Proposed Re-evaluation Decision PRVD2016-10

Tetramethrin

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Overview

Proposed Re-evaluation Decision for Tetramethrin

After a re-evaluation of the insecticide tetramethrin, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration of products containing tetramethrin for sale and use in Canada.

An evaluation of available scientific information found that most uses of products containing tetramethrin do not present unacceptable risks to human health or the environment when used according to the proposed label directions. As a requirement of the continued registration of tetramethrin, new risk-reduction measures are proposed for the end-use products registered in Canada, including the cancellation of certain uses. Theses uses are proposed for cancellation to address potential risks of concern from postapplication exposure. No additional data are being requested at this time.

This proposal affects all end-use products containing tetramethrin registered in Canada. Once the final re-evaluation decision is made, registrants will be instructed on how to address any new requirements.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for tetramethrin and presents the reasons for the proposed re-evaluation decision. It also proposes new risk-reduction measures to further protect human health and the environment.

This consultation document is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the assessment of tetramethrin.

The PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document. Please forward all comments to Publications (please see contact information indicated on the cover page of this document).

What Does Health Canada Consider When Making a Re-evaluation Decision?

The PMRA's pesticide re-evaluation program considers potential risks, as well as value, of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2012-02, *Re-evaluation Program Cyclical Re-evaluation*, presents the details of the current re-evaluation approach.

For more details on the information presented in this overview, please refer to the Science Evaluation of this consultation document.

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

What Is Tetramethrin?

Tetramethrin is a synthetic pyrethroid insecticide registered for use on a broad spectrum of insect pests on a variety of sites including: structural sites (indoors and outdoors), indoor house plants, outdoor wasp and hornet nests, outdoor ornamentals and outdoor residential sites. Tetramethrin acts on the nervous system of insects, disturbing the function of neurons by interaction with the sodium channels. It is a non-systemic insecticide with contact action. All tetramethrin end use products are co-formulated with other active ingredients, such as piperonyl butoxide , N-octyl bicycloheptene dicarboximide, (S)-methoprene and pyriproxyfen (insect growth regulators) pyrethrins and other pyrethroids. It can be applied by the general public and professional applicators, using ready to use spray solutions or pressurized spray cans.

Health Considerations

Can Approved Uses of Tetramethrin Affect Human Health?

Tetramethrin is unlikely to affect human health used according to the proposed label directions, which include additional risk-reduction measures and the cancellation of indoor broadcast and perimeter treatments as well as broadcast treatments to gardens.

Potential exposure may occur when handling and applying products containing tetramethrin or by entering treated sites. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only those uses where exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when using pesticide products according to label directions.

In laboratory animals, tetramethrin was of slight or low acute toxicity by the oral and inhalation routes and of low acute toxicity by the dermal route. It was minimally irritating to the eye, not irritating to the skin and did not cause an allergic skin reaction.

Short and long-term (lifetime) animal toxicity tests supplied by the registrant, as well as information from the published scientific literature were assessed for the potential of tetramethrin to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints used for risk assessment included effects on the liver and nervous system. There was no indication that the young were more sensitive than the adult animal. Longer-term dosing with tetramethrin resulted in testicular tumors in rats, but not in mice.

The risk assessment protects against these and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in Drinking Water and Food

Dietary risks from food and drinking water are not of concern.

Dietary exposure from tetramethrin is not expected as there are no registered food uses in Canada. Residues in drinking water are expected to be negligible.

Risks in Residential Environments

Based on the human health risk assessment , certain uses of tetramethrin in residential settings are proposed for cancellation.

Residential exposure may occur from the application of products containing tetramethrin inside and outside residential structures. Residential postapplication exposure may occur while performing activities on treated areas. Exposure would be predominantly dermal and also by inhalation. Incidental oral exposure may also occur for children (1 to <2 years old) playing in treated areas.

For all domestic class products, the target dermal and inhalation Margins of Exposure (MOEs) were met for adults applying tetramethrin and are not of concern.

Residential postapplication non-cancer risks are not of concern. However, potential residential postapplication cancer risks were identified for indoor broadcast and perimeter treatments, as well as broadcast treatments to gardens. These uses are proposed for cancellation.

Incidental oral scenarios were aggregated with postapplication dermal and inhalation scenarios. The resulting non-cancer aggregate risk estimates met the target MOE for all uses and are not of concern.

Occupational Risks from Tetramethrin

Occupational risks are not of concern when tetramethrin is used according to label directions.

Commercial applicators may be exposed to tetramethrin while spraying ready to use outdoor aerosol wasp and hornet treatments. Based on the label precautions and directions for use reviewed for this re-evaluation, the risk estimates for applying tetramethrin are not of concern.

Environmental Considerations

What Happens When Tetramethrin Is Introduced into the Environment?

When used according to the proposed label directions, tetramethrin does not pose an unacceptable risk to the environment.

Tetramethrin is used primarily in and around homes as a domestic insecticide. Because of this use pattern, environmental exposure is expected to be minimal. If tetramethrin is released into the environment it can enter soil and surface water. Tetramethrin is non-persistent in soil, breaking down in the presence of microbes. In water, tetramethrin is broken down by hydrolysis. Tetramethrin is not expected to enter the atmosphere and be subject to long-range transport. Laboratory studies indicate that tetramethrin is not likely to move downward through the soil, indicating that it has a low potential to leach to ground water.

Tetramethrin poses negligible risk to terrestrial organisms other than invertebrates. At high enough doses it can be toxic to aquatic invertebrates and fish. However, due to the use pattern, the potential exposure of terrestrial and aquatic non-target organisms is expected to be minimal and consequently, risk to these organisms is not of concern.

Value Considerations

What is the Value of Tetramethrin?

Tetramethrin can be of benefit to the homeowner in the management of pests in and around the home.

Tetramethrin is registered for use on a broad spectrum of pests such as earwigs, ants, spiders, flies, wasps, cockroaches and bedbugs. Ants and earwigs are the most prevalent types of crawling insects targeted in homes, while wasps are the most commonly sprayed flying pest. Tetramethrin products are formulated as ready to use solutions or pressurized spray cans which can be used to spray the target pests. Many pests are challenging to control, typically requiring multiple control strategies that have to be repeated.

Tetramethrin products can be of benefit to the homeowner to use with other control methods such as prevention and non-chemical treatments in the management of pests in and around the home.

Proposed Measures to Minimize Risk

Labels of registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law. As a result of the re-evaluation of tetramethrin, the PMRA is proposing further risk-reduction measures in addition to those already identified on tetramethrin product labels. Additional risk-reduction measures are discussed below.

Additional Key Risk-Reduction Measures

Human Health

- Revisions to the labels are proposed to provide consistency across common products, update label statements and minimize unnecessary exposure. The proposed label amendments are listed in Appendix VI.
- To protect the public from exposure in residential settings, the following residential uses of tetramethrin are proposed to be cancelled (removed from labels): garden broadcast treatments; indoor broadcast treatments; indoor perimeter treatments.

Environment

- Due to the limited outdoor use, the risk to environment is expected to be minimal. However, as tetramethrin is toxic to terrestrial invertebrates and aquatic organisms, hazard statements are proposed to protect bees and aquatic organisms.

What Additional Scientific Information is required?

There are no additional data required under section 12 of the *Pest Control Products Act*.

Next Steps

During the consultation period, registrants and stakeholder organizations may submit further data that could be used to refine risk assessments (cancer mode of action data, exposure or use information), which could result in revised risk-reduction measures. Stakeholders who are planning to provide information of this type are advised to contact the PMRA early in the consultation period, for advice on studies or information that could be submitted to help refine the relevant risk assessments. Before making a final re-evaluation decision on tetramethrin, the PMRA will consider all comments received from the public in response to this consultation document. A science-based approach will be applied in making a final decision on tetramethrin. The PMRA will then publish a Re-evaluation Decision[2] that will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

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

Science Evaluation

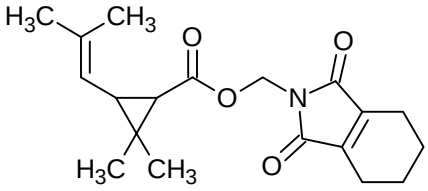
1.0 Introduction

Tetramethrin is under re-evaluation in Canada as announced by the PMRA in the 20 December 2011 Re-evaluation Note REV2011-05, *Re-evaluation of Pyrethroids, Pyrethrins and Related Active Ingredients*. Tetramethrin is a broad spectrum contact synthetic pyrethroid belonging to the Insecticide Resistance Management Mode of Action (MOA) group 3A. Tetramethrin acts on the nervous system of insects, disrupting the function of neurons by interaction with the sodium channels. Following the re-evaluation announcement for tetramethrin, Sumitomo Chemical Co. Ltd., the registrant of the technical grade active ingrediate and primary data provider in Canada, indicated continued support for all registered label uses.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name		Tetramethrin
Function		Insecticide
Chemical Family		Pyrethroid
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	(1,3,4,5,6,7-hexahydro-1,3-dioxo-2*H*-isoindol-2-yl)methyl (1*RS*,3*RS*;1*RS*,3*SR*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate or (1,3,4,5,6,7-hexahydro-1,3-dioxo-2*H*-isoindol-2-yl)methyl (1*RS*)-*cis*-*trans*-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate or cyclohex-1-ene-1,2-dicarboximidomethyl (±)-*cis*-*trans*-chrysanthemate
2	**Chemical Abstracts Service (CAS)**	(1,3,4,5,6,7-hexahydro-1,3-dioxo-2*H*-isoindol-2-yl)methyl 2,2-dimethyl-3-(2-methyl-1-propen-1-yl)cyclopropanecarboxylate

CAS Registry Number	7696-12-0
Molecular Formula	$C_{19}H_{25}NO_4$
Structural Formula	
Molecular Weight	331.42
Purity of the Technical Grade Active Ingredient	95%
Registration Number	18534

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Vapour pressure at 25°C	2.1 mPa
Ultraviolet (UV) / visible spectrum	No absorption at $\lambda > 350$ nm
Solubility in water at 25°C	1.83 mg/L
n-Octanol/water partition coefficient at 25°C	Log K_{ow}= 4.6
Dissociation constant	No dissociable functionalities

2.3 Description of Registered Tetramethrin Uses

Appendix I list all tetramethrin products that are registered under the authority of the *Pest Control Products Act*. Appendix II lists all Commercial and Domestic Class uses for which tetramethrin is presently registered. All uses were supported by the registrant at the time of re-evaluation initiation and were therefore considered in the health and environmental risk assessments of tetramethrin.

Tetramethrin domestic products are registered for use indoors in homes and buildings to target flying and crawling insects, directing sprays into areas that may harbour pests such as voids and

hollow spaces in walls, cracks and crevices, surface sprays to target crawling pests on locations such as carpets and pet premises, as well as proximal sites such as mattresses, indoor houseplants and plantscapes. Outdoors it can be applied to residential gardens and turf, structures (including patios, garages and foundations), window and door frames and wasp and hornet nests attached to structures. The only registered commercial use of tetramethrin is as a structural wasp and hornet nest treatment.

3.0 Impact on Human and Animal Health

3.1 Toxicological Summary

Tetramethrin is a Type I synthetic pyrethroid insecticide that is a racemic mixture of 4 stereoisomers, [1R, trans], [1R, cis], [1S, trans] and [1S, cis], in approximately a 4:1:4:1 ratio. It is also referred to as Neopynamin. The primary target of Type I pyrethroids is the nervous system through interference with axonal sodium channels in the nerve membrane. This interference with sodium channels leads to the repetitive firing of affected nerves, generating signs of neurotoxicity which could include hyperexcitability, muscle spasms, tremors, paralysis and death.

A detailed review of the toxicological database for tetramethrin was conducted. The majority of available toxicity studies were conducted with tetramethrin; however studies conducted with a compound called Neopynamin Forte were included in this review. Neopynamin Forte is a mixture of the two stereoisomers of tetramethrin which have the highest insecticidal activity, [1R, trans] and [1R, cis], in a ratio of 4:1. The registrant indicated that Neopynamin Forte was more toxic than tetramethrin; the only clear evidence supporting the higher potency of Neopynamin Forte was found in an acute oral mouse study, in which Neopynamin Forte was approximately twice as toxic as tetramethrin. In all other acute and repeat-dose scenarios in which a direct comparison was possible there was no clear evidence of Neopynamin Forte's increased potency. Consequently, it was determined that tetramethrin and Neopynamin Forte were toxicologically equivalent for the purpose of this review. While toxicology data conducted with tetramethrin was considered foremost in the review, data conducted with Neopynamin Forte was considered supportive, particularly in cases where isomeric-relevant studies were not available or had limitations.

Available toxicokinetic data for tetramethrin are based on radiolabel studies in which rats were administered cis or trans isomers as a single low dose, single high dose or repeat low dose. Tetramethrin's rapid absorption was inferred from the excretion of >90% of administered dose within 48 hours in both single and repeat dosing scenarios. Tissue samples contained less than 0.5% of the radiolabelled dose 7 days post-dosing. The highest levels of radioactivity recovered for both isomers were in the blood followed by hair, skin, and thyroid. Measurable levels were also recovered from the kidney, liver and spleen following dosing with the cis-isomer. Female rats had higher tissue levels than males in blood, kidney and spleen following single dose administration. While not varying greatly, cis-isomers generally appeared to produce higher residues than trans-isomers. Tissue residues were generally higher with the alcohol-labelled isomers compared to the acid-labelled isomers.

Tetramethrin was rapidly and almost completely eliminated within 7 days of dosing. Higher levels of radioactivity were excreted via the feces compared to the urine with the cis isomer. Increased fecal excretion was observed with a single high dose as compared to a single low dose; repeat dosing had little effect on the excretion pattern of the cis isomer. For the trans isomer, low and high single dose regimes had comparable excretion in the urine and feces however fecal excretion was slightly reduced with repeated administration. Negligible amounts were expired in air in a preliminary study. Urinary excretion was higher in females as compared to males in all dosing regimens.

No qualitative differences in metabolism were noted in relation to dose regime or gender in excreta pooled over 2 days post-dosing. Biotransformation involved cleavage of the ester linkage followed by ring opening, hydroxylation, oxidation and incorporation of the sulfonic acid group to the 1,2-double bond of the 3,4,5,6-tetrahydrophthalimide (THPI) moiety. Metabolism was extensive with numerous metabolites seen in both urine and feces. The main fecal metabolites were sulphonate derivatives and the main urinary metabolites were alcohols, dicarboxylic acid and reduced metabolites derived from the THPI moiety. Some metabolites arise from trans ↔ cis isomerization.

Acute oral toxicity in the rat was low for both tetramethrin and Neopynamin Forte. In mice, acute oral toxicity was low for tetramethrin and slight for Neopynamin Forte. Clinical signs noted in the tetramethrin studies included: hypersensitivity, muscular fibrillation, tremor, clonic convulsion, and decreased spontaneous activity. Hyperexcitation, irregular respiration, ataxia, lacrimation and salivation were additionally seen in the Neopynamin Forte mouse study. Acute toxicity was slight via the inhalation route in a study using Neopynamin Forte. The observed clinical signs from this route of exposure included: hyperexcitation, muscular fibrillation, irregular respiration, ataxia, limb paralysis and salivation. Toxicity from the dermal route was low with both tetramethrin and Neopynamin Forte. Tetramethrin was non-irritating to rabbit skin and minimally irritating to the rabbit eye. Tetramethrin was non-sensitizing to the skin of guinea pigs using the Buehler method.

In short term dietary studies with tetramethrin (mice and dogs) or Neopynamin Forte (rats), the primary target organ across all species was the liver. The observed effects included increases in liver weights, cholesterol, hepatic glycogen, bilirubin, hypertrophy and focal necrosis. Additional effects in mice included decreases in thyroid, ovary and adrenal weights and increases in relative testes weight; no histopathological correlates to these weight changes were observed. Nervousness, tremors, decreased ovarian weight and inhibition of estrus were observed in a 6 month dietary study in dogs but were not reproduced in two one-year studies in dogs. In the 6-month study, nervousness and tremors were noted once in one animal of each sex at the mid-dose and in 3/6 males at the high dose. Of the 4/6 females affected at the high dose, two showed repeated occurrences of this neurological observation. In a 90-day inhalation study with tetramethrin effects included clinical signs, altered liver and kidney weights and pathology and changes in haematology and clinical chemistry. No systemic effects or irritation were observed up to and including the limit dose in a 21-day dermal study performed with tetramethrin in rats. Long term dietary studies with tetramethrin showed the liver and the testes as the major target organs in rats and mice. In addition to increased liver weights, decreased thyroid and pituitary weights in males were observed in one of the two mouse studies and an increase in the incidence

of amyloidosis and increased testicular weights were recorded in the second study. The latter effects were seen above the limit dose. In rats, liver effects included increases in weights, number of hepatocytes and vacuolation; bile duct proliferation was also seen in one of two studies. Testes effects included enlarged and firm testes, increased weights, atrophy, degeneration, hypospermatogenesis and aspermatogenesis.

A significant increase in the incidence of interstitial cell tumours (Leydig cell tumours) was demonstrated in two rat carcinogenicity studies in two different strains of rats. No mode of action (MOA) data were submitted to address these tumours. No evidence of treatment-related carcinogenicity in mice was observed.

The battery of genotoxicity studies included two in vitro chromosome aberration studies that were positive with metabolic activation. All other genotoxicity studies were negative. Overall, tetramethrin is not considered to be genotoxic.

Effects on reproductive and developmental toxicity were minimal. One and two-generation dietary reproduction studies were available in rats, the latter with Neopynamin Forte. Parental and offspring effects consisted of effects on body weight in both studies. Females from the F1 generation in the 2-generation study showed an increase in bile duct hyperplasia, while there was a slight decrease in the fertility index in parents in the 1-generation study. In a non-guideline reproductive function and fertility study with tetramethrin in mice, there were no effects at doses in excess of the limit dose in parents or offspring.

Three gavage developmental toxicity studies with tetramethrin were available for rats. In two non-guideline studies, parental/maternal effects were observed at 1000 mg/kg bw/day, namely decreases in body weight and increases in liver and kidney weights. A divergent response in ovarian weights was seen in maternal animals in these studies. In the non-guideline study with pre-gestational and early gestational exposure, there was a slight decrease observed in the number of corpora lutea per litter which led to decreases in the number of implantations and live fetuses per litter. In the same study, there was a biologically significant decrease in fetal body weight and ossification at the same dose that elicited maternal toxicity. Consistent with the non-guideline study with gestational exposure only, the guideline study resulted in decreased body weight gain in the high dose maternal animals, and no observed fetal toxicity to the highest dose tested.

In rabbits, gavage developmental toxicity studies with tetramethrin included a range-finding study, a main study and a supplemental study. The main study showed a decrease in maternal body weight gain at the two highest doses and no effects in the fetus. At higher levels in the range-finding study, abortions and increased late resorptions were observed at levels producing maternal mortality. Decreased fetal bodyweight was seen in the supplemental study at a dose higher than those used in the acceptable study. Overall, there was no evidence of sensitivity of the young in either rats or rabbits in these studies.

There were four neurotoxicity studies included in this database consisting of two acute gavage neurotoxicity range finding studies, a short-term dietary neurotoxicity study and a special non-guideline inhalation motor activity study in juveniles. The initial acute neurotoxicity range-

finding study with tetramethrin did not reveal any systemic or neurotoxic effects at the highest dose tested in rats. There was some concern that the choice of vehicle in this study, carboxymethylcellulose (CMC), may have masked neurotoxic effects as has been shown with other pyrethroids (for example, deltamethrin). A subsequent acute neurotoxicity range finding study conducted with tetramethrin using corn oil vehicle or no vehicle, showed no evidence of neurotoxicity. The data suggest that tetramethrin is either resilient to the influence of the CMC vehicle or the toxicity of tetramethrin is low regardless of vehicle. It was concluded that the vehicles used in the tetramethrin studies were adequate and no further data would be required to address acute neurotoxicity.

