Proposed Re-evaluation Decision PRVD2019-10

Pyriproxyfen and Its Associated End-use Products

Consultation Document

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Proposed Re-evaluation Decision

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

Pyriproxyfen is an insect growth regulator that contributes to the management of white flies in greenhouse vegetable and ornamental production, flea control in indoor, non-food areas of structures and management of fleas on cats and dogs. Commercial products are formulated as solutions, and are applied by ground application equipment by greenhouse workers and professional applicators. Domestic-class indoor products are applied to indoor environments as a trigger pump sprayer or pressurized product. Domestic-class pet treatment products are applied to dogs as a shampoo, or to dogs and cats as a spot-on treatment. Currently registered products containing pyriproxyfen can be found in the Pesticide Label Search and in Appendix I.

This document presents the proposed regulatory decision for the re-evaluation of pyriproxyfen including the proposed risk mitigation measures to further protect human health and the environment, as well as the science evaluation on which the proposed decision was based. All products containing pyriproxyfen registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period, during which the public including the pesticide manufacturers and stakeholders may submit written comments and additional information to the PMRA. The final re-evaluation decision will be published taking into consideration the comments and information received.

Outcome of Science Evaluation

Pyriproxyfen contributes to the management of white flies in greenhouse vegetable and ornamental production, flea control in indoor, non-food areas of structures and management of fleas on cats and dogs.

With respect to human health, dietary, residential and aggregate risks from the use of pyriproxyfen and associated end-use products have been shown to be acceptable. Occupational risks have been shown to be acceptable with label statements updated to standard baseline personal protective equipment. For indoor uses to control fleas and ticks, label amendments are proposed to standardize precautionary statements, to add best practice statements as per Regulatory Proposal PRO2018-04, *Structural Pest Control Products: Label Updates* and to clarify label directions to reflect actual use conditions.

When used according to the proposed label directions, potential risks to the environment from the use of pyriproxyfen and associated end-use products have been shown to be acceptable.

Proposed Regulatory Decision for Pyriproxyfen

An evaluation of available scientific information found that all uses of pyriproxyfen products meet current standards for protection of human health and the environment when used according to proposed label directions. Under the authority of the *Pest Control Products Act*, Health Canada is proposing that products containing pyriproxyfen are acceptable for continued registration in Canada.

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment and must be followed by law. No products or uses are proposed for cancellation. The proposed label amendments are summarized below. Refer to Appendix VII for details.

Human Health

- To protect mixer/loaders and applicators, updated label statements for personal protective equipment are proposed.
- Label statements are also proposed to address the following:
    - Preventing recycled greenhouse water from being applied to outdoor food crops
    - Prevent contamination of food and food surfaces during indoor applications
    - Clarifying and/or ensuring consistency regarding use directions and precautionary statements.
    - Adding best practice label statements as per PRO2018-04, *Structural Pest Control Products: Label Updates*
- Due to lack of data to assess occupational exposure, label statements prohibiting application using handheld mist blower or handheld fogging equipment are proposed.

Environment

- Standard label statements to inform users of the potential toxic effects of pyriproxyfen to aquatic organisms are proposed.

International Context

Pyriproxyfen is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including the United States, the European Union, and Australia.

As of 11 March 2019, no decision by an OECD member country to prohibit all uses of pyriproxyfen for health or environmental reasons has been identified.

Next Steps

The public including the registrants and stakeholders are encouraged to submit comments during the 90-day public consultation period[1] upon publication of this proposed re-evaluation decision.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of re-evaluation decision document,[2] which could result in revised risk mitigation measures. The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with Health Canada's responses.

Additional Scientific Information

No additional information is required at this time.

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

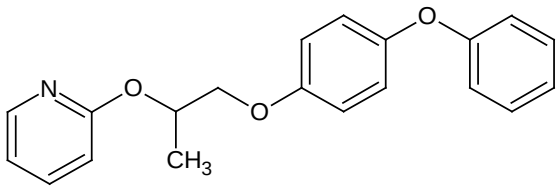
2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Science Evaluation

1.0 Introduction

2.0 Technical Grade Active Ingredient

2.1 Identity

Common name	Pyriproxyfen
Function	Insect Growth Regulator
Chemical Family	pyridine-based pesticide
Chemical name	
1 International Union of Pure and Applied Chemistry (IUPAC)	*rac*-2-{[(2*R*)-1-(4-phenoxyphenoxy)propan-2-yl]oxy}pyridine
2 Chemical Abstracts Service (CAS)	2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine
CAS Registry Number	95737-68-1
Molecular Formula	$C_{20}H_{19}NO_3$
Structural Formula	
Molecular Weight	321.37 g/mol
Purity of the Technical Grade Active Ingredient	98.7%
Registration Number	25105

2.2 Physical and Chemical Properties

Property	Result
Vapour pressure at 25°C	< 0.013 mPa
Ultraviolet (UV) / visible spectrum	λ_{max} ~ 270 nm (pH 3-11) λ_{max} 278 nm (pH 1)
Solubility in water at 25°C	0.367 mg/L

Property	Result
n-Octanol/water partition coefficient	Log K_{ow} = 5.37
Dissociation constant	~ 3.62 (calculated)

2.3 Description of Registered Pyriproxyfen Uses

In Appendix I, Table 1 lists all pyriproxyfen products that are registered under the authority of the *Pest Control Products Act*. In Appendix I, Table 2 lists all Commercial Class uses for which pyriproxyfen is presently registered, while in Appendix I, Table 3 lists all Domestic Class uses for which pyriproxyfen 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 pyriproxyfen.

3.0 Human Health Assessment

3.1 Toxicology Summary

Pyriproxyfen is a pyridine insecticide that is an analogue of insect juvenile hormone. A detailed review of the toxicological database for pyriproxyfen was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Most of 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 pyriproxyfen.

Toxicokinetic investigations were conducted in rats following gavage administration of phenyl- or pyridyl-radiolabelled pyriproxyfen. Administration of a single low dose of pyriproxyfen resulted in rapid but low absorption. Males showed higher peak concentrations in blood than females in the first 24 hours after administration. Maximum tissue concentrations were observed at eight hours post-dosing with highest concentrations in the liver, blood, kidneys and adipose tissue. In rats receiving single low, single high or repeated low doses, the highest tissue concentrations at seven days post-dosing were observed in adipose tissue with other tissues showing negligible amounts. Pyriproxyfen was extensively and rapidly eliminated in the feces of rats within 48 hours. Minor amounts of the administered radioactivity were eliminated in urine, with negligible amounts in expired air. There were no differences in tissue distribution or elimination attributable to sex, dose level, dosing regimen or position of radiolabel. Fecal metabolites consisted primarily of 4'-OH-pyr with lesser amounts of unchanged pyriproxyfen. Minor fecal metabolites included 5"4'-OH-pyr and, depending on the position of the radiolabel, POPA, 2'-OH-pyr, 5"-OH-pyr, DPH-pyr and sulfate and glucuronide conjugates of some of the identified metabolites. Unchanged pyriproxyfen and 4'-OH-pyr were either absent, or seen in minor amounts in the urine of treated rats. Other urinary metabolites, all representing less than 5% of the administered dose, included PYPAC and sulfate conjugates. Chemical names of the metabolites that were further characterized can be found in Appendix II, Table 1.

