOR USE section, add or replace “Do not use on fruits or vegetables” with: “**DO NOT** apply to plants grown for food or feed (e.g., fruits, vegetables, herbs).”

Commercial and domestic products used on plants:

Ensure that only the registered crop/site from the table below is included in your particular product label. Retain product application rate ranges but do not exceed maximum application rates as indicated in table below. For domestic product labels, do not convert product rate to active ingredient rate but include maximum number of applications per year.

On all labels replace the site cereals with barley, oats, rye, triticale and wheat. Replace the site cole crops with broccoli, Brussels sprouts, cabbage and cauliflower.

Sites	Maximum Application rate (g a.i./ha)	Maximum Cumulative Application rate per year (g a.i./ha)	Maximum Number of Applications Per Year; re-treatment interval (RTI) and pre-harvest interval (PHI)
Commercial woodland: conifers	70	70	1
Commercial woodland: deciduous plants	70	70	1
Greenhouse cucumber	100	600	6; 10 days (RTI); 1 day (PHI)
Greenhouse tobacco	124	124	1

Sites	Maximum Application rate (g a.i./ha)	Maximum Cumulative Application rate per year (g a.i./ha)	Maximum Number of Applications Per Year; re-treatment interval (RTI) and pre-harvest interval (PHI)
Greenhouse tomatoes	150	900	6; 10 days (RTI); 1 day (PHI)
Mushroom houses	0.033 g a.i./m ³	2.08 g a.i./m ³	Maximum of 20 applications per crop cycle (including breaks). DO NOT APPLY more than 63 applications in a year. 1 day (RTI); 1 day PHI
Forestry nursery greenhouses: conifer seedlings	25	50	2; 21 days (RTI)
Greenhouse ornamentals	100	600	6; 7 days (RTI)
Apples	Drench application: 168 Foliar application: 200	536	3(2 drench and 1 foliar application are allowed per year); 14 days (RTI); 7 days (PHI)
Asparagus	150	150	2 (only 1 aerial application is allowed per year); 7 days (RTI); 2 days (PHI)
Barley, oats, rye, triticale and wheat	150	150	2 (only 1 aerial application is allowed per year); 7 days (RTI); 7 days (PHI)
Canola, rape	150	150	2 (only 1 aerial application is allowed per year); 7 days (RTI). Do NOT make any applications after the 5 leaf stage.
Carrots	150	300	2 (only 1 aerial application is allowed per year); 14 days (RTI); 2 days (PHI)
Corn (excluding sweet corn)	150	150	2 (only 1 aerial application is allowed per year); 7 days (RTI); 30 days (PHI)

Sites	Maximum Application rate (g a.i./ha)	Maximum Cumulative Application rate per year (g a.i./ha)	Maximum Number of Applications Per Year; re-treatment interval (RTI) and pre-harvest interval (PHI)
Beets (garden)	150	150	2 (only 1 aerial application is allowed per year); 7 days (RTI); 2 days (PHI)
Blueberries, vegetative year only	70	70	1 (PHI is not applicable)
Broccoli	150	300	4 (only 1 aerial application is allowed per year); 7 days (RTI); 7 days (PHI)
Brussels sprouts, cabbage, cauliflower	150	300	4 (only 1 aerial application is allowed per year); 7 days (RTI); 3 days (PHI)
Chinese broccoli	70	280	4; 7 days (RTI); 7 days (PHI)
Chinese cabbage	70	280	4; 7 days (RTI); 3 days (PHI)
Flax, sunflowers	150	150	2 (only 1 aerial application is allowed per year); 7 days (RTI). Do NOT make any applications after the 5 leaf stage.
Ginseng	150	300	2; 14 days (RTI); 40 days (PHI)
Grapes	138.2	553	4; 7 days (RTI); 7 to 21 days (PHI) based on PHI which is already on the label.
Horseradish, radish	70	280	4; 7 days (RTI); 2 days (PHI)
Lentils	150	150	2 (only 1 aerial application is allowed per year); 7 days (RTI); 7 days (PHI)
Lettuce	150	150	2 (only 1 aerial application is allowed per year); 7 days (RTI); 1 day (PHI)
Nectarines, peaches	200	400	2; 14 days (RTI); 7 days (PHI)

Sites	Maximum Application rate (g a.i./ha)	Maximum Cumulative Application rate per year (g a.i./ha)	Maximum Number of Applications Per Year; re-treatment interval (RTI) and pre-harvest interval (PHI)
Onions (dry bulb and green)	150	150	2 (only 1 aerial application is allowed per year); 7 days (RTI); 1 day (PHI)
Bok choy	70	280	4; 7 days (RTI); 3 days (PHI)
Peanuts	70	280	4; 7 days (RTI); 14 days (PHI)
Peas (succulent, dry)	150	150	2 (only 1 aerial application is allowed per year); 7 days (RTI); 7 days (PHI)
Pears	425	425	2; 7 days (RTI); 7 days PHI for application rates of 200 g a.i./ha; and 14 days PHI for application rates greater than 200 g a.i./ha.
Plums	212.5	425	2; 14 days (RTI); 7 days (PHI)
Peppers	150	300	4; 7 days (RTI); 1 day (PHI)
Potatoes	150	600	4 (only 1 aerial application is allowed per year); 7 days (RTI); 1 day (PHI)
Snap beans (succulent, podded)	100	300	3; 10 days (RTI); 7 day (PHI)
Sugar beets	150	150	2 (only 1 aerial application is allowed per year); 7 days (RTI); 2 days (PHI)
Sweet corn	144	576	4 (only 1 aerial application is allowed per year); 3 days (RTI); 1 day (PHI)
Tobacco	140	140	2; 7 days (RTI); 55 days (PHI)
Tomatoes	140	700	5; 7 days (RTI); 1 day (PHI)

Sites	Maximum Application rate (g a.i./ha)	Maximum Cumulative Application rate per year (g a.i./ha)	Maximum Number of Applications Per Year; re-treatment interval (RTI) and pre-harvest interval (PHI)
Turnip	70	210	3; 7 days (RTI); 1 day (PHI)
Wasabi	70	280	4; 7 days (RTI); 7 days (PHI)

MUSHROOM HOUSES:

- Amend the directions for mushroom houses as follows:

MUSHROOM HOUSES:

For the control of sciarid and phorid adults in mushroom houses.

