Proposed Re-evaluation Decision PRVD2020-09

Piperonyl butoxide and associated end-use products

Consultation Document

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Proposed re-evaluation decision

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

Piperonyl butoxide is a synergist that is always co-formulated with an insecticide. It does not have a direct pesticidal mode of action, but acts to increase the overall efficacy of other active ingredients. It is registered for use in restricted, commercial and domestic products on outdoor ornamentals, pastures, livestock, companion animals, structural sites (indoor and outdoor), clothing, stored grains, home and garden, and lakes, ponds, and reservoirs. Products containing piperonyl butoxide are available in various formulations including dusts, pressurized products, pastes, solutions, and emulsifiable concentrates. A list of the registered products in Canada that contain piperonyl butoxide can be accessed through the PMRA's label transcription service.[1]

Most piperonyl butoxide-containing products were registered prior to the development of modern standardized label language and the labels do not contain comprehensive use directions. Considering the very large number of piperonyl butoxide products currently registered and the variability with regards to the description of their uses on the labels, a scenario-based approach was used to identify the piperonyl butoxide use pattern, rather than a label-based approach. High-level use pattern summary tables were prepared that outlined the different use scenarios for piperonyl butoxide and these tables were shared with registrants and user groups for consultation, and for their comments and clarifications. These tables were used as the basis for the risk assessment of piperonyl butoxide.

As a result of the use pattern consultation, it was determined that the dietary assessment would be limited to specific scenarios on commercial class piperonyl butoxide product labels. In addition, uses for which no data were available, such as application to stored grain and seeds, water, and pastures; space sprays when livestock (other than chickens) are present; spot on application to poultry; dust application in food-handling establishments; and all food and garden uses on domestic-class products, were not included in the dietary risk assessment. Summary tables of the uses that were used as the basis of the risk assessment can be found in Appendix I.

This document presents the proposed regulatory decision for the re-evaluation of piperonyl butoxide including the proposed risk mitigation measures to protect human health and the environment, as well as the science evaluation on which the proposed decision was based. All products containing piperonyl butoxide registered in Canada are subject to this proposed 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

This document is subject to a 90-day public consultation period, during which the public, including the pesticide manufacturers and stakeholders, may submit written comments and additional information to the PMRA. The final re-evaluation decision will be published taking into consideration the comments and information received.

Outcome of science evaluation

Piperonyl butoxide is of value to users as it enhances the effectiveness of other co-formulated active ingredients that control a broad spectrum of insect pests on a wide variety of sites, including commercial and domestic agricultural and structural uses. Piperonyl butoxide is a component of the integrated pest management of common household pests, such as bed bugs, cockroaches, fleas, and indoor ants. When used for treatment of lice on mattresses, bedding, furniture, and garments, piperonyl butoxide does not have acceptable value.

With respect to human health, risks have been shown to be acceptable with mitigation measures required for most uses considered in the risk assessment. As previously discussed, some uses for which no data were available were not included in the dietary risk assessment (for example, application to stored grain, water, and pastures; space sprays when livestock are present; all food and garden uses on domestic-class products). For several uses, risk associated with consumers, bystanders or workers have not been shown to be acceptable. These include domestic-class products used as total release foggers, indoor use of domestic-class dust products, indoor space sprays for domestic-class pressurized products; outdoor insect control using pressurized domestic- and commercial-class products; and broadcast application for bed bug control on commercial-class dust and pressurized product labels. Exposure from the remaining uses is unlikely to affect human health when used according to the proposed label directions.

In terrestrial environments, piperonyl butoxide is not expected to pose a risk to populations of birds, mammals, earthworms, non-target arthopods and terrestrial plants. Because piperonyl butoxide is always co-formulated with an insecticide, the labels for all co-formulated insecticides include mitigation measures that will also reduce the risks associated with piperonyl butoxide. In aquatic environments, spray buffer zones required for insecticides that are co-formulated with piperonyl butoxide will help mitigate potential risks associated with piperonyl butoxide. When used according to instructions on end-use product labels, environmental risks associated with piperonyl butoxide are acceptable.

Proposed regulatory decision for piperonyl butoxide

Under the authority of the *Pest Control Products Act* and based on the evaluation of currently available scientific information, Health Canada is proposing continued registration of piperonyl butoxide in Canada, provided that the proposed risk mitigation measures are in place to protect human health and the environment. Several uses, where the value or risks associated with consumers, bystanders or workers have not been shown to be acceptable, are proposed for cancellation.

In addition, where data were unavailable to support certain uses that could result in dietary exposure, cancellation is also proposed. Furthermore, only the uses explicitly identified in the summary tables outlined in Appendix I were included in the risk assessment. All other uses are proposed for cancellation due to lack of supporting use information.

Proposed risk mitigation measures

As a result of the re-evaluation of piperonyl butoxide, Health Canada is proposing further risk-reduction measures, in addition to those already included on piperonyl butoxide labels. The updated label statements and mitigation measures, required as a result of the re-evaluation of piperonyl butoxide, are summarized below. Refer to Appendix IX (proposed label amendments) for details.

Human health

- Data were not available to support certain uses that could result in dietary exposure. Therefore, the following risk mitigation measures are proposed:
    - Cancellation of: uses on pastures; direct application to stored grain and seeds; direct application to ponds, lakes, reservoirs, and streams; spot-on application to poultry; space spray application while livestock, other than poultry, are present; and garden and greenhouse food uses on domestic class product labels.
    - The application rate of space spray applications while poultry are present is to be limited to 0.12 g a.i/m^3 or less.
    - Dust application is to be limited to areas that do not affect food, feed, or livestock used to produce food commodities (for example, voids, non-food areas).

- The following uses are proposed for cancellation due to potential risks to consumers, bystanders (including children) or workers:
    - All domestic-class pressurized products used as total release foggers.
    - Indoor uses on domestic-class dust product labels.
    - Indoor space spray uses (not including metered release) on domestic-class pressurized product labels.
    - Outdoor mosquito, fly or gnat control uses on domestic- and commercial-class pressurized product labels.
    - Broadcast application for bed bug control on commercial-class dust and pressurized product labels.

- To protect consumers from dietary exposure, the following risk reduction measures are proposed:
    - Revocation of the MRL for raw cereals.
    - The number of applications for all outdoor uses, as described in Appendix I (for example: campgrounds, roadsides, and grassy areas), are to be reduced such that the yearly cumulative rate is less than 1100 g active ingredient (a.i.)/ha.
    - Structural labels are to be updated as per the 2020 PMRA Guidance Document, *Structural Pest Control Products: Label Updates*.

- To protect consumers, and bystanders (including children) who may be using the product or entering treated sites, the following risk reduction measures are proposed:
    - For surface spray applications, label directions must be added or revised to specify the pests controlled, the application rate and application type (for example, perimeter/spot, crack and crevice) that was shown to have acceptable risk in the human health risk assessment (Appendix IX, Sections 3.2 and 3.3). This includes label statements that clearly define and establish the conditions of use for residential areas where children may be present versus non-residential areas where children are not expected to be present.
    - A 2-hour restricted-entry interval for commercial-class products applied as an indoor space spray in residential environments (not applicable to metered release devices). The commercial applicator is responsible for notifying the occupants and others of the re-entry period requirement.
    - Limit the application rate for metered release devices.
    - A label statement prohibiting use of handheld airblast/mistblower or mechanically-pressurized handheld equipment on domestic-class labels.
    - A label statement prohibiting use of domestic-class greenhouse end-use products in commercial greenhouses.
    - Additional label statements for domestic and commercial products used as structural pest control products as per the 2020 PMRA Guidance Document, *Structural Pest Control Products: Label Updates*.

- To protect workers using or entering treated sites following application of commercial-class products, the following risk reduction measures are proposed:
    - Personal protective equipment.
    - Limit the amount of product handled per day.
    - Restricted-entry intervals for agricultural sites.
    - Restricted-entry intervals for non-agricultural sites.
    - Limit the application rate for metered release devices.
    - Updated labels statements and clarifications to ensure product use is consistent with the assumptions used in the human health risk assessment.

Environment

To protect the environment, the following risk mitigation measures are proposed:

- Updated label statements to identify potential risks to bees, beneficial arthropods and aquatic organisms, and restrictions on application timing to protect pollinators. As piperonyl butoxide is always co-formulated with an insecticide, the labels will include mitigation measures for the co-formulated insecticide that will also reduce the risks identified for piperonyl butoxide.

- Precautionary statements and additional application instructions on product labels with foliar applications (commercial and domestic) to prevent terrestrial plant damage/death are proposed.

Value

- Label claims related to killing lice on mattresses, bedding, furniture, and garments are proposed for cancellation.

International context

Piperonyl butoxide is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including Australia, the European Union and the United States. No decision by an OECD member country to prohibit all uses of piperonyl butoxide for health or environmental reasons has been identified.

Next steps

The public, including the registrants and stakeholders, are encouraged to submit additional information that could be used to refine risk assessments during the 90-day public consultation period[2] upon publication of this proposed re-evaluation decision.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of the re-evaluation decision document,[3] which could result in revised risk mitigation measures. The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with Health Canada's responses.

Additional scientific information

Data are required to confirm that the application rates and use directions on current product labels are consistent with the rates used in the residential, bystander and occupational risk assessments. Many current labels do not have any rate specified, or the rate is presented in a form that cannot be used for risk assessment purposes (for example, spray for five seconds). Registrants are required to provide data that bridges the use directions and/or the rate on the label, to a rate that can be expressed in units of the amount of piperonyl butoxide per surface area (for example, mg a.i./cm^2) for surface applications, or amount of piperonyl butoxide per air volume (for example, mg a.i./m^3) for space spray or fogging applications. Data are required for the following products:

- All ready-to-use, commercial-class products for all formulations (for example, pressurized products, dusts) used for structural pest control, unless current label directions have very clear application directions and rates.

- All domestic-class products for all formulations (for example, pressurized products, dusts) for all uses, except pet/livestock and greenhouse uses.

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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.*

In addition, for several uses where risks were shown to be acceptable at the highest rate assessed, limited label rate use/directions are available. Consequently, additional label information is required to support the risk assessment proposal, and further confirm what use directions/mitigation will be required in the final re-evaluation decision.

Registrants are encouraged to contact the PMRA for guidance on how to meet this data requirement. Only products supported by data demonstrating that the rates used in the risk assessments are not exceeded will be considered for continued registration. A Notice, pursuant to paragraph 19(1)(a) of the *Pest Control Products Act*, will be issued to affected registrants in the near future and will include additional guidance on how to satisfy this data requirement.

Although not required during the consultation period, the registrants and other stakeholders may submit information that may address uncertainties in the available information database of piperonyl butoxide to support refinement of the risk assessment and, subsequently, change the proposed mitigation. Providing data, or an acceptable rationale to waive data, is recommended if registrants wish to maintain certain limited uses, such as the restricted use with rotenone for direct application to ponds, lakes, reservoirs, and streams.

For the dietary assessment, registrants may also propose alternative mitigation measures, provided these result in acceptable dietary exposure. For example, registrants may wish to propose a lower maximum application rate instead of reducing the number of applications, or may propose to revoke additional MRLs to allow for higher cumulative outdoor application rates in Canada. In addition, stakeholders are encouraged to comment on the feasibility of the proposed mitigation and their potential impact on associated pest management practices.

Revisions to the proposed mitigation measures for occupational and residential uses may be considered if clarifications to the piperonyl butoxide use pattern or chemical-specific studies are provided during the comment period. Examples of this information include (but are not limited to):

- Application equipment, directions, amount applied per day, and rates for outdoor mosquito, fly or gnat control uses on commercial-class product labels;
- Application directions, amount applied per day (for example, proportion of can), and rates for outdoor mosquito, fly, or gnat control uses on domestic-class product labels;
- Application directions, amount applied per day, and rates for indoor space spray uses on commercial- and domestic-class product labels;
- Application directions, amount applied per day, and rates for commercial- and domestic-class indoor surface-directed spray products;
- For commercial and domestic class products, specify which specific pests are to appear on the product labels for each use site;
- Clarifications on weight and sizes of ready-to-use commercial- and domestic-class

products (for example, single vs. bulk packaging);

- Chemical-specific studies that monitor the concentration of piperonyl butoxide in the air during and following outdoor mosquito, fly or gnat control pressurized product applications;

- Chemical-specific studies that monitor the deposition of piperonyl butoxide following indoor surface spray applications.

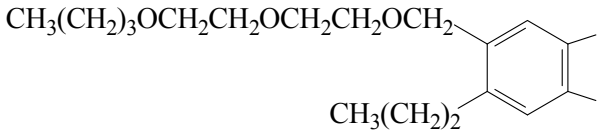
Science evaluation

1.0 Introduction

At the time that the piperonyl butoxide re-evaluation was initiated, all uses were supported by the registrants. As of 9 January 2020, there are three technical grade active ingredient products, 14 manufacturing products, 103 commercial class products, 206 domestic class products, and one restricted-class product. A list of the registered products containing piperonyl butoxide in Canada can be accessed through the PMRA's label transcription service.[4]

2.0 Technical grade active ingredient

2.1 Identity

Common name		Piperonyl butoxide
Function		Insecticide
Chemical family		Methylenedioxybenzene
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	5-[2-(2-butoxyethoxy)ethoxymethyl]-6-propyl-1,3-benzodioxole or 2-(2-butoxyethoxy)ethyl 6-propylpiperonyl ether
2	**Chemical Abstracts Service (CAS)**	5-[[2-(2-butoxyethoxy)ethoxy]methyl]-6-propyl-1,3-benzodioxole
CAS registry number		51-03-6
Molecular formula		$C_{19}H_{30}O_5$
Structural formula		
Molecular weight		338.4

[4] The 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.

Registration number	Purity of the technical grade active ingredient
27451	96.57%
30351	96.57%
31822	96.57%

2.2 Physical and chemical properties

Property	Result	Interpretation
Vapour pressure at 60 °C	0.02 mPa	*Not expected to volatilise*
Ultraviolet (UV) /visible spectrum	Not expected to absorb at λ > 350 nm	Not expected to undergo direct photolysis in the environment
Solubility in water at 20–25 °C	14.3 mg/L	Soluble in water
n-Octanol/water partition coefficient	Log K_{ow} = 4.75	Potential to bioaccumulate
Dissociation constant	Not applicable	No dissociable function groups

2.3 Description of registered piperonyl butoxide uses

Piperonyl butoxide is registered for use on outdoor ornamentals, pastures, livestock, companion animals, structural sites (indoor and outdoor), clothing, stored grains, home and garden, and lakes, ponds, and reservoirs. Piperonyl butoxide products are available in various formulations, including dusts, solutions, emulsifiable concentrates, and pressurized products.

3.0 Human health assessment

3.1 Toxicology summary

Piperonyl butoxide is a pesticide synergist used to enhance the pesticidal properties of other active ingredients, such as pyrethrins and synthetic pyrethroids. It works by directly binding to microsomal enzymes in insects, which prevents the breakdown of other active ingredients. Since piperonyl butoxide lacks pesticidal properties of its own, there are no products that contain only piperonyl butoxide.

A detailed review of the toxicology database for piperonyl butoxide was conducted. The database was considered complete and consisted of the full array of toxicity studies currently required for hazard assessment purposes. A number of mechanistic studies were also available to support a proposed mode of action (MOA).

The toxicology database supporting piperonyl butoxide was based on studies available from the registrant as well as published literature studies and was considered adequate to characterize the potential health hazards associated with piperonyl butoxide.

In oral toxicokinetic studies with radiolabelled piperonyl butoxide in rats, the plasma levels of radioactivity increased slowly with maximum blood levels noted between 4 and 6 hours post-dosing dropping to approximately half of the peak level by 24 hours post-dosing. When administered by gavage, the highest levels of radiolabel were found in the gastrointestinal tract and its contents. Levels of radioactivity were also retained in the fat, liver, prostate, muscle, kidney and seminal vesicles at 48 hours post-dosing. After 168 hours, less than 1.5% of the administered radioactivity was present in tissues.

Excretion of phenyl-labeled piperonyl butoxide in rats occurred via urine and feces with most of the radiolabel recovered 12–24 hours post-dosing. The amount of radiolabel recovered after 24 hours was low, and less than 1% of the excreted dose was recovered at the 72-hour post-dosing timepoint. The amount of recovered radioactivity found in the feces was greater than that eliminated in the urine. No significant dose or gender differences were apparent.

Metabolism of piperonyl butoxide was extensive with no significant differences noted in the metabolic profile between genders, dosage levels or in studies with different dosing regimens. Piperonyl butoxide has four potential sites for metabolism: the methylenedioxy ring, the 2-(2-butoxyethoxy)ethoxymethyl side-chain, the phenyl ring and the propyl side-chain. In mice and rats, the major metabolic pathway for the metabolism of piperonyl butoxide involved the cleavage of the methylene-dioxyphenyl moiety by oxidation. This cleavage resulted in opening of the methylenedioxy ring to form a catechol that could then undergo methylation. Sequential oxidation of the 2-(2-butoxyethoxy) ethoxy methyl side chain also occurred producing a number of alcohols and acids. Metabolites also underwent conjugation with sulphate or glucuronide. The major metabolites in the feces were unchanged piperonyl butoxide and piperonyl butoxide opened at the methylene dioxy ring. Approximately 20 radioactive peaks were identified in the urine with none of these individual peaks exceeding 5% of the administered radioactivity. No unchanged piperonyl butoxide was detected in the urine.

Piperonyl butoxide was of low acute toxicity by the oral route in rats, dermal route in rabbits and inhalation route in rats. Clinical signs of toxicity noted in these acute toxicity studies included ruffled fur, piloerection, salivation, lacrimation, nasal discharge, anogenital staining, laboured breathing, lethargy and tremors. Piperonyl butoxide was minimally irritating to the eyes and skin of rabbits and was non-sensitizing to the skin of guinea pigs.

In both short-term and long-term repeat-dose oral toxicity studies in mice, rats and dogs, the target organ of toxicity was the liver. In these different species, hepatic toxicity following exposure to piperonyl butoxide was characterized by increased organ weight, alterations in clinical chemistry parameters, enzyme levels and histopathology including hypertrophy, hyperplasia and necrosis (mice and rats only). Male animals were slightly more sensitive than females. In a 21-day dermal toxicity study in rabbits, no treatment-related systemic effects were observed. Signs of dermal irritation in the form of very slight erythema, edema and desquamation were noted along with acanthosis, hyperkeratosis and inflammation of the

epidermis at the test sites exposed to piperonyl butoxide. In a 90-day inhalation toxicity study in rats, histopathological changes in the respiratory tract that included hyperplasia and metaplasia were noted in the larynx starting from the lowest exposure concentration. At the highest concentration, effects on the liver (organ weight, enzymes and pathology) were also observed.

Several long-term dietary toxicity studies examined potential carcinogenicity in mice and rats following exposure to piperonyl butoxide. In mice, an increased incidence of hepatocellular tumours (adenomas, in some cases accompanied by progression to carcinomas) was noted in three chronic toxicity/carcinogenicity studies. In the first study, a supplemental 52-week dietary carcinogenicity study in CD-1 mice, an increased incidence of liver adenomas and carcinomas was observed in males and females. An increased incidence of hemangioendothelial sarcomas was also noted in males and females at a very high dose level in this 52-week study. At this dosage level, an increased number of mortalities occurred and the maximum tolerated dose was exceeded. As the hemangiosarcomas were observed at a dose level resulting in excessive toxicity, they were not considered relevant to the human health risk assessment. In the second study, an acceptable 78-week dietary carcinogenicity study in CD-1 mice, there was an increased incidence of hepatocellular adenomas in both sexes and an increased incidence of hepatocellular carcinomas in males. In a third study, a supplemental 2-year chronic toxicity/carcinogenicity study in B6C3F1 mice, female mice demonstrated an increased incidence of hepatocellular carcinomas, while there were no treatment-related tumours noted in the livers of male mice. In this study, there was also a slight increase in the incidence of lacrimal gland adenomas in males at the highest dose level tested. However, the relation to treatment of this tumour with piperonyl butoxide was considered equivocal. This was based on the lack of statistical significance by pairwise comparison, the supplemental nature of the study (limitations included significantly fewer animals in the control group compared to treatment groups and the lack of individual data), and the fact that similar tumours were not observed in any of the other long-term toxicity studies conducted with mice. Also, there was no evidence of progression of these tumours to malignancy. For these reasons, there was a low level of concern for the observed lacrimal gland tumours.

An increased incidence of treatment-related hepatocellular adenomas and/or carcinomas was observed in two of the four chronic toxicity/carcinogenicity studies conducted in rats exposed to piperonyl butoxide. No evidence of carcinogenicity was noted in an acceptable 2-year carcinogenicity study in Sprague-Dawley rats. In one supplemental 2-year carcinogenicity study in F344 rats, an increased incidence of lymphoreticular malignant lymphomas was observed in females. The evidence for a treatment-related increase in this tumour was considered to be equivocal. This was based on the supplemental nature of the study (limitations included significantly fewer animals in the control group compared to treatment groups and the lack of individual data) and the fact that a similar increase in this tumour type was not observed in any of the other long-term rat or mouse toxicity studies. Furthermore, this is a common tumour type in F344 rats and there was a relatively high incidence of this tumour noted in male control animals, with the incidence being higher than in any of the female treatment groups. Male and female F344 rats exposed to piperonyl butoxide for two years (in a second supplemental study) had an increased incidence of hepatocellular adenomas and carcinomas at high dose levels. In this same study, an increased incidence of hemangiosarcomas was noted in male and female F344 rats; however, these tumours were noted at a dosage level that resulted in extensive

systemic toxicity and was considered in excess of the maximum tolerated dose. As such, these tumours were not considered relevant to the human health risk assessment. In another supplemental study, slight increases in the incidences of hepatocellular carcinomas as well as "neoplastic nodules" in the liver were noted in male F344 rats exposed to piperonyl butoxide for 107 weeks.

Piperonyl butoxide did not cause genetic damage when tested in a series of in vitro assays including a bacterial reverse mutation assay (*Salmonella typhimurium*), a chromosomal aberration test (Chinese hamster ovary cells), a sister chromatid exchange assay (Chinese hamster ovary cells), an unscheduled DNA synthesis assay (rat primary hepatocytes) and a cell transformation assay (Syrian hamster embryo cells). A positive response was noted in an in vitro gene mutation assay in mouse lymphoma cells when tested without metabolic activation (not conducted with metabolic activation). However, piperonyl butoxide did not induce gene mutations in Chinese hamster V79 cells when tested with or without metabolic activation. Overall, the weight of evidence did not suggest that piperonyl butoxide has genotoxic potential.

There was an extensive number of published studies available for piperonyl butoxide that suggested a plausible MOA to explain the increased incidence of hepatocellular adenomas and carcinomas in mice and rats. Based on this information, the likely MOA involved hepatic P450 enzyme induction. This nuclear-receptor-mediated MOA involved aryl hydrocarbon receptor (AhR), constitutive androstane receptor (CAR) and pregnane X receptor (PXR) activation, leading to increased hepatocellular proliferation and ultimately hepatocellular tumours. Activation of these nuclear-receptors produced a cascade of alterations in gene transcription that led to increased hepatocellular proliferation which is a critical event in the development of liver tumours. In a series of mechanistic studies in mice and rats, activation of these nuclear receptors was apparent at the messenger ribonucleic acid, protein (demonstrated by increases in the CYP1A, CYP2B and CYP3A families) and enzyme level. Activation of these nuclear receptors resulted in increased liver weights, hepatocellular hypertrophy and proliferation which then led to the formation of pre-neoplastic and neoplastic lesions. When taken together, the mechanistic and repeat-dose toxicity studies for both mice and rats support a threshold approach for cancer risk assessment.

A dietary two-generation reproductive toxicity study was conducted with Sprague-Dawley rats. Decreased body weight and body weight gain were noted at the same dose level in both parental animals and offspring, while no treatment-related effects on reproductive endpoints occurred. Two acceptable gavage developmental toxicity studies were conducted in rats. In one study with Sprague-Dawley rats, fetotoxicity was noted in the form of unossified cervical centra at a dosage level that resulted in maternal toxicity. The other developmental toxicity study in Wistar rats demonstrated no treatment-related signs of toxicity in either the maternal animals or fetuses at comparable dose levels. In the rabbit gavage developmental toxicity study, there was no evidence of sensitivity or serious endpoints as the fetuses showed no treatment-related effects, while a slight effect was noted on body weight in the maternal animals.

A non-guideline gavage developmental toxicity study in mice was available in which the mice were exposed to piperonyl butoxide on gestation day (GD) 9 only. In this study, an increased number of forelimb deformities was noted in the fetuses at the same dosage level at which

maternal animals exhibited decreased body weight gain, abortions and increased resorptions. Another non-guideline gavage developmental toxicity study in rats was performed with dosing on GDs 11 and 12. In this study, fetal effects in the form of external limb deformities were noted at a dosage level that resulted in an effect on body weight in maternal animals. It should be noted that in both studies, limb deformities were only observed at a dose level that resulted in significant maternal toxicity.

Clinical signs of neurotoxicity were not observed in guideline studies conducted in mice, rats, rabbits or dogs. However, in a non-guideline 6-week dietary neurotoxicity study in mice, an effect on motor activity (increased number of turnings and distance traveled) was noted. In a series of non-guideline developmental neurotoxicity studies in mice exposed to piperonyl butoxide, an effect on pup weight, olfactory orientation and surface righting was noted. In contrast to the extensive examinations conducted in the offspring, the assessments conducted for maternal animals were limited as the focus of the studies was to determine potential neurotoxicity in the pups following in utero exposure to piperonyl butoxide. The signs of toxicity that were noted in maternal animals were considered to be minimal; however, it was likely that hepatic hypertrophic responses were present in the dams at levels producing the developmental neurotoxicity based upon consideration of the database as a whole.

Results of the toxicology studies conducted on laboratory animals with piperonyl butoxide, along with the toxicology reference values for use in the human health risk assessment, are summarized in Appendix II, Tables 1 and 2.

3.1.1 Epidemiology data

In a prospective cohort study in New York, United States the neurodevelopment of children at 36 months of age who were born to mothers for which there was evidence of potential exposure to piperonyl butoxide during the third trimester of pregnancy was assessed. The results of this study revealed that children from these mothers with high levels of piperonyl butoxide in personal air samples scored lower on mental development tests than those with lower exposure levels. However, there were no significant associations noted between maternal exposure to piperonyl butoxide for 48 hours and the motor development of their offspring at 36 months of age (PMRA# 2418556). The lack of internal measures of piperonyl butoxide exposure in the mother, fetus or the 36-month-old child is a significant limitation in this study.

3.1.2 *Pest Control Products Act* hazard characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for piperonyl butoxide. The database contains the full complement of required studies including developmental toxicity studies in rats (two studies) and

rabbits (one study) and a two-generation reproductive toxicity study in rats. Two non-guideline developmental toxicity studies were also available for piperonyl butoxide (one in mice and one in rats). Four non-guideline developmental neurotoxicity studies that investigated a variety of dosage levels with different durations were also available in mice. Guideline neurotoxicity studies were not available for piperonyl butoxide but given the lack of neurotoxic findings throughout the database, the results of such studies would not be expected to significantly affect the risk assessment.

With respect to potential prenatal and postnatal toxicity, decreased pup weight was noted in the first and second generations of the two-generation rat reproduction toxicity study at a dose level that resulted in decreased body weight, body weight gain and food consumption in parental animals. In one of the two developmental toxicity studies in rats, there was an increased incidence of unossified cervical centra in the presence of maternal toxicity. In the second developmental toxicity study in rats and the developmental toxicity study in rabbits, no evidence of malformations or sensitivity of the young was noted. In a non-guideline developmental toxicity study in mice, an increased incidence of forelimb deformities was noted at a dose level that resulted in significant maternal toxicity in the dams following exposure to piperonyl butoxide on GD 9. In a non-guideline developmental toxicity study in rats with dosing on GDs 11 and 12, external limb deformities and decreased body weight were noted in fetuses at a dosage level that resulted in an effect on body weight in maternal animals. It should be noted that the limb deformities in mice and rats only occurred at doses in excess of the limit dose.

A series of non-guideline developmental neurotoxicity studies were conducted in piperonyl butoxide-exposed mice. These studies did not include a comprehensive assessment of maternal toxicity; only minimal effects were reported for the dams. In contrast, effects on body weight, olfactory orientation and surface righting were noted in the offspring. It was likely that hepatic hypertrophic responses were present in the dams at levels producing the developmental neurotoxicity based on overall consideration of the database.

Overall, the database for piperonyl butoxide is adequate for determining potential sensitivity of the young. The available studies indicated that there was a low degree of concern for potential sensitivity of the young provided endpoints protective of the hepatic hypertrophic responses were selected for risk assessment. As a result the *Pest Control Products Act* factor (PCPA factor) has been reduced to onefold.

3.2 Dietary exposure and risk assessment

In a dietary exposure assessment, Health Canada determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to piperonyl butoxide from potentially treated imported foods is also included in the assessment. These dietary assessments are age specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults.

Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

Heath Canada considers limiting the use of a pesticide when exposure exceeds 100% of the reference dose. The PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute and chronic risk assessment procedures.

Residue estimates used in the dietary risk assessment may be based conservatively (using upper bound estimates) on the maximum residue limits (MRLs) or the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency (CFIA) National Chemical Residue Monitoring Program and the United States Department of Agriculture's Pesticide Data Program. Theoretical and experimental processing factors as well as specific information regarding the percent of crops treated may also be incorporated to the greatest extent possible.

In situations where the need to mitigate dietary exposure has been identified, the following options are considered. Dietary exposure from Canadian agricultural uses can be mitigated through changes in the use pattern. Revisions of the use pattern may include such actions as reducing the application rate or the number of seasonal applications, establishing longer pre-harvest intervals (PHIs), and/or removing uses from the label. In order to quantify the impact of such measures, new residue chemistry studies that reflect the revised use pattern would be required. These data would also be required in order to amend the Canadian maximum residue limits (MRLs) to the appropriate level. Imported commodities that have been treated also contribute to the dietary exposure and are routinely considered in the risk assessment. The mitigation of dietary exposure that may arise from treated imports is generally achieved through the amendment or specification of MRLs.

The assessed uses are shown in Appendix I. Certain uses that could result in dietary exposure are proposed for cancellation due to lack of supporting data. Sufficient information was available to adequately determine the dietary exposure and risk to piperonyl butoxide for the remaining uses. Additionally, there are limitations to the available residue chemistry data, which may need to be addressed for future use expansions.

Acute and chronic dietary (food and drinking water) exposure and risk assessments for piperonyl butoxide were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™; Version 4.02, 05-10-c) program, which incorporates food consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) dietary survey for the years 2005–2010 available through the Centers for Disease Control and Prevention's National Center for Health Statistics. For more information on dietary risk estimates or residue chemistry information used in the dietary assessment, see Appendices III and IV.

The acute and chronic exposure estimates for food are considered to be refined, as percent crop treated, an experimental processing factor, domestic/import data, and monitoring data were used to the extent possible. However, the assessments retained a certain level of conservatism due to the use of MRLs/tolerances, anticipated residues (from relevant studies), and modelled Estimated Environmental Concentrations (EECs) for drinking water.

3.2.1 Acute Reference Dose (ARfD)

To estimate acute dietary risk, the NOAEL of 151 mg/kg bw/day from the 20-day dietary toxicity study in mice was selected for risk assessment. Decreased body weight and food consumption during the first few days of the study were observed at the next dosage level of 459 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The PCPA factor was reduced to onefold as discussed in the Pest Control Products Act Hazard Characterization section resulting in a composite assessment factor (CAF) of 100.

$$\textbf{ARfD} = \frac{\textbf{NOAEL}}{\textbf{CAF}} = \frac{\textbf{151 mg/kg bw/day}}{\textbf{100}} = \textbf{1.5 mg/kg bw of piperonyl butoxide}$$

3.2.2 Acute dietary exposure and risk assessment

The acute dietary risk was calculated considering the highest ingestion of residues of piperonyl butoxide that would be likely on any one day, and using food consumption values. The expected intake of residues is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the estimated exposure is less than the ARfD, the acute dietary exposure is acceptable.

The acute exposure assessment was conducted using maximum values from monitoring data, anticipated residues from relevant studies, or MRLs/tolerances. Residues were adjusted with domestic/import statistics, and experimental processing factors, when available, and all crops were assumed to have been 100% treated. Theoretical processing factors were used when experimental processing factors were not available. Drinking water contribution to the exposure was accounted for by direct incorporation of the acute (daily) EEC value obtained from water modelling (see Section 3.3.1) into the dietary assessment.

Based on the assessed use pattern, acute dietary risk was shown to be acceptable; however, as indicated in Section 3.2.4 below, the chronic dietary risk was not shown to be acceptable (see Section 3.2.4). As a result of the chronic and aggregate assessments, potential residues in raw cereals were removed from the dietary assessment, and an EEC from a lower cumulative application rate was incorporated (see Section 3.3.1 Concentrations in Drinking Water). With these mitigation measures, the acute dietary exposure estimates at the 95th percentile for the general population and all subpopulations range from 4–14% of the ARfD, with the highest exposure for children 1–2 years of age subpopulation. Therefore, acute risk is shown to be acceptable.

3.2.3 Acceptable daily intake (ADI)

To estimate risk from repeated dietary exposure, the NOAEL of 2.9 mg/kg bw/day from the 12-month dog dietary toxicity study was selected. At the LOAEL of 15.5 and 16.3 mg/kg bw/day (for males and females, respectively), decreased body weight and body weight gain and increased relative liver weight were noted in both males and females, along with decreased food consumption, increased alkaline phosphatase and mild atrophy of the testis in males. This study provides the lowest NOAEL in the database and is also of appropriate duration. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold, resulting in a CAF of 100.

$$\textbf{ADI} = \frac{\textbf{NOAEL}}{\textbf{CAF}} = \frac{\textbf{2.9 mg/kg bw/day}}{\textbf{100}} = \textbf{0.03 mg/kg bw/day of piperonyl butoxide}$$

The ADI provides a margin of greater than 700 to the lowest NOAEL for developmental toxicity in the mouse and is thus considered protective of all populations including pregnant women and their fetuses, infants and children. This ADI also provides a margin of greater than 1000 to the lowest NOAEL of 30 mg/kg bw/day for hepatocellular adenomas in male mice, and margins of greater than 8000 to the dose levels at which equivocal increases in lymphoreticular malignant lymphomas in female rats and lacrimal gland adenomas in male mice were observed.

3.2.4 Chronic (non-cancer and cancer) dietary exposure and risk assessment

The chronic dietary risk from food and drinking water was calculated using the average consumption of different foods and water, and the average residue values on those foods and water. This estimated exposure to piperonyl butoxide was then compared to the ADI. When the estimated exposure is less than the ADI, the chronic dietary exposure is shown to be acceptable.

The chronic assessment was conducted using monitoring data, anticipated residues from relevant studies, or MRLs/tolerances. Residues were adjusted with percent crop treated data and domestic/import statistics, and experimental processing factors, when available. Theoretical processing factors were used when experimental processing factors were not available. Drinking water contribution to the exposure was accounted for by direct incorporation of the chronic (yearly) EEC value obtained from water modelling (see Section 3.3.1) into the dietary assessment.

Based on the assessed use pattern, chronic risk was not shown to be acceptable, with raw cereals and drinking water residues driving the risk assessment. Potential residues in raw cereals were removed, and the EEC from a lower cumulative application rate was incorporated. With these mitigation measures, the chronic exposure estimates for the general population and all subpopulations range from 16–64% of the ADI, with the highest exposure for the children 1–2 years of age subpopulation. Therefore, chronic risk is shown to be acceptable.

Since potential residues from raw cereals were removed from the dietary assessment and the use is proposed for cancellation, the MRL for raw cereals is proposed for revocation in order to prevent imports with residues of piperonyl butoxide.

3.2.5 Cancer assessment

As previously discussed, an increased incidence of liver tumours was observed in mice and rats following long-term dosing. There was adequate evidence to support a threshold-based MOA for the liver tumours in mice and rats. The ADI and selected toxicology reference values for occupational and residential risk assessment provide sufficient margins to the dose levels at which these tumours were observed.

Also, as previously discussed, increased incidences of hemangioendothelial sarcomas in male and female CD-1 mice in a supplemental 52-week dietary carcinogenicity study and hemangiosarcomas in male and female F344 rats in a supplemental 2-year carcinogenicity study were not considered relevant to the human health risk assessment since they were observed at dose levels exceeding the maximum tolerated dose. For both the lacrimal gland adenomas noted in the supplemental 2-year chronic toxicity/carcinogenicity study in male B6C3F1 mice and the lymphoreticular malignant lymphomas observed in female F344 rats from a supplemental 2-year carcinogenicity study, the evidence for their relation to treatment was considered to be equivocal. Overall, the toxicology reference values selected for the non-cancer risk assessment are protective of any residual concerns regarding the carcinogenic potential of piperonyl butoxide.

3.2.6 Cancer dietary exposure and risk assessment

As noted above in Section 3.2.5, the ADI is protective of the observed tumours. As the chronic dietary risk was shown to be acceptable when the proposed mitigation is considered, the dietary cancer risk is also shown to be acceptable.

3.3 Exposure from drinking water

3.3.1 Concentrations in drinking water

Estimated environmental concentrations (EECs) of piperonyl butoxide combined residues (piperonyl butoxide and three transformation products) in potential drinking water sources were calculated using the Pesticides in Water Calculator (PWC V 1.52) model. Modelling for surface water used a standard Level 1 scenario, a small reservoir adjacent to an agricultural field. EECs in groundwater were calculated by selecting the highest EEC from a set of standard scenarios representing different regions of Canada. All scenarios were run for 50 years. (Refer to Appendix VII, Table 2 for information on the transformation products).