The major pathway of pyriproxyfen metabolism in rats involves hydroxylation at the 4'-position of the terminal phenyl ring. Minor pathways include hydroxylation at the 2'-position of the terminal phenyl ring and at the 5''-pyridyl position, dephenylation, cleavage of ether linkages, and formation of glucuronide and sulfate conjugates. There were no significant effects of sex or dose on the metabolic pattern of pyriproxyfen in rats. With repeated dosing, the amount of metabolite produced by oxidation at the 4' position was significantly greater in females as compared to males.

Pyriproxyfen was of low acute toxicity in rats when administered via the oral and dermal routes of exposure and of slight acute toxicity via the inhalation route. Clinical signs of toxicity following acute oral exposure included diarrhea, soft feces and reduced spontaneous activity. Transient clinical signs following acute inhalation exposure included salivation and urinary incontinence. Pyriproxyfen was minimally irritating to the eyes and non-irritating to the skin of rabbits, and was not a dermal sensitizer in guinea pigs in the Maximization assay.

The liver was identified as a target organ throughout the database. In short-term dietary or capsule administration studies, increased liver weights were seen in rats, mice and dogs; cytoplasmic changes and increased cholesterol and phospholipids were also noted in rats and dogs. At high dose levels, dogs also exhibited increased serum enzyme levels, increased triglycerides, centriacinar fibrosis and bile duct hyperplasia. The kidney was also a target of toxicity with increased weights in rats and dogs and tubular nephrosis with dilation of the renal tubules and focal mineralization in mice. The hematological system was affected in the rodent short-term dietary studies, as demonstrated by decreased red blood cell, hematocrit and hemoglobin counts. Decreased bodyweight was often concomitant with the observed effects on the liver, kidney or hematological system.

No treatment-related effects were noted in a short-term dermal toxicity study in rats at the limit dose of testing (1000 mg/kg bw/day). A NOAEC of 0.48 mg/L was established for rats exposed via inhalation for four weeks based on transient salivation, decreased bodyweights and absolute lung weights in males at the limit dose concentration of 1 mg/L.

In a dietary chronic toxicity study in rats, effects included reductions in bodyweight, increases in liver weight, and transient increases in cholesterol, phospholipids and urinary protein. In a dietary oncogenicity study in mice, survival was reduced in males, resulting in a study NOAEL of 16 mg/kg bw/day. The primary cause of death was identified as amyloidosis. Although the overall incidence of amyloidosis in decedents was unaffected by treatment, males that died showed an increased severity of amyloidosis, particularly of the kidney, thyroid, parathyroid and stomach. Males and females at a higher dose level showed effects on kidneys (increased incidences of chronic progressive nephropathy, mineralized tubules), liver (increased weight), and blood (decreased red blood cells, hemoglobin and hematocrit) as well as decreased bodyweight and accelerated development and severity of amyloidosis. Reduced survival in females occurred at this dose level. No treatment-related increase in tumour incidences was evident in either the rat or mouse studies.

Pyriproxyfen was negative in a battery of genotoxicity assays including a bacterial reverse mutation assay, several in vitro assays (mammalian gene mutation assay, unscheduled DNA synthesis assay and chromosome aberration assay) and an in vivo micronucleus assay.

In the dietary two-generation reproductive toxicity study in rats, there was no evidence of sensitivity of the young. Increased liver and kidney weights were recorded in F_1 males which progressed to pathological changes at the highest dose level. Decreases in bodyweight during the pre-mating phase were apparent at the latter level in both generations. Pup bodyweights were reduced at the highest dose level tested in both generations. There was no effect on reproductive parameters in the study.

Three gavage developmental toxicity studies in rats were available, assessing different windows of exposure, namely pre-implantation, during organogenesis, and post-organogenesis through lactation. No evidence of sensitivity of the young was apparent in these studies. Maternal toxicity occurred at the same dose level in all three studies and consisted of decreased bodyweight and food consumption and increased liver and kidney weights. At higher dose levels, mortality was noted in pregnant dams after several doses during organogenesis or post-organogenesis. No adverse effects on fetal development were noted at the limit dose in the non-guideline pre-implantation exposure study; however, a slight decrease in the number of corpora lutea was seen in the dams at this level. In the study with exposure during organogenesis, an increased incidence of a variation (opening of the seventh cervical vertebra foramen transversium) was noted in fetuses. In this study, a subgroup of dams was allowed to deliver their young. Findings in these offspring at the highest dose level tested included an increased incidence of renal pelvic dilatation in three and eight-week-old pups and increased kidney weights in eight-week-old pups. No effects were evident on the sensory function, behavior, motor co-ordination, learning ability or reproductive performance in pups from this study. In the non-guideline study with pyrifproxyfen exposure occurring post-organogenesis through lactation, the offspring NOAEL of 100 mg/kg bw/day was based on reduced pup weights at birth and throughout lactation and an increased incidence of dilatation of the renal pelvis in three-week-old pups. A decrease in pup viability at postnatal day (PND) 21 was also observed, which was deemed equivocal at this dose level due to the magnitude of the response. At a higher dose level, pup viability was clearly affected at birth and throughout the lactation period, reflected in reduced mean litter size. A slight delay in vaginal opening was also noted in pups at the high-dose level. Increased pre-implantation loss was observed in high-dose pups that were assessed during adulthood for reproductive performance, but sensory function, behavior, motor coordination and learning ability were unaffected by treatment. Overall, the data suggest that the most sensitive window of exposure was post-organogenesis through lactation; the potential mobilization of pyriproxyfen fat stores during lactation could play a role in this sensitivity.

In a gavage rabbit developmental toxicity study, maternal toxicity was evident based on the occurrence of abortions or premature deliveries as well as decreased weight gain with a resultant NOAEL of 100 mg/kg bw/day. Although the abortions/premature deliveries co-occurred with a reduction or absence of food intake in the affected dose, it was unknown if this was a causal factor or merely a correlation with the occurrence of the abortions/premature deliveries.

At the highest dose level tested (limit dose), additional effects in maternal animals included weight loss and mortality. Fetal effects were limited to an increased incidence of a variation (abnormal location of posterior vena cava) at the highest dose level.

There was no evidence of selective neurotoxicity in either the acute gavage or 90-day dietary neurotoxicity studies in the rat. Effects in the acute neurotoxicity study were limited to a transient reduction in motor activity on the day of dosing in male animals at a high dose level. Reduced bodyweight and food consumption were the only effects observed in the 90-day neurotoxicity study.

No adverse effects were noted in a 28-day dietary immunotoxicity study in mice. A dietary range-finding study conducted in mice with higher dose levels showed effects on bodyweight as well as liver and kidney toxicity. Overall, there was no evidence of immune dysregulation.