The only neurotoxicity study with any observed effects was the short-term dietary neurotoxicity study with tetramethrin in rats. A decrease in brain weights occurred in both sexes and an increase in landing foot splay was observed in mid and high dose males. This study had a threshold LOAEL based on marginal effects on body weight and body weight gain at the dose below the occurrence of any neurotoxic findings. In the special inhalation study with tetramethrin, muscarinic acetylcholine receptor density was increased in the brain of juvenile rats; however, motor activity was not affected on either PND 17 or at 4 months post-dosing. The only other studies in the database with neurotoxic findings were the 6 month dog study with nervousness and tremors, the 90-day inhalation study in rats (irregular respiration and bradypnea) and acute oral studies in mice.

Studies from the published literature indicate that pharmacodynamics and pharmacokinetic factors, notably age-dependent maturation of key metabolic processes, may lead to increased susceptibility of the young to pyrethroid toxicity. Young animals have incomplete maturation of the enzyme systems that detoxify pyrethroids, particularly the carboxylesterases and cytochrome P450s. Consequently, pyrethroid concentrations in target tissues (for example, brain) may be higher in young animals than in adults given the same dose. In general, pyrethroid neurotoxicity is correlated to peak concentrations of the compound, with gavage dosing patterns resulting in greater internal doses compared to dietary administration. The pyrethroids are regarded as having a narrow window of time-to-peak-effect. The design of a DNT study does not consider time-to-peak-effect and may miss the window of peak toxicity for the pyrethroids. Accordingly a developmental neurotoxicity study is not required for tetramethrin. In the recent evaluation of other pyrethroids by the PMRA, a comparative oral gavage neurotoxicity study in pups, weanlings and adults has been required to address residual uncertainty with regards to potential susceptibility of the young; in the absence of this data, the application of a database uncertainty factor was deemed necessary. This factor has not been applied for tetramethrin in view of the minimal evidence of neurotoxicity in the animal toxicity database.

In the dietary immunotoxicity study with tetramethrin in rats, plaque-forming cell counts, while increased relative to controls, were too variable to be deemed treatment-related. Thymus weight was decreased at the mid and high dose along with body weight compared to controls.

Results of the toxicology studies conducted on laboratory animals with tetramethrin, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Tables 1 and 2 of Appendix III.

3.1.1 *Pest Control Products Act* Hazard Consideration

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. This factor should take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, as well as potential pre- and post-natal 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, several pre-natal developmental toxicity studies in rats and rabbits were available as well as a one and two-generation reproduction study in rats. Other non-guideline studies were also used in support of the analysis of pre- and post-natal toxicity.

With respect to potential pre- and post-natal toxicity, effects on both reproductive and developmental toxicity were minimal. Effects in the reproduction studies were limited to reductions in offspring bodyweight at maternally toxic levels. In a non-guideline developmental toxicity study in rats, a decrease in corpora lutea was observed at the limit dose; this dose also resulted in maternal toxicity and reductions in fetal bodyweight and ossification. In a range finding study conducted in rabbits an increase in abortions and late resorptions was observed at high dose levels, in the presence of significant maternal toxicity. By contrast, in the main and supplemental studies, fetal effects in rabbits were limited to reductions in bodyweight at the same levels that resulted in effects on maternal weight gain. Juvenile animals did not show any effects on motor activity following inhalation exposure. Overall, there was no evidence of sensitivity of the young or serious effects in either rats or rabbits at doses relevant for risk assessment from any studies in the database.

While an age-comparative neurotoxicity study was not available, there was a low level of concern for neurotoxic potential and sensitivity of the young for tetramethrin. The results of such a study are not expected to have an impact on the risk assessment.

In consideration of the above, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Dietary Exposure and Risk Assessment

Dietary exposure from tetramethrin is not expected as there are no registered food uses in Canada.

3.2.1 Acute Reference Dose

Establishment of an acute reference dose is not required as there are no registered food uses. Residues in food and drinking water are expected to be negligible.

3.2.2 Acceptable Daily Intake

Establishment of an acceptable daily intake is not required as there are no registered food uses. Residues in food and drinking water are expected to be negligible.

3.3 Occupational and Residential Risk Assessment

Occupational and residential (non-occupational) 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. However, MOEs less than the target MOE require measures to mitigate (reduce) risk.

3.3.1 Toxicology Endpoint Selection for Occupational and Bystander Risk Assessment

3.3.1.1 Short-term Incidental Oral Exposure Endpoint

The 6-month dietary study with tetramethrin in dogs with a NOAEL of 31 mg/kg bw/day was selected for use in risk assessment. At the LOAEL of 63 mg/kg bw/day, effects included increased liver weight as well as nervousness and tremors. The target MOE of 100 was established, which included standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold.

3.3.1.2 Short/Intermediate-term Dermal Endpoint

The 21-day dermal toxicity study with tetramethrin in rats was selected for use in risk assessment. There were no treatment-related effects noted in the study. The NOAEL was 1000 mg/kg bw/day. The dermal study did not assess histopathology of the testes, one of the target organs after extended dosing. Despite this, only the mouse 13-week range-finding study suggested that there was an impact on the testes, following short- to intermediate-term exposure and only at doses exceeding the limit dose. No strong evidence of increased toxicity with increasing duration of dosing over short to intermediate-term was observed. Accordingly, the selected study was deemed suitable for use in both short- and intermediate term risk assessment. A target MOE of 100 was established, which included standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability. For residential exposures, the *Pest Control Products Act* factor was reduced to 1-fold.

3.3.1.3 Long-term Dermal Endpoint

The 1-year toxicity study with tetramethrin in dogs with a NOAEL of 8.2 mg/kg bw/day was selected for use in risk assessment. While there was consideration of using the 21-day dermal study, it did not assess histopathology of the testes, which was a target organ identified with long-term dosing. The effects at the LOAEL of 36 mg/kg bw/day from the selected study were increased liver/gallbladder weight in both sexes, as well as increases in cholesterol, phospholipid

and hepatic glycogen in males. A target MOE of 100 was required to account for standard uncertainty factors of 10-fold for inter-species extrapolation and intra-species variability. For residential exposure, the *Pest Control Products Act* factor was reduced to 1-fold.

3.3.1.4 Short/Intermediate/Long-term Inhalation Endpoint

The 90 day rat inhalation toxicity study with tetramethrin with a NOAEL of 4.1 mg/kg bw/day was selected for use in risk assessment. At the LOAEL of 26 mg/kg bw/day, effects included increases in the incidence of clinical signs, decreases in body weight gain, changes in hematology and clinical chemistry, hepatocellular hypertrophy, an increase in the incidence of hyaline droplets in kidney, and increased kidney and liver weight. A target MOE of 100 was established, which included standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability. For residential exposures, the *Pest Control Products Act* factor was reduced to 1-fold.

3.3.1.5 Cancer endpoint

In the absence of evidence to support an MOA, a linear low dose extrapolation was conducted on the Leydig cell tumours noted in the long-term rat study. A q_1* of 6.24×10^{-3} $(mg/kg\ bw/day)^{-1}$ was determined for these tumours.

3.3.1.6 Dermal Absorption

As no dermal absorption studies were available for tetramethrin, a weight-of-evidence approach to estimating the dermal absorption was taken. Based on information from the toxicology database and in consideration of the physical-chemical properties of tetramethrin, the dermal absorption factor was reduced from 100% to 50%. A dermal absorption factor is required for all long-term dermal risk assessment scenarios, as well as all dermal cancer risk assessments scenarios.

3.3.2 Occupational Exposure and Risk Assessment

Workers can only be exposed to tetramethrin through the application of a tetramethrin wasp and hornet treatment, as this is the sole commercial use registered. Postapplication exposure to workers is not expected from this use as there are no associated postapplication activities.

3.3.2.1 Occupational Applicator Exposure and Risk Assessment (non-cancer)

The following scenario was assessed:

- aerosol applications outdoors

Occupational applicator exposure is considered to be of short-term duration. Handler exposure was estimated based on the levels of personal protection described on the product labels:

- **Applying:** Long sleeves, long pants and chemical resistant gloves.

Dermal and inhalation exposures were estimated using data from the *Pesticide Handlers Exposure Database* (PHED), *Version 1.1*. 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 (PPE). PHED data was used to assess dermal and inhalation exposure for pest control operators (PCOs) using commercial class aerosol end use products. All data were normalized for kg of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency.

The PHED light inhalation rate of 17 litres per minute was used for the commercial products since they are lightweight aerosol cans that can be used only outdoors.

PHED did not contain appropriate data sets to evaluate exposure to workers wearing personal protective equipment (PPE). This was estimated by incorporating a protection factor into the unit exposure data. Where warranted, a 90% protection factor was incorporated into the dermal data for chemical resistant gloves.

The results of the occupational applicator risk assessment are presented in Appendix IV.

Based on the label precautions and directions for use reviewed for this re-evaluation, non-cancer risk estimates associated with occupational application activities are not of concern.

3.3.2.2 Occupational Applicator Exposure and Risk Assessment (cancer)

The cancer risk for occupational workers was determined by calculating the lifetime average daily dose from dermal and inhalation exposure. The lifetime average daily dose (LADD) was then compared to the q_1* to obtain cancer risk estimates. Occupational cancer risk is calculated assuming a working career of 16 years over a 78-year lifetime. A 50% dermal absorption value, along with the assumption of 2 exposure days per year was applied in calculating the cancer risk for commercial applicators. The product of the expected exposure LADD and the cancer potency factor q_1* estimates the lifetime cancer risk as a probability. A lifetime cancer risk in the range of 1×10^{-5} in worker populations is generally considered acceptable.

The occupational applicator exposure cancer risk estimates are summarized in Appendix IV. The calculated risks for all currently registered/supported uses are not of concern.

3.3.2.3 Occupational Postapplication Risk Assessment

Occupational cancer and non-cancer postapplication risk assessments were not required for tetramethrin as there are no postapplication activities associated with the registered commercial uses.

3.3.3 Residential Exposure and Risk Assessment

Residential (non-occupational) risk assessment involves estimating risks to the general population, including youth and children, during or after pesticide application.

The United States Environmental Protection Agency (USEPA) has generated standard default assumptions for developing residential exposure assessments for both applicator and postapplication exposures when chemical- and/or site-specific field data are limited. These assumptions 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 assumptions are outlined in the Standard Operating Procedures (SOP) for Residential Pesticide Exposure Assessments.

The following sections from the Residential SOPs were used to assess residential applicator exposure for tetramethrin:

- Section 4: Gardens and Trees
- Section 5: Outdoor Fogging & Misting Systems
- Section 7: Indoor Environments

3.3.3.1 Residential Applicator Exposure and Risk Assessment (non-cancer)

A residential applicator would be an adult who purchased a domestic class tetramethrin product for use in and around the home. Residential applicators are assumed to be wearing shorts, short-sleeve shirts, shoes, and socks. Residential applicator exposure is considered to be of short- to intermediate-term duration.

Based on the registered uses, the following scenarios were assessed:

- aerosol and trigger spray applications indoors
- aerosol applications outdoors
- aerosol/fog applications outdoors

The results of the residential applicator risk assessment are presented in Appendix IV. Based on the label precautions and directions for use, residential applicator non-cancer risks are not of concern.

3.3.3.2 Residential Postapplication Exposure and Risk Assessment (non-cancer)

Postapplication exposure occurs when an individual is exposed through dermal, inhalation, and/or incidental oral (non-dietary ingestion) routes as a result of being in a residential environment that has been previously treated with a pesticide.

Postapplication residential exposure to tetramethrin is generally expected to be short- to intermediate term (30-90 days) in duration, with the exception of bedbug treatments. There is potential for short to intermediate-term and long-term exposure to adults, youth, and children entering areas treated for bedbugs. Adults and youth have the potential for dermal and inhalation exposure, while children also have the potential for incidental oral exposure (both hand-to-mouth

and object-to-mouth). Postapplication exposure estimates were generated on the basis of assumptions in the USEPA Residential Standard Operation Procedure (SOP) (2012). The following scenarios were assessed for short- to intermediate-term postapplication exposure for residential use of products containing tetramethrin:

- Adults, youth, and children (1 to <2 years old) dermal and inhalation exposure resulting from activities indoors.
- Adults, youth, and children (6 to <11 years old) dermal exposure resulting from activities in gardens, trees, and indoor plants.
- Adult, youth, and children (1 to <2 years old) dermal exposure from residue deposited on turf from outdoor spray applications.
- Incidental oral (hand-to-mouth and object-to-mouth) exposure to children (1 to <2 years old) in indoor environments and from residues deposited on turf after spraying with an outdoor spray.

Bedbug treatments potentially result in long-term exposure (>180 days). The following scenarios were assessed for long-term postapplication exposure for residential use of products containing tetramethrin for bedbugs:

- Adult, youth, and children (1 to <2 years old) dermal and inhalation exposure to surface directed spray applications of aerosol products used in indoor environments,
- Incidental oral (hand-to-mouth) exposure to children (1 to <2 years old) from aerosol formulation products used in indoor environments

Postapplication dermal exposure incurred during the removal of stinging insect nests treated with pesticides was considered to be minimal as there is a 48 hour period recommended before disposing of treated nests. Inhalation exposure to outdoor applications was considered to be minimal due to low vapour pressure and expected dilution in outdoor air.

For residential risk assessments, it is assumed that individuals contact previously treated surfaces on the same day the pesticide treatment is applied. Therefore, the assessment of postapplication exposure must be representative of the day of application residues (that is, Day 0).

The results of the residential postapplication risk assessment are presented in Tables 3- 12 of Appendix IV. Based on the label precautions and directions for use reviewed for this re-evaluation, residential non-cancer risk estimates associated with postapplication activities are not of concern.

3.3.3.3 Residential Applicator Exposure and Risk Assessment (cancer)

The cancer risk for residential applicators was determined by calculating the lifetime average daily dose from dermal and inhalation exposure. The lifetime average daily dose (LADD) was then compared to the q_1* to obtain cancer risk estimates. The product of the expected exposure LADD and the cancer potency factor q_1* estimates the lifetime cancer risk as a probability. A lifetime cancer risk of less than one-in-a-million (in other words, 1×10^{-6}) for the residential populations is generally considered acceptable.

A deterministic cancer risk assessment was conducted for residential applicators of tetramethrin. A 50% dermal absorption value, along with the assumption of 2-10 exposure days per year was applied in calculating the cancer risk for residential applicators. The domestic applicator exposure cancer risk estimates are summarized in Table 14 of Appendix IV. The calculated risks for all currently registered uses are not of concern.

3.3.3.4 Residential Postapplication Exposure and Risk Assessment (cancer)

The cancer risk for residential postapplication populations was determined by calculating the lifetime average daily dose from dermal and inhalation exposure. The lifetime average daily dose (LADD) was then compared to the q_1* to obtain cancer risk estimates. The product of the expected exposure LADD and the cancer potency factor q_1* estimates the lifetime cancer risk as a probability. Cancer risk estimates for children, youths and adults were then summed to determine a Lifetime Cancer Risk (LCR). A lifetime cancer risk of less than one-in-a-million (that is, 1×10^{-6}) for residential populations is generally considered acceptable. For tetramethrin, the cancer risk assessment was refined through the selection of inputs more consistent with lifetime exposures. While there are uncertainties and conservatisms with this approach, the data used represents the most reliable information available to the PMRA. Conservatisms include the dermal absorption value of 50%, which is most likely an over-estimation. In consideration of these factors, estimated cancer risks of up to 3×10^{-6} are not of concern.

A 50% dermal absorption value (along with the assumption of 30 exposure days per year) was applied in calculating the cancer risk for residential postapplication populations.

The residential postapplication exposure dermal cancer risk estimates are summarized in Table 15 of Appendix IV. The calculated risks for some registered uses are of concern, specifically outdoor uses on gardens and indoor broadcast (for example, floors or carpets) and perimeter treatments (for example, baseboards).

The residential postapplication exposure inhalation cancer risk estimates are summarized in Table 16 of Appendix IV (space sprays) and Table 17 of Appendix IV (surface sprays). The calculated risks for the currently registered uses are not of concern.

The residential long-term postapplication incidental hand to mouth cancer risk estimates are summarized in Table 18 (indoors) and Table 19 (outdoors) of Appendix IV. The calculated risks for the currently registered uses are not of concern.

3.3.3.5 Lifetime Cancer Risk Estimates

For the combined lifetime postapplication cancer risk assessment, all sources and routes of exposure are considered per lifestage before being summed into a single lifetime risk estimate.

For tetramethrin, the relevant compartments of the lifestages for the lifetime cancer risk are as follows:

Lifestage	Carpet Hand-to-Mouth	Applicator Broadcast Dermal	Applicator Broadcast Inhalation	Postapplication Broadcast Dermal	Postapplication Broadcast Inhalation	Mattress Dermal
adult	n/a	✓	✓	✓	✓	✓
youth		n/a		✓	✓	✓
child	✓			✓	✓	✓

Children:
(dermal and inhalation cancer exposure following a perimeter/spot treatment) + (hand-to-mouth exposure) + (dermal exposure following a mattress treatment)

Youth:
(dermal and inhalation exposure following a perimeter/spot treatment) + (dermal exposure following a mattress treatment)

Adults:
(dermal and inhalation exposure for residential applicators) + (dermal and inhalation exposure following a perimeter/spot treatment) + (exposure following a mattress treatment).

The LADD values from the appropriate exposure scenarios are summed per lifestage.

for example:
$\mathbf{LADD_{Child} = LADD_{HtM} + LADD_{PA\ Broadcast\ Dermal} + LADD_{PA\ Broadcast\ Inhalation} + LADD_{Mattress\ Dermal}}$

The summed LADD values for adults, youth and children are then compared to the established q_1* value to determine a cancer risk per lifestage. Finally, the lifestage cancer risks are summed to provide a total lifetime cancer risk estimate. The combined lifestage and lifetime cancer risk estimates are based on exposure values from this review and are summarized in Tables 20 and 21 of Appendix IV. Unless broadcast application is excluded in the estimation of the total lifetime cancer risk, the calculated total lifetime cancer risks for all currently registered indoor broadcast and perimeter treatments, as well as broadcast treatments to gardens are of concern.

3.3.4 Aggregate Risk Assessment (non-cancer)

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).

3.3.4.1 Short/Intermediate-term Aggregate Endpoint

The primary effect of concern for aggregation was liver toxicity. Clinical signs of neurotoxicity were also considered for aggregation. When manifested, clinical signs were observed at the same levels as those producing liver toxicity. For oral exposure, the 6-month dietary dog study with a NOAEL of 31 mg/kg bw/day (increased liver weight and nervousness and tremors) was selected as the critical point of departure. For inhalation exposure, the 90-day rat inhalation study with a NOAEL of 4 mg/kg bw/day (increased liver weight/hypertrophy and irregular respiration and

bradypnea) was selected as the critical point of departure. It was considered appropriate to not include the dermal route in the short/intermediate-term aggregate risk assessment as there were no signs of hepatotoxicity or neurotoxicity in the 21-day dermal toxicity study up to the limit dose. For both oral and inhalation routes of exposure, a target MOE of 100 was selected which includes a 10-fold uncertainty factor for interspecies extrapolation, a 10-fold uncertainty factor for intraspecies variability and a *Pest Control Products Act* factor of 1-fold.

