Proposed Registration Decision PRD2018-20

1R-*trans* Prallethrin, and Related End-use Products

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

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

Canada

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Overview

Proposed Registration Decision for 1R-*trans* Prallethrin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing registration for the sale and use of 98ETOC, Thermacell Area Repellent II, Thermacell Area Repellent II Camping Lantern, Thermacell Area Repellent II Bronze Camp Lantern, Thermacell Area Repellent II Compact Appliance, Thermacell Area Repellent II Lantern, Thermacell Area Repellent II Camp Lantern, Thermacell Skeeter Reliever Mosquito Repelling Lantern II, Thermacell Area Repellent II Flameless Torch and Thermacell Area Repellent II Patio Lantern, containing the technical grade active ingredient 1R-*trans* prallethrin, as an area repellent device to kill and repel mosquitos in an area up to 4.5 metres (m) from the device for up to 4 hours.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of 1R-*trans* prallethrin, Thermacell Area Repellent II, Thermacell Area Repellent II Camping Lantern, Thermacell Area Repellent II Bronze Camp Lantern, Thermacell Area Repellent II Compact Appliance, Thermacell Area Repellent II Lantern, Thermacell Area Repellent II Camp Lantern, Thermacell Skeeter Reliever Mosquito Repelling Lantern II, Thermacell Area Repellent II Flameless Torch and Thermacell Area Repellent II Patio Lantern (the end-use products hereinafter referred to as Thermacell II Devices).

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The *Pest Control Products Act* also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "…the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of Canada.ca.

Before making a final registration decision on 1R-*trans* prallethrin and Thermacell II Devices, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration Decision[4] on 1R-*trans* prallethrin and related end-use products, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

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

What Is 1R-*trans* Prallethrin?

1R-*trans* prallethrin is an insecticide which kills on contact by acting on the insect nervous system and also has mosquito repellent properties.

Health Considerations

Can Approved Uses of 1R-*trans* Prallethrin Affect Human Health?

Thermacell II Devices, containing 1R-*trans* prallethrin, are unlikely to affect your health when used according to label directions.

Potential exposure to 1R-*trans* prallethrin may occur when handling, and from the use of the Thermacell II Devices. 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). As such, sex and gender are taken into account in the risk assessment. Only uses for which the 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 dose levels more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide-containing products are used according to label directions.

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

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

In laboratory animals, the technical grade active ingredient 1R-*trans* prallethrin was of high acute toxicity via the oral route of exposure, of low acute toxicity via the dermal route, and was slightly acutely toxic via the inhalation route. Consequently, the signal word and hazard statement "DANGER-POISON" are required on the label. 1R-*trans* prallethrin was minimally irritating to the eyes and not irritating to the skin, and did not cause an allergic skin reaction.

All of the Thermacell II Devices use a cellulose mat impregnated with a liquid 1R-*trans* prallethrin formulation, which is vaporized upon heating. The liquid formulation was of low acute toxicity via the oral route of exposure. It was considered slightly acutely toxic via the inhalation route; consequently, the signal word and hazard statement "CAUTION-POISON" are required on the label. The cellulose mat impregnated with the 1R-*trans* prallethrin formulation was of low acute toxicity via the dermal route of exposure, was not irritating to the eyes or skin, and did not cause an allergic skin reaction.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of 1R-*trans* prallethrin to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoint for risk assessment was clinical signs of neurotoxicity. There is some concern for increased susceptibility of the young exposed to pyrethroids, such as 1R-*trans* prallethrin. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose level at which these effects occurred in animal tests.

Residues in Water and Food

The use pattern of the Thermacell II Devices is for non-food uses, thus dietary risks from food and water are not of concern.

Occupational Risks From Handling Thermacell II Devices

Thermacell II Devices are domestic-class products; therefore, no quantitative occupational assessments were conducted.

Risks in Residential and Other Non-Occupational Environments

Estimated risk for residential exposure is not of concern provided that use directions specified on the label are followed.

A risk assessment conducted for individuals performing different outdoor activities while they are in the vicinity of the Thermacell II Devices indicated that risks to adults, youth and children are not of concern when these products are used according to label directions.

Environmental Considerations

What Happens When 1R-*trans* Prallethrin Is Introduced Into the Environment?

1R-*trans* Prallethrin is not expected to pose risks of concern to the environment when used according to product label directions.

1R-*trans* Prallethrin enters the environment when used outdoors in various lanterns, lamps and other appliances, which heat the active ingredient and allow it to be released to the air as a repellent vapour against mosquitoes. Significant deposition of 1R-*trans* prallethrin in the environment is unlikely due to the volatile nature of the compound and limited exposure to the air, soil or water through this type of use. Exposure to non-target organisms is unlikely and risks of concern to the environment are not expected when the products are used according to label directions.

Value Considerations

What Is the Value of Thermacell II Devices?

Thermacell II Devices have value as they reduce the prevalence and nuisance from mosquitoes in the treated area.

While area repellents do not protect users from mosquito bites, they reduce the chance of getting bit by mosquitoes. Thermacell II Devices provide an area of mosquito repellency up to 4.5 m from the device for up to 4 hours.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the labels to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

No risks to human health are expected from using the Thermacell II Devices when used according to label directions.

Environment

A label statement indicating toxicity to aquatic organisms is required.

Next Steps

Before making a final registration decision on 1R-*trans* prallethrin and Thermacell II Devices, Health Canada's PMRA will consider any comments received from the public in response to this consultation document. Health Canada will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

Other Information

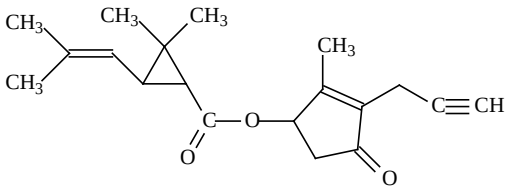
When the Health Canada makes its registration decision, it will publish a Registration Decision on 1R-*trans* pralletherin and related end-use products (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

1R-*trans* Prallethrin and Thermacell II Devices

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	1R-*trans* Prallethrin
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(*RS*)-2-methyl-4-oxo-3-prop-2-ynylcyclopent-2-enyl (1*RS*,3*RS*;1*RS*,3*SR*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate
2. Chemical Abstracts Service (CAS)	2-methyl-4-oxo-3-(2-propyn-1-yl)-2-cyclopenten-1-yl 2,2-dimethyl-3-(2-methyl-1-propen-1-yl)cyclopropanecarboxylate
CAS number	23031-36-9
Molecular formula	$C_{19}H_{24}O_3$
Molecular weight	300.4
Structural formula	
Purity of the active ingredient	93.0%

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product—98ETOC

Property	Result
Colour and physical state	Dark red liquid
Odour	No odour
Melting range	Not applicable
Boiling point or range	313.5 °C
Density	1.0330 g/mL

Vapour pressure at 20 °C	< 0.013 mPa
Henry's law constant at 20°C	4.8×10^{-6} atm mol/m^3
Ultraviolet-visible spectrum	No absorption between 300–800 nm
Solubility in water at 20 °C	8.03 g/mL
Solubility in organic solvents at 20 °C	Miscible with light mineral oil. Completely miscible with methanol and hexane when added in a 2:1 ratio.
n-Octanol-water partition coefficient (K_{ow})	Log K_{ow} = 4.49
Dissociation constant (pK_a)	The compound does not dissociate.
Stability (temperature, metal)	Stable to low temperatures and reducing agents. Not stable to high temperatures or oxidizing agents.

End-Use Products—Thermacell II Devices

Property	Result
Colour	Blue
Odour	Pleasant, aromatic-like
Physical state	Solid
Formulation type	device
Guarantee	1R-*trans* prallethrin … 10.86%
Container material and description	Metal, plastic, paper Foil sealed cellulose mat, rigid plastic butane cartridge, boxed and shrink wrapped 2–30 1.7 grams, mats 1–10 12 grams, cartridges 1–4 appliance
Density	0.519 g/mL
pH of 1% dispersion in water	Non-aqueous
Oxidizing or reducing action	No oxidizing or reducing action
Storage stability	Stable for 2 weeks at 54 °C
Corrosion characteristics	No corrosion after storage for 2 weeks at 54 °C
Explodability	Not explosive

1.3 Directions for Use

One 1R-*trans*-prallethrin mat is inserted into a Thermacell II device, which is turned on to heat up the mat. The heated 1R-*trans*-prallethrin mat releases a vapour which kills and repels mosquitoes in an area up to 4.5 m from the product. Devices do not work immediately, but should be left to run for 30 minutes. Devices are for outdoor use only, and should be used in an area protected from wind to ensure product performance.