A battery of endocrine-related studies was conducted for the United States Endocrine Disruptor Screening Program. In in vitro assays, pyriproxyfen was negative for estrogen and androgen receptor binding and aromatase inhibition and did not affect testosterone production, but was a weak inducer of estradiol production in the steroidogenesis assay. Pyriproxyfen did not show endocrine-related toxicity in either the uterotrophic or Hershberger assays conducted via gavage in rats. In the female pubertal assay, rats gavage-dosed with pyriproxyfen showed a slight delay for incomplete vaginal opening and a reduction in females cycling regularly at the limit dose level concurrent with evidence of hepatic and renal toxicity; the time for complete vaginal opening was unaffected by treatment. Minimal evidence of thyroid toxicity was present in this study. In the male pubertal assay, rats gavage-dosed with pyriproxyfen showed decreases in serum testosterone levels and in the weights of androgen sensitive organs as well as a slight delay for complete preputial separation. These effects occurred in the presence of hepatic and renal toxicity. Slight changes in thyroid pathology were also evident in this study but thyroid hormones were unaffected by treatment. Androgen-related effects (decreased testosterone as well as weights of androgen-sensitive organs, delayed preputial separation) were also observed in a mechanistic study in gavage-dosed pubertal male rats. In addition to the co-occurring indicators of hepatic and renal toxicity in this study (organ weight changes, clinical chemistry alterations and histopathology), liver enzyme induction was evident. No effect on 17β-hydroxysteroid dehydrogenase activity in the testis was evident. The data suggest that the potential anti-androgenic effects could be secondary to the increased metabolism of testosterone by the liver.

Concern was raised in the public domain regarding the relationship between pyriproxyfen and the increase in microcephaly cases in Brazil in 2015 and 2016. Pyriproxyfen was added to the drinking water supply to combat the larva of mosquitos that carried the Zika virus. Although the increase in microcephaly has been strongly correlated with the mosquito-borne Zika virus, one publication considered a possible link with pyriproxyfen exposure (PMRA #2857241). The authors speculated that pyriproxyfen has cross-reactivity with retinoic acid, a known developmental toxicant, but did not provide data to support this claim. The authors cited a decrease in relative brain weight seen in eight-week-old male pups from dams that received 300 mg/kg bw/day in the rat developmental toxicity study (PMRA #1143907) as supporting evidence for their concern. This observation was not considered treatment-related by the PMRA for several reasons including: lack of a dose relationship, lack of a similar response in female

pups, the lack of an effect on absolute brain weight (considered to be a better measure of response due to the conserved nature of brain weight) and the lack of a similar observation in the reproductive toxicity assay.

Results of a published case-control study (PMRA #2857240) did not identify an association between microcephaly and pyriproxyfen; however, there was a strong association between microcephaly and the Zika virus. In a published ecological study (PMRA #2857242), there was no difference in the prevalence of microcephaly between Brazilian municipalities using pyriproxyfen and those using *Bacillus thuringiensis israelensis*. Although these epidemiological studies had limitations, the findings did not support a concern for pyriproxyfen. Results of an additional published study (PMRA #2857243) did not reveal evidence of brain malformations or significant changes in the number of stem cells in the developing central nervous system in zebrafish embryos. The findings in these studies, taken together with the absence of treatment-related malformations in the developmental and reproductive toxicity studies, do not suggest that pyriproxyfen was a causal factor in the increase in microcephaly cases in Brazil.

Further data in the scientific literature included two in vitro studies that indicated weak estrogenic activity, and two in vitro studies that demonstrated cytotoxicity. The findings in these studies did not substantially impact the current understanding of pyriproxyfen toxicity.

The mammalian metabolites 4'-OH-pyr, 5''-OH-pyr, DPH-pyr, POPA and PYPAC were of low acute oral toxicity in the mouse and negative in a bacterial reverse mutation assay. Slight acute oral toxicity in mice and negative findings in a bacterial reverse mutation assay were noted for 2,5-OH-py, a minor metabolite noted in the lactating goat metabolism study. A plant metabolite, 2-OH-py, was of high acute toxicity in the mouse; however, it was considered a minor metabolite. It was also negative in a bacterial reverse mutation assay.

Results of the toxicology studies conducted on laboratory animals with pyriproxyfen are summarized in Appendix II, Table 2. The toxicology reference values for use in the human health risk assessment are summarized in Appendix II, Table 3.

3.1.1 *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 full complement of required studies including gavage developmental toxicity studies in rats and rabbits and a dietary two-generation reproductive toxicity study in rats. Additional data on the young were available from gavage pubertal assays conducted in juvenile rats with pyriproxyfen.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of fetuses or offspring compared to parental animals in the reproductive and developmental toxicity studies. Minor developmental effects (increased incidence of fetal variations) were observed in the rat and rabbit guideline developmental toxicity studies; however, these effects occurred in the presence of maternal toxicity. A serious effect, abortion/premature delivery, was noted in maternal animals in the rabbit developmental toxicity study. Each of the affected animals ceased consuming food and lost weight for several days prior to litter loss. It was unknown whether the abortions/premature deliveries were the consequence of a direct effect on the fetus or secondary to overt toxicity in the maternal animal. A reduction in the number of corpora lutea was noted in rats administered pyriproxyfen prior to the implantation period in a non-guideline developmental toxicity study; however, this effect was only noted at the limit dose of testing and in the presence of significant maternal toxicity including mortality. In a non-guideline developmental toxicity study in rats in which dams were dosed post-organogenesis through lactation, pups at the mid-dose level exhibited renal effects, decreased weight at birth and throughout lactation, and an equivocal decrease in viability at PND 21. The equivocal decrease in viability at this dose level was deemed a low concern due to the small magnitude of the effect. At a higher dose level, pup effects included clearly reduced viability at birth and throughout lactation, delayed sexual development and an increase in pre-implantation loss when these pups were mated at adulthood. In the rat reproductive toxicity study, pup weight was reduced in both generations at a dose level that resulted in parental toxicity (effects on liver, kidney and bodyweight). Delayed sexual development was noted in young male and female rats in the pubertal assays but occurred concurrently with other systemic toxicity (liver, kidney and bodyweight effects).

Overall, endpoints in the young were well-characterized and there was no evidence of sensitivity. Endpoints considered serious in nature included the abortions/premature deliveries in rabbits, the decrease in corpora lutea in rats and the clear effects on rat pup viability. On the basis of this information, the *Pest Control Products Act* factor (PCPA factor) was reduced to threefold when these endpoints were used as the point of departure for risk assessment. In scenarios where other endpoints were selected, the risk assessment was protective of the serious endpoints and the PCPA factor was reduced to onefold.