3.3.4.2 Long-term Aggregate Endpoints

Liver toxicity was identified as the common endpoint for a long term aggregate risk assessment, and the 1-year dietary dog study with NOAEL of 8.2 mg/kg bw/day was selected as the critical point of departure for a long term aggregate exposure scenario. Route-specific studies of appropriate duration were not available. The use of the oral study was deemed preferable to selecting route specific studies with additional uncertainty factors, for potential durational effects. A target MOE of 100 was selected which includes a 10-fold uncertainty factor for interspecies extrapolation, a 10-fold uncertainty factor for intraspecies variability and a *Pest Control Products Act* factor of 1-fold.

3.3.4.3 Residential Aggregate Exposure and Risk Assessment

For tetramethrin, the relevant scenarios for aggregation are as follows:

- short-term hand-to-mouth (HtM) and postapplication inhalation exposure from hard surfaces following a broadcast spray (child)
- short-term HtM and postapplication inhalation exposure from space sprays (child)
- long-term HtM exposure and postapplication inhalation exposure from hard surfaces following a broadcast spray (child)

All target MOEs were met; non-cancer aggregate risk estimates are not of concern.

3.4 Exposure from Drinking Water

The use pattern of tetramethrin is expected to lead to minimal environmental exposure and consequently the potential exposure of drinking water sources to tetramethrin is expected to be minimal.

3.5 Cumulative Risk

The Pest Control Products Act requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Tetramethrin belongs to a group of chemicals classified as pyrethroids. Pyrethroids and pyrethrins have a common mechanism of toxicity wherein they all possess the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity. Upon completion of the re-evaluation of the individual chemicals in the pyrethroid group, it will be determined whether a cumulative effects assessment is necessary and if so, this will be performed with all relevant chemicals of the common mechanism group.

3.6 Incident Reports

As of 23 April 2015, 59 human incidents, 44 domestic animal incidents, and 17 packaging failure incidents involving the active ingredient tetramethrin have been reported to the PMRA. Most incidents were minor in severity and involved the normal use of sprays or foggers used in or around the home. The human incident data indicated a potential issue with incidental inhalation and dermal exposure to domestic class insecticide sprays, even when these products were used according to label directions. In the review of domestic animal incidents, contact with a treated area following the application of an insecticide spray indoors was identified as a potential issue. The current language on most products is somewhat vague and non-specific. Revisions to the labels have been proposed as a result of the re-evaluation to provide consistency across common products and minimize unnecessary human and domestic animal exposure.

There were no environmental incidents involving tetramethrin in the PMRA or USEPA databases.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Tetramethrin is used primarily in and around homes as a domestic insecticide. Based on the use pattern, environmental exposure is expected to be minimal.

Data on the fate and behaviour of tetramethrin are summarized in Table 1, Appendix V.

In soil, tetramethrin transforms through biotransformation and is non-persistent, with a half-life of 12.5-14 days. Results from American field studies indicate that d-phenothrin quickly dissipates in soil ($t_{1/2}$ 3 hr) and the transformation products were not detected below 15 cm.

In aquatic environments, tetramethrin undergoes hydrolysis ($t_{1/2}$ 13-25 d) at environmentally relevant pH and, therefore, is slightly persistent in aquatic environment. Tetramethrin has a low solubility in water.

The vapour preasure indicates that tetramethrin is slightly volatile and Henry's Law Constant indicates that it is sligtly volatile in moist soil or water. The log K_{ow} value of 4.6 indicates that tetramethrin has potential for bioaccumulation. However, the minimal environmental exposure indicates that bioaccumulation is not expected to be of concern. Based on the high K_{oc} value (1249-2939), the results of terrestrial field dissipation studies and because of the limited use-pattern, tetramethrin is not expected to leach to groundwater.

The photolysis of tetramethrin in air is expected to be rapid based on its reaction with ozone.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology

information to estimate the potential for adverse effects on non-target species. Available toxicity data for tetramethrin is presented in Table 2, Appendix V.

The use pattern indicates that the exposure of environmental compartments (soil, aquatic systems and food sources for birds and mammals) to tetramethrin will be minimal. Therefore expected environmental concentrations were not calculated and a quantitative risk assessment was not conducted.

4.2.1 Risks to Terrestrial Organisms

Due to the use pattern, the potential exposure of terrestrial non-target organisms is not expected to be significant. Therefore, the risk to terrestrail organisms is expected to be negligible.

4.2.2 Risks to Aquatic Organisms

Due to the limited outdoor use, exposure of aquatic habitats is expected to be minimal. Therefore, the risk to aquatic organisms is expected to be negligible.

5.0 Value

5.1 Value of Tetramethrin

Tetramethrin is registered for use on a broad spectrum of pests such as earwigs, ants, spiders, flies, wasps, cockroaches and bedbugs. Resistance to tetramethrin has been documented for some of the pests including German cockroaches and house flies. Ants and earwigs are the most prevalent types of crawling insects targeted in homes, while wasps are the most commonly sprayed flying pest. Tetramethrin products are formulated as ready to use solutions or pressurized spray cans which can be used to directly spray the target pests. Tetramethrin products may be of benefit to the homeowner to use with other control methods such as prevention and non-chemical treatments in the management of pests in and around the home. Many pests are challenging to control, typically requiring multiple control strategies that have to be repeated.

All Commercial Class and Domestic Class uses of tetramethrin are supported by the registrant and are listed in Appendix II.

5.2 Alternatives to Domestic Class Products

Tetramethrin is a broad spectrum contact synthetic pyrethroid. Tetramethrin end use products are formulated as ready to use solutions or pressurized products. The majority of domestic class insecticides registered for the same pests and sites as the tetramethrin use pattern are pyrethroids. Other active ingredients registered for some of the same labelled pests are the following: borates; conventional chemistries such as propoxur (bait trays), dichlorvos and naphthalene; abamectin, chlorpyrifos and thiamethoxam ant and/or cockroach baits; and German cockroach extract and (Z)-9-tricosene that trap and kill German cockroaches and house flies, respectively. Non-conventional insecticides against some of the labelled pests include diatomaceous earth/silicon

dioxide, d-limonene and soybean oil.

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 [those that meet all four criteria outlined in the policy: in other words, 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*].

During the review process, tetramethrin and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[3] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Tetramethrin does not meet Track 1 criteria, and is not considered a Track 1 substance. See Table 3 (Appendix V) for comparison with Track 1 criteria.

- Tetramethrin does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical 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*[4]. The list is used as described in the PMRA Notice of Intent NOI2005-01[5] and is based on existing policies and regulations including DIR99-03 and DIR2006-02[6], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade tetramethrin and the end-use products do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

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3 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*.

4 *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.*

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

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

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.[4]

7.0 Organisation for Economic Co-operation and Development Status of Tetramethrin

Canada is part of the Organisation for Economic Co-operation and Development (OECD), which groups member countries and provides a forum in which governments can work together to share experiences and seek solutions to common problems.

As part of the re-evaluation of an active ingredient, the PMRA takes into consideration recent developments and new information on the status of an active ingredient in other jurisdictions, including OECD member countries. In particular, decisions by an OECD member to prohibit all uses of an active ingredient for health or environmental reasons are considered for relevance to the Canadian situation.

Tetramethrin is currently acceptable for use in other OECD countries, including the United States and Australia. As of September 9, 2015, no decision by an OECD member country to prohibit all uses of tetramethrin for health or environmental reasons has been identified.

8.0 Proposed Re-evaluation Decision

After a re-evaluation of the insecticide tetramethrin, Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration of tetramethrin and associated end-use products for certain uses, provided that the risk-reduction measures described in this document are implemented.

The proposed regulatory actions for tetramethrin are summarized in the following sections. The labels of Canadian end-use products must be amended to include the risk-reduction measures listed in Appendix VI.

8.1 Proposed Regulatory Actions

8.1.1 Proposed Regulatory Action Related to Human Health

Potential cancer risks of concern were identified for certain uses. Consequently, the following residential uses are proposed to be cancelled (removed from labels):

- indoor broadcast treatments (for example, floors or carpets)
- indoor perimeter treatments (for example, baseboards).
- outdoor broadcast garden treatments

Based on the exposure assessments, the following label amendments are proposed to mitigate exposure:

- harmonizing instructions concerning re-entry into treated areas
- the requirement for gloves during the removal of treated nests

- the removal of any directions to repeat treatments as necessary
- Addition of standard use precautions:
  - "keep out of reach of children and pets"
  - "do not use in food handling, storage or preparation areas while food is present"

For domestic products:

- Limiting outdoor uses to turf and trees
- Limiting outdoor uses to spot treatments and/or crack and crevice treatments
- Limiting indoor uses to house plants, bedbug treatments and space sprays (for example, openings leading to voids and hollow spaces in walls)

8.1.2 Proposed Regulatory Action Related to the Environment

In order to mitigate the potential effects of tetramethrin on non-target organisms in terrestrial and aquatic habitats, the statements listed below are proposed for product labels.

- All labels: Toxic to aquatic organisms.
- For tetramethrin products that are registered for outdoor use (not for products that are registered for indoor use only): Toxic to bees. Do not spray bees.

List of Abbreviations

abs.	absolute
A	Applicator
ACH	air exchanges per hour
AChE	acetylcholinesterase
AD	administered dose
ADD	Absorbed Daily Dose
ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
atm	atmosphere
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
bw	bodyweight
bwg	body weight gain
CAS	chemical abstracts service
CF	Conversion Factor
CHAT	choline acetyltransferase
cm^2	square centimeters
cm^2/h	square centimetres per hour
cm^2/kg	square centimetres per kilogram
CMC	carboxymethylcellulose
C_o	initial concentration
cont'd	continued
CR	Cancer Risk
DA	Dermal Absorption
DACO	Data Code
DE	Dermal Exposure
DFR	Dislodgeable Foliar Residue
DR	Deposited Residue
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
DT_{75}	dissipation time 75% (the time required to observe a 75% decline in concentration)
DT_{90}	dissipation time 90% (the time required to observe a 90% decline in concentration)
dw	dry weight
d/yr	days per year
EC_{05}	effective concentration on 5% of the population
EC_{10}	effective concentration on 10% of the population
EC_{25}	effective concentration on 25% of the population
EDE	estimated daily exposure
EEC	estimated environmental exposure concentration
ER_{25}	effective rate on 25% of the population
ER_{50}	effective rate on 50% of the population
et al	and others

e-PRS	PMRA's Electronic Pesticide Regulatory System
ET	Exposure Time
EUPs	End Use Products
F	fraction of residue transferred
F0	parental generation
F1	first filial generation
F_{ai}	fraction of residue available for transfer
F_{AR}	fraction of a.i. as dislodgeable residue following application
Fc	Food consumption
F_D	fraction of residue that dissipates daily
FIR	food ingestion rate
F_M	fraction of hand surface area mouthed/event
FOB	functional observational battery
$Freq_H$	number of hand-to-mouth events per hour
$Freq_O$	number of object-to-mouth contact events per hour
g	gram
g a.i./m^2	grams of active ingredient per square meter
g a.i./m^3	grams of active ingredient per cubic meter
GD	gestation day
ha	hectare
HDT	Highest Dose Tested
HPLC	high performance liquid chromatography
hr	hours
HR	Hand Residue loading
hr/d	hours per day
HtM	Hand-to-Mouth
i.p.	intraperitoneal
IR	Inhalation Rate
IUPAC	International Union of Pure and Applied Chemistry
k	first order decay rate
Koc	organic-carbon partition coefficient
K_{ow}	octanol-water partition coefficient
Kd	soil-water partition coefficient
kg	kilogram
kg a.i.	kilograms of active ingredient
kg a.i./can	kilograms of active ingredient per can
kg ai/ha	kilograms of active ingredient per hectare
kg bw	kilograms of bodyweight
lb	pound
lb/ft^2	pound per square foot
lb/ft^3	pound per cubic foot
L	litre
LADD	Lifetime Average Daily Dose
LC_{50}	median lethal concentration
LD50	lethal dose 50%
LCR	Lifetime Cancer Risk
LD_{50}	median lethal dose
LOAEL	lowest observed adverse effect level

LOEC	lowest observed effect concentration
LOD	limit of detection
LOQ	limit of quantitation
M	Mass of a.i. applied
m	meters
m^2	square meters
m^3	cubic meters
m^3/hr	cubic meters per hour
mAChR	Muscarinic acetylcholine receptor
mg	milligram
mg/cm^2	milligrams per square centimeter
mg/kg bw	milligrams per kilogram of bodyweight
mg/kg bw/d	milligrams per kilogram of bodyweight per day
mg/kg/d	milligrams per kilogram per day
mg/m^3	milligrams per cubic meter
mL	millilitre
M/L/A	Mixer/Loader/Applicator
mo	month
MOA	Mode of action
MOE	Margin of Exposure
mPa	millipascal
N/A	not applicable
NOAEL	No Observed Adverse Effect Level
NOEC	no observed effect concentration
NOEL	no observed effect level
N/R	not required
OC	organic carbon content
OM	organic matter content
ORETF	Outdoor Residential Exposure Task Force
Pa	Pascal
PCP	Pest Control Product
PHED	Pesticide Handlers Exposure Database
pKa	dissociation constant
PND	Post natal day
PPE	Personal Protective Equipment
PMRA	Pest Management Regulatory Agency
q1*	quantitative dose response factor
R	residues available for transfer
RA	Risk Assessment
RED	Reregistration Eligibility Decision Document
REI	Restricted Entry Interval
ROLD	Repeat oral low dose
s	second
SGPT	Serum glutamic pyruvic transaminase
SN	Solution
SOHD	Single oral high dose
SOLD	Single oral low dose
SOP	Standard Operating Procedure

t	time
t1/2	half-life
TC	Transfer Coefficient
THPI	3,4,5,6-tetrahydrophthalimide
TR	Transferable Residue
TSMP	Toxic Substances Management Policy
UDS	unscheduled DNA synthesis
UE	Unit Exposure
µg	micrograms
µg a.i./cm2	micrograms of active ingredient per square centimeter
µg/cm2	micrograms per square centimeter
µg/hr	micrograms per hour
µg/kg bw/d	micrograms per kilograms of bodyweight per day
µg/kg ai	micrograms per kilogram of active ingredient
USC	Use-site Category
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WBC	white blood cell
wk	week
wt	weight
yr	year
♂	males
♀	females
↑	increased
↓	decreased

Appendix I Products containing Tetramethrin that are registered in Canada as of 13 August 2013

Registration Number	Marketing Class[1]	Registrant Name and Registrant Code	Product Name	Formulation Type	Guarantee
15337	D	JOH - S.C. JOHNSON AND SON LTD	RAID HOUSE & GARDEN BUG KILLER	PP-PRESSURIZED PRODUCT	PYRETHRIN 0.176%; PIPERONYL BUTOXIDE 1.21%; TETRAMETHRIN 0.09%
15411	D	JOH - S.C. JOHNSON AND SON LTD	RAID FLYING INSECT KILLER PRESSURIZED SPRAY	PP-PRESSURIZED PRODUCT	PYRETHRIN 0.14%; PIPERONYL BUTOXIDE 0.97%; TETRAMETHRIN 0.078%; N-OCTYL BICYCLOHEPTENE DICARBOXIMIDE 1.00%
16063	D	JOH - S.C. JOHNSON AND SON LTD	RAID FLYING INSECT BUG KILLER	PP-PRESSURIZED PRODUCT	PIPERONYL BUTOXIDE 0.97%; TETRAMETHRIN 0.067%; N-OCTYL BICYCLOHEPTENE DICARBOXIMIDE 1.00%; D-CIS, TRANS ALLETHRIN 0.15%
18534	T	SUG - SUMITOMO CHEMICAL COMPANY, LIMITED	NEO-PYNAMIN TECHNICAL GRADE	SO-SOLID	TETRAMETHRIN 95%
18984	M	MGK - MCLAUGHLIN GORMLEY KING COMPANY	EVERCIDE INTERMEDIATE 2132	EC-EMULSIFIABLE CONCENTRATE OR EMULSION	PERMETHRIN 8.89%; TETRAMETHRIN 8.89%
19597	D	JOH - S.C. JOHNSON AND SON LTD	RAID FLEA KILLER	PP-PRESSURIZED PRODUCT	PYRETHRIN 0.14%; PIPERONYL BUTOXIDE 0.97%; TETRAMETHRIN 0.07%; N-OCTYL BICYCLOHEPTENE DICARBOXIMIDE 1.00%
20796	D	JOH - S.C. JOHNSON AND SON LTD	RAID HOME INSECT KILLER	PP-PRESSURIZED PRODUCT	PIPERONYL BUTOXIDE 1.21%; TETRAMETHRIN 0.09%; D-TRANS ALLETHRIN 0.176%

Registration Number	Marketing Class[1]	Registrant Name and Registrant Code	Product Name	Formulation Type	Guarantee
22261	M	MGK - MCLAUGHLIN GORMLEY KING COMPANY	MULTICIDE NEO-PYNAMIN TECHNICAL	DU-DUST OR POWDER	TETRAMETHRIN 95%
23130	D	JOH - S.C. JOHNSON AND SON LTD	RAID HOUSE & GARDEN BUG KILLER - OUTDOOR FRESH SCENT	PP-PRESSURIZED PRODUCT	PYRETHRINI 0.176%; PIPERONYL BUTOXIDE 0.97%; TETRAMETHRIN 0.086%
23325	D	MGK - MCLAUGHLIN GORMLEY KING COMPANY	EVERCIDE PREMISE SPRAY 2132	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%
24201	D	JOH - S.C. JOHNSON AND SON LTD	RAID YARD GUARD 1 BUG KILLER	PP-PRESSURIZED PRODUCT	PYRETHRIN 0.176%; PIPERONYL BUTOXIDE 0.97%; TETRAMETHRIN 0.081%
24580	D	JOH - S.C. JOHNSON AND SON LTD	RAID FLEA KILLER PLUS 1 CARPET & ROOM SPRAY	PP-PRESSURIZED PRODUCT	PYRETHRIN0.14%; PIPERONYL BUTOXIDE 1.0%; TETRAMETHRIN 0.064%; METHOPRENE 0.015%; N-OCTYL BICYCLOHEPTENE DICARBOXIMIDE 1.0%
24581	D	JOH - S.C. JOHNSON AND SON LTD	RAID FLEA KILLER PLUS 2 CARPET & ROOM SPRAY	PP-PRESSURIZED PRODUCT	METHOPRENE 0.015%; PYRETHRIN 0.14%; PIPERONYL BUTOXIDE 1.0%; TETRAMETHRIN 0.064%
24819	M	MGK - MCLAUGHLIN GORMLEY KING COMPANY	MULTICIDE INTERMEDIATE 2084	SN-SOLUTION	D-PHENOTHRIN 7.17%; TETRAMETHRIN 12.50%