1.4 Mode of Action

1R-*trans*-prallethrin is a contact pyrethroid insecticide which paralyzes and kills mosquitoes by preventing sodium channel closure, permanently depolarizing the axonal membrane. 1R-*trans*-prallethrin vapour also repels mosquitoes from the treated area.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

1R-*trans* prallethrin is a Type I synthetic pyrethroid insecticide comprised of two isomers, *cis* and *trans*, at a ratio of 2:98, respectively. It differs from prallethrin in terms of the isomeric ratio in that prallethrin is comprised of *cis*- and *trans*-isomers at a ratio of 20:80, respectively. Synthetic pyrethroids induce neurotoxic effects primarily by binding to voltage-dependent channels in neurons, thereby delaying the closing of sodium channels and causing the depolarization of neurons. This affects action potentials and results in either repetitive activity (Type I pyrethroids) or blockage of nerve conduction (Type II pyrethroids). Type I pyrethroids, such as 1R-*trans* prallethrin, lack an alpha-cyano moiety and typically induce a syndrome of behaviours described as the “T-syndrome”, which consist of aggressive sparring, altered sensitivity to external stimuli, and fine tremor progressing to whole-body tremor and prostration in rats.

The applicant requested to fulfill the toxicology data requirements for 1R-*trans* prallethrin with toxicology data for prallethrin. This request was supported with bridging information consisting of acute toxicity (with the exception of inhalation) data and an in vitro bacterial mutation assay for 1R-*trans* prallethrin, as well as comparative 28-day gavage neurotoxicity studies in rats with both isomeric ratios.

On the basis of the results of these studies, which identified similar effects and effect levels for 1R-*trans* prallethrin and prallethrin, these two chemicals are considered toxicologically equivalent and the request to bridge to the prallethrin toxicology database was supported.

The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to characterize the potential health hazards associated with 1R-*trans* prallethrin.

The absorption, distribution, metabolism, and excretion of C^{14}-radiolabelled 1R-*trans* or 1R-*cis* prallethrin were investigated in rats following gavage administration of single or repeated low oral doses, a single high oral dose, or a single low subcutaneous dose. For the repeated-dose regimen, rats were administered non-radiolabelled test material for 14 days followed by administration of radio-labelled test material on day 15. In all cases, the test material was rapidly absorbed, distributed, metabolized, and excreted in the urine and feces. Levels of radioactivity in blood and tissues peaked within three hours of administration. The highest levels of radioactivity seven days post-dosing were found in the kidneys, liver and whole blood for both sexes, both isomers and all dose groups. Radioactivity in tissues seven days after administration of single or repeated doses accounted for less than 0.5% of the administered dose, with females retaining slightly greater amounts in tissues compared to males in one study. Urine was the major route of elimination for the *trans*-isomer and feces was the major route of elimination for the *cis*-isomer. The pattern of excretion was similar in both sexes; however, a greater proportion of radioactivity was excreted in the urine of females compared to males in one study. Elimination via expired air was negligible. The major pathway of elimination of prallethrin involved ester cleavage to form a number of cyclopentenyl-derived products and their corresponding conjugates. There was no difference between sexes or administration routes in the nature or amount of metabolites in the excreta. A toxicokinetic investigation in male mice that were administered a single high dose of C^{14}-radiolabelled prallethrin via gavage identified the highest tissue residues in kidney and liver 24 hours post-dosing, and confirmed that prallethrin reached the bone marrow under the same conditions as in the mouse micronucleus assay.

In acute toxicity testing in rats, 1R-*trans* prallethrin was highly toxic via the oral route of exposure, of low toxicity via the dermal route, and was slightly toxic via the inhalation route. 1R-*trans* prallethrin was minimally irritating to the eyes, and not irritating to the skin of rabbits. It was not a dermal sensitizer when tested in guinea pigs using the Buehler method. Clinical signs of toxicity following acute oral, dermal and inhalation exposure to 1R-*trans* prallethrin or prallethrin were consistent with effects following exposure to Type I pyrethroids and included tremors, decreased spontaneous activity, irregular respiration, salivation, and limb paralysis.

The Thermacell II Devices contain a cellulose mat impregnated with a liquid 1R-*trans* prallethrin end-use formulation which is vaporized upon heating. The liquid formulation was of low acute toxicity in rats via the oral route of exposure. Based on the results of the acute inhalation toxicity study with 1R-*trans* prallethrin in rats, it is considered slightly acutely toxic. The cellulose mat was of low acute dermal toxicity to rats, not irritating to the eyes or skin in rabbits, and negative in a skin sensitization study in guinea pigs using the Buehler method.

Repeat-dose administration of prallethrin to rats, dogs and rabbits via oral gavage or capsule resulted in clinical signs of neurotoxicity. Similar clinical signs were not observed in mice or rats following dietary administration. Clinical signs of neurotoxicity included tremors, convulsions, salivation, irregular respiration or decrease in spontaneous activity, and appeared within half an hour to two hours after dose administration. This is consistent with the toxicokinetic profile of prallethrin in which tissue levels peaked within three hours after oral administration. The dog appeared to be the most sensitive with respect to clinical signs of neurotoxicity. No neuropathological lesions were observed in the central and peripheral nervous system tissues in any of the studies.

The liver (mice, rats and dogs), kidneys (mice and rats) and thyroid (rats) were identified as targets of toxicity for prallethrin following repeated dietary exposure in mice and rats, or repeated oral capsule administration in dogs. In addition to weight changes in these organs, histopathological alterations were observed in some studies including hepatocyte vacuolation, hypertrophy, and histiocytic infiltration in mice and rats. An increased incidence of pigment in the renal tubular epithelium of the kidneys was observed in dogs following 52 weeks of exposure to prallethrin via oral capsule, as well as in the two-generation dietary reproductive toxicity study in rats. Thyroid effects included an increased number of small follicles and follicular hypertrophy or hyperplasia which were observed in rats in the 90-day dietary and the reproductive toxicity study, respectively. Effects on the thyroid were not observed following chronic dietary administration in rats, the difference possibly attributed to the fact that the chronic study was conducted with a different strain of rat (Fischer) from that utilized in the balance of the toxicology database (Sprague Dawley).

There were some effects on spleen, thymus, and bone marrow in the dog studies. Although spleen weights were decreased in the 52-week study, there were no histopathological correlates. Decreased thymus weights, along with lymphocyte disintegration in the thymus and other lymphatic organs, were observed in the decedent females of the 90-day study. Thymus weights were increased, however, in the 52-week study and were without histopathological correlates. Proliferation of granulocyte juvenile cells in the sternal and femoral bone marrow, accompanied by a significantly altered hematopoietic cell composition, was observed in one male in the 90-day study. However, no such lesions were observed following 52-weeks of dosing and no effects on blood total or differential leucocyte counts were noted in either dog study. Overall, these findings, coupled with the lack of adverse effects on the organs of the immune system in rats and mice, do not suggest that 1R-*trans* prallethrin is an immunotoxicant.

Following repeated dermal exposure of rats to prallethrin for 21 days, clinical signs of neurotoxicity were observed, including prolonged gaze with fixed posture, increased vocalization, twitching, writhing spasms, tremors, increased pawing behaviour and increased sensitivity to stimuli. Clinical signs appeared within the first few days of dosing and disappeared during the 6-hour treatment period. Body weight loss and decreases in body weight gain were also observed in this study. Transient mild skin reactions were noted only at the highest dose level.

In a 28-day inhalation toxicity study in which rats were exposed to prallethrin aerosolized in deodorized kerosene, findings included clinical signs suggestive of neurotoxicity (decreased spontaneous activity and urinary incontinence), as well as irregular respiration and nasal discharge. At a higher concentration, increased salivation was noted. Vehicle control animals which received only the deodorized kerosene also displayed these clinical signs; however, signs were observed earlier, or at a higher incidence, in the prallethrin test groups and were therefore considered to be exacerbated by exposure to prallethrin.

There was some indication in the database of increased toxicity with increased duration of dosing, as evidenced in mice when comparing the effect levels in the dietary 90-day and 80-week prallethrin toxicity studies. In addition, there was some indication of increased toxicity in rats over the intermediate- to long-term duration; however, the comparison for rats was confounded by the use of different strains in the subchronic and chronic dietary studies with prallethrin. Increased duration of dosing did not appear to have an effect on toxicity in dogs. No pronounced sex sensitivity was observed in the available database. Although female dogs seemed more sensitive than their male counterparts following oral capsule dosing for 90 days, these differences were not observed following dosing at comparable dose levels for 52 weeks.

In long-term dietary studies conducted with prallethrin, there was no evidence of oncogenicity in rats or mice. Prallethrin tested negative in a battery of in vivo and in vitro genotoxicity studies, with the exception of one in vitro study. Positive results for inducing structural aberrations (chromatid gaps, breaks and exchanges) occurred in Chinese hamster ovary cells (CHO-K1 cells) in the presence of metabolic activation. Based on the fact that prallethrin was negative in the in vivo micronucleus assay and unscheduled DNA synthesis assay, the overall weight of evidence did not suggest prallethrin, and thus 1R-*trans* prallethrin, had genotoxic potential.