3.2 Dietary Exposure and Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in meat and milk, may be ingested with the daily diet. Exposure to pyriproxyfen from potentially treated imported foods is also included in the assessment. Dietary exposure assessments are age-specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children’s eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

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

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

Sufficient information was available to adequately assess the dietary exposure and risk from pyriproxyfen. The chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02, 05-10-c) program which incorporates consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the years 2005-2010 available through the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS). Further details on the consumption data are available in Science Policy Note SPN2014-01, *General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments*.

3.2.1 Determination of Acute Reference Dose

An acute reference dose (ARfD) was not required as no endpoint of concern attributable to a single exposure was identified.

3.2.2 Acute Dietary Exposure and Risk Assessment

An acute dietary exposure and risk assessment was not required.

3.2.3 Determination of Acceptable Daily Intake

To estimate risk from repeated dietary exposure, the mouse oncogenicity study with a NOAEL of 16 mg/kg bw/day was selected. At the LOAEL of 79 mg/kg bw/day, reduced survival and increased severity of amyloidosis were observed. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the Pest Control Products Act Hazard Characterization Section, the PCPA factor was reduced to onefold. The composite assessment factor (CAF) is thus 100.

The acceptable daily intake (ADI) is calculated according to the following formula:

$$ADI = \frac{NOAEL}{CAF} = \frac{16 \text{ mg/kg bw/day}}{100} = 0.2 \text{ mg/kg bw/day of pyriproxyfen}$$

The ADI provides a margin of 500 or greater to the NOAELs for abortions/premature deliveries in rabbits and reduced corpora lutea and pup viability in rats.

3.2.4 Chronic Dietary Exposure and Risk Assessment

Generally, the chronic dietary risk is calculated using average consumption of different foods and the average residue values on those foods. For pyriproxyfen specifically, the average consumption values were used and the maximum potential residues as noted below were used. This would result in conservative (high-end) estimates of exposure. The estimated exposure was then compared to the ADI, which is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects. When the estimated exposure is less than the ADI, the chronic dietary exposure is shown to be acceptable.

The exposure assessment was conducted using the Canadian maximum residue limits (MRLs) or American tolerances for pyriproxyfen (whichever was greater). Available CODEX MRLs were used for commodities without Canadian MRLs or American tolerances. For agricultural crops, 100% crop treated was assumed. Available experimental processing factors were also used in the assessment.

In the United States, a tolerance of 0.1 ppm pyriproxyfen has been established for all commodities not listed as having specific American tolerances. This tolerance is intended for residues on foods resulting from the use of pyriproxyfen products in food handling establishments. Use of pyriproxyfen in food handling establishments is not a registered use in Canada. However, in consideration of potential food imports to Canada from the United States, the American tolerance of 0.1 ppm was used in the dietary exposure assessment for all commodities for which no MRL or tolerance has been established. For these commodities, 4.65% were considered to be treated based on percent of food handling establishments treated in the United States. In addition, commodities with existing Canadian MRLs lower than 0.1 ppm were assigned the 0.1 ppm for the dietary assessment, since as noted above, the highest value of either the Canadian MRL or American tolerance was used in the assessment.

CFIA and USDA PDP residue monitoring data for pyriproxyfen were available but were not used in this assessment; there was no need for this level of residue refinement at this time. The monitoring data showed non-detect values for the majority of commodities, with only a few detected residues but at levels lower than the established MRLs or tolerances.

The chronic dietary risk assessment was conducted for the general population and all population subgroups. The chronic dietary exposure for the general population was approximately 5% of the ADI. Chronic exposures for population subgroups ranged from approximately 4% of the ADI to 13% of the ADI. Children 1–2 years old were the subpopulation expected to be subject to the highest exposures relative to bodyweight. Pyriproxyfen dietary risk was, therefore, shown to be

acceptable for the general population and all population subgroups. For more information on the dietary risk estimates or the residue chemistry information used in the dietary assessment, see Appendix III.

Best practice label statements are proposed to clarify label directions as it relates to potential residues on food as follows:

- As there are no field uses of pyriproxyfen, label statements to prevent recycled greenhouse water from being applied to outdoor food crops;
- Label statements to prevent contamination of food and food surfaces during indoor applications for control of fleas and ticks.

See Appendix VII for specific label statements.

3.2.5 Cancer Assessment

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

3.3 Exposure from Drinking Water

Given that pyriproxyfen is registered for greenhouse and indoor uses only, exposure of drinking water sources was deemed minimal and, therefore, drinking water contribution to the dietary exposure was not considered in this assessment. Label statements are being proposed to prevent residues from entering drinking water sources. See Appendix VII for specific label statements.

3.4 Occupational and Non-Occupational Exposure and Risk Assessment

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

3.4.1 Toxicology Reference Values

Short- and Intermediate-Term Dermal and Inhalation

For short- and intermediate-term dermal and inhalation risk assessment for adults, the oral developmental toxicity study in rabbits was selected. A NOAEL of 100 mg/kg bw/day was established. At 300 mg/kg bw/day, an increase in abortions/premature deliveries was observed in the presence of maternal toxicity. Although short-term dermal and inhalation toxicity studies were available, they were not chosen for reference value selection since the design of those studies does not allow for the assessment of the relevant endpoint of concern. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies

variability were applied. For residential scenarios, as discussed in the *Pest Control Products Act* Hazard Characterization Section, the PCPA factor was reduced to threefold, resulting in a target margin of exposure (MOE) of 300. For occupational scenarios, the target MOE was also 300 reflecting the use of an additional threefold factor for a serious effect in the presence of maternal toxicity.

For short and intermediate-term dermal and inhalation risk assessment for children, the oral developmental toxicity study in rats that included a postnatal phase was selected. A NOAEL of 100 mg/kg bw/day was established. At 300 mg/kg bw/day, pup weight was reduced along with an equivocal reduction in pup viability. Although short-term dermal and inhalation toxicity studies were available, they were not chosen for reference value selection since the design of those studies does not allow for the assessment of the relevant endpoint of concern. A target MOE of 100 was established based on standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, along with a PCPA factor of onefold, as discussed in the *Pest Control Products Act* Hazard Characterization Section.

Long-term Dermal and Inhalation

For long-term dermal and inhalation risk assessment, the mouse oncogenicity study with a NOAEL of 16 mg/kg bw/day was selected. At the LOAEL of 79 mg/kg bw/day, reduced survival and increased severity of amyloidosis were observed. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied resulting in a target MOE of 100. For residential scenarios, the PCPA factor was reduced to onefold as discussed in the *Pest Control Products Act* Hazard Characterization Section.

Non-Dietary Oral Ingestion (Children, Short-term)

For non-dietary oral ingestion, the 90-day oral toxicity study in rats with a NOAEL of 24 mg/kg bw/day in rats was selected for risk assessment. At the LOAEL of 118 mg/kg bw/day, effects were noted on the liver and hematological system. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, along with a PCPA factor of onefold, as discussed in the *Pest Control Products Act* Hazard Characterization Section, resulted in a target MOE of 100.

Dermal Absorption

No chemical-specific dermal absorption studies were submitted to the PMRA. Therefore, dermal absorption of 100% was used in the risk assessment.