Registration Number	Marketing Class[1]	Registrant Name and Registrant Code	Product Name	Formulation Type	Guarantee
24820	M	MGK - MCLAUGHLIN GORMLEY KING COMPANY	MULTICIDE INTERMEDIATE 2086	SN-SOLUTION	D-PHENOTHRIN 8.90%; TETRAMETHRIN 8.90%
24823	D	MGK - MCLAUGHLIN GORMLEY KING COMPANY	MULTICIDE CRAWLING INSECT KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.20%; TETRAMETHRIN 0.20%
24824	D	MGK - MCLAUGHLIN GORMLEY KING COMPANY	MULTICIDE HOUSE & GARDEN INSECT KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.20%; TETRAMETHRIN 0.20%
24825	D	KMS - KUUS INC	KNOCK DOWN FLYING INSECT KILLER 1	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.15%; TETRAMETHRIN 0.25%
24829	M	MGK - MCLAUGHLIN GORMLEY KING COMPANY	MULTICIDE INTERMEDIATE 2317	EC-EMULSIFIABLE CONCENTRATE OR EMULSION	D-PHENOTHRIN 9.23%; TETRAMETHRIN 12.30%
24959	D	KGS - K-G SPRAY-PAK INC	K-G HOUSE & GARDEN INSECT KILLER VI	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.20%; TETRAMETHRIN 0.20%
24960	D	KGS - K-G SPRAY-PAK INC	K-G FLYING INSECT KILLER III	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.15%; TETRAMETHRIN 0.25%
25181	D	JOH - S.C. JOHNSON AND SON LTD	OFF! AREA BUG SPRAY (YARD & DECK)	PP-PRESSURIZED PRODUCT	PYRETHRIN 0.176%; PIPERONYL BUTOXIDE 0.97%; TETRAMETHRIN 0.081%
25491	D	MGK - MCLAUGHLIN GORMLEY KING COMPANY	NYLAR PRESSURIZED SPRAY 2618	PP-PRESSURIZED PRODUCT	PYRIPROXYFEN 0.015%; D-PHENOTHRIN 0.30%; TETRAMETHRIN 0.40%

Registration Number	Marketing Class[1]	Registrant Name and Registrant Code	Product Name	Formulation Type	Guarantee
25741	D	JOH - S.C. JOHNSON AND SON LTD	RAID WASP & HORNET KILLER 4	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%
25745	D	JOH - S.C. JOHNSON AND SON LTD	RAID WASP & HORNET KILLER 5	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.124%; TETRAMETHRIN 0.119%
26179	D	SGZ - SURE-GRO IP INC	C-I-L FLEA KILLER SURFACE SPRAY	PP-PRESSURIZED PRODUCT	PYRIPROXYFEN 0.015%; D-PHENOTHRIN 0.300%; TETRAMETHRIN 0.400%
26208	D	SGZ - SURE-GRO IP INC	CIL HOUSE AND GARDEN INSECT KILLER 2	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.20%; TETRAMETHRIN 0.20%
26502	D	HAC - ROLF C. HAGEN INC	SERGEANT'S PRETECT HOUSEHOLD FLEA SPRAY	PP-PRESSURIZED PRODUCT	PYRIPROXYFEN 0.015%; D-PHENOTHRIN 0.3%; TETRAMETHRIN 0.4%
26836	D	SGZ - SURE-GRO IP INC	SCHULTZ HOUSE PLANT INSECT SPRAY	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.20%; TETRAMETHRIN 0.20%
26932	D	JOH - S.C. JOHNSON AND SON LTD	RAID MAX HOUSE & GARDEN MULTI-BUG KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.20%; TETRAMETHRIN 0.20%
26997	M	MGK - MCLAUGHLIN GORMLEY KING COMPANY	MULTICIDE INTERMEDIATE 2660	SN-SOLUTION	D-PHENOTHRIN 6.25%; TETRAMETHRIN 10.00%
26998	D	MGK - MCLAUGHLIN GORMLEY KING COMPANY	MULTICIDE WASP & HORNET KILLER 2695	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.200%
27280	D	JOH - S.C. JOHNSON AND SON LTD	RAID FLYING INSECT BUG KILLER 3	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.10%; TETRAMETHRIN 0.35%; D-CIS, TRANS ALLETHRIN 0.10%

Registration Number	Marketing Class[1]	Registrant Name and Registrant Code	Product Name	Formulation Type	Guarantee
27282	D	JOH - S.C. JOHNSON AND SON LTD	RAID FLYING INSECT BUG KILLER 4	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.09%; TETRAMETHRIN 0.291%
27283	D	JOH - S.C. JOHNSON AND SON LTD	RAID DOUBLE ACTION FLYING INSECT KILLER	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.10%; TETRAMETHRIN 0.35%; D-CIS, TRANS ALLETHRIN 0.10%
27333	D	JOH - S.C. JOHNSON AND SON LTD	RAID OUTDOOR BARRIER BUG KILLER	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.2%; TETRAMETHRIN 0.21%
27498	D	PFP - PROFESSIONAL PET PRODUCTS INC	CYCLEBLOCK HOME & CARPET SPRAY	PP-PRESSURIZED PRODUCT	PYRIPROXYFEN 0.015%; D-PHENOTHRIN 0.30%; TETRAMETHRIN 0.400%
27628	D	JOH - S.C. JOHNSON AND SON LTD	RAID REACH & KILL WASP & HORNET BUG KILLER	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%
27708	D	MGK - MCLAUGHLIN GORMLEY KING COMPANY	EVERCIDE PUMP SPRAY 21321	SN-SOLUTION	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%
27861	D	GAX - GARDEX CHEMICALS LTD	GARDEX BUG-KILL MAXX	SN-SOLUTION	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%
27874	D	CRU - CRC INDUSTRIES INC	CRC BUG BLAST WASP AND HORNET KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.20%
27931	D	NPB - NPI BUGCON	BUGCON MEGA CRAWLING INSECT KILLER SOLUTION	SN-SOLUTION	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%
28104	D	JOH - S.C. JOHNSON AND SON LTD	RAID DOUBLE ACTION MOSQUITO AND FLY KILLER	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.10%; TETRAMETHRIN 0.35%; D-CIS, TRANS ALLETHRIN 0.10%

Registration Number	Marketing Class[1]	Registrant Name and Registrant Code	Product Name	Formulation Type	Guarantee
28147	D	NPB - NPI BUGCON	PROTECT PLUS	SN-SOLUTION	PERMETHRIN 0.20; TETRAMETHRIN 0.20;
28148	D	NPB - NPI BUGCON	STEVE'S TOTAL EXTERMINATOR	SN-SOLUTION	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%
28273	D	NPB - NPI BUGCON	S.D. RESIDUAL MULTI-PURPOSE INSECT KILLER	SN-SOLUTION	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%
28290	D	NGI - AGRIUM ADVANCED TECHNOLOGIES RP INC	PRO BUG-X READY-TO-USE INSECTICIDE	SN-SOLUTION	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%
28380	C	SIB - STATE INDUSTRIAL PRODUCTS	ZERO IN WAS WASP & HORNET KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.200%
28685	D	JOH - S.C. JOHNSON AND SON LTD	RAID DOUBLE ACTION MOSQUITO AND FLY KILLER 2	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.10%; TETRAMETHRIN 0.35%; D-CIS, TRANS ALLETHRIN 0.10%
28686	D	JOH - S.C. JOHNSON AND SON LTD	RAID WASP & HORNET KILLER 6	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.2%; TETRAMETHRIN 0.2%
28788	D	SGZ - SURE-GRO IP INC	WILSON ONE SHOT HOUSE AND GARDEN INSECT KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.20%; TETRAMETHRIN 0.20%
28841	D	WLM - WAL-MART CANADA INC	GREAT VALUE® HOUSE AND HOME INSECT KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
29085	D	JLC - THE JOHN LIM CO. LTD	SURE KILLER YELLOW RTU INSECTICIDE	SN-SOLUTION	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%
29204	D	SHP - SHOPPERS DRUG MART/PHARMAPRIX	LIFE BRAND HOUSE & HOME INSECT KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.20%; TETRAMETHRIN 0.20%

Registration Number	Marketing Class[1]	Registrant Name and Registrant Code	Product Name	Formulation Type	Guarantee
29402	D	PUG - PUROGUARD INSECTICIDES LTEE	THE EXTERMINATOR P-42	SN-SOLUTION	PERMETHRIN 0.2%; TETRAMETHRIN 0.2%
29423	D	SGZ - SURE-GRO IP INC	SCHULTZ HOUSEPLANT INSECT SPRAY	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.20%; TETRAMETHRIN 0.20%
29426	D	SGZ - SURE-GRO IP INC	WILSON ONESHOT HOUSE AND INDOOR GARDEN INSECT KILLER	PP-PRESSURIZED PRODUCT	TETRAMETHRIN 0.20%; D-PHENOTHRIN 0.20%
29555	D	SGZ - SURE-GRO IP INC	C-I-L HOUSE AND INDOOR GARDEN INSECT KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
29696	D	JOH - S.C. JOHNSON AND SON LTD	RAID MAX CRAWLING INSECT BUG KILLER 2	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
29697	D	JOH - S.C. JOHNSON AND SON LTD	RAID ANT, ROACH & EARWIG BUG KILLER 18	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
29699	D	JOH - S.C. JOHNSON AND SON LTD	RAID SPIDER BLASTER BUG KILLER 3	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
29753	C	KGS - K-G SPRAY-PAK INC	KG WASP & HORNET KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.200%
29776	D	JOH - S.C. JOHNSON AND SON LTD	RAID WASP & HORNET BUG KILLER 7	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.200%

Registration Number	Marketing Class[1]	Registrant Name and Registrant Code	Product Name	Formulation Type	Guarantee
29792	D	JOH - S.C. JOHNSON AND SON LTD	RAID MOSQUITO & FLY KILLER	PP-PRESSURIZED PRODUCT	PIPERONYL BUTOXIDE 0.97%; TETRAMETHRIN 0.067%; N-OCTYL BICYCLOHEPTENE DICARBOXIMIDE 1.0%; D-CIS, TRANS ALLETHRIN 0.15%
29946	D	KGS - K-G SPRAY-PAK INC	BETTER THAN BEDBUG BUG KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2; TETRAMETHRIN 0.2
29947	D	PRQ - LES PRODUITS DE CONTROLE SUPERIEUR INC/ SUPERIOR CONTROL PRODUCTS INC	PRO MAXX BEDBUG BUG DESTROYER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30033	D	NDI - NATURES' INNOVATION INC	BEDBUG BUG PATROL BEDBUG BUG KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30034	D	KMS - KUUS INC	KNOCK DOWN BEDBUG BUG KILLER I	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30069	D	BQS - BRODI SPECIALTY PRODUCTS LTD	BRODI BEDBUG BUG KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30070	D	LTI - ALTI PACKAGING SYSTEMS INC	KABLAMO BEDBUG BUG KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30084	D	KMS - KUUS INC	PROTEX BEDBUG BUG KILLER .20% D-PHENOTHRIN	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30085	D	KMS - KUUS INC	KNOCKDOWN TOTAL HOME MULTI FLYING & CRAWLING	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%

Registration Number	Marketing Class[1]	Registrant Name and Registrant Code	Product Name	Formulation Type	Guarantee
			INSECT KILLER		
30098	D	MAE - MAHEU & MAHEU INC	RAMPEX	SN-SOLUTION	PERMETHRIN 0.2%; TETRAMETHRIN 0.2%
30125	D	JOH - S.C. JOHNSON AND SON LTD	OFF! AREA BUG SPRAY CAMPSITE AND BACKYARD	PP-PRESSURIZED PRODUCT	PYRETHRIN 0.176%; PIPERONYL BUTOXIDE 0.97%; TETRAMETHRIN 0.081%
30126	D	NBG - NIGHT BUG ENR	NIGHT BUGS BEDBUG BUG KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30158	D	SGZ - SURE-GRO IP INC	GREEN EARTH HOMECARE BEDBUG BUG TRAVEL SPRAY	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30191	D	SGZ - SURE-GRO IP INC	C-I-L WASP & HORNET LONG SHOT	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.2%
30192	D	SGZ - SURE-GRO IP INC	WILSON ONESHOT WASP & HORNET LONG SHOT	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.2%
30209	D	COP - LA COOP DU QUEBEC	ELIMINATOR PLUS WASP & HORNET KILLER INSECTICIDE I	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.2%
30212	D	PRQ - LES PRODUITS DE CONTROLE SUPERIEUR INC/ SUPERIOR CONTROL PRODUCTS INC	SUPER HUNTER WASP & HORNET KILLER INSECTICIDE I	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.2%
30273	D	KGS - K-G SPRAY-PAK INC	BETTER THAN WASP & HORNET KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0..125%; TETRAMETHRIN 0.2%

Registration Number	Marketing Class[1]	Registrant Name and Registrant Code	Product Name	Formulation Type	Guarantee
			1		
30285	D	DVB - DCG VISION MARKETING & SALES INTERNATIONAL LTD	POWER SHOT BEDBUG BUG KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30286	D	MME - LES MARQUES METRO S.E.N.C	SELECTION HOUSE & HOME INSECT KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30287	D	NCH - NCH CANADA INC	X-PIRE	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30302	D	LLD - LLOYDS LABORATORIES	WASP & HORNET BLASTER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.20%
30303	D	NVE - NOVELLA BRANDS INC	BLAZE WASP & HORNET KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.20%
30306	D	DLS - DIRECT LINE SALES & SUPPLIES CORP.	ONGUARD T 20	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.20%
30425	C	FCA - CANTOL CORP.	WASP & HORNET SPRAY	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.20%
30432	D	SGZ - SURE-GRO IP INC	GREEN EARTH HOMECARE FLYING & CRAWLING INSECT KILLER (1)	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30466	D	BHD - BUSINESS HELPERS' DEPOT INC	FIGHT BACK INSECTICIDE M-1	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%

Registration Number	Marketing Class[1]	Registrant Name and Registrant Code	Product Name	Formulation Type	Guarantee
30557	D	SSX - SCOTTS CANADA LTD	ORTHO® HOME DEFENSE® MAX, HORNET & WASP ELIMINATOR SPRAY	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.200%
30578	D	BHD - BUSINESS HELPERS' DEPOT INC	FIGHT BACK INSECTICIDE M-3-2	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.2%
30636	D	KMS - KUUS INC	KNOCK DOWN TOTAL IN-AND-AROUND THE HOUSE INSECT KILLER	SN-SOLUTION	PERMETHRIN 0.2%; TETRAMETHRIN 0.2%
30689	D	CVU - CONSEAL INTERNATIONAL, INC	BEDBUG BUG FIX	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30701	D	AUO - AURA PRO SOLUTIONS, INC	ZONE GUARD, BEDBUG BUG KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30706	D	AUO - AURA PRO SOLUTIONS, INC	ZONE GUARD, WASP & HORNET BLASTER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.20%
30744	D	JOH - S.C. JOHNSON AND SON LTD	RAID® OUTDOOR ANT NEST DESTROYER 2	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30745	D	MGK - MCLAUGHLIN GORMLEY KING COMPANY	EVERCIDE® WASP & HORNET KILLER 20861	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.2%
30746	D	JOH - S.C. JOHNSON AND SON LTD	RAID® MAX WASP & HORNET FOAM	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.20%

Registration Number	Marketing Class[1]	Registrant Name and Registrant Code	Product Name	Formulation Type	Guarantee
			BUG KILLER 2		
30777	D	ULT - ULTRASOL INDUSTRIES LTD	DOKTOR DOOM WASP & HORNET NEST ANNIHILATOR	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.200;
30779	D	KMS - KUUS INC	KNOCK DOWN PEST CONTROL PT INSECT KILLER	SN-SOLUTION	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%;
30781	D	AOK - AEROKURE INTERNATIONAL INC	INSECT STOP BEDBUG BUG KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.2%; TETRAMETHRIN 0.20%
30879	D	SFR - WOODSTREAM CANADA CORPORATION	TERRO® WASP & HORNET KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.20%
30880	D	SFR - WOODSTREAM CANADA CORPORATION	TERRO® HOME INSECT KILLER	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%
30882	D	SFR - WOODSTREAM CANADA CORPORATION	TERRO® ANT KILLER PLUS	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%
30885	D	SFR - WOODSTREAM CANADA CORPORATION	TERRO® ANT AND SPIDER KILLER	PP-PRESSURIZED PRODUCT	PERMETHRIN 0.20%; TETRAMETHRIN 0.20%
30965	D	KMS - KUUS INC	KNOCK DOWN HORNET & WASP BLASTER SPRAY KILLER	PP-PRESSURIZED PRODUCT	TETRAMETHRIN 0.200%; D-PHENOTHRIN 0.125%
30975	D	URC - UR-CAN INC	ECO-GUARD WASP & HORNET	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.2%

Registration Number	Marketing Class[1]	Registrant Name and Registrant Code	Product Name	Formulation Type	Guarantee
			BLASTER		
30994	D	NVE - NOVELLA BRANDS INC	BLAZE PROFESSIONAL WASP & HORNET KILLER	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.20%
31042	D	KMS - KUUS INC	KNOCK DOWN PROFESSIONAL HORNET & WASP BLASTER SPRAY KILLER I	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.125%; TETRAMETHRIN 0.200%
31057	D	BHD - BUSINESS HELPERS' DEPOT INC	FIGHT BACK INSECTICIDE M-17	PP-PRESSURIZED PRODUCT	D-PHENOTHRIN 0.200%; TETRAMETHRIN 0.200%

[1] C=commercial, D=domestic, M=manufacturing and T=technical

Appendix II Registered Domestic and Commercial Class uses of Tetramethrin in Canada as of 13 August 2013

Site (s)[1]	Application equipment	Metric Conversion of USEPA Rate of Active Ingredient[2]
Commercial Class Products		
USC[3] 20 (Structures) and USC 25 (Human Habitat and Recreational areas)		
Wasp and hornet nests	Pressurized spray can	Not specified
Domestic Class Products		
USC 20: Structures (pet quarters, crack and crevices, baseboards, indoor and outdoor window and door frames, localized areas of floor and floor coverings, behind sinks, stoves, refrigerators, and cabinets and around garbage cans, plumbing and other utility installations, porches, patios, garages, between different elements of construction, between equipment and floors, openings leading to voids and hollow spaces in walls, equipment legs and bases).	Pressurized spray can, spray container	0.056 g a.i/m^3 or 0.17 g a.i./m^2
USC 20: Structures outdoors	Pressurized spray can	0.17 g a.i./m^2
USC 26: Human skin, clothing and Proximal sites (Mattress, baseboards, floorboards, bedframes, door and window frames, window treatment hardware)		Not specified
USC 27: Outdoor Ornamentals		0.17 g a.i./m^2
USC 28: Indoor Plants and Plantscapes		0.056 g a.i./m^3
USC 33: Residential Outdoors		0.17 g a.i./m^2

[1] All uses were supported by the technical registrant.

[2] The application rates are not stated on the Canadian labels. The technical registrant did not provide any additional information of use and usage information on tetramethrin end use products for inclusion in PMRA's risk assessment. Therefore application rates from the United States Environmental Protection Agency Reregistration Eligibility Decision (RED) Document for Tetramethrin Revised April 2010 were used in the assessment for the equivalent or corresponding site, formulation type and application.

[3] USC = Use-site Category

Appendix III Toxicology Assessment for Tetramethrin

Table 1 Summary of Risk Assessment Endpoints

Exposure Scenario	Endpoint	Study/NOAEL	MOE [a]
Short-term Incidental oral	Increased liver weight as well as nervousness and tremors	6-month dietary study in dogs NOAEL: 31 mg/kg bw/day	100
Long-term Incidental Oral	Liver toxicity (increased liver/gallbladder weight, increased cholesterol, phospholipid and hepatic glycogen)	1-yr dietary study in dogs NOAEL: 8.2 mg/kg bw/day	100
Short/Intermediate-term Dermal	No treatment related effects	21-day dermal toxicity study in rats NOAEL: 1000 mg/kg bw/day	100
Short/Intermediate /Long-term Inhalation	Increases in the incidence of clinical signs, decreased bwg, changes in hematology and clinical chemistry, increased liver and kidney toxicity	90 day rat inhalation toxicity study in rats NOAEL: 4.1 mg/kg bw/day	100
Long-term Dermal [b]	Liver toxicity (increased liver/gallbladder weight, increased cholesterol, phospholipid and hepatic glycogen)	1-yr dietary study in dogs NOAEL: 8.2 mg/kg bw/day	100
Short/Intermediate-term Aggregate	Increased liver weight as well as nervousness and tremors	6-month dietary study in dogs NOAEL: 31 mg/kg bw/day	100
Long--term Aggregate	Liver toxicity (increased liver/gallbladder weight, increased cholesterol, phospholipid and hepatic glycogen)	1-yr dietary study in dogs NOAEL: 8.2 mg/kg bw/day	100
Cancer Endpoint	q_1* value rat interstitial cell (♂) = 6.24×10^{-3} (mg/kg bw/day)$^{-1}$		

a - MOE refers to target MOE for occupational or residential assessments
b – Since an oral NOAEL was selected a dermal absorption factor was used in route-to-route extrapolation

Table 2 Toxicity Profile of Tetramethrin

NOTE: Studies have been conducted with tetramethrin unless otherwise noted. 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 weight and relative organ to bodyweights unless otherwise noted.