Prallethrin did not adversely affect fertility or reproductive performance in rats following dietary exposure over two generations. Effects in offspring were limited to decreases in body weight occurring at dose levels that also caused toxicity to the dams as evidenced by decreases in body weight and body weight gain, as well as pathology in the liver, thyroid, and pituitary.

Developmental toxicity studies were conducted with prallethrin in rats and rabbits via oral gavage administration. No evidence of developmental toxicity was observed in guideline studies at dose levels that resulted in maternal toxicity which included clinical signs of neurotoxicity and reduced body weights, and in the case of the rat study, death at the highest dose level. In the rabbit developmental toxicity study report, it was stated that tremors occurred in dams in the range-finding study at 100 mg/kg bw/day. The time of occurrence was not specified nor was the range-finding study available. However, there were no signs of maternal toxicity at this dose level in the more robust main study. A non-guideline modified developmental toxicity study in rats conducted via the subcutaneous route was also available which, in addition to examination of fetuses following caesarean section, included additional investigations on pups from dams that were allowed to deliver naturally. These pups were assessed for postnatal development, sensory functions, learning ability and reproductive performance. There were no treatment-related effects on these parameters in offspring or on fetal development. Maternal animals displayed clinical signs of neurotoxicity in addition to decreased body weight gain and food consumption at this dose level. The results of the postnatal developmental phase were considered supplemental due

to limited group size and extent of histopathological assessment of nervous system tissue. Moreover, the study was not conducted via a relevant route of exposure for risk assessment purposes. That being said, the study did provide some information that contributes to the overall interpretation of effects on the young.

The neurotoxic potential of 1R-*trans* prallethrin and prallethrin was investigated in rats. An acute gavage neurotoxicity study and a 90-day dietary neurotoxicity study were available for prallethrin in addition to the aforementioned subcutaneous modified developmental toxicity study. Comparative 28-day gavage neurotoxicity studies were also provided for 1R-*trans* prallethrin and prallethrin. Following a single oral dose of prallethrin, decreased exploratory behaviour was observed at the time of peak effect (2 hours). Reduced total motor activity and total number of rears were also observed, with the decrease in motor activity persisting until day 14 in male rats. In females, mortality and transient tremors were also observed. Following repeated oral dosing for 28 days, mortality, tremors, convulsions, and prostrate posture were observed with prallethrin and 1R-*trans* prallethrin at the same dose levels. Ataxia, impairments to mobility and gait, uncoordinated air righting reflex, a more energetic startle response and decreased rearing were additionally noted in the study with 1R-*trans* prallethrin. There was no evidence of neurotoxicity in the 90-day dietary neurotoxicity study in rats, consistent with findings in other dietary studies in the prallethrin database. As previously noted, there were no neuropathological findings in any of the studies.

Studies from the published literature indicate that pharmacodynamic 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 P450 enzyme families. Consequently, pyrethroid concentrations in target tissues may be higher in young animals than in adults given the same dose level. In general, pyrethroid neurotoxicity is correlated to peak concentrations of the compound; gavage dosing results 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 developmental neurotoxicity study does not consider time-to-peak-effect and may miss the window of peak toxicity for the pyrethroids. Accordingly, a developmental neurotoxicity study was not required for 1R-*trans* prallethrin.

Recently, the results of work undertaken by the Council for Advancement of Pyrethroid Human Risk Assessment to address potential sensitivity of the young were submitted to the PMRA. The Council for Advancement of Pyrethroid Human Risk Assessment data may have implications to the entire class of pyrethroids, and consequently these data are being addressed separately from assessments for individual pyrethroids. Until these data are evaluated, residual uncertainty regarding sensitivity of the young is reflected in the form of a database uncertainty factor.

Results of the toxicology studies conducted on laboratory animals with prallethrin and 1R-*trans* prallethrin and its associated end-use products are summarized in Appendix I, Tables 1 and 2. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 3.

3.1.1 Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA. Information on the reporting of incidents can be found on the PMRA website. As of 21 March 2018, four human and 15 domestic animal incidents involving prallethrin were submitted to the PMRA. All incidents involved American prallethrin products co-formulated with other active ingredients.

The human incidents were classified as major (three American incidents) or minor (1 Canadian incident). None of the three major incidents were considered to be related to the reported product. The symptoms reported in incidents either resulted from factors other than the described pesticide exposure or were not typical of the signs and symptoms usually associated with the reported active ingredients. The Canadian incident involved an American prallethrin product and the individual reported non-specific minor tongue paraesthesia after using the product.

Nine incidents, involving 11 American domestic animal deaths, were considered to be related to the reported pesticide exposure. Reported exposure scenarios involved cats or dogs coming in contact with, or resting in areas treated with a product, as well as pet rodents or fish exposed to a product when surrounding areas were treated. The signs reported in animals included seizure, difficulty walking, pupil dilation, drooling or dyspnea. The signs could not be directly attributed to prallethrin as the prallethrin products reported in the animal incidents are co-formulated with other active ingredients. Furthermore, the products involved in the incidents have a different use pattern than the proposed product and therefore, the reported exposure scenarios are of limited relevance.

Based on the incident report review, no additional risk mitigation measures are proposed.

3.1.2 *Pest Control Products Act* Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the standard complement of required studies, including gavage developmental toxicity studies in rats and rabbits and a dietary two-generation reproductive toxicity study in rats. Additionally, a non-guideline modified developmental toxicity study in rats conducted via the subcutaneous route was available for prallethrin which also examined sensory functions and functional learning ability in pups exposed in utero.

With respect to concerns relevant to the assessment of risk to infants and children, there was no evidence suggestive of increased sensitivity of the young compared to parental animals in the reproductive and guideline developmental toxicity studies. In these developmental toxicity studies, there were no effects in rat or rabbit fetuses at maternally toxic dose levels. In the two-generation reproductive toxicity study, decreases in body weight in offspring were observed at a

dose level that also elicited maternal toxicity. In the subcutaneous modified developmental toxicity study in rats, there were no adverse effects on postnatal development, sensory functions, learning ability or reproductive performance at maternally toxic dose levels.

Young animals have incomplete maturation of enzyme systems which detoxify pyrethroids and thus may be more susceptible due to higher and prolonged brain concentrations, compared to adults. The database lacks additional information to fully characterize the potential for juvenile sensitivity to the neurotoxic effects of 1R-trans prallethrin. Thus, an adequate assessment of sensitivity of the young is currently not available, and residual uncertainty remains concerning susceptibility of the young to potential neurotoxic effects of 1R-trans prallethrin. Recently, the results of work undertaken by the Council for Advancement of Pyrethroid Human Risk Assessment to address potential sensitivity of the young were submitted to the PMRA. Until these data are evaluated, this residual uncertainty is reflected in the form of a database uncertainty factor of threefold in the risk assessment. Since these concerns were addressed with a database uncertainty factor, the Pest Control Products Act factor was reduced to onefold.

3.2 Acute Reference Dose

An acute reference dose is not required as there are no proposed food uses, and contamination of drinking water sources is not expected.

3.3 Determination of Acceptable Daily Intake

An acceptable daily intake is not required as there are no proposed food uses, and contamination of drinking water sources is not expected.

3.4 Residential Risk Assessment

3.4.1 Toxicological Reference Values

Residential exposure to the Thermacell II Devices is characterized as short-term in duration and is predominantly by the inhalation route for adults, youth and children.

Short- and Intermediate-term Inhalation

For short- and intermediate-term inhalation risk assessments, the No Observed Adverse Effect Concentration (NOAEC) of 0.001 mg/L (0.174 mg/kg bw/day) from the 28-day inhalation toxicity study with prallethrin in rats was selected. At the Lowest Observed Adverse Effect Concentration (LOAEC) of 0.0044 mg/L (0.765 mg/kg bw/day), decreased spontaneous activity, irregular respiration, nasal discharge and urinary incontinence were observed. This short-term study represents the relevant route of exposure for this scenario and was considered appropriate for assessment of the intermediate-term duration scenarios as well, since there was no pronounced evidence in the supporting toxicology database of increased toxicity with increased duration of dosing over the short- to intermediate-term duration. Use of this study is considered protective of all populations including the unborn children of exposed women. The target Margin of Exposure (MOE) is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a database uncertainty factor of

threefold for concerns relating to potential sensitivity of the young. As discussed in the *Pest Control Products Act* Hazard Characterization section, residual uncertainty regarding susceptibility of the young has been captured under the database uncertainty factor. Consequently, the *Pest Control Products Act* factor was reduced to onefold.