3.4.2 Residential Exposure and Risk Assessment

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

The USEPA has generated standard default 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 (USEPA, 2012).

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

- Section 7: Indoor Environments
- Section 8: Treated Pets

3.4.2.1 Residential Applicator Exposure and Risk Assessment

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

There is potential exposure to residential applicators applying pyriproxyfen inside homes and to pets (dogs and cats). Based on typical use patterns, the representative scenarios identified were:

- Applying pressurized product formulations to indoor environments
- Applying liquid formulations using ready-to-use trigger pump sprayers to indoor environments
- Applying liquid formulations as a shampoo to dogs
- Applying liquid formulations using a ready-to-use spot-on application to dogs and cats

Residential applicators have the potential for short-to-intermediate term exposure (<6 months) due to seasonality of the pests listed on the label (for example, fleas, ticks and mosquitoes).

Route-specific MOEs for residential applicators are outlined in Appendix V, Table 1. Calculated MOEs for dermal, inhalation, and combined (dermal + inhalation) exposures for residential applicators of pyriproxyfen exceeded target MOEs for all scenarios, and therefore, risks were shown to be acceptable.

3.4.2.2 Residential Postapplication Exposure and Risk Assessment

Residential postapplication exposure refers to an exposure scenario in which an individual is exposed through dermal, inhalation, and/or incidental oral (non-dietary ingestion) routes as a result of being in a residential environment or contacting a surface that has been previously treated with a pesticide. The surface could have been treated by a residential applicator using a domestic-class product or a commercial applicator hired to treat the residential area.

There is potential for intermittent, short- to intermediate-term exposure to adults and children through contact with transferable residues following application of pyriproxyfen to indoor environments and to pets. Adults and children have the potential for postapplication dermal exposure; children aged 1 to <2 years old also have the potential for incidental oral exposure. Since children aged 1 to 2 years have the greatest potential for exposure, risk outcomes for this population of children are presented. Inhalation exposure is considered to be minimal compared to dermal exposure, since pyriproxyfen has a low vapour pressure and meets the criteria for an inhalation waiver based on low volatility. Thus, a residential postapplication inhalation exposure assessment was not required.

The following scenarios were assessed for residential use of products containing pyriproxyfen:

- Indoor Environments:
    - Adults and children (1 to <2 years old) dermal exposure resulting from activities indoors.
    - Incidental oral (hand-to-mouth, object-to-mouth) exposure to children (1 to <2 years old) in indoor environments.

- Treated Pets:
    - Adults and children (1 to <2 years old) dermal exposure resulting from activities with treated pets.
    - Incidental oral (hand-to-mouth) exposure to children (1 to <2 years old) from treated pets.

The highest application rate was used in the postapplication risk assessment for pyriproxyfen. It is assumed that individuals contact previously treated surfaces and pets on the same day the pesticide treatment is applied. Multiple applications were not assessed for indoor and pet uses of pyriproxyfen since exposure on the day of application (Day 0) without any dissipation was assumed for the entire duration of exposure. These assumptions would result in conservative or high-end estimates of exposure.

Dermal Exposure

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

Calculated dermal MOEs for residential postapplication exposure to pyriproxyfen exceeded target MOEs for all populations and scenarios, and therefore, risks are shown to be acceptable. The residential dermal postapplication risk assessment is outlined in Appendix V, Table 2.

Incidental Oral Exposure

Postapplication incidental oral exposure assumes that pesticide residues are transferred to the skin of children's (1 to <2 years old) hands while playing on treated indoor surfaces or with treated pets, and are subsequently ingested as a result of hand-to-mouth transfer. For indoor applications, residues that could result on children's toys and which could subsequently be ingested as a result of mouthing activity with the toy are also considered (object-to-mouth transfer).

Calculated incidental oral MOEs for residential postapplication exposure to pyriproxyfen exceeded target MOEs, and therefore, risks are shown to be acceptable. The residential incidental oral postapplication risk assessment is outlined in Appendix V, Table 3.

3.4.2.3 Label Statements

For end-use products with directions for indoor uses to control fleas and ticks, label amendments are proposed as follows:

- Clarifying and/or ensuring consistency regarding use directions and precautionary statements.
- Adding best practice label statements as per PRO2018-04, *Structural Pest Control Products: Label Updates*.

See Appendix VII for specific label statements for pyriproxyfen.

3.4.3 Occupational Exposure and Risk Assessment

There is potential for exposure to pyriproxyfen in occupational scenarios from workers handling the pesticide during the application process, and potential for postapplication exposure from workers entering into areas or handling pets previously treated with pyriproxyfen.

3.4.3.1 Mixer, Loader, and Applicator Exposure and Risk Assessment

There are potential exposures to mixers, loaders, and applicators. The following scenarios were assessed:

- Application to greenhouse crops
- Application in indoor structures, including homes, using the commercial-class product
- Application of domestic-class spot-on or shampoo products to pets by workers

Typically, it is assumed that commercial applicators or workers would not be using domestic-class products. However, for pyriproxyfen, since there are no commercial-class products registered for application to pets, it was assumed that workers would be using domestic-class products (for example, in veterinary clinics).

Greenhouse and Indoor Structures

For greenhouse and indoor structures, the following application equipment were assessed:

- Backpack application to greenhouse ornamentals, tomatoes, cucumbers, peppers and eggplants
- Manually-pressurized handwand application to indoor structures and greenhouse ornamentals, tomatoes, cucumbers, peppers and eggplants
- Mechanically-pressurized handgun application to greenhouse ornamentals, tomatoes, cucumbers, peppers and eggplants

Farmers and commercial applicators may handle pyriproxyfen for short to intermediate periods of time depending on the crop and use site. Therefore, the short-to-intermediate endpoints were used for all scenarios.

Exposure was estimated for baseline personal protective equipment (PPE): long pants, long-sleeved shirt, chemical-resistant gloves, socks and shoes.

No appropriate chemical-specific handler exposure data were available for pyriproxyfen. Therefore, dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database Version 1.1 (PHED). 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 PPE.

In addition, for application to indoor structures, a passive dosimetry study that monitored exposure of pest control operators (PCOs) applying liquid products indoors as a surface spray using a manually-pressurized handwand was used.

Data were not available to assess exposures when using handheld mist blower or handheld fogging equipment. Therefore, label statements prohibiting application with these equipment are proposed.

Route-specific MOEs for mixer/loaders and applicators are outlined in Appendix IV, Table 1. Calculated MOEs from dermal, inhalation, and combined (dermal + inhalation) routes for mixer/loaders and applicators of pyriproxyfen exceeded target MOEs for all scenarios, and therefore, risks are shown to be acceptable.

Since the assessment was conducted with handlers wearing baseline PPE, label statements are proposed to be added to labels currently lacking this PPE. Specifically, to protect mixer/loaders and applicators applying in indoor environments to control fleas, baseline PPE is proposed.