Study Type/ Animal/ PMRA #	Study Results
Metabolism/Toxicokinetic Studies	
Toxicokinetic, metabolism cis vs. trans isomers Sprague Dawley rats PMRA - 1923015 1923016 ^{14}C-labelled at the 1,2 double bond of the THPI moiety	**SOLD (2 mg/kg bw), SOHD (250 mg/kg bw) or ROLD (2 mg/kg bw/day)** **Absorption** Rapid absorption based on > 90% of administered dose (AD) excreted within 2 days **Distribution** Tissue residues less than 0.5% of dose. Highest levels noted in blood; levels also found in hair, skin, thyroid (both isomers) and kidney, liver, lung and spleen (cis isomer). No sex difference in tissue distribution except for higher levels in blood, kidney and spleen of single low and high dose ♀ compared to ♂ **Metabolism** No qualitative differences in metabolism were noted in relation to dose regime or gender in excreta pooled over 2 days post-dosing. 22-23 urinary metabolites were detected; all except 3-OH-HPI-1(3-hydroxy-1,2-cyclohexanedicarboximide) (1.9-23%AD) were < 5%. Repeated dosing decreased the amount of unchanged parent compound excreted in the feces (3-3.9% with cis-isomer, 0.7-2.2% with trans isomer compared to the low and high dose single dose groups 13-32.4% with cis isomer, 4.8-23.2% with trans isomer). 33-34 fecal metabolites were detected; major metabolites included TPI-SA (1-sulfo-1,2-cyclohexanedicarboximide) (6-18%) and in the case of the cis-isomer, two unknowns (6-15% and 3-7% respectively). Biotransformation occurred as cleavage of the ester linkage followed by ring opening, hydroxylation, oxidation and incorporation of the sulfonic acid group to the1,2-double bond of the THPI moiety. **Excretion** Rapidly and almost completely eliminated (95-101%) within 7 days in feces and urine. % AD in feces, urine resp. (cis-isomer) SOLD: 66-75%, 21-31% SOHD: 88-91%, 9-12% ROLD: 69-78%, 23-32% % AD in feces, urine resp. (trans isomer) SOLD: 38-53%, 42-58% SOHD: 41-58%, 43-58% ROLD: 29-39%, 63-71%

Study Type/ Animal/ PMRA #	Study Results
	Urinary excretion was higher in ♀ compared to ♂ in all dosing regimens. Negligible amounts were expired in air in a preliminary study.
Toxicokinetics, metabolism , cis vs. trans isomers Sprague Dawley rats PMRA – 1144131 ^{14}C-labelled at carbonyl group of the acid or alcohol moiety	**SOLD (3-5 mg/kg bw)** **Absorption** Rapid absorption inferred from radioactivity in the content of the stomach and intestines at 6 and 24 hours but not at 72 hours in whole-body autoradiography **Distribution** Highest tissue concentrations 7 days post-dosing were in the blood and hair. In general, the residue levels did not differ between the sexes but the cis-isomer appeared to produce higher residues compared to the trans-isomer. Tissue residues were generally higher with the alcohol-labelled tetramethrin compared to the acid-labelled tetramethrin. **Metabolism** A small amount of parent (1%) was found in the feces of rats treated with the cis-isomer; no parent was found in the feces of rats treated with the trans-isomer or in the urine from either group. The metabolites derived from the acid moiety of the trans or cis-isomer were found in free and glucuronide form and were detected in the urine and feces. The metabolites are identified as t-CA, *ωt*-acid-t-CA, *ωc*-acid-t-CA, *ωt*-alcohol-t-CA, *ωt*-alcohol-c-CA, *ωc*-alcohol-c-CA and *ωt*-acid-c-CA; some of the metabolites were attributed to trans ↔ cis isomerisation. The most abundant metabolite was free form *ωt*-acid-t-CA in both ♂ and ♀ dosed with trans-tetramethrin (15.5% and 12.4% respectively in urine). In ♀ treated with trans-tetramethrin, the glucuronide form ωt-alcohol-t-CA was also fairly abundant at 11% in urine. All other metabolites from the acid moiety of either the cis or trans isomer were ≤5%. The alcohol derived metabolites were the same for both isomers, but the amounts of the metabolites differed. The main trans-isomer urinary metabolite in both ♂ and ♀ was 2-OH-HPI (10.1 and 8.5% respectively). The other urinary and fecal metabolites for both isomer forms included TPI in free and glutathione conjugate form, HPI, 3-OH-TPI, TPIA, 3-OH-HPI and 4-OH-HPI; none exceeded 4%. . **Excretion** For both moieties recoveries at 7 days ranged from 94-101%. - Urinary excretion was 27-46% for the cis isomer and 42-67% for the trans isomer. Fecal excretion was 52-68% for the cis isomer and 27-50% for the trans isomer. Urinary excretion was higher in ♀ compared to ♂ .No difference was noted in excretion pattern between radiolabel positions. Negligible amounts were excreted via CO_2 (≤3%). Tween 80 vehicle

Study Type/ Animal/ PMRA #	Study Results
Acute Toxicity Studies	
Acute oral toxicity (gavage in corn oil) DD mice PMRA - 1143977	**LD_{50}:** 1920 mg/kg bw ♂, 2000 mg/kg bw ♀ **≥1000 mg/kg bw:** hypersensitivity, muscular fibrillation, tremor and clonic convulsion Low acute toxicity
Acute oral toxicity (gavage in corn oil) ddY mice **Neopynamin Forte** PMRA - 1185235	**LD_{50}:** 1060 mg/kg bw ♂, 1040 mg/kg bw ♀ **≥200 mg/kg bw:** slight ↓ in spontaneous activity **≥385 mg/kg bw:** hyperexcitation, muscular fibrillation, tremor, irregular respiration, deep respiration, laboured respiration, ataxic gait, **≥845 mg/kg bw:** limb and/or whole body ataxia, weak respiration, lacrimation and salivation Slight acute toxicity
Acute oral toxicity (gavage in corn oil) Sprague Dawley rats PMRA - 1143977	**LD_{50}:** >5000 mg/kg bw Low acute toxicity
Acute oral toxicity (gavage in corn oil) Sprague Dawley rats PMRA - 1143978	**LD_{50}:** >5000 mg/kg bw **≥2500 mg/kg bw:** urinary incontinence **5000 mg/kg bw:** decreased spontaneous activity, excretion of oily substance. Low acute toxicity
Acute oral toxicity (gavage in corn oil) Sprague Dawley rats **Neopynamin Forte** PMRA - 1185235	**LD_{50}:** >5000 mg/kg bw Low acute toxicity
Oral range finding (capsule) Beagle dogs PMRA - 1143979	**Supplemental** No mortality ≤ 5000 mg/kg bw **≥ 1000 mg/kg bw:** white compound-like material present in emesis and/or stools **5000 mg/kg bw:** enlarged thymus in all animals receiving second dose of 5000 mg/kg bw.

Study Type/ Animal/ PMRA #	Study Results
Acute dermal toxicity DD mice PMRA - 1143977	**LD_{50}:** >5000 mg/kg bw Low acute toxicity
Acute dermal toxicity ddY mice **Neopynamin Forte** PMRA - 1185235	**LD_{50}:** >5000 mg/kg bw **≥2500 mg/kg bw:** muscular fibrillation**,** irregular respiration Low acute toxicity
Acute dermal toxicity Sprague Dawley rats PMRA - 1143977	**LD_{50}:** >5000 mg/kg bw Low acute toxicity
Acute dermal toxicity Sprague Dawley rats **Neopynamin Forte** PMRA - 1185235	**LD_{50}:** >5000 mg/kg bw Low acute toxicity
Acute dermal toxicity New Zealand White rabbits PMRA – 1143980	**LD_{50}:** >2000 mg/kg bw Low acute toxicity
Acute inhalation toxicity Sprague Dawley rats **Neopynamin Forte** PMRA - 1185237	**LC_{50}:** >1.18 mg/L **0.131 mg/L:** ↓ spontaneous activity, salivation, hyperexcitability, hyperpnea, irregular respiration, urinary incontinence, muscular fibrillation, ataxia, limb paralysis and other toxic signs were observed Slight acute toxicity
Primary eye irritation New Zealand White rabbits PMRA - 1143962	Minimally irritating
Primary skin irritation New Zealand White rabbits PMRA – 1143962	Non-irritating

Study Type/ Animal/ PMRA #	Study Results
Dermal sensitization (Buehler Method) Hartley Guinea pig PMRA - 1143963	Non-sensitizer
Short-Term Toxicity Studies	
13-Week toxicity (dietary, range finding) B6C3F1 mice PMRA - 1143968	**LOAEL: 117/149 mg/kg bw/day** ≥117/149 mg/kg bw/day: ↓ adrenal wt (♂); ↓ thyroid wt (♀) ≥393/430 mg/kg bw/day: ↓bw, ↑ rel liver wt. (♂); ↓ adrenal wt , ↓ ovary weight (♀) 1342/1593 mg/kg bw/day: ↓bw, bwg, ↑fc, ↓ pituitary wt.; ↑ rel. testes wt., ↑ rel. brain wt., ↓ thyroid wt. (♂); ↑ rel. liver wt., (♀).
30-Day toxicity (dietary) Sprague Dawley rats **Neopynamin Forte** PMRA - 1185238	**NOAEL = 30 mg/kg bw/day** ≥ 300 mg/kg bw/day: ↑ urinary bilirubin, SGPT and cholesterol, enlarged livers, focal necrosis and hepatocellular hypertrophy; ↓ bwg ♀
6-Month toxicity (dietary) Sprague Dawley rats **Neopynamin Forte** PMRA - 1185239	**NOAEL = 57.9 mg/kg bw/day** ≥ 17.1 mg/kg bw/day: ↑liver weight at 6 months (♂) (*non-adverse*) 57.9/71.4 mg/kg bw/day: ↑cholesterol and ↑urinary protein at 3 and 6 months; ↑liver wt at 3 months (♂); ↑liver wt at 6 months, ↑rel liver wt at 3 months (♀) (*non-adverse*) 178/214 mg/kg bw/day: ↓bw and bwg,↑ liver swelling and luster surface, ↑eosinophilic bodies in renal tubular epithelial cells (♂)
3 & 6-Month toxicity (dietary) Sprague Dawley rats **Neopynamin Forte** PMRA - 1185240	**NOAEL = 10.75 mg/kg bw/day** ≥2.64 mg/kg bw/day: transient ↓triglycerides (*non-adverse*) ≥5.29 mg/kg bw/day: transient ↓phospholipids (*non-adverse*) 10.75 mg/kg bw/day: ↓bw and bwg, ↑WBC (*non-adverse*)
6-Month toxicity (dietary) Beagle dogs PMRA – 1143969	**NOAEL = 31.25 mg/kg bw/day** ≥ 62.5 mg/kg bw/day: ↑ liver wt, nervousness and tremors. 125 mg/kg bw/day: inhibition of estrus, ↓ ovarian wt, and no *corpora lutea* (♀)

Study Type/ Animal/ PMRA #	Study Results
21-Day dermal toxicity Sprague Dawley rats PMRA - 1143970	**NOAEL = 1000 mg/kg bw/day (HDT)** **LOAEL** = not established
90-Day inhalation toxicity Sprague Dawley rats PMRA - 1143971 PRMA - 1143973	**NOAEL = 19.8/20.3 mg/m^3 (3.8/4.1 mg/kg bw/day)** ≥19.8/20.3 mg/m^3: ↑ liver wt. (rel.); ↑ kidney wt. (abs.) (♀) (*non-adverse*) ≥ 134 mg/m^3(26/27 mg/kg bw/day): ↑ clinical signs, (irregular respiration and bradypnea), ↓ bwg, changes in hematology (↓ monocyte count, mean corpuscular volume, mean corpuscular haemoglobin and mean corpuscular hemoglobin concentration; ↑prothrombin time and fibrinogen), clinical chemistries (↑urinary bilirubin, urobilinogen, serum protein, serum lipidase and gamma glutamyl transpeptidase), gross necropsy findings in liver (dark red discoloration, soft liver and enlarged liver), hepatocellular hypertrophy, hyaline droplets in kidney, ↑ kidney and liver wt. 824 mg/m^3 (158/166 mg/kg bw/day): ↓A/G ratio
52-Week oral toxicity (capsule) Beagle dogs PMRA – 2126759, 2126760, 2126761, 2126762, 2126763	**NOAEL = 300 mg/kg bw/day** **LOAEL = not established.** **≥ 100 mg/kg bw/day:** transient ↑ cholesterol (♂) (*non-adverse*)
52-Week oral toxicity (dietary) Beagle dogs PMRA - 2126740	**NOAEL = 8.2/9.2 mg/kg bw/day** ≥ 36.1/35.5 mg/kg/day: ↑ liver/gallbladder wt.;↑ cholesterol and phospholipid, ↑ hepatic glycogen (♂) 147/157 mg/kg bw/day: ↑cholesterol and phospholipid (♀) 286/325 mg/kg bw/day: ↑chronic inflammatory renal lesions (♂); ↑ hepatic glycogen (♀)
Neurotoxicity Studies	
Range finding study for an acute functional observation battery comparison study (gavage) Sprague Dawley rats PMRA – 2395173	Supplementary No effects reported at 2500 mg/kg bw (in corn oil) or at 5500 mg/kg bw (undiluted)

Study Type/ Animal/ PMRA #	Study Results
Acute neurotoxicity screening battery (gavage in CMC) Sprague Dawley rats PMRA - 2126769	NOAEL = 2000 mg/kg bw (HDT)
Subchronic neurotoxicity (dietary) Sprague Dawley rats PMRA - 2202500	**LOAEL (threshold) = 71 mg/kg bw/day (♂); NOAEL = 85 mg/kg bw/day (♀)** ≥71 mg/kg bw/day: slight ↓ bw,↓ bwg (♂) ≥172 mg/kg bw/day: ↓ brain wt.; ↑ landing foot splay (♂)
Chronic Toxicity/Oncogenicity Studies	
Chronic toxicity and oncogenicity (dietary) B6C3F1 mice PMRA – 1144034 1144035 1144048 1144049 1144051 1144052	**No NOAEL established** ≥ 10.8 mg/kg bw/day: non-dose related ↓ thyroid/parathyroid wt., ↓pituitary wt. (♂) 265/268 mg/kg bw/day: ↑rel. liver wt. (wk 53) (♂) No evidence of carcinogenicity
Oncogenicity (dietary) CD-1Mice PMRA - 2126799	**NOAEL = 484/566 mg/kg bw/day** ≥484/566 mg/kg bw/day: ↑ liver wt (♂)(*non-adverse*) 1134/1326 mg/kg bw/day: amyloidosis (in liver kidney, glandular stomach, small intestine); ↑ testes/epididymis wt. (♂); ↑ liver wt. (♀) No evidence of carcinogenicity
Chronic toxicity and oncogenicity (dietary) Sprague Dawley rats PMRA – 1144016 1144017	**NOAEL = 48 /61mg/kg bw/day** >48/61 mg/kg bw/day: ↓ fc (no dose response pattern); ↑ rel. liver wt., ↑ abs. liver wt. (wk 52) (♀) (*non-adverse*) ≥171/203 mg/kg bw/day: ↓ bw and bwg, ↑rel. liver weight; ↑ enlarged and firm testes, ↑interstitial cell tumours, ↑ number of hepatocytes in midzonal area of liver (♂) 295/327 mg/kg bw/day: ↑ vacuolation in hepatocytes (mild-moderate), ↑ testicular atrophy (slight) (♂) Incidence of interstitial cell adenoma at 0, 48, 171 and 295 mg/kg bw/day resp. is 4, 8, 23 and 40%
Carcinogenicity and chronic toxicity (dietary) Sprague Dawley and	**NOAEL = 41 mg/kg bw/day** **The chronic phase of this study was preceded by an in utero exposure phase (parental animals exposed one week pre-mating, during mating, gestation and lactation; main study animals exposed in utero through to 104 weeks). Only male offspring used for chronic phase.**

Study Type/ Animal/ PMRA #	Study Results
Long Evans rats PMRA – 1144015 1144026 1144036 1144038 1144039	**<u>In Utero phase only</u>** ***Long Evans strain*** ≥ 41mg/kg bw/day: ↓bwg during one-week pre-mating period (♂) 218 mg/kg bw/day: ↓bw, bwg during one-week pre-mating period ***Sprague Dawley strain*** 207 mg/kg bw/day: ↓bwg during one-week pre-mating period; ↓ group mean litter weights of ♂ pups (PND 7, 14 & 21) **<u>Chronic phase</u> (♂) <u>only</u>** ***Both strains*** 207-218 mg/kg bw/day: ↓bw & bwg, ↑ liver wt., ↑ testicular degeneration, hypospermatogenesis & aspermatogenesis, ***Sprague Dawley strain*** 207 mg/kg bw/day: ↓fc, ↑ rel. testes wt., ↑interstitial cell tumor ***Long Evans strain*** 218 mg/kg bw/day: ↑ testes wt., ↑ bile duct proliferation, ↑interstitial cell tumor
Developmental/Reproductive Toxicity Studies	
One-generation reproduction (dietary) Sprague Dawley rats (non-guideline) PMRA - 1144020	**Parental NOAEL = 56/68 mg/kg bw/day** ≥160/197 mg/kg bw/day: ↓ bwg, bw **Reproductive NOAEL = 56/68 mg/kg bw/day** ≥160/197 mg/kg bw/day: ↓ fertility index **Offspring NOAEL = 68 mg/kg bw/day** ≥197 mg/kg bw/day: ↓ lactation index , ↓ bw No evidence of sensitivity of the young
Two-generation reproduction (dietary) **Neopynamin Forte** Sprague Dawley rats PMRA - 1185244	**Parental NOAEL = 25 mg/kg bw/day** 150 mg/kg bw/day: ↓bw and fc , F0 and F1; ↑bile duct hyperplasia, F1(♀) **Reproductive NOAEL = 150 mg/kg bw/day** **Offspring NOAEL = 25 mg/kg bw/day** 150 mg/kg bw/day: ↓bw No evidence of sensitivity of the young
Reproductive function and fertility (dietary) (non-guideline) Swiss mice PMRA – 1257455	**Parental NOAEL = 2000 mg/kg bw/day** **Reproductive/Offspring NOAEL = 2000 mg/kg bw/day** No evidence of sensitivity of the young