3.4.2 Residential Exposure and Risk

3.4.2.1 Residential Handler Exposure and Risk Assessment

These domestic-class insect repellents are ready-to-use and do not require mixing or loading. However handlers may replace or insert the mat into the devices. These exposures are expected to be short-term in duration. The USEPA Residential SOP (standard operating procedure) (2012) for the candles, coils, torches and mats (CCTM) scenario under outdoor fogging/misting systems considers handler exposure, both dermal and inhalation, to be negligible as the application activity (in other words, product activation) does not involve application (for example, spraying liquids or spreading granules) in the typical sense.

3.4.2.2 Postapplication Residential Exposure and Risk

This risk assessment addressed only the postapplication inhalation exposure for adults, youth and children. Dermal and incidental oral exposures were not estimated since the USEPA Residential SOP (Section 5) considers them insignificant for this scenario. Potential inhalation exposure is expected from the use of these products to people performing different outdoor activities while they are in the vicinity of these domestic-class products.

3.4.2.2.1 Postapplication Inhalation Exposure and Non-Cancer Risk Assessment

Inhalation exposure to residues resulting from the airborne emission, released by the products when in use, is expected for adults, youth and children, since the label does not prohibit children from being in the vicinity of these products.

Section 5 (CCTMs) of the USEPA Residential SOP provides standard methods for estimating potential inhalation exposure to pesticides from the use of CCTMs for the purpose of outdoor pest control.

The SOP uses the well-mixed box model to estimate inhalation exposure to CCTMs. This model considers air concentrations within an enclosed, fixed volume (in other words, a box), over time and during the constant emission of a pesticide from such products. Therefore, using the well-mixed box model is a conservative approach for estimating exposures occurring on an open patio or deck where dissipation is expected to be greater than that in an enclosed space, as depicted by the model.

The mats of the Thermacell II Devices contain 1R-*trans* prallethrin at a guarantee of 10.86%. The directions specify to use one mat per 20 m^2 (4.5 m × 4.5 m). This area fits within the typical area identified in the SOP (21.2 m^2; 4.6 m × 4.6 m).

Airflow is defined as the volume of air that uniformly passes through a given area over a specified period of time. The airflow used in this risk assessment is that of calm air (0.1 m/s) passing through a cross-sectional area of treated space (11 m^2).

Vaporization efficiency is the percentage of active ingredient in the product released as a result of heating and which becomes available for inhalation. For an actual estimation of the vaporization efficiency, the registrant conducted a study to estimate the weight loss from 10 Thermacell II mosquito repellent mats, containing *trans:cis* prallethrin in a ratio of 98:2. The product used in the study is similar to the one proposed for registration. The mats were burned on a pre-heated MR300 emitter, at approximately 170 °C for a duration of four hours. The heat from the MR300 emitter was monitored each minute by a picologger data unit. The average weight of the mat was 1.6953 g, which was comprised of a blank cellulose mat and the liquid concentrate. The weight loss was calculated by subtracting the weight of the mat after burning from that at the start. To further confirm the amount of active ingredient lost, the replicates of the burned mats were assayed, along with the unburned mats, using a high-performance liquid chromatography method. Despite the minor limitations, this study was considered acceptable to estimate the vaporization efficiency.

Each mat, at the start of the experiment, contained an average of 191.35 mg a.i. ± 1.87, which is slightly higher than that proposed. After four hours of burning, an average of 83.65 mg a.i. ± 17.59 remained in the burned mats. Thus, an average of 107.7 mg a.i. was released from the mat resulting in a vaporization efficiency of 56.3% (107.7/191.35=0.563), which was considered in the inhalation risk assessment.

The risk estimates in Table 3.4.2.2-1 indicate that inhalation exposure to adults, youth and children (1<2 years) resulted in MOEs exceeding the target MOE of 300. Therefore, no risks of concern are expected from the postapplication inhalation exposures to adults, youth and children.

Table 3.4.2.2-1 Inhalation Exposure Risk Estimates

Life Stage	Emission rate[1] (mg a.i./hr)	IR[2] (m^3/hr)	Airflow Q[3] (m^3/hr)	V_E[4]	Exposure Time[5] (hrs/day)	Volume of Treated space[6] (m^3)	Exposure[7] (mg/kg/day)	Inhalation MOE[8, 9]
Adult > 16	47.75	0.64	3960	0.563	2.3	51	0.000124	1400
Youth 11 < 16 years	47.75	0.63	3960	0.563	1.9	51	0.000142	1200
Children 1 < 2 years	47.75	0.33	3960	0.563	2.3	51	0.000466	370

[1]ER = emission rate = The amount of a.i. in mat (191 mg ai) × number of products used (1)/useful life of product (4h)
[2]IR = Inhalation rate (m^3/hr)
[3]Q = airflow (m^3/hr) = air velocity (0.1 m/s) × conversion factors (s/h) × cross-section of outdoor space treated (11 m^2)
[4]V_E = vaporization efficiency = 56.3% based on study estimating the amount of active ingredient lost after 4 hours
[5]ET = exposure time (hr/day; Exposure factors handbook, 2011, using the arithmetic mean)
[6]V= volume of treated space (51m^3; USEPA Residential SOP, 2012)
[7]E = exposure (mg/kg bw/day)

$$E = [((IR \times \bullet V_E \times ER/Q) \times (ET - v/Q)) \times AF]/ BW$$

AF= inhalation absorption factor (100%)
BW= Body weight (kg); Adults: 80, Youths: 57 and Children 1 < 2: 11.

[8]MOE = Inhalation NOAEL / Exposure

[9]Inhalation NOAEL is 0.174 mg/kg bw/day; Target MOE = 300.

3.4.2.2.2 Postapplication Dermal and Non-Dietary Ingestion Exposure Assessment

The 2012 USEPA Residential SOP for CCTM specifies that these exposures are expected to be negligible. No residues deposited on patios or other surfaces are expected from using CCTM products. Due to the particle sizes released from the activation of CCTM products, particles are expected to remain airborne rather than be deposited on surfaces. Therefore, dermal and incidental oral postapplication exposures to surface residues do not need to be quantitatively assessed and are not aggregated with postapplication inhalation exposure.

3.5 Cancer Assessment

There was no evidence of carcinogenicity; therefore, a cancer risk assessment was not necessary.

3.6 Cumulative Assessment

The *Pest Control Products Act* requires the PMRA to consider the cumulative effects of pest control products that have a common mechanism of toxicity. 1R-*trans* prallethrin belongs to a group of insecticides commonly known as the pyrethroids. Pyrethroids and pyrethrins have a common mechanism of toxicity wherein they 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.

3.7 Food Residues Exposure Assessment

A food residue exposure assessment was not required for the non-food/feed uses of Thermacell II Devices.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

1R-*trans* prallethrin is not expected to persist in the terrestrial environment as it is subject to rapid aerobic soil biotransformation, with 50% dissipation time (DT_{50}) values of 3.4 to 6.9 days under laboratory conditions. Hydrolysis is not an important route of transformation at environmentally relevant pH. Based on the vapour pressure (<0.013 mPa at 20 ºC) and the Henry's law constant (4.8×10^{-6} atm mol/m^3 at 20 ºC), 1R-*trans* prallethrin is expected to volatilize from water surfaces or moist soils.

This is consistent with the proposed use of the end-use products. The photodegradation half-life of 1R-*trans* prallethrin in water was 13.6 hours (irradiated), indicating that breakdown in water is rapid. Movement through soil is not expected to be significant for IR-*trans* prallethrin.

Data on the environmental fate and behaviour of 1R-*trans* prallethrin are summarized in Appendix I, Table 4.

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. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level).

The environmental risk assessment for 1R-*trans* prallethrin was qualitative as the use patterns of the end-use products will result in limited environmental exposure. The exposure cannot be quantified using standard scenarios for environmental risk assessment, as the use of these products will not result in significant deposition of the active ingredient on soil, water, or plants.

4.2.1 Risks to Terrestrial Organisms

1R-*trans* prallethrin is practically non-toxic to earthworms, slightly toxic to birds and wild mammals, and highly toxic to bees (Appendix I, Table 5). When the active ingredient is released as a vapour from insecticide-impregnated mats, it acts as mosquito repellent in relatively small areas before it dissipates further into the surrounding air. Given the method of use of the end-use products in impregnated mats, the exposure and, therefore, any risk to non-target terrestrial organisms will be negligible.

4.2.2 Risks to Aquatic Organisms

1R-*trans* prallethrin is very highly toxic to aquatic organisms (Appendix I, Table 5). However, due to the method of use of the end-use products, the risk to non-target aquatic organisms will be negligible. Exposure to the aquatic environment would be expected to be negligible since the active ingredient enters the environment as a vapour and will then dissipate rapidly into the air. Deposition onto water surfaces would not be expected.