Table 3.1 Level 1 estimated environmental concentrations of the combined residue of piperonyl butoxide and PBO-alcohol, PBO-aldehyde and PBO-acid in potential sources of drinking water

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
26 applications of 336 g a.i./ha with an interval of 7 days (8736 g a.i./ha per year)	522	515	145	46
35 applications at 31.25 g a.i./ha with intervals of 3 days (1094 g a.i./ha per year)	65	65	16	3.9

[1] 90th percentile of daily concentrations
[2] 90th percentile of 365-day moving average concentrations
[3] 90th percentile of 1-day concentrations from each year
[4] 90th percentile of yearly average concentrations

When piperonyl butoxide is used according to the maximum label directions (for outdoor uses), the yearly groundwater EEC of 515 µg/L for 26 applications of 336 g a.i./ha with an interval of 7 days (8736 g a.i./ha per year) was considered appropriate for use in the chronic risk assessment. The daily groundwater EEC of 522 µg/L was considered appropriate for use in the acute risk assessment.

For the purposes of risk mitigation, EECs were also determined for a reduced use pattern such that the number of applications for outdoor uses was reduced from a yearly cumulative rate of 8736 g a.i./ha to less than 1100 g a.i./ha. While it is noted that the lower rate of 1094 g a.i./ha was based on a pasture use (that is proposed for cancellation), it was determined that the remaining outdoor uses could be represented by this EEC, and that the yearly cumulative rate was the appropriate value upon which to set reduced rates.

When piperonyl butoxide is used according to the proposed reduced use pattern, the yearly groundwater EEC of 65 µg/L for 35 applications at 31.25 g a.i./ha with intervals of 3 days (1094 g a.i./ha per year) was considered appropriate for use in the risk assessment. The daily groundwater EEC of 65 µg/L was considered appropriate for use in the acute risk assessment.

3.3.2 Drinking water exposure and risk assessment

Drinking water exposure estimates were combined with food exposure estimates, with EEC values incorporated directly in the dietary (food and drinking water) assessments. Please refer to Sections 3.2.2 and 3.2.4 for details and conclusions.

3.4 Occupational and non-occupational exposure and risk assessment

The use pattern that formed the basis of the occupational and residential risk assessments of piperonyl butoxide is summarized in Appendix I, Tables 1.1 and 1.2. The highest available application rates were used in the assessments, which included consideration of products with the highest concentration of piperonyl butoxide or largest net contents of product. When available, lower application rates were used for refinement purposes.

Occupational and residential risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce potential risk would be required.

3.4.1 Toxicology reference values

3.4.1.1 Short- and intermediate-term dermal

For short- and intermediate-term dermal occupational and residential risk assessments, the NOAEL of 1,000 mg/kg bw/day from the rabbit 21-day dermal toxicity study was selected. In this study, there were no treatment-related effects noted at the NOAEL of 1000 mg/kg bw/day (the highest dose tested). The target organ identified in oral studies, the liver, was adequately assessed in this dermal study. For residential and occupational scenarios, the target margin of exposure (MOE) is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. For residential scenarios, the PCPA factor was reduced to onefold as discussed in the *Pest Control Products Act* Hazard Characterization Section. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed women.

3.4.1.2 Long-term dermal

For long-term dermal occupational and residential risk assessments, the NOAEL of 1000 mg/kg bw/day from the rabbit 21-day dermal toxicity study was selected. In this study, there were no treatment-related effects noted at the NOAEL (highest dose tested) of 1000 mg/kg bw/day. The target organ identified in oral studies, the liver, was adequately assessed in this dermal study. For residential and occupational scenarios, the target MOE is 300, which accounted for a 10-fold uncertainty factor for interspecies extrapolation, a 10-fold uncertainty factor for intraspecies variability and an additional threefold factor to account for potential durational effects when using a short-term study for a long-term exposure scenario. For residential scenarios, the PCPA factor was reduced to onefold, as outlined in the *Pest Control Products Act* Hazard Characterization section. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed women.

3.4.1.3 Short- and intermediate-term inhalation

For short- and intermediate-term inhalation occupational and residential risk assessments, the LOAEC of 0.015 mg/L (~3.9 mg/kg bw/day) from the 90-day inhalation toxicity study in rats was selected. This LOAEC was based on an increased incidence of pseudostratified ciliated/nonciliated columnar epithelium-squamous/squamoid metaplasia/hyperplasia in the ventral seromucous glands of the larynx and dried red nasal discharge in males and females at this concentration. The target organ identified in oral studies, the liver, was adequately assessed in this inhalation study. For residential and occupational scenarios, the target MOE is 300, which accounted for a 10-fold uncertainty factor for interspecies extrapolation, a 10-fold uncertainty

factor for intraspecies variability and an additional threefold factor to account for the use of a LOAEC. As outlined in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to threefold for residential scenarios. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed women.

3.4.1.4 Long-term inhalation

For long-term inhalation occupational and residential risk assessments, the LOAEC of 0.015 mg/L (~3.9 mg/kg bw/day) from the 90-day inhalation toxicity study in rats was selected. At this LOAEC an increased incidence of pseudostratified ciliated/nonciliated columnar epithelium squamous/squamoid metaplasia/hyperplasia in the ventral seromucous glands of the larynx and dried red nasal discharge was noted in males and females at this concentration. The target organ identified in oral studies, the liver, was adequately assessed in this inhalation study. For residential and occupational scenarios, the target MOE is 1,000. A 10-fold uncertainty factor for interspecies extrapolation and a 10-fold uncertainty factor for intraspecies variability were applied, along with an additional 10-fold factor to account for the use of a LOAEC and to account for potential durational effects when using a short-term study for a long-term exposure scenario. As outlined in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold for residential scenarios. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed women.

3.4.1.5 Short-term non-dietary incidental oral ingestion

For short-term non-dietary oral ingestion risk assessment, the 12-month dietary toxicity study in the dog was chosen. A point of departure of 15.5 mg/kg bw/day was selected based on decreased body weight and body weight gain noted by 4 weeks at the next dosage level of 53 mg/kg bw/day, which was considered relevant for this duration. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold. The target MOE for this scenario was 100.

3.4.1.6 Intermediate- and long-term non-dietary incidental oral ingestion

For intermediate- and long-term non-dietary oral ingestion risk assessment, the 12-month dietary toxicity study in the dog was chosen. For the intermediate-term scenario, a NOAEL of 2.9 mg/kg bw/day was selected based on decreased body weight and body weight gain noted by 13 weeks at the next dosage level of 15.5 mg/kg bw/day. For the long-term scenario, a NOAEL of 2.9 mg/kg bw/day was selected based on decreased body weight and body weight gain, increased liver weight and mild atrophy of the testis in males noted at study termination at 52 weeks at the next dosage level of 15.5 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold. The target MOE for this scenario was 100.

3.4.1.7 Cancer risk assessment

As noted in Section 3.2.5, the selected toxicology reference values for occupational and residential risk assessment provide sufficient margins to the dose levels at which tumours were observed. Therefore, when margins of exposure are greater than the target MOE, both cancer and non-cancer risks are shown to be acceptable.

3.4.1.8 Dermal absorption

A dermal absorption value is not required since the toxicology reference values for dermal exposures were derived from a dermal toxicity study.

3.4.2 Residential exposure and risk assessment

Residential risk assessment involves estimating risks to the general population, including children, during or after pesticide application.

The USEPA has generated standard default procedures for developing residential exposure assessments for both applicator and post-application exposures when chemical- and/or site-specific field data are limited. These procedures may be used in the absence of, or as a supplement to, chemical- and/or site-specific data and generally result in high-end estimates of exposure. These procedures are outlined in the Standard Operating Procedures (SOP) for Residential Pesticide Exposure Assessments (USEPA, 2012).

The following sections from the USEPA Residential SOPs were used to assess residential exposure to piperonyl butoxide:

- Section 3: Lawns and Turf
- Section 4: Gardens and Trees
- Section 5: Outdoor Fogging/Misting Systems
- Section 7: Indoor Environments
- Section 8: Treated Pets

There are some uses on domestic-class piperonyl butoxide product labels that are not addressed in the USEPA Residential SOPs. For application to livestock, applicator and post-application exposure was determined based on the procedures for treated pets and modified for the livestock use, such as rates and numbers of animals. For applications to greenhouse ornamentals, which is specified on domestic-class labels only, exposure was determined based on Health Canada's standard approach for commercial greenhouses, modified for specific inputs related to non-commercial greenhouses, such as size. Since the greenhouse assessment is specific for non-commercial greenhouses, a label statement is proposed prohibiting use of piperonyl butoxide in commercial greenhouses.

In addition, the assessment for post-application exposure from swimming in treated bodies of water was based on the approach used in the USEPA occupational/residential risk assessment for rotenone (USEPA, 2006).

Several chemical-specific studies or scenario-specific studies that can be used in a generic manner were also used for the piperonyl butoxide assessment, as described below.

3.4.2.1 Residential applicator exposure and risk assessment

Residential applicators are adults who apply domestic-class piperonyl butoxide products that are registered for use inside and outside the home. Applicators are assumed to be adults (>16 years old) and to wear shorts, short-sleeved shirts, shoes and socks.

There is potential exposure to residential applicators applying piperonyl butoxide in and around homes and to pets (dogs/cats) and livestock. Based on typical use patterns, the representative scenarios identified were:

- Applying liquid formulations using a hose-end sprayer, backpack, and sprinkler can to outdoor ornamentals.
- Applying ready-to-use (RTU) pressurized products to indoor/greenhouse and outdoor ornamentals; general outdoor sites (including wasp and hornet nests); animal premises; inside homes and other indoor sites (including for control of bed bugs and clothing moths); and pets and livestock.
- Applying pressurized products as a total release fogger in indoor sites.
- Applying RTU liquid formulations using a hose-end sprayer to outdoor ornamentals.
- Applying RTU liquid formulations using a trigger spray bottle to indoor/outdoor ornamentals; general outdoor sites (including hornet and wasp nests), animal premises; inside homes and other indoor sites (including for control of bed bugs); and pets and livestock.
- Applying dust formulations using a bulb duster, plunger duster, shaker can, hand crank duster, and electric/power duster to outdoor ornamentals; animal premises; inside homes and other indoor sites (including control of bed bugs).
- Applying liquid formulations using a manually-pressurized handwand to indoor/greenhouse and outdoor ornamentals; animal premises; inside homes and other indoor sites (including for control of bed bugs and clothing moths).
- Applying liquid formulations as a fog to indoor/greenhouse and outdoor ornamentals; inside homes and other indoor sites (including for control of bed bugs).
- Applying RTU liquid formulation of shampoo and ear drops to pets.
- Applying RTU paste formulations as wipe-on (with cloth) to livestock.
- Loading pressurized products into a metered release automatic dispenser (space spray) in animal premises, inside homes and other indoor sites.

Residential applicators have the potential for short-to-intermediate term exposure when applying products containing piperonyl butoxide.

Route-specific MOEs for residential applicators are presented in Appendix V, Table 1. For dermal exposure, calculated MOEs exceeded the target MOE and risks were shown to be acceptable using the highest available application rates for all scenarios assessed. For inhalation exposure, calculated MOEs exceeded the target MOE and risks were shown to be acceptable except for indoor dust application using a shaker can. As it is not possible to prohibit specific

dust application equipment on domestic-class product labels, this use is proposed for cancellation. It may be possible to revisit this proposed cancellation if information regarding the use pattern (for example, application rates, product sizes, application directions, etc.) as well as how much is typically applied per day, is provided during the PRVD consultation period.

Total release foggers were assessed in the same way as RTU pressurized products for indoor space spray use; however, there are no data available to assess indoor or outdoor application for residential applicators using a handheld mister/fogger or mechanically-pressurized handheld sprayer for mists, aerosols, and fogs. Therefore, label directions are proposed to prohibit application using this type of equipment. It may be possible to revisit this proposed cancellation if further information is provided during the consultation period regarding the type of application equipment that would produce a fog-like spray and that would be used by residential applicators.

3.4.2.2 Residential post-application exposure and risk assessment

Residential post-application exposure refers to an exposure scenario in which an individual is exposed through dermal, inhalation, and/or incidental oral (non-dietary ingestion) routes as a result of being in a residential environment or contacting a surface that has been previously treated with a pesticide. Pesticide treatment could be by a residential applicator using a domestic-class product or a commercial applicator hired to treat the residential area or pet. The residential environment includes areas treated inside homes and other indoor areas where children would be present (for example, schools, hotel rooms, barns), areas treated outside the home (for example, gardens, yards, campgrounds), treated bodies of water (lakes, ponds, reservoirs) and treated pets and other animals (for example, horses). Since there are domestic-class products with label directions for livestock and livestock housing, agricultural premises were assessed as residential sites. Also, since there are domestic-class products with greenhouse uses, an assessment was conducted for individuals contacting treated ornamental plants in non-commercial greenhouses. For application to general outdoor areas, for example mosquito control in campgrounds, a standard assessment for outdoor fogging and turf uses was conducted. However, for application to golf courses, a golfer assessment was not conducted. Label directions were vague regarding the use in golf courses. Based on use information submitted for pyrethrins which is co-formulated with piperonyl butoxide, Health Canada assumed that the golf course use would be in marshy areas only. Health Canada is proposing a label statement to clarify that piperonyl butoxide is not to be applied to golf course greens, fairways and tees, which is where golfer exposure would occur.

Adults and children have the potential for post-application dermal exposure. Children aged 1 to < 2 years old also have the potential for incidental oral exposure. Although piperonyl butoxide itself is not volatile, inhalation exposure was considered when there is potential inhalation exposure of spray droplets, aerosols or dusts, depending on the formulation or application equipment (for example, space spray or fogging application).

For all scenarios, except for bed bug control, short- to intermediate-term exposure to adults and children was assumed. For applications to control bed bugs, post-application exposure may be long-term. While some scenarios may be of short-term duration only, given that toxicology reference values for dermal and inhalation exposures were the same for short- and intermediate-

term exposures, all scenarios were considered short- to intermediate-term in duration (which did not impact the risk assessments for short-term only durations). For incidental oral exposures, separate toxicology reference values were established for short-term and intermediate-term exposures. Although the incidental oral exposure for some scenarios may be short-term, the intermediate-term reference value was used for all scenarios, resulting in conservative estimates of risk

While exposure may occur for people of all ages, adults (>16 years old), youth (11 to <16 years old), and children (6 to <11 years old, 3 to <6 years old, and 1 to <2 years old) were chosen as the index lifestages to assess based on behavioral characteristics and the quality of the available data. For many scenarios it is assumed that younger children (in other words, 1 to <2 years old) would have higher exposure in these areas when playing or engaging in the types of activities associated with this lifestage (for example, crawling or mouthing) than would older children (in other words, >3 years old). For these scenarios, children 2 to <11 years were not assessed separately because their exposure is expected to be lower. The exception to this is for post-application exposure from swimming in treated waters; children 6 to <11 years were assessed separately based on the approach used in the USEPA assessment for rotenone (USEPA, 2006).

The following residential post-application exposure scenarios and sub-populations were assessed:

Residential Areas:

- Adults and children (1 to <2 years) dermal and inhalation exposure resulting from activities indoors (including agricultural premises) after space sprays, including metered release and total release foggers.
- Adults and children (1 to <2 years) dermal exposure resulting from activities indoors (including agricultural premises) after surface sprays.
- Children (1 to <2 years) incidental oral exposure resulting from activities indoors (including agricultural premises) after indoor surface and space sprays (including metered release and total release foggers).
- Adults, and children (1 to <2 years) dermal exposure resulting from activities on turf following applications to general outdoor areas, including for mosquito, fly or gnat control, and outdoor space spray applications.
- Adults and children (1 to <2 years) inhalation exposure resulting from activities on turf following applications to general outdoors including for mosquito, fly or gnat control, and outdoor space spray applications.
- Children (1 to <2 years) incidental oral exposure resulting from activities on turf following applications to general outdoors including for mosquito, fly or gnat control, and outdoor space spray applications.
- Adults, youth (11 to <16 years), and children (6 to <11 years) dermal and incidental oral exposure resulting from swimming following outdoor water applications
- Adults and children (6 <11 years) dermal exposure resulting from activities with treated indoor and outdoor ornamentals/plants.

Pets:

- Adult, and children (1 to <2 years) dermal exposure resulting from exposure to treated pets.
- Children (1 to <2 years) incidental oral exposure from treated pets.

For indoor sites (except greenhouses) and pets, it is assumed that individuals contact previously treated surfaces and pets on the same day the pesticide treatment is applied. Multiple applications were not assessed since exposure on the day of application (Day 0) without any dissipation was assumed for the entire duration of exposure. These assumptions would result in conservative or high-end estimates of exposure.

For outdoor sites and greenhouses, the application number and intervals varied greatly on labels. Survey data from the Outdoor Residential Exposure Task Force (ORETF) indicated that the average number of applications to gardens and trees for insect control by a residential applicator is 3 applications, with a 2-week interval between applications. This information was used in the post-application assessment for outdoor ornamentals. For non-commercial greenhouses, no data was available. It was assumed that the number of applications and frequency would be the same as for outdoor sites. Multiple applications were assessed assuming a dissipation rate of 10% and 2% per day for outdoor sites and greenhouse ornamentals, respectively.

Dermal exposure

Post-application dermal exposure can result from pesticide residue transfer to the skin of individuals who contact previously treated lawns, gardens, trees, pets, and indoor surfaces, and during activities such as recreation, gardening, or housework. Post-application dermal exposure was calculated using activity-specific transfer coefficients for treated foliage, surfaces and treated pet fur; dislodgeable/transferrable residue (residue transfer to skin); and exposure time.

A transfer coefficient is a factor that relates exposure to dislodgeable/transferrable residues and the amount of treated surface that a person contacts while performing activities in a given time period (usually expressed in units of cm^2 per hour). It is specific to a particular sub-population and activity/location (for example, children playing on soft surfaces such as carpets).

Post-application dermal exposure from swimming in treated bodies of water was calculated using the maximum chemical concentration of piperonyl butoxide in water, permeability constant, population-specific body surface areas, exposure times, and body weights.

Calculated dermal MOEs for residential post-application exposure exceeded the target MOEs for all populations and scenarios, and therefore, risks are shown to be acceptable. The residential dermal post-application risk assessment is outlined in Appendix V, Tables 2.1 to 2.4.

Inhalation exposure

Inhalation exposure to piperonyl butoxide was assessed for indoor and outdoor aerosol space sprays.

For outdoor mosquito, fly or gnat control applications using commercial class products (including truck-mounted and handheld fogging), inhalation MOEs were greater than the target MOE and risks were shown to be acceptable, except for pressurized products (rate of 0.0336 g a.i./m^2). To mitigate potential risks, it is proposed to cancel the mosquito, fly or gnat control use on commercial-class pressurized products.

For outdoor space sprays using domestic-class pressurized products for mosquito, fly or gnat control, the inhalation MOE did not exceed the target MOE and risks were not shown to be acceptable. To mitigate potential risks, it is proposed to cancel these domestic-class products.

Inhalation exposure from indoor space spray applications was assessed using the highest available rates for domestic- and commercial-class liquid and pressurized products (including total release foggers), and using two chemical-specific studies that monitored piperonyl butoxide air concentrations up to 2 hours following a pressurized product indoor space spray. Risks were not shown to be acceptable for all sub-populations when the study results were scaled to the highest available rates for piperonyl butoxide. However, the studies showed that aerosols settle after 2 hours and therefore, risks are considered to be acceptable provided that a 2-hour restricted-entry interval is implemented. For commercial-class products, a restricted-entry interval of 2 hours is proposed for indoor space spray uses. The commercial applicator is responsible for notifying workers, the homeowner, and others of the re-entry period requirement. As risk-based restricted-entry intervals are not considered a practical mitigation measure for domestic-class products; therefore, this use will be proposed for cancellation.

For metered release indoor space sprays, a chemical-specific study was available that monitored piperonyl butoxide air concentrations during a metered-release application over 12 days. Using the results from this study, calculated MOEs were greater than the target MOE and risks were shown to be acceptable under the conditions of the chemical-specific study.

As it is unknown how the rate in this study compares to the rates on labels of registered metered release products, the application rate for all metered release sprays will be limited to the application rate in this study (maximum of 1.07 mg a.i. released every 15 minutes).

It may be possible to revisit these proposed cancellations and mitigation measures due to inhalation exposure to aerosols if information regarding the use pattern (for example, application rates, product sizes, application directions, etc.), as well as the amount typically applied per day, is provided during the PRVD consultation period.

The results of the post-application inhalation risk assessment are summarized in Appendix V, Tables 3.1 and 3.2.

Incidental oral exposure

Post-application incidental oral exposure assumes that pesticide residues are transferred to the skin of children's (1 to <2 years old) hands while playing on treated grass, contacting indoor surfaces or interacting with treated pets, and are subsequently ingested as a result of hand-to-mouth transfer.

For indoor applications, residues that could result on children's toys and which could subsequently be ingested as a result of mouthing activity with the toy are also considered (object-to-mouth transfer). Soil can also be ingested while playing on treated grass as a result of normal mouthing activities.

Post-application incidental oral exposure from swallowing water while swimming in treated bodies of water was also considered for adults, youth (11 to <16 years), and children (6 to <11 years). Exposure was calculated using the potential maximum concentration of piperonyl butoxide in water, population-specific water ingestion rates, exposure duration, and body weights.

For incidental oral exposure from treated pets and outdoor scenarios, including swimming, calculated MOEs exceeded the target MOE and risks were shown to be acceptable. Exposure estimates are presented in Appendix V, Tables 4.1 and 4.2.

For indoor environments (including agricultural premises), calculated MOEs for hand-to-mouth exposure were greater than the target MOE and risks were shown to be acceptable, except for broadcast surface applications using the highest available rates for commercial and domestic-class products (Appendix V, Table 4.1). For object-to-mouth short- to intermediate-term incidental oral exposure scenarios, calculated MOEs were greater than the target MOE and risks were shown to be acceptable for some scenarios (for example, space spray, crack and crevice) but were not shown to be acceptable for broadcast, perimeter/spot, and bed bug surface spray applications using the highest available rates (Appendix V, Tables 4.3). As a result, further analysis and assessments were conducted for the surface spray uses taking into consideration formulation type, treatment type, and lower available application rates. When this mitigation is considered, calculated object-to-mouth MOEs were greater than the target MOE and risks were shown to be acceptable for at least one rate for all application methods (for example, broadcast, perimeter/spot) (Appendix V, Table 4.4).

For bed bug surface spray applications, an assessment for incidental oral exposure for the long-term duration of exposure was also conducted. Only the bed bug application scenarios for which risks were shown to be acceptable for the short- and intermediate-term object-to-mouth risk assessment were assessed. When the mitigation required for the short- to intermediate-term assessment is considered, calculated object-to-mouth MOEs were greater than the target MOE and risks were shown to be acceptable for the long-term duration for at least one rate for all application methods (for example, broadcast, perimeter) (Appendix V, Table 4.5).

Mitigation measures proposed for addition to product labels that are based on risk from incidental oral exposure are presented under the section on assessment of aggregate risks (see Section 3.5).

3.4.2.3 Bystander exposure and risk assessment

Piperonyl butoxide was detected in ambient air in urban and rural areas in France. A bystander inhalation assessment was conducted based on air concentrations from this study. It was assumed that bystanders would be exposed to these concentrations for several months (in other words,

intermediate-term duration). Using the highest measured air concentration, calculated MOEs for adults and toddlers were greater than the target MOE and, therefore, risks were shown to be acceptable (Appendix V, Table 7).

3.4.3 Occupational exposure and risk assessment

There is potential for exposure to piperonyl butoxide in occupational scenarios from workers handling the pesticide during the application process, and potential for post-application exposure from workers entering areas or handling pets previously treated with piperonyl butoxide.

3.4.3.1 Mixer, loader, and applicator exposure and risk assessment

For commercial-class products, there are potential exposures to piperonyl butoxide for mixers, loaders, applicators and other handlers. Workers handling piperonyl butoxide have the potential for short- and intermediate- term durations of exposure. Based on typical use patterns, the major scenarios identified were:

- Mixing/loading of liquids for automatic, stationary foggers and mistblowers, as well as stationary ULV aerosol generators or mechanical aerosol generators (space spray).
- Mixing/loading of liquids for airblast, aerial, boat, groundboom, truck-mounted ULV/fogging equipment, handheld airblast/mistblower, and mechanically-pressurized handheld sprayer for mists, aerosols, and fogs.
- Mixing/loading and applying liquids using handheld sprayers (in other words, mechanically-pressurized handgun, backpack, manually-pressurized handwand, mechanical aerosol generator /ULV aerosol generators (surface spray)).
- Applying liquids using truck-mounted ULV/fogging equipment.
- Applying liquids and pressurized products using handheld airblast/mistblower and mechanically-pressurized handheld sprayer for mists, aerosols, and fogs.
- Applying pressurized products using RTU can (including as a total release fogger).
- Applying liquids using airblast and groundboom.
- Applying liquids using aerial equipment.
- Applying liquids using boat equipment.
- Loading and applying dusts using bulb duster, plunger duster, hand crank duster.
- Applying dusts using shaker can, and electric/power duster.
- Applying pressurized products using metered release automatic dispensers.
- Applying liquids using trigger pump sprayer.
- Applying liquids and pressurized products as wipe-on (with cloth) to livestock.
- Applying liquids using dropper bottle to pets.
- Commercial applicator entering previously treated site to move/adjust total release fogger or automated fogger during application.

Personal protective equipment:

The exposure estimates for mixer/loaders and applicators are based on different levels of personal protective equipment (PPE) and engineering controls:

- Baseline PPE – long pants, long-sleeved shirt and chemical-resistant gloves.
- Maximum-Level PPE – chemical-resistant coveralls with a chemical-resistant hood over a long-sleeved shirt, long pants, socks and shoes, chemical-resistant gloves, and a respirator.
- Dust Mask – a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested.
- Respirator – a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides.

Inhalation exposures were based on light inhalation rates (17 L/min) except for backpack and handheld airblast/mistblower applicator scenarios, which are based on moderate inhalation rates (27 L/min).

Exposure data:

No appropriate chemical-specific handler exposure data were available for piperonyl butoxide. Therefore, dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database Version 1.1 (PHED), the Agricultural Handler Exposure Task Force (AHETF), the Outdoor Residential Exposure Task Force (ORETF) and other worker exposure studies. Data from the USEPA Residential SOPs (2012) were also used for application equipment not included in PHED, AHETF or ORETF.

PHED is a compilation of generic mixer/loader applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of personal protective equipment.

The AHETF was formed in 2001 with the objective of providing more up-to-date generic exposure data to replace the data currently being used in the PHED. The open cab airblast, open cab groundboom, closed cockpit aerial, and open mix/load liquid studies from AHETF were used.

For handheld airblast/mistblower (HH AB/MB) application equipment, (also referred to as "mechanically-pressurized handheld sprayer for mists, aerosols, and fogs"/MPHS for non-agricultural scenarios), unit exposures were determined from two worker exposure studies; one of these studies is from the Non-Dietary Exposure Task Force (NDETF). These studies were reviewed by Health Canada and the calculated dermal and inhalation unit exposures were determined to be representative of workers wearing a maximum level of personal protective equipment including chemical-resistant coveralls with a chemical-resistant hood and a respirator. These studies are also considered to address uses with ULV aerosol generators or mechanical aerosol generators and MPHS. Furthermore, where labels indicated application with pressurized products by mechanical equipment to produce fogs, it was assumed that this application equipment was most closely represented by HH AB/MB.

In addition, for application to indoor structures, a passive dosimetry study that monitored exposure of pest control operators (PCOs) applying liquid products indoors as a surface spray, using a manually-pressurized handwand, was used. This scenario was also used to address exposure for workers using mechanically-pressurized handheld ULV equipment for surface-directed sprays.The PHED data for manually-pressurized handwand were used for outdoor applications.

Where exposure data from the USEPA Residential SOPs were used, the clothing worn is representative of what a homeowner would wear (short-sleeved shirt, shorts, no gloves), which is considered to be an overestimate of exposure for commercial applicators who would wear standard work clothing (that is, long-sleeved shirt, long pants, chemical-resistant gloves). For application of dust products, it was necessary to account for the additional personal protective clothing (PPE) worn by commercial applicators. As the underlying studies for this scenario were not available to Health Canada, the unit exposure values for this application equipment from the USEPA Occupational Pesticide Handler Unit Exposure Surrogate Reference Table were used in the assessment.

There is one commercial-class product registered for application to pets, specifically by ear drop application. This use was assessed assuming that exposure would be less than that of liquid spot-on applications to pets. The spot-on application assessment was based on the USEPA Residential SOPs modified for commercial applicators (for example, number of animals treated). Also, there are a number of domestic-class products registered for application to pets with no similar commercial-class product registered. These include aerosol, trigger spray and shampoo applications. It is possible that commercial handlers (for example, veterinarians, groomers) may use these domestic-class products to treat pets. Occupational exposure from domestic-class pet products was assessed qualitatively in relation to the residential applicator assessment.

While there are limitations in the use of the above studies/data and approaches, these exposure data and methods represent the most reliable information currently available.

Risk assessment outcomes:

Route-specific MOEs for mixer/loaders and applicators are outlined in Appendix V, Table 5. Exposure for the dermal and inhalation routes of exposure did not need to be combined as they did not contribute to the same adverse toxicology endpoint. Calculated dermal and inhalation MOEs are greater than the target MOEs and, therefore, risks were shown to be acceptable for all scenarios at baseline PPE, except for scenarios noted below. Since risks were shown to be acceptable for most application equipment when handlers were wearing baseline PPE, label statements are proposed to be added to labels currently lacking this PPE.

The following additional PPE or other mitigation is proposed for the scenarios listed below:

- Application using a mechanically-pressurized handgun (MPHG) – respirator
- Application using handheld airblast/mistblowers (HH AB/MB) or mechanically-pressurized handheld sprayer (MPHS) for mists, aerosols, and fogs – maximum PPE, a

chemical-resistant hood, respirator; and workers must not handle more than 0.27 kg a.i. per day
- Indoor dust application – filtering facepiece respirator (dust mask)

For commercial handlers using domestic-class spot-on or shampoo products to treat pets, exposure was compared to the residential applicator in terms of amount of product handled, number of pets treated, PPE worn, and margins of exposure. For commercial users, the extent of exposure is uncertain; however, these workers typically wear PPE when applying pet products, such as a laboratory coat/apron. The number of animals treated per day by a worker with spot-on or shampoo products in animal facilities may be higher than for residential applicators treating their own pets. However, it was assumed that applying pet products is only one of many tasks that workers would do in a typical day, and it may not always be the same product being applied. Risks were shown to be acceptable for residential applicators (see Section 3.4.2), and based on the exposure considerations above, risks are expected to be acceptable for commercial users as well.

3.4.3.2 Post-application worker exposure and risk assessment

There is potential piperonyl butoxide exposure to workers entering treated sites, contacting treated surfaces, or handling treated pets. The occupational post-application assessment was conducted for the following uses:

- **Outdoor Scenarios**: workers conducting activities associated with outdoor ornamentals, pastures, outdoor residential sites such as campgrounds and golf courses.
- **Indoor Scenarios**: Workers entering treated residential, commercial, industrial or institutional locations (for example, food processing plants, warehouses, homes, schools, hotels and motels, pet kennels, livestock housing, etc.)
- **Livestock and Pet Uses (direct animal treatment)**: Veterinarians or other workers handling treated pets or livestock.
- **Treated bodies of water (lakes, ponds, reservoirs)**: Workers in or in contact with treated water.

No appropriate chemical-specific data were available to assess post-application exposure to workers.

Outdoor scenarios

A worker post-application assessment is conducted for outdoor ornamentals or other uses where workers enter treated areas to conduct agronomic activities involving foliar contact (for example, scouting). For outdoor ornamentals, post-application exposure activities include, but are not limited to, scouting, pruning, weeding. For golf courses and pastures, worker activities include scouting. Other activities were not considered for golf courses. Label directions were vague regarding the use in golf courses. Based on use information submitted for pyrethrins which is co-formulated with piperonyl butoxide, Health Canada assumed that the golf course use would be in marshy areas only. Health Canada is proposing a label statement to clarify that piperonyl

butoxide is not to be applied to golf course greens, fairways and tees, which is where significant worker activity and exposure can occur.

Based on the registered use pattern, there is potential for short- to intermediate-term post-application exposure to piperonyl butoxide residues for workers.

Post-application exposure would be primarily via the dermal route. Based on the vapour pressure of piperonyl butoxide, inhalation exposure would be low, provided that the minimum restricted entry interval is followed.

Potential dermal exposure to post-application workers was estimated using activity-specific transfer coefficients (TCs) and dislodgeable foliar residue (DFR) or turf transferrable residue (TTR) values. The DFR and TTR refer to the amount of residue that can be dislodged or transferred from a surface, such as the leaves of a plant or turf. The TC is a measure of the relationship between exposure and DFR/TTRs for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies. The TCs are specific to a given crop and activity combination, and reflect standard clothing worn by adult workers. Activity-specific TCs from the Agricultural Re-entry Task Force (ARTF) were used. For more information about estimating worker post-application exposure, refer to Health Canada's Regulatory Proposal PRO2014-02, *Updated Agricultural Transfer Coefficients for Assessing Occupational Post-application Exposure to Pesticides*.

Since no acceptable chemical-specific DFR/TTR studies were available for piperonyl butoxide, default values were used (peak DFR of 25% and TTR of 1% of the application rate and a dissipation rate of 10% per day). For further information on these default values, refer to the PMRA's Science Policy Note SPN2014-02, *Estimating Dislodgeable Foliar Residues and Turf Transferable Residues in Occupational and Residential Post-application Exposure Assessments*.

For workers entering a treated site, restricted-entry intervals (REIs) are calculated to determine the minimum length of time required before people can safely enter after application. An REI is the duration of time that must elapse before residues decline to a level where performance of a specific activity results in exposures above the target MOE.

The post-application exposure assessment is outlined in Appendix V, Table 6. Worker risks were shown to be acceptable at an REI of 12 hours for outdoor ornamentals and pastures, and when the sprays have dried for golf courses.

Exposure for post-application workers in outdoor residential areas, such as campgrounds, was assessed qualitatively. It was assumed that risks to post-application workers in these areas would be similar to or less than post-application risks for workers assessed above, such as workers working for 8 hours doing agronomic tasks for outdoor ornamentals, and is therefore acceptable.

Indoor scenarios

Exposure for post-application workers in commercial, industrial, institutional and residential locations was assessed qualitatively. Risks to post-application workers in these areas was assumed to be similar to or less than post-application risks determined for individuals living in

residential areas, since the time an individual spends in residential areas was assumed to be longer than their respective times in workplaces. For the majority of scenarios, risks were shown to be acceptable for residential post-application scenarios for adults (Section 3.4.2). For space spray applications (not including metered release), a 2-hour restricted-entry interval was proposed to mitigate potential inhalation risks. This mitigation measure would also be applicable for all commercial, industrial and institutional sites.

In residential sites, post-application risks from incidental oral exposure in children required mitigation. However, for commercial indoor sites (for example, food processing plants), where children are not expected to be present, risks are considered to be addressed by the residential dermal assessment for adults, for which risks were shown to be acceptable for broadcast application at the highest rate. Therefore, the mitigation required to address risks to children in residential sites would not be required for non-residential sites. Statements need to be added to all relevant labels to clearly define and establish the conditions of use for residential areas where children may be present versus non-residential areas where only adults would be present.

Exposure following applications in animal housing, including poultry houses, was assessed in the residential assessment as agricultural premises (Section 3.4.2). The agricultural premises were addressed in the same manner as all indoor residential sites. Therefore, worker exposure in animal housing would be addressed by the residential assessment, as noted above, including the requirement of a 2-hour restricted-entry interval for space spray applications (not including metered release), and different mitigation measures depending on whether the animal housing is considered a residential site where children could be present versus a non-residential site where children are not present.

Livestock and pet uses (direct animal treatment)

Exposure for post-application workers in contact with treated pets and livestock was assessed qualitatively. It was assumed that risks to workers handling treated animals would be similar to or less than a pet owner in contact with their own treated animal, since the time an individual spends in contact with their pet is assumed to be longer than that for farmers in contact with livestock (for example, cows) or for veterinarians or other workers handling treated pets. The residential assessment is discussed in Section 3.4.2.

Treated bodies of water (lakes, ponds, reservoirs)

It is unknown whether workers would enter treated bodies of water after application of piperonyl butoxide or whether workers would handle the treated water. Regardless, the residential assessment conducted for swimmers immediately following application would address this scenario for workers. Risks were shown to be acceptable for residential swimmers (Section 3.4.2).

3.5 Aggregate exposure and risk assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation).

3.5.1 Toxicology reference values for aggregate risk assessment

For short- and intermediate-term oral and inhalation aggregate risk assessment for all populations, toxicology endpoints related to hepatotoxicity were selected for aggregation. It was not necessary to aggregate exposure via the dermal route owing to the absence of hepatotoxic effects at the limit dose of 1000 mg/kg bw/day in a 21-day dermal toxicity study conducted in rabbits with piperonyl butoxide. For the oral route, the point of departure of 15.5 mg/kg bw/day from the 12-month oral toxicity study in dogs was selected based on increased liver weight, elevated enzyme levels and altered pathology at 53 mg/kg bw/day. For the inhalation route, the point of departure of 40.4 mg/kg bw/day from the 90-day inhalation toxicity study in rats was selected based on increased liver weight, elevated enzyme levels and pathology of the liver at 134 mg/kg bw/day. A target MOE of 100 was derived for both the oral and inhalation aggregate risk assessments, which included standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As discussed in the *Pest Control Products* Act Hazard Characterization Section, the PCPA factor was reduced to onefold.

For long-term aggregate risk assessment for all populations, it was not necessary to aggregate exposure via the inhalation route since this route was not considered relevant to the exposure scenario. It was also determined to be unnecessary to aggregate exposure via the dermal route owing to the absence of systemic toxicity or hepatotoxicity at the limit dose of 1000 mg/kg bw/day in the 21-day rabbit dermal toxicity study. For the assessment of long-term oral aggregate exposure via the diet, drinking water and non-dietary incidental oral ingestion, the NOAEL of 2.9 mg/kg bw/day in the 12-month dog dietary toxicity study with piperonyl butoxide was selected. This NOAEL was selected based on decreased body weight and body weight gain and increased relative liver weight, which were noted in both males and females along with decreased food consumption, increased alkaline phosphatase and mild atrophy of the testis in males at the LOAEL of 15.5 mg/kg bw/day. This study provides the lowest NOAEL in the database and is also of appropriate duration. A target MOE of 100 was selected which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The PCPA factor was reduced to onefold as discussed in the *Pest Control Products Act* Hazard Characterization Section.