Study Type/ Animal/ PMRA #	Study Results
Developmental toxicity (gavage in CMC) Sprague Dawley rats PMRA - 2126753	**Maternal NOAEL = 500 mg/kg bw/day** 1000 mg/kg bw/day: ↓ bwg, fc (GD 6-9) **Developmental NOAEL = 1000 mg/kg bw/day** No evidence of sensitivity of the young
Developmental toxicity (range-finding) (gavage in CMC) New Zealand White rabbits PMRA - 2202499	**Supplemental** **Maternal** ≥500 mg/kg bw/day: ↑ abortions (2, 4, 5 in 500, 1000 & 1500 mg/kg bw/day, respectively), mortality (1, 4, 1 in 500, 1000 & 1500 mg/kg bw/day, respectively) ≥1000 mg/kg bw/day: ↓ bw **Developmental** ≥1000 mg/kg bw/day: ↑ late resorptions
Developmental toxicity (gavage in CMC) New Zealand white rabbits PMRA - 2202499	**Maternal NOAEL = 100 mg/kg bw/day** ≥ 300 mg/kg bw/day: ↓ bwg **Developmental NOAEL = 420 mg/kg bw/day** LOAEL = not established. No evidence of sensitivity of the young
Fertility and development toxicity (gavage in CMC) (non-guideline) Sprague-Dawley rats PMRA – 2126744	**Parental NOAEL = 300 mg/kg bw/day** **≥ 300 mg/kg bw/day:** ↑ liver wt. (abs./rel.) (♂) (*non-adverse*) **1000 mg/kg bw/day**:↑ liver wt. (abs.) / (rel.) , ↑ kidney wt. (abs.) / (rel.) , ↑ water consumption (♂); transient ↓ bw , fc , ovary wt. (abs.)(♀) **Reproductive NOAEL = 300 mg/kg bw/day** **1000 mg/kg bw/day:** ↓*corpora lutea*/litter, implantations/litter, live fetuses/litter **Developmental NOAEL = 300 mg/kg bw/day** 1000 mg/kg bw/day: ↓bw, body length, ↓ ossification (proximal phalanges of forepaw, sacral and coccygeal vertebrae, sternebrae) No evidence of malformations or sensitivity of the young
Fertility and development toxicity (gavage in CMC) (non-guideline) Sprague-Dawley rats PMRA – 1144012	**Maternal NOAEL = 300 mg/kg bw/day** 1000 mg/kg bw/day: transient ↓ bw, bwg, fc, ↑ water consumption, liver wt. ovary wt. and kidney wt. **Offspring NOAEL = 1000 mg/kg bw/day** No evidence of malformations or sensitivity of the young

Study Type/ Animal/ PMRA #	Study Results
Developmental toxicity (gavage in CMC) (non-guideline) Japanese white rabbits PMRA - 1144013	**Supplemental** **Maternal** 500 mg/kg bw/day: ↓bwg, fc **Developmental** 500 mg/kg bw/day: ↓ bw
Genotoxicity Studies	
Gene mutation (Ames assay) S. typhimurium and E. coli PMRA – 1144027	Negative both with and without activation up to 5000 µg/plate
Gene mutation S. typhimurium TA 100, 98, 1535, 1537 & 97 (his-) E. coli (WP2uvrA) PMRA - 1144033	Negative ≥ 2000 µg/plate: precipitation without activation 5000 µg/plate: precipitation with activation
In vitro chromosome aberration Chinese Hamster Ovary cells (CHO-K1) PMRA - 1144030	Positive with activation at ≥50 µg/ml ↓mitotic index at 100 µg/ml; no metaphases observed at 125 µg/ml
In vitro chromosome aberration Chinese Hamster Ovary cells (CHO-WBL) PMRA - 1144031	Positive with activation ≥ 75.3 µg/ml (cytotoxic ≥ 150 µg/ml)
In vivo chromosome aberration (i.p.) ICR mice PMRA – 1144028	≥ 1200 mg/kg bw: ↓bw Negative for bone marrow chromosome aberrations at doses ≤ 5000 mg/kg bw.

Study Type/ Animal/ PMRA #	Study Results
In vivo chromosome aberration (i.p.) ICR mice PMRA – 2126764, 2126768, 2126903	Negative for bone marrow chromosome aberrations at ≤2000 mg/kg bw
In vitro unscheduled DNA synthesis Sprague Dawley rat hepatocytes PMRA - 1144032	Negative for UDS at 0.2 to 30 µg/mL Cytotoxic at 100 µg/mL
Special Studies	
Motor activity in juveniles (inhalation w/ Polyethylene Glycol 400 vehicle) (non-guideline) NMRI mice PMRA – 1171418	Motor activity was not affected on either PND 17 or at 4 months post-dosing. With up to 40 mg/m^3 (12 mg/kg bw/day) on PND 10-16 Muscarinic acetylcholine receptor (mAChR) density in the brain cortex of all treated groups was significantly increased in a dose-dependent manner in PND 17 ♂ mice, but not at four months post-dosing Acetylcholinesterase (AChE) and choline acetyltransferase (CHAT) were unaffected by treatment.
Immunotoxicity study (dietary) Sprague Dawley rats PMRA - 2385860	**NOAEL = 102 mg/kg bw/day** ≥ 257 mg/kg bw/day: ↓ thymus wt., ↓bwg 545 mg/kg bw/day: ↓bw

Appendix IV Occupational and Non-occupational Risk Assessments

Table 1 Occupational Applicator Exposure Estimates and MOEs

Use Scenario	Form [a]	Application Equipment	Application Rates [b] (kg a.i./can)	Amount Handled per day [c] (cans)	Daily Exposure (mg/kg bw/d)		Margins of Exposure	
					Dermal [d]	Inhalation [e]	Dermal [f]	Inhalation [g]
Label PPE: (long sleeves, long pants, socks, chemical resistant gloves								
outdoor wasp and hornet nests	PP	pressurized spray can	0.0012	14	0.031	0.0003	32500	12000

[a] PP = Pressurized Product
[b] Maximum listed label rate in kilograms of active ingredient per container (kg a.i./can).
[c] Based on the US EPA RED for piperonyl butoxide, which states that a commercial applicator can be expected to treat 7 homes per day and use 2 cans per home.
[d] Where dermal exposure mg/kg bw/d = unit exposure × amount handled × × rate)/80 kg bw
[e] Where inhalation exposure mg/kg bw/d = (unit exposure × × area treated × × rate)/80 kg bw
[f] Based on a dermal NOAEL of 1000 mg/kg bw/d and a target MOE of 100.
[g] Based on an inhalation NOAEL of 4.1 mg/kg bw/d and a target MOE of 100.

Table 2 Residential Applicator Exposure Assessment and MOEs

Use Scenario	Form [a]	Application Equipment	Application Rates [b] (kg a.i./can)	Amount Handled per day [c] (cans)	Daily Exposure (mg/kg bw/d)		Margins of Exposure	
					Dermal [d]	Inhalation [e]	Dermal [f]	Inhalation [g]
PPE: (short sleeves, shorts, socks)								
indoor, broadcast	SN	trigger-spray bottle	0.002	1	4.69E-03	3.25E-06	210000	1300000
indoor, perimeter/spot	SN	trigger-spray bottle	0.002	0.5	2.35E-03	1.63E-06	430000	2500000
indoor, broadcast	PP	aerosol can	0.0039	1	3.98E-02	3.22E-04	25000	13000
indoor, perimeter/spot (coarse);	PP	aerosol can	0.0039	0.5	1.99E-02	1.61E-04	50000	25000
indoor bedbugs, perimeter/spot; crack and crevice (pin stream)	PP	aerosol can	0.0012	0.5	6.12E-03	4.96E-05	160000	83000
indoor, space spray	PP	aerosol can	0.0023	0.25	5.86E-03	4.75E-05	170000	86000
indoor houseplants, perimeter/spot (coarse)	PP	aerosol can	0.0014	0.5	7.14E-03	5.78E-05	140000	71000

Use Scenario	Form [a]	Application Equipment	Application Rates [b] (kg a.i./can)	Amount Handled per day [c] (cans)	Daily Exposure (mg/kg bw/d)		Margins of Exposure	
					Dermal [d]	Inhalation [e]	Dermal [f]	Inhalation [g]
outdoor, ornamentals	PP	aerosol can	0.0012	2	2.45E-02	1.98E-04	41000	21000
outdoor space spray (fogger)	PP	aerosol can	2.84E-04	1	2.89E-03	2.34E-05	350000	180000

[a] PP = Pressurized Product; SN = Solution
[b] Maximum listed label rate in kilograms of active ingredient per container (kg a.i./can), except for outdoor space spray, which is a calculated application rate in kilograms of active ingredient per day (kg a.i./day).
[c] Based on default assumptions from the US EPA Residential SOPs (2012).
[d] Where dermal exposure mg/kg bw/day = unit exposure × amount handled × rate)/80 kg bw
[e] Where inhalation exposure mg/kg bw/day = (unit exposure × amount handled × rate)/80 kg bw
[f] Based on a short- to intermediate-term dermal NOAEL of 1000 mg/kg bw/d and a target MOE of 100.
[g] Based on a short- to intermediate-term inhalation NOAEL of 4.1 mg/kg bw/d and a target MOE of 100.

Table 3 Short- to Intermediate-term Postapplication Dermal Exposure from Floor and Carpets (non-bedbug)

Exposure Scenario		Life Stage	Transferable Residue ($\mu g/cm^2$) [a]	Transfer Coefficient (cm^2/hr) [b]	Exposure Time (hr/d) [c]	Dermal Dose (mg/kg bw/d) [d]	MOE [e]
Broadcast	Carpet	Adults	1.02	6800	8	6.94E-01	1400
		Youth		5600	5	5.01E-01	2000
		Children		1800	4	6.68E-01	1500
	Hard Surface	Adults	1.36	6800	2	2.31E-01	4300
		Youth		5600	1	1.34E-01	7500
		Children		1800	2	4.45E-01	2200
Perimeter/Spot (coarse and pin stream)	Carpet	Adults	0.51	6800	8	3.47E-01	2900
		Youth		5600	5	2.51E-01	4000
		Children		1800	4	3.34E-01	3000
	Hard Surface	Adults	0.68	6800	2	1.16E-01	8700
		Youth		5600	1	6.68E-02	15000
		Children		1800	2	2.23E-01	4500
Crack and Crevice	Carpet	Adults	0.10	6800	8	6.94E-02	14000
		Youth		5600	5	5.01E-02	20000
		Children		1800	4	6.68E-02	15000
	Hard Surface	Adults	0.14	6800	2	2.31E-02	43000
		Youth		5600	1	1.34E-02	75000
		Children		1800	2	4.45E-02	22000
Space Spray	Carpet	Adults	0.02	6800	8	1.33E-02	75000
		Youth		5600	5	9.63E-03	100000

Exposure Scenario		Life Stage	Transferable Residue ($\mu g/cm^2$) [a]	Transfer Coefficient (cm^2/hr) [b]	Exposure Time (hr/d) [c]	Dermal Dose (mg/kg bw/d) [d]	MOE [e]
		Children		1800	4	1.28E-02	78000
	Hard Surface	Adults	0.03	6800	2	4.44E-03	230000
		Youth		5600	1	2.57E-03	390000
		Children		1800	2	8.55E-03	120000

[a] Where Transferable Residue ($\mu g/cm^2$) = Residue ($\mu g/cm^2$) × Fraction Transferred (%). Deposited residues were calculated based on maximum label application rates or calculated amount applied using the US EPA Residential SOPs (2012) algorithms for all scenarios.
[b] Transfer Coefficient (cm^2/hr) default values obtained from the US EPA Residential SOPs (2012).
[c] Exposure Time (hr/d) default values obtained from the US EPA Residential SOPs (2012).
[d] Where Dermal Dose (mg/kg bw/d) = (Transferable Residue ($\mu g/cm^2$) × 0.001 mg/µg × Transfer Coefficient (cm^2/hr) × Exposure Time (hr/d))/Body Weight (kg). Body weights of 80, 57 and 11 kg were used for adults, youths (11 <16 years), and children (1 <2 years) respectively, as stated in the US EPA Residential SOPs (2012). Dermal absorption not required because the short- to intermediate-term dermal NOAEL is based on a dermal toxicity study.
[e] MOE = margin of exposure; MOE = NOAEL ÷ exposure, based on a dermal NOAEL of 1000 mg/kg bw/d and a target MOE of 100 applicable to short- intermediate-term scenarios.

Table 4 Long-term Postapplication Dermal Exposure from Floor and Carpets (bedbug)

Exposure Scenario		Life Stage	Transferable Residue ($\mu g/cm^2$) [a]	Transfer Coefficient (cm^2/hr) [b]	Exposure Time (hr/d) [c]	Dermal Dose (mg/kg bw/d) [d]	MOE [e]
Perimeter/Spot (coarse and pin stream)	Carpet	Adults	9.0E-02	4700	8	2.12E-02	390
		Youth		3900	5	1.54E-02	530
		Children		1300	4	2.13E-02	390
	Hard Surface	Adults	1.35E-01	4700	2	7.93E-03	1000
		Youth		3900	1	4.62E-03	1800
		Children		1300	2	1.60E-02	510
Perimeter/Spot (pin stream)	Carpet	Adults	2.20E-02	4700	8	5.17E-03	1600
		Youth		3900	5	3.76E-03	2200
		Children		1300	4	5.20E-03	1600
	Hard Surface	Adults	3.30E-02	4700	2	1.94E-03	4200
		Youth		3900	1	1.13E-03	7300
		Children		1300	2	3.90E-03	2100
Crack and Crevice	Carpet	Adults	6.00E-03	4700	8	1.41E-03	5800
		Youth		3900	5	1.03E-03	8000
		Children		1300	4	1.42E-03	5800
	Hard Surface	Adults	9.00E-03	4700	2	5.29E-04	16000
		Youth		3900	1	3.08E-04	27000
		Children		1300	2	1.06E-03	7700

[a] Where Transferable Residue ($\mu g/cm^2$) = Residue ($\mu g/cm^2$) × Fraction Transferred (%). Default deposited residue values were obtained from the US EPA Residential SOPs (2012) since an application rate was not provided for bed bug products. The 50th percentile values for Fraction Transferred were used for long-term risk assessments (Carpet = 0.02, Hard surface = 0.03) (US EPA, 2012).
[b] Transfer Coefficient (cm^2/hr) default values obtained from the US EPA Residential SOPs (2012).
[c] Exposure Time (hr/d) 50th percentile values obtained from the US EPA Residential SOPs (2012).

[d] Where Dermal Dose (mg/kg bw/d) = (Transferable Residue (µg/cm^2) × 0.001 mg/µg × Transfer Coefficient (cm^2/hr) × Exposure Time (hr/d) × Dermal Absorption (%))/Body Weight (kg). Body weights of 80, 57 and 11 kg were used for adults, youths (11 <16 years), and children (1 <2 years) respectively, as stated in the US EPA Residential SOPs (2012). A dermal absorption value of 50% was selected based on available data.
[e] MOE = margin of exposure; MOE = NOAEL ÷ exposure, based on an oral NOAEL of 8.2 mg/kg bw/d and a target MOE of 100 applicable to long-term scenarios.

Table 5 Short- to Intermediate- term Postapplication Dermal Exposure from Mattresses

Exposure Scenario	Life Stage	Deposited Residue (µg/cm^2) [a]	Surface Area/Body Weight Ratio (cm^2/kg) [b]	Dermal Dose (mg/kg bw/d) [c]	MOE [d]
mattress	Adults	4.5	280	1.89E-02	53000
	Youth		280	1.89E-02	53000
	Children		640	4.32E-02	23000

[a] Default deposited residue value was obtained from the US EPA Residential SOPs (2012) since an application rate was not provided for products applied to mattresses.
[b] Values were obtained from the US EPA Residential SOPs (2012) based on body weights of 80 kg for adults, 57 kg for youth, and 11 kg for children (1<2 years).
[c] Where Dermal Dose (mg/kg bw/d) = 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 (0.06) × Protection Factor (0.5).
[d] MOE = margin of exposure; MOE = NOAEL ÷ exposure, based on an dermal NOAEL of 1000 mg/kg bw/d and a target MOE of 100 applicable to short-, intermediate-term dermal scenarios.

Table 6 Short- to Intermediate-term Postapplication Dermal Exposure from Gardens, Trees and Indoor Plants [a]

Exposure Scenario	Life Stage	DFR_t (ug/cm^2) [b]	Transfer Coefficient (cm^2/hr) [c]	Exposure Time (hour) [d]	Dermal Dose (mg/kg bw/d) [e]	MOE [f]
Gardens	Adults	5.22	8400	2.2	1.21E+00	800
	Youth		6900	1.1	6.95E-01	1400
	Children		4600	1.1	8.26E-01	1200
Trees and Retail Plants	Adults		1700	1	1.11E-01	9000
	Youth		1400	0.5	6.41E-02	15600
	Children		930	0.5	7.59E-02	13200
Indoor Plants	Adults	4.25	220	1	1.17E-02	85600
	Youth		180	0.5	6.71E-03	149000
	Children		120	0.5	7.97E-03	125500

[a] The risk assessment was conducted without chemical-specific DFR since no studies were provided. Default values obtained from US EPA Residential SOPs (2012).
[b] Where DFR_t = Application Rate (kg ai/ha) × Transferrable a.i. × (1-(Dissipated Residue)^t (day after application (0)). Based on 2 applications 2 weeks apart for gardens and trees.
[c] Transfer Coefficient (cm^2/hr) default values obtained from the US EPA Residential SOPs (2012).
[d] Exposure Time (hr/d) default values obtained from the US EPA Residential SOPs (2012).
[e] Where Dermal Dose (mg/kg bw/d) = (DFR_t (µg/cm^2) × Transfer Coefficient (cm^2/hr) × Exposure Time (hr)/Body Weight (kg). Body weights of 80, 57 and 32 kg were used for adults, youths, and children (6 <11 years) as stated in US EPA Residential SOPs (2012). Dermal absorption not required because the dermal NOAEL is based on a dermal toxicity study.
[f] MOE = margin of exposure; MOE = NOAEL/Exposure, based on a dermal NOAEL of 1000 mg/kg bw/d and a target MOE of 100 applicable to short- intermediate-term scenarios.

Table 7 Short-to Intermediate-term Postapplication Dermal Exposure from Outdoor Aerosol Space Spray (foggers) [a]

Exposure Scenario	Life Stage	Deposited Residue (kg ai/m^2) [b]	Transfer Coefficient (cm^2/hr) [c]	Exposure Time (hour) [d]	Dermal Dose (mg/kg bw/d) [e]	MOE [f]
Outdoor Space Spray (fogger)	Adults	9.41E-08	180000	1.5	0.032	31000
	Youth		148000	1.3	0.032	31000
	Children		49000	1.5	0.063	16000

[a] The risk assessment was conducted without chemical-specific TTR since no studies were provided. Default values obtained from US EPA Residential SOPs (2012).
[b] Where Deposited Residue = Application Rate (kg ai/ha) × (1-(Dissipated Residue)^t (day after application (0)). Based on 2 applications 2 weeks apart for outdoor aerosol space sprays (foggers).
[c] Transfer Coefficient (cm^2/hr) default values obtained from the US EPA Residential SOPs (2012).
[d] Exposure Time (hr/day) default values obtained from the US EPA Residential SOPs (2012).
[e] Where Dermal Dose (mg/kg bw/day) = (Deposited Residue (kg/m^2) × Transfer Coefficient (cm^2/hr) × Exposure Time (hr) × 1.0E+06 mg/kg × 0.0001 m^2/cm^2 ÷ Body Weight (kg). Body weights of 80, 57 and 32 kg were used for adults, youths, and children (6 <11 years) as stated in US EPA Residential SOPs (2012). Fraction transferred was taken into consideration when calculating residues after multiple applications. Dermal absorption not required because the dermal NOAEL is based on a dermal toxicity study.
[f] MOE = margin of exposure; MOE = NOAEL÷ Exposure, based on a dermal NOAEL of 1000 mg/kg bw/day and a target MOE of 100 applicable to short- to intermediate-term scenarios.