- DO NOT APPLY** more than two applications between each break.
- DO NOT APPLY** more than once daily.
- Maximum of 20 applications per crop cycle (including breaks). **DO NOT APPLY** more than 63 applications in a year.
- DO NOT APPLY** within 1 day of manual or mechanical harvesting (1 day PHI).
- DO NOT USE** when air temperature is less than 12° C or greater than 30° C as this could reduce the effectiveness of (insert name of product).
- For manual mushroom harvesting (hand picking) operations:** Use (insert name of product) prior to filling, during cool down, during spawning, up to pinning and during post-production operations (between crop cycles). Make applications when there are no mushrooms above the substrate surface. The application must be such that the mushrooms will not be contacted with product during the application. If an application is required anytime when mushrooms are above the substrate surface the crop must be covered prior to application with an impermeable material to avoid direct contact to the mushrooms, for example between breaks. These restrictions are to minimize worker exposure.
- For mechanical mushroom harvesting operations:** Use (insert name of product) prior to filling, during cool down, during spawning, up to pinning, between breaks and during post-production operations (between crop cycles). **DO NOT** allow manual harvesting of mushrooms.

Prepare the building and apply following these steps:

- Close all doors, windows and ventilators.
- Lock or barricade all entrances, turn off pilot lights, post warning signs and take precautions to prevent persons and animals from entering the area.
- Apply a fogging or aerosol treatment at the rate of (*insert product rate*) per 1 L of water per 1000 m³.
- Length of exposure time should be limited to one hour, and then fully ventilate the mushroom house with forced air circulation or the aid of exhaust fans to minimize surface deposits.

Routine procedures for reducing fly populations need to be carefully followed to ensure adequate adult fly control in the mushroom crop and to reduce the necessity for pesticide applications. Consult provincial mushroom specialist for details of integrated Pest Management programs to be followed for sciarid and phorid fly control in mushroom houses.

STRUCTURAL AND GENERAL OUTDOOR USES:

- Labels with structural uses must be amended to adopt the revised definitions for application types outlined in the PMRA publication Regulatory Proposal *PRO2018-04, Structural Pest Control Products: Label Updates* or the most up to date version of this document. The types of application methods permitted should appear in the DIRECTIONS FOR USE section under the header “How to Apply”. The following methods of surface applications are permitted for permethrin products:

Product class	Location of Use	Surface Application Type Permitted	Label statements Required
Domestic	Indoor surface spray	Indoor Perimeter Spot Void	DO NOT apply indoors as a broadcast spray. For products only applied as a surface spray, add: DO NOT apply as a space spray.
	Outdoor surface spray	Crack and Crevice Outdoor Structural Broadcast Outdoor Perimeter Spot	
Commercial/ Restricted	Indoor surface spray (Residential areas)	Crack and Crevice Indoor Perimeter Spot Void	DO NOT apply indoors in residential areas* as a broadcast application.
	Indoor surface spray (Non-residential areas)	Crack and Crevice Indoor Broadcast Indoor Perimeter Spot Void	*Residential areas are defined as any use site where the general public, including children, could be exposed during or after application. For structural uses, in residential sites, this includes homes, schools, restaurants, public buildings, modes of transport in areas where passengers are present, or any other areas where the general public including children may potentially

Product class	Location of Use	Surface Application Type Permitted	Label statements Required
			be exposed.” <i>For products only applied as a surface spray, add: DO NOT apply as a space spray.</i>
	Outdoor surface spray (Residential and Non-residential)	Crack and Crevice Outdoor Structural Broadcast Outdoor Perimeter Spot	

- The use directions for indoor and outdoor uses must be separated out and clearly describe where the product can be applied on both the primary display panel and in the DIRECTIONS FOR USE section.

Location	Primary Panel Statement and Header in the DIRECTIONS FOR USE
Indoor uses at buildings or structures*	FOR INDOOR USE ONLY AT (LISTED) BUILDINGS/STRUCTURES*
Outdoors on the exterior surfaces of buildings**	LIMITED OUTDOOR USE ON THE EXTERIOR SURFACES OF (LISTED) BUILDINGS
Outdoors on the exterior surfaces of structures (for example, buildings, porches, patios, etc.)	FOR OUTDOOR USE ON THE EXTERIOR SURFACES OF LISTED STRUCTURES*
General outdoor uses (for example, ant nests, wasp nests, mosquito control)	FOR LISTED OUTDOOR USES or a specific use such as FOR MOSQUITO CONTROL OUTDOORS AROUND BUILDINGS

*Specific structures (for example, transportation vehicles, garbage cans) must be identified on the label.

** Under Restrictions in the DIRECTIONS FOR USE section of the label, the following statements must be added: “**DO NOT** treat soil, turf or other plants adjacent to the building. **DO NOT** treat patios, porches, decks, gazebos or play structures. This product is only for use on the exterior surfaces of buildings.”

- The DIRECTIONS FOR USE section must be organized with general instructions coming first followed by more pest specific instructions. Examples of acceptable formatting include:

Concentrate product:	Ready-To-Use:
General information that applies to all uses (for example, non-safety adverse effects, shake well before using)	
How to apply (See definitions under Regulatory Proposal PRO2018-04, Structural Pest Control Products: Label Updates or the most up to date version of this document)	
Use locations (for example, buildings, transport vehicles)	

When to apply (for example, Treat when pests are found.)	
Mixing Instructions	List of pests
<p>Tables for indoor use and limited outdoor use on the exterior surfaces of structures.</p> <p>Tables should be structured manner that:</p> <ul style="list-style-type: none"> -indicates the use (for example, limited outdoor use on exterior surfaces of listed structures); -Restrictions specific to that use (forexample, maximum rate on the exterior surfaces of restricted structures) -Specific instructions by pest including the dilution to use. 	Pest specific instructions

- Amend the phrase “Stored Product Insects and hibernating stages of Indian Meal Moth and Cluster Flies” to “Indian Meal Moth and Hibernating Cluster Flies”.
- For termites, all instructions must be located in the RESTRICTED USE section of the label.
- Commercial class products must have the following statements:

Product permits use in food/feed areas:	Products not permitted for use in food/feed areas:
<p>Instructions/Precautions for all locations: DO NOT contaminate food/feed. DO NOT spray food/feed or food/feed packages. Remove or cover all food/feed. Remove or cover all food/feed processing surfaces, equipment and utensils or thoroughly wash them following treatment.</p> <p>Additional Limitations Specific to Food/Feed Handling Establishments*: DO NOT apply when a food/feed processing is in operation</p> <p>*A food/feed handling establishment is a place other than private residences in which food/feed is held, processed, prepared and/or served. Non-food/feed areas of food/feed handling establishments includes garbage rooms, lavatories, floor drains to sewers, entries and vestibules, offices, locker rooms, machine rooms, boiler rooms, garages, mop closets, and storage for canned, bottled or packaged products.</p>	<p>Instructions/Precautions for all locations: For use only in non-food/non-feed areas*. DO NOT contaminate food/feed. DO NOT apply to surfaces that may come into contact with food/feed.</p> <p>*Non-food/feed areas includes garbage rooms, lavatories, floor drains to sewers, entries and vestibules, offices, locker rooms, machine rooms, garages, mop closets, and storage.</p>