3.5.2 Residential and dietary aggregate exposure and risk assessment

In an aggregate risk assessment, the combined potential risk associated with food, drinking water and various residential exposure pathways is assessed. A major consideration is the likelihood of co-occurrence of exposures and durations of exposures. Additionally, only exposures from routes that share common toxicology endpoints can be aggregated. As noted above, dermal exposures were not included in the aggregate assessment due to the absence of a common toxic effect (hepatotoxicity).

Aggregate assessments were conducted for the following scenarios which are expected to co-occur:

- Following application of commercial-class products for mosquito, fly and gnat control in outdoor residential areas (for example, campgrounds, parks, etc.):

    - For adults, post-application inhalation exposure + dietary exposure (food + drinking water)
    - For children, post-application incidental oral exposure + dietary exposure (food + drinking water)

- Following application of domestic-class products to non-commercial greenhouse ornamentals and outdoor ornamentals (for example, gardens, trees):
    - For adults, applicator inhalation exposure + dietary exposure (food + drinking water)

- Following application of commercial-class or domestic-class products to indoor surfaces and spaces to control all relevant pests except bed bugs, and not including metered release automatic dispensers (for example, homes, hotels/motels, agricultural premises as noted on domestic-class labels, etc.):
    - For adults, applicator inhalation exposure + dietary exposure (food + drinking water)
    - For children, post-application incidental oral exposure + dietary exposure (food + drinking water)

- Following application of commercial-class or domestic-class products to indoor surfaces and spaces to control bed bugs, and <u>not including</u> metered release automatic dispensers (for example, homes, hotels/motels, agricultural premises as noted on domestic-class labels, etc.):
    - For children, post-application incidental oral exposure + dietary exposure (food + drinking water)

- Following indoor application of commercial-class or domestic-class metered release automatic dispenser products (for example, homes, hotels/motels, agricultural premises as noted on domestic-class labels, etc.):
    - For adults, post-application inhalation exposure + dietary exposure (food + drinking water)
    - For children, post-application inhalation exposure + incidental oral exposure + dietary exposure (food + drinking water)

- Following application of commercial-class or domestic-class products to pets or livestock (livestock that appear on domestic-class labels):
    - For adults, applicator inhalation exposure + dietary exposure (food + drinking water)
    - For children, post-application incidental oral exposure + dietary exposure (food + drinking water)

There would also be potential aggregate exposure to swimmers following application of piperonyl butoxide to bodies of water (post-application dermal and/or incidental oral) or bystanders exposed to ambient air (inhalation) with chronic and dietary exposure. These scenarios were considered qualitatively. The pathway- and route-specific MOEs for these

scenarios exceeded the target MOE by several orders of magnitude, and therefore the contribution to the total aggregate exposure (diet and drinking water) is minimal and aggregate risks are acceptable.

All aggregate scenarios were considered to be short- to intermediate-term in duration, with the exception of application to indoor surfaces to control bed bugs, which was considered to be long-term.

For short- and intermediate-term aggregate risk, oral and inhalation routes of exposure were aggregated. Although for most residential scenarios, dermal exposure was the predominant route for adults, and both oral and dermal routes were predominant for children, the dermal route did not have a common toxic effect and was not included in the aggregate assessment. There were limited scenarios with co-occurrence of oral or inhalation exposures. In some situations, aggregation was limited to oral exposures only, such as for children with incidental oral exposures aggregated with dietary (food and drinking water exposures.)

The results of the short- to intermediate-term aggregate risk assessment are summarized in Appendix VI, Table 1. All scenarios had MOEs greater than the target MOEs, and therefore, risks were shown to be acceptable provided that the mitigation measures considered for route-specific assessments were considered.

The results of the long-term aggregate risk assessment (in other words, post-application risks to children following surface spray application to control bed bugs) are presented in Appendix VI, Table 2. The aggregate risk assessment was conducted based on the mitigation measures proposed for the route-specific assessments. Even with these mitigation measures, the MOEs for broadcast application with commercial-class dust and pressurized products were less than target MOE, even at the lowest available application rate. Therefore, for these uses risks were not shown to be acceptable and these uses are proposed for cancellation. Risks for the remaining scenarios were shown to be acceptable, provided that the application rates and treatment type (for example, perimeter/spot, crack and crevice) are restricted as noted in the assessment outlined in Appendix IX Tables 1 and 3.

In conclusion, for indoor surface applications, aggregate risks were shown to be acceptable for the following uses:

Commercial-class liquid products:

- Applications at lowered label rates, or current rates depending on treatment type.

Commercial-class pressurized products:

- For all pests except bed bugs, applications as broadcast, perimeter/spot, crack and crevice, at lowered or current label rates, depending on treatment type.
- For bed bugs, applications as perimeter/spot at lowered label rates. These products may also be applied at current label rates for crack and crevice treatments with specific label directions for bed bugs (for example, tufts and seams of mattresses only).

Commercial-class dust products:

- For all pests except bed bugs, applications at current label rates.
- For bed bugs, applications as perimeter/spot or crack and crevice at current label rates with specific label directions for bed bugs.

Domestic-class products:

- For all pests, applications for liquid products at lowered label rates.
- For all pests except bed bugs, applications for pressurized products at current or lowered rates, depending on treatment type.
- For bed bugs, applications for pressurized products at lowered label rates, with specific directions for bed bugs.

3.6 Cumulative assessment

The *Pest Control Products Act* requires that Health Canada consider the cumulative exposure to pest control products with a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for piperonyl butoxide. Health Canada did not identify information indicating that piperonyl butoxide shares a common mechanism of toxicity with other pest control products. Therefore, there is no requirement for a cumulative health risk assessment at this time.

3.7 Incident reports

Health incident reports

As of 14 January 2020, Health Canada received 1337 domestic animal and 274 human incidents involving piperonyl butoxide. In most of these incidents, the reported piperonyl butoxide product was co-formulated with pyrethrins and/or other active ingredients (for example, synthetic pyrethroids, MGK-264, s-methoprene). The products reported in incidents were used either on companion animals or at residential sites.

Incidents involving products for use on companion animals

Piperonyl butoxide incidents involving companion animals mainly involved pets (cats and dogs) treated with an animal spray or shampoo product used in the control of fleas and ticks (1039 reports). The piperonyl butoxide products reported in Canadian incidents also frequently contained the active ingredient pyrethrins. The reported effects in animals were mainly minor (for example, itchy skin) or moderate (for example, tremors) in severity. The potential for life-threatening effects including death was considered low given the few serious incidents reported over a 12-year period. In addition, no consistent patterns were noted in the serious incident reports.

Overall, the high number of incident reports as well as the minor nature of the signs reported in animals suggests a potential for adverse effects in cats and dogs when products are being used as per label directions. It is therefore proposed that the labels of all co-formulated piperonyl butoxide sprays or shampoo products be updated to inform the consumer of possible side effects

that may be expected in their pets following the use of these products. The proposed recommendations are similar to those outlined in the 2019 PMRA Guidance Document, Label Improvements for Spot-on Pesticides Used on Companion Animals. In addition, it is recommended that the product labels be amended to reflect the statements as outlined in DIR2002-01, Canadian Label Improvement for Pesticides used on Companion Animals, in order to address the deficiencies and/or inconsistencies noted in the precautionary and use direction statements across the various registered products.

Incidents involving products used at residential sites

Piperonyl butoxide incidents at residential sites were mainly associated with domestic class residential sprays or foggers (202 reports). The products reported in incidents were co-formulated with pyrethrins and/or synthetic pyrethroids. A trend analysis conducted on incidents involving synthetic pyrethroid products (2011 Report on Pesticide Incidents), as well as the review of human incidents involving co-formulated pyrethrins products identified a potential for inhalation or dermal exposure to people and pets following or during treatment of indoor areas. The reported exposure scenarios in people included inhaling the product mist when applying the product in enclosed areas or coming in contact with treated surfaces.

In general, the symptoms reported in people following exposure were mainly minor or moderate in severity and included signs such as respiratory tract irritation or nausea. There were 12 serious incidents (1 Canadian, 11 American) that were considered to be related to the reported product. In the Canadian incident, a person reported respiratory irritation for a period of over six months after misapplication of a domestic class product containing piperonyl butoxide and other synthetic pyrethroids. No action was taken by Health Canada given the manner in which the product was used and the vague details on the reported product exposure. In the serious American incidents, the reported exposure scenarios included product application or residing in treated areas. The signs reported in people included respiratory distress, seizures, muscle weakness, burns or chest discomfort. In the American incident involving death, a person with a pre-existing chronic respiratory condition experienced cardiac arrest after remaining in a home treated with a pesticide fogger co-formulated with piperonyl butoxide, pyrethrins and other synthetic pyrethroids. In this incident, the label directions of the United States product were not followed.

Overall, the review of human incidents involving piperonyl butoxide products containing pyrethrins and/or synthetic pyrethroids (for example, permethrin) for use at residential sites indicates a potential of incidental oral and/or dermal exposure to people when products are used as per label directions. The current label language on co-formulated piperonyl butoxide products that were most frequently reported in incidents were found to be somewhat vague and non-specific. Label amendments as outlined in the PMRA 2020 Guidance Document: Structural Pest Control Products: Label Updates are therefore proposed for all domestic class co-formulated piperonyl butoxide products for use at residential sites in order to minimize the likelihood of exposure of people and animals following product use.

4.0 Environmental assessment

4.1 Fate and behaviour in the environment

A summary of environmental fate data for piperonyl butoxide is presented in Appendix VII, Table 1.

Behaviour in Soil
In aerobic soil, piperonyl butoxide is slightly to moderately persistent, with biodegradation and photolysis being major transformation pathways. Two major transformation products, piperonyl butoxide -acid and M2 (2-[(6-propyl-1,3-benzodioxol-5-yl)methoxy] ethoxy}acetic acid) are formed as a result of microbial degradation, neither of which are expected to be persistent in soil. On soil surfaces, sunlight breaks down piperonyl butoxide rapidly (<3 days), forming piperonyl butoxide -alcohol, piperonyl butoxide -acid and piperonyl butoxide -aldehyde. Piperonyl butoxide has a high affinity to bind to soil particles and is not expected to leach through soil and reach groundwater, except in sandy soils.

Behaviour in water
Piperonyl butoxide is soluble and is not expected to volatilise from the surface of water or moist soil. A portion of the piperonyl butoxide in aerobic water systems is expected to partition to sediment. Piperonyl butoxide is slightly persistent in aerobic water, with biodegradation and photolysis being major routes of degradation. The major transformation products produced include piperonyl butoxide -aldehyde, piperonyl butoxide -alcohol, piperonyl butoxide -acid and M2 (2-[(6-propyl-1,3-benzodioxol-5-yl)methoxy] ethoxy}acetic acid) which are all soluble in water, non-persistent and are not expected to partition to sediment in aquatic systems. In anaerobic aquatic systems, piperonyl butoxide is moderately persistent, with the major transformation product being piperonyl butoxide-acid.

Behaviour in air
Piperonyl butoxide and major transformation products are not expected to volatilize from water surfaces or moist soil (Henry's law constant (1/H) for piperonyl butoxide of 1.57E+12) and are not persistent in air.

Bioaccumulation
Piperonyl butoxide has a log K_{ow} of 4.8, which suggests it has potential to bioaccumulate. Studies demonstrate that piperonyl butoxide is rapidly eliminated from fish tissue and, therefore, bioaccumulation is not expected.

4.2 Environmental risk characterization

A summary of ecotoxicity data for piperonyl butoxide is presented in Appendix VII, Table 3.

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. EECs are calculated for pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models, which take into consideration the

application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints.

Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

The EECs for the screening level were based the highest registered single application rate, which is of 732 g a.i./ha for commercial outdoor ornamental use. Labels do not identify a minimum application interval, but they do identify a maximum number of applications per season (10). As such, for the screening level risk assessment, a conservative approach was used, assuming application up to 10 times with 1-day application interval, resulting in a maximum cumulative application per season of 6943 g a.i./ha. The screening level environmental risk assessment conducted for piperonyl butoxide is conservative in that it assumes application at the highest registered application rate every day for 10 consecutive days.

To determine exposure to birds and mammals via piperonyl butoxide contaminated food items, it was assumed that 100% of the spray droplets are deposited directly onto vegetation and other food sources. For pollinators, during spray application, adult forager bees may be exposed to spray droplets during flight through direct contact. Pollinators can also be exposed to piperonyl butoxide residues via food sources, and as such, screening level EECs are based on piperonyl butoxide residues on tall grass as a surrogate for residues in pollen and nectar of flowers that are directly sprayed. For both contact and dietary exposures, levels were based on the maximum single application rate for commercial outdoor ornamentals.

For aquatic organisms, screening level EECs for piperonyl butoxide in water were calculated assuming a conservative scenario of direct application to water bodies of two different depths (80 and 15 cm). The 80 cm water body was chosen to represent a permanent body of water and 15 cm was chosen to represent a seasonal body of water. The permanent body of water was used to assess the risk to aquatic organisms that depend on a permanent water body (in other words, fish) whereas, the seasonal body of water was used to assess the risk to organisms that use seasonal bodies of water (in other words, amphibians). The pesticide is assumed to be instantaneously and completely mixed within the water body.

Other registered uses have application rates that are 16–73 times lower than the rates used in the screening level assessment. In addition, potential risks identified at the screening level for piperonyl butoxide are relatively low as compared to potential risks associated with co-formulated insecticides.

For greenhouse uses, terrestrial and aquatic environmental exposure is not expected outside of the greenhouse and, therefore, risks to pollinators and non-target arthropods are expected to be limited to those found inside the treated greenhouse.

4.2.1 Risks to terrestrial organisms

Results of the terrestrial risk assessment are presented in Appendix VII, Table 4.

The potential for acute risk to pollinators, earthworms, beneficial insects (aphid parasitoids and predatory mites), birds, and terrestrial plants as well as chronic risks to earthworms and birds were assessed. At the screening level, no risks of concern were identified for earthworms, predatory mites or parasitic aphids.

Pollinators
At the screening level, potential risks to pollinators were identified on an acute oral basis (RQ values up to 34). Because piperonyl butoxide is always co-formulated with another insecticide, the labels for all co-formulated insecticides include mitigation measures that will also reduce the risks associated with piperonyl butoxide to pollinators. Risks to pollinators are acceptable when mitigation instructions on end-use product labels are followed.

Birds and mammals
At the screening level, potential risks were identified for birds (RQ up to 16) and mammals (RQ up to 5) based on conservative assumptions (highest application rates, 10 applications applied once a day over a 10-day period). Piperonyl butoxide is always co-formulated with an insecticide. All registered co-formulated products have terrestrial spray buffer zones that help limit spray drift to non-target areas. As a result, risks to birds and mammals are considered to be acceptable when mitigation instructions on end-use product labels are followed.

Terrestrial vascular plants
Potential risks identified at the screening level for terrestrial vascular plants are low (RQ = 4.5). Given the conservative nature of the screening level risk assessment, risks are considered acceptable when the formulated product is used according to label instructions.

4.2.2 Risks to aquatic organisms

Results of the aquatic risk assessment are presented in Appendix VII, Table 4.

The potential for risks to freshwater invertebrates, freshwater fish, amphibians, freshwater algae, marine fish, marine invertebrates, and marine bivalves were evaluated in this assessment. At the screening level, no risks of concern were identified for freshwater algae, invertebrates and bivalves. Potential risks of concern were identified for freshwater invertebrates, freshwater fish, amphibians and marine fish.

The aquatic screening level risk assessment was conducted using the highest cumulative application rate for commercial application on ornamentals. This conservative assessment assumes 10 applications at 1-day intervals, which is unlikely. This results in EECs of 4.63 mg/L in the 15 cm deep scenario and 0.87 mg/L in the 80 cm deep scenario. Available monitoring data had a maximum detection of 0.45 µg/L, with only two detections in 242 surface water samples. Data from the United States detected PBU in 7.34% of 13893 samples, with a maximum detection of 1.43 µg/L. These concentrations are orders of magnitude lower than those estimated in the screening level risk assessment. Other registered uses are domestic applications with rates that are 16–73 times lower than the rate used for the screening level. Considering that the estimated risk quotients are relatively low at the screening level, it can be reasonably expected that the other uses would be proportionately lower than indicated at the screening level. Overall, risks to aquatic organisms are acceptable when end-use label directions are followed.

Synergistic effects associated with the co-formulation of piperonyl butoxide with other insecticides have been assessed through the evaluations of other pesticides. Risk mitigation measures required for co-formulated end-use products provide adequate mitigation for risks associated with the use of piperonyl butoxide in the formulation.

Ecotoxicity endpoints for sediment dwelling amphipods (*Hyalella azteca*) were available for three major transformation products (piperonyl butoxide-alcohol, piperonyl butoxide-acid and piperonyl butoxide-aldehyde), but the risks could not be assessed as fate data to calculate EECs for the transformation products was lacking. Conservatively assuming that the transformation products are present at levels comparable to the parent (piperonyl butoxide), results in slight risks of concern on an acute basis for piperonyl butoxide-alcohol and piperonyl butoxide-aldehyde, but not for piperonyl butoxide-acid. Risks to sediment dwelling amphipods from piperonyl butoxide transformation products are acceptable.

4.2.3 Environmental incident reports

Canadian Incident Reports

As of 28 June 2019, 31 environment incidents involving products containing piperonyl butoxide were submitted to Health Canada. The incidents were classified as either minor (30 reports) or moderate (1 report). The incidents involved effects on herbaceous plants (25 incidents), trees or shrubs (4 incidents), and songbirds (1 incident).

As piperonyl butoxide is a synergist, end-use products are always co-forumulated with a pesticide active ingredient. Environment incidents with pyrethrin products co-formulated with piperonyl butoxide frequently occurred at residential sites. Scotts Ecosense Bug-B-Gon Ready to Use Insecticide (PCP Reg. No. 28379) was commonly reported in incidents (20 reports), with the product being applied to either lawns, various types of plants (tomato, beans, ornamentals, marijuana etc.) or fruit trees. Damage reported in plants included visible injury, leaf discoloration or plant mortality. In addition to the above incidents, there was one minor incident involving barn swallows (songbird). In this incident, a pyrethrin product co-formulated with piperonyl butoxide was applied to horses in a barn. Sometime following application, the caller reported finding three to four dead barn swallows in a barn stall. The majority of the reports for plant incidents were assigned causality levels of either possible or probable given i) the consistency of the damage reported in the incidents and ii) results from a published study which indicated non-lethal plant damage to commercially grown greenhouse plants following application of a product containing piperonyl butoxide at recommended application rates. The incident regarding barn swallows did not provide sufficient information to determine if exposure had occurred and was classified as such.

United States environmental incidents

The U.S. EIIS (Ecological Incident Information System) database was queried for environment incidents involving pyrethrins that occurred in the U.S. As of October 2015, there were 22 incidents involving pyrethrins. Most pyrethrin incidents involved plants (34 reports). Most these incidents were assigned the certainty index of "possible" or higher (20 incidents). Other incidents involved aquatic organisms (2) and terrestrial organisms (9). Aquatic organisms included fish, flounder, grass shrimp or fluke; plants included ornamentals, roses or sunflowers; and terrestrial organisms included honeybees, bumblebees, monarch butterflies or Canada goose. Exposure scenarios reported in incidents include direct treatment with a product containing piperonyl butoxide in agricultural or residential areas, product ingestion as well as drift/run-off from treated sites. Reported signs in plants following exposure was noted as plant damage and mortality. In terrestrial and aquatic organisms, mortality was noted following exposure.

In two incidents, fish mortality was reported in unknown fish species either following run-off from an intentional misuse of a pyrethrin product formulated as a dust or from exposure to a pyrethrin dip product that was applied to a dog.

Given the trends observed in the current and previous review of the environmental incident data, the following label statements are proposed for products containing pyrethrins and piperonyl butoxide in order to minimize the likelihood of plant damage or death.

- Do not wet plants to the point of run-off or drip.
- Before making widespread applications of this product, treat a limited number of plants and observe for plant damage over a 10-day period.

5.0 Value assessment

Piperonyl butoxide is a synergist that is co-formulated with other insecticides. It does not have a direct pesticidal mode of action, but acts to increase the overall efficacy of other active ingredients.

Pyrethrins and pyrethroids are a component of a successful integrated pest management program to control domestic pests, such as bed bugs, cockroaches, fleas, and indoor ants. Since the majority of commercial products used to control these pests contain both piperonyl butoxide and pyrethrins or pyrethroids, retaining piperonyl butoxide will maintain effective pest control options for pest control operators. One exception is the label claim related to killing lice on mattresses, bedding, furniture, and garments. Lice die in the absence of a host; therefore, infestations on mattresses, bedding, furniture, and garments would cease on their own or in conjunction with cultural control strategies (for example, laundry for garments and vacuuming). There is little to no value in treating various lice species when off the host; therefore, these claims are proposed for cancellation.

6.0 Pest control product policy considerations

6.1 Toxic substances management policy considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, in other words, those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

- During the review process, piperonyl butoxide and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-031 and evaluated against the Track 1 criteria. Health Canada has reached the conclusion that piperonyl butoxide and its transformation products do not meet all of the TSMP Track 1 criteria.

See Appendix VII, Table 5 for comparison with Track 1 criteria.

6.2 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the technical grade active ingredient and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada*

Gazette.[5] The list is used as described in the Health Canada Notice of Intent NOI2005-01[6] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[7] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). Health Canada has reached the following conclusions:

- Technical grade piperonyl butoxide does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*
- End-use products do not contain any formulants of health or environmental concern identified in the *Canada Gazette* with the exception of the end-use product Prentox Nusyn-Noxfish Fish Toxicant (Reg. No. 19985), which is co-formulated with rotenone and contains aromatic petroleum distillates (APDs). Health Canada will seek to reduce APD levels or substitution with another less toxic formulant. The following statement will be added to the label for the end-use product Nusyn-Noxfish Fish Toxicant (PCP# 19985): "This product contains aromatic petroleum distillates that are toxic to aquatic organisms."

The use of formulants in registered pest control products is assessed on an ongoing basis through Health Canada formulant initiatives and Regulatory Directive DIR2006-02.[8]

7.0 Conclusion of science evaluation

Value

Piperonyl butoxide is of value to users as it enhances the effectiveness of other co-formulated active ingredients that control a broad spectrum of insect pests. Piperonyl butoxide is an important component of integrated pest management of common household pests, such as bed bugs, cockroaches, fleas, and indoor ants. Piperonyl butoxide does not have value in treating various lice species when off the host.

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5 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

6 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

7 DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

8 DIR2006-02, *PMRA Formulants Policy*.

Health

With respect to human health, the health risks associated with the use of piperonyl butoxide and associated end-use products are acceptable when these products are used according to the proposed revised label directions, including cancellation of some uses (Appendix IX).

Data are required to confirm that the application rates and use directions on current product labels are consistent with the rates used in the residential, bystander and occupational risk assessments.

Although not required, the registrants and other stakeholders may submit information that may address uncertainties in the available information database of piperonyl butoxide to support refinement of the risk assessment and, subsequently, change the proposed mitigation.

Environment

In terrestrial environments, piperonyl butoxide is not expected to pose a risk to populations of birds, mammals, earthworms, non-target arthopods and terrestrial plants. Because piperonyl butoxide is always co-formulated with another insecticide, the labels for all co-formulated insecticides include mitigation measures that will also reduce the risks associated with piperonyl butoxide. In aquatic environments, spray buffer zones required for other insecticides that are co-formulated with piperonyl butoxide will help mitigate potential risks associated with piperonyl butoxide. When used according to instructions on end-use product labels, environmental risks associated with piperonyl butoxide are acceptable.

List of abbreviations

↑	increased
↓	decreased
µg	microgram(s)
♀	females
♂	males
8-OHdG	8-hydroxydeoxyguanosine
a.i.	active ingredient
abs	absolute
ACET-OH	acetanilide hydroxylation
ADI	acceptable daily intake
AHETF	Agricultural Handler Exposure Task Force (AHETF)
AhR	aromatic hydrocarbon-responsive receptor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APD	aromatic petroleum distillates
AR	applied radioactivity
ARfD	acute reference dose
ARα	androgen receptor
ARTF	Agricultural Re-entry Task Force
AST	aspartate aminotransferase
atm	Atmospheres
BCF	bioconcentration factor
BUN	blood urea nitrogen
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Society
CFIA	Canadian Food Inspection Agency
ChE	cholinesterase
CHO	Chinese hamster ovary
CI	Confidence Interval
cm	centimeters
d	day(s)
DEEM-FCID	Dietary Exposure Evaluation Model - Food Commodity Intake Database
°C	degrees Celsius
DEN	N-diethylnitrosamine
DT_{50}	Dissipation Time to 50%
DFR	dislodgeable foliar residue
EC_{50}	Effective Concentration to 50%
EbC50	Effective Concentration to 50% biomass reduction
ErC50	Effective Concentration to 50% growth rate reduction
EDE	Estimated Daily Exposure
EEC	Estimated Environmental Concentration
EFED	Environmental Fate and Effects Division (USEPA)
EMD	ethylmorphine N-demethylase
ER	effective rate

EROD	ethoxyresorufin-O-deethylase
ERα	estrogen receptor
F_0	parental generation
F_1	first generation
F_2	second generation
fc	food consumption
g	gram(s)
GC	Gas Chromatograph
GD	gestation day
GRx	glutathione reductase
GST	glutathione S-transferase
h	hour(s)
ha	hectare
Hct	hematocrit
HDT	highest dose tested
Hgb	hemoglobin
HH AB/MB	handheld airblast/mistblower
HHRA	Human Health Risk Assessment
HPLC	High Performance Liquid Chromatography
hr(s)	hour(s)
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
K	Henry's Law Constant
K_d	Adsorption Coefficient
kg	Kilogram(s)
K_{oc}	Organic carbon partition coefficient
K_{ow}	Octanol-water partition coefficient
LC_{50}	concentration estimated to be lethal to 50% of the test population
LD	lactation day
LD_{50}	dose estimated to be lethal to 50% of the test population
L	Litre
LIFR	leukemia inhibitory factor receptor
Log K_{ow}	Octenol-water partition coefficient
LOAEC	lowest observable adverse effect concentration [mg a.i./kg diet or mg a.i./L]
LOAEL	lowest observable adverse effect dose level [mg a.i./kg bw]
LOD	limit of detection
LOAEL	lowest observable adverse effect dose level [mg a.i./kg bw]
LOEC	lowest observable effect concentration [mg a.i./kg diet or mg a.i./L]
LOEL	lowest observable dose level [mg a.i./kg bw]
LOQ	limit of quantitation
m	metre(s)
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MFOs	mixed function oxidase enzymes
mg	milligram
min	minute
mm Hg	millimetre mercury
mL	millilitre

MOA	mode of action
MOE	margin of exposure
mol	moles
mPa	millipascal
MPHG	mechanically-pressurized handgun
MPHS	mechanically-pressurized handheld sprayer for for mists, aerosols, and fogs
MRID	Master Record Identifier number
MRL	maximum residue limit
MTD	maximum tolerated dose
NDETF	Non-Dietary Exposure Task Force
NHANES	National Health and Nutrition Examination Survey
nm	nanometre
NOAEC	no observed adverse effect concentration
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NOErC	No Observed Effect Concentration for growth rate
NOEL	No Observed Effect Level
nm	nanometre
OC	organic carbon
OECD	Organisation for Economic Co-operation and Developmet
OM	organic matter
ORETF	Outdoor Residential Exposure Task Force
PBU	piperonyl butoxide
PCNA	proliferating cell nuclear antigen
PCO	pest control operator
PCPA	*Pest Control Products Act*
pH	-log10 hydrogen ion concentration
PHED	Pesticide Handlers Exposure Database
PHI	pre-harvest interval
pKa	-log10 acid dissociation constant
PMRA	Pest Management Regulatory Agency
POD	point of departure
Por	NADPH-cytochrome P450 oxidoreductase
PP	pressurized product
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
PROD	7-pentoxyresorufin-O-deethylase
PWC	Pesticides in Water Calculator
RBC	red blood cells
RD	residue definition
RfD	reference dose
ROS	reactive oxygen species
RQ	risk quotient
SER	smooth endoplasmic reticulum
SHE	Syrian hamster embryo
$t_{1/2}$	first-order half-life
TC	transfer coefficient

TRR	turf transferrable residue
TSMP	Toxic Substance Management Policy
UDPGTR	uridine diphosphate glucuronyltransferase
USDA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency
µg	microgram
UV	Ultraviolet
vp	Vapour Pressure
WBC	white blood cells
wc	water consumption
wt	weight
WWEIA	"What We Eat in America"
γ-GGT	gamma-glutamyl transpeptidase

Appendix I Summary of the registered uses of piperonyl butoxide used as the basis of the risk assessment

Table 1.1 Use pattern assessed for commercial-class products

Scenario	Site	Application type	Form.	Application equipment	Max. application rate	Max. # apps per year	Min. interval between apps (days)
Outdoor (use-site category 2)	**Restricted use** – Lakes, ponds, reservoirs, preimpoundment treatment above dam	Direct application to water	Liquid	Aerial, boat, backpack	0.123 g a.i./m^3	As needed	14
Animals (use-site category 8, 9, 24)	**Livestock** (Horses, ponies, beef and dairy cattle, swine, poultry, other livestock)	Direct animal treatment	PP	Aerosol can RTU with cloth	1.09 g a.i./animal	180 PYR	1
			Liquid	HH AB/MB (mist over poultry)	0.24 g a.i./m^3		
			Liquid	Handheld spray equipment (MPHW, MPHG, backpack), spray with cloth	0.52 g a.i./animal		
Outdoor (use-site category 27)	**Outdoor ornamentals** [a] (African Violet, Aster, Azalea, Begonia, Calceolaria, Calendula, Calla, Camellia, Carnation, Cineraria, Chrysanthemum, Cypress, Daffodil, Dahlia, Dogwood, Elm Eucalyptus, Fern, Ficus, Geranium, Gladiolus, Gypsophila, Holly Juniper, Lily, Marigold, Oak, Peony, Petunia, Philodendron, Pine, Roses, Snapdragon, Sweet Pea, Tulips, Viburnum, Wandering Jew, Yew, Zinnia; evergreens and small ornamental deciduous trees, shrubs and vines, etc.)	Foliar spray	Liquid	Airblast, handheld spray equipment (MPHW, MPHG, backpack), HH AB/MB, groundboom	732.24 g a.i./ha (0.0732 g a.i./m^2) (1.93 g a.i./L)	10 PYR	1
			PP	Aerosol can RTU	8 g a.i./container		
Outdoor (use-site category 13)	**Pastures**	Foliar spray	Liquid	HH AB/MB, truck-mounted fogging equipment	0.003125 g a.i./m^2 (31.25 g a.i./ha) (17.86 g a.i./L)	25 PYR	1

Scenario	Site	Application type	Form.	Application equipment	Max. application rate	Max. # apps per year	Min. interval between apps (days)
			PP	HH AB/MB, aerosol "fog"	0.0336 g a.i./m^2 PYR (336 g a.i./ha)		
Indoor (use-site category 3)	**Empty Food and Feed Storage Structures and Areas** (Transit, truck beds, boxcars and ships' holds before loading (empty), etc.)	Surface broadcast spray	Liquid	Handheld spray equipment (MPHW, backpack); MechPH-ULV	0.58 g a.i./m^2	As needed	1
Indoor (use-site category 20)	**Agricultural premises** (Farm buildings, barns, poultry houses, stables, milk rooms, stables, etc.)	Space spray (metered release)	PP	Automatic aerosol dispenser	0.294 g a.i./m^3 50 g a.i./container	12 PYR	1
		Space spray	Liquid	MPHS, stationary fogger	0.24 g a.i./m^3	As needed	1 PYR
			PP	Aerosol can RTU	40 g a.i./container		
					0.0018 g a.i./m^3		
		Surface broadcast spray	Liquid	Handheld spray equipment (MPHW, backpack); MechPH-ULV	0.398 g a.i./m^2		
		Surface spot spray	PP	Aerosol can RTU	40 g a.i./container		
					0.77 g a.i./m^2 PYR		
Indoor (use-site category 12)	**Stored Food and Feed** (Stored grains)	Surface broadcast spray	Liquid	MPHS	1.65 g a.i./m^2	6 PYR	14 PYR
Indoor (use-site category 12, 20)	**Food handling establishments; Commercial/industrial/institutional** (Food processing plants, flour and feed mills, bakeries, canneries, packing houses, bottling plants, breweries, restaurants and wherever foodstuffs are handled; hotels, motels, stores, public buildings, industrial settings; warehouses, etc.)	Space spray (metered release)	PP	Automatic dispenser	0.294 g a.i./m^3	12 PYR	1
		Space spray	Liquid	MPHS, stationary fogger	0.24 g a.i./m^3	As needed	1 PYR
			PP	Aerosol can RTU	40 g a.i./container		
				Aerosol can RTU, total release fogger	0.027 g a.i./m^3 8 g a.i./container		
		Surface broadcast spray	Liquid	Handheld spray equipment (MPHW, backpack); MechPH-ULV	2.76 g a.i./m^2		

Scenario	Site	Application type	Form.	Application equipment	Max. application rate	Max. # apps per year	Min. interval between apps (days)
			PP	Aerosol can RTU	40 g a.i./container 0.406 g a.i./m^2		
		Surface application	Dust	Bulbous/Plunger Duster; Shaker Can; Hand-crank Duster; Electric/Power Duster	0.6 g a.i./m^2 PYR 0.097 g a.i./g dust		
Indoor (use-site category 20)	**Dwellings and indoor sites** (Homes, apartments, institutions, hospitals, office buildings, hotels, motels, theatres, schools, transport vehicles; garages, basements, enclosed porches, patios, utility rooms, storage sheds, workshops, etc.)	Space spray	Liquid	MPHS, stationary fogger	0.05 g a.i./m^3	As needed	1 PYR
			PP	Aerosol can RTU	40 g a.i./container		
				Aerosol can RTU, total release fogger	0.027 g a.i./m^3 8 g a.i./container		
		Space spray (metered release)		Automatic dispenser	0.294 g a.i./m^3		
		Surface broadcast spray	Liquid	Handheld spray equipment (MPHW, backpack); MechPH-ULV	0.21 g a.i./m^2		
			PP	Aerosol can RTU	40 g a.i./container 1.2 g a.i./m^2 PYR		
		Surface spray: Bed bug treatment (incl. mattresses); Clothing moth treatment	Liquid	Handheld spray equipment (MPHW, backpack); MechPH-ULV	0.21 g a.i./m^2	As needed	7 PYR
			PP	Aerosol can RTU	40 g a.i./container 0.77 g a.i./m^2 PYR		
			Dust	Bulbous/Plunger Duster; Shaker Can; Hand-crank Duster; Electric/Power Duster	0.6 g a.i./m^2 PYR 0.097 g a.i./g dust		

Scenario	Site	Application type	Form.	Application equipment	Max. application rate	Max. # apps per year	Min. interval between apps (days)
		Surface application (incl. bed bugs and wasp nests indoors)	Dust	Bulbous/Plunger Duster; Shaker Can; Hand-crank Duster; Electric/Power Duster	0.6 g a.i./m^2 PYR 0.097 g a.i./g dust		
Indoor (use-site category 20)	**Pet premises** (Kennels, pet sleeping quarters, bedding, floors and floor coverings where pets are kept, etc.)	Space spray (metered release)	PP	Automatic aerosol dispenser	0.294 g a.i./m^3	As needed	1 PYR
		Surface broadcast spray	Liquid	Handheld spray equipment (MPHW, backpack); MechPH-ULV	2.76 g a.i./m^2		
Outdoor (use-site category 13, 16, 20)	**General outdoors** (Campgrounds, corrals, drive-in-restaurants, drive-in-theatres, dumpsters, feedlots, garbage dumps, golf courses, junkyards, kennels, lath houses, parks, recreational areas, sewers, swine yards and zoos; shrubbery and vegetation; pastures; waste areas, roadsides; residential and recreational areas, other outdoor/open areas, etc.)	C&C spray	Liquid	Handheld spray equipment (MPHW, MPHG, backpack)	0.01875 g a.i./m^2 PYR (187.5 g a.i./ha)	52 PYR	7 PYR
Outdoor (use-site category 13, 16, 20, 25)	**Mosquito, Fly, Gnat Control** (Campgrounds, corrals, drive-in-restaurants, drive-in-theatres, dumpsters, feedlots, garbage dumps, golf courses, junkyards, kennels, lath houses, parks, recreational areas, sewers, swine yards and zoos; shrubbery and vegetation; pastures; waste areas, roadsides; residential and recreational areas, other outdoor/open areas, etc.; Gardens, trees, lawns, grassy areas)	Broadcast spray	Liquid	HH AB/MB, handheld spray equipment (MPHW, MPHG, backpack), truck-mounted fogging equipment	0.003125 g a.i./m^2 (31.25 g a.i./ha) (17.86 g a.i./L)	26 PYR	1
			PP	HH AB/MB, aerosol 'fog'	0.0336 g a.i./m^2 PYR (336 g a.i./ha)	26 PYR	7 PYR
Animals (use-site category 24)	**Pets** (Dogs and cats)	Direct animal treatment	Liquid/ RTU	Ear dropper	20 drops/animal 1.97 g a.i./container	As needed	14

Form = Formulation; PP = pressurized product; Liquid = emulsifiable concentrate, suspension, or solution; C&C = crack and crevice; MechPH-ULV = Mechanically-pressurized handheld ULV equipment; MPHW = manually-pressurized handwand, MPHG = mechanically-pressurized handgun; MPHS = mechanically-pressurized handheld sprayer for mists, aerosols, and fogs; HH AB/MB = handheld airblast/mistblower; Max = maximum; # = number; Min = minimum; Apps = applications; RTU = ready-to-use
PYR = based on information from the pyrethrins use pattern.
[a] This scenario includes application by a commercial applicator to domestic gardens and outdoor ornamentals in residential areas.