Application to Pets

There are no specific exposure data for commercial handlers (for example, veterinarians, groomers) using domestic-class spot-on or shampoo products to treat pets. Therefore, exposure was compared to the residential applicator in terms of amount of product handled, number of pets treated, PPE worn, and margins of exposure. For commercial users, the extent of exposure is uncertain; however, these workers typically wear PPE when applying pet products, such as a laboratory coat/apron. The number of animals treated per day by a worker with spot-on or shampoo products in animal facilities may be higher than for residential applicators treating their own pets. However, it was assumed that applying pet products is only one of many tasks that workers would do in a typical day, and it may not always be the same product being applied. Risks were shown to be acceptable for residential applicators (see Section 3.4.2), and based on the exposure considerations above, risks are expected to be acceptable for commercial users as well.

3.4.3.2 Postapplication Worker Exposure and Risk Assessment

There is potential exposure to workers entering treated sites or handling treated pets. Possible occupational postapplication worker scenarios include:

- Agriculture: Workers entering treated greenhouses to conduct agronomic activities
- Indoor Structures: Workers entering treated commercial, industrial or institutional locations
- Pet Uses: Veterinarians or other workers handling treated pets.

No chemical-specific data were available to assess postapplication exposure to workers.

Agriculture

The postapplication occupational risk assessment considered exposures to workers who enter treated sites to conduct agronomic activities involving foliar contact (for example, scouting). Based on the use of pyriproxyfen in greenhouse crops, there is potential for long-term postapplication exposure to pyriproxyfen residues for workers.

Potential exposure to postapplication workers was estimated using updated activity-specific transfer coefficients (TCs), and default dislodgeable foliar residue (DFR) values, since chemical-specific DFR data were not available (see below). The DFR refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant. The TC is a measure of the relationship between exposure and DFRs for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies. The TCs are specific to a given crop and activity combination, and reflect standard agricultural work clothing worn by adult workers. Activity-specific TCs from the Agricultural Re-entry Task Force (ARTF) were used. Postapplication exposure activities for agricultural crops include (but are not limited to): harvesting, weeding and scouting.

For more information about estimating worker postapplication exposure, refer to the PMRA's Regulatory Proposal PRO2014-02, *Updated Agricultural Transfer Coefficients for Assessing Occupational Postapplication Exposure to Pesticides*.

Since no acceptable chemical-specific DFR studies were available for pyriproxyfen, default values were used (peak DFR of 25% of the application rate for all crops). For further information on these default values, refer to the PMRA's Science Policy Note SPN2014-02, *Estimating Dislodgeable Foliar Residues and Turf Transferable Residues in Occupational and Residential Postapplication Exposure Assessments*.

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

Postapplication exposure would be primarily via the dermal route. Based on the vapour pressure of pyriproxyfen, inhalation exposure would be low, provided that the minimum 12-hour REI is followed.

The postapplication exposure assessment is outlined in Appendix IV, Table 2. At a 12-hour REI, postapplication risks to workers performing activities such as thinning, pruning, and harvesting, were shown to be acceptable.

Indoor Structures and Pet Uses

For indoor structural uses and for pet uses, there is potential for short- to intermediate-term exposure for workers entering treated areas or handling treated pets.

Exposure for postapplication workers in these scenarios was assessed qualitatively. It was assumed that risks to postapplication workers in these scenarios would be similar to or less than residential postapplication risks, since time spent in residential areas or time spent handling pets in the home is assumed to be longer than the respective times in workplaces. Risks were shown to be acceptable for residential postapplication scenarios for adults after commercial applications in homes and after handling treated pets (see Section 3.4.2). Based on the exposure considerations above, risks are expected to be acceptable for workers as well.

3.5 Aggregate Exposure and Risk Assessment

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

3.5.1 Toxicology Reference Values for Aggregate Risk Assessment

Short- and Intermediate-term Aggregate

For short- and intermediate-term aggregate assessment for adults, the oral developmental toxicity study in rabbits was selected. A NOAEL of 100 mg/kg bw/day was established. At 300 mg/kg bw/day, an increase in abortions/premature deliveries was observed in the presence of maternal toxicity. This finding was considered relevant for all routes of exposure. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, along with a PCPA factor of threefold, as discussed in the *Pest Control Products Act* Hazard Characterization Section, resulted in a target MOE of 300.

For short and intermediate-term aggregate assessment for children, the oral developmental toxicity study in rats that included a postnatal phase was selected. A NOAEL of 100 mg/kg bw/day was established. At 300 mg/kg bw/day, pup weight was reduced along with an equivocal reduction in pup viability. This finding was considered relevant for all routes of exposure. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, along with a PCPA factor of onefold, as discussed in the *Pest Control Products Act* Hazard Characterization Section, resulted in a target MOE of 100.

3.5.2 Residential and Dietary Aggregate Exposure and Risk Assessment

In an aggregate risk assessment, the combined potential risk associated with food, drinking water and various residential exposure pathways is assessed. A major consideration is the likelihood of co-occurrence of exposures and durations of exposures.

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

- Following commercial application to control fleas in residential areas:
    - Postapplication dermal exposure to adults and children + incidental oral exposure to children + dietary exposure (food only) for adults and children
- Following application of a domestic-class product indoors to control fleas and ticks:
    - For adults, applicator dermal and inhalation exposure + postapplication dermal exposure + dietary exposure (food only)
    - For children, postapplication dermal exposure + incidental oral exposure + dietary exposure (food only)
- Following application of a domestic-class product to pets:
    - For adults, applicator dermal and inhalation exposure + postapplication dermal exposure + dietary exposure (food only)
    - For children, postapplication dermal exposure + incidental oral exposure + dietary exposure (food only)

Calculated MOEs for aggregate exposure to pyriproxyfen exceeded target MOEs and therefore, risk is shown to be acceptable. The aggregate risk assessment is outlined in Appendix VI, Table 1.

3.6 Cumulative Assessment

The *Pest Control Products Act* requires that the PMRA considers the cumulative exposure to pesticides with a common mechanism of toxicity. For the current re-evaluation, the PMRA did not identify information indicating that pyriproxyfen shares a common mechanism of toxicity with other pest control products. Therefore there is no requirement for a cumulative risk assessment at this time.

3.7 Incident Reports

As of 6 December 2018, the PMRA had received 73 human and 6058 domestic animal incidents involving pyriproxyfen. The pyriproxyfen products reported in incidents are mostly co-formulated with other active ingredients (for example, synthetic pyrethroids, pyrethrins, imidacloprid).

Forty-nine human incidents were considered to be possibly related to the reported pyriproxyfen product. The co-formulated pyriproxyfen products reported in incidents involved companion animal spot-on products and indoor sprays or foggers. Minor skin and eye irritation were the most common signs in people and the reported exposure scenarios include treating pets, coming in contact with treated pets or indoor areas, and during product application. There were six serious American incidents with co-formulated pyriproxyfen products. Signs reported in these incidents include effects such as temporary blindness, respiratory distress or muscular weakness. The described exposure scenarios include ocular exposure when treating a pet, excessive application of a pesticide, applying a product in non-ventilated areas or living in treated areas. In one serious American incident involving cardiac arrest and death, the label directions of the American product were not followed.