Table 8 Postapplication Inhalation Exposure from Indoor Space Sprays

Exposure Scenario	Life Stage	Initial Concentration C_o (mg/m^3) [a]	Inhalation Dose (mg/kg bw/d) [b]	MOE [c]
Space Spray	Adults	1.34	0.01	290
	Youth		0.02	210
	Children		0.05	77

[a] Initial concentration expressed in mg/m^3
[b] Inhalation Dose (mg/kg bw/d) = $[(C_o \times IR) \div (ACH \times BW] \times (1 - e^{(-ACH \times ET)})$
Where IR = Inhalation Rate (m^3/hour) 0.64, 0.63, and 0.33 m^3/hr for adult, youth and children (1<2 years old) respectively, ACH = Air Exchange per hour (0.45 hr^{-1}), ET = Exposure Time (2 hr), BW = Body Weight (80 kg for adults, 57 kg for youth, and 11 kg for children (1<2 years old). Default values were obtained from the US EPA Residential SOPs (2012).
[c] MOE = margin of exposure; MOE = NOAEL ÷ Exposure, based on an inhalation NOAEL of 4.1 mg/kg bw/d and a target MOE of 100 applicable to short- to intermediate term exposure. Shaded cells indicate those inhalation MOEs which failed to reach the target MOE of 100.

Table 9 Short- to intermediate term postapplication Inhalation Exposure from Indoor Surface Directed Sprays

Exposure Scenario	Life Stage	Mass of a.i. (mg) [a]	Exposure Time (hour) [b]	Inhalation Dose (mg/kg bw/d) [c]	MOE [d]
Surface Directed Spray	Adults	3900	16	3.60E-03	1100
	Youth	3900	15	4.60E-03	890
	Children	3900	18	1.50E-02	270

[a] Where Mass (M_{Label}) = Application Rate (kg a.i./can) × Amount Handled (1 can) × 1.00E06 mg/kg.
[b] Exposure Time (hr/d) default values obtained from the US EPA Residential SOPs (2012).
[c] Where inhalation exposure (mg/kg bw/d) = $((IR \times M) \div ACH \times V \times BW) \times [1 – ((ACH \times e^{-k \times ET}) – (k \times e^{-ACH \times ET})) \div (ACH – k)]$
The equation assumes 100% absorption through inhalation, air exchanges (ACH) = 0.45 hr^{-1}, volume of a room (V) = 28 m^3, decay rate (k) = 9.5E-06 hr^{-1}, M = mass of a.i., ET = exposure time. Inhalation rates (IR) of 0.64, 0.63 and 0.33 m^3/hr and body weights (BW) of 80, 57 and 11 kg were used for adults, youth and children (1<2 years old) respectively, as stated in the US EPA Residential SOPs (2012).
[d] MOE = margin of exposure; MOE = NOAEL ÷ Exposure, based on an inhalation NOAEL of 4.1 mg/kg bw/d and a target MOE of 100 applicable to short- to intermediate term exposure.

Table 10 Short-term Postapplication Hand-to-Mouth Exposure to Children from Indoor Environments

Exposure Scenario		Hand Residue Loading (mg/cm^2) [a]	Oral Dose (mg/kg bw/d) [b]	MOE [c]
Broadcast	Carpet	3.67E-03	1.00E-01	310
	Hard Surface	2.45E-03	3.34E-02	930
Perimeter/Spot (coarse and pin stream)	Carpet	1.84E-03	5.01E-02	620
	Hard Surface	1.22E-03	1.67E-02	1900
Crack and Crevice	Carpet	3.67E-04	1.00E-02	3100
	Hard Surface	2.45E-04	3.34E-03	9300
Space Spray	Carpet	7.05E-05	1.92E-03	16000
	Hard Surface	4.70E-05	6.42E-04	48000

[a] Based on the dermal postapplication exposure from indoor applications without the body weight × fraction of a.i. on hands compared to body (0.15).
[b] Where Oral Dose (mg/kg bw/d) = [Hand Residue (mg/cm^2) × (Fraction of hand mouthed/event (0.13) × Surface Area of one hand (150 cm^2)) × (Exposure Time (hr) × Replenishment Intervals (4/hr)) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (20)} \div \text{Replenishment Intervals (4/hr)}}$)] ÷ Body Weight (11 kg). Exposure times for carpets and hard surfaces were 4, and 2 hrs, respectively, as stated in the US EPA Residential SOPs (2012).
[c] MOE = margin of exposure; Oral MOE = oral NOAEL ÷ oral exposure, based on the short-term incidental oral NOAEL 31 mg/kg bw/d and a target MOE of 100.

Table 11 Short-term Postapplication Hand-to-Mouth Exposure to Children from Outdoor Environments

Exposure Scenario		Hand Residue Loading (mg/cm^2) [a]	Oral Dose (mg/kg bw/d) [b]	MOE [c]
Outdoor Space Spray to Gardens and Trees	Turf	1.38E-04	1.32E-03	23000

[a] Based the dermal postapplication exposure from indoor applications without the body weight × fraction of a.i. on hands compared to body (0.06).
[b] Where Oral Dose (mg/kg bw/d) = [Hand Residue (mg/cm^2) × (Fraction of hand mouthed/event (0.13) × Surface Area of one hand (150 cm^2)) × (Exposure Time (hr) × Replenishment Intervals (4/hr)) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (13.9)} \div \text{Replenishment Intervals (4/hr)}}$)] ÷ Body Weight (11 kg). Exposure time for outdoor scenarios is 1.5 hrs, as stated in the US EPA Residential SOPs (2012).
[c] MOE = margin of exposure; Oral MOE = oral NOAEL ÷ oral exposure, based on the short-term incidental oral NOAEL 31 mg/kg bw/d and a target MOE of 100.

Table 12 Short-term Postapplication Object-to-Mouth Exposure to Children from Indoor Environments

Exposure Scenario		Object Residue (ug/cm^2) [a]	Oral Dose (mg/kg bw/d) [b]	MOE [c]
Broadcast	Carpet	1.02	1.33E-02	2300
	Hard Surface	1.36	8.89E-03	3500
Perimeter/Spot (coarse and pin stream)	Carpet	5.10E-01	6.67E-03	4700
	Hard Surface	6.80E-01	4.44E-03	7000
Crack and Crevice	Carpet	1.02E-01	1.33E-03	23000
	Hard Surface	1.36E-01	8.89E-04	35000
Space Spray	Carpet	1.96E-02	2.56E-04	120000
	Hard Surface	2.61E-02	1.71E-04	180000

[a] Where Object Residue = Deposited Residue (ug/cm^2) × Fraction of residue transferred (6% for carpets and 8% for hard surfaces). Deposited residue based on maximum application rate provided on the labels.
[b] Where Oral Dose (mg/kg bw/d) = [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)) $^{\text{Number events per hour (14)} \div \text{Replenishment Intervals (4/hr)}}$)]÷ Body Weight (11 kg). Exposure times for carpets and hard surfaces were 4 and 2 hrs, respectively as stated in the US EPA Residential SOPs (2012).
[c] MOE = margin of exposure; Oral MOE = oral NOAEL ÷ oral exposure, based on the short-term incidental oral NOAEL 31 mg/kg bw/d and a target MOE of 100.

Table 13 Occupational Applicator Cancer Risk Estimates

Use Scenario	Form [a]	Application Equipment	Application Rates [b] (kg a.i./can)	Amount Handled per day [c] (cans)	Lifetime Average Daily Dose (LADD) [d] (mg/kg bw/d)		Cancer Risk [e]		
					Dermal	Inhalation	Dermal	Inhalation	Combined
Label PPE: (long sleeves, long pants, socks, chemical resistant gloves									
outdoor wasp and hornet nests	PP	pressurized spray can	7.50E-04	14	1.62E-04	2.16.E-04	1E-06	2E-08	1E-06

[a] PP = Pressurized Product
[b] Average label rate in kilograms of active ingredient per container (kg a.i./can).
[c] Based on the US EPA RED for piperonyl butoxide, which states that a commercial applicator can be expected to treat 7 homes per day and use 2 cans per home.
[d] Where LADD = (Treatment Frequency × Working Duration) ÷ (365 d/yr × Life Expectancy). A 50% dermal absorption factor was applied. Treatment frequency is 30 days/year.
[e] Where Risk = LADD × q_1*. Based on a q_1* value of 6.24E-03 $(mg/kg\ bw/d)^{-1}$.

Table 14 Residential Applicator Cancer Risk Estimates

Use Scenario	Form [a]	Application Equipment	Application Rates [b] (kg a.i./can)	Amount Handled per day [c] (cans)	Lifetime Average Daily Dose (LADD) [d] (mg/kg bw/d)		Cancer Risk [e]		
					Dermal	Inhalation	Dermal	Inhalation	Combined
PPE: (short sleeves, shorts, socks)									
indoor, broadcast	SN	trigger-spray bottle	1.10E-03	1	2.85E-05	3.96E-08	2E-07	2E-10	2E-07
indoor, perimeter/spot	SN	trigger-spray bottle	1.10E-03	0.5	1.43E-05	1.98E-08	9E-08	1E-10	9E-08
indoor, broadcast	PP	aerosol can	2.00E-03	1	2.26E-04	3.66E-06	1E-06	2E-08	1E-06
indoor, perimeter/spot (coarse); crack & crevice (pin stream)	PP	aerosol can	2.00E-03	0.5	1.13E-04	1.83E-06	7E-07	1E-08	7E-07
indoor bedbugs, perimeter/spot (pin stream)	PP	aerosol can	6.50E-04	0.5	3.67E-05	5.94E-07	2E-07	4E-09	2E-07
indoor, space spray	PP	aerosol can	1.20E-03	0.25	3.38E-05	5.49E-07	2E-07	3E-09	2E-07
indoor houseplants, perimeter/spot (coarse)	PP	aerosol can	9.00E-04	0.5	1.02E-05	1.65E-07	6E-08	1E-09	6E-08
outdoor, ornamentals	PP	aerosol can	5.00E-04	2	2.26E-05	3.66E-07	1E-07	2E-09	1E-07
outdoor space spray (fogger)	PP	aerosol can	2.84E-04	1	6.40E-06	1.04E-07	4E-08	6E-10	4E-08

[a] PP = Pressurized Product
[b] Average label rate in kilograms of active ingredient per container (kg a.i./can), except for outdoor space spray, which is a calculated application rate in kilograms of active ingredient per day (kg a.i./day).

[c] Based on standard assumptions from the US EPA Residential SOP (2012).
[d] Where LADD = (ADD × Treatment Frequency × Working Duration) ÷ (365 d/yr × Life Expectancy). A 50% dermal absorption factor was applied. Treatment frequency is 2-10 days/year.
[e] Where Risk = LADD × q_1*. Based on a q_1* value of 6.24E-03 (mg/kg bw/d)$^{-1}$.

Table 15 Residential Postapplication Dermal Cancer Risk Estimates

Use Scenario	Life stage	Deposited Residue (ug/cm^2)	Transferrable Residue [a] (ug/cm^2)	Transfer Coefficient [b]	Exposure Time [c] (hr/d)	Lifetime Average Daily Dose (LADD) [d] (mg/kg/d)	Cancer Risk	
						Dermal	Dermal [e]	Lifetime [f]
broadcast, carpet	adults	17.0	3.40E-01	4700	8	5.30E-03	3E-05	4E-05
	youths			3900	5	3.06E-04	2E-06	
	children			1300	4	4.23E-04	3E-06	
broadcast, hard surfaces	adults		5.10E-01	4700	2	1.99E-03	1E-05	1E-05
	youths			3900	1	9.19E-05	6E-07	
	children			1300	2	3.18E-04	2E-06	
perimeter/spot /coarse, carpet	adults	8.5	1.70E-01	4700	8	2.65E-03	2E-05	2E-05
	youths			3900	5	1.53E-04	1E-06	
	children			1300	4	2.12E-04	1E-06	
perimeter/spot /coarse, hard surfaces	adults		2.55E-01	4700	2	9.95E-04	6E-06	7E-06
	youths			3900	1	4.60E-05	3E-07	
	children			1300	2	1.59E-04	1E-06	
crack and crevice, carpet	adults	1.70	3.40E-02	4700	8	5.30E-04	3E-06	4E-06
	youths			3900	5	3.06E-05	2E-07	
	children			1300	4	4.23E-05	3E-07	
crack and crevice, hard surfaces	adults		5.10E-02	4700	2	1.99E-04	1E-06	1E-06
	youths			3900	1	9.19E-06	6E-08	
	children			1300	2	3.18E-05	2E-07	
space spray, carpets	adults	0.33	6.53E-03	4700	8	1.02E-04	6E-07	7E-07
	youths			3900	5	5.89E-06	4E-08	
	children			1300	4	8.13E-06	5E-08	
space spray, hard surfaces	adults		9.80E-03	4700	2	3.82E-05	2E-07	3E-07
	youths			3900	1	1.77E-06	1E-08	
	children			1300	2	6.10E-06	4E-08	

[a] Where Transferable Residue (µg/cm^2) = Residue (µg/cm^2) × Fraction Transferred (%). Deposited residues were calculated based on maximum label application rates or calculated amount applied using the US EPA Residential SOPs (2012) algorithms for all scenarios.
[b] Transfer Coefficient (cm^2/hr) 50th percentile values obtained from the US EPA Residential SOPs (2012).
[c] Exposure Time (hr/d) default values obtained from the US EPA Residential SOPs (2012).
[d] Where LADD = LADD = (ADD × Exposure Frequency × Years of Exposure) ÷ (365 d/yr × Life Expectancy). Dermal Dose (mg/kg bw/d) = (Transferable Residue (µg/cm^2) × 0.001 mg/µg × Transfer Coefficient (cm^2/hr) × Exposure Time (hr/d))/Body Weight (kg). Body weights of 80, 57 and 11 kg were used for adults, youths (11 <16 years), and children (1 <2 years) respectively, as stated in the US EPA Residential SOPs (2012). A dermal absorption factor of 50% was applied in the cancer risk assessment. Exposure frequency is 30 days/year.
[e] Where Risk = LADD × q_1*. Based on a q_1* value of 6.24E-03 (mg/kg bw/d)$^{-1}$.
[f] Where Lifetime Cancer Risk(LCR) = $CR_{children}$ + CR_{youths} + CR_{adults}. Shaded cells indicate those LCRs that are of concern. Estimated cancer risks of up to 3×10–6 are not of concern, when conservatisms in the risk assessment are considered (See Section 3.3.3.4).

Table 15 Residential Postapplication Dermal Cancer Risk Estimates (cont'd)

Use Scenario	Life stage	DFR or TR [a]	Transfer Coefficient [b]	Exposure Time [c] (hr/d)	Lifetime Average Daily Dose (LADD) [d] (mg/kg/d)	Cancer Risk	
					Dermal	Dermal [e]	Lifetime [f]
indoor houseplants	adults	1.29	200	0.5	5.36E-05	3E-07	4.E-07
	youths		160	0.25	2.39E-06	1E-08	
	children		110	0.25	2.93E-06	2E-08	
gardens	adults	1.29	3200	1.4	2.40E-03	2E-05	2.E-05
	youths		2600	0.7	1.09E-04	7E-07	
	children		1800	0.7	1.34E-04	8E-07	
trees	adults		1700	0.5	4.56E-04	3E-06	3.E-06
	youths		1400	0.25	2.09E-05	1E-07	
	children		930	0.25	2.47E-05	2E-07	
mattresses	adults	4.50	n/a		2.09E-04	1E-06	2E-06
	youths				1.66E-05	1E-07	
	children				3.79E-05	2E-07	

[a] The risk assessment was conducted without chemical-specific DFR since no studies were provided. Default values obtained from US EPA Residential SOPs (2012). Where DFR_t = Application Rate (kg ai/ha) × Transferrable a.i. × (1-(Dissipated Residue)$^{t\ (day\ after\ application\ (0))}$. Based on a time weighted average over 30 days using an average application rate of 8.93 µg/cm^2 for houseplants, gardens and trees, and 2 applications 2 weeks apart for gardens and trees.

[b] 50th percentile Transfer Coefficient (cm^2/hr) values obtained from the US EPA Residential SOPs (2012).

[c] 50th percentile Exposure Time (hr/d) values obtained from the US EPA Residential SOPs (2012).

[d] Where LADD = (ADD × Exposure Frequency × Years of Exposure) ÷ (365 d/yr × Life Expectancy). Absorbed Dermal Dose (mg/kg bw/d) = (DFR_t (µg/cm^2) × Transfer Coefficient (cm^2/hr) × Exposure Time (hr)/Body Weight (kg). Body weights of 80, 57 and 32 kg were used for adults, youths, and children (6 <11 years) as stated in US EPA Residential SOPs (2012). A dermal absorption factor of 50% was applied in the cancer risk assessment. Exposure frequency is 30 days/year.

[e] Where Risk = LADD × q_1*. Based on a q_1* value of 6.24E-03 (mg/kg bw/d)$^{-1}$.

[f] Where Lifetime Cancer Risk = $CR_{children}$ + CR_{youths} + CR_{adults} Shaded cells indicate those LCRs that are of concern.

Table 16 Postapplication Cancer Risk from Inhalation Exposure from Indoor Space Sprays

Exposure Scenario	Life Stage	Initial Concentration (mg/m^3) [a]	TWA Air Concentration (mg/m^3) [b]	LADD (mg/kg bw/d) [c]	Cancer Risk [d]	Lifetime Cancer Risk [e]
Space Spray	Adults	1.34	0.10	7.21E-05	5E-07	6E-07
	Youth			7.91E-06	5E-08	
	Children			2.15E-05	1E-07	

[a] Initial concentration expressed in mg/m^3 and is based on the maximum application arate, as average application rates were not available.

[b] For space sprays, a time-weighted average (TWA) air concentration value was determined over 120 minutes using the air exchange rate (ACH) of 1.26 (hr^{-1}) as per the US EPA SOP (US EPA, 2012).

[c] Where LADD = (ADD × Exposure Frequency × Years of Exposure) ÷ (365 d/yr × Life Expectancy). Exposure frequency is 30 days/year.

[d] Where Risk = LADD × q_1*. Based on a q_1* value of 6.24E-03 (mg/kg/d)$^{-1}$.