Table 1.2 Use pattern assessed for domestic-class products

Scenario	Site	Application type	Form.	Application equipment	Maximum application rate	Max # applications per year	Min interval between apps (days)
Treated Pets/Animals (use-site category 24)	**Pets** (Dogs, cats, birds, rabbits, etc.)	Direct animal treatment	Liquid	Shampoo RTU, trigger-pump sprayer	20.6 g a.i./container 0.12 g a.i./kg bw	16 PYR	7 PYR
			Liquid /RTU	Ear Dropper	0.193 g a.i./container, or 20 drops/animal	As needed	2
			PP	Aerosol can RTU	14.4 g a.i./container 0.2 g a.i./kg bw	12 PYR	7 PYR
Treated Pets/Animals (use-site category 9, 24)	**Livestock** (Cattle, horses, ponies, etc.)	Direct animal treatment	Paste	Wipe-on (with cloth)	0.85 g a.i./container	As needed	1
			Liquid	Shampoo, trigger-pump sprayer, spot-on	1.2 g a.i./animal (9.5 g a.i./container)		
			PP	Aerosol can RTU	6.5 g a.i./container		
Indoor Environments (use-site category 20)	**Animal premises** (Pet premises, animal quarters, barns, etc.)	Surface application	Dust	Bulbous/Plunger Duster; Shaker Can; Hand-crank Duster; Electric/Power Duster	50 g a.i./container (0.01 kg a.i./kg dust) 0.04 g a.i./m^2	As needed	1
		Space spray (metered release)	PP	Automatic dispenser	50 g a.i./container 0.006 g a.i./m^3 (1.06 g a.i./170 m^3/day)	52 PYR	1
		Surface broadcast spray	Liquid	MPHW, trigger-pump sprayer	0.55 g a.i./m^2 (9.5 g a.i./container)	As needed	1
			PP	Aerosol can RTU	32.5 g a.i./container 1.4 g a.i./m^2 PYR		

Scenario	Site	Application type	Form.	Application equipment	Maximum application rate	Max # applications per year	Min interval between apps (days)
Indoor Environments (use-site category 20, 26)	**Dwellings and indoor sites** (Homes, apartments, institutions, hospitals, office buildings, hotels, motels, theatres, schools, transport vehicles; garages, basements, enclosed porches & patios, utility rooms, storage sheds, workshops, etc.)	Space spray	Liquid	Stationary fogger	0.0158 g a.i./m^3 (0.474 g a.i./30 m^3)	As needed	1
		Space spray	PP	Aerosol can RTU; Automatic dispenser (metered release); total release fogger	50 g a.i./container		
					0.0055 g a.i./7.5 minutes		
					0.03 g a.i./m^3		
		Bed bug treatment (incl. mattresses);	Dust	Bulbous/Plunger Duster; Shaker Can; Hand-crank Duster; Electric/Power Duster	50 g a.i./container (0.01 kg a.i./kg dust)	As needed	1
					0.58 g a.i./m^2		
			Liquid	MPHW, trigger-pump sprayer	2.76 g a.i./m^2 USEPA		
					36.8 g a.i./container (73.76 g a.i./L)		
			PP	Aerosol can RTU	32.5 g a.i./container		
					0.21 g a.i./m^2 PYR		
		Surface application	Dust	Bulbous/Plunger Duster; Shaker Can; Hand-crank Duster; Electric/Power Duster	50 g a.i./container (0.01 kg a.i./kg dust)	As needed	1
					0.04 g a.i./m^2		
		Surface broadcast spray	Liquid	MPHW, trigger-pump sprayer	9.5 g a.i./container 0.55 g a.i./m^2		
					36.8 g a.i./container (73.76 g a.i./L)		
			PP	Aerosol can RTU	32.5 g a.i./container		
					1.4 g a.i./m^2 PYR		
Clothing (use-site category 26)	**Clothes**	Surface spray: clothing moth treatment	PP	Aerosol can RTU	9 g a.i./container	52	7
					0.21 g a.i./m^2 PYR		
			Liquid	Trigger-pump sprayer	10.13 g a.i./container		
					0.7 g a.i./m^2 PYR		

Scenario	Site	Application type	Form.	Application equipment	Maximum application rate	Max # applications per year	Min interval between apps (days)
Gardens/Trees (indoor plants) (use-site category 6, 28)	**Indoor and domestic greenhouse ornamentals** (African violets, Asters, Azaleas, Begonias, Camellias, Carnations, Chrysanthemums, Dahlias, Delphiniums, Dogwood, English Ivy, Euonymus, Fuschia, Geraniums, Crassula, Gladioli, Kentia Palm, Laurel, Marigold, Rhododendron, Rose, Rubber Plant, Snapdragon, Stocks, Wandering Jew, Zinnia, etc.)	Foliar spray	Liquid	MPHW, trigger-pump sprayer	9.5 g a.i./container 0.55 g a.i./m^2	As needed	1
			PP	Aerosol can RTU	9.69 g a.i./container		
					0.175 g a.i./m^2 PYR		
Gardens/Trees (use-site category 27)	**Outdoor ornamentals** (Incl. ornamentals, gardens, trees, cut flowers, shrubs, etc.)	Surface application	Dust	Bulbous/Plunger Duster; Shaker Can; Hand-crank Duster; Electric/Power Duster	0.05 g a.i./m^2 USEPA	3 PYR	14 PYR
					50 g a.i./container 0.01 kg a.i./kg dust		
		Foliar spray	Liquid	Handheld spray equipment (MPHW, MPHG, backpack), trigger-pump sprayer	39.9 g a.i./container		
					0.922 g a.i./m^2 PYR		
			PP	Aerosol can RTU	9.7 g a.i./container		
					0.016 g a.i./m^2 PYR		
Gardens/Trees, Lawns/Turf (use-site category 33)	**General outdoors** (Incl. around structures, yards, groundcovers, decks, patios, etc.)	Broadcast spray, spot spray	PP	Aerosol can RTU	18.6 g a.i./container	20 PYR	7 PYR
					0.0096 g a.i./m^2 PYR		
		Space spray		Aerosol can RTU	3.395 g a.i./container		

Form = Formulation; PP = pressurized product; Liquid = emulsifiable concentrate, suspension, or solution; C&C = crack and crevice; MechPH-ULV = Mechanically-pressurized handheld ULV equipment;MPHW = manually-pressurized handwand,

MPHG = mechanically-pressurized handgun; Max = maximum; # = number; Min = minimum; Apps = applications; RTU = ready-to-use PYR = rate based on information from the pyrethrins use pattern.
USEPA = label rate is based on the USEPA draft HHRA (2017) as a rate on the Canadian label could not be determined.

Appendix II Toxicology information for health risk assessment

Table 1 Toxicity profile of piperonyl butoxide

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

Study type/animal/PMRA#	Study results
Toxicokinetic Studies	
Swiss-Webster - mice Single gavage dose of ^{14}C labelled piperonyl butoxide PMRA# 2407827	Excretion: Forty-eight hrs after administration of methylene-labelled piperonyl butoxide, 97% of the radiolabel was recovered with 76% as carbon dioxide, 6% in urine, 4% in the feces and ≤2.5% in the intestines and the liver. 48 hrs after administration of piperonyl butoxide labelled in the 2(2-butoxyethoxy) ethoxymethyl side-chain, 75% of the radiolabel was recovered, with 65% in urine, 8% in feces and <1% in each of the intestines, liver, carcass and as carbon dioxide. Metabolism*:* The major metabolic pathway involved cleavage of the methylene-dioxyphenyl moiety by oxidation. Most of the compounds excreted in the 0–12 hr urine samples lacked the methylenedioxy-phenyl moiety. 6-propylpiperonylic acid and 6-propylpiperonylglycine, each representing less than 0.5% of the administered radioactivity, were also found in the urine. At least 18 metabolites appeared in the urine with piperonyl butoxide labelled in the 2(2-butoxyethoxy) ethoxymethyl side-chain while only 12 metabolites were evident with methylene-labelled piperonyl butoxide.
Rats Single gavage dose of ^{14}C labelled piperonyl butoxide Daily gavage dose of piperonyl butoxide for 13 days followed by a single gavage dose of ^{14}C labelled piperonyl butoxide PMRA# 2132127, 2132162, 2407827, 2408291, 2420520	Single dosing regimen: Absorption: The plasma levels of radioactivity increased slowly with maximum blood levels noted 4 to 6 hrs post-dosing with lesser amounts present 12 and 24 hrs post-dosing. Twenty-four hrs-post dosing, plasma radioactivity dropped to ~ half the peak level.

Study type/animal/PMRA#	Study results
Distribution: At each interval, the highest levels of radiolabel were found in the gastrointestinal tract and its contents. The fat, liver, prostate, muscle, kidney and seminal vesicles retained the most radioactivity based on the 48-hr sample time. Less than 1.5% of the administered radioactivity was present in tissues after 168 hrs. Excretion: Most of the radiolabel was recovered 12–24 hrs post-dosing. The amount of radiolabel recovered after 24 hours was low, and less than 1% of the excreted dose was recovered at the 72 hour post-dosing timepoint. Collectively, the data show most of the administered radioactivity was found in the feces (47–85%) with lesser amounts eliminated in the urine (11–38%). No significant dose or gender differences were apparent. In a study lacking fecal recovery, the total radioactivity recovered 48 hrs post-dosing was 72% with 66% as carbon dioxide and 6% in urine after the administration of methylene-labelled piperonyl butoxide. After administration of piperonyl butoxide labelled in the 2(2-butoxyethoxy) ethoxymethyl side-chain, 74% of the radiolabel was recovered, with 73% in urine and <1% as carbon dioxide. Metabolism: Metabolism of piperonyl butoxide was extensive with no significant differences noted in the metabolic profile between the genders or dosage levels. The major metabolic pathway involved cleavage of the methylene-dioxyphenyl moiety by oxidation. This resulted in opening of the methylenedioxy ring to form a catechol that could then undergo methylation. Sequential oxidation of the 2-(2-butoxyethoxy) ethoxy methyl side chain also occurred producing a number of alcohols and acids. Metabolites also underwent conjugation with sulphate or glucuronide. The major metabolites in the feces (~20%) were unchanged piperonyl butoxide and M3 (piperonyl butoxide opened at the methylene dioxy ring). Urine contained numerous metabolites (~20) with none exceeding 5% of the administered radioactivity. No unchanged piperonyl butoxide was detected in the urine. Multiple dosing regimen: Similar tissue distribution and excretion patterns as that noted following a single oral dose were observed.	
Sprague-Dawley rats Single intravenous dose of piperonyl butoxide labelled with ^{14}C in the methylenedioxy or the α-methylene side-chain. PMRA# 2400364 Excretion:	

Study type/animal/PMRA#	Study results
After treatment with methylenedioxy- labelled piperonyl butoxide, ~40% of the label was recovered as carbon dioxide, <1% in urine and 3% in bile by 7 hrs. After treatment with α-methylene-labelled piperonyl butoxide, 25-47% of the label was found in the bile and ~5% in urine after 7 hrs post-dosing while almost no radioactivity was detected in expired air.	
The peak amount of label was detected in bile <30 minutes after injection with either compound and in urine ~25 hrs later. Significant amounts of radioactivity were present in both urine and bile 8 hrs later. Metabolism: More than 10 metabolites were detected but not identified in urine and bile; unchanged piperonyl butoxide was identified only in fat (9–18% of the total radiolabel) and lung (15-25%) after 8 hrs.	
Acute Toxicity Studies	
Acute Oral Study Sprague-Dawley rats PMRA# 2132120	LD_{50} = 4570/7220 mg/kg bw ♂/♀ Clinical signs included ruffled fur, prostration, tremors, lethargy, dark ocular staining, dark nasal staining and piloerection. Low acute toxicity
Acute Dermal Study New Zealand White rabbits PMRA# 2132120	LD_{50} > 2000 mg/kg bw Signs of dermal irritation included well defined erythema and very slight-slight edema on day 1 with animals appearing normal after day 2. Low acute toxicity
Acute Inhalation Study Sprague-Dawley rats PMRA# 2132140	LC_{50} > 5.9 mg/L Clinical signs included lacrimation, salivation, nasal discharge, anogenital staining and laboured breathing. Low acute toxicity
Primary Eye Irritation Study New Zealand White rabbits PMRA# 2132120	Minimally irritating
Primary Dermal Irritation Study New Zealand White rabbits PMRA# 2132120	Mildly to minimally irritating

Study type/animal/PMRA#	Study results
Dermal Sensitization Study - Modified Buehler Hartley guinea pigs PMRA# 2132120	Negative
Short-Term Toxicity Studies	
2-wk Dietary Range-finding Study CD-1 mice PMRA# 2132142	≥623 mg/kg bw/day: ↓ bw, bwg and fc, ↑ liver size 1490 mg/kg bw/day: dietary aversion Supplemental study
20-day Dietary Study CD-1 mice PMRA# 2400366	NOAEL = 151/188 mg/kg bw/day ≥459/518 mg/kg bw/day: ↑ cholesterol; ↓ bw and fc (first few days), ↑ relative liver wt, ↑ γ-GGT and total serum protein (♂); ↑ triglycerides and phospholipids, ↑ absolute liver wt (♀) 1441/1276 mg/kg bw/day: ↓ bwg, ↓ absolute kidney and spleen wt, centrilobular cell infiltration, hypertrophic hepatocytes and single-cell necrosis; ↑ triglycerides and phospholipids (♂); ↓ bw and fc, ↑ relative liver wt, ↑ γ-GGT and total serum protein (♀)
90-day Dietary Range-finding Study CD-1 mice PMRA# 2132142	≥10.3 mg/kg bw/day: ↑ liver wt, minimal-mild hepatocellular hypertrophy (♂) ≥30.8 mg/kg bw/day: minimal hepatocellular hypertrophy (♀) ≥309/318 mg/kg bw/day: moderate-marked hepatocellular hypertrophy (♂); ↑ liver wt, minimal-moderate hepatocellular hypertrophy (♀) 1127/1054 mg/kg bw/day: ↓ bw and bwg, hepatocellular necrosis, polymorphonuclear cell infiltrates; ↓ absolute kidney wt and ↑ relative brain wt (♂) Supplemental study

Study type/animal/PMRA#	Study results
4-wk Dietary Range-finding Study Sprague-Dawley rats PMRA# 2400364	≥62.5 mg/kg bw/day: eosinophilia and loss of vacuolation in hepatocytes ≥250 mg/kg bw/day: ↑ relative liver wt (♂) ≥500 mg/kg bw/day: ↑ absolute liver wt; ↓ bwg, ↑ relative liver wt (♀) ≥1000 mg/kg bw/day: ↑ relative adrenal, kidney and brain wts, necrosis of hepatocytes and cytoplasmic inclusions; ↓ bwg (♂) 2000 mg/kg bw/day: prominent backbone, thinness, poor fur condition with brown staining and piloerection Supplemental study
13-wk Dietary Range-finding Study F344 rats PMRA# 2400304	≥125 mg/kg bw/day: ↑ liver wt; ↓ bwg, ↑ relative kidney wt (♂) ≥500 mg/kg bw/day: ↓ bw (♂); ↑ relative kidney wt (♀) ≥1000 mg/kg bw/day: ↓ bw and bwg (♀) 1500 mg/kg bw/day: hepatocellular hypertrophy and focal necrosis; ↑ absolute kidney wt (♂); ↓ absolute kidney wt (♀) Supplemental study
13-wk Dietary Study F344 rats PMRA# 2400405	LOAEL = 300 mg/kg bw/day ≥300 mg/kg bw/day: ↑ nose bleeds and abdominal distension, ↑ liver and relative kidney wt, ↑ γ-GGT; ↓ triglycerides (♂); ↓ bw, ↑ total protein (♀) ≥600 mg/kg bw/day: ↓ bw (♂); ↓ Hgb (♀) 1200 mg/kg bw/day: ↓ fc and wc, ↓ absolute kidney wt, ↑ serum protein, cholesterol and BUN, enlargement of the liver, hepatocellular hypertrophy and vacuolation, coagulative necrosis and oval-cell proliferation; ↓ Hgb, bilirubin and glucose, atrophy of the epithelium of the proximal convoluted tubules in the renal cortex, black pigment in the liver (♂); ↓ MCH, ↑ phospholipids, ↓ ChE levels, uterine atrophy (♀)

Study type/animal/PMRA#	Study results
8-wk Dietary Range-finding Study Beagle dogs PMRA# 2132144	≥14.7 mg/kg bw/day: ↑ liver/gallbladder wt, hepatic hypertrophy (♂) ≥31.9/37.0 mg/kg bw/day: ↓ bwg ≥62.5/61.4 mg/kg bw/day: ↑ ALP; ↓ cholesterol, ↓ testes/epididymis wt (♂); ↑ absolute liver/gallbladder wt, hepatic hypertrophy (♀) 89.2/85.4 mg/kg bw/day: inappetance and ↓ defecation, ↓ fc and bw, ↓ cholesterol; thin appearance (♀) Supplemental study
12-month Dietary Study Beagle dogs PMRA# 2132143	NOAEL = 2.9/2.7 mg/kg bw/day ≥15.5/16.3 mg/kg bw/day: ↓ bw and bwg, ↑ relative liver wt; ↓ fc, mild atrophy of the testis (♂); ↑ absolute liver wt (♀) 52.8/71.0 mg/kg bw/day: ↑ absolute liver wt, ↑ ALP, diffuse hepatocellular hypertrophy; ↓ RBC, cyst in the gall bladder (♂); ↓ cholesterol, ↑ thyroid/parathyroid wt (♀)
21-day Dermal Study New Zealand White rabbits PMRA# 2423238	NOAEL (systemic toxicity) > 1000 mg/kg bw/day ≥100 mg/kg bw/day: very slight erythema and edema, desquamation, mild acanthosis, hyperkeratosis and inflammation of the epidermis; moderate hyperkeratosis and inflammation of the epidermis (♀) ≥300 mg/kg bw/day: slight erythema, moderate hyperkeratosis and inflammation of the epidermis; dermal fissure and moderate acanthosis (♀) 1000 mg/kg bw/day: moderate acanthosis (♂); severe acanthosis and hyperkeratosis (♀)

Study type/animal/PMRA#	Study results
90-day Inhalation Study Sprague-Dawley rats PMRA# 2132115	LOAEC = 0.015 mg/L (~3.9 mg/kg bw/day) ≥0.015 mg/L (~3.9 mg/kg bw/day): ↑ incidence of pseudostratified ciliated/nonciliated columnar epithelium-squamous/squamoid metaplasia/hyperplasia in the ventral seromucous glands of the larynx and dried red nasal discharge ≥0.155 mg/L (~40.4 mg/kg bw/day): ↑ incidence of secretory activity, nasal discharge, matted fur, anogenital staining and dried material on facialarea and extremities, ↑ liver wt 0.512 mg/L (~134 mg/kg bw/day): ↑ relative kidney wt, ↓ AST, ALT and glucose, ↑ BUN, total protein and albumin levels, yellow anogenital staining, vesiculation and vacuolation of the hepatocellular cytoplasm, metaplasia/hyperplasia in the ventral diverticulum, chronic inflammation of the larynx, hyperplasia and hyperkeratosis of the squamous epithelium of the larynx
Chronic Toxicity/Oncogenicity Studies	
52-wk Dietary Toxicity/Carcinogenicity Study CD-1 mice PMRA# 2419729, 2428494	≥816/876 mg/kg bw/day: ↓ bw, ↑ liver wt, ↓ RBC, Hgb and Hct, ↑ γ-GGT, AST and ALT, hepatocellular hyperplasia; ↑ hepatocellular adenomas and carcinomas (♂) 1692/2004 mg/kg bw/day: postnecrotic peliosis, hemangioendothelial sarcomas; ↑ mortalities (♂); ↑ number of early deaths, ↑ hepatocellular adenomas and carcinomas (♀) Incidence of hepatocellular adenomas (♂) was 1/49, 7/52 and 21/81 at respective dose levels of 0, 816 and 1692 mg/kg bw/day and (♀) was 0/50, 0/50 and 10/63 at respective dose levels of 0, 876 and 2004 mg/kg bw/day. Incidence of hepatocellular carcinomas (♂) was 0/49, 6/52 and 43/81 at respective dose levels of 0, 816 and 1,692 mg/kg bw/day and (♀) was 0/50, 0/50 and 24/63 at respective dose levels of 0, 876 and 2004 mg/kg bw/day. Incidence of hemangioendothelial sarcomas (♂) was 0/49, 1/52 and 36/81 at respective dose levels of 0, 816 and 1692 mg/kg bw/day and (♀) was 0/50, 0/50 and 21/63 at respective dose levels of 0, 876 and 2004 mg/kg bw/day. **Evidence of carcinogenicity** Supplemental study

Study type/animal/PMRA#	Study results
78-wk Dietary Toxicity/Carcinogenicity Study CD-1 mice PMRA# 2132119, 2407823	NOAEL = 30 mg/kg bw/day (♂); 100 mg/kg bw/day (♀) ≥100 mg/kg bw/day: ↑ relative liver wt; hepatocellular hypertrophy and adenomas (♂) ≥300 mg/kg bw/day: hepatocellular hemorrhage and hyperplasia; ↓ bw and bwg, hepatic necrosis, ↑ hepatocellular carcinomas (♂); hepatocellular hypertrophy and adenomas (♀) Incidence of hepatocellular adenomas (♂) was 8/60, 7/60, 13/60, 21/60 and 34/60 at respective dose levels of 0, 0, 30, 100 and 300 mg/kg bw/day and (♀) was 2/60, 2/60, 1/60, 1/60 and 12/60 at respective dose levels of 0, 0, 30, 100 or 300 mg/kg bw/day. Incidence of hepatocellular carcinomas (♂) was 3/60, 3/60, 2/60, 2/60 and 5/60 at respective dose levels of 0, 0, 30, 100 or 300 mg/kg bw/day. **Evidence of carcinogenicity in ♂; Evidence of tumorigenicity in ♀**
2-yr Dietary Toxicity/Carcinogenicity Study B6C3F1 mice PMRA# 1233678	≥155 mg/kg bw/day: ↓ bw, alopecia (♀) 421 mg/kg bw/day: ↑ lacrimal gland adenomas (equivocal) (♂); hepatocellular carcinomas (♀) Incidence of lacrimal gland adenomas (♂) was 0/20, 0/49 and 4/50 at respective dose levels of 0, 155 and 421 mg/kg bw/day. Incidence of hepatocellular carcinomas (♀) was 1/20, 2/50 and 5/50 at respective dose levels of 0, 155 and 421 mg/kg bw/day. **Evidence of carcinogenicity in ♀** Supplemental study
2-year Dietary Toxicity/Carcinogenicity Study Sprague-Dawley rats PMRA# 2407823	NOAEL = 30 mg/kg bw/day ≥100 mg/kg bw/day: ↑ liver and kidney wt, ↑ pigment in thyroid follicles, hepatocellular hyperplasia, hypertrophy and enlarged eosinophilic cells; hepatic mixed cell foci, hyperplasia of thyroid follicles and chronic interstitial glomerulonephritis (♀) 500 mg/kg bw/day: ↓ bw, bwg and fc, ↓ glucose, ↓ AST and ALT levels, enlarged thyroid glands; hepatic mixed cell and

Study type/animal/PMRA#	Study results
	eosinophilic cell foci (♂); ↑ cholesterol and BUN, adrenal and ovarian enlargement, degenerative changes in the ovaries (♀) **No evidence of carcinogenicity**
2-yr Dietary Toxicity/Carcinogenicity Study F344 rats PMRA# 2419730	≥547/537 mg/kg bw/day: ↓ bw and bwg, ↑ hypochromic and microcytic anaemia, ↓ Hgb and Hct, ↓ ChE activity and triglycerides; abnormal shaped erythrocytes, thrombocythemia, enlargement and hemorrhagic effects on the cecum, ↓ MCV, MCH and cholesterol, hepatocellular hyperplasia (♂); ↑ liver wt, ↑ BUN, black kidneys (♀) ≥1052/1061 mg/kg bw/day: enlarged platelets, ↑ hepatocellular adenomas; ↑ mortality, ↑ liver wt, black kidneys, white spotting in the lungs, ↑ hepatocellular carcinomas (♂); ↓ absolute lung wt, enlargement and hemorrhagic effects on the cecum, misshaped kidneys (♀) 1877/2002 mg/kg bw/day: rough hair, lethargy, epistaxis, ↓ fc, ↑ AST, ↓ absolute lung, kidney, spleen and heart wts, stomach haemorrhage, tubular dilatation, distension of Bowman's space and interstitial fibrosis of the kidneys, ↓ erythrocytes, glucose, prothrombin index, ↑ hemangiosarcomas; ↑ BUN, ↓ absolute testicular wt (♂); ↓ MCV, ↑ cholesterol, ↓ absolute ovarian wt, ↑ hepatocellular carcinomas (♀) Incidence of hepatocellular adenomas (♂) was 0/25, 0/23, 8/15 and 5/25 at respective dose levels of 0, 547, 1052 and 1877 mg/kg bw/day and (♀) was 0/24, 0/27, 4/25 and 9/26 at respective dose levels of 0, 537, 1061 and 2002 mg/kg bw/day. Incidence of hepatocellular carcinomas (♂) was 0/25, 0/23, 4/15 and 20/25 at respective dose levels of 0, 547, 1052 and 1877 mg/kg bw/day and (♀) was 0/24, 0/27, 0/25 and 15/26 at respective dose levels of 0, 537, 1061 and 2002 mg/kg bw/day. Incidence of hemangiosarcomas (♂) was 0/30, 0/30, 2/30 and 15/33 at respective dose levels of 0, 547, 1052 and 1877 mg/kg bw/day and (♀) was 0/30, 0/30, 0/30 and 8/33 at respective dose levels of 0, 537, 1061 and 2002 mg/kg bw/day. **Evidence of carcinogenicity** Supplemental study

Study type/animal/PMRA#	Study results
2-year Dietary Toxicity/Carcinogenicity Study F344 rats PMRA# 2407749	≥250 mg/kg bw/day: ↓ bw, hyperplasia of the adrenal gland, alveolar epithelial hyperplasia; ↑ lymphoreticular malignant lymphomas (equivocal) (♀) Incidence of lymphoreticular malignant lymphomas (♀) was 1/20, 7/50 and 15/50 at respective dose levels of 0, 250 and 500 mg/kg bw/day. Supplemental study
107-wk Dietary Toxicity/Carcinogenicity Study F344 rats PMRA# 2400304	≥250 mg/kg bw/day: ↑ mortalities, ↓ bw; presence of ulcers with inflammatory-cell infiltration and granulation, regenerative hyperplasia, ulcers and ossification in the ileocaecal mucosa and haemorrhage of the caecum and colon (♂) 500 mg/kg bw/day: ↑ hepatocellular carcinomas and neoplastic nodules in the liver (♂); regenerative hyperplasia and ulcers of the ileocaecal mucosa and haemorrhage of the caecum and colon (♀) Incidence of hepatocellular carcinomas (♂) was 0/48, 0/48 and 2/46 at respective dose levels of 0, 250 and 500 mg/kg bw/day. Incidence of neoplastic liver nodules (♂) was 2/48, 2/48 and 6/46 at respective dose levels of 0, 250 and 500 mg/kg bw/day. **Evidence of carcinogenicity in ♂** Supplemental study
Genotoxicity Studies	
In vitro Studies	
Bacterial Reverse Mutation Assay *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 PMRA# 2400364, 2419596	**Negative ± metabolic activation.** Tested up to a limit concentration.

Study type/animal/PMRA#	Study results
Bacterial Reverse Mutation Assay *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 PMRA# 2420020	No ↑ in the number of revertants ± metabolic activation Tested up to a limit concentration. Supplemental study
Bacterial Reverse Mutation Assay *S. typhimurium* strains TA98, TA100 and TA1537 PMRA# 2419732	**Negative ± metabolic activation.** Tested up to a limit concentration.
In vitro Forward Mutation Assay in Mammalian Cells Mouse Lymphoma L5178Y cells PMRA# 2407758	**Positive in the absence of metabolic activation.** Not tested with metabolic activation. ≥30 µg/mL: weak positive response ≥50 µg/mL: positive response 100 µg/mL: cytotoxic
In vitro Forward Mutation Assay in Mammalian Cells Chinese hamster V79 cells PMRA# 2400364, 2419596	**Negative ± metabolic activation.** Tested up to a limit concentration.
In vitro Mammalian Cell Chromosomal Aberration Test CHO cells PMRA# 2132146	**Negative ± metabolic activation.** Tested up to a limit concentration.
In vitro Mammalian Cell Chromosomal Aberrations Test CHO cells PMRA# 2400364, 2419596	**Negative ± metabolic activation** Tested up to a limit concentration.

Study type/animal/PMRA#	Study results
In vitro Mammalian Cell Chromosomal Aberration Test CHO-W-B1 cells PMRA# 2420034	**Negative ± metabolic activation** Tested up to a limit concentration.
Unscheduled DNA Synthesis Rat Primary Hepatocytes PMRA# 2400364, 2419596	**Negative** Tested up to a cytotoxic concentration.
Sister Chromatid Exchange Assay CHO-W-B1 cells PMRA# 2420034	**Negative**
Cell Transformation Assay SHE50 and SHE53 cells PMRA# 2428489	**Negative**
Unscheduled DNA synthesis Human liver slices PMRA# 2400364	**Negative**
Reproductive/Developmental Toxicity Studies	
2-Generation Dietary Reproduction Study Sprague-Dawley rats PMRA# 2400364, 2419596	Parental NOAEL = 89/102 mg/kg bw/day 469/528 mg/kg bw/day: ↓ bw, bwg and fc Reproductive NOAEL = 469/528 mg/kg bw/day No treatment-related signs of toxicity. Offspring NOAEL = 102 mg/kg bw/day 528 mg/kg bw/day: ↓ pup bw and bwg (F_1 and F_2) **No evidence of sensitivity of the young**

Study type/animal/PMRA#	Study results
Developmental Toxicity Study (gavage) Sprague-Dawley rats PMRA# 2132145	Maternal NOAEL = 200 mg/kg bw/day ≥500 mg/kg bw/day: ↓ bwg and fc, red urogenital discharge and perinasal encrustration 1000 mg/kg bw/day: urogenital wetness and urinary staining, ↑ liver wt Developmental NOAEL = 200 mg/kg bw/day ≥500 mg/kg bw/day: ↑ incidence of unossified cervical centrums #5 and #6 **No evidence of malformations or sensitivity of the young**
Developmental Toxicity Study (gavage) Wistar rats PMRA# 2407754	Maternal NOAEL = 500 mg/kg bw/day No treatment-related signs of toxicity. Developmental NOAEL = 500 mg/kg bw/day No treatment-related signs of toxicity. **No evidence of malformations or sensitivity of the young**
Range-finding Developmental Toxicity Study (gavage) New Zealand white rabbits PMRA# 2400364	Maternal 100 mg/kg bw/day: 1 abortion 200 mg/kg bw/day: ↓ bwg ≥300 mg/kg bw/day: 2 abortions 400 mg/kg bw/day: 2 abortions, ↓ defecation Supplemental study
Developmental Toxicity Study (gavage) New Zealand White rabbits PMRA# 2400364, 2419596	Maternal NOAEL = 50 mg/kg bw/day ≥100 mg/kg bw/day: ↓ defecation and bw Developmental NOAEL = 200 mg/kg bw/day No treatment-related signs of toxicity. **No evidence of malformations or sensitivity of the young**

Study type/animal/PMRA#	Study results
Special Reproductive/Developmental Toxicity Studies (Non-guideline)	
Developmental Toxicity Study (gavage on GD9) CD-1 mice PMRA# 2407761	Maternal NOAEL = 1,065 mg/kg bw ≥1385 mg/kg bw: 1 dam aborted and 1 litter resorbed, ↑ total resorptions, ↓ bwg 1800 mg/kg bw: 2 dams aborted and 3 litters resorbed Developmental NOAEL = 1,065 mg/kg bw ≥1385 mg/kg bw: ↑ number of early resorptions and late resorptions, ↑ total resorptions, oligodactyly in the forelimbs 1800 mg/kg bw: ↓ fetal bw, ↓ sex ratio
Developmental Toxicity Study (gavage on GDs 11-12) CD rats PMRA# 2407751	Maternal NOAEL = 630 mg/kg bw/day ≥1065 mg/kg bw/day: ↓ bwg 1800 mg/kg bw/day: 2 litters totally resorbed, ↑ total resorption rate Developmental NOAEL = 630 mg/kg bw/day ≥1065 mg/kg bw/day: ↓ fetal bw, ↑ number of fetuses with external limb deformities (oligodactyly and syndactyly) 1800 mg/kg bw/day: ↓ number of viable fetuses and average litter size, ↑ number of fetuses with external limb deformities (polydactyly)
Special Studies (non-guideline)	
6-wk Dietary Neurotoxicity Study CD-1 mice PMRA# 2407755	LOAEL = 236 mg/kg bw/day ≥236 mg/kg bw/day: ↑ defecation, alterations in motor activity (↑ number of turnings, total distance traveled and average distance traveled) ≥448 mg/kg bw/day: ↓ fc, alterations in motor activity (↑ number of movements and movement time) 880 mg/kg bw/day: alterations in motor activity (↓ number of horizontal activities)

Study type/animal/PMRA#	Study results
Dietary Developmental Neurotoxicity Study - 4 wks prior to mating of F_0 generation until F_1 generation was 8 wks old CD-1 mice PMRA# 2428495	Parental LOAEL = 225 mg/kg bw/day ≥225 mg/kg bw/day: ↓ ambulation and rearing Offspring LOAEL = 225 mg/kg bw/day ≥225 mg/kg bw/day: ↓ pup and litter wt, ↓ olfactory orientation and ambulation; ↓ rearing (♂) 900 mg/kg bw/day: ↓ survival, ↓ surface righting, negative geotaxis; ↑ jumping (♂); ↓ rearing (♀)
Dietary Developmental Neurotoxicity Study - 5 wks of age of F_0 generation to 9 wks of age of F_1 generation CD-1 mice PMRA# 2418571	Parental (F_0 generation) NOAEL ≥ 176 mg/kg bw/day No treatment-related signs of toxicity. Offspring (F_1 generation) NOAEL = 21 mg/kg bw/day ≥58 mg/kg bw/day: delayed surface righting, ↓ olfactory orientation, ↑ total distance travelled (♂) 176 mg/kg bw/day: ↑ average distance and speed (♂)
Dietary Developmental Neurotoxicity Study - 5 wks of age of F_0 generation to 12 wks of age of F_1 generation CD-1 mice PMRA# 2428496	Parental (F_0 generation) LOAEL = 34 mg/kg bw/day ≥34 mg/kg bw/day: slightly ↑ vertical time (♀) Offspring (F_1 generation) NOAEL = 34 mg/kg bw/day 107 mg/kg bw/day: ↓ bw 313 mg/kg bw/day: ↓ average litter wt; delayed cliff avoidance, accelerated development of swimming direction (♂); delayed surface righting, ↑ number of movements, movement time, total distance and number of turnings (♀)
Dietary Developmental Neurotoxicity Study - 5 wks of age of F_0 generation to weaning of F_2 generation CD-1 mice PMRA# 2407759	Parental No NOAEL established due to limited observations. ≥675/719 mg/kg bw/day: ↓ fc (F_0 and F_1) Offspring LOAEL = 205 mg/kg bw/day ≥205 mg/kg bw/day: ↓ litter wt and size at birth (F_2), ↓ pup wt and surface righting (F_2) ≥387 mg/kg bw/day: ↓ pup wt (F_1 and F_2), ↓ olfactory orientation (F_2)

Study type/animal/PMRA#	Study results
	≥719 mg/kg bw/day: ↓ litter wt and size at birth (F_1), ↓ surface righting and olfactory orientation (F_1) 1533 mg/kg bw/day: ↓ survival index (F_1 and F_2) and cliff avoidance (F_2)
Acute Hepatotoxicity Study (intraperitoneal) Swiss ♂ mice PMRA# 2407826	160 mg/kg bw: inhibition of dimethyl-aminopyrine and hexobarbital hydroxylase 1 hr after administration
Acute Hepatotoxicity Study (intraperitoneal) Swiss-Webster ♂ mice PMRA# 2407829	450 mg/kg bw: inhibition of hepatic MFOs and cytochrome P-450 several hrs following administration of piperonyl butoxide; however, after 24–72 hrs, an induction of MFOs and P-450 content was noted, prolongation of hexobarbital sleeping time was also induced
Acute Hepatotoxicity Study (intraperitoneal) C57BL/6 and DBA/2 (Ah receptor deficient) ♂ mice PMRA# 2407820	≥104 mg/kg bw: ↑ CYP1A1 mRNA, protein and enzyme activity in the liver 24 hrs following administration of piperonyl butoxide
Acute Hepatotoxicity Study (intraperitoneal) C57BL/6 and DBA/2 (Ah receptor deficient) ♂ mice PMRA# 2407828	400 mg/kg bw: ↑ CYP1A1 and CYP1A2 mRNA levels in the liver 24 hrs following administration of piperonyl butoxide Piperonyl butoxide induced hepatic CYP1A1 considerably more in C57BL/6 than in DBA/2 mice
Acute Hepatotoxicity Study (intraperitoneal) C57BL/6 and DBA/2 (Ah receptor deficient) mice PMRA# 2428302	400 mg/kg bw: ↑ CYP1B1 mRNA levels in the liver, lung and kidney 24 hrs following administration of piperonyl butoxide Piperonyl butoxide induced hepatic CYP1B1 considerably more in DBA/2 than in C57BL/6 mice without any difference between the genders. The kidney expressed CYP1B1 at a lower level than that identified in the liver or lung.
Acute Hepatotoxicity Study (intraperitoneal) AHR knock-out ♂ mice PMRA# 2428303	200 mg/kg bw: ↑ CYP1A2 and CYP1B1 mRNA levels 24 hrs following administration of piperonyl butoxide AhR-independent pathway(s) may be involved in induction of CYP1A2 and CYP1B1