5.0 Value

Value information, submitted in support of the claim that the Thermacell II Devices will kill and repel mosquitoes, consisted of three efficacy trials. Two trials were conducted outdoors in screened enclosures and tested the product against mosquitoes. One of these semi-field trials tested mosquito repellency, while the second tested mosquito mortality. A laboratory trial was also submitted as additional supporting information. The outdoor repellency trial demonstrated that Thermacell II Devices will repel at least 80% of mosquitoes from an area up to 4.5 m from the device. The mortality trial demonstrated that these products will also kill at least 50% of mosquitoes within the treated area. The results of the laboratory trial were consistent with the semi-field trial results.

Registered alternative active ingredients used as area repellents against mosquitoes are d-*cis*/*trans*-allethrin, metofluthrin, garlic juice, and garlic oil. While 1R-*trans*-prallethrin is a new mosquito area repellent active ingredient, it does not provide a new mode of action against mosquitoes. However, the development of resistance to 1R-*trans*-prallethrin mosquito area repellents is not expected.

Thermacell II Devices reduce the prevalence and nuisance from mosquitoes in the treated area. While area repellents do not protect users from mosquito bites, they reduce the chance of getting bit by mosquitoes. The submitted value information was sufficient to support a claim that Thermacell II Devices will kill and repel mosquitoes from an area up to 4.5 m from the device for up to 4 hours.

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), bioaccumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, 1R-*trans* prallethrin was assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- 1R-*trans* prallethrin does not meet all Track 1 criteria, and is not considered a Track 1 substance (See Appendix I, Table 6 for comparison with Track 1 criteria).
- 1R-*trans* prallethrin does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

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

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

- Technical grade 1R-*trans* prallethrin and its end-use products, Thermacell II Devices**,** do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

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

7.0 Summary

7.1 Human Health and Safety

The toxicology database is considered adequate to characterize the potential health hazards associated with 1R-*trans* prallethrin. The primary target of toxicity was the nervous system. The liver, kidneys and thyroid were also target organs. There was no evidence of carcinogenicity in rats or mice after longer-term dosing and 1R-*trans* prallethrin is not considered genotoxic. There was no evidence of malformations or effects suggestive of immune dysregulation. There is some concern for increased susceptibility of the young exposed to pyrethroids, such as 1R-*trans* prallethrin. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

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

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

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

The non-cancer inhalation risks to children, youth and adults were acceptable. Dermal and incidental non-dietary oral ingestion exposures were not assessed as the 1R-*trans* prallethrin particles released from the activation of the products are expected to remain airborne and not to be deposited on surfaces.

In light of the above, the residential exposure from using the Thermacell II Devices according to label directions does not likely to result in any human health risks of concern.

7.2 Environmental Risk

1R-*trans* prallethrin is to be used as an outdoor mosquito repellent when heated and released to the air from lanterns, lamps and other appliances. When used according to the label directions of the Thermacell II Devices, environmental releases of 1R-*trans* prallethrin are expected to be minimal and risks of concern to the environment are not expected.

7.3 Value

Thermacell II Devices reduce the prevalence and nuisance from mosquitoes in the treated area. The submitted value information supported a claim that the Thermacell II Devices will kill and repel mosquitoes in an area up to 4.5 m from the device for up to 4 hours.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing registration for the sale and use of 98ETOC and Thermacell II Devices, containing the technical grade active ingredient 1R-trans prallethrin, as an area repellent device to kill and repel mosquitos in an area up to 4.5 m from the device for up to 4 hours.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

List of Abbreviations

µg	micrograms
a.i.	active ingredient
AD	administered dose
atm	atmosphere
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
bwg	body weight gain
CAS	Chemical Abstracts Service
CCTM	candles, coils, torches and mats
CEPA	*Canadian Environmental Protection Act*
CHO	Chinese hamster ovary
cm	centimetres
d	days
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
dw	dry weight
EC_{50}	effective concentration on 50% of the population
E_bC_{50}	effect concentration 50% (total biomass)
E_rC_{50}	effect concentration 50% (growth rate)
EEC	environmental exposure concentration
F_1	first filial generation
F_2	second filial generation
fc	food consumption
g	gram
GD	gestation day
h	hour
ha	hectare(s)
HDT	highest dose tested
IUPAC	International Union of Pure and Applied Chemistry
ICR	Institute of Cancer Research
kg	kilogram
km	kilometre
K_{oc}	organic-carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
LOC	level of concern
LOEC	Low Observed Effect Concentration
LOQ	limit of quantitation
m	metres

mg	milligram
mL	millilitre
MAS	maximum average score
MIS	maximum irritation score
MOE	margin of exposure
N/A	not applicable
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
P	parental generation
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
ppb	parts per billion
ppm	parts per million
rel	relative
SOP	standard operating procedure
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
wk(s)	week(s)
wt	weight
wc	water consumption
♂	male
♀	female
↓	decrease
↑	increase

Appendix I Tables and Figures

Table 1 Toxicity Profile of Thermacell II Devices

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity (Up and Down Procedure) (Liquid 1R-*trans* prallethrin formulation) Sprague Dawley rat PMRA #2622430	LD_{50} = 3129 mg/kg bw **Low toxicity** Clinical signs included hypoactivity, irregular respiration, bluish-green feces, anogenital staining, and death.
Acute dermal toxicity (cellulose mat) Sprague Dawley rat PMRA #2622432	LD_{50} > 5000 mg/kg bw **Low toxicity**
Acute inhalation toxicity PMRA #2622433	Waiver request to default to the acute inhalation hazard profile of 1R-*trans* prallethrin technical. The Thermacell II Devices contain a cellulose mat that is impregnated with a solution containing the active ingredient which is vaporized upon heating. Given that it is the active ingredient that is released when the mat is heated, the waiver request was considered acceptable. LC_{50} (1R-*trans* prallethrin) = 0.855/0.658 mg/L (♂/♀) **Slight toxicity**
Eye irritation (cellulose mat) New Zealand White rabbit PMRA #2622434	MAS (24, 48, 72 hrs) = 0 MIS = 0 **Non-irritating**
Dermal irritation (cellulose mat) New Zealand White rabbit PMRA #2622435	MAS (24, 48, 72 hrs) = 0 MIS = 0 **Non-irritating**

Dermal sensitization (Buehler method) (cellulose mat) Hartley guinea pigs PMRA #2622436	**Negative**

Table 2 Toxicity Profile of 1R-*trans* Prallethrin

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted. Effects observed above the LOAEL(s) have not been reported in this table for reasons of brevity.)

Study Type/Animal/PMRA #	Study Results
Toxicokinetics Single gavage dose of 150 mg/kg bw of 1R-*trans* and 1R-*cis* prallethrin in corn oil (radiolabeled with ^{14}C at the C-2 position in the alcohol moiety) Prallethrin ICR mice (♂) The study was conducted to examine the in vivo transfer of prallethrin to bone marrow under the same conditions as in the mouse micronuclei test. Liver, blood, kidney, brain, bone and bone marrow were assessed for radioactivity. PMRA #1144194	**Distribution:** At 6 hrs after dosing, levels in bone marrow and blood were 4.51 and 6.85 ppm, respectively. After 24 hrs, levels in bone marrow and blood were 0.48 and 0.79 ppm, respectively. Highest tissue residues at 24 hrs post-dosing were in the liver (4.4%) and kidney (1.9%). Levels in blood, bone and bone marrow were < 1% AD. The percent of radiolabel in bone marrow vs. that in blood was 66% and 61% at 6 and 24 hrs after dosing, respectively. Study results confirmed the in vivo transfer of prallethrin to bone marrow under the same conditions as in the mouse micronucleus assay.

Study Type/Animal/PMRA #	Study Results
Toxicokinetics Single gavage or subcutaneous dose of 1R-*trans* or 1R-*cis* prallethrin at 2 mg/kg bw in 10% Tween 80 (radiolabeled with ^{14}C at the C-2 position in the alcohol moiety) Sprague Dawley rat PMRA #1144217	**Absorption and Excretion**: Both isomers were almost completely eliminated in urine and feces within 7 days after single oral or subcutaneous dosing (96–104% of administered radioactivity recovered). Urinary excretion of radioactivity was greater with the *trans*-isomer (60–78%) than with the *cis*-isomer (17–32%), whereas fecal excretion was less for the *trans*-isomer (23–42%) compared to the *cis*-isomer (70–83%). Less than 0.1% of administered radioactivity was eliminated in expired air. The excretion pattern was similar between sexes and administration routes. **Distribution**: Levels of radioactivity in blood and tissues reached their maximum within 3 hr after oral administration of both the *cis*- and *trans*-isomers and decreased rapidly thereafter. Tissue residues 7 days after dosing were low, with the highest levels of radioactivity noted in blood, liver and kidney (0.3–3.2% of the administered dose). Tissue residues were similar between the sexes and administration routes. **Metabolism**: Numerous metabolites were identified in both urine and feces following administration of both the *cis*- and *trans*-isomers. Proposed metabolic pathways involved 1) oxidation at the methyl groups of the isobutenyl group in the acid moiety and at the C-1 or C-2 position of the propynyl in the alcohol moiety, 2) cleavage of the ester linkage, and 3) conjugation of the resultant hydroxyl derivatives with glucuronic acid. The majority of the metabolites resulting from ester cleavage were excreted in the urine, whereas the metabolites retaining ester bonds were excreted primarily in the feces. Very little to no unchanged parent compound was detected in analysed tissues within 1 hr after administration. There was no difference between sexes or administration routes with respect to the nature and amount of metabolites in the excreta.