<p>Food/feed areas of food/feed handling establishments includes areas of receiving; serving; storing of dry, cold, frozen or raw foods/feed; packaging such as canning, bottling, wrapping and boxing; preparing such as cleaning, slicing, cooking and grinding; storing edible waste and enclosed processing systems such as mills, dairies, edible oils and syrups.</p>	
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- For Domestic class products, the followings statements must be present on the label: “**DO NOT** contaminate food/feed. **DO NOT** apply to surfaces that may come into contact with food/feed.”
- For Commercial class products used in livestock housing, ensure that only the registered sites are included in your particular product label. Retain the product rates on the labels. Registrants are responsible for converting the active ingredient rate to product rate, based on individual product considerations such as specific gravity. Update the DIRECTIONS FOR USE instructions for any uses with mitigation requirements, as outlined in this re-evaluation decision.
- For Commercial class products used in outdoor feedlots, ensure that only the registered sites are included in your particular product label. Retain the product rates on the labels. Maximum of 960 g a.i./ha with one application.
- For Domestic class products used in livestock housing, ensure that only the registered sites are included in your particular product label. Retain the product rates on the labels. Update the labels with a maximum of 12 applications per year. Re-treatment interval 14 days.
- For Commercial and Domestic class products used on residential yards, retain the product rates on the labels. Maximum of 0.123 g a.i./ha.

Appendix IV Additional Published Toxicology Studies for Permethrin

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in absolute weight and relative (to bodyweight) weight unless otherwise noted.

Study Type/Species/Strain/P MRA#	Doses/Purity	Study Results
Special Studies (non-guideline, all considered supplemental for risk assessment purposes)		
Glucose metabolism following permethrin exposure with low- and high-fat diets Mice, C57BL/6J (♂) PMRA# 2878511	Low-fat diet (4 w/w % fat): 0, 0.06, 0.59 or 6.18 mg/kg bw/day permethrin in the diet for 12 wks High-fat diet (20 w/w % fat): 0, 0.07, 0.61 or 6.42 mg/kg bw/day permethrin in the diet for 12 wks Appeared to range from 3-8 ♂/group 40:60 cis:trans isomer ratio 98% Purity	Permethrin appeared potentiated high-fat diet-induced insulin resistance; insulin signalling was potentially impaired via the Akt signalling pathway; permethrin potentially targeted AMPK, fatty acid oxidation and energy expenditure
Glucose metabolism following permethrin exposure with low- and high-fat diets Mice, C57BL/6J (♀) PMRA# 2878512	Low-fat diet (4 w/w % fat): 0, 0.03, 0.33 or 3.39 mg/kg bw/day permethrin in the diet for 12 wks High-fat diet (20 w/w % fat): 0, 0.03, 0.37 or 3.49 mg/kg bw/day permethrin in the diet for 12 wks Appeared to range from 4-6 ♀/group 40:60 cis:trans isomer ratio 98% Purity	Permethrin appeared potentiated high-fat diet-induced insulin resistance; insulin signalling was potentially impaired via the Akt signalling pathway
Hepatotoxicity following oral (gavage) exposure to permethrin Rats, Wistar (♂)	0, 12, 30 or 75 mg/kg bw/day permethrin (in corn oil) by gavage for 90 days 5 ♂/group	No treatment-related effect on liver brain, heart, spleen, kidney, testes or adrenal wts, clinical chemistry, histopathology of the liver or antioxidant enzyme levels.

Study Type/Species/Strain/P MRA#	Doses/Purity	Study Results
PMRA# 2878515	Cis:trans isomer ratio N/S >95% Purity	<p>≥12 mg/kg bw/day: ↑ lipid peroxidation in liver (↑ TBARS level, poor dose-response);</p> <p>≥30 mg/kg bw/day: ↓ bw;</p> <p>75 mg/kg bw/day: ↑ incidence of tremors.</p>
<p>Reproductive toxicity following oral (gavage) exposure to permethrin and the effect of naringenin</p> <p>Rats, albino (♂)</p> <p>PMRA# 2878517</p>	<p>0 or 70 mg/kg bw/day permethrin (in corn oil) by gavage for 6 wks; one group was given a 3 wks recovery period, one group was co-administered 50 mg/kg bw/day naringenin (a naturally occurring flavanone)</p> <p>6 ♂/group</p> <p>25:75 cis:trans isomer ratio</p> <p>93% Purity</p>	<p>70 mg/kg bw/day: ↓ testicular wt, ↓ epididymal sperm count and ↓ serum testosterone levels, markedly distorted/shrunken seminiferous tubules with irregular and thickened basement membrane, homogenous material in the lumen, ↓ spermatozoa, ↓ number of layers of germinal epithelium, apoptotic, sloughed or vacuolated germinal epithelial spermatogenic cells, interstitium filled with acidophilic hyaline material, ↑ intercellular spaces between germinal epithelial cells, irregular nuclei and prominent nucleoli of Sertoli cells, ultrastructural damage, ↓ epithelial height of seminiferous tubules, ↓ area percentage of positive c-Kit immunoreactions in cytoplasm of germinal epithelial cells.</p> <p>70 mg/kg bw/day + recovery: partial recovery of effects.</p> <p>70 mg/kg bw/day + 50 mg/kg bw/day naringenin: testicular effects ameliorated by co-administration of naringenin.</p> <p>Note: number of animals with specified lesions not provided</p>
Reproductive toxicity following oral (gavage) exposure to permethrin	0, 20 or 40 mg/kg bw/day permethrin (in saline) by gavage for 14 days. After the last dose, ovarian tissue	≥20 mg/kg bw/day: ↑ immunoreactivity of caspase-3 reactivity in atretic follicles (moderate), loss of cellular contacts