Study type/animal/PMRA#	Study results
Acute Hepatotoxicity Study (intraperitoneal) C57BL/6 ♂ mice PMRA# 2428298	338 mg/kg bw: ↑ CYP1A1, CYP1A2 and CYP2B10 mRNA and protein levels, ↑ EROD, ACET-OH and PROD
Acute Hepatotoxicity Study (intraperitoneal) C57BL/6 (Ah receptor) and DBA/2 (Ah receptor deficient) mice PMRA# 2428297	Study #1 (C57BL/6 mice): ≥52 mg/kg bw: ↑ P450 complex in hepatic microsomes, ↑ CYP1A1, CYP1A2 and CYP2B10 mRNA levels, ↑ EROD, PROD and ACET-OH ≥104 mg/kg bw: ↑ CYP1A2 and CYP2B10 protein levels ≥156 mg/kg bw: ↑ CYP1A1 protein levels Study #2 (both strains): ≥254 mg/kg bw: ↑ CYP1A1, CYP1A2, CYP2B10 and EROD The protein levels of CYP1A2 and CYP2B10 in both C57BL/6 and DBA/2 mice were elevated above control but showed little difference between the different strains. The increased protein level of CYP2B10 appeared to be higher in C57BL/6 mice as compared to that noted in DBA/2 mice.
7 and 42-day Dietary Hepatotoxicity Study CD-1 ♂ mice PMRA# 2420879	≥9.5 mg/kg bw/day: ↑ EROD, PROD and EMD ≥27.1 mg/kg bw/day: ↑ microsomal protein content ≥94.1 mg/kg bw/day: ↑ relative liver wt, midzonal hepatic hypertrophy, ↑ microsomal cytochrome P450 content 284 mg/kg bw/day: ↑ replicative DNA synthesis Phenobarbital: ↑ relative liver wt, centrilobular hepatic hypertrophy, ↑ replicative DNA synthesis, ↑ microsomal cytochrome P450 content, microsomal protein content and MFOs (EROD, PROD and EMD)
1, 4 or 8-wk Dietary Hepatotoxicity Study ICR ♂ mice PMRA# 2428301	600 mg/kg bw/day: ↓ bw and bwg, ↑ liver wt, centrilobular hypertrophy, ↑ lipofuscin deposition in hepatocellular cytoplasm, ↑ ROS in liver microsomes, ↑ CYP1A1, CYP2A5, CYP2B9 and CYP2B10, ↑ Por, Cyclin D1 and Xrcc5 gene

Study type/animal/PMRA#	Study results
8-wk Dietary Hepatotoxicity Study ICR ♂ mice PMRA# 2428299	600 mg/kg bw/day: ↓ bw, ↑ liver wt, vacuolar degeneration and hypertrophy of centrilobular hepatocytes, ↑ ROS in liver microsomes (higher than group with DEN initiation), ↑ γ-GGT-positive foci, PCNA-positive cells and hepatic AhR receptor, ↑ CYP1A1, CYP2A5, CYP2B9 and CYP2B10, ↑ Por, abcc2, abcc3, abcc4, Nqo1, Nrf2, c-myc and Cyclin D1 600 mg/kg bw/day + DEN: ↓ bw, ↑ liver wt, ↑ ROS in liver microsomes, ↑ γ-GGT-positive foci (higher than piperonyl butoxide alone) and PCNA-positive cells (higher than piperonyl butoxide alone), ↑ hepatic AhR receptor, ↑ CYP1A1, CYP2A5, CYP2B9 and CYP2B10, ↑ Por, abcc3, abcc4, Nqo1, Nrf2, c-fos, c-jun, c-myc, ATF3 and Cyclin D1, ↑ area and number of altered hepatic foci and ATF3-negative hepatic foci
25-wk Dietary Hepatotoxicity Study ICR ♂ mice PMRA# 2428300	Exposure to piperonyl butoxide had no effect on oxidative DNA damage as assessed by 8-OHdG 600 mg/kg bw/day + DEN: ↓ bw, ↑ liver wt, ↑ ROS in liver microsomes, ↑ CYP1A1, CYP2A5 and CYP2B10, ↑ Por, Nqo1, c-Myc, Cyclin D1 and E2f1, ↓ Egfr and Ogg1, ↑ PCNA-positive ratio in non-tumour hepatocytes, ↑ incidence of liver proliferative lesions (altered foci, adenomas and carcinomas), majority of proliferative lesions (altered foci, adenomas and carcinomas) were strongly CK8/18-positive lesions (number/cm^2)
1, 4 and 27-wk Dietary Hepatotoxicity Study C3H/HeNcrl (wild-type and CAR knock-out) ♂ mice PMRA# 2428220	Study #1: Wild-type mice: 750 mg/kg bw/day: ↓ bw, ↑ liver wt, centrilobular-midzonal hepatocellular hypertrophy, mild neutrophil infiltration, ↑ CYP2B10, CYP3A11, CYP1A2, Gadd45beta and P450 reductase Phenobarbital: ↑ liver wt, centrilobular hepatocellular hypertrophy, ↑ CYP2B10, CYP3A11, CYP1A1, CYP1A2, Gadd45beta and P450 reductase CAR-KO mice: 750 mg/kg bw/day: ↑ liver wt, centrilobular-midzonal hepatocellular hypertrophy, mild neutrophil infiltration, mild focal necrosis, mild hepatocyte vacuolation, ↑ CYP2B10, CYP3A11, CYP1A1, CYP1A2, CYP4A10, Gadd45beta and P450 reductase Phenobarbital: ↓ relative liver wt, ↑ CYP2B10 (significantly lower than wild-type) and CYP3A11 Study #2:

Study type/animal/PMRA#	Study results
	Wild-type mice: 750 mg/kg bw/day: ↓ bw, ↑ liver wt, ↑ PCNA-positive cells Phenobarbital: ↑ liver wt, ↑ PCNA-positive cells CARKO mice: 750 mg/kg bw/day: ↑ liver wt, ↑ PCNA-positive cells Phenobarbital: no treatment-related effects noted Study #3: Wild-type mice: 750 mg/kg bw/day + DEN: ↓ bw, ↑ liver wt, moderate-marked hepatocellular hypertrophy, mild-moderate karyocytomegaly, mild neutrophil infiltration, mild focal necrosis, mild yellow pigment deposition, eosinophilic altered foci and adenomas, basophilic altered foci and adenomas, other type of altered foci and adenomas Phenobarbital: ↑ liver wt, marked hepatocellular hypertrophy, mild to moderate karyocytomegaly, mild yellow pigment deposition, eosinophilic altered foci and adenomas, basophilic altered foci and adenomas, other type of altered foci and adenomas CARKO mice: 750 mg/kg bw/day + DEN: ↓ bw, ↑ liver wt, mild-marked hepatocellular hypertrophy, mild karyocytomegaly, mild-moderate focal necrosis, mild yellow pigment deposition, mild
	Moderate centrilobular vacuolation, eosinophilic altered foci and adenomas, basophilic altered foci and adenomas, other type of altered foci and adenomas Phenobarbital: ↓ bw, ↓ liver wt, mild yellow pigment deposition, basophilic altered foci and adenomas, no incidence of eosinophilic or other type of altered foci or adenomas
In vitro Study Wistar rats Isolated rat mast cells PMRA# 2428490	Piperonyl butoxide, at concentrations up to 50 µM did not induce histamine release on its own. However, at a concentration of 50 µM, piperonyl butoxide inhibited the histamine release induced by a histamine releasing agent in the absence of calcium from isolated rat mast cells.
2 days, 1, 2 or 4 wk Dietary Hepatotoxicity Study F344 ♂ rats PMRA# 2418561	≥50 mg/kg bw/day: ↑ SER ≥180 mg/kg bw/day: ↑ relative liver wt, ↓ Cx32-positive spots/hepatocyte, ↑ PCNA-positive nuclei in hepatocytes

Study type/animal/PMRA#	Study results
	1800 mg/kg bw/day: ↓ bwg and fc, ↑ liver wt, centrilobular hypertrophy, eosinophilic intracytoplasmic inclusions in hypertrophic hepatocytes Phenobarbital: ↑ liver wt, centrilobular hypertrophy, ↑ SER, ↓ Cx32-positive spots/hepatocyte, ↑ PCNA-positive nuclei in hepatocytes
2-wk Dietary Hepatotoxicity Study F344 ♂ rats PMRA# 2418565	Comet assay: No effect on the comet tail length or percentage of DNA in comet tails Liver initiation assay: There was no significant difference noted in liver wt or the number and area of GST-P positive foci between control and piperonyl butoxide-exposed animals
4 or 13-wk Dietary Hepatotoxicity Study GPT Delta ♂ rats PMRA# 2428223	2000 mg/kg bw/day: ↓ bw, ↑ liver wt, ↑ CYP1A1, CYP1A2 and CYP2B1, ↑ 8-OHdG and PCNA, centrilobular hepatocellular hypertrophy, no effect on gpt or red/gam mutant frequencies in livers or on GST-P Phenobarbital: ↑ liver wt, ↑ CYP2B1, centrilobular hepatocellular hypertrophy, no effect on gpt or red/gam mutant frequencies in livers or on GST-P
6-wk Dietary Hepatotoxicity Study F344 ♂ rats PMRA# 2428222	Study #1: ≥125 mg/kg bw/day + DEN: ↑ liver wt, ↑ UDPGTr-2, CYP1A1, Gpx-2 and Mrp3 ≥250 mg/kg bw/day + DEN: ↓ bw, centrilobular hypertrophy, ↑ GST-P positive foci and Akr7a3, ↑ ROS in liver microsomes 500 mg/kg bw/day + DEN: ↑ PCNA-positive labelling index and Nqo-1. No effect on Sic7a5 or GRx Study #2: ≥30 mg/kg bw/day + DEN: ↑ UDPGTr-2, CYP1A1 and Mrp3 60 mg/kg bw/day + DEN: ↑ relative liver wt, ↓ PCNA-positive labelling index, ↑ Gpx-2 Results compared to DEN control

Study type/animal/PMRA#	Study results
6-wk Dietary Hepatotoxicity Study F344 ♂ rats PMRA# 2428221	≥1000 mg/kg bw/day + DEN: ↓ bw, ↑ liver wt, centrilobular hypertrophy, ↑ GST-p positive foci, ↑ CYP1A1, Nqo1, GRx, UDPGTR-2, Gpx2, Abcc3, Akr7a3, Slc7a5 and Me1 2000 mg/kg bw/day + DEN: ↑ ROS in liver microsomes and level of 8-OHdG Results compared to DEN control
3 day, 4 or 13-wk Dietary Hepatotoxicity Study F344 ♂ rats PMRA# 2418554	2000 mg/kg bw/day: ↓ hepatic ERα mRNA, AR mRNA and LIFR expression, ↑ CD36 expression Phenobarbital: ↓ hepatic AR mRNA and CD36 expression, ↑ LIFR Clofibrate: ↓ hepatic ERα mRNA, AR mRNA and LIFR expression, ↑ CD36 expression
3 days, 4 or 13-wk Dietary Hepatotoxicity Study F344 ♂ rats PMRA# 2428491	2000 mg/kg bw/day: ↑ relative liver wt, diffuse hepatocellular hypertrophy, ↑ CYP1A1 and Grin2c gene Phenobarbital: ↑ relative liver wt, centrilobular hepatocellular hypertrophy, ↑ CYP2B and Grin2c gene Clofibrate: ↑ relative liver wt, diffuse hepatocellular hypertrophy, ↑ Aquaporin 3 and Grin2c genes
7 and 42-day Dietary Hepatotoxicity Study F344 ♂ Rats PMRA# 2420879	≥99.7 mg/kg bw/day: ↑ relative liver wt, periportal/midzonal hypertrophy, ↑ microsomal protein and cytochrome P450 content, ↑ EMD and PROD ≥557.3 mg/kg bw/day: ↓ bw and fc, ↑ replicative DNA synthesis (7 days), ↑ EROD 1059 mg/kg bw/day: ↑ replicative DNA synthesis (42 days), minimal hepatic cell necrosis 1848 mg/kg bw/day: minimal-mild hepatic cell necrosis Phenobarbital: ↑ fc, ↑ relative liver wt, centrilobular hepatic hypertrophy, ↑ replicative DNA synthesis (7 days), ↓ replicative DNA synthesis (42 days), ↑ microsomal protein and cytochrome P450 content, ↑ EROD, PROD and EMD
1, 4 or 8-wk Dietary Hepatotoxicity Study Sherman ♂ rats PMRA# 2407825	Study #1: ≥100 mg/kg bw/day: ↓ fc, ↑ relative liver wt, ↑ P450 content and glucuronyl transferase activity ≥500 mg/kg bw/day: ↑ hexobarbital oxidase, nitroreductase, aniline hydroxylase and O-demethylase, ↑ hepatic microsomal

Study type/animal/PMRA#	Study results
	protein and P450 content, enlargement and extensive proliferation of hepatic SER, enlarged hepatocytes, ↑ number of lipid vacuoles in hepatocytes, dilation of the tubules of the SER, double membranes around mitochondria and strands of electron-dense material in the mitochondria which resembled myelin figures 1000 mg/kg bw/day: ↓ bwg, inclusions in hepatic cytoplasm Study #2: Both regimes: 1000 mg/kg bw/day: ↑ relative liver wt, ↑ microsomal protein, cytochrome P450, cytochrome b5, hexobarbital oxidase, aniline hydroxylase, O-demethylase, nitroreductase and glucuronyl transferase, ↑ number of lipid vacuoles in hepatocytes and proliferation of SER
1, 2, 4 or 12-wk Dietary Hepatotoxicity and Renal Toxicity Study F344 ♂ rats PMRA# 2400209	≥600 mg/kg bw/day: ↓ bw, ↑ liver wt, ↑ cholesterol, albumin, total protein, phospholipids, BUN and γ-GGT, ↓ triglycerides and glucose, mild enlargement of hepatocytes and hepatic nuclei, single cell hepatic necrosis, prominent nucleoli in liver, hepatic oval cell proliferation, bile duct hyperplasia, vacuolation of hepatocytes in the periportal area, hepatic microgranuloma, marked atrophy of proximal tubules, dilation of tubules, cell infiltration, fibrosis and yellow/brown pigment in proximal tubular cell of the kidney ≥1200 mg/kg bw/day: ↓ absolute kidney wt, ↓ AST, focal hepatic necrosis, hepatic cell infiltration, multinucleated hepatocytes 2400 mg/kg bw/day: ↑ AST, ↑ relative kidney wt, vacuolation of hepatocytes in the terminal portal area, severe enlargement of hepatocytes and nuclei, atrophy of proximal tubules and cell infiltration of the kidney
Human study (considered supplemental)	
Human Study PMRA# 2400364	Antipyrine metabolism unaffected by a single oral dose of piperonyl butoxide at 0.71 mg/kg bw

Table 2 Toxicology reference values for use in the human health risk assessment of piperonyl butoxide

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or target MOE
Acute Dietary (all populations)	20-day dietary toxicity study - mice	NOAEL = 151 mg/kg bw/day	100

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or target MOE
		↓ body weight and food consumption during the first few days	
	ARfD = 1.5 mg/kg bw		
Chronic Dietary (all populations)	12-month dietary toxicity study - dogs	NOAEL = 2.9 mg/kg bw/day ↓ body weight, body weight gain and food consumption, ↑ relative liver weight and mild testicular atrophy	100
	ADI = 0.03 mg/kg bw/day		
Short- and Intermediate-Term Dermal (all populations)	21-day dermal toxicity study - rabbits	NOAEL = 1,000 mg/kg bw/day (HDT)	100
Long-Term Dermal (all populations)	21-day dermal toxicity study - rabbits	NOAEL = 1,000 mg/kg bw/day (HDT)	300
Short- and Intermediate-Term Inhalation (all populations)	90-day inhalation toxicity study - rats	LOAEC = 0.015 mg/L (~ 3.9 mg/kg bw/day) Histopathological changes in the larynx and clinical signs of toxicity	300
Long-Term Inhalation (all populations)	90-day inhalation toxicity study - rats	LOAEC = 0.015 mg/L (~ 3.9 mg/kg bw/day) Histopathological changes in the larynx and clinical signs of toxicity	1,000
Incidental Oral Short-Term (children)	12-month dietary toxicity study - dogs	NOAEL = 15.5 mg/kg bw/day ↓ body weight and body weight gain during the first 4 wks	100
Incidental Oral Intermediate-Term (children)	12-month dietary toxicity study - dogs	NOAEL = 2.9 mg/kg bw/day ↓ body weight and body weight gain by wk 13	100
Incidental Oral Long-Term (children)	12-month dietary toxicity study - dogs	NOAEL = 2.9 mg/kg bw/day ↓ body weight and body weight gain, ↑ relative liver weight and mild testicular atrophy at 52 wks	100
Aggregate Short- and Intermediate-Term (Oral, Inhalation) (all populations)	Oral: 12-month dietary toxicity study - dogs Inhalation: 90-day inhalation toxicity study - rats	Common endpoint: hepatotoxicity ↑ liver weight, ↑ hepatic enzyme levels, liver pathology Oral NOAEL = 15.5 mg/kg bw/day Inhalation NOAEL = 40.4 mg/kg bw/day	 100 100
Aggregate Long-Term (Oral) (all populations)	Oral (diet, drinking water and incidental oral ingestion): 12-month dietary toxicity study - dogs	Oral NOAEL = 2.9 mg/kg bw/day ↓ body weight and body weight gain, ↑ relative liver weight and mild testicular atrophy	100
Cancer	Evidence of carcinogenicity based on increased incidences of liver tumours in rats and mice, and equivocal evidence of tumours of the lacrimal gland (in mice) and lymphatic system (in rats). Cancer risk (threshold) was addressed through the selected toxicology reference values.		

1 CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments.

Appendix III Dietary exposure and risk assessments for piperonyl butoxide

Table 1 Refined chronic risk assessment – food alone

Population subgroup	Dietary exposure (mg/kg bw/day)	% ADI
General Population	0.042647	142
All Infants (<1 year old)	0.116392	388
Children 1—2 years old	0.094481	315
Children 3–5 years old	0.091368	305
Children 6–12 years old	0.065892	220
Youth 13–19 years old	0.048410	161
Adults 20–49 years old	0.038706	129
Adults 50–99 years old	0.024192	81
Female 13–49 years old	0.034107	114

Acceptable Daily Intake (ADI): 0.03 mg/kg bw/day
Cancer risk (threshold) was addressed through the selected ADI.

Table 2 Refined chronic risk estimates – food alone, with proposed mitigation

Population subgroup	Dietary exposure (mg/kg bw/day)	% ADI
General Population	0.004978	17
All Infants (<1 year old)	0.010252	34
Children 1–2 years old	0.017345	58
Children 3–5 years old	0.012021	40
Children 6–12 years old	0.006922	23
Youth 13–19 years old	0.004033	13
Adults 20–49 years old	0.004044	14
Adults 50–99 years old	0.003627	12
Female 13–49 years old	0.003709	12

Acceptable Daily Intake (ADI): 0.03 mg/kg bw/day
Cancer risk (threshold) was addressed through the selected ADI.

Table 3 Refined chronic risk assessment – food, with proposed mitigation, and drinking water, using an EEC of 515 µg a.i./L

Population subgroup	Dietary exposure (mg/kg bw/day)	% ADI
General Population	0.015383	51
All Infants (<1 year old)	0.049120	164
Children 1–2 years old	0.031655	106
Children 3–5 years old	0.023665	79
Children 6–12 years old	0.015580	52
Youth 13–19 years old	0.011368	38
Adults 20–49 years old	0.014382	48
Adults 50–99 years old	0.013680	46
Female 13–49 years old	0.013871	46

EEC = estimated environmental concentration; Acceptable Daily Intake (ADI): 0.03 mg/kg bw/day
Cancer risk (threshold) was addressed through the selected ADI.

Table 4 Refined chronic risk assessment – food, with poposed mitigation, and drinking water with proposed mitigation, using an EEC of 65 µg a.i./L

Population subgroup	Dietary exposure (mg/kg bw/day)	% ADI
General Population	0.006291	21
All Infants (<1 year old)	0.015158	51
Children 1–2 years old	0.019151	64
Children 3–5 years old	0.013491	45
Children 6–12 years old	0.008014	27
Youth 13–19 years old	0.004959	17
Adults 20–49 years old	0.005349	18
Adults 50–99 years old	0.004896	16
Female 13–49 years old	0.004991	16

EEC = estimated environmental concentration; Acceptable Daily Intake (ADI): 0.03 mg/kg bw/day
Cancer risk (threshold) was addressed through the selected ADI.

Table 5 Refined acute risk assessment – food, with proposed mitigation, and drinking water, using an EEC of 65 µg a.i./L

Population subgroup	Dietary exposure (mg/kg bw/day)	% ARfD
General Population	0.082253	5
All Infants (<1 year old)	0.145889	10
Children 1–2 years old	0.216394	14
Children 3–5 years old	0.188335	13
Children 6–12 years old	0.104628	7
Youth 13–19 years old	0.073146	5
Adults 20–49 years old	0.066914	4
Adults 50–99 years old	0.053238	4
Female 13–49 years old	0.061886	4

EEC = estimated environmental concentration; Acute Reference Dose (ARfD): 1.5 mg/kg bw

Table 6 Summary of chronic (non-cancer and cancer) exposure, with proposed mitigation, for aggregate risk assessment

Custom subpopulation	Dietary exposure (mg/kg bw/day)
Adult (16–80 years old)	0.005160
Youth (11–16 years old)	0.005227
Children (6–11 years old)	0.009224
Infants (1–2 years old)	0.017924

Appendix IV Food residue chemistry summary

Metabolism in livestock and plants

The nature of the residue in plant and animal commodities is adequately understood based on available metabolism studies in goat, hens, cotton, lettuce and potato. The residue definition (RD) in plant and animal commodities was established in previous petitions as piperonyl butoxide, which is consistent with the residue definition established by other regulatory jurisdictions (USEPA and JMPR/Codex).

Residue Definition

No changes are being proposed to the current residue definition for piperonyl butoxide in Canada: 5-[[2-(2-butoxyethoxy)ethoxy]methyl]-6-propyl-1,3-benzodioxole

The residue definition for risk assessment in drinking water is the sum of piperonyl butoxide, piperonyl butoxide-acid, piperonyl butoxide-aldehyde, and piperonyl butoxide-alcohol (see Appendix VII, Table 2).

Analytical Methodology

Various analytical methods exist for quantitation of the residues of piperonyl butoxide. Available methods include colorimetric methods, liquid chromatography-tandem mass spectrometry, high performance liquid chromatography with fluorescence or ultraviolet/visible light detection, gas chromatography/electron capture detector, gas-liquid chromatography with flame ionization detection or electron capture detector, and gas chromatography-tandem mass spectrometry. Enforcement methods are listed in the Canadian Food Inspection Agency's Pesticide Residues Unit Analytical Methods Manual and the US Food and Drug Administration's Pesticide Analytical Manual, via gas chromatography-tandem mass spectrometry, gas-liquid chromatography and high performance liquid chromatography with fluorescence detection.

Magnitude of the Residue

There are insufficient data to assess the risk from direct application to stored grains and seeds; pastures; ponds, lakes, reservoirs, and streams; spot-on application to poultry; space spray application while livestock, other than poultry, are present; dust application to food storage, food processing, or food-handling establishments; and domestic class label food uses which do not have a commercial equivalent. For the remaining uses, sufficient data are available to adequately assess the dietary exposure and risk from exposure to piperonyl butoxide.

Processing Studies

An experimental processing factors from a study on potato (for the processed commodity of dry flakes) was applied in the risk assessment. While other processing studies were submitted, they were not used in the risk assessment as they did not have adequate storage stability data to support their use in the derivation of processing factors. Theoretical processing factors, where available, were used in the risk assessment for other commodities.

Livestock, Poultry, Egg and Milk Residue Data

A study for direct application of piperonyl butoxide to lactating cattle was found to be adequate for the re-evaluation. A study for laying hens exposed to a space spray application of piperonyl butoxide was found to be adequate for the re-evaluation. As the study was at a lower rate than the maximum label rate for space spray in animal housing, it is proposed that labels which include use while poultry are present be limited to the study rate or lower.

Data Gaps

Sufficient information was available to adequately determine the dietary exposure and risk to piperonyl butoxide for the assessed uses. As noted above, certain food uses are proposed for cancellation due to data gaps. Additionally, there are limitations to the available residue chemistry data which may need to be addressed for future use expansions.

Appendix V Residential and occupational exposure and risk assessment tables

Table 1 Residential applicator exposure and risk assessment

Sites	Form.	Application equipment	Treatment type	Maximum application rate [a]	ATPD [b]	Exposure (mg/kg bw/day) [c]		MOE	
						Dermal	Inhalation	Dermal [d] (T = 100)	Inhalation [e] (T = 300)
Indoor and non-commercial greenhouse ornamentals; Outdoor ornamentals; gardens, trees, shrubs	Liquid	MPHW	Foliar application (Broadcast), Nest Spray	0.000922 kg a.i./m^2	111.48 m^2	1.78E-01	5.14E-05	5600	76000
		Hose-end Sprayer, sprinkler can				1.64E-01	3.98E-06	6100	980000
		Backpack				3.68E-01	3.98E-04	2700	9800
	RTU	Aerosol RTU Can	Surface spray (Broadcast), Nest Spray	0.0186 kg a.i/can	2 cans	3.79E-01	3.07E-03	2600	1300
		Trigger spray Bottle		0.0399 kg a.i./bottle	2 bottles	1.87E-01	1.30E-04	5300	30000
		Hose-end Sprayer		0.000922 kg a.i./m^2	111.48 m^2	1.77E-02	9.64E-05	56000	40000
	Dust	Plunger Duster, Bulb Duster	Surface application (Broadcast)	0.00005 kg a.i./m^2	111.48 m^2	3.84E-02	2.61E-04	26000	15000
		Shaker Can, Electric/Power Duster, Hand Crank Duster				6.61E-01	2.78E-03	1500	1400
General outdoors; mosquito, fly, gnat control (Around structures, yards, groundcovers, decks, patios, etc.)	RTU	Aerosol RTU can	Space Spray	0.00339 kg a.i./can	1 can	3.46E-02	2.81E-04	29000	14000
Dwellings and indoor sites, incl. animal premises (for example, barns); incl. bed bug treatment	Liquid	MPHW	Surface spray (Broadcast,)	0.0738 kg a.i./L	1.89 L	2.65E-01	4.23E-03	3800	920
	RTU	Aerosol RTU Can (incl. total release foggers)	Surface spray (Broadcast,); Space spray	0.05 kg a.i./can	1 can	5.10E-01	4.13E-03	2000	940
		Aerosol RTU Can (incl. automatic dispensers)	Space spray: Metered Release	Applicator exposure from loading automatic dispensers is expected to be low compared to other scenarios.					

Sites	Form.	Application equipment	Treatment type	Maximum application rate [a]	ATPD [b]	Exposure (mg/kg bw/day) [c]		MOE	
						Dermal	Inhalation	Dermal [d] (T = 100)	Inhalation [e] (T = 300)
		Trigger Spray Bottle	Surface spray (Broadcast,)	0.0369 kg a.i./bottle	1 bottle	8.65E-02	5.99E-05	12000	65000
	Dust	Bulb Duster	Surface application (Broadcast,)	0.01 kg a.i./kg dust	0.113 kg dust	7.79E-03	5.30E-05	130000	74000
		Plunger	Surface application (Broadcast,)		0.227 kg dust	1.56E-02	1.06E-04	64000	37000
		Electric/power, Hand Crank Duster				2.69E-01	1.13E-03	3700	3500
		Shaker Can		0.05 kg a.i./can	1 can	5.92E+00	2.48E-02	170	160
Livestock and pets (Cattle, horses, ponies, dogs, cats, birds, rabbits, etc.)	RTU	Shampoo, paste [f]	Livestock, direct animal treatment	0.0012 kg a.i./animal	24 animals	1.59E+00	2.30E-04	630	17000
		Spot-on				9.52E-02	Minimal	11000	Minimal
		Trigger spray Bottle				6.51E-01	2.62E-03	1500	1500
		Aerosol RTU Can		0.00325 kg a.i./animal		1.76E+00	7.10E-03	570	550
		Shampoo, ear drops [f]	Pets, direct animal treatment [g]	0.0125 kg a.i./animal	2 animals	1.38E+00	2.00E-04	720	19000
		Trigger Spray Bottle				5.66E-01	2.28E-03	1800	1700
		Aerosol RTU Can		0.0209 kg a.i./animal		9.43E-01	3.80E-03	1100	1000

Form = formulation; max = maximum; ATPD = area treated per day; MOE = margin of exposure; RTU = ready-to-use; MPHW = manually-pressurized handwand; Incl. = including; T = target; Minimal = Exposure is expected to be low compared to other application scenarios
Shaded cells indicate that the target MOE was not met and further mitigation is required.

[a] Highest available rates for each scenario/application equipment. Trigger sprayer, aerosol can and space spray application rates could also be based on net contents, maximum concentration of PBU, and density.

[b] Based on Residential SOP inputs (USEPA, 2012), except the value for livestock which was based on data from Statistics Canada (2016).

[c] Where exposure (mg/kg bw/day) = (unit exposure × area treated per day × application rate)/80 kg.

[d] Dermal MOEs for short- to intermediate-term exposure durations are based on a NOAEL of 1000 mg/kg bw/day from a 21-day rabbit dermal toxicity study and a target MOE of 100.

[e] Inhalation MOEs for short- to intermediate-term exposure durations are based on a LOAEL of 3.9 mg/kg bw/day from a 90-day inhalation toxicity study in rats and a target MOE of 300.

[f] Exposure from shampoo will address exposure from ear drops and paste.

[g] Application rates for liquid and pressurized products (0.12 g a.i./kg bw pet and 0.2 g a.i./kg bw pet, respectively) calculated based on assumption of 230 lbs (104 kg) for a large dog (mastiff).

Table 2.1 Residential post-application dermal exposure and risk assessment – outdoor areas and non-commercial greenhouse

Exposure Scenario			Lifestage	DFR or TTR (µg/cm^2)	TC [a] (cm^2/hr)	ET [b] (hr/day)	Dermal Exposure [c] (mg/kg bw/day)	MOE [d] (T = 100)
Outdoor ornamentals; gardens, trees, shrubs; indoor and non-commercial greenhouse ornamentals	Liquid, Aerosol RTU can	Gardens	Adult	29.5 [e]	8400	2.2	6.82E+00	150
			Child (6<11)		4600	1.1	4.67E+00	210
		Trees	Adult		1700	1	6.28E-01	1600
			Child (6<11)		930	0.5	4.29E-01	2300
		Indoor Plants / Greenhouses	Adult	53.5 [f]	220	1	1.47E-01	6800
			Child (6<11)		120	0.5	1.00E-01	10000
	Dust	Gardens	Adult	1.6 [g]	8400	2.2	3.70E-01	2700
			Child (6<11)		4600	1.1	2.53E-01	3900
		Trees	Adult		1700	1	3.40E-02	29000
			Child (6<11)		930	0.5	2.33E-02	43000
		Indoor Plants / Greenhouses	Adult	2.9 [h]	220	1	7.98E-03	130000
			Child (6<11)		120	0.5	5.44E-03	180000
Mosquito, fly, gnat control (in general outdoor residential, for example, campgrounds, parks; and commercial/ industrial/institutional areas)	Aerosol RTU can		Adult	0.12 [i]	180000	1.5	3.97E-01	2500
			Children (1<2)		49000	1.5	7.85E-01	1300
	Liquid and PP		Adult	0.31 [j]	180000	1.5	1.06E+00	940
			Children (1<2)		49000	1.5	2.10E+00	480

DFR or TTR = dislodgeable foliar or turf transferable residue; TC = transfer coefficient; ET = exposure time; MOE = margin of exposure; T = target; RTU = ready-to-use; PP = pressurized product

[a] Transfer coefficient values from USEPA Residential SOPs (2012) were used.

[b] Exposure time values from USEPA Residential SOPs (2012) were used.

[c] Dermal exposure (mg/kg bw/day) = DFR or TTR × TC × ET/body weight (kg). Body weights of 80, 32 and 11 kg were used for adults, children (6 to <11 years), and children (1 to <2 years), respectively, as stated in the USEPA Residential SOPs (2012).

[d] Dermal MOEs for short- to intermediate-term exposure durations are based on a NOAEL of 1000 mg/kg bw/day from a 21-day rabbit dermal toxicity study and a target MOE of 100.

[e] Based on maximum domestic-class liquid application rate of 0.922 g a.i./m^2 (3 applications per year; 14 day interval). Default peak DFR 25% of application rate and 10%/day dissipation outdoors.

[f] Based on maximum domestic-class liquid application rate of 0.922 g a.i./m^2 (3 applications per year; 14 day interval). Default peak DFR 25% of application rate and 2%/day dissipation in greenhouses.

[g] Based on maximum domestic-class agriculture dust rate of 0.05 g a.i./m^2 (3 applications per year, 14 day interval). Default peak DFR 25% of application rate and 10%/day dissipation outdoors.

[h] Based on maximum domestic-class agriculture dust rate of 0.05 g a.i./m^2 (3 applications per year, 14 day interval). Default peak DFR 25% of application rate and 2%/day dissipation in greenhouses.

[i] Based on maximum domestic-class product can size of 350 g (9.7% PBU) (3 applications per year; 14 day interval). Default peak TTR 1% of application rate and 10%/day dissipation outdoors.

[j] Based on maximum commercial-class product rate of 0.0336 g a.i./m^2 (26 applications per year; 1 day interval). Default peak TTR 1% of application rate and 10%/day dissipation outdoors.

Table 2.2 Residential post-application dermal exposure and risk assessment – indoor areas (short- to intermediate-term) and pets

Exposure scenario			Lifestage	TR [a] (µg/cm^2)	TC [b] (cm^2/hr)	ET [c] (hr/day)	Dermal exposure [d] (mg/kg bw/day)	MOE [e] (T = 100)
Indoor residential and commercial/ industrial/institutional sites, incl. dwellings, food handling establishments, agricultural premises (for example, barns), etc.	Broadcast [f]	Soft Surface	Adults	5.52	6800	8	3.75E+00	270
			Children (1<2)		1800	4	3.61E+00	280
		Hard Surface	Adults	13.8	6800	2	2.35E+00	430
			Children (1<2)		1800	2	4.52E+00	220
	Perimeter/Spot/Bed bug (Coarse and Pin Stream) [f]	Soft Surface	Adults	2.76	6800	8	1.88E+00	530
			Children (1<2)		1800	4	1.81E+00	550
		Hard Surface	Adults	6.9	6800	2	1.17E+00	850
			Children (1<2)		1800	2	2.26E+00	440
	Bed bug crack and crevice (Commercial application only) [f]	Soft Surface	Adults	1.38	6800	8	9.38E-01	1100
			Children (1<2)		1800	4	9.03E-01	1100
		Hard Surface	Adults	3.45	6800	2	5.87E-01	1700
			Children (1<2)		1800	2	1.13E+00	890
	Crack and Crevice (Commercial application only) [f]	Soft Surface	Adults	0.552	6800	8	3.75E-01	2700
			Children (1<2)		1800	4	3.61E-01	2800
		Hard Surface	Adults	1.38	6800	2	2.35E-01	4300
			Children (1<2)		1800	2	4.52E-01	2200
	Fogger (liquid) [g]	Soft Surface	Adults	1.17	6800	8	7.96E-01	1300
			Children (1<2)		1800	4	7.66E-01	1300
		Hard Surface	Adults	2.93	6800	2	4.97E-01	2000
			Children (1<2)		1800	2	9.58E-01	1000
	Space Spray (PP, incl. total release fogger) [h]	Soft Surface	Adults	0.15	6800	8	9.95E-02	10000
			Children (1<2)		1800	4	9.58E-02	10000
		Hard Surface	Adults	0.37	6800	2	6.22E-02	16000

Exposure scenario			Lifestage	TR [a] (µg/cm^2)	TC [b] (cm^2/hr)	ET [c] (hr/day)	Dermal exposure [d] (mg/kg bw/day)	MOE [e] (T = 100)
			Children (1<2)		1800	2	1.20E-01	8400
	Space Spray (PP) - Metered Release [i]	Soft Surface	Adults	0.91	6800	8	6.21E-01	1600
			Children (1<2)		1800	4	5.98E-01	1700
		Hard Surface	Adults	2.28	6800	2	3.88E-01	2,600
			Children (1<2)		1800	2	7.48E-01	1,300
	Animal Barn Misting Systems [i]	Residues on hard surfaces	Adult	2.28	6800	4	7.77E-01	1,300
			Children (1<2)	Refer to Space Spray (PP) – Metered Release				
Treated Pets	Dog (liquids) [j]	All Sizes [l]	Adults	0.011	5200	0.77	5.57E-01	1800
			Children (1<2)		1400	1	1.42E+00	710
	Cat (liquids) [j]		Adults	0.001	5200	0.77	6.06E-02	17000
			Children (1<2)		1400	1	1.54E-01	6500
	Dog (pressurized products) [k]	All Sizes [l]	Adults	0.079	5200	0.77	3.93E+00	250
			Children (1<2)		1400	1	1.00E+01	100
	Cat (pressurized products) [k]		Adults	0.009	5200	0.77	4.27E-01	2300
			Children (1<2)		1400	1	1.09E+00	920

TR = transferable residue; TC = transfer coefficient; ET = exposure time; MOE = margin of exposure; T = target; PP = pressurized product; Incl. = including

[a] Transferable residue calculated based on the application rate and the exposure scenario using chemical-specific fraction transferred values of 2% for soft surfaces, 5% for hard surfaces.

[b] Transfer coefficient values from USEPA Residential SOPs (2012) were used.

[c] Exposure time values from USEPA Residential SOPs (2012) were used.

[d] Dermal exposure (mg/kg bw/day) = TR × TC × ET/BW (kg). Body weights of 80, 19, and 11 kg were used for adults, children (3 to <6 years), and children (1 to <2 years), respectively, as stated in the USEPA Residential SOPs (2012).

[e] Dermal MOEs for short- to intermediate-term exposure durations are based on a NOAEL of 1000 mg/kg bw/day from a 21-day rabbit dermal toxicity study and a target MOE of 100.

[f] Based on maximum commercial-class liquid product rate of 2.76 g a.i./m^2. Deposited residues are calculated as fractions of the label rate: 100% for broadcast, 50% for perimeter/spot/bed bug, 25% for commercial applicator-only bed bug crack and crevice, and 10% for standard crack and crevice treatment. Bed bug crack and crevice: Assumes pest control operators (PCO) will treat for bed bugs using crack & crevice treatment as well as on tufts and seams of mattresses and furniture. This results in greater exposure than the standard crack & crevice method, but less than the perimeter/spot method.