Study Type/Animal/PMRA #	Study Results
Toxicokinetics Single low (2 mg/kg bw) or single high (100 mg/kg bw) gavage dose of ^{14}C-radiolabeled 1R-*trans* or 1R-*cis* prallethrin in corn oil, or repeated low dose (2 mg/kg bw/day) of unlabeled compounds followed by a single ^{14}C-radiolabeled dose of 1R-*trans* or 1R-*cis* prallethrin (radiolabeled at the C-2 position in the alcohol moiety) Sprague Dawley rat PMRA #1144205	**Excretion**: 95–107% of the administered radioactivity was eliminated in urine and feces in ♂ and ♀ 7 days after single (low or high dose) or repeated low dosing. Urinary excretion of the radiolabel was larger with the *trans*-isomer (45–62%) than with the *cis*-isomer (13–23%). Fecal excretion was lower with the *trans*-isomer (34–50%) compared to the *cis*-isomer (77–-91%). The pattern of excretion was similar in both sexes and in all dose groups; however, a greater proportion of radioactivity was excreted in the urine of ♀ compared to ♂. **Distribution**: Radioactivity in tissues plus carcass at 168 hrs accounted for < 0.5% of the administered dose. More radioactivity (1.13–1.9-fold) was retained in the tissues of ♀ at sacrifice compared to ♂ for both isomers and all dose groups. The highest tissue residue levels were in the kidneys, liver and whole blood for both sexes, both isomers and all dose groups. **Metabolism**: The major metabolites in urine and feces were from ester cleavage. The metabolite profiles in the excreta were similar between the sexes and across dose groups.
Acute oral toxicity 1R-*trans* prallethrin Sprague Dawley rat PMRA #1779657	LD_{50} (♂) = 667 mg/kg bw LD_{50} (♀) = 417 mg/kg bw **High toxicity** Clinical signs of toxicity included ↓ spontaneous activity, tremors, ataxic gait, irregular respiration, lacrimation, salivation, excretion of oily substance, urinary incontinence, death.
Acute oral toxicity Prallethrin Sprague Dawley rat PMRA #1144140	LD_{50} (♂) = 640 mg/kg bw LD_{50} (♀) = 460 mg/kg bw **High toxicity** Clinical signs of toxicity included ↓ spontaneous activity, limb paralysis, irregular respiration, dyspnea, lacrimation, salivation, muscular fibrillation, tremors, and death.
Acute dermal toxicity 1R-*trans* prallethrin Sprague Dawley rat PMRA #2621395	LD_{50} > 2000 mg/kg bw **Low toxicity** Clinical signs included urinary incontinence and hypersensitivity.
Acute dermal toxicity Prallethrin Sprague Dawley rat PMRA #1144141	LD_{50} > 5000 mg/kg bw **Low Toxicity** Clinical signs included muscular fibrillation, ↓ spontaneous activity (both sexes), tremors, limb paralysis, irregular respiration, urinary incontinence, and death.

Study Type/Animal/PMRA #	Study Results
Acute inhalation toxicity (nose-only) 1R-*trans* prallethrin Sprague Dawley rat PMRA #2892235	LC_{50} (♂) = 0.855 mg/L LC_{50} (♀) = 0.658 mg/L **Slight toxicity** Clinical signs included tremor of the tail, hypersensitivity, lateral position, tremor, ataxic gait, tip toe gait, stains and/or wet fur.
Acute inhalation (whole-body) Prallethrin Sprague Dawley rat PMRA #1144143	LC_{50} (♂) = 0.29 mg/L LC_{50} (♀) = 0.33 mg/L **Moderate toxicity** Clinical signs included salivation, lacrimation, nasal discharge, hyperpnea, tremors, and death.
Eye irritation 1R-*trans* prallethrin New Zealand White rabbit PMRA #2621396	Irrigated eyes: MAS (24, 48, 72 hrs) = 2.0 MIS = 4.0, at 1 hr **Minimally irritating** Non-irrigated eyes: MAS (24, 48, 72 hrs) = 1.8 MIS = 2.7, at 24 and 48 hrs **Minimally irritating**
Eye irritation Prallethrin New Zealand White rabbit PMRA #1144144	MAS (24, 48, 72 hrs) = 0.1 MIS = 3.7 at 1 hr **Minimally irritating**
Dermal irritation 1R-*trans* prallethrin New Zealand White rabbits PMRA #2621396	MAS (24, 48, 72 hrs) = 0 MIS = 0 **Non-irritating**
Dermal irritation Prallethrin New Zealand White rabbit PMRA #1144144	MAS (24, 48, 72 hrs) = 0 MIS = 0 **Non-irritating**

Study Type/Animal/PMRA #	Study Results
Dermal sensitization (Buehler) 1R-*trans* prallethrin Hartley guinea pig PMRA #2621397	Negative **Not a dermal sensitizer**
Dermal sensitization (Maximization) Prallethrin Hartley guinea pigs PMRA #1144145	Negative **Not a dermal sensitizer**
7-day oral toxicity (gavage) range-finding 1R-*trans* prallethrin Sprague Dawley rat PMRA #2621402	NOAEL not established as study was considered supplemental. Effects at 200 mg/kg bw/day: ↑ mortality (1 ♂ found dead on day 7, 2 ♀ euthanized in extremis on days 1 and 3), tremors, clonic convulsions, prostration (in animals that died/were sacrificed in extremis and in survivors, clear/red/yellow material around nose, eyes, mouth, tail and/or urogenital area; ↓ fc, ↓ bw/bwg (♂).
7-day oral toxicity (gavage) range-finding Prallethrin Sprague Dawley rat PMRA #26521403	NOAEL not established as study was considered supplemental. Effects at 200 mg/kg bw/day: ↑ mortality (1 ♂ euthanized in extremis on day 1, 2 ♀ found dead on days 1 and 5), tremors, clonic convulsions, prostration (in animals that died/were sacrificed in extremis and in survivors); red material around nose/eyes, clear material around mouth, ↓ fc, ↓ bw/bwg (♂)
21-day dermal toxicity Prallethrin Sprague Dawley rat PMRA #1164872	NOAEL (systemic) = 30 mg/kg bw/day LOAEL (systemic) = 150 mg/kg bw/day NOAEL (dermal irritation) = 750 mg/kg bw/day (HDT) Effects at the LOAEL: ↑ fixation (prolonged gaze with fixed posture); ↑ vocalization, twitching, writing spasms, ↑ sensitivity to stimuli, bw loss (days 0–3), ↓ overall bwg (♂); abnormal gait (♀) Effects at the next highest dose level of 750 mg/kg bw/day: tremors; ↑ pawing behaviour, ↑activity, vocalization, twitching , ↑ sensitivity to stimuli, transient mild skin reactions (erythema and edema) (♀)

Study Type/Animal/PMRA #	Study Results
28-day inhalation toxicity (whole body exposure in deodorized kerosene) Vehicle and negative (compressed air) control groups included Prallethrin Sprague Dawley rat PMRA #1144136	NOAEC = 0.001 mg/L (0.174 mg/kg bw/day) LOAEC = 0.0044 mg/L (0.765 mg/kg bw/day) Effects at the LOAEC: ↓ spontaneous activity,↑ incidence of irregular respiration, nasal discharge (appeared within 30 minutes of dosing; reversible within 1 hr following removal from the inhalation chambers); urinary incontinence (♀)
90-day oral toxicity (dietary) Prallethrin ICR mouse PMRA #1144146	NOAEL = 374/444 mg/kg bw/day LOAEL = 808/890 mg/kg bw/day Effects at the LOAEL: ↑ creatinine, ↓ urea nitrogen, enlarged liver, generalized hepatocyte enlargement (minimal/moderate), ↑ liver wt; yellow staining of fur in urogenital and ventral regions, ↓ platelets, moderate centrilobular midzonal hepatic enlargement (♂); ↑ cholesterol (♀)
90-day oral toxicity (dietary) Prallethrin Sprague Dawley rat PMRA #1144147	NOAEL = 79/82 mg/kg bw/day LOAEL = 230/244 mg/kg bw/day Effects at the LOAEL: ↓ bw, ↓ fc (wk 1), ↑ cholesterol, ↑ phospholipids, enlarged liver and thyroid, ↑ perilobular hepatocellular hypertrophy, ↑ number of small follicles in thyroid; ↑ neutrophils, ↑ thyroid wt (♂); ↓ bwg, ↑ rel kidney wt (♀)
90-day oral toxicity (capsule) Prallethrin Beagle dog PMRA #1144134	NOAEL = 3 mg/kg bw/day LOAEL = 10 mg/kg bw/day Effects at the LOAEL: tremors, convulsions, enlarged liver; ↓ bwg (♂); ↑ ovary wt, ↑ uterus wt (♀)
52-week oral toxicity (capsule) Prallethrin Beagle dog PMRA #1144135	NOAEL = 2.5 mg/kg bw/day LOAEL = 5 mg/kg bw/day Effects at the LOAEL: ↑ incidence and severity of brown pigment (lipofuscin) deposition in renal tubular epithelium; mortality of 1 ♀ in wk 44 [this dog exhibited trembling at wk 4, convulsions on 2 occasions (wk 19 and then the day before death) and panting, salivation, rapid eye blinking and muscle twitching (day before death)].