Study Type/Species/Strain/PMRA#	Doses/Purity	Study Results
<p>Rats, Wistar (♀)</p> <p>PMRA# 2878518</p>	<p>was collected and examined.</p> <p>8 ♀/group</p> <p>25:75 cis:trans isomer ratio</p> <p>Purity N/S</p>	<p>and ↑ formation of pyknotic cells in granulosa cell layer of follicles, vacuolization, dispersed cytoplasm and degenerated cellular contacts in the luteal cell layer of the corpus luteum, disrupted cytoplasm and mitochondrial degeneration in Graaf follicle cells, ↑ degeneration in the corpus luteum;</p> <p>40 mg/kg bw/day: ↑ immunoreactivity of caspase-3 in the atretic and growing follicles (intense), irregular shape of nuclear membranes of Graaf follicles, degeneration and swollen mitochondria, excessive dilated SER tubules, intense clusters of large lipid droplets and vacuolar spaces detected in the cytoplasm of corpus luteum cells.</p> <p>Note: number of animals with specified lesions not provided</p>
<p>In vitro modulation of estrogen receptor</p> <p>MCF-7 CLONE B17 and SK-N-BE human cell lines</p> <p>PMRA# 2878520</p> <p>(in vivo data reported in separate entry)</p>	<p>Permethrin ranging from 1 nM to 10 μM was added alone or with 1 nM 17β-estradiol to cell cultures for 24 hrs.</p> <p>25:75 cis:trans isomer ratio</p> <p>94% Purity</p>	<p>MCF-7 Clone B17 cells: Permethrin: no effect on ERα activity. Permethrin + 17β estradiol: permethrin antagonized the effect of 17β estradiol on ERα.</p> <p>SK-N-BE Cells: Permethrin: ↓ ERα activity (not dose-related) and no effect on ERβ activity. Permethrin + 17β estradiol: permethrin antagonized the effect of ERα and ERβ.</p>
<p>Comparison of ASR, and brain and plasma concentrations of permethrin in adult (♂) and PND 15 rats (♂ and ♀) following oral (gavage) exposure to</p>	<p>Animals (15 ♂ adults/group or 16 pups/sex/dose [only 1/sex/litter/dose]) were administered 5 ml/kg corn oil by gavage and tested in 100 ASR trials 2 hrs post-dosing. The animals were</p>	<p>Experiment 1: Adults: 60 mg/kg bw: ↑ ASR (6 hrs); ≥90 mg/kg bw: ↑ incidence of salivation (2 ♂s 4 hrs), ↑ ASR (4, 6 and 8 hrs); 120 mg/kg bw: ↑ incidence of</p>

Study Type/Species/Strain/PMRA#	Doses/Purity	Study Results
<p>permethrin</p> <p>Rats, Sprague-Dawley</p> <p>PMRA# 2905889</p>	<p>then assigned to dose groups based on the average ASR and administered a single gavage dose of 0, 60, 90 or 120 mg/kg bw of permethrin. Animals were tested at 2, 4, 6 and 8 hrs post-dosing with 100 ASR trials per timepoint.</p> <p>In a separate experiment, a single gavage dose of 0, 60, 90 or 120 mg/kg bw of permethrin was administered to PND15 pups (8/sex/dose/timepoint from 32 different litters) or ♂ adults (8 ♂/dose/timepoint) and plasma and brain concentrations of cis- and trans-permethrin were determined at 2, 4, 6 or 8 hrs post-dosing.</p> <p>43:57 cis:trans isomer ratio</p> <p>>95% Purity</p>	<p>tremors (3 ♂s 6 and 8 hrs post-dosing) and salivation (1 ♂ 4 hrs post-dosing).</p> <p>PND 15 pups: ≥60 mg/kg bw: ↑ incidence of tremors (all rats, ↑ severity w/increasing doses, peak 6 hrs) and salivation, ↑ ASR (2, 4 and 6 hrs); 90 mg/kg bw: mortalities (1 ♂ and 1 ♀ 8 hrs), ↑ incidence of salivation, ↑ ASR (2 hrs); 120 mg/kg bw: mortalities (2 ♂s and 1 ♀ 6 hrs, 3 ♂s and 1 ♀ 8 hrs), ↑ incidence of salivation, ↑ ASR (2 hrs) and ↓ ASR (4, 6 and 8 hrs).</p> <p>Experiment 2: After the same dose of permethrin, PND 15 rats had greater concentrations of cis- and trans-permethrin in the brain and plasma compared with that noted in adults.</p>
<p>(Anti)-estrogenic activity in human and rat estrogen receptor α-mediated reporter gene assays</p> <p>Transiently transfected CV-1 cells</p> <p>PMRA# 2879066</p>	<p>CV-1 cells were transiently transfected with hERα or rERα during an incubation period of 12 hrs. The cells were then treated with permethrin or 3-PBA in 0.1% ethanol for 24 hrs at 10^{-8} to 10^{-4} M followed by the measurement of luciferase activity.</p> <p>Cis:trans isomer ratio N/S</p> <p>94% Purity</p>	<p>Permethrin showed weak estrogenic activity and no anti-estrogenic activity with hERα or rERα transfected cells. Maximum estrogenic potential of permethrin was achieved at a concentration of 10^{-4} M.</p> <p>3-PBA showed no estrogenic activity and weak anti-estrogenic activity with hERα or rERα transfected cells.</p>
<p>Dopaminergic system modulation, behavioral changes and oxidative</p>	<p>0 or 34 mg/kg bw/day permethrin (in corn oil) by gavage once daily from</p>	<p>No clinical signs of toxicity, effect on body weight or on plasma membrane fluidity of the striatum or</p>