[g] Based on maximum commercial-class liquid product rate of 0.24 g a.i./m^3.

[h] Based on commercial-class pressurized product with largest amount of active ingredient for all pressurized products (50 g a.i./container; 10% PBU, 500 g).

[i] Based on maximum commercial-class metered release (automated dispenser) product with 10% PBU.

[j] Based on maximum domestic-class liquid product rate of 0.12 g a.i./kg body weight of pet.
[k] Based on maximum domestic-class PP application rate of 0.20 g a.i./kg body weight of pet.
[l] Showing only the values based on large dogs (104 kg) and cats (11 kg), which would result in the highest post-application exposure to people.

Table 2.3 Residential post-application dermal exposure and risk assessment – indoor areas (long-term, for bed bugs)

Exposure scenario			Lifestage	TR [a] (µg/cm^2)	TC [b] (cm^2/hr)	ET [c] (hr/day)	Dermal exposure [d] (mg/kg bw/day)	MOE (T = 300) [e]
Indoor residential and commercial/ industrial/institutional sites, incl. dwellings, food handling establishments, agricultural premises (for example, barns), etc.	Broadcast	Soft Surface	Adults	5.52	4700	8	2.59E+00	390
			Children (1<2)		1300	4	2.61E+00	380
		Hard Surface	Adults		4700	2	6.49E-01	1500
			Children (1<2)		1300	2	1.30E+00	770
	Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	Adults	2.76	4700	8	1.30E+00	770
			Children (1<2)		1300	4	1.30E+00	770
		Hard Surface	Adults		4700	2	3.24E-01	3100
			Children (1<2)		1300	2	6.52E-01	1500
	Bed bug crack and crevice [f] (Commercial application only)	Soft Surface	Adults	1.38	4700	8	6.49E-01	1500
			Children (1<2)		1300	4	6.52E-01	1500
		Hard Surface	Adults		4700	2	1.62E-01	6200
			Children (1<2)		1300	2	3.26E-01	3100
	Crack and Crevice (Commercial application only)	Soft Surface	Adults	0.552	4700	8	2.59E-01	3900
			Children (1<2)		1300	4	2.61E-01	3800
		Hard Surface	Adults		4700	2	6.49E-02	15000
			Children (1<2)		1300	2	1.30E-01	7700

TR = transferable residue; TC = transfer coefficient; ET = exposure time; MOE = margin of exposure; T = target; PP = pressurized product; Incl. = including
[a] Transferable residue calculated based on the application rate and the exposure scenario using (50th percentile) chemical-specific fraction transferred values of 2% for both soft and hard surfaces. Application rate for bed bugs is based on maximum indoor surface rate for liquid products (2.76 g a.i./m^2). Deposited residues are calculated as fractions of the label rate: 100% for broadcast, 50% for perimeter/spot/bed bug, 25% for commercial applicator-only bed bug crack and crevice, and 10% for standard crack and crevice treatment.
[b] Transfer coefficient values from USEPA Residential SOPs (2012) were used.
[c] Exposure time values from USEPA Residential SOPs (2012) were used.
[d] Dermal exposure (mg/kg bw/day) = TR × TC × ET/BW (kg). Body weights of 80 and 11 kg were used for adults and children (1 to <2 years), respectively, as per the USEPA Residential SOPs (2012).

[e] Dermal MOEs for the long-term exposure duration are based on a NOAEL of 1000 mg/kg bw/day from a 21-day rabbit dermal toxicity study and a target MOE of 300.
[f] Bed bug crack and crevice: Assumes pest control operators (PCO) will treat for bed bugs using crack & crevice treatment as well as on tufts and seams of mattresses and furniture. This results in greater exposure than the standard crack & crevice method, but less than the perimeter/spot method.

Table 2.4 Residential post-application dermal exposure and risk assessment – mattresses (long-term, for bed bugs)

Exposure scenario	Life stage	Deposited residue (µg/cm^2) [a]	Surface area/body weight ratio (cm^2/kg)[b]	Dermal exposure (mg/kg bw/day) [c]	MOE [d] (T = 300)
Bed bugs (highest available application rate of 2.76 g a.i./m^2)					
Application to mattress	Adults	138	280	0.1932	5200
	Children (1 to <2)		640	0.4416	2300

MOE = margin of exposure
[a] Deposited residue for mattresses is based on the USEPA Residential SOPs (2012).
[b] Values were obtained from the USEPA Residential SOPs (2012) for adults and children (1 to <2 years).
[c] Dermal exposure (mg/kg bw/day) = (Deposited Residue (µg/cm^2) × 0.001 mg/µg × Surface Area/Body Weight Ratio (cm^2/kg) × Fraction of skin in contact with mattress (0.5) × Fraction transferred (0.02) × Protection Factor (0.5). The fraction transferred value is chemical-specific and the same for all exposure durations for soft surfaces such as mattresses.
[d] Dermal MOEs for the long-term exposure duration are based on a NOAEL of 1000 mg/kg bw/day from a 21-day rabbit dermal toxicity study and a target MOE of 300.

Table 3.1 Residential post-application inhalation exposure and risk assessment (not including metered release applications)

Exposure scenario			Lifestage	C_0 or AR [a]	ET [b] (hr/day)	Inhalation exposure [c] (mg/kg bw/day)	MOE [d] (T = 300)
Highest available application rates							
Mosquito, fly, gnat control (in general outdoor residential, for example, campgrounds, parks; and commercial/industrial/institutional areas)	Domestic PP- max rate [e]		Adult	3395 mg a.i./day	N/A	5.03E-03	780
			Children (1<2)			1.89E-02	210
	Commercial PP- max rate [f] (incl. HH AB/MB applications)		Adult	67.2 mg a.i./m^3	1.5	8.06E-03	480
			Children (1<2)			3.02E-02	130
	Commercial Liquid- max rate [g] (incl. truck-mounted fogging applications)		Adult	6.3 mg a.i./m^3	1.5	7.50E-04	5200
			Children (1<2)			2.81E-03	1400
Indoor residential and commercial/ industrial/institutional sites, incl. dwellings, food handling establishments, agricultural premises (for example, barns), etc.	Commercial PP- max rate [h]	Incl. total release foggers	Adult	30 mg a.i./m^3	2	3.16E-01	12
			Children (1<2)		2	1.19E+00	3
	Domestic PP- max rate [i]		Adult	379 mg a.i./m^3	2	4.00E+00	1
			Children (1<2)		2	1.50E+01	0.3
	Commercial Liquid- max rate [j] (incl. MPHS)		Adult	240 mg a.i./m^3	2	2.53E+00	2
			Children (1<2)		2	9.49E+00	0.4

ET = exposure time; MOE = margin of exposure; OASS = outdoor aerosol space sprays; incl. = including; T = target; max = maximum; HH AB/MB = handheld airblast/mistblower; MPHS = mechanically-pressurized handheld sprayer for mists, aerosols, and fogs
Shaded cells indicate target MOE not met and further mitigation is required.
[a] Application rate (AR) or C_0 = initial air concentration (mg/m^3) following an indoor space spray determined from the label application rate if available, or from the maximum product size and highest concentration of PBU.
[b] Exposure time values from USEPA Residential SOPs (2012) were used.
[c] Generally, inhalation exposure (mg/kg bw/day) = Exposure (mg/day) × ET (hr) /BW (kg). Body weights of 80 and 11 kg were used for adults and children (1 to <2 years), respectively, as stated in the USEPA Residential SOPs (2012). Refer to footnotes 'e' through 'j' for additional calculation information.
[d] Inhalation MOEs for short- to intermediate-term exposure durations are based on a LOAEL of 3.9 mg/kg bw/day from a 90-day inhalation toxicity study in rats and a target MOE of 300.
[e] Based on maximum domestic-class pressurized product can size of 350 g (9.7% PBU). Inhalation exposure (mg/kg bw/day) = IR × AR /Q × BW. Where IR = inhalation rate; 0.64 m^3/hr for adults, 0.33 m^3/hr for children (1 to <2 years); AR = application rate (mg a.i./day); Q = airflow through the treated area (5400 m^3/hr); values from USEPA Residential SOPs (2012).
[f] Based on maximum commercial-class pressurized product rate of 0.0336 g a.i./m^2. Exposure (mg/day) = AR × F × IR. Where AR = application rate, calculated as the amount applied to 1 m × 1 m × 0.5 m space (mg/m^3); F = fraction of chemical available in outdoor air for exposure (0.01); IR = inhalation rate (m^3/hr), values from USEPA Residential SOPs (2012).
[g] Based on maximum commercial-class liquid product rate of 0.003125 g a.i.m^2. Exposure calculated as in footnote 'e'.
[h] Based on maximum commercial-class pressurized product rate of 0.03 g a.i./m^3. Inhalation exposure (mg/kg bw/day) = $[(C_0 \times IR)/(ACH \times BW)] \times [1 - e^{(-ACH \times ET)}]$. Where IR = inhalation rate (m^3/hr); ACH = air exchanges per hour (0.45 hr^{-1}); values from USEPA Residential SOPs (2012).
[i] Based on maximum domestic-class pressurized product can size of 500 g (10% PBU), and assuming 0.25 of the can is applied to a 33 m^3 room. Rate is calculated as 0.38 g a.i./m^3. Inhalation exposure is calculated as in footnote 'h'.
[j] Based on maximum commercial-class liquid product rate of 0.24 g a.i./m^3. Inhalation exposure is calculated as in footnote 'h'.

Table 3.2 Residential post-application inhalation exposure and risk assessment (metered release applications)

Exposure scenario		Lifestage	Air concentration (µg/m^3) [a]	Exposure time (hr/day) [b]	Inhalation exposure (mg/kg bw/day) [c]	MOE [d] (T = 300)
Indoor residential and commercial/ industrial/institutional sites, incl. dwellings, food handling establishments, agricultural premises (for example, barns), etc.	Metered Release /Automatic Dispensers	Adult	18.74	16	2.40E-03	1600
		Children (1 to <2)		18	1.01E-02	390

MOE = margin of exposure; T = target
[a] Average air concentration from chemical-specific study (peak to end of study) after metered release spray at 1.8 metres away from the device.
[b] Exposure Time (hr/day) values obtained from the USEPA Residential SOPs (2012) for vapours for indoor residential environments.
[c] Inhalation exposure (mg/kg bw/day) = AC × IR × ET/BW. Where AC = air concentration obtained from study (following release of 55 mg insecticide every 15 minutes); IR = Inhalation Rate (m^3/hour) 0.64 and 0.33 m^3/hr for adult and children (1 to <2 years old), respectively. Body Weight values were 80 kg for adults and 11 kg for children (1 to <2 years old). Values from USEPA Residential SOPs (2012).
[d] Inhalation MOEs for short- to intermediate-term exposure durations are based on a LOAEL of 3.9 mg/kg bw/day from a 90-day inhalation toxicity study in rats and a target MOE of 300.

Table 4.1 Intermediate-term residential post-application incidental oral exposure and risk assessment

Exposure scenario			Hand residue (mg/hour) [a] or concentration in water (mg/L) [b]	ET (hr/day) [c]	Oral exposure (mg/kg bw/day) [d]	Oral MOE [e] (T = 100)
Hand-to-Mouth Exposure (indoors/outdoors/pets) – Children (1 to <2 years)						
Mosquito, fly, gnat control (in general outdoor residential, for example, campgrounds, parks; and commercial/industrial/institutional areas)	Aerosol RTU can [f]	Residues deposited on lawns/turf	0.173	1.5	2.75E-03	1100
	Liquid and PP [g]		0.462	1.5	7.36E-03	390
Indoor residential and commercial/ industrial/institutional sites, incl. dwellings, food handling establishments, agricultural premises (for example, barns), etc.	Broadcast [h]	Soft Surface	0.745	4	3.39E-02	86
		Hard Surface	1.863	2	4.24E-02	68
	Perimeter/Spot/Bed bug (Coarse and Pin Stream) [h]	Soft Surface	0.373	4	1.69E-02	170
		Hard Surface	0.931	2	2.12E-02	140
	Bed bug crack and crevice (Commercial application only) [h]	Soft Surface	0.186	4	8.47E-03	340
		Hard Surface	0.466	2	1.06E-02	270
	Crack and Crevice (Commercial application only) [h]	Soft Surface	0.0745	4	3.39E-03	860
		Hard Surface	0.186	2	4.24E-03	680
	Fogger (liquid) [i]	Soft Surface	0.158	4	7.19E-03	400
		Hard Surface	0.395	2	8.98E-03	320
	Space Spray (PP, incl. total release fogger) [j]	Soft Surface	0.0198	4	8.98E-04	3200
		Hard Surface	0.0494	2	1.12E-03	2600
	Space Spray (PP) - Metered Release [k]	Soft Surface	0.123	4	5.61E-03	520
		Hard Surface	0.308	2	7.01E-03	410
Treated Pets [l]	Dog – liquid	All sizes	0.312	1	3.55E-03	820
	Cat – liquid	All sizes	0.143	1	1.63E-03	1800
	Dog – PP	All sizes	0.520	1	5.91E-03	490
	Cat – PP	All sizes	0.239	1	2.72E-03	1100
Ingestion Exposure (treated water) – Non-Competitive Adult, Youth, and Child Swimmers						
Lakes, ponds, reservoirs, preimpoundment treatment above dam		Adult	0.2	1	6.25E-05	46000
		Youth (11<16)		1	1.75E-04	17000
		Child (6<11)		1	3.13E-04	9300

HtM = hand-to-mouth; MOE = margin of exposure; ET = exposure time; incl. = including; PP = pressurized product; RTU = ready-to-use; T = target

[a] For mosquito, fly, gnat control and indoor sites: Hand residue is based on the dermal post-application exposure × fraction of a.i. on hands compared to body (0.15). For treated pets: Based the post-application dermal exposure from spot-on applications /(dermal exposure time (hour) × replenishment intervals (intervals/hr)) × fraction of a.i. on hands compared to body (0.04).

[b] For treated water: Maximum concentration (2 ppm) as indicated on product label for co-formulant rotenone and assumes for PBU since both are found in the same concentration

in the product (2.5% a.i.)).
[c] Exposure time based on values from the USEPA Residential SOPs (2012), except for swimming, where exposure time is 1 hr for all lifestages, based on the USEPA SwiModel.
[d] For all scenarios except treated pets and treated water: Oral Exposure (mg/kg bw/day) = [Hand Residue loading (mg/hr) × Fraction of hand mouthed (0.13)) × Exposure Time (1.5 hr) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (14)/)/Replenishment Intervals (4/hr)}}$)]/Body Weight (11 kg). For treated pets: Oral Exposure (mg/kg bw/day) = [Hand Residue loading (mg/hr) × Fraction of hand mouthed (0.13)) × Exposure Time (1hr) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (20)/)/Replenishment Intervals (4/hr)}}$)]/Body Weight (11 kg). For treated water: Oral Exposure (mg/kg bw/day) = [Concentration in water (mg/L) × ingestion rate (L/hr) × exposure duration (hrs)]/BW. Body weights of 80, 57, 32, and 11 kg for adults, youth (11 to <16), children (6 to <11), and children (1 to <2 years), respectively, as stated in the USEPA Residential SOPs (2012).
[e] Oral MOEs for the intermediate-term exposure duration are based on a NOAEL of 2.9 mg/kg bw/day from a 12-month oral toxicity study in dogs and a target MOE of 100.
[f] Based on maximum domestic-class product can size of 350 g (9.7% PBU).
[g] Based on maximum commercial-class product rate of 0.0336 g a.i./m^2.
[h] Based on the overall maximum liquid application rate of 2.76 g a.i./m^2. Bed bug crack and crevice: Assumes pest control operators (PCO) will treat for bed bugs using crack & crevice treatment as well as on tufts and seams of mattresses and furniture. This results in greater exposure than the standard crack & crevice method, but less than the perimeter/spot method.
[i] Based on maximum commercial-class liquid product rate of 0.24 g a.i./m^3.
[j] Based on maximum commercial-class pressurized product rate of 0.03 g a.i./m^3. Showing only the commercial-class rate as domestic-class PPs for space spray use have been proposed for cancellation.
[k] Based on maximum commercial-class metered release (automated dispenser) product with 10% PBU.
[l] Based on maximum application rate (0.12 g a.i./kg bw pet for liquids and 0.20 g a.i./kg bw pet for pressurized products). Showing only the values based on large dogs (104 kg) and cats (11 kg), which would result in the highest post-application exposure to people.

Table 4.2 Post-application incidental soil ingestion exposure and risk assessment for children (1 to <2 years)

Exposure scenario	Application rate	Ingestion rate (mg/day)	Soil volume to weight conversion factor	Oral exposure (mg/kg bw/day) [a]	MOE [b]
Residues deposited on lawns/turf following applications for mosquito, fly, gnat control	0.0336 g a.i./m^2	50	0.67 cm^3/g soil	1.0E-05	280000

[a] Where Oral Exposure (mg/kg bw/day) = Application rate × fraction available in the top cm of soil (1) × soil volume to weight conversion factor (0.67) × soil ingestion rate (50 mg/day)/BW (11 kg). Application rate is based on maximum commercial-class product rate for this scenario; other inputs from the USEPA Residential SOPs (2012).
[b] Oral MOE for the intermediate-term exposure duration is based on a NOAEL of 2.9 mg/kg bw/day from a 12-month oral toxicity study in dogs and a target MOE of 100.

Table 4.3 intermediate-term residential post-application object-to-mouth exposure and risk assessment for children (1 to <2 years)

Exposure scenario			Object residue (µg/cm^2) [a]	ET (hr/day) [b]	Oral exposure (mg/kg bw/day) [c]	OtM MOE [d] (T = 100)
Indoor residential and commercial/ industrial/institutional sites, incl. dwellings, food handling establishments, agricultural premises (for example, barns), etc.	Broadcast [e]	Soft Surface	5.52	4	7.21E-02	40
		Hard Surface	13.8	2	9.02E-02	32
	Perimeter/Spot/Bed bug (Coarse and Pin Stream) [e]	Soft Surface	2.76	4	3.61E-02	80
		Hard Surface	6.90	2	4.51E-02	64
	Bed bug crack and crevice	Soft Surface	1.38	4	1.80E-02	160

Exposure scenario			Object residue (µg/cm^2) [a]	ET (hr/day) [b]	Oral exposure (mg/kg bw/day) [c]	OtM MOE [d] (T = 100)
	(Commercial application only) [e]	Hard Surface	3.45	2	2.25E-02	130
	Crack and Crevice (Commercial application only) [e]	Soft Surface	0.552	4	7.21E-03	400
		Hard Surface	1.38	2	9.02E-03	320
	Fogger (liquid) [f]	Soft Surface	1.17	4	1.53E-02	190
		Hard Surface	2.926	2	1.91E-02	150
	Space Spray (PP, incl. total release fogger) [g]	Soft Surface	0.146	4	1.91E-03	1500
		Hard Surface	0.366	2	2.39E-03	1200
	Space Spray (PP) - Metered Release [h]	Soft Surface	0.914	4	1.19E-02	240
		Hard Surface	2.28	2	1.49E-02	190

OtM = object-to-mouth; MOE = margin of exposure; ET = exposure time; incl. = including; PP = pressurized product; T = target

[a] Object residue is based on the deposited residue and chemical-specific fraction transferred values of 2% for soft surfaces, 5% for hard surfaces.

[b] Exposure time based on values from the USEPA Residential SOPs (2012).

[c] Oral Exposure (mg/kg bw/day) = [Object Residue (ug/cm^2) × 0.001 mg/ug × Surface Area of object mouthed (10 cm^2/event) × (Exposure Time (hr) × Replenishment Intervals (4/hr)) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (14)/Replenishment Intervals (4/hr)}}$)]/Body Weight (11 kg), as in the USEPA Residential SOPs (2012).

[d] OtM Oral MOEs for the intermediate-term exposure duration are based on a NOAEL of 2.9 mg/kg bw/day from a 12-month oral toxicity study in dogs and a target MOE of 100.

[e] Based on the overall maximum liquid application rate of 2.76 g a.i./m^2. Bed bug crack and crevice: Assumes pest control operators (PCO) will treat for bed bugs using crack & crevice treatment as well as on tufts and seams of mattresses and furniture. This results in greater exposure than the standard crack & crevice method, but less than the perimeter/spot method.

[f] Based on maximum commercial-class liquid product rate of 0.24 g a.i./m^3.

[g] Based on maximum commercial-class pressurized product rate of 0.03 g a.i./m^3. Showing only the commercial-class rate as domestic-class PPs for space spray use have been proposed for cancellation.

[h] Based on maximum commercial-class metered release (automated dispenser) product with 10% PBU.

Table 4.4 intermediate-term residential post-application object-to-mouth exposure and risk assessment for children (1 to <2 years) – indoor surface applications only

Form.	Rate [a]	Exposure scenario		Object residue (µg/cm^2) [b]	ET (hr/day) [c]	Oral exposure (mg/kg bw/day) [d]	OtM MOE [e] (T = 100)
Commercial-Class Products							
Liquid	2.76 g a.i./m^2 (highest indoor rate, intended for FHEs and pet premises)	Broadcast	Soft Surface	5.520	4	7.21E-02	40
			Hard Surface	13.800	2	9.02E-02	32
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	2.760	4	3.61E-02	80
			Hard Surface	6.900	2	4.51E-02	64
		Bed bug crack and crevice	Soft Surface	1.380	4	1.80E-02	160
			Hard Surface	3.450	2	2.25E-02	130
		Crack and Crevice	Soft Surface	0.552	4	7.21E-03	400

Form.	Rate [a]	Exposure scenario		Object residue (µg/cm^2) [b]	ET (hr/day) [c]	Oral exposure (mg/kg bw/day) [d]	OtM MOE [e] (T = 100)
			Hard Surface	1.380	2	9.02E-03	320
	0.21 g a.i./m^2 (indoor/dwelling rate)	Broadcast	Soft Surface	0.420	4	5.49E-03	530
			Hard Surface	1.050	2	6.86E-03	420
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	0.210	4	2.74E-03	1100
			Hard Surface	0.525	2	3.43E-03	850
PP	1.2 g a.i./m^2 (highest indoor/dwelling rate)	Broadcast	Soft Surface	2.400	4	3.14E-02	92
			Hard Surface	6.000	2	3.92E-02	74
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	1.200	4	1.57E-02	180
			Hard Surface	3.000	2	1.96E-02	150
		Bed bug crack and crevice	Soft Surface	0.600	4	7.84E-03	370
			Hard Surface	1.500	2	9.80E-03	300
		Crack and Crevice	Soft Surface	0.240	4	3.14E-03	920
			Hard Surface	0.600	2	3.92E-03	740
	0.77 g a.i./m^2 (indoor/dwelling rate, intended for bed bugs)	Broadcast	Soft Surface	1.540	4	2.01E-02	140
			Hard Surface	3.850	2	2.52E-02	120
DU	0.6 g a.i./m^2 (highest rate)	Broadcast	Soft Surface	1.200	4	1.57E-02	180
			Hard Surface	3.000	2	1.96E-02	150
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	0.600	4	7.84E-03	370
			Hard Surface	1.500	2	9.80E-03	300
		Bed bug crack and crevice	Soft Surface	0.300	4	3.92E-03	740
			Hard Surface	0.750	2	4.90E-03	590
		Crack and Crevice	Soft Surface	0.120	4	1.57E-03	1800
			Hard Surface	0.300	2	1.96E-03	1500
Domestic-Class Products							
Liquid	2.76 g a.i./m^2 (indoor/dwelling rate intended for bed bugs)	Broadcast	Soft Surface	5.520	4	7.21E-02	40
			Hard Surface	13.800	2	9.02E-02	32
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	2.760	4	3.61E-02	80
			Hard Surface	6.900	2	4.51E-02	64
	0.55 g a.i./m^2 (indoor/dwelling rate)	Broadcast	Soft Surface	1.100	4	1.44E-02	200
			Hard Surface	2.750	2	1.80E-02	160
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	0.550	4	7.19E-03	400
			Hard Surface	1.375	2	8.99E-03	320
PP	1.4 g a.i./m^2 (highest indoor/dwelling rate)	Broadcast	Soft Surface	2.800	4	3.66E-02	79
			Hard Surface	7.000	2	4.57E-02	63
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	1.400	4	1.83E-02	160
			Hard Surface	3.500	2	2.29E-02	130

Form.	Rate [a]	Exposure scenario		Object residue (µg/cm²) [b]	ET (hr/day) [c]	Oral exposure (mg/kg bw/day) [d]	OtM MOE [e] (T = 100)
	0.21 g a.i./m² (indoor/dwelling rate, intended for bed bugs)	Broadcast	Soft Surface	0.420	4	5.49E-03	530
			Hard Surface	1.050	2	6.86E-03	420
DU	0.58 g a.i./m² (highest rate)	Broadcast	Soft Surface	1.160	4	1.52E-02	190
			Hard Surface	2.900	2	1.90E-02	150
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	0.580	4	7.58E-03	380
			Hard Surface	1.450	2	9.48E-03	310

Form. = formulation; OtM = object-to-mouth; MOE = margin of exposure; ET = exposure time; incl. = including; PP = pressurized product; DU = dust; T = target; FHE = food handling establishment

[a] All rates from Appendix V, Tables 1.1 and 1.2 were considered as "general use" indoor rates for this assessment. When risk mitigation was required, only lower label rates (for example, 0.21 g a.i./m² from 2.76 g a.i./m²) are shown for specific treatment types (for example, broadcast, perimeter).

[b] Object residue is based on the deposited residue and chemical-specific fraction transferred values of 2% for soft surfaces, 5% for hard surfaces.

[c] Exposure time based on values from the USEPA Residential SOPs (2012).

[d] Oral exposure (mg/kg bw/day) = [Object Residue (ug/cm²) × 0.001 mg/ug × Surface Area of object mouthed (10 cm²/event) × (Exposure Time (hr) × Replenishment Intervals (4/hr)) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (14)/Replenishment Intervals (4/hr)}}$)]/Body Weight (11 kg), as in the USEPA Residential SOPs (2012).

[e] OtM Oral MOEs for the intermediate-term exposure duration are based on a NOAEL of 2.9 mg/kg bw/day from a 12-month oral toxicity study in dogs and a target MOE of 100.

Table 4.5 long-term residential post-application object-to-mouth exposure and risk sssessment for children (1 to <2 years) – surface applications only

Form.	Rate [a]	Exposure scenario [b]		Object residue (µg/cm²) [c]	ET (hr/day) [d]	Oral exposure (mg/kg bw/day) [e]	OtM MOE [f] (T = 100)
Commercial-Class Products							
Liquid	2.76 g a.i./m² (highest indoor rate, intended for FHEs and pet premises)	Bed bug crack and crevice	Soft Surface	1.380	4	1.73E-02	170
			Hard Surface		2	8.63E-03	340
		Crack and Crevice	Soft Surface	0.552	4	6.90E-03	420
			Hard Surface		2	3.45E-03	840
	0.21 g a.i./m² (indoor/dwelling rate)	Broadcast	Soft Surface	0.420	4	5.25E-03	550
			Hard Surface		2	2.63E-03	1100
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	0.210	4	2.63E-03	1100
			Hard Surface		2	1.31E-03	2200
		Bed bug crack and crevice	Soft Surface	0.105	4	1.31E-03	2200
			Hard Surface		2	6.56E-04	4400
		Crack and Crevice	Soft Surface	0.042	4	5.25E-04	5500
			Hard Surface		2	2.63E-04	11000

Form.	Rate [a]	Exposure scenario [b]		Object residue (µg/cm^2) [c]	ET (hr/day) [d]	Oral exposure (mg/kg bw/day) [e]	OtM MOE [f] (T = 100)
PP	1.2 g a.i./m^2 (highest indoor/dwelling rate)	Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	1.200	4	1.50E-02	190
			Hard Surface		2	7.50E-03	390
		Bed bug crack and crevice	Soft Surface	0.600	4	7.50E-03	390
			Hard Surface		2	3.75E-03	770
		Crack and Crevice	Soft Surface	0.240	4	3.00E-03	970
			Hard Surface		2	1.50E-03	1900
	0.77 g a.i./m^2 (indoor/dwelling rate, intended for bed bugs)	Broadcast	Soft Surface	1.540	4	1.93E-02	150
			Hard Surface		2	9.63E-03	300
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	0.770	4	9.63E-03	300
			Hard Surface		2	4.81E-03	600
		Bed bug crack and crevice	Soft Surface	0.385	4	4.81E-03	600
			Hard Surface		2	2.41E-03	1200
		Crack and Crevice	Soft Surface	0.154	4	1.93E-03	1500
			Hard Surface		2	9.63E-04	3000
DU	0.6 g a.i./m^2 (highest rate)	Broadcast	Soft Surface	1.200	4	1.50E-02	190
			Hard Surface		2	7.50E-03	390
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	0.600	4	7.50E-03	390
			Hard Surface		2	3.75E-03	770
		Bed bug crack and crevice	Soft Surface	0.300	4	3.75E-03	770
			Hard Surface		2	1.88E-03	1500
		Crack and Crevice	Soft Surface	0.120	4	1.50E-03	1900
			Hard Surface		2	7.50E-04	3900
Domestic-Class Products							
Liquid	0.55 g a.i./m^2	Broadcast	Soft Surface	1.100	4	1.38E-02	210
			Hard Surface		2	6.88E-03	420
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	0.550	4	6.88E-03	420
			Hard Surface		2	3.44E-03	840
PP	1.4 g a.i./m^2 (highest indoor rate)	Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	1.400	4	1.75E-02	170
			Hard Surface		2	8.75E-03	330
	0.21 g a.i./m^2 (indoor rate intended for bed bugs)	Broadcast	Soft Surface	0.420	4	5.25E-03	550
			Hard Surface		2	2.63E-03	1100
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	0.210	4	2.63E-03	1100
			Hard Surface		2	1.31E-03	2200
DU	0.58 g a.i./m^2	Broadcast	Soft Surface	1.160	4	1.45E-02	200
			Hard Surface		2	7.25E-03	400

Form.	Rate [a]	Exposure scenario [b]		Object residue (µg/cm²) [c]	ET (hr/day) [d]	Oral exposure (mg/kg bw/day) [e]	OtM MOE [f] (T = 100)
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	Soft Surface	0.580	4	7.25E-03	400
			Hard Surface		2	3.63E-03	800

Form. = formulation; OtM = object-to-mouth; MOE = margin of exposure; ET = exposure time; incl. = including; PP = pressurized product; DU = dust; T = target; FHE = food handling establishment

[a] All rates from Appendix V, Tables 1.1 and 1.2 were considered as "general use" indoor rates for this assessment. When risk mitigation was required, only lower label rates (for example, 0.21 g a.i./m^2 from 2.76 g a.i,/m^2) are shown for specific treatment types (for example, broadcast, perimeter).

[b] Assessed only those scenarios for which risks were shown to be acceptable in the refined intermediate-term object-to-mouth risk assessment (Appendix V, Table 4.4).

[c] Object residue is based on the deposited residue and chemical-specific (50^{th} percentile) fraction transferred values of 2% for both soft and hard surfaces.

[d] Exposure time based on values from the USEPA Residential SOPs (2012).

[e] Oral exposure (mg/kg bw/day) = [Object Residue (ug/cm^2) × 0.001 mg/ug × Surface Area of object mouthed (10 cm^2/event) × (Exposure Time (hr) × Replenishment Intervals (4/hr)) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (12)/Replenishment Intervals (4/hr))}}$]/Body Weight (11 kg), as in the USEPA Residential SOPs (2012).

[f] OtM Oral MOEs for the long-term exposure duration are based on a NOAEL of 2.9 mg/kg bw/day from a 12-month oral toxicity study in dogs and a target MOE of 100.

Table 5 occupational MLA exposure and risk assessment

Sites	Form.	Application equipment	Treatment type [a]	Max application rate [b]	ATPD /AHPD	Exposure [c] (mg/kg bw/day)		MOE	
						Dermal	Inhalation	Dermal [d] (T=100)	Inhalation [e] (T=300)
PPE for all except HH AB/MB: Baseline (long pants, long-sleeved shirt, CR gloves) PPE for HH AB/MB: CR coveralls with a CR hood over long-sleeved shirt, long pants, CR gloves, socks, CR footwear and a respirator [f]									
Lakes, ponds, reservoirs, preimpoundment treatment above dam (water treatment)	Liquid	Boat [g]	Direct application to water	0.123 g a.i./m^3	600000 m^3	7.96E-02	2.19E-03	13000	1800
		Aerial –ML			61700 m^3	5.55E-03	5.98E-05	180000	65000
		Aerial –A				2.53E-04	9.19E-07	3900000	4200000
		Backpack [g]			12300 m^3	1.78E-02	8.55E-04	56000	4600
Outdoor ornamentals; gardens, trees, shrubs	Liquid	Airblast	Foliar application	732 g a.i./ha	20 ha	7.01E-01	1.78E-03	1400	2200
		Groundboom			26 ha	2.00E-02	5.50E-04	50000	7100
		HH AB/MB			0.81 ha	2.42E-01	2.92E-02	4100	130
		MPHG		1.93 g a.i./L [h]	3800 L	5.12E-01	1.38E-02	2000	280
		MPHW			150 L	3.41E-03	1.64E-04	290000	24000
		Backpack			150 L	1.97E-02	2.25E-04	51000	17000
	PP	Aerosol RTU can		8 g a.i./can	14 cans	2.05E-01	2.30E-03	4900	1700
Pastures; General outdoor residential (for	Liquid	Truck-mounted sprayer (fogger) [i]	Mosquito, fly, gnat	31.25 g a.i./ha	1200 ha	1.79E+00	4.55E-03	560	860

Sites	Form.	Application equipment	Treatment type [a]	Max application rate [b]	ATPD /AHPD	Exposure [c] (mg/kg bw/day)		MOE	
						Dermal	Inhalation	Dermal [d] (T=100)	Inhalation [e] (T=300)
example, campgrounds, parks, etc.) and commercial/industrial/institutional areas		HH AB/MB	control		0.81 ha	1.03E-02	1.25E-03	97000	3100
	PP	Aerosol RTU can		336 g a.i./ha	0.81 ha	4.99E-01	5.60E-03	2000	700
		HH AB/MB [j]				1.11E-01	1.34E-02	9000	290
General outdoor residential and commercial/industrial/institutional areas	Liquid	MPHW	Outdoor surface sprays	187.5 g a.i./ha	0.81 ha	1.79E-03	8.58E-05	560000	45000
		Backpack				1.03E-02	1.18E-04	97000	33000
		MPHG			4 ha	5.24E-02	1.42E-03	19000	2800
Livestock [k]	Liquid	MPHW	Direct animal treatment	0.52 g a.i./animal	6440 animals	3.95E-02	1.89E-03	25000	2100
		Backpack				2.28E-01	2.60E-03	4400	1500
		MPHG				2.34E-01	6.32E-03	4300	620
		Spray with Cloth [l]			120 animals	6.53E-01	1.21E-03	1500	3200
	PP	Aerosol RTU Can	Direct animal treatment	1.09 g a.i./animal	120 animals	2.40E-01	2.69E-03	1500	3200
		Aerosol Can with Cloth [m]				8.93E-01	3.90E-03	1100	1000
Pet treatment	Liquid	Dropper bottle [n]	Direct animal treatment	0.00433 g a.i./animal	8 animals	1.15E-04	Lower	8700000	Lower
Poultry	Liquid	MPHW	Direct animal treatment	0.52 g a.i./animal	20000 animals	1.23E-01	5.88E-03	8200	660
		Backpack				7.08E-01	8.07E-03	1400	480
		MPHG				7.26E-01	1.96E-02	1400	200
Poultry buildings (birds present)	Liquid	HH AB/MB	Space spray (mist over birds)	0.24 g a.i./m^3 [(o)]	2540 m^3	2.49E-01	3.00E-02	4000	130
Indoor residential and commercial/ industrial/institutional sites, incl. dwellings, food handling establishments, agricultural premises (for example, barns), etc.	PP	Aerosol RTU can (incl. total release foggers)	Space and Surface sprays	40 g a.i./can	14 cans	1.03E+00	1.15E-02	970	340
		Aerosol RTU can (incl. automatic dispensers)	Space spray: Metered Release	Applicator exposure from loading automatic dispensers is expected to be low compared to other scenarios. [p]					
	Liquid	Auto/Stationary fogger –ML	Space spray	0.24 g	2540 m^3	4.46E-04	4.80E-06	2200000	810000

Sites	Form.	Application equipment	Treatment type [a]	Max application rate [b]	ATPD /AHPD	Exposure [c] (mg/kg bw/day)		MOE	
						Dermal	Inhalation	Dermal [d] (T=100)	Inhalation [e] (T=300)
		MPHS		a.i./m^3		2.49E-01	3.00E-02	4000	130
		PCO MPHW, MechPH-ULV	Surface spray (Broadcast), Bed bug	2.76 g a.i./m^2	1040 m^2	3.08E+00	1.18E-02	320	330
	DU	Bulbous/Plunger Duster	Surface application (Broadcast), bed bug, nests	0.6 g a.i./m^2	111 m^2	1.30E-01	2.27E-03	7700	1700
		Shaker Can, Hand-crank Duster, Electric/Power Duster				2.03E-01	3.23E-02	4900	120
For HH AB/MB: Limit amount handled per day [q]									
Outdoor ornamentals	Liquid	HH AB/MB	Foliar application	0.27 kg a.i./day		1.08E-01	1.31E-02	9300	300
Poultry buildings (birds present)			Space spray (mist over birds)						
Required Mitigation (PPE): Baseline (long pants, long-sleeved shirt, CR gloves) and respirator [f]									
Poultry	Liquid	MPHG	Direct animal treatment	0.52 g a.i./animal	20000 animals	7.26E-01	1.96E-03	1400	2000

ML = mixer/loader; A = applicator; Form. = formulation; RTU = ready-to-use; PP = pressurized product; liquid = solution, emulsifiable concentrate, and/or suspension; DU = dust; PCO = pest control operator; MechPH-ULV = Mechanically-pressurized handheld ULV equipment;MOE = margin of exposure; MPHW = manually-pressurized handwand; MPHG = mechanically-pressurized handgun; CR = chemical resistant; HH AB/MB = handheld airblast/mistblower; MPHS = mechanically-pressurized handheld sprayer for mists, aerosols, and fogs; ATPD = area treated per day; AHPD = amount handled per day; PPE = personal protective equipment; T = target
Lower = MLA exposure is expected to be low compared to other application scenarios. Shaded cells indicate that the target MOE was not met and further mitigation is required.
[a] Surface applications include broadcast, perimeter/spot, or crack/crevice treatment types.
[b] Highest available rates for each scenario/application equipment are presented. Aerosol can and space spray application rates could also be based on net contents, maximum concentration of PBU, and density.
[c] Where exposure (mg/kg bw/day) = (unit exposure × area treated per day × application rate)/80 kg. Unit exposures: for HH AB/MB and MPHS, based on Thouvenin (2015) and Testman (2015); for PCO MPHW, based on Krolski (2014); for bulbous/plunger duster, based on ORETF garden pump duster; and for shaker can, hand-crank duster, electric/power duster, based on USEPA dust unit exposure table (2018).