The domestic animal incidents mainly involved spot-on pyriproxyfen products registered for use on cats and dogs (5967 reports). The review of spot-on incidents involving pyriproxyfen and the proposed mitigation measures for all spot-on products are discussed under Regulatory Proposal PRO2018-01, *Consultation on Proposed Regulatory Changes for Pesticide Products Used on Companion Animals*. Of the remaining 91 incidents, the majority were considered to be possibly related to the reported pyriproxyfen product. Three minor incidents occurred in the Canada, while the remainder were serious American incidents mainly involving cats. The reported exposure scenarios include treatment with an American shampoo containing a pyriproxyfen formulation not registered for use in Canada or exposure to an indoor spray/powder. The minor signs reported in animals include symptoms such as drooling, lethargy, anorexia or vomiting. In animals that died, reported signs include more serious effects like ataxia or convulsion.

Overall, the review of incident reports suggests that the synthetic pyrethroids and/or pyrethrins present in the co-formulated pyriproxyfen products may have contributed to the adverse effects reported in people and animals. The labels of Canadian pyriproxfen spot-on products reported in incidents have protective measures (in other words, use of rubber gloves), as well as precautionary statements, to minimize the likelihood of exposure in people. Domestic class Canadian pyriproxyfen products registered for use in indoor areas are co-formulated with the synthetic pyrethroids, d-phenothrin or tetramethrin. A trend analysis conducted on incidents

involving synthetic pyrethroid products (2011 Report on Pesticide Incidents), including those containing d-phenothrin and tetramethrin, identified concerns pertaining to inhalation and dermal exposure of people and animals following or during the treatment of indoor areas. Label amendments as outlined in PRO2018-04, *Structural Pest Control Products: Label Updates* are therefore proposed to minimize the likelihood of human or animal exposure to pyriproxyfen products co-formulated with synthetic pyrethroids.

4.0 Environmental Assessment

4.1 Fate and Behaviour in the Environment

Pyriproxyfen is sparingly soluble in water and is hydrolytically stable. Pyriproxyfen is not expected to volatilize from dry or moist surfaces and, based on an adsorption/desorption study, is immobile in soil. Pyriproxyfen is non-persistent in aerobic soil under laboratory and field conditions. Biotransformation is the principal route of dissipation in soil. No major transformation products are formed. Considering its immobility and non-persistence in soil and its low water solubility, pyriproxyfen is not expected to leach into groundwater. Pyriproxyfen is also non-persistent in aerobic water, but was shown to be persistent under anaerobic water conditions. Pyriproxyfen is not expected to bioaccumulate in organisms.

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. For greenhouse uses of pyriproxyfen, potential exposure was assessed for beneficial arthropods and pollinators (typically those used inside greenhouses for production purposes) and aquatic organisms (potential for exposure of adjacent aquatic habitats to discharge of process waters from the greenhouse), and a qualitative risk assessment was considered.

4.2.1 Risks to Terrestrial Organisms

Based on the current use pattern (indoor use), minimal exposure to earthworms, birds, wild mammals, and non-target terrestrial vascular plants is expected. Pyriproxyfen is an insect growth regulator and effects on beneficial terrestrial invertebrates (bees, predatory and parasitic arthropods) are expected. For greenhouse uses, a label statement to inform users of potential risks to beneficial non-target invertebrates is already present on the label. No additional risk reduction measures are proposed.

4.2.2 Risks to Aquatic Organisms

Pyriproxyfen is highly toxic to freshwater invertebrates, freshwater fish, estuarine/marine fish, and is very highly toxic to estuarine/marine invertebrates. Based on the current indoor use pattern, direct exposure of pyriproxyfen to aquatic organisms is not expected. However, the potential for indirect exposure to the discharge of greenhouse process water was considered. Therefore, to minimize the potential exposure of aquatic organisms from the discharge of greenhouse process water, the current label for the end-use product includes use directions prohibiting the discharge of greenhouse process water.

In conclusion, the potential risks to non-target terrestrial and aquatic organisms from pyriproxyfen are considered to be acceptable when the associated end-use products are used according to the label directions. However, for consistency and to meet current labelling standards, environmental precaution/disposal statements are proposed to be updated. For additional details on the environmental assessment of pyriproxyfen, please refer to Proposed Regulatory Decision Document PRDD2006-04, *Pyriproxyfen* and Registration Decision RD2007-03, *Pyriproxyfen*.

4.2.3 Environmental Incident Reports

As of 19 March 2019, one environment incident involving pyriproxyfen has been submitted to the PMRA database. A queen bee mortality incident was received by the PMRA in 2018 associated with a pet treatment product which contains three active ingredients (including pyriproxyfen). A causality assessment concluded that exposure to pyriproxyfen was unlikely to have contributed to the mortality observed.

The United States EIIS database was also searched for environment incidents in the United States (data as of October 2015). There were two incidents involving honey bees. One incident was assigned the certainty index of ‘possible’ while the other was considered as ‘unlikely’. In the incident considered as possible, the reported product use site was an almond orchard where 2000 bee hives were impacted. No other details were available. These incidents occurred at outdoor sites, which are not relevant to currently registered uses in Canada.

No additional mitigation measures are recommended based on the review of environmental incident reports.

5.0 Value Assessment

Pyriproxyfen is a valuable tool for the management of whiteflies, an economically important pest in greenhouse vegetable and ornamental production. It is mainly used at the end of a production cycle, to reduce whitefly populations before the next production cycle. For greenhouse vegetables, it is generally not applied when the fruit are present, but applied when the harvest is complete, and the vegetative part of the plant is still present. Since whitefly feeding can adversely affect the appearance and hence marketability of vegetables and ornamentals, maintaining high quality and visual appeal is critical to these sectors.

Pyriproxyfen is a valuable tool for the control of fleas in indoor, non-food areas of structures. Pyriproxyfen is also co-formulated with other insecticides to broaden the pest spectrum, including control of ticks in structures, on furniture and carpets.

Pyriproxyfen contributes to the management of companion animal pests (for example, fleas, ticks, lice and mosquitoes) due to its long residual activity (5 months).

6.0 Pest Control Product Policy Considerations

6.1 Assessment of the Active Ingredient under the Toxic Substances Management Policy

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

During the review process, pyriproxyfen 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 conclusion that pyriproxyfen and its transformation products do not meet all of the TSMP Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the active ingredient as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*[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 the Toxic Substances Management Policy and Formulants Policy,[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 conclusion that pyriproxyfen and its end-use products do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

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

4 SI/2005-114, last amended on 25 June 2008. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*

5 PMRA's Notice of Intent 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 the PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Conclusion of Science Evaluation

Pyriproxyfen is an insect growth regulator belonging to juvenile hormone mimics. Pyriproxyfen is a valuable tool in the management of white flies in greenhouse vegetable and ornamental production, flea control in indoor, non-food areas of structures and management of fleas on cats and dogs.