Study Type/Species/Strain/PMRA#	Doses/Purity	Study Results
<p>stress following early life oral (gavage) exposure to permethrin</p> <p>Rats, Wistar</p> <p>PMRA# 2916596</p>	<p>PND 6 to 15. On PND 35, 10 ♂/group were weighed, sacrificed and the striatum was dissected out. Litters weighed at PNDs 1, 7, 14 and 21.</p> <p>Open-field studies (PNDs 21 and 35): 10 ♂s/group; Blood collection (PND 35): 4-6 ♂/group</p> <p>25:75 cis:trans isomer ratio</p> <p>94% Purity</p>	<p>erythrocytes was noted.</p> <p>PND 21: 34 mg/kg bw/day: no treatment-related alterations in behavioral activities (locomotion, rearing or grooming).</p> <p>PND 35: 34 mg/kg bw/day: ↑ in spontaneous locomotor activity, ↓ DA and ↑ HVA levels, ↓ GPx activity, ↑ carbonyl group content in striatum, ↓ GSH levels in the striatum, ↑ oxidation index in erythrocytes, ↓ superoxide anion production in monocytes.</p>
<p>Hepatotoxicity following oral (gavage) exposure to permethrin in early life or during adolescence</p> <p>Rats, Wistar</p> <p>PMRA# 2916632</p> <p>(data for neonatal exposure reported in separate entry)</p>	<p>0 or 150 mg/kg bw/day permethrin (in corn oil) by gavage once daily for 60 days to 5-week old animals. After 60 days of treatment the rats were sacrificed and livers removed for analysis.</p> <p>Permethrin group: 12♂; control group: 9♂</p> <p>25:75 cis:trans isomer ratio</p> <p>94% Purity</p>	<p>150 mg/kg bw/day: No treatment-related effect on clinical signs of toxicity or body weight, ↑ carbonyl groups and lipid peroxidation, ↓ fluidity in the hydrophilic-hydrophobic region of the bilayer of liver cell membranes, ↑ CAT and GST levels and ↓ GPx and GSH levels in liver cells.</p>
<p>Reproductive toxicity following oral (gavage) exposure to permethrin during puberty</p> <p>Mice, ICR (♂)</p> <p>PMRA# 2879069</p>	<p>0, 25, 50 or 100 mg/kg bw/day (+)-cis, (-)-cis, (+)-trans or (-)-trans-permethrin (enantiomers were separated by preparative HPLC) by gavage from PNDs 21 to 42.</p> <p>5 ♂/group</p> <p>>95% Purity</p>	<p>≥25 mg/kg bw/day: ↓ testicular mRNA levels of HMGC_oA synthase ((+)-cis, (-)-cis, (+)-trans and (-)-trans), PBR ((+)-cis), StAR ((+)-cis and (-)-trans), P450scc ((+)-cis and (-)-trans) and 17β-SHD ((+)-cis);</p> <p>≥50 mg/kg bw/day: ↓ testicular mRNA levels of HMGC_oA reductase ((+)-cis), P450scc ((-)-cis and (+)-trans) and ↓ 3β-SHD ((+)-cis);</p> <p>100 mg/kg bw/day: ↓ testicular wt ((+)-cis, (-)-cis and (-)-trans), ↓ number of spermatogenic cells and ↑</p>

Study Type/Species/Strain/PMRA#	Doses/Purity	Study Results
		number of large interstitial spaces in seminiferous tubules ((+)-cis, (-)-cis and (-)-trans), ↓ serum testosterone level ((+)-cis, (-)-cis and (-)-trans), ↓ testicular mRNA levels of PBR ((-)-cis, (+)-trans or (-)-trans), StAR ((-)-cis and (+)-trans), 3β-SHD ((-)-cis) and 17β-SHD ((-)-cis, (+)-trans or (-)-trans).
<p>In vitro study of permethrin and 3-PBA on sperm motility</p> <p>Sperm suspensions from Sprague-Dawley Rats (♂)</p> <p>PMRA# 2879070</p>	<p>Permethrin and 3-PBA were diluted with DMSO and added to sperm suspensions at 0, 1, 4, 16 or 64 mmol/L. The sperm suspensions were then incubated for 1, 2 or 4 hrs.</p> <p>10 samples/group</p> <p>99% Purity</p>	<p>≥16 mmol/L: ↓ straight-line velocity (1 and 2 hrs), linearity (1 and 2 hrs) and curvilinear velocity (4 hrs);</p> <p>64 mmol/L: ↓ straight-line velocity (4 hrs), linearity (4 hrs), ↓ beat cross frequency (1, 2 and 4 hrs), ↓ straightness (1, 2 and 4 hrs), ↓ curvilinear velocity (2 hrs), ↑ average path velocity (1, 2 and 4 hrs), no motile sperm (3 samples after 2 hrs, 6 samples after 4 hrs).</p> <p>3-PBA: no treatment-related alterations in sperm motility at any concentration or incubation period examined.</p>
<p>Effects following oral (gavage) exposure of neonatal animals to permethrin</p> <p>Rats, Wistar</p> <p>PMRA# 2878513, 2878520, 2879060, 2879061, 2879062, 2879063, 2879064, 2879065, 2916632</p>	<p>0 or 34 mg/kg bw/day permethrin (in corn oil) by gavage from PNDs 6 to 21. On PND 1, ♀ pups were discarded and 2 ♂ pups were assigned to each dam until weaning on PND 21. Various studies were performed on the animals at different periods post-dosing (reported separately). All assays conducted on 6 ♂s/group unless specified below</p> <p>T-maze at PND 50: 10 or 12 ♂/group</p> <p>DA analysis at PND 60: 7 ♂/group</p>	<p>PND 21 (PMRA# 2879060): 90% of the 3-PBA was excreted within 24 hrs post-dosing and was completely eliminated after 96 hrs.</p> <p>PND 30 (PMRA# 2878520): ↓ DA and Nurr1 and ↑ ERα gene expression in striatum, co-administration of 10 µg/kg bw/day of 17β-estradiol resulted in more pronounced ↓ DA and Nurr1 gene expression and down-regulation of ERα expression in striatum.</p> <p>PND 50 (PMRA# 2878513): no effect on motor co-ordination, ↓ % of correct responses and ↑ number of incorrect choices in a T-maze.</p> <p>PND 60 (PMRA# 2878513): ↓ DA in striatum, ↓ TH immune-reactivity at the level of the substantia nigra pars</p>

Study Type/Species/Strain/P MRA#	Doses/Purity	Study Results
	<p>Immunohistochemical analysis of brain at PND 60: 3 ♂/group</p> <p>Motor co-ordination tests at PND 50, 100 and 150: 8 ♂/group</p> <p>L-dopa challenge test at PND 150: 8 ♂/group</p> <p>Neurobehavioral assays at PND 500: 7 ♂/group</p> <p>Monoamine and metabolite levels at PND 500: 3 ♂/group</p> <p>25:75 cis:trans isomer</p> <p>94% purity</p>	<p>compacta and ↓ number of TH-positive neurons.</p> <p>PND 100 (PMRA# 2878513): no effect on motor co-ordination.</p> <p>PND 150 (PMRA# 2878513): significant motor coordination deficits on rotarod test (↓ latency to fall off the rotarod) and beam walking task (asymmetric posture, frequent limp or dragging of hind-limbs and ↑ number of foot slips), single gavage administration of >10 mg/kg bw L-Dopa 1 hr prior to motor co-ordination testing reversed motor deficits.</p> <p>PND 300:</p> <p>PMRA# 2879065: ↓ expression of Nurr-1 mRNA in striatum, ↓ glutamate level in hippocampus, ↓ calcium level in striatum, hippocampus and leukocyte tissue homogenates, ↓ calcium plasma level, ↓ NO level in striatum and hippocampus, ↑ plasma levels of NO, ↓ plasma SOD level, ↑ lipid peroxidation.</p> <p>PMRA# 2879064: ↑ DNA damage in cardiac cells (↑ % tail DNA in comet assay), ↓ cholesterol level in heart mitochondria, ↑ cholesterol level in plasma and cardiac cells, ↓ heart cell membrane fluidity, ↑ protein and lipid peroxidation in cardiac cells, ↓ GSH levels and ↑ glutathione peroxidase activity in heart cells, ↓ albumin concentration in plasma, ↑ plasma content of cytokines.</p> <p>PMRA# 2916632: ↑ carbonyl formation and lipid peroxidation in liver cells, ↑ in fluidity of hydrophobic region of the bilayer in liver cell membranes.</p> <p>PND 500:</p> <p>PMRA# 2879061: ↑ Nrf2 gene expression, ↑ intracellular calcium</p>