[d] Dermal MOEs for short- to intermediate-term exposure durations are based on a NOAEL of 1000 mg/kg bw/day from a 21-day rabbit dermal toxicity study and a target MOE of 100.
[e] Inhalation MOEs for short- to intermediate-term exposure durations are based on a LOAEL of 3.9 mg/kg bw/day from a 90-day inhalation toxicity study in rats and a target MOE of 300.
[f] NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH-approved canister approved for pesticides.
[g] Assessed using unit exposures for AHETF open cab groundboom (for boat) and PHED low pressure handwand (for backpack). Based on approach used in USEPA assessment for rotenone (2007).
[h] Maximum application rate was calculated based on a spray volume of 380 L/ha and the application rate for outdoor ornamentals (732 g a.i./ha).
[i] Airblast application equipment was used as surrogate for truck-mounted ULV sprayer application equipment.
[j] The application instructions for this PP described the application as a fog. To address the potential that it could be used with a handheld fogger, the HH AB/MB equipment was assumed. This addresses potential scenarios where the PP has a 'fogging' nozzle and it is applied as a RTU 'fog' from the aerosol can.
[k] Includes horses, ponies, beef and dairy cattle, sheep, goats, swine (and other livestock).
[l] Assessed using unit exposures for AHETF liquid (M/L) + PHED paintbrush (A)
[m] Assessed using unit exposures for PHED aerosol + PHED paintbrush
[n] Assumed 1 drop = 0.05 mL. Rate was calculated based on 20 drops (1 mL) per animal (0.5% PBU).
[o] Rate is expressed in m^3 and not per animal since the product is applied as mist over the birds.
[p] Exposure data was not available for loading aerosol cans into a metered release dispenser; however, exposure is considered to be less than aerosol can application. As MOEs for all aerosol can application scenarios were greater than the target MOE, exposure from loading a metered release device is considered to be acceptable.
[q] Limit on amount handled for HH AB/MB equipment is required to reach target MOEs for outdoor ornamentals and poultry buildings.

Table 6 Post-application worker exposure and risk assessment

Site	Activity	TC (cm^2/hr) [a]	DFR or TTR (µg/cm^2) [b]	Rate (kg a.i./ha) [c]	Max # of apps per year	Min interval between apps (days)	Dermal exposure (mg/kg bw/day) [d]	MOE (Day 0) (T=100) [e]	REI
Pastures [f]	Scouting	1100	7.8573	0.336	26	1	0.86	1200	12 hours
Outdoor ornamentals	Cut flower, hand harvesting, disbudding, and pruning (full foliage)	4000	11.9231	0.73224	10	1	4.77	210	
	Hand set/hand line irrigation related activities involving workers contacting foliage	1750					2.09	480	
	Container Moving, Pinching, Plant support/staking, Pruning (Hand), Scouting, Transplanting, Weeding (Hand)	230					0.27	3600	

Site	Activity	TC (cm^2/hr) [a]	DFR or TTR (µg/cm^2) [b]	Rate (kg a.i./ha) [c]	Max # of apps per year	Min interval between apps (days)	Dermal exposure (mg/kg bw/day) [d]	MOE (Day 0) (T=100) [e]	REI
Golf courses [g]	Scouting	1000	0.0644	0.336	52	7	0.01	160000	Until sprays have dried

TC = transfer coefficient; DFR or TTR = dislodgeable foliar or turf transferable residue; ET = exposure time; MOE = margin of exposure; T = target; RTU = ready-to-use; PP = pressurized product; REI = restricted entry interval; max = maximum; min = minimum; apps = applications; # = number

[a] Transfer coefficient values from the Agricultural Re-entry Task Force (ARTF).

[b] Since no DFR or TTR studies were submitted, a peak default DFR value of 25% of the application rate was used for all crops and a peak TTR value of 1% of the application rate was used for turf. A 10% dissipation rate per day was used for all crops.

[c] Highest available rates for each scenario were assessed.

[d] Dermal exposure (mg/kg bw/day) = DFR or TTR × TC × ET (8 hrs)/BW (80 kg).

[e] Dermal MOEs for short- to intermediate-term exposure durations are based on a NOAEL of 1000 mg/kg bw/day from a 21-day rabbit dermal toxicity study and a target MOE of 100.

[f] TCs for forage crop activities were used as surrogate for pastures.

[g] Label directions were vague regarding the use in golf courses. Based on use information submitted for pyrethrins which is co-formulated with piperonyl butoxide, the PMRA assumed that the golf course use would be in marshy areas only. Therefore, only a scouting post-application assessment was performed as other golf course maintenance activities are not expected in the application region.

Table 7 Bystander inhalation exposure and risk assessment

Lifestage	Air concentration [a] (mg/m^3)	Exposure time (hrs)	Inhalation exposure [b] (mg/kg bw/day)	MOE [c] (T = 100)
Adult	6.63E-04	1.5	7.96E-06	490000
Toddlers (6 to <12 months)		2.3	3.93E-05	99358

MOE = margin of exposure; T = target

[a] Maximum value from literature study (Désert*, et al.,*2018).

[b] Inhalation exposure (mg/kg bw/day) = air concentration × inhalation rate × exposure time /body weight. Inhalation rate was 0.64 m^3/hr for adults and 0.23 m^3/hr for toddlers (6 to <12 months). Exposure times were 1.5 and 2.3 h/day for adults and children (6 to <12 months), respectively.

[e] Inhalation MOEs for short- to intermediate-term exposure durations are based on a LOAEL of 3.9 mg/kg bw/day from a 90-day inhalation toxicity study in rats and a target MOE of 300.

Appendix VI Aggregate exposure and risk assessment tables

Table 1 Short- to intermediate-term aggregate exposure and risk assessment

Treatment type	Lifestage	Inhalation exposure (mg/kg bw/day) [a]	Inhalation MOE [b]	Incidental oral exposure (mg/kg bw/day) [c]	Chronic dietary exposure (mg/kg bw/day) [d]	Total oral exposure (mg/kg bw/day) [e]	Total oral MOE [f]	Aggregate MOE [g] (T=100)
Outdoor ornamentals; gardens, trees, shrubs; indoor and non-commercial greenhouse ornamentals								
Foliar application	Adult	2.76E-03	15000	--	5.16E-03	--	3000	2500
Mosquito, fly, gnat control (in residential areas; for example, campgrounds, parks, etc.)								
Broadcast	Adult	7.50E-04	54000	--	5.16E-03	--	3000	2800
	Children (1<2)	2.81E-03	14000	6.84E-04	1.79E-02	1.86E-02	830	790
Indoor residential and commercial/industrial/institutional sites, incl. dwellings, food handling establishments, agricultural premises (for example, barns), etc.								
Surface and space sprays (excl. metered release)	Adult	4.23E-03 [h]	9500	--	5.16E-03	--	3000	2300
	Children (1<2)	Minimal [i]	--	1.91E-02 [j] (Fogging)	1.79E-02	3.70E-02	--	420
				2.52E-02 [k] (Surface spray)	1.79E-02	4.31E-02	--	360
Space sprays (metered release, automatic dispensers)	Adult	2.40E-03	17000	--	5.16E-03	--	3000	2500
	Children (1<2)	1.01E-02 [l]	4000	1.49E-02 [m]	1.79E-02	3.29E-02	470	420
Treated Pets								
Direct application to animals	Adult	7.10E-03	5700	--	5.16E-03	--	3000	2000
	Children (1<2)	--	--	5.91E-03 [n]	1.79E-02	4.29E-02	--	360

MOE = margin of exposure; T = target; incl. = including; excl. = excluding

[a] Inhalation exposure = Handler inhalation exposure (for adults) + Post-application inhalation exposure. Highest inhalation exposure scenario was used for the aggregate risk assessment.

[b] Inhalation MOEs for short- to intermediate-term exposure durations are based on a NOAEL of 40.4 mg/kg bw/day from a 90-day inhalation toxicity study in rats and a target MOE of 100.

[c] Incidental oral exposure used for aggregate risk assessment is the highest between hand-to-mouth or object-to mouth exposure.

[d] Chronic dietary exposure is based on information provided in the dietary risk assessment (Appendix III).

[e] Total Oral Exposure (mg/kg bw/day) = HtM or OtM exposure (for children) + Chronic dietary exposure.

[f] Total Oral MOEs for short- to intermediate-term exposure durations are based on a NOAEL of 15.5 mg/kg bw/day from a 12-month oral toxicity study in dogs and a target MOE of 100.

[g] Aggregate MOE = $1/((1/MOE_{inhalation}) + (1/MOE_{oral}))$.

[h] Based on handler inhalation exposure from liquid applications (handheld equipment). Value from Appendix V, Table 1. Post-application inhalation exposure from indoor applications (other than metered release) is expected to be minimal.

[i] Post-application inhalation exposure from indoor applications (other than metered release) is expected to be minimal, provided that a 2-hour restricted-entry interval is followed for aerosols applied by a commercial handler.

[j] Based on post-application object-to-mouth exposure from liquid (fogger) applications. Values from Appendix V, Table 4.3.

[k] Based on post-application object-to-mouth exposure from pressurized product applications. Values from Appendix V, Table 4.4.

[l] Based on post-application inhalation exposure from metered release applications. Value from Appendix V, Table 3.2.

[m] Based on post-application object-to-mouth exposure from metered release applications. Value from Appendix V, Table 4.3.

[n] Based on post-application hand-to-mouth exposure from large dogs treated with pressurized products. Value from Appendix V, Table 4.1.

Table 2 Long-term aggregate exposure and risk assessment for children (1 to <2 years) – indoor surface applications

Form.	Rate [a]	Treatment type [b]	Incidental oral exposure (mg/kg bw/day) [c]	Chronic eietary exposure (mg/kg bw/day) [d]	Aggregate MOE [e] (T=100)
Commercial-class products					
Liquid	2.76 g a.i./m^2 (highest indoor rate, intended for FHEs and pet premises)	Bed bug crack and crevice	1.73E-02	1.79E-02	82
		Crack and Crevice	6.90E-03		120
	0.21 g a.i./m^2 (indoor/dwelling rate)	Broadcast	5.25E-03		130
PP	1.2 g a.i./m^2 (highest indoor/dwelling rate)	Perimeter/Spot/Bed bug (Coarse and Pin Stream)	1.50E-02	1.79E-02	88
		Bed bug crack and crevice	7.50E-03		110
		Crack and Crevice	3.00E-03		140
	0.77 g a.i./m^2 (indoor/dwelling rate, intended for bed bugs)	Perimeter/Spot/Bed bug (Coarse and Pin Stream)	9.63E-03		110
DU	0.6 g a.i./m^2 (highest rate)	Broadcast	1.50E-02	1.79E-02	88
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	7.50E-03		110
		Bed bug crack and crevice	3.75E-03		130
		Crack and Crevice	1.50E-03		150
Domestic-class products					
Liquid	0.55 g a.i./m^2	Broadcast	1.38E-02	1.79E-02	92
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	6.88E-03		120
PP	1.4 g a.i./m^2 (highest indoor rate)	Perimeter/Spot/Bed bug (Coarse and Pin Stream)	1.75E-02	1.79E-02	82
	0.21 g a.i./m^2 (indoor rate intended for bed bugs)	Broadcast	5.63E-03	1.79E-02	120
		Perimeter/Spot/Bed bug (Coarse and Pin Stream)	2.81E-03		140

Form. = formulation; OtM = object-to-mouth; MOE = margin of exposure; ET = exposure time; PP = pressurized product; DU = dust; T = target; FHE = food handling establishment

[a] All rates from Appendix V, Tables 1.1 and 1.2 were considered as "general use" indoor rates for this assessment. When risk mitigation was required, only lower label rates (for example, 0.21 g a.i./m^2 from 2.76 g a.i,/m^2) are shown for specific treatment types (for example, broadcast, perimeter).

[b] Showing only results from treatment to soft surfaces as this scenario presents greater exposure and risk than treatment to hard surfaces. Treatment type is differentiated by deposited residue (fraction of label application rate): 100% for broadcast, 50% for perimeter/spot, 25% for commercial applicator-only bed bug crack and crevice, and 10% for crack and crevice. Bed bug crack and crevice: Assumes pest control operators (PCO) will treat for bed bugs using crack & crevice treatment as well as on tufts and seams of mattresses and furniture. This results in greater exposure than the standard crack & crevice method, but less than the perimeter/spot method.

[c] Incidental oral exposure used for the aggregate risk assessment was object-to mouth since it was a higher value than hand-to-mouth.

[d] Chronic dietary exposure is based on information provided in the dietary risk assessment (Appendix III).

[e] Aggregate MOE = NOAEL/($EXPO_{OtM}$ + $EXPO_{Dietary}$), where NOAEL (2.9 mg/kg bw/day from the 12-month oral toxicity study in dogs) is the endpoint selected for long-term aggregate oral exposure; EXPO is exposure (mg/kg bw/day); and the target MOE is 100.

Appendix VII Environmental assessment

Table 1 Fate and behaviour in the environment

Type of study (PMRA#)	Endpoint	Endpoint value	Comments
Hydrolysis PMRA# 2994681	Half-life	pH 5: stable pH 7: stable pH 9: stable	Not an important route of transformation (MRID 43595601)
Phototransformation in water PMRA# 2994681	Half-life	8.4 h	May be an important route of transformation (MRID 43637201 and 1999 Arnold) Two major transformation products: PBO-alcohol 50% AR at 24 h and PBO-aldehyde 10% AR at 24 h
Phototransformation on soil PMRA# 2994681	Half-life	2.1 days	May be an important route of transformation very rapid degradation observed in both the irradiated and dark control samples may preclude a definitive determination of whether photodegradation was a significant factor in the degradation of the compound (MRID 43720801)
Phototransformation in air	Half-life	3.6 h	Not expected to undergo long range atmospheric transport AopWin v1.92 estimate based on overall hydroxyl radical rate constant of 107.0380 × 10-12 cm3·molecule^{-1}·second^{-1}
Aerobic biotransformation in water/sediment PMRA# 2994681 and 3019853	DT_{50}	133 days (USEPA) At 12 °C: 102.4 and 104.3 days Normalised to 20 °C: 58.81 and 59.90 days; 213 days (3019853)	Not an important route of transformation. Slightly Persistent USEPA: Max. concentration of transformation products PBO-alcohol 3.8% AR (water), 0.8% AR (sediment) day 30; PBO aldehyde 18% AR (water), 0.9% AR (sediment) at day 30; PBO-acid 3.4% AR (water), 1.5% AR (sediment) at day 30. EFSA (3019853): identified M2 {2-[(6-propyl-1,3-benzodioxol-5-yl)methoxy] ethoxy}acetic acid as major transformation product (reached a max of 40.7% AR after 100 days in creek water sediment system and 21.4% AR in pond system. PBO acid reached a max of 6.6% AR total pond system and another (minor) transformation product, M1 [(6-propyl-1,3-benzodioxol-5-yl)methoxy] acetic acid, reached 7.6%AR in pond system 1999 Arnold (PMRA# 3019854): reports sandy loam soil water sediment system showed PBU partitioned to sediment (60% AR) and water (40% AR). Minor transformation products PBO-alcohol and PBO-acid formed at 5%AR
Anaerobic biotransformation in water/sediment PMRA# 2713733	DT_{50}	Sandy-loam = 121.6 days Loam = 120.3 days	Moderately Persistent Max. concentration of major transformation product: Sandy loam: PBU-acid = 24.2% AR (water), 5.4% AR (sediment). Loam: PBU-acid = 18.6% AR (water), 4.1% AR (sediment).

Type of study (PMRA#)	Endpoint	Endpoint value	Comments
Aerobic biotransformation in soil PMRA# 1448938 and 3019853	DT_{50}	EPA (2994681) and EFSA (3019853) - Sandy loam: 14 days (25 degrees C) – normalised to 20 degrees C half-life = 19.8 days EFSA (3019853) Loamy sand: 64 days Silt loam: 29 days Sandy loam: 23 days	Important route of transformation. Moderately persistent USEPA (2994681) and EFSA (3019853): Max. concentration of transformation products PBO-acid 17% AR at day 30; PBO prop-i-one 3% AR day 30; PBO prop-1-one benzaldehyde 6% AR at day 7 and M8 9% AR at day 30. ---------- EFSA (3019853): Four major metabolites reported, 120 day test period M12 (PBU acid) max 16.1 % AR (loamy sand) and 19.4 % AR (silt loam) and 7.5% AR (sandy loam) M2 reached max 14.4% AR (sandy loam) after 70 days Metabolite EN 1-101/4 reached max 6.6% AR (sandy loam) M1 max 5.9% AR (sandy loam) M8 max 9% AR (30 days, sandy loam)
Adsorption/Desorption PMRA# 2994681	*K*oc	Sand: 399 Sandy loam: 490 Clay loam: 708 Silt loam: 830	Low mobility in clay and silt loam soils, moderate mobility in sandy loam and sand soils. May have potential for leaching
Volatilization (1999 Arnold)	Rate	250 g a.i./ha	Not important route of dissipation, low volatility Non-guideline test conducted using French bean leaves and [14C]PBU. Approx 9% PBU volatilised withing 24 h.
Bioaccumulation PMRA# 3019853	log K_{ow}	4.8	Potential for bioaccumulation
Bioconcentration factors PMRA# 3019853		450 L/kg nonedible tissue 290 L/kg whole fish 99 L/kg edible tissue	Kinetic mean BCF factors reported for bluegill sunfish *Lepomis macrochirus*

Table 2 Identification of the transformation products included in the drinking water residue definition

Title	Data/information
Common Name	PBU-alcohol
CAS Chemical Name	3,4-methylene-6-propylbenzyl alcohol
CAS Number	21809-60-9

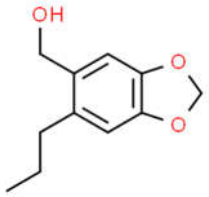
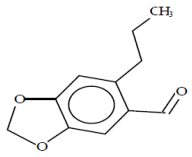
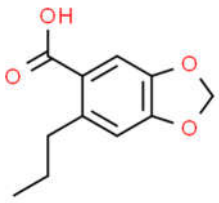
Title	Data/information
Structural Formula	
SMILES String	O(CC1=CC2=C(C=C1CCC)OCO2)[H]
Common name	PBU-aldehyde
CAS Chemical Name	3,4-methylene-6-propylbenzaldehyde
CAS Number	Not available
Structural Formula	
Molecular Formula	$C_{11}H_{12}O_3$
Molecular Weight (g/mol)	192.22
SMILES String	O=CC1=CC2=C(C=C1CCC)OCO2
Common name	PBU acid
CAS Chemical Name	3,4-methylene-6-propylbenzoic acid
CAS Number	23505-33-1
Structural Formula	
Molecular Formula	$C_{11}H_{12}O_4$
Molecular Weight (g/mol)	208.22
SMILES string	CCCc1cc2c(cc1C(=O)O)OCO2

Table 3 Toxicity to non-target species

PMRA#	Species	Type of test	Toxicity endpoint	Comments
Terrestrial Organisms				
2132139	Honey bee (*Apis mellifera*)	48-h Acute contact	LD50> 25 µg a.i./bee	Relatively non-toxic
3019853	Honey bee (*Apis mellifera*)	48-h Acute contact	LD50 = 0.294 mg a.i./bee	Highly toxic
3019853	Honey bee (*Apis mellifera*)	48-h Acute oral	LD50 = 0.6116 mg a.i./bee	Highly toxic
3019853	Earthworm (*Eisenia Fetida)*	14-day Acute	LC50 = 143.8 mg a.i./kg soil dw	-
3019853	Earthworm (*Eisenia Fetida)*	56-day Chronic (reproductive)	NOEC = 10.2 mg a.i./kg soil dw	-
3019853	Aphid parasitoid (*Aphidius rhopalosiphi)*	48-h Acute	LR50 >4.8 kg a.i./ha	-
3019853	Predatory mite *(Typhlodromus pyri)*	7-day Acute	LR50 = 0.319 kg a.i./ha	-
3019853	Bobwhite quail	14-day Acute oral	LD50 > 2250 mg a.i./kg bw/day	Practically non-toxic
3019853	Mallard duck	5-day Acute Dietary	LC50 >5620 mg a.i./kg bw/diet	Practically non-toxic
2994681	Bobwhite quail	Reproductive	NOEC = 300 mg a.s./kg diet (equivalent to 27 mg a.s./kg bw/d	Male body weight
2994681	Mallard duck	Reproductive	NOEC = 300 mg a.i./kg diet (equivalent to 47 mg a.i./kg bw/d	Eggs laid, eggs laid per female, percentage of eggs cracked, eggshell thickness, viable embryos, live 3-week embryos, 14-day survivors, normal hatchlings, food consumption, hatchling and adult body weights
3019853	Rat	Acute oral	LD50 (females) > 5000 mg a.i./kg bw LD50 (males) > 2000 mg a.i./kg bw	Practically non-toxic
3019853	Rat	Reproductive	NOAEL = 1000 mg/kg/day	developmental
1448938	Rat	Reproductive 2-generational	NOAEC = 89 mg/kg/day	decreased body weight gain (12%) in the mother and decreased body weight gain in pups (12%)
3019853	Terrestrial plants	Vegetative vigour	ER50> 3250 g a.i./ha	Limit test conducted on 6 species of plants (2006)
Aquatic Organisms – Freshwater				
3019853	*(Americamycis bahia)*	96-h Acute toxicity Flow-through	EC50 = 0.32 mg a.i./L	Highly toxic
3021061	Waterflea *(Ceriodaphnia dubia)*	96-h acute toxicity	0.650 mg a.i./L (C.I. 0.610 – 0.690 mg a.i./L)	Highly toxic

PMRA#	Species	Type of test	Toxicity endpoint	Comments
3019853 and 1448938 (USEPA RED)	*Daphnia magna*	48-h acute toxicity Flow-through	EC50 = 0.51 mg a.i./L	Highly toxic
2713734	Amphipod *(Hyalella azteca)*	96-h acute toxicity	EC50 = 42 mg a.i./L (95% C.I. 37–47 mg a.i./L)	Slightly toxic
2713729	Amphipod *(Hyalella azteca)*	96-h acute toxicity PBU-alcohol	EC50 = 0.97 (95% C.I. 0.75 – 1.2) mg a.i./L	Highly toxic
2173730 and 3019853	Amphipod *(Hyalella azteca)*	96-h Acute toxicity PBU-acid	EC50 = 31 mg a.i./L (95% C.I. = 27-37 mg a.i./L)	Slightly toxic
2713731	Amphipod *(Hyalella azteca)*	96-h Acute toxicity PBU-aldehyde	EC50 = 1.0 mg a.i./L (95% C.I. = 0.82 – 1.3 mg a.i./L)	Highly toxic
2713728	*Daphnia magna*	Chronic – 21-day Life-cycle toxicity	NOEC = 0.019 mg a.i./L based on cumulative no. of off-spring	NOEC endpoint was adjusted from 0.030 mg a.i./L to reflect low analytical recovery of the lowest test concentration (mean 63%)
3019853	*Chironomus riparius*	Chronic – 28-day NOEC (spiked sediment system)	NOEC = 0.093 mg a.i./dry weight of sediment	-
3019853	*Chironomus dilutus*	Chronic – 63-day NOEC (spiked sediment system)	NOEC = 0.44 mg a.i./dry weight of sediment	-
3019853	*Hyalel/a azteca*	Chronic – 42-day NOEC (spiked sediment system)	NOEC = 39 mg a.i./dry weight of sediment	-
3019853 and 2006 EFED 2994681	Rainbow trout *(Oncorhynchus mykiss)*	96-h Acute – flow through	96 h LC50 = 6.12 mg a.i./L	Moderately toxic
2713734	Rainbow trout *(Oncorhynchus mykiss)*	96-h Acute	96 h LC50 = 2.90 mg a.i./L	Moderately toxic
USEPA RED	Rainbow trout *(Oncorhynchus mykiss)*	96-h Acute - static	96 h LC50 = 1.9 mg a.i./L	Moderately toxic
2006 EFED 2994681	Rainbow trout *(Oncorhynchus mykiss)*	96-h Acute - static	96 h LC50 = 3.4 mg a.i./L	Moderately toxic
3019853 and 2006 EFED 2994681	Bluegill Sunfish (*Lepomis macrochirus*)	96-h Acute – flow-through	96 h LC50 = 5.37 mg a.i./L	Moderately toxic
2006 EFED 2994681	Bluegill Sunfish (*Lepomis macrochirus*)	96-h Acute - static	96 h LC50 = 9.7 mg a.i./L	Moderately toxic
2006 EFED 2994681	Bluegill Sunfish (*Lepomis macrochirus*)	96-h Acute - static	96 h LC50 = 4.2 mg a.i./L	Moderately toxic
2713727	Fathead Minnow (*Pimphales promelas*)	Early life-stage (35-day, flow through)	NOEC = 0.18 mg a.i./L based on growth and mean wet weight.	-

PMRA#	Species	Type of test	Toxicity endpoint	Comments
1448938 USEPA RED	Fathead Minnow (*Pimphales promelas*)	Early life-stage (35-day, flow through)	NOEC = 0.04 mg a.i./L based on reproductive capacity.	-
2713726	Bluegill sunfish (*Lepomis macrochirus*)	28-day bioconcentration	Depuration half-lives (DT50): Edible tissue – 0.67 days Nonedible tissue – 1.6 days Whole fish – 1.3 days BCF factors Edible tissue – 91 Nonedible tissue – 260 Whole fish – 380	Not expected to bioconcentrate
3019855 1970 Sanders[b]	Amphibians Western chorus frog (*Pseudacris Triseriata)* -1 week old tadpoles	96-h static	LC50 = 1.0 mg a.i/L. 0.10 – 9.0 mg a.i./L)	Study temperature reported to be 15.5 °C
3021061	Amphibians *Xenopus laevis* (South African clawed frog)	96-h Acute	LC50 = 68 mg a.i./L	Slightly toxic
3019853	Freshwater Green Alga (*Selenastrum capricornutum*)	72-h Static	ErC50 =3.89 mg a.i./L EbC50 = 2.09 mg a.i./L NOE_rC = 0.824 mg a.i./L	
Aquatic Organisms - Marine				
3019853 and 1448938 USEPA RED	Sheepshead Minnow (*Cyprinodon variegatus*)	96-h Acute – flow through	LC50 = 3.94 mg a.i./L	Moderately toxic
2713732	Sheepshead Minnow (*Cyprinodon variegatus*)	Early life-stage	NOEC = 0.053 mg a.i./L	
3019853 and 1448938 USEPA RED	Eastern Oyster (*Crassostrea virginica*)	96-h – Shell deposition	96-h EC50 = 0.23 mg a.i./L	Highly toxic
3019853	Mysid shrimp (*Mysidopsis bahia*)	96 h Acute	96-h LC50 = 0.32 mg ai./L	Highly toxic
1448938 USEPA RED	Mysid shrimp (*Mysidopsis bahia*)	96 h Acute – flow through	96-h EC50 = 0.49 mg ai./L	Highly toxic
3019853	*Leptocheirus plumulosus*	96-h Acute	5.37 mg a.i./L	Moderately toxic

Table 4 Screening level risk assessment on non-target species for highest cumulative application rate of PBU to outdoor ornamentals at 732 g a.i./ha with 10 applications per season and a minimum, assumed application interval of 1 day

PMRA#	Species	Type of test	Toxicity endpoint	Uncertainty factor	Toxicity endpoint adjusted for uncertainty	EECs	Risk quotient
Terrestrial Organisms							
2132139	Honey bee (*Apis mellifera*)	48-h Acute contact	>25 ug a.i./bee	1	25 mg a.i./bee	*1.76	0.07
3019853	Honey bee (*Apis mellifera*)	48-h Acute contact	LD50 = 0.294 mg a.i./bee	1	0.294 mg a.i./bee	*1.76	**5.99**
3019853	Honey bee (*Apis mellifera*)	48-h Acute oral	LD50 = 0.6116 mg a.i./bee	1	0.612 mg a.i./bee	*20.95	**34.25**
3019853	Earthworm (Eisenia Fetida)	14-day Acute	LC50 = 143.8 mg a.i./kg soil	2	7.19 mg a.i./kg soil dw	3.07	0.43
3019853	Earthworm (*Eisenia Fetida)*	56-day Chronic	NOEC= 10.2 mg a.i./kg soil dw	n/a	10.2 mg a.i./kg soil dw	3.07	0.30
3019853	Aphid parasitoid	48-h Acute	LR50 >4.8 kg a.i./ha (4800 g a.i./ha)	10	480 g a.i./ha	5304	0.76
3019853	Predatory mite *Typhlodromus pyri*	7-day Acute	LR50 = 0.319 kg a.i./ha (319 g a.i./ha)	10	31.9 g a.i./ha	5304	0.76
3019853	Bobwhite quail	14-day Acute oral	LD50 > 2250 mg a.i./kg bw/day	10	225 mg a.i./kg bw	EDE (mg a.i./kg bw) Small bird: 237.24 Mediu m bird: 185.14 Large bird: 119.59	**Small = 1.92** **Med = 1.50** **Large = 8.06**
3019853	Bobwhite quail	Reproductiv e	NOEC = 27 mg a.i./kg bw/d		27 mg a.i./kg bw	EDE (mg a.i./kg bw) Small bird: 237.24	**Small =15.99** **Medium = 12.48**

PMRA#	Species	Type of test	Toxicity endpoint	Uncertainty factor	Toxicity endpoint adjusted for uncertainty	EECs	Risk quotient
						Medium bird: 185.14 Large bird: 119.59	**Large = 8.06**
3019853	Rat	Acute oral	LD50 (females) > 5000 mg a.i./kg bw		500 mg a.i./kg bw	Mammals EDE (mean nomogram) (mg a.i./kg bw) Small: 136.45 Medium: 264.65 Large: 141.41	**Small = 1.24** **Medium = 2.41** **Large = 1.29**
1448938	Rat	Reproductive 2-gen	NOAEC = 89 mg/kg/day		89 mg a.i./kg bw	Mammals EDE (mean nomogram) (mg a.i./kg bw) Small: 136.45 Med: 264.65 Large: 141.41	**Small = 2.79** **Med = 5.41** **Large = 2.89**
3019853	Terrestrial plants	Vegetative vigour	ER50> 3250 g a.i./ha ER25 = 3250/2 = 1625	n/a	1625	7320	**4.50**
Freshwater Aquatic Organisms							
1448938 and 3019853	*Daphnia magna*	48-h Acute flow through	EC50= 0.51 mg a.i./L	2	0.051 mg a.i./L	0.87	**3.41**

PMRA#	Species	Type of test	Toxicity endpoint	Uncertainty factor	Toxicity endpoint adjusted for uncertainty	EECs	Risk quotient
3021061	Waterflea *Ceriodaphnia dubia*	48-h Acute flow through	EC50 = 0.650 mg a.i./L	2	0.065 mg a.i./L	0.87	**2.68**
2713728	*Daphnia magna*	Chronic (Life-cycle toxicity)	NOEC = 0.019 mg a.i./L based on cumulative no. of off-spring	n/a	0.019 mg a.i./L	0.87	**45.79**
3019853	Midge, *(Chironomus riparius)*	28-day Spiked sediment	NOEC = 0.093 mg a.i./dry weight of sediment	n/a	0.093 mg a.i./L	0.87	**9.35**
3019853	Midge, *Chironomus dilutes*	Chronic, 63-day spiked sediment	NOEC = 0.44 mg .a.i./dry weight of sediment	n/a	0.44 mg a.i./L	0.87	**1.98**
2173730 and 3019853	Amphipod, *Hyalella azteca*	96-h Acute	EC50 = 42 mg a.i./L	10	4.2 mg a.i./L	0.87	0.04
2713729	Amphipod, *Hyalella azteca*	96-h Acute (PBU-alcohol)	EC50 = 0.97 (95% C.I. 0.75 – 1.2) mg a.i./L	10	0.097 mg a.i./L	0.87	**1.79**
2173730 and 3019853	Amphipod, *Hyalella azteca*	96-h Acute (PBU-acid)	EC50 = 31 mg a.i./L (95% C.I. = 27-37 mg a.i./L)	10	3.1 mg a.i./L	0.87	0.06
2713731	Amphipod, *Hyalella azteca*	96-h Acute (PBU-aldehyde)	EC50 = 1.0 mg a.i./L (95% C.I. = 0.82 – 1.3 mg a.i./L)	10	0.1 mg a.i./L	0.87	**1.74**
3019853	Amphipod, *Hyalella azteca*	Chronic 42-day spiked sediment	NOEC = 39 mg a.i./kg dry weight sediment	n/a	39 mg a.i./L	0.87	0.02
2994681 and 3019853	Rainbow trout *(Oncorhynchus mykiss)*	96-h Acute flow through	LC50 = 6.12 mg a.i./L	10	0.612 mg a.i./L	0.87	**1.42**
2713734	Rainbow trout *(Oncorhynchus mykiss)*	96-h Acute	LC50 = 2.90 mg a.i./L	10	0.29 mg a.i./L	0.87	**3.00**
USEPA RED	Rainbow trout *(Oncorhynchus mykiss)*	96-h Acute static	LC50 = 1.90 mg a.i./L	10	0.19 mg a.i./L	0.87	**4.58**
2006 EFED and 2994681	Rainbow trout *(Oncorhynchus mykiss)*	96-h Acute static	LC50 = 3.4 mg a.i./L	10	0.34 mg a.i./L	0.87	**2.56**
3019853 and 2006 EFED 2994681	Bluegill Sunfish (*Lepomis macrochirus*)	96-h Acute flow through	LC50 = 5.37 mg a.i./L	10	0.537 mg a.i./L	0.87	**1.62**

PMRA#	Species	Type of test	Toxicity endpoint	Uncertainty factor	Toxicity endpoint adjusted for uncertainty	EECs	Risk quotient
2006 EFED 2994681	Bluegill Sunfish (*Lepomis macrochirus*)	96-h Acute static	LC50 = 9.7 mg a.i./L	10	0.97 mg a.i./L	0.87	0.90
2006 EFED 2994681	Bluegill Sunfish (*Lepomis macrochirus*)	96-h Acute static	LC50 = 4.2 mg a.i./L	10	0.42 mg a.i./L	0.87	**2.07**
3019855	**Amphibians Western chorus frog (*Pseudacris Triseriata*) -1 week old tadpoles	96-h acute static	LC50 = 1.0 mg a.i/L. (0.10 – 9.0 mg a.i./L)	10	0.1 mg a.i./L	4.63	**46.30**
3021061	Amphibians *Xenopus laevis* (South African clawed frog)	96-h Acute	LC50 = 68 mg a.i./L	10	6.8 mg a.i./L	4.63	0.68
2713727	Fathead Minnow (*Pimphales promelas*)	Early life-stage (35-day flow through)	NOEC = 0.18 mg a.i./L based on growth and mean wet weight	n/a	0.18 mg a.i./L	0.87	**4.83**
1448938 (USEPA RED)	Fathead Minnow (*Pimphales promelas*)	Early life-stage (35-day flow through)	NOEC = 0.04 mg a.i./L based on reproductive capacity	n/a	0.04 mg a.i./L	0.87	**21.75**
3019853	Freshwater Green Alga, (*Selenastrum capricornutum*)	72-h static	EbC50 = 2.09 mg a.i./L	2	1.05 mg a.i./L	0.87	0.83
Marine Aquatic Organisms							
3019853 and 1448938	Sheepshead Minnow (*Cyprinodon variegatus*)	96-h Acute flow through	LC50 = 3.94 mg a.i./L	10	0.394 mg a.i./L	0.092	0.23
2713732	Sheepshead Minnow (*Cyprinodon variegatus*)	Early life-stage	LC50 = 0.053 mg a.i./L	n/a	0.053 mg a.i./L	0.092	**1.74**
3019853	*Americamycis bahia*	96-h Acute toxicity Flow through	EC50 =0.32 mg ai./L	10	0.032 mg a.i./L	0.092	0.58
3019853	Mysid shrimp (*Mysidopsis bahia*)	96-h Acute	LC50 = 0.32 mg ai./L	10	0.032 mg a.i./L	0.092	0.58

PMRA#	Species	Type of test	Toxicity endpoint	Uncertainty factor	Toxicity endpoint adjusted for uncertainty	EECs	Risk quotient
3019853 and 1448938	Mysid shrimp (*Mysidopsis bahia*)	96-h Acute flow through	LC50 = 0.49 mg ai./L	10	0.049 mg a.i./L	0.092	0.38
3019853 and 1448938 USEPA RED	Eastern Oyster (*Crassostrea virginica*)	96-h Shell deposition	EC50 = 0.23 mg a.i./L	10	0.023 mg a.i./L	0.092	0.80

*For pollinators, the maximum single application rate of 732 g a.i./ha is used to determine exposure.
** USEPA RED (2006) incorrectly reports acute LC50 of 0.210 ppm for Western chorus frog tadpoles. It appears the USEPA also incorrectly referenced the source as Mayer 1986, the correct reference is H.O. Sanders (1970; PMRA# 3019855). The correct endpoint (obtained from the 1970 H.O. Sanders study) is reported here as LC50 = 1.0 mg a.i/L. 0.10 – 9.0 mg a.i./L. Reference to another amphibian endpoint for Fowler's toad (LC50 = 1.0 ppm) cannot be located in either Mayer (1986) or H.O Sanders (1970).