[e] Where Lifetime Cancer Risk = $CR_{children}$ + CR_{youths} + CR_{adults}

Table 17 Postapplication Cancer Risk from Inhalation Exposure from Indoor Surface Directed Sprays

Exposure Scenario	Life Stage	Mass of a.i. (mg) [a]	Exposure Time (hour) [b]	LADD (mg/kg bw/d) [c]	Cancer Risk [d]	Lifetime Cancer Risk [e]
Surface Directed Spray	Adults	2000	16	1.22E-04	8E-07	1E-06
	Youth		15	1.24E-05	8E-08	
	Children		18	4.16E-05	3E-07	

[a] Mass of a.i. expressed in mg and is based on an average application rate of 0.002 kg a.i./can.
[b] Exposure Time (hr/d) default values obtained from the US EPA Residential SOPs (2012).
[c] Where LADD = (ADD × Exposure Frequency × Years of Exposure) ÷ (365 d/yr × Life Expectancy) Exposure frequency is 30 days/year.
[d] Where Risk = LADD × q_1*. Based on a q_1* value of 6.24E-03 $(mg/kg/d)^{-1}$.
[e] Where Lifetime Cancer Risk = $CR_{children} + CR_{youths} + CR_{adults}$

Table 18 Postapplication Cancer Risk from Hand-to-Mouth Exposure to Children from Indoor Environments

Exposure Scenario		Hand Residue Loading (mg/cm^2) [a]	Oral Dose (mg/kg bw/d)	LADD (mg/kg bw/d) [b]	Cancer Risk [c]
Broadcast	Carpet	8.84E-04	2.08E-02	1.10E-04	7E-07
	Hard Surface	6.63E-04	7.80E-03	4.11E-05	3E-07
Perimeter/Spot/Bedbug (coarse and pin stream)	Carpet	4.42E-04	1.04E-02	5.48E-05	3E-07
	Hard Surface	3.32E-04	3.90E-03	2.05E-05	1E-07
Crack and Crevice	Carpet	8.84E-05	2.08E-03	1.10E-05	7E-08
	Hard Surface	6.63E-05	7.80E-04	4.11E-06	3E-08
Space Spray	Carpet	1.70E-05	4.00E-04	2.11E-06	1E-08
	Hard Surface	1.27E-05	1.50E-04	7.89E-07	5E-09

[a] Hand residue values in mg/cm^2.
[b] Where LADD = (ADD × Exposure Frequency × Years of Exposure) ÷ (365 d/yr × Life Expectancy). Exposure frequency is 30 days/year.
[c] Where Risk = LADD × q_1*. Based on a q_1* value of 6.24E-03 $(mg/kg\ bw/d)^{-1}$.

Table 19 Postapplication Cancer Risk from Hand-to-Mouth Exposure to Children from Outdoor Environments

Exposure Scenario		Hand Residue Loading (mg/cm^2) [a]	Oral Dose (mg/kg bw/d)	LADD (mg/kg bw/d) [b]	Cancer Risk [c]
Outdoor Aerosol Space Spray	Turf	1.38E-04	1.29E-03	6.79E-06	4.E-08

[a] Hand residue values in mg/cm^2.
[b] Where LADD = LADD = (ADD × Exposure Frequency × Years of Exposure) ÷ (365 d/yr × Life Expectancy). Exposure frequency is 30 days/year.
[c] Where Risk = LADD × q_1*. Based on a q_1* value of 6.24E-03 $(mg/kg\ bw/day)^{-}$

Table 20 Lifetime Cancer Risk Estimates

Lifestage	Carpet HtM LADD [a] (mg/kg/d)	Carpet HtM Cancer Risk [b]	Applicator Broadcast Dermal LADD [a] (mg/kg/d)	Applicator Broadcast Dermal Cancer Risk [b]	Applicator Broadcast Inhalation LADD [a] (mg/kg/d)	Applicator Broadcast Inhalation Cancer Risk [b]	PA Broadcast Dermal LADD [a] (mg/kg/d)	PA Broadcast Dermal Cancer Risk [b]	PA Broadcast Inhalation LADD [a] (mg/kg/d)	PA Broadcast Inhalation Cancer Risk [b]	Mattress Dermal LADD [a] (mg/kg/d)	Mattress Dermal Cancer Risk [b]
adult	n/a		2.26E-04	1E-06	3.66E-06	2E-08	5.30E-03	3E-05	1.22E-04	8E-07	2.09E-04	1E-06
youth			n/a				3.06E-04	2E-06	1.24E-05	8E-08	1.66E-05	1E-07
child	1.10E-04	7E-07					4.23E-04	3E-06	4.16E-05	3E-07	3.79E-05	2E-07

[a] Where LADD = (ADD × Exposure Frequency × Years of Exposure) ÷ (365 d/yr × Life Expectancy). Exposure frequency is 30 days/year.
[b] Where Risk = LADD × q_1*. Based on a q_1* value of 6.24E-03 $(mg/kg/d)^{-1}$.

Table 21 Total Lifetime Cancer Risk Estimates

Lifestage	Total LADD [a] (mg/kg/d)	Cancer Risk [b]	Lifetime Cancer Risk [c]
adult	5.86E-03	4E-05	4E-05[d]
youth	3.35E-04	2E-06	
child	6.13E-04	4E-06	

[a] Where Total LADD = sum of all selected LADD values for that lifestage.
[b] Where Risk = Total LADD × q_1*. Based on a q_1* value of 6.24E-03 $(mg/kg/d)^{-1}$.
[c] Where Lifetime Cancer Risk = $CR_{children} + CR_{youths} + CR_{adults}$ Shaded cells indicate those LCRs that are of concern.
[d] Not of concern if the broadcast application is not considered in the estimation of Total Lifetime Cancer Risk

Appendix V Environmental Exposure and Risk Assessment for Tetramethrin

Table 1 Fate and Behaviour in the Environment

Property	Test substance	Value	Transformation products	Comments	PMRA#
Abiotic transformation					
Hydrolysis		$t_{1/2}$ 13-25 d		Slightly persistent	1144063 2199810 2199811
Phototransformation on soil				No data	
Phototransformation in air		$t_{1/2}$ = 30 min (base on reaction with ozone)		Non persistent	2199810 2199811
Biotransformation					
Biotransformation in aerobic soil		$t_{1/2}$ 12.5-14 d		Non persistent	1172456
Biotransformation in anaerobic soil				No data	
Mobility					
Adsorption / desorption in soil		K_d = 8.5 Koc = 1249		Low mobility	1144064 2199810 2199811
Soil leaching				No data	
Volatilization				No data	
Field studies					
Field dissipation		DT50=3hr		California site	2199810 2199811
Field leaching					

Table 2 Toxicity to Non-Target Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Invertebrates					
Earthworm	Acute		No data available		
Bee	Oral		No data available		
	48 h-Contact		LD50 = 0.155 µg/bee	Highly toxic	1144082 1144083 2199810 2199811
	Foliar residue		<3 hrs post treatment		
Predatory arthropod	Contact		No data available		

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Parasitic arthropod	Contact		No data available		
Birds					
Bobwhite quail	Acute		LD50>2250 mg/kg bw	Practically non-toxic	1144071 2199810 2199811
	8 d-Dietary		LC50>5620 mg/kg bw		1144072 2199810 2199811
	Reproduction		No data available		
Mallard duck	Acute		No data		
	8 d-Dietary		LC50>5620 mg/kgbw		1144073 2199810 2199811
	Reproduction		No data		
Mammals					
Rat	Acute		LD50>5000 mg/kgbw	Practically non-toxic	2199810 2199811
	Dietary		No data		
	2-generation Reproduction		NOEC=25 mg/kg/day		
	2-generation Reproduction		NOEC=25 mg/kg/day		
Freshwater species					
Daphnia magna	48 h-Acute		LC50 = 35 µg ai/L NOEC=24 µg ai/L	Very highly toxic	1144076 2199810 2199811
Rainbow trout	96 h-Acute		LC50 = 3.7 µg ai/L NOEC=2.2 µg ai/L	Very highly toxic	1144078 2199810 2199811
Bluegill sunfish	96 h-Acute		LC50 = 16 µg ai/L NOEC<12 µg ai/L	Very highly toxic	1144077 2199810 2199811

Table 3 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Tetramethrin Are criteria met?
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes	Yes
Predominantly anthropogenic[2]	Yes	Yes

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Tetramethrin Are criteria met?
Persistence[3]	Soil	Half-life ≥ 182 days	No: Half-life = 12.5-14 d
	Water	Half-life ≥ 182 days	No: Half-life = 13-25 d
	Sediment	Half-life ≥ 365 days	Half-life not available
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (0.944 mPa) and Henry's Law Constant (6.801×10^{-2} $Pa\cdot m^3$/mole).
Bioaccumulation[4]	Log $K_{OW} \geq 5$		No: 4.6
	BCF ≥ 5000		Not available
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

[a] All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criterion may be refined if required (in other words, all other TSMP criteria are met).
[b] The policy considers a substance "predominantly anthropogenic" if, based on expert judgment, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[c] 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.
[d] The log K_{OW} and/or bioconcentraion factor (BCF) and/or bioaccumulation factor (BAF) are preferred over log K_{OW}.

Appendix VI Label Amendments for Products Containing Tetramethrin

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

End Use Product Label Statement Changes

I) The following statements must be removed from all product labels:

- Any statement describing "Repeat as Necessary" applications.
- Any statement targeting stray insects in the home.

II) The following statements must be added labels under 'Directions for Use' to all applicable indoor domestic product labels:

- "Do not use tetramethrin in food handling, storage or preparation areas while food is present."

III) The following alterations must be made to all labels under 'Directions for Use' for all commercial and domestic products targeting wasp and hornet nests:

Remove:
- Any statements concerning removal of the treated nest.

Add:
- "After 48 hours wear gloves to remove the treated nest."

IV) The following alterations must be made to all labels under 'Use Precautions' for all commercial products and all domestic products:

Add:
- "Keep out of reach of children and pets."

For all domestic products, remove:
- Any statement concerning re-entry.

Add as necessary:
- "Remove animals for a minimum of 1 hour when spraying room. Following treatment, ventilate all rooms, do not access for a minimum of 15 minutes and do not re-enter before ventilation is complete. Avoid contact with treated surfaces until dry."

V) The following statements must be included in a section entitled ENVIRONMENTAL HAZARDS:

All labels:

- "Toxic to aquatic organisms."

For tetramethrin products that are registered for outdoor use (not for products that are registered for indoor use only):

- " Toxic to bees. Do not spray bees."

References

A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT

Chemistry

PMRA No.	Title
1488670	1990, Munsell Color Determination of Neo-Pynamin. , DACO: 2.14.1
1488678	1990, Odor Determination of Neo-Pynamin. , DACO: 2.14.3
1488697	1990, Physical State Determination of Neo-Pynamin. , DACO: 2.14.2
1488699	1990, Density Determination of Neo-Pynamin. , DACO: 2.14.6
1488702	1990, Vapor Pressure Determination of Neo-Pynamin. , DACO: 2.14.9
1488703	1990, Stability of Neo-Pynamin Technical Grade. , DACO: 2.14.13
1488705	1990, Melting Point/Melting Range Determination of Neo-Pynamin. , DACO: 2.14.4
1488739	1990, Neo-Pynamin- Determination of Octanol/Water Partition Coefficient. , DACO: 2.14.11
1488741	1990, Neo-Pynamin- Determination of Water Solubility. , DACO: 2.14.7
1488743	1990, Organic Solvent Solubility Determination of Neo-Pynamin. , DACO: 2.14.8
1488960	1978, Analyses of [CBI removed] compounds in Neo-Pynamin technical grade. , DACO: 0.8,2.13.3
1487962	T-1-223 Memo for Neo-Pynamin (Tetramethrin). Submitted November 30, 1983.
1527508	1999, Enforcement Analytical Methods of Neo-Pynamin Technical Grade; Certification of Ingredient Limits of Neo-Pynamin Technical Grade; Preliminary Analysis of Neo-Pynamin Technical Grade., DACO: 2.13,2.13.1,2.13.2
1527569	Description of Starting Materials and Manufacturing Process; Discussion of the Formation of Impurities; Certification of Ingredient Limits; Analytical Methods to Verify Certifieid Limits of Neo-Pynamin Technical Grade., DACO: 2.11.1,2.11.2,2.11.4,2.13
1527582	1991, Storage Stability of Neo-Pynamin Technical Grade at Ambient Temperature for One Year., DACO: 2.14.14
1879911	1982, [Privacy Information Removed] Spectral data of Neo-Pynamin technical grade (GC, UV, IR, NMR & MS), DACO: 2.14.12

Toxicology

PMRA #	Reference
1143962	PRIMARY EYE AND SKIN IRRITATION TESTS WITH NEO-PYNAMIN IN RABBITS (IT-00-0217;2022), DACO: 4.2.4,4.2.5
1143963	SKIN SENSITIZATION TEST WITH NEO-PYNAMIN IN GUINEA PIGS (BUEHLER'S METHOD)(IT-00-0218;2023), DACO: 4.2.6
1143969	NEOPYNAMIN: SUBCHRONIC TOXICITY STUDY IN DOGS FINAL REPORT (IT-11-0098;343-127), DACO: 4.3.1
1143970	21-DAY DERMAL TOXICITY STUDY IN RATS WITH NEO-PYNAMIN FINAL REPORT (IT-11-0238;343-232), DACO: 4.3.4
1143971	THREE-MONTH INHALATION TOXICITY STUDY OF NEO-PYNAMIN IN RATS (DETERMINATION OF THE NO OBSERVED EFFECT LEVEL)(IT-10-0238;2279), DACO: 4.3.6
1143973	THREE-MONTH INHALATION TOXICITY STUDY OF NEO-PYNAMIN IN RATS (IT-10-0239;2189)(CONT'D ON ROLL#1039), DACO: 4.3.6
1143977	ACUTE ORAL AND DERMAL TOXICITIES OF NEOPYNAMIN IN RATS AND MICE (IT-70-0003), DACO: 4.2.1,4.2.2
1143978	ACUTE ORAL TOXICITY STUDY OF NEO-PYNAMIN IN RATS (IT-00-0224;2139), DACO: 4.2.1
1143979	ORAL DOSE RANGE FINDING STUDY IN DOGS NEOPYNAMIN FINAL REPORT (IT-00-0106;343-142), DACO: 4.2.9
1143980	ACUTE DERMAL TOXICITY OF NEOPYNAMIN IN RABBITS (IT-70-0207), DACO: 4.2.2

1144012	REPRODUCTION TEST OF NEOPYNAMIN PART 2: TERATOLOGY STUDY IN RATS (IT-01-0076), DACO: 4.5.2
1144013	REPRODUCTION TEST OF NEOPYNAMIN PART 3: TERATOLOGY STUDY IN RABBITS (IT-01-77;IT-91-0077), DACO: 4.5.2
1144015	CHRONIC TOXICITY STUDY IN RATS NEO-PYNAMIN TECHNICAL FINAL REPORT (IT-11-0097;343-117)(CONT'D ON ROLL#1040), DACO: 4.4.1
1144016	TWO-YEAR DIETARY ADMINISTRATION IN THE RAT NEO-PYNAMIN FINAL REPORT (IT-41-0024;343-107), DACO: 4.4.1
1144017	TWO-YEAR DIETARY ADMINISTRATION IN THE RAT NEO-PYNAMIN ADDENDUM I FINAL REPORT (IT-61-0203;343-195;343-107), DACO: 4.4.1
1144020	NEO-PYNAMIN: ONE GENERATION REPRODUCTION STUDY-RATS FINAL REPORT (IT-41-0042;343-106), DACO: 4.5.1
1144026	(CONT'D FROM ROLL#1039) CHRONIC TOXICITY STUDY IN RATS NEO-PYNAMIN TECHNICAL FINAL REPORT (IT-11-0097;343-117), DACO: 4.4.1
1144027	MUTAGENICITY OF TETRAMETHRIN (NEOPYNAMIN) (IT-70-0206), DACO: 4.4.2
1144028	IN VIVO CHROMOSOMAL ABERRATION TEST OF NEOPYNAMIN IN MOUSE BONE MARROW CELLS (IT-60-0197), DACO: 4.4.2
1144030	IN VITRO CHROMOSOMAL ABERRATION TEST OF NEO-PYNAMIN (PURE) WITH METABOLIC ACTIVATION IN CHINESE HAMSTER OVARY CELLS (CHO-K1) PRELIMINARY STUDY (IT-90-0215), DACO: 4.4.2
1144031	MUTAGENICITY TEST ON NEO-PYNAMIN IN AN IN-VITRO CYTOGENETIC ASSAY MEASURING CHROMOSOMAL ABERRATION FREQUENCIES IN CHINESE HAMSTER OVARY CELLS FINAL REPORT (IT-91-0216;10825-0-437;20990), DACO: 4.4.2
1144032	IN VIVO UNSCHEDULED DNA SYNTHESIS (UDS) ASSAY OF NEOPYNAMIN IN RAT HEPATOCYTES (IT-80-0213;1280), DACO: 4.4.2
1144033	REVERSE MUTATION TEST OF NEOPYNAMIN IN SALMONELLA TYPHIMURIUM AND ESHERICHIA COLI (IT-70-0205; MUT86021), DACO: 4.4.2
1144034	COMBINED CHRONIC TOXICITY AND ONCOGENICITY IN MICE: NEO-PYNAMIN FINAL REPORT (IT-61-0193;343-136)(CONT'D ON ROLL#1041), DACO: 4.4.1,4.4.2
1144035	COMBINED CHRONIC TOXICITY AND ONCOGENICITY IN MICE: NEO-PYNAMIN FINAL REPORT (IT-61-0193;343-136)(CONT'D ON ROLL#1041), DACO: 4.4.1,4.4.2
1144036	CHRONIC TOXICITY STUDY IN RATS NEOPYNAMIN TECHNICAL ADDENDUM TO FINAL REPORT (IT-31-0159;343-117), DACO: 4.4.1
1144038	CHRONIC TOXICITY STUDY IN RATS NEO-PYNAMIN TECHNICAL ADDENDUM TO FINAL REPORT (IT-61-0191;343-117), DACO: 4.4.1
1144039	CHRONIC TOXICITY STUDY IN RATS NEO-PYNAMIN TECHNICAL ADDENDUM III TO FINAL REPORT (IT-61-0204;343-117), DACO: 4.4.1
1144048	(CONT'D FROM ROLL#1040) COMBINED CHRONIC TOXICITY AND ONCOGENICITY IN MICE: NEO-PYNAMIN FINAL REPORT (IT-61-0193;343-136)(CONT'D ON ROLL#1042), DACO: 4.4.1,4.4.2
1144049	(CONT'D FROM ROLL#1040) COMBINED CHRONIC TOXICITY AND ONCOGENICITY IN MICE: NEO-PYNAMIN FINAL REPORT (IT-61-0193;343-136)(CONT'D ON ROLL#1042), DACO: 4.4.1,4.4.2
1144051	(CONT'D FROM ROLL#1041) COMBINED CHRONIC TOXICITY AND ONCOGENICITY IN MICE: NEO-PYNAMIN FINAL REPORT (IT-61-0193:343-136), DACO: 4.4.1,4.4.2
1144052	COMBINED CHRONIC TOXICITY AND ONCOGENICITY STUDY IN MICE NEO-

	PYNAMIN TECHNICAL AMENDMENT TO FINAL REPORT (IT-71-0210;343-136), DACO: 4.4.1,4.4.2
1171418	MOTOR ACTIVITY MEASUREMENTS IN MALE AND FEMALE MICE POSTNATALLY EXPOSED TO TETRAMETHRIN BY INHALATION (INCLUDING MEASUREMENTS OF MUSCARINIC ACETYLCHLOLINE RECEPTORS IN THE BRAIN)(T3059027;25749;IT-0277)(NEO-PYNAMIN)(SUBN# 96-0724), DACO: 4.5.12
1185235	BRIDGING ARGUMENT FOR USE OF REPRODUCTIVE TOXICITY DATA FOR NEO-PYNAMIN FORTE TO SUPPORT 83-4 GUIDELINE REQUIREMENT FOR NEO-PYNAMIN. ACUTE ORAL, SUBCUTANEOUS, INTRAPERITONEAL AND DERMAL NEO-PYNAMIN FORTE IN RATS AND MICE. H.KOHDA ET.AL.. DACO: 4.2.1
1185237	BRIDGING ARGUMENT FOR USE OF REPRODUCTIVE TOXICITY DATA FOR NEO-PYNAMIN FORTE TO SUPPORT 83-4 GUIDELINE REQUIREMENT FOR NEO-PYNAMIN. ACUTE AND SUBACUTE INHALATION TOXICITY STUDIES OF NEO-PYNAMIN FORTE IN RATS. T.SUZUKI ET.AL. DACO: 4.2.3,4.3.7
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