Study Type/Species/Strain/P MRA#	Doses/Purity	Study Results
		<p>influx in heart cells and ↓ in heart surface area, no effect on NF-kB gene expression.</p> <p>PMRA# 2879062: ↑ plasma NO, sodium and 25-hydroxy-vitamin D levels, ↓ plasma calcium, adrenaline, noradrenaline, cholesterol and urea levels, ↓ urinary sodium levels.</p> <p>PMRA# 2879060: significantly slower choice reaction time in the alternating T-maze test (no effect on % correct responses or number of consecutive incorrect choices), no effect on spatial reference memory in Morris water maze or on anxiety-like behavior in elevated plus maze or on feeding or locomotor activity, ↑ glucose and ↓ lactate levels in the medial prefrontal cortex, ↓ L-DOPA, DA and DOPAC (only striatum) levels in the striatum and in the hippocampus, ↑ HVA levels in the striatum and hippocampus, ↑ NE and ↓ MHPG levels in the striatum, hippocampus and the medial prefrontal cortex, ↓ 5-HT and ↑ 5-HIAA in the medial prefrontal cortex, ↑ turnover ratios of DOPAC/DA and HVA/DA in the striatum and the hippocampus, ↓ MHPG/NE turnover ratios in the striatum, hippocampus and the medial prefrontal cortex, ↑ turnover ratio of 5-HIAA/5-HT in the medial prefrontal cortex.</p> <p>PMRA# 2879063: ↓ Nurr-1 mRNA level and ↑ Nurr-1 protein expression in striatum, ↑ Nurr-1 mRNA level and ↓ NF-kB p65 protein expression in hippocampus, ↑ Nurr-1, Nrf-2, NF-kB p65 mRNA levels and NF-kB p65 protein expression in cerebellum, ↑ NF-kB p65 protein expression in pre-frontal cortex, ↓ glutamate level in cerebellum, ↑</p>

Study Type/Species/Strain/P MRA#	Doses/Purity	Study Results
		calcium level in striatum, prefrontal cortex and cerebellum, ↓ calcium level in hippocampus, ↓ NO production in cerebellum.

Appendix V Updated Occupational Exposure and Risk Estimates

During the PRVD consultation period for permethrin (PRVD2017-18), new exposure information became available to the PMRA. This included a worker exposure study conducted by the French Agency for Food, Environment and Occupational Health and Safety (ANSES) (Thouvenin, 2015), which measured dermal exposure during applications using mechanically-pressurized handheld sprayer for mists, aerosols, and fogs. A Non-Dietary Exposure Task Force (NDETF) study (Testman, 2015) was also submitted, which measured inhalation exposure during ultra-low volume (ULV) fogger applications to various indoor commercial areas. The Thouvenin and Testman studies collectively were considered acceptable to estimate the dermal and inhalation exposure when using a mechanically-pressurized handheld sprayer for mists, aerosols, and fogs. A passive dosimetry study (Krolski, 2014) that monitored exposure of pest control operators (PCOs) applying liquid products indoors as a surface spray using a manually pressurized handwand was submitted to the PMRA by Bayer CropScience. Pest Handler Exposure Database (PHED) unit exposure values for rod and sub-slab injection for termiticide application, showing higher exposure than the previous assessment, were available from the USEPA (2018). Mushroom house use information, relevant to the permethrin risk assessment, was available from other actives.

The studies and information were used to conduct applicator risk assessments for mechanically-pressurized handheld sprayer for mists, aerosols, and fogs, and postapplication exposure in mushroom houses, as well as update the indoor manually pressurized handwand and rod and sub-slab injector applicator risk assessments. The calculated risks for commercial applicators were shown to be acceptable for most of the application equipment, provided additional mitigation measures are implemented, when necessary. Cancer risk for the electric mistblower application into attic spaces was shown to be unacceptable and cannot be mitigated.

In PRVD2017-18, a postapplication exposure assessment could not be conducted for mushroom houses due to a lack of exposure data for this scenario. While no exposure data or comments were submitted during the consultation the mushroom house risk assessment was reconsidered based on recent use information available from other submissions. The updated mushroom house assessment indicated that postapplication inhalation exposure is not expected after the bunker or tunnel (pre-composting) is treated, as permethrin is not volatile, and it is not likely to be airborne after sprays are allowed to dry and settle overnight. Following spawn application, dermal contact with treated surfaces is minimal; mostly automated monitoring; and only checking temperature and humidity conditions, as needed. Dermal contact with treated walls, floors, shelving, and treated beds may occur during harvesting, but is considered to be incidental while undertaking typical work activities. The re-entry activity that results in the most contact with the growth media or the mushrooms is hand harvesting. If the application of permethrin is restricted to when postapplication workers are not present and when the crop is not present above the substrate (and/or covered), dermal and inhalation occupational exposures from postapplication re-entry into mushroom houses are expected to be low.

Table 1 Short, Intermediate, and Long-term Exposure Estimates and MOEs for Occupational Handlers