Study Type/Animal/PMRA #	Study Results
80-week oral toxicity (dietary) Prallethrin ICR mouse PMRA #1144161, #1144171	NOAEL (♂) = 68 mg/kg bw/day NOAEL (♀) = 778 mg/kg bw/day (HDT) LOAEL (♂) = 347 mg/kg bw/day LOAEL (♀) not established Effects at the LOAEL: ↓ bw, ↓ bwg, ↑ liver wt, ↓ white blood cells, ↓ lymphocytes (wk 80) (♂); ↑ kidney wt (♀ interim sacrifice only) No evidence of oncogenicity
106-week oral toxicity (dietary) Prallethrin Fischer 344 rat PMRA #1144137	NOAEL = 16/19 mg/kg bw/day LOAEL = 84/103 mg/kg bw/day Effects at the LOAEL: ↑ alopecia, ↑ cholesterol, ↑ phospholipids, ↑ crystals, casts and pH in urine, ↑ thyroid wt (wk 106) (♂); ↓ bw, ↓ bwg, ↑ liver wt, histiocytic infiltration in liver, ↑ thyroid wt (wk 52) (♀) No evidence of oncogenicity
One-generation reproduction (dietary) range-finding Prallethrin Sprague Dawley rat PMRA #1144183	NOAEL not established as study was considered supplemental. Parental effects at 57/63 mg/kg bw/day: ↑ liver wt; ↓ bwg during premating, ↓ fc 1st wk of premating (♀) Offspring effects at 182 mg/kg bw/day: ↓ bw PND 14 and 21 No reproductive effects up to 275/288 mg/kg bw/day (HDT).
Two-generation reproduction (dietary) Prallethrin Sprague Dawley rat PMRA #1144156, 1144157	Parental NOAEL = 39/46 mg/kg bw/day Parental LOAEL = 196/228 mg/kg bw/day Effects at the parental LOAEL: ↓ bw/bwg during premating period (P/F_1), ↓ fc 1st wk of premating (P), ↑ liver wt (P/F_1), ↑ hepatocellular hypertrophy (P/F_1), ↑ thyroid follicular hypertrophy/hyperplasia (P/F_1); ↑ pigment in cortical tubules of kidney (P/F_1♂), ↑ vacuolation and hypertrophy of anterior lobe of pituitary (P/F_1♂); ↓ bw during gestation (P♀) Offspring NOAEL = 46 mg/kg bw/day Offspring LOAEL = 228 mg/kg bw/day Effects at the offspring LOAEL: ↓ bw PND 21(F_1/F_2) Reproductive NOAEL = 397/446 mg/kg bw/day (HDT) Reproductive LOAEL not established No evidence of increased sensitivity to the young.

Study Type/Animal/PMRA #	Study Results
Developmental toxicity (gavage) Prallethrin Sprague Dawley rat PMRA #1144162	Maternal NOAEL = 10 mg/kg bw/day Maternal LOAEL = 30 mg/kg bw/day Effects at the maternal LOAEL: tremors, salivation, chromorrhinorrhea (all appeared within 2–9 days of dosing, persisting for 1–2 days), slight bw loss after first dose, ↓ fc during dosing period Developmental NOAEL = 300 mg/kg bw/day (HDT) Developmental LOAEL not established. No evidence of increased sensitivity of the young.
Modified developmental toxicity (subcutaneous) Prallethrin Sprague Dawley rat PMRA #1144165 1 group of dams subjected to caesarean section on GD 21; 1 group of dams allowed to deliver naturally (to produce F_1 pups). All F_1 pups (except 2/sex/litter – see below) were assessed for sensory functions (visual placing, auditory, righting and pain reflexes) on PND 20, and then necropsied on PND 21. 1/sex/litter - subjected to functional learning ability tests (open field, rotarod, multiple T-maze), then sacrificed at 8 wks. 1/sex/litter - subjected to reproduction performance testing (to produce F_2 pups, sacrificed on PND 7).	Non-guideline study. Maternal NOAEL = 25 mg/kg bw/day Maternal LOAEL = 50 mg/kg bw/day Effects at the maternal LOAEL: clinical signs (tremors, exaggerated reflex to external stimuli - appeared within 3 days of dosing, disappeared post-dosing), ↓ bwg, fc and wc (after first administration) Developmental NOAEL = 50 mg/kg bw/day (HDT) Developmental LOAEL not established. Offspring/Reproductive NOAEL = 50 mg/kg bw/day (HDT) Offspring/Reproductive LOAEL not established. No evidence of increased sensitivity of the young.

Study Type/Animal/PMRA #	Study Results
Developmental toxicity (gavage) Prallethrin New Zealand White rabbit PMRA #1144164	Maternal NOAEL = 100 mg/kg bw/day Maternal LOAEL = 200 mg/kg bw/day Effects at the maternal LOAEL: clinical signs (tremors on GD 13–19, lasting for 1–2 days), ↓ bwg and ↓ fc during dosing period Developmental NOAEL = 200 mg/kg bw/day (HDT) Developmental LOAEL not established. No evidence of increased sensitivity of the young.
Developmental toxicity (gavage) range-finding Prallethrin New Zealand White rabbit (study results summarized within main study report; PMRA #1144164)	NOAELs not established as study was considered supplemental. Maternal effects at 100 mg/kg bw/day: ↑ tremors No effects on number of corpora lutea, implantations, litter sizes, live fetuses, resorptions, sex ratios, fetal bw or percent resorbed conceptuses/litter.
Bacterial mutation 1R-*trans* prallethrin S. typhimurium (TA98, TA100, TA1535, TA1537); E. coli (WP2*uvr*A) PMRA #2621399	Negative with and without metabolic activation.
Bacterial mutation Prallethrin S. typhimurium (TA100, TA98, TA153, TA1537, TA1538); E. coli (WP2*uvr*A) PMRA #1144159	Negative with and without metabolic activation.
Mammalian cytogenetics (in vitro) Prallethrin Chinese hamster lung cells (V9) PMRA #1144160	Negative with and without metabolic activation.

Study Type/Animal/PMRA #	Study Results
Mammalian chromosomal aberration (in vitro) Prallethrin Chinese hamster ovary cells (CHO-K1) PMRA #1144169	Positive with metabolic activation: ↑ was not clearly dose-related Negative without metabolic activation
Bone marrow micronucleus assay (in vivo) Prallethrin ICR mouse PMRA #1144170	Negative with and without metabolic activation.
Unscheduled DNA synthesis (in vivo) Prallethrin Sprague Dawley rat (♂), primary hepatocytes PMRA #1144158	Negative with and without metabolic activation.
Acute neurotoxicity (gavage) Prallethrin Sprague Dawley rat PMRA #1164890	NOAEL = 100 mg/kg bw LOAEL = 300 mg/kg bw Effects at the LOAEL: ↓ exploratory behaviour at time of peak effect (2 hrs), ↓ motor activity (on day 0 in ♀; persisting until day 14 in ♂), ↓ total number of rears; ↑ mortality (2 ♀, days 1 and 2), tremors (marginal, isolated and transient, on the day of dosing in 2 ♀, one of which died the next day) (♀)
28-day neurotoxicity (gavage) 1R-*trans* prallethrin Sprague Dawley rat PMRA #2621401	NOAEL = 75 mg/kg bw/day LOAEL = 150 mg/kg bw/day Effects at the LOAEL: mortality/moribundity (2 ♂, 3 ♀ euthanized in extremis on study days 1or 2), tremors, clonic convulsions, prostrate posture, clear/red/yellow material around mouth/nose/urogenital area, slight salivation; ataxia, slightly impaired mobility, slight gait impairment, slightly uncoordinated air righting reflex, and more energetic startle response (1 ♂), ↓ rearing count (♂)

Study Type/Animal/PMRA #	Study Results
28-day neurotoxicity (gavage) Prallethrin Sprague Dawley rat PMRA #2621400	NOAEL = 75 mg/kg bw/day LOAEL = 150 mg/kg bw/day Effects at the LOAEL: tremors, clonic convulsions, and/or prostrate posture, red/yellow and/or clear material around mouth and/or nose, yellow material around urogenital area; mortality/moribundity (♀) [1 ♀ each found dead/euthanized in extremis on study day 1]
90-day neurotoxicity (dietary) Prallethrin Sprague Dawley rat PMRA #1164874, 1164879	NOAEL = 74/88 mg/kg bw/day LOAEL = 363/420 mg/kg bw/day Effects at the LOAEL: ↓ fc, ↓ bw

Table 3 Toxicology Reference Values for Use in the Human Health Risk Assessment for 1R-trans prallethrin

Exposure Scenario	Study	Point of Departure and Endpoint	Target MOE[1]
Short- to intermediate-term inhalation	Rat 28-day inhalation toxicity	NOAEC of 0.001 mg/L (0.174 mg/kg bw/day); decreased spontaneous activity, irregular respiration, nasal discharge, urinary incontinence	300
Cancer	A cancer risk assessment was not required.		