Table 5 Toxic substances management policy considerations-comparison to TSMP track 1 criteria

TSMP track 1 criteria	TSMP track 1 criterion value		Active ingredient endpoints	Transformation products endpoints
CEPA-toxic or CEPA-toxic equivalent	Yes		PBU is considered toxic to certain terrestrial invertebrates and aquatic organisms	No toxicity information is available for the major transformation product 2-[(6-propyl-1,3-benzodioxol-5-yl)methoxy] ethoxy}acetic acid Limited aquatic ecotoxicity data were available for PBU-aldehyde and PBU-acid. PBU-aldehyde is considered toxic to aquatic organisms PBU-acid does not appear to be toxic to aquatic organisms. No terrestrial ecotoxicity data were avaible for PBU-aldehyde and PBU-acid.
Predominantly anthropogenic	Yes		-	-
Persistence	Soil	Half-life ≥ 182 days	Half-life = 19.8 - 64 days PBU does not meet the soil persistence criterion	No soil degradation information is available for major transformation products.
	Water	Half-life ≥ 182 days	Half-life = 58.8 – 104.3 days PBU does not meet the aquatic persistence criterion	No aquatic degradation information is available for major transformation products.
	Sediment	Half-life ≥ 365 days	No kinetic data were available for sediment	No sediment degradation information is available for major transformation products.
	Air	Half-life ≥ 2 days or evidence of	3.6 hours: Not expected to persist in air thus not expected to undergo long-range atmospheric	Data not available

TSMP track 1 criteria	TSMP track 1 criterion value		Active ingredient endpoints	Transformation products endpoints
		long-range transport	transport	
Bioaccumulation	Log $K_{OW} \geq 5$		4.8 PBU may be expected to bioaccumulate	Data not available
	BCF ≥ 5000		450 L/kg non-edible tissue 290 L/kg whole fish 99 L/kg edible tissue Not expected to bioaccumulate	Data not available
	BAF ≥ 5000		No data available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No	No

[1]All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (in other words, all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

Appendix VIII Water monitoring

Based on available monitoring data from potential drinking water sources, piperonyl butoxide was detected in 8% of 281 groundwater samples from Ontario and Quebec up to a maximum concentration of 0.028 µg/L. The maximum concentration detected in all Canadian potential sources of drinking water was 0.45 µg/L. Samples analyzed for piperonyl butoxide in the United States had a maximum concentration of 1.43 µg/L detected from a lake in California in 2011. Although there were a relatively high number of samples in the United States, the detection frequency and peak concentrations were low. In total for Canada and the United States, there were 22,607 samples analyzed for drinking water and potential drinking water sources; with 1020 detections (<5% detection frequency).

Appendix IX Proposed label amendments for products containing piperonyl butoxide

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

Piperonyl butoxide is co-formulated with other active ingredients. When updating the label statements, follow the more stringent label directions of all the actives for which a given product is co-formulated.

1. USES PROPOSED FOR CANCELLATION

1.1 Restricted-Class Products

The following uses and any references to these uses are proposed to be removed from restricted-class product labels:

- Direct application to ponds, lakes, reservoirs, and streams

1.2 Commercial-Class Products

The following uses and any references to these uses are proposed to be removed from commercial-class product labels:

- Application to pastures
- Direct application to stored grain and seeds
- Spot-on application to poultry
- Space spray application while livestock, other than poultry, are present
- Outdoor mosquito, fly, or gnat control on pressurized product labels.
- Broadcast surface spray/treatment for bed bugs on pressurized product and dust product labels
- Lice on mattresses, bedding, furniture, and garments
- Spot-on application to poultry
- Space spray application while livestock, other than poultry, are present

1.3 Domestic-Class Products

The following uses and any references to these uses are proposed to be removed from domestic-class product labels:

- Garden and greenhouse food uses
- Total release fogger use on pressurized product labels
- Indoor space spray use on pressurized product labels. This does not apply to metered-release uses.
- Outdoor mosquito, fly, or gnat control on pressurized product labels
- Indoor uses on dust product labels
- Lice on mattresses, bedding, furniture, and garments

2. GENERAL LABEL IMPROVEMENTS (ALL LABELS)

Most piperonyl butoxide-containing products were registered prior to the development of modern standardized label language and the labels do not contain comprehensive use directions. After making a final re-evaluation decision for piperonyl butoxide, which will be communicated in the re-evaluation decision document (RVD), registrants will be required to update registered labels to current standards by including use directions that reflect the final risk assessment and required mitigation. The following aspects will require updating:

- Identification of specific pests that are controlled. For example, simply stating "crawling insects" is not sufficient.
- More detailed application instructions, including but not limited to the following:
    - Specific information about how much product is to be applied, which can be related to the application rates used for the health risk assessment and which would be easily understood by users, including consumers
    - Frequency of application
    - Type of application (for example, broadcast, perimeter/spot, crack and crevice)
    - Use directions or restrictions (for example, inside cupboards only, areas inaccessible to children)
    - Clear identification of application sites such as specific areas of the home (for example, kitchen, living areas), items on which application occurs (for example, carpets, mattresses), specific outdoor sites (for example, playing fields, parks, industrial areas)
- Consideration of whether some application sites listed on domestic-class labels should be removed from domestic-class products, as these are not intended for commercial uses (for example, greenhouses, livestock housing).

3. LABEL AMENDMENTS

3.1 For Technical Grade of the Active Ingredient and Manufacturing Concentrate:

The following statements are proposed to be added under the ENVIRONMENTAL PRECAUTIONS section:

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

The following statements are proposed to be added under the DISPOSAL section:

> "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."

3.2 For commercial-class end-use products:

Label statements for commercial-class products are proposed below. In addition, all labels are to be updated as per the 2020 PMRA Guidance Document: *Structural Pest Control Products: Label Updates.* Specific label statements, including those from the 2020 PMRA Guidance Document, are proposed for each of the various use scenarios on commercial-class products and are outlined in Table 2 below. Note that some product labels may include more than one scenarios. In these situations, it is important that the statements proposed for each use scenario be included on the label, with the exception of statements that are identical.

Use Precautions

The following precautionary statement is proposed to be added to commercial-class product labels with outdoor uses under PRECAUTIONS:

> "Apply only when the potential for drift beyond the area to be treated is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings."

Personal Protective Equipment

The following personal protective equipment statements are proposed to be added to all commercial-class labels under PRECAUTIONS:

> "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair."
>
> "In addition, for applications using mechanically-pressurized handguns, wear a NIOSH-approved organic-vapour removing cartridge with a prefilter approved for pesticides OR a NIOSH-approved canister approved for pesticides during mixing, loading, and application."

For dust products:

> "For indoor applications, wear a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested."

For products with fogging or space spray applications:

> "When using handheld airblast/mistblower application equipment wear chemical-resistant coveralls with a chemical-resistant hood over a long-sleeved shirt and long pants, chemical-resistant footwear, socks, 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. **DO NOT** handle more than [0.27 kg a.i. to be reported as a product equivalent value] per person, per day when using a handheld airblast/mistblower (droplet sizes 0.1–100 μm). These restrictions are in place to minimize exposure to individual applicators.

Application may need to be performed over multiple days or using multiple applicators." As indicated by the square brackets above, the active ingredient amount in this statement (in other words 0.27 kg a.i.) is to be converted into the corresponding amount of product by the registrant for each product."

"If entering treated indoor areas prior to venting, wear chemical-resistant coveralls with a chemical-resistant hood over long-sleeved shirt, long pants, chemical-resistant footwear, socks, chemical-resistant gloves, and a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH-approved canister approved for pesticides."

Restricted-entry Interval

For commercial-class labels with use instructions for outdoor ornamentals, pastures, or golf courses, the following statements are proposed to be added under PRECAUTIONS:

"For outdoor ornamentals and pastures, **DO NOT** enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours."

"For golf courses, **DO NOT** enter or allow entry into treated areas until sprays have dried."

For commercial-class labels with use instructions for indoor space spray (not including metered release products), the following statements are proposed to be added under PRECAUTIONS:

"**DO NOT** allow people or pets to enter treated area until 2 hours after application. The commercial applicator is responsible for notifying workers, the homeowner, and others of the re-entry period requirement."

Directions for Use

All Commercial-Class End-use Labels

"**DO NOT** apply in greenhouses or to greenhouse crops."

Products with Outdoor Uses

The number of applications for outdoor uses are to be reduced such that the yearly cumulative rate is less than 1100 g a.i./ha.

All Products Formulated As Dusts

Application of dust products is to be limited to areas that do not impact food, feed, or livestock that are used to produce food commodities (for example, voids, non-food areas).

Golf Courses

If golf courses are on the product label, the following statement is proposed:

> "**DO NOT** apply to golf course greens, fairways, or tees."

Space Spray Applications While Poultry Are Present

The application rate of space spray applications while poultry are present is to be limited to 0.12 g a.i/m^3 or less. The active ingredient amount (in other words 0.12 g a.i./m^3) is to be converted into the corresponding amount of product by the registrant for each applicable product.

Pressurized Products with Indoor Metered Release Space Spray Applications

For indoor metered release space spray applications of pressurized products, limit the maximum application rate of piperonyl butoxide to 1.07 mg of piperonyl butoxide released every 15 minutes. The active ingredient amount (in other words 1.07 mg a.i.) is to be converted into the corresponding amount of product by the registrant for each applicable product.

Indoor Surface Applications in Residential Areas

Use directions on labels need to be clearly defined in terms of pests controlled and of application site and area (see Section 2 above, General Label Improvements). The application sites and areas must be reflective of the pests controlled. In addition, application sites and areas must be separated into residential sites and non-residential sites.

The definition of residential sites must be added to the labels as follows:

> "Residential areas are defined as any use site where bystanders including children could be exposed during or after application. This includes in and around homes, schools, public buildings, parks, playing fields or any other areas where the general public including children could be exposed."

For indoor surface applications in residential areas, it is proposed to limit the maximum application rate of piperonyl butoxide for each treatment type as outlined in Table 1 below. The treatment type and rate would be based on the pests to be controlled. As noted in Table 2, it is also proposed that the definitions of each treatment type be added to labels where the current label instructions are absent or ambiguous. Directions for the application rates on the labels must be easily understood by applicators and must be converted into the corresponding amount of product by the registrant for each applicable product.

In addition, for pressurized products and dust products, the following statement must be added:

> "**DO NOT** apply as broadcast treatment for bed bugs"

Table 1 Maximum proposed rates for indoor surface applications for commercial-class products

Formulation	Treatment type [a]	Maximum application rate
Liquid	Broadcast	0.21 g a.i./m^2
	Perimeter/spot	
	Bed bug crack and crevice	
	Crack and crevice	2.76 g a.i./m^2
Pressurized product	Broadcast [NO BED BUGS] [b]	0.77 g a.i./m^2
	Perimeter/spot	
	Bed bug crack and crevice	1.2 g a.i./m^2
	Crack and crevice	
Dust	Broadcast [NO BED BUGS] [b]	0.6 g a.i./m^2
	Perimeter/spot	
	Bed bug crack and crevice	
	Crack and crevice	

[a] Definitions of these treatment types are as follows:
Indoor Broadcast: Indoor broadcast application is to broad expanses of indoor structural surfaces such as walls, floors, ceilings and indoor foundation walls/crawlspaces.
Crack and Crevice: 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."
Indoor Perimeter (coarse droplet or particle size): 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: Spot application is localized to a surface area not more than 0.2 m^2. Spots are not to be adjoining. The combined area of spots is not to exceed 10% of the total surface area of a room.
Bed bug crack and crevice: Assumes pest control operators (PCO) will treat for bed bugs using crack & crevice treatment as well as on tufts and seams of mattresses and furniture. This results in greater exposure than the standard crack & crevice method, but less than the perimeter/spot method.
[b] For commercial-class pressurized and dust products: DO NOT apply as broadcast treatment for bed bugs.

Indoor Surface Applications in Non-Residential Areas

Table 1 refers to the rates and treatment types required for residential areas. For non-residential areas (where children are not expected to be present), the above mitigation is not required. However, the PMRA strongly recommends that the label directions be updated as noted above in Section 2. General Label Improvements. In particular, non-residential sites should be clearly defined on labels. For example, for restaurants, specifying areas of restaurants where the general public do not enter.

Table 2 Label statements for piperonyl butoxide commercial-class product by use scenario

Scenario	Registered use	Form. [a]	Proposed label statements
Indoor surface [b] application	All	All	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**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." • "**DO NOT** apply when people or pets [or livestock] [c] are present, unless otherwise specified." • "**DO NOT** apply to surfaces that may come into contact with food/feed."
Indoor surface [b] application	All	Liquid & PP	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** allow people or pets [or livestock] [c] to enter treated areas until sprays have dried, unless otherwise specified." • "**DO NOT** allow spray to drip or allow drift onto non-target surfaces."
			If the product is registered as a surface spray and does not also have application instructions for use as a space spray, then the following statement are proposed to be added under **PRECAUTIONS**: • "**DO NOT** apply as a space spray."
Indoor surface [b] application	All	Dusts	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** allow people or pets [or livestock] [c] to enter treated areas until sprays have settled." • "**DO NOT** allow dust to deposit onto non-target surfaces."
Indoor surface [b] application	Food/feed processing facilities	All	For products registered for use in food/feed processing facilities, the following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** apply when a food/feed processing facility is in operation."

Scenario	Registered use	Form. [a]	Proposed label statements
Indoor surface [b] application	Not registered for use on stored food and feed	All	For products not registered for use on stored food and feed, the following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • **"DO NOT** apply to surfaces that may come into contact with food/feed." • "Cover or remove all food/feed. Cover all food/feed processing surfaces, equipment, and utensils or thoroughly wash following treatment."
Indoor surface [b] application	All	All	The label must contain clear instructions that define areas and locations that can be treated. The treatment type also needs to be defined. If this is absent or ambiguous, include the following definitions under "'**DIRECTIONS OF USE**". DO NOT add these statements to product labels if similar information or more restrictive application instructions are already present: • "Indoor Broadcast: Indoor broadcast application is to broad expanses of indoor structural surfaces such as walls, floors, ceilings and indoor foundation walls/crawlspaces." • "Indoor Perimeter (coarse droplet or particle size): 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: Spot application is localized to a surface area not more than 0.2 m^2. 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: 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." • "Bed Bug Crack & Crevice: Crack & crevice treatment as defined above, as well as on tufts and seams of mattresses and furniture." • "Void: Void application applies to inaccessible, enclosed empty spaces of a structure. For example, hollow walls and suspended ceilings."
Indoor surface [b] application	Void application	All	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "Care should be taken to avoid the pesticide exiting the void. Any residue deposits on non-target surfaces must be removed by the applicator."
Indoor surface [b] application	Clothing treatment	All	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently

Scenario	Registered use	Form. [a]	Proposed label statements
			specified on the label, integrate it in the statements below, as applicable. • "Remove all objects before treatment of furniture, luggage, closets or other areas where clothing, toys, towels, and other items are stored. Treated furniture and treated surfaces must be dry before replacing stored items." • "Only apply to clothing which can be laundered. Treated clothing must be laundered prior to wearing."
Indoor surface [b] application	Mattress and furniture treatment	All	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** use on items which can be laundered (e.g. pillows, bedding, toys, etc)." • "Remove bedding before treating mattresses. Treated mattress must be dry before replacing laundered bedding. • "Remove all objects before treatment of furniture, luggage, closets or other areas where clothing, toys, towels, and other items are stored. Treated furniture must be dry before replacing stored items." When approved for tuft and/or seam application only, add: • "**DO NOT** apply to the entire mattress or piece of furniture. Apply to tufts [and/or] seams only." When approved for application to voids, add: • "Care should be taken to avoid the pesticide exiting the void. Any residue deposits on non-target surfaces must be removed by the applicator."
Indoor surface [b] application			The label must contain clear instructions that define areas and locations that can be treated. The treatment type also needs to be defined. If this is absent or ambiguous, include the following definitions under '**DIRECTIONS OF USE**.' DO NOT add these statements to product labels if similar information or more restrictive application instructions are already present: • Furniture Treatment, including but not limited to upholstered furniture, hard surface furniture, mattresses, box spring, pet bedding, bed frames, dressers, curtains, picture frames, wall coverings, hollow furniture legs, etc. • "Broadcast –Broadcast furniture application covers large areas or the entire surface of listed items." • "Spot – Spot furniture application is up to 10% of the surface of the treated item." • "Crack and crevice – Crack and crevice furniture treatments are applications to junction points on items." • "Tufts and seams (mattresses and upholstered furniture only) – Tufts and seam treatment is to the junction of two or more pieces of fabric and any decorative trim (for example buttons). • "Void –Void furniture treatment targets inaccessible empty spaces of items. For example, inside the dust

Scenario	Registered use	Form. [a]	Proposed label statements
			cover on the underside of furniture or hollow table legs."
Indoor surface [b] application	Not registered for use on mattress, clothing or furniture		For products not registered for use on mattresses, clothing, or furniture, the following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** apply to [furniture, mattresses] [d], linens, pet bedding, toys or clothing.
Indoor surface [b] application	All	Liquid	The following personal protective equipment statements are proposed to be added to commercial-class product labels under **PRECAUTIONS**: • "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair." • For broadcast, perimeter and spot spray applications, add "Use a coarse droplet size and low pressure spray not exceeding 345 kPa (50 psi) to avoid splashing onto non-target surfaces."
Indoor surface [b] application	All	PP	The following personal protective equipment statements are proposed to be added to commercial-class agricultural product labels under **PRECAUTIONS**: • "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during application, clean-up and repair."
Indoor Space Spray [e] Application	All	All (not MR)	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** allow people, pets, or livestock to enter treated areas until sprays have settled." • "When applying to overhead areas or in confined spaces, wear 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." • "**DO NOT** apply when people or pets [or livestock] [c] are present." • "**DO NOT** remain in treated areas after application." • "Cover or remove all food/feed. Cover all food/feed processing surfaces, equipment and utensils or thoroughly wash following treatment."
Indoor Space Spray [e] Application	Food/feed processing facilities	All (not MR)	For products registered for use in food/feed processing facilities, the following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable.

Scenario	Registered use	Form. [a]	Proposed label statements
			• "**DO NOT** apply when a food/feed processing facility is in operation."
Indoor Space Spray [e] Application	All [f]	All (not MR)	The following statement is proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** allow people or pets to enter treated area until 2 hours after application. The commercial applicator is responsible for notifying workers, the homeowner, and others of the re-entry period requirement."
Indoor Space Spray [e] Application	All	Liquid	The following personal protective equipment statements are proposed to be added to commercial-class product labels under **PRECAUTIONS**: "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair." "When using handheld airblast/mistblower application equipment wear chemical-resistant coveralls with a chemical-resistant hood over a long-sleeved shirt and long pants, chemical-resistant footwear, socks, 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. **DO NOT** handle more than [0.27 kg a.i. to be reported as a product equivalent value] per person, per day when using a handheld airblast/mistblower (droplet sizes 0.1-100 µm). These restrictions are in place to minimize exposure to individual applicators. Application may need to be performed over multiple days or using multiple applicators." As indicated by the square brackets above, the active ingredient amount in this statement (in other words 0.27 kg a.i.) is to be converted into the corresponding amount of product by the registrant for each product." "If entering treated indoor areas prior to venting, wear chemical-resistant coveralls with a chemical-resistant hood over long-sleeved shirt, long pants, chemical-resistant footwear, socks, chemical-resistant gloves, and a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH-approved canister approved for pesticides."
			The definition of a space spray application method is proposed to be added to product labels where space spray application is currently specified: • "Space spray: Space application is a suspension of fine droplets (0.1 to 100 µm) in the air within an indoor space."

Scenario	Registered use	Form. [a]	Proposed label statements
Indoor Space Spray [e] Application	All	PP (not MR)	The following personal protective equipment statements are proposed to be added to commercial-class agricultural product labels under **PRECAUTIONS**: "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during application, clean-up and repair."
	All	PP (not MR)	The definition of a space spray application method is proposed to be added to product labels where space spray application is currently specified: • "Space spray: Space application is a suspension of fine droplets in the air within an indoor space."
Indoor Space Spray [e] Application	All	MR	Include the following definitions under "**DIRECTIONS OF USE**". DO NOT add these statements to product labels if similar information or more restrictive application instructions are already present: "**DO NOT** allow release of more than [1.07 mg a.i. every 15 minutes]."
Outdoor structural, surface, and/or perimeter application	All (except nest application)	All	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** apply to overhead areas or in confined spaces without appropriate respiratory and eye protection." • "**DO NOT** apply when people or pets [or livestock] [c] are present." • "**DO NOT** allow people or pets [or livestock] [c] to enter treated areas until sprays have dried." • "**DO NOT** allow spray to drip or allow drift onto non-target surfaces."
			The label must contain clear instructions that define areas and locations that can be treated. The treatment type also needs to be defined. If this is absent or ambiguous, include the following definitions under '**DIRECTIONS OF USE**.' DO NOT add these statements to product labels if similar information or more restrictive application instructions are already present: • "Outdoor Structural Broadcast: Outdoor broadcast application is to large outdoor structural surfaces (in other words, roofs, walls, doors, windows and foundations) [g]." • "Outdoor Perimeter: Outdoor perimeter application is 1 m or less out from the building's foundation and to a maximum height of 1 m starting where the foundation meets the ground."
Outdoor structural, surface, and/or perimeter application		Liquid	The following personal protective equipment statements are proposed to be added to commercial-class agricultural product labels under **PRECAUTIONS**: • "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair."
			The following statements are proposed be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable.

Scenario	Registered use	Form. [a]	Proposed label statements
			• "Apply only when the potential for drift beyond the area to be treated is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings."
Outdoor structural, surface, and/or perimeter application		PP	The following personal protective equipment statements are proposed to be added to commercial-class agricultural product labels under **PRECAUTIONS**: • "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during application, clean-up and repair."
Outdoor wasp, bee, hornet, etc. and/or nest application	Wasp/hornet and/or Nest application	Liquid & PP	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • • "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks during application, clean-up and repair." • • "**DO** NOT apply when people or pets [or livestock][c] are present." • • "**DO NOT** allow people or pets [or livestock] [c] to enter treated areas until sprays have dried." • • "**DO** NOT allow spray to drip or allow drift onto non-target surfaces."
Outdoor Application for Mosquitos, Flies, and/or Gnats	All	Liquid	The following personal protective equipment statements are proposed to be added to commercial-class product labels under **PRECAUTIONS**: • "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair." • "When using handheld airblast/mistblower application equipment wear chemical-resistant coveralls with a chemical-resistant hood over a long-sleeved shirt and long pants, chemical-resistant footwear, socks, 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. **DO NOT** handle more than [0.27 kg a.i. to be reported as a product equivalent value] per person, per day when using a handheld airblast/mistblower (droplet sizes 0.1-100 μm). These restrictions are in place to minimize exposure to individual applicators. Application may need to be performed over multiple days or using multiple applicators." As indicated by the square brackets above, the active ingredient amount in this statement (in other words 0.27 kg a.i.) is to be converted into the corresponding amount of product by the registrant for each product."
			The following statements are proposed be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable.

Scenario	Registered use	Form. [a]	Proposed label statements
			• "**DO NOT** allow people or pets [or livestock] [c] to enter treated areas until sprays have dried." • "Apply only when the potential for drift beyond the area to be treated is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings."
Outdoor Ornamentals and Pastures	All	All	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours."
Outdoor Ornamentals and Pastures		Liquid	The following personal protective equipment statements are proposed to be added to commercial-class product labels under **PRECAUTIONS**: • "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair." • "When using handheld airblast/mistblower application equipment wear chemical-resistant coveralls with a chemical-resistant hood over a long-sleeved shirt and long pants, chemical-resistant footwear, socks, 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. **DO NOT** handle more than [0.27 kg a.i. to be reported as a product equivalent value] per person, per day when using a handheld airblast/mistblower (droplet sizes 0.1-100 μm). These restrictions are in place to minimize exposure to individual applicators. Application may need to be performed over multiple days or using multiple applicators." As indicated by the square brackets above, the active ingredient amount in this statement (in other words 0.27 kg a.i.) is to be converted into the corresponding amount of product by the registrant for each product."
Outdoor Ornamentals		PP	The following personal protective equipment statements are proposed to be added to commercial-class product labels under **PRECAUTIONS**: • "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair."

[a] Form = formulation. Liquid = emulsifiable concentrate, solution; PP = pressurized product; MR= metered-release pressurized product

[b] A surface application is a directed application to a surface (floor, wall, foundation, ceiling, mattress, furniture, etc.). This includes but is not limited to broadcast, perimeter, spot, crack and crevice and void applications etc. It includes all indoor sites currently registered on commercial-class product labels, such as homes, commercial/industrial/institutional site, vehicles, agricultural premises, pet premises, horse stables and barns, etc.

[c] Statement to be modified, as applicable, based on uses registered on product labels.

[d] Modify to remove applications (furniture and/or mattresses) that are currently registered on the label.

[e] A space spray application is an application of a pesticide as a suspension of fine droplets in air within an indoor space. This definition does not include fumigants, outdoor fogging and outdoor misting systems. This term may not be specifically included on the current product label.

[f] "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 or any other areas where the general public including children may potentially be exposed. Non-residential areas include, but are not limited to: industrial/commercial indoor sites (for example, laboratories, warehouses, food granaries); modes of transport in areas where passengers are not present (for example, buses, railcars, trailers); and animal housing (for example, livestock and poultry housing, and pet kennels)."
[g] Other locations can be included in a case-by-case basis (for example, porches, patios) depending on the uses registered on product labels.

3.3 For domestic-class end-use products:

Label statements for domestic-class products are proposed below. In addition, all labels are to be updated as per the 2020 PMRA Guidance Document: *Structural Pest Control Products: Label Updates.* Specific label statements, including those from the 2020 PMRA Guidance Document, are proposed for each of the various use scenarios on domestic-class products are outlined in Table 4 below. Note that some product labels may include more than one scenario. In these situations, it is important that the statements are proposed for each use scenario be included on the label, with the exception of statements that are identical.

Precautions

For all domestic-class products, except dust formulations, the following must be added under PRECAUTIONS:

> "**DO NOT** apply by handheld airblast/mistblower or mechanically-pressurized handheld equipment for mists, aerosols, and fogs"

Directions for Use

Indoor Surface Applications

For indoor surface applications specified on domestic-class product labels, the following changes are proposed under **DIRECTIONS FOR USE**.

Use directions on labels need to be clearly defined in terms of pests controlled and of application site and area (see Section 2 above, General Label Improvements). The application sites and areas must be reflective of the pests controlled.

It is proposed to limit the maximum application rate of piperonyl butoxide for each treatment type as outlined in Table 3 below. The treatment type and rate would be based on the pests to be controlled. As noted in Table 4, it is also proposed that the definitions of each treatment type be added to labels where the current label instructions are absent or ambiguous. Directions for the application rates on the labels must be easily understood by consumers. For each end-use product, information must be provided to Health Canada to confirm that the application rate directions on the label are consistent with the rates used in the health risk assessment, as noted in Table 3. The rates on the label must be provided in terms of the amount of product.

Table 3 Maximum proposed domestic rates for indoor surface applications

Formulation	Treatment type[a]	Maximum application rate
Liquid	Broadcast	0.55 g a.i./m^2
	Perimeter/Spot/Bed bugs	
Pressurized product	Broadcast	0.21 g a.i./m^2
	Perimeter/spot [NO BED BUGS] [b]	1.4 g a.i./m^2
	Perimeter/Spot/Bed bugs	0.21 g a.i./m^2

[a]Definitions of these treatment types are as follows:
Indoor Broadcast: Indoor broadcast application is to broad expanses of indoor structural surfaces such as walls, floors, ceilings and indoor foundation walls/crawlspaces.
Indoor Perimeter (coarse droplet or particle size): 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: Spot application is localized to a surface area not more than 0.2 m^2. Spots are not to be adjoining. The combined area of spots is not to exceed 10% of the total surface area of a room.
[b] For domestic-class pressurized products: the maximum rate permitted for bed bug treatment is 0.21 g a.i./m^2. Other pest treatments are permitted a rate up to 1.4 g a.i./m^2.

Pressurized Products

Under directions for use, the following must be added:

"This product must not be applied as a total release fogger."

Dust Products

Under directions for use, the following must be added:

"For outdoor use only. Do not use indoors."

Application of dust products is to be limited to areas which do not impact food, feed, or livestock which are used to produce food commodities. See Table 4 for statements from the 2020 PMRA Guidance Document.

Products with Greenhouse Uses

Under directions for use, the following must be added:

- "**DO NOT** use in commercial greenhouses."

Space Spray Applications While Poultry Are Present

The application rate of space spray applications while poultry are present is to be limited to 0.12 g a.i/m^3 or less. The active ingredient amount (in other words 0.12 g a.i./m^3) is to be converted into the corresponding amount of product by the registrant for each applicable product.

Pressurized Products with Indoor Metered Release Space Spray Applications

For indoor metered release space spray applications of pressurized products, limit the maximum application rate of piperonyl butoxide to 1.07 mg of piperonyl butoxide released every 15 minutes. The active ingredient amount (in other words 1.07 mg a.i.) is to be converted into the corresponding amount of product by the registrant for each applicable product.

Table 4 Label statements for piperonyl butoxide domestic-class product by use scenario

Scenario	Registered Use	Form[a]	Proposed Label Statements
Indoor surface [b] application	All	Liquid & PP	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**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] [c] are present, unless otherwise specified." • **"DO NOT** apply to surfaces that may come into contact with food/feed." • "**DO NOT** allow spray to drip or allow drift onto non-target surfaces."
			If the product is registered as a surface spray and does not also have application instructions for use as a space spray, then the following statement are proposed to be added under **PRECAUTIONS**: • "**DO NOT** apply as a space spray."

Scenario	Registered Use	Form[a]	Proposed Label Statements
Indoor surface [b] application	All	All	The label must contain clear instructions that define areas and locations that can be treated. If these are absent or ambiguous, include the following definitions under "**DIRECTIONS OF USE**". DO NOT add these statements to product labels if similar information or more restrictive application instructions are already present: • "Indoor Broadcast: Indoor broadcast application is to broad expanses of indoor structural surfaces such as walls, floors, ceilings and indoor foundation walls/crawlspaces." • "Indoor Perimeter (coarse droplet or particle size): 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: Spot application is localized to a surface area not more than 0.2 m^2. 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: 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." • "Void: Void application applies to inaccessible, enclosed empty spaces of a structure. For example, hollow walls and suspended ceilings."
Indoor surface [b] application	Void application	All	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "Care should be taken to avoid the pesticide exiting the void. Any residue deposits on non-target surfaces must be removed by the applicator."
Indoor surface [b] application	Clothing treatment	All	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "Remove all objects before treatment of furniture, luggage, closets or other areas where clothing, toys, towels, and other items are stored. Treated furniture and treated surfaces must be dry before replacing stored items." • "Only apply to clothing which can be laundered. Treated clothing must be laundered prior to wearing."
Indoor surface [b] application	Mattress and furniture treatment	All	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on

Scenario	Registered Use	Form[a]	Proposed Label Statements
			the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** use on items which can be laundered (e.g. pillows, bedding, toys, etc)." • "Remove bedding before treating mattresses. Treated mattress must be dry before replacing laundered bedding. • "Remove all objects before treatment of furniture, luggage, closets or other areas where clothing, toys, towels, and other items are stored. Treated furniture must be dry before replacing stored items." When approved for tuft and/or seam application only, add: • "DO NOT apply to the entire mattress or piece of furniture. Apply to tufts [and/or] seams only." When approved for application to voids, add: • "Care should be taken to avoid the pesticide exiting the void. Any residue deposits on non-target surfaces must be removed by the applicator."
			The label must contain clear instructions that define areas and locations that can be treated. If these are absent or ambiguous, include the following definitions under "**DIRECTIONS OF USE**". DO NOT add these statements to product labels if similar information or more restrictive application instructions are already present: • Furniture Treatment, including but not limited to upholstered furniture, hard surface furniture, mattresses, box spring, pet bedding, bed frames, dressers, curtains, picture frames, wall coverings, hollow furniture legs, etc. • "Broadcast – Broadcast furniture application covers large areas or the entire surface of listed items." • "Spot – Spot furniture application is up to 10% of the surface of the treated item." • "Crack and crevice – Crack and crevice furniture treatments are applications to junction points on items." • "Tufts and seams (mattresses and upholstered furniture only) – Tufts and seam treatment is to the junction of two or more pieces of fabric and any decorative trim (for example buttons). • "Void – Void furniture treatment targets inaccessible empty spaces of items. For example, inside the dust cover on the underside of furniture or hollow table legs."
Indoor surface [b] application	Not registered for use on mattress, clothing or furniture		For products not registered for use on mattresses, clothing, or furniture, the following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If

Scenario	Registered Use	Form[a]	Proposed Label Statements
			more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** apply to [furniture, mattresses] [d], linens, pet bedding, toys or clothing.
Indoor Space Spray [e] Application	All	All (not MR)	The following statements is proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** allow people, pets, or livestock to enter treated areas until sprays have settled." • "When applying to overhead areas or in confined spaces, wear 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." • "**DO NOT** apply when people or pets [or livestock] [c] are present." • "**DO NOT** remain in treated areas after application." • "Cover or remove all food/feed. Cover all food/feed processing surfaces, equipment and utensils or thoroughly wash following treatment."
Indoor Space Spray [e] Application	All	Liquid	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** apply by handheld airblast/mistblower or mechanically-pressurized handheld equipment for mists, aerosols, and fogs"
			The definition of a space spray application method is proposed to be added to product labels where space spray application is currently specified: • "Space spray: Space application is a suspension of fine droplets in the air within an indoor space."
Indoor Space Spray [e] Application	All	MR	Include the following definitions under "**DIRECTIONS OF USE**". DO NOT add these statements to product labels if similar information or more restrictive application instructions are already present: "**DO NOT** allow release of more than [1.07 mg a.i. every 15 minutes]."
Outdoor structural, surface, and/or perimeter application	All (except nest application)	All	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** apply to overhead areas or in confined spaces (for example eaves, soffits)."

Scenario	Registered Use	Form[a]	Proposed Label Statements
			• "**DO NOT** apply when people or pets [or livestock] [c] are present." • "**DO NOT** allow people or pets [or livestock] [c] to enter treated areas until sprays have dried." • "**DO NOT** allow spray to drip or allow drift onto non-target surfaces."
			The label must contain clear instructions that define areas and locations that can be treated. If these are absent or ambiguous, include the following definitions under "**DIRECTIONS OF USE**" DO NOT add these statements to product labels if similar information or more restrictive application instructions are already present: • "Outdoor Structural Broadcast: Outdoor broadcast application is to large outdoor structural surfaces (in other words, roofs, walls, doors, windows and foundations) [f]." • "Outdoor Perimeter: Outdoor perimeter application is 1 m or less out from the building's foundation and to a maximum height of 1 m starting where the foundation meets the ground."
Outdoor wasp, bee, hornet, etc. and/or nest application	Wasp/hornet and/or Nest application	Liquid & PP	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** apply when people or pets [or livestock] [c] are present." • "**DO NOT** allow people or pets [or livestock] [c] to enter treated areas until sprays have dried." • "**DO NOT** allow spray to drip or allow drift onto non-target surfaces."
Outdoor and indoor (greenhouse) ornamental	Foliar applications	All	The following statement is proposed to be added under **DIRECTIONS FOR USE**: • "**DO NOT** use in commercial greenhouses."
			The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "**DO NOT** apply when people or pets [or livestock] [c] are present." • "**DO NOT** allow people or pets [or livestock] [c] to enter treated areas until sprays have dried." • "**DO NOT** allow spray to drip or allow drift onto non-target surfaces."
Pet Application	All	All	The following statements are proposed to be added under **PRECAUTIONS**. Replace similar wording on the label with these statements. If more stringent mitigation is currently specified on the label, integrate it in the statements below, as applicable. • "Use ONLY in well-ventilated area, preferably outdoors." • "Avoid contact with treated animals until dried."

Scenario	Registered Use	Form[a]	Proposed Label Statements
			• "**DO NOT** allow product to contact non-target surfaces."

[a] Form = formulation. Liquid = emulsifiable concentrate, solution; PP = pressurized product; MR= metered-release pressurized product
[b] A surface application is a directed application to a surface (floor, wall, foundation, ceiling, mattress, furniture, etc.). This includes but is not limited to broadcast, perimeter, spot, crack and crevice and void applications etc.
[c] Statement to be modified, as applicable, based on uses registered on product labels.
[d] Modify to remove applications (furniture and/or mattresses) that are currently registered on the label.
[e] A space spray application is an application of a pesticide as a suspension of fine droplets in air within an indoor space. This definition does not include fumigants, outdoor fogging and outdoor misting systems. This term may not be specifically included on the current product label.
[f] Other locations can be included in a case-by-case basis (for example, porches, patios) depending on the uses registered on product labels.

3.4 For all end-use proudcts (commercial- and domestic-class):

The following statements are proposed to be added under the ENVIRONMENTAL PRECAUTIONS section:

"TOXIC to aquatic organisms."

"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 of this product when heavy rain is forecast."

"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 ornamental uses that are highly attractive to pollinators or when using managed bees for pollination services:

"DO NOT apply during the plant blooming period."

"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. Piperonyl butoxide 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."

For all other uses:

"Avoid application during the plant blooming period. If applications must be made during the 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. Piperonyl butoxide 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."

For all 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."

The following statements are proposed to be added under the DIRECTION FOR USE section:

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

For ornamentals that are attractive to pollinators:

"Toxic to bees. DO NOT apply during the plant 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."

For all other ornamental uses:

"Toxic to bees. Avoid application during the plant blooming period. If applications must be made during the plant blooming period, restrict applications to evening when most bees are not foraging. When using managed bees for pollination services, DO NOT apply during the plant 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."

For all greenhouse uses:

"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."

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

For all other crops on label:

"DO NOT wet plants to the point of run-off or drip."

"Before making widespread applications of this product, treat a limited number of plants and observe for plant damage over a 10-day period."

References

A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT

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2132145	Developmental toxicity evaluation of piperonyl butoxide administered by gavage to CD (Sprague-Dawley) rats, 1991. DACO 4.5.2.
2132144	Evaluation of piperonyl butoxide in an eight week toxicity study in dogs, 1993. DACO 4.4.5.
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