Site	Application Equipment	Application Rate	ATPD	PPE	Exposure ^a (µg/kg bw/day)		MOE ^b	
					Dermal	Inhalation	Dermal	Inhalation
Commercial Woodlots	MPHS	0.07 kg a.i./ha	0.4047 ha	ML: Single layer, CR gloves A: CR coveralls over a single layer, CR gloves, respirator	10.29	1.40	49000	47000
Agricultural Premises (surface)	Indoor MPHWH	0.00192 kg a.i./L	40 L	MLA: Single layer, CR gloves	82.37	0.32	6100	210000
Agricultural Premises (space)	MPHS	9.6×10^{-6} kg/m ³	28300 m ³	ML: Single layer, CR gloves A: CR coveralls over a single layer, CR gloves, respirator	98.68	13.38	5100	4900
Mushroom Houses	MPHS	3.3×10^{-5} kg a.i./m ³	5660 m ³		67.84	9.20	7400	7100
Structures and surrounding soil (termites)	Rod & Sub-slab Injector	0.0096 kg a.i./L	860 L	MLA: Single layer, CR gloves	81.94	0.50	6100	130000
Mosquito Abatement	MPHS	0.1134 kg a.i./ha	0.4047 ha	ML: Single layer, CR gloves A: CR coveralls over a single layer, CR gloves, respirator	16.67	2.26	30000	29000
Indoor (attic space)	Electric Mistblower	0.05 kg a.i./L	40 L		726.46	98.52	690	660
Indoor (surface)	Indoor MPHWH	0.005 kg a.i./L		MLA: Single layer, CR gloves	214.50	0.82	2300	79000
Indoor (space)	MPHS	4.8×10^{-6} kg/m ³	680 m ³	ML: Single layer, CR gloves A: CR coveralls over a single layer, CR gloves, respirator	1.19	0.16	420000	400000
Outdoor sites	MPHS	0.005 kg a.i./L	150 L		272.42	36.94	1800	1800
Aircraft Disinsection (surface)	Indoor MPHWH	0.005 kg a.i./L	40 L	MLA: Single layer, CR gloves	214.50	0.82	2300	79000

MOE = margin of exposure; MPHWH = mechanically-pressurized handheld sprayer for mists, aerosols, and fogs; MPHWH = manually pressurized handwand; ATPD = area treated per day; PPE = personal protective equipment; ML = mixer/loader, A = applicator, CR = chemical-resistant. Single layer = long-sleeved shirt, long pants

^a Where dermal/inhalation exposure = (unit exposure × area treated per day × application rate)/80 kg.

^b Based on a short-, intermediate-, long-term dermal NOAEL of 500 mg/kg bw/day and a short-, intermediate-, long-term inhalation NOAEC of 65 mg/kg bw/day with a target MOE of 300. All calculated MOEs exceed the target MOE.

Table 2 Cancer Exposure and Risk Estimates for Occupational Handlers

Site	Application Equipment	Application Rate	ATPD	PPE	Work days/Year ^a	LADD ^b (µg/kg bw/day)	Cancer Risk ^c
Commercial Woodlots (agricultural)	MPHS	0.07 kg a.i./ha	0.4047 ha	ML: Single layer, CR gloves A: CR coveralls over a single layer, CR gloves, respirator	30	0.1109	1 × 10 ⁻⁶
Agricultural Premises (surface)	Indoor MPHWH	0.00192 kg a.i./L	40 L	MLA: Single layer, CR gloves	30	0.4299	4 × 10 ⁻⁶
Agricultural Premises (space)	MPHS	9.6 × 10 ⁻⁶ kg/m ³	28300 m ³	ML: Single layer, CR gloves A: CR coveralls over a single layer, CR gloves, respirator	30	1.063	1 × 10 ⁻⁵
Mushroom Houses (agricultural)	MPHS	3.3 × 10 ⁻⁵ kg a.i./m ³	5660 m ³		63	1.535	2 × 10 ⁻⁵
Structures and surrounding soil (termites)	Rod & Sub-slab Injector (PCO)	0.0096 kg a.i./L	860 L	MLA: Single layer, CR gloves	60	0.3483	3 × 10 ⁻⁶
Mosquito Abatement	MPHS (PCO)	0.1134 kg a.i./ha	0.4047 ha	ML: Single layer, CR gloves A: CR coveralls over a single layer, CR gloves, respirator	30	0.0718	7 × 10 ⁻⁷
Indoor (attic space)	Electric Mistblower (PCO)	0.05 kg a.i./L	40 L		30	3.131	3 × 10 ⁻⁵
Indoor (surface)	Indoor MPHWH (PCO)	0.005 kg a.i./L	40 L	MLA: Single layer, CR gloves	30	0.4478	4 × 10 ⁻⁶
Indoor (space)	MPHS (PCO)	4.8 × 10 ⁻⁶ kg/m ³	680 m ³	ML: Single layer, CR gloves A: CR coveralls over a single layer, CR gloves, respirator	30	0.0051	5 × 10 ⁻⁸
Outdoor sites	MPHS (PCO)	0.005 kg a.i./L	150 L		30	1.174	1 × 10 ⁻⁵
Aircraft Disinsection (surface)	Indoor MPHWH (PCO)	0.005 kg a.i./L	40 L	MLA: Single layer, CR gloves	30	0.4478	4 × 10 ⁻⁶

MPHS = mechanically-pressurized handheld sprayer for mists, aerosols, and fogs; MPHWH = manually pressurized handwand; PCO = pesticide control operator; ATPD = area treated per day; PPE = personal protective equipment; ML = mixer, loader; A = applicator; CR = chemical-resistant; LADD = lifetime average daily dose;

^a Work days per year are based on the number of applications per year, 30 applications are assumed when the number of applications were not provided on the label.

^b LADD = Absorbed Daily Dose (ADD) × treatment frequency × working duration/(365 days × 78 years). Working duration = 40 years for agricultural scenarios and 16 years for PCOs. ADD is a sum of exposures from Appendix IV, Table 1. A dermal absorption value of 12% was applied to the dermal component of the ADD.

^c A q₁* value of 0.00987 (mg/kg bw/day)⁻¹ was considered appropriate to use in the cancer risk assessment. Cancer risks in the range of 1 × 10⁻⁵ were considered to be acceptable.