[1] MOE refers to a target MOE for occupational and residential assessments

Table 4 Fate and Behaviour in the Environment

Study	Test substance	Value	Remarks	Reference (PMRA #)
Hydrolysis	Technical Grade Active Ingredient	Half-life at 25 ºC and pH 9: 4.9 d Stable at pH 5 and 7	Is not an important route of transformation.	1301676
Phototransformation	Technical Grade Active Ingredient	Phototransformation in Water: pH 5 Alcohol labelled: Half-life: 13.6 hours (irradiated) Half-life: 1028 hours (43 days) (dark)	Rapidly degrades in natural sunlight.	2621410
		Phototransformation in Soil: Acid labelled: Half- life: 24.8 days (irradiated) Half-life: > 1 year (dark)	Undergoes natural sunlight photodegradation.	2621411 2621412

		Alcohol labelled: Half-life: 26.9 days (irradiated) Half-life: 198 days (dark)		
Biotransformation Soil	Technical Grade Active Ingredient	Aerobic Parent DT_{50}: 3.5–6.9 days (10 ppb level) DT_{50}: 3.4–5.3 days (100 ppb level)	Is an important route of transformation of the parent compound.	2621413
Biotransformation (Aquatic Systems)	Technical Grade Active Ingredient	Anaerobic Aquatic Sediment Acid labelled: Half-life: 33 days Alcohol labelled: Half-life: 35 days		2621415 2621416
Adsorption/desorption in soil	Technical Grade Active Ingredient	K_{oc} (Adsorption): 1361–3769 K_{oc} (Desorption): 1570–6636	Low to slightly mobile in soil.	2621408
Bioaccumulation	Technical Grade Active Ingredient	BCF (edible tissue): 81–236 BCF (non-edible tissue): 2210–3130	Does not bioaccumulate significantly.	2621434

Table 5 Toxicity to Non-Target Organisms

Organism	Study type	Test substance	Endpoint value	Degree of toxicity [a]	Reference (PMRA #)
Terrestrial Non-Target Organisms					
Earthworm (*Eisenia fetida*)	Acute (7-day)	Technical Grade Active Ingredient	LC_{50}: = 67.9 mg a.i./kg dw NOEC (survival): = 25 mg a.i./kg dw LOEC (survival) = 50 mg a.i./kg dw	N/A	2621421
	Acute (14-day)	Technical Grade Active Ingredient	LC_{50}: = 53.8 mg a.i./kg dw NOEC (survival): = 25 mg a.i./kg dw LOEC (survival): = 50 mg a.i./kg dw NOEC (weight change): = 6.25 mg a.i./kg dw LOEC (weight change): = 12.5 mg a.i./kg dw		

Honey bees (*Apis mellifera*)	Acute (48-h contact)	Technical Grade Active Ingredient	LD_{50}: = 0.028 µg a.i./bee NOEC: = 0.0125 µg a.i./bee	Highly toxic	1144174
Bobwhite quail (*Colinus virginianus*)	Acute (Oral)	Technical Grade Active Ingredient	LD_{50}: = 1171 mg a.i./kg bw NOEL (mortality effects): = 250 mg a.i./kg bw	Slightly toxic	1144228
	Dietary (5-d)	Technical Grade Active Ingredient	LC_{50}: > 5620 ppm NOEC (mortality): = 3160 ppm	Practically non-toxic	1144251
Mallard duck (*Anas platyrhynchos*)	Acute (Oral)	Technical Grade Active Ingredient	LD_{50}: > 2000 mg a.i./kg bw NOEL (mortality): = 500 mg a.i./kg bw	Practically non-toxic	1144240
	Dietary (5-d)	Technical Grade Active Ingredient	LC_{50}: > 5620 ppm NOEC (mortality): = 5620 ppm	Practically non-toxic	1144263
Rat	Acute (Oral)	Technical Grade Active Ingredient	LD_{50}: = 417–667 mg a.i./kg body weight	Slightly toxic	1144140

Organism	Study type	Test substance	Endpoint value	Degree of toxicity[a]	Reference (PMRA #)
Aquatic Organisms					
Water fleas (*Daphnia magna*)	Acute (48-h)	Technical Grade Active Ingredient	EC_{50}: = 23–24 µg a.i./L NOEC (sub-lethal effects): < 6 µg a.i./L	Very highly toxic	2621424
	Chronic (21-day)	Technical Grade Active Ingredient	LOEC: = 1.3 µg a.i./L NOEC (reproductive): = 0.65 µg a.i./L		2621425
Freshwater green alga (*Pseudokirchneriella subcapitata*)	Acute (72-h)	Technical Grade Active Ingredient	E_bC_{50} (total biomass): = 2.0 mg a.i./L NOEC (biomass): = 0.55 mg a.i./L E_rC_{50} (growth rate): = 4.5 mg a.i./L NOEC (growth rate): = 1.3 mg a.i./L	Moderately toxic	2621435
Rainbow trout (*Oncorhynchus mykiss*)	Acute (96-h) (Static renewal	Technical Grade Active Ingredient	LC_{50}: = 28 µg a.i./L NOEC (mortality): = 19 µg a.i./L	Very highly toxic	2621431

Organism	Study type	Test substance	Endpoint value	Degree of toxicity[a]	Reference (PMRA #)
	conditions)				
	Acute (96-h) (Flow through renewal conditions)	End-use product (6.41% as prallethrin)	LC_{50}: = 5.1 µg a.i./L NOEC (mortality): = 2.4 µg a.i./L		2621430
	Early life stage (90 day)	Technical Grade Active Ingredient	NOEC: = 3 µg a.i./L LOEC: > 3 µg a.i./L		2621432
Bluegill sunfish (*Lepomis macrochirus*)	Acute (96-h)	Technical Grade Active Ingredient	LC_{50}: = 22 µg a.i./L NOEC (sub-lethal effects): = 8.63 µg a.i./L	Very highly toxic	1144172
Sheepshead minnow *(Cyprinodon variegatus)*	Acute (96-h)	Technical Grade Active Ingredient	LC_{50}: = 3.9 µg a.i./L NOEC (sub-lethal effects): = 11 µg a.i./L	Very highly toxic	2621433
Mysids *(Mysidopsis bahia)*	Acute (96-h)	Technical Grade Active Ingredient	LC_{50}: = 3.9 µg a.i./L NOEC (sub-lethal effects): = 2.1 µg a.i./L	Very highly toxic	2621428
Eastern oyster (*Crassostrea virginica*)	Acute (96-h)	Technical Grade Active Ingredient	EC_{50}: = 0.58.mg a.i./L NOEC (sub-lethal effects): = 0.41mg a.i./L	Very highly toxic	2621429
Freshwater amphipod (*Hyalella azteca*)	Acute (96-h)	Technical Grade Active Ingredient	LC_{50}: = 6.4 µg a.i./L NOEC (mortality): = 2.0 µg a.i./L	Very highly toxic	2621426

[a] Based on Atkins et al. (1981) for bees, and US-EPA (Technical Overview of Ecological Risk Assessment - Analysis Phase: Ecological Effects Characterization, for other organisms, where applicable.

Table 6 Toxic Substances Management Policy Considerations

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		1R-*trans* prallethrin endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]	Soil	Half-life ≥ 182 days	DT_{50}: 3.4–6.9 days

	Water	Half-life ≥ 182 days	
	Sediment	Half-life ≥ 365 days	DT_{50}: 2.8 days
	Air	Half-life ≥ 2 days or evidence of long range transport	
Bioaccumulation[4]	Log K_{ow} ≥ 5		4.49
	BCF ≥ 5000		BCF (edible tissue): 81–236 BCF (non-edible tissue): 2210–3130
	BAF ≥ 5000		N/A
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

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

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A. List of Studies/Information Submitted by Registrant

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