Appendix VI References Considered Following Publication of PRVD2017-18

A. Information Considered in the Toxicological Assessment

Additional Information Considered

Published Information

PMRA Document Number	Reference
2407825	1973. Effects of Purified and Technical Piperonyl Butoxide on Drug-Metabolizing Enzymes and Ultrastructure of Rat Liver - Toxicology and Applied Pharmacology, 26: 444-458, DACO 4.8
2407829	1971. Response of Hepatic Microsomal Mixed-Function Oxidases to Various Types of Insecticide Chemical Synergists Administered to Mice - Biochemical Pharmacology, 20: 1607-1618, DACO 4.8
2420879	1997. Effect of Piperonyl Butoxide on Cell Replication and Xenobiotic Metabolism in the Livers of CD-1 Mice and F344 Rats - Fundamental and Applied Toxicology, 38: 64-74, DACO 4.8
2878511	2018. Exposure to permethrin promotes high fat diet-induced weight gain and insulin resistance in male C57BL/6J mice. Food and Chemical Toxicology, 111: 405-416, DACO: 4.8
2878512	2017. Permethrin alters glucose metabolism in conjunction with high fat diet by potentiating insulin resistance and decreases voluntary activities in female C57BL/6J mice. Food and Chemical Toxicology, 108: 161-170, DACO: 4.8
2878513	2017. Early life exposure to permethrin: a progressive animal model of Parkinson's disease. Journal of Pharmacological and Toxicological Methods, 83: 80-86, DACO: 4.8
2878515	2017. Subchronic toxicity of low dose propoxur, permethrin, and their combination on the redox status of rat liver. Chemico-Biological Interactions, 272: 21-27, DACO: 4.8
2878517	2016. Efficacy of naringenin against permethrin-induced testicular toxicity in rats. International Journal of Experimental Pathology, 97(1): 37-49, DACO: 4.8
2878518	2015. The effects of permethrin on rat ovarian tissue morphology. Experimental and Toxicologic Pathology, 67(3): 279-285, DACO: 4.8
2878520	2014. Effect of 17 β -estradiol on striatal dopaminergic transmission induced by permethrin in early childhood rats. Chemosphere, 112: 496-502., DACO: 4.8
2879060	2013. Effects of early life permethrin exposure on spatial working memory and on monoamine levels in different brain areas of pre-senescent rats. Toxicology, 303: 162-168., DACO: 4.8
2879061	2013. Early life permethrin treatment leads to long-term cardiotoxicity. Chemosphere, 93(6): 1029-1034, DACO: 4.8
2879062	2013. Early life permethrin exposure leads to hypervitaminosis D, nitric oxide and catecholamines impairment. Pesticide Biochemistry and Physiology, 107(1): 93-97., DACO: 4.8
2879063	2013. Early life permethrin exposure induces long-term brain changes in Nurr1,

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- 2879064 2011. Early life permethrin insecticide treatment leads to heart damage in adult rats. *Experimental Gerontology*, 46(9): 731-738, DACO: 4.8
- 2879065 2012. The impact of early life permethrin exposure on development of neurodegeneration in adulthood. *Experimental Gerontology*, 47(1): 60-66, DACO: 4.8
- 2879066 2014. Pyrethroid and their metabolite, 3-phenoxybenzoic acid showed similar (anti)estrogenic activity in human and rat estrogen receptor-mediated reporter gene assays. *Environmental Toxicology and Pharmacology*, 37(1): 371-377, DACO: 4.8
- 2905889 2018. Effects of acute exposure of permethrin in adult and developing Sprague-Dawley rats on acoustic startle response and brain and plasma concentrations. *Toxicological Sciences*, 165(2): 361-371, DACO: 4.8
- 2916596 2007. Dopaminergic system modulation, behavioral changes, and oxidative stress after neonatal administration of pyrethroids. *Toxicology*, 229(3): 194-205, DACO: 4.8
- 2916626 2014. Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study. *Environmental Health Perspectives*, 122(10): 1103-1109, DACO: 4.8
- 2916627 2013. Urinary metabolites of organophosphate and pyrethroid pesticides and behavioral problems in Canadian children. *Environmental Health Perspectives*, 121(11-12): 1378-1384, DACO: 4.8
- 2916628 2017. Neurodevelopmental delay diagnosis rates are increased in a region with aerial pesticide application. *Frontiers in Pediatrics*, 5(116): 1-9, DACO: 4.8
- 2916629 2017. Prenatal exposure to pyrethroid pesticides and childhood behavior and executive functioning. *NeuroToxicology*, 62: 231-238, DACO: 4.8
- 2916630 2015. Pyrethroids: exposure and health effects - an update. *International Journal of Hygiene and Environmental Health*, 218: 281-292, DACO: 4.8
- 2916631 2017. Nonoccupational exposure to pyrethroids and risk of coronary heart disease in the Chinese population. *Environmental Science & Technology*, 51: 664-670, DACO: 4.8
- 2916632 2013. Imbalance in redox system of rat liver following permethrin treatment in adolescence and neonatal age. *Xenobiotica*, 43(12): 1103-1110, DACO: 4.8

B. Additional Information Considered in the Occupational and Residential Assessment

List of Additional Studies/Information Submitted by Registrant/Available to PMRA

Published

PMRA Document Number	Reference
2572745	2015. Agricultural Handler Exposure Scenario Monograph: Open Pour Mixing and Loading of Liquid Formulations. Report Number AHE1003-1. March 31, 2015. DACO 5.4, 5.5.
2988355	US EPA 2018. Occupational Pesticide Handler Exposure Unit Exposure Surrogate Reference Table. June 2018.

Unpublished

PMRA Document Number	Reference
2449137	2014. Observational Study to Determine Dermal and Inhalation Exposure to Pest Control Operator (PCO) Workers Applying Deltamethrin and/or β -Cyfluthrin Using Hand-held Equipment in a Crack and Crevice Application. SynTech Research Laboratory Services Stilwell, KS & Eurofins Agrosociences Services, Inc., GA. Bayer Report No. RGDAY016. Unpublished.
2873196	2015. Determination of operator dermal exposure and protective factors provided by personal protective equipment during foliar application using backpack sprayer in vineyards. ANSES. STAPHYT study No. ChR-15-19603, 10 July 2015. Unpublished.
2905452	2015. An Observational Study for the Determination of Air Concentration in the Applicator's Breathing Zone and Deposition of Pyrethrins, Piperonyl Butoxide and MGK 264 from the Use of a ULV Fogger in Various Commercial Applications. Golden Pacific Laboratories. GPL Report No. 110392. Non-Dietary Exposure Task Force (NDETF). Mar.30, 2015.

C. Information Considered in the Environmental Assessment

Additional Information Considered

Published

PMRA Document Number	Reference
2969329	Robinson, C. A., Ghaffarzadeh, M. and Cruse, R. M. 1996. Vegetative filter strip effects on sediment concentration in crop land runoff. Journal of Soil and Water Conservation. 51 (3): 227-230.

2969334	USDA-NRCS. 2000. Conservation Buffers to Reduce Pesticide Losses. United States Department of Agriculture, Natural Resources Conservation Service. Washington, DC. 25 pp.
2969340	Schmitt, T.J., M.G. Dosskey, and K.D. Hoagland. 1999. Filter strip performance and processes for different vegetation, widths, and contaminants. <i>Journal of Environmental Quality</i> 28: 1479-1489.
2969345	Abu-Zreig, M., R.P. Rudra, M.N. Lalonde, H.R. Whiteley, and N.K. Kaushik. 2004. Experimental investigation of runoff reduction and sediment removal by vegetated filter strips. <i>Hydrological Processes</i> 18: 2029-2037.
2969351	Syversen, N. 2005. Effect and design of buffer zones in the Nordic climate: The influence of width, amount of surface runoff, seasonal variation and vegetation type on retention efficiency for nutrient and particle runoff. <i>Ecological Engineering</i> 24: 483-490.