With respect to human health, the health risks associated with the use of pyriproxyfen and associated end-use products are acceptable when these products are used according to the proposed revised label directions (Appendix VI).

When used according to the proposed label directions, potential risks to the environment from the use of pyriproxyfen and associated end-use products have been shown to be acceptable.

List of Abbreviations

abs	absolute
AD	administered dose
ADI	acceptable daily intake
ALK	alkaline phosphatase
ALT	alanine aminotransferase
AR	androgen receptor
ARfD	acute reference dose
AST	aspartate aminotransferase
BUN	blood urea nitrogen
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CYP	cytochrome P450 enzyme(s)
DEHP	di-2-ethylhexyl phthalate
DNA	deoxyribonucleic acid
EC10	effective concentration to produce a 10% response
ER	estrogen receptor
F0	parental generation
F1	first generation
F2	second generation
fc	food consumption
Hct	hematocrit
Hgb	hemoglobin
hr(s)	hour(s)
GD	gestation day
kg	kilogram(s)
L	litre(s)
LABC	levator ani-bulbocavernosus muscle complex
LC50	lethal concentration to 50%
LD	lactation day
LDH	lactate dehydrogenase
LD50	lethal dose to 50%
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
M	molar
MAS	maximum average score for 24, 48 and 72 hours
MCH	mean cell hemoglobin
MCV	mean cell volume
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
MOE	margin of exposure
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NOAEC	no observed adverse effect concentration

NOAEL	no observed adverse effect level
NRI50	neutral red incorporation to 50%
PCPA	Pest Control Products Act
PMRA	Pest Management Regulatory Agency
PND	postnatal day
ppm	parts per million
RBC	red blood cell
rel	relative
S9	metabolic activation
sRBC	sheep red blood cells
T3	triiodothyronine
T4	thyroxine
TSH	thyroid stimulating hormone
UGT	uridine 5'-diphospho-glucuronosyltransferase
µM	micromolar
wt	weight
wc	water consumption
wk(s)	week(s)

Appendix I Lists of Pyriproxyfen Products and Uses

Table 1 Registered Pyriproxyfen Products in Canada as of 1 May 2019 excluding discontinued products or products with a submission for discontinuation

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Active Ingredient
25105	Technical Grade Active Ingredient	Sumitomo Chemical Company Ltd.	SUMILARV TECHNICAL GRADE	Solid	Pyriproxyfen 98.7%
25489	Manufacturing Concentrate	McLaughlin Gormley King Company	NYLAR 50% CONCENTRATE	Solution	Pyriproxyfen 50%
27545		Rolf C. HAGEN Inc.	PERMETHRIN NYLAR SQUEEZE ON MANUFACTURING BLEND	Solution	Pyriproxyfen 1.9% Permethrin 45%
27705			ETOFENPROX NYLAR SQUEEZE ON MANUFACTURING BLEND		Pyriproxyfen 2.2% Etofenprox 55%
25490	Commercial	McLaughlin Gormley King Company	NYGUARD IGR CONCENTRATE	Emulsifiable Concentrate	Pyriproxyfen 10%
28414		VALENT Canada Inc.	DISTANCE	Emulsifiable Concentrate	Pyriproxyfen 103 g/L
27581	Domestic	BAYER Inc.	ADVANTAGE II SMALL DOG	Solution	Pyriproxyfen 0.46% Imidacloprid 9.1%
27582			ADVANTAGE II LARGE DOG		
27583			ADVANTAGE II MEDIUM DOG		
27584			ADVANTAGE II EXTRA LARGE DOG		
27585			ADVANTAGE II SMALL CAT		
27586			ADVANTAGE II LARGE CAT		
29777			K9 ADVANTIX II SMALL DOG		Pyriproxyfen 0.44% Permethrin 44% Imidacloprid 8.8%
29778			K9 ADVANTIX II		

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Active Ingredient
			MEDIUM DOG		
29779			K9 ADVANTIX II EXTRA LARGE DOG		
29780			K9 ADVANTIX II LARGE DOG		
31517			ADVANTAGE II KITTENS		Pyriproxyfen 0.46% Imidacloprid 9.1%
31119	Domestic	HARTZ Canada Inc.	HARTZ ULTRAGUARD PLUS FLEA & TICK HOME SPRAY	Solution	Pyriproxyfen 0.015% D-phenothrin 0.40% Piperonyl butoxide 1%
31749			HARTZ ULTRAGUARD PRO FLEA & TICK SHAMPOO FOR DOGS	Emulsifiable Concentrate	Pyriproxyfen 0.075% D-phenothrin 0.270% S-methoprene 0.04%
25491	Domestic	McLaughlin Gormley King Company	NYLAR PRESSURIZED SPRAY 2618	Pressurized product	Pyriproxyfen 0.015% D-phenothrin 0.30% Tetramethrin 0.40%
31941	Domestic	Neogen Corporation	PROZAP PET GUARD IGR FLEA SPRAY	Pressurized product	Pyriproxyfen 0.015% D-phenothrin 0.30% Tetramethrin 0.40%
26179	Domestic	Premier Tech Ltd.	C-I-L FLEA KILLER SURFACE SPRAY	Pressurized product	Pyriproxyfen 0.015% D-phenothrin 0.300% Tetramethrin 0.400%
26502	Domestic	Rolf C. HAGEN Inc.	SERGEANT'S PRETECT HOUSEHOLD FLEA SPRAY	Pressurized product	Pyriproxyfen 0.015% D-phenothrin 0.3% Tetramethrin 0.4%
28113			SERGEANT'S PRETECT SQUEEZE-ON FLEA, TICK & MOSQUITO CONTROL FOR DOGS (UP TO 15 KG)	Liquid	Pyriproxyfen 1.9% Permethrin 45%
28280			SEARGEANT'S PRETECT SQUEEZE-ON FLEA, TICK & MOSQUITO CONTROL FOR DOGS (OVER 30 KG)	Solution	
28281			SERGEANTS PRETECT SQUEEZE-ON FLEA, TICK &MOSQUITO CONTROL FOR DOGS (15-30 KG)		

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Active Ingredient
28610			SERGEANT'S PRE TECT SQUEEZE-ON FLEA CONTROL FOR CATS AND KITTENS		Pyriproxyfen 2.2%
31608			SENTRY FLEA SQUEEZE-ON FOR CATS AND KITTENS		
31609			SENTRY FLEA, TICK & MOSQUITO SQUEEZE-ON FOR DOGS (15 TO 30 KG)		Pyriproxyfen 1.9% Permethrin 45%
31610			SENTRY FLEA, TICK & MOSQUITO SQUEEZE-ON FOR DOGS (OVER 30 KG)		
31611			SENTRY FLEA, TICK & MOSQUITO SQUEEZE-ON FOR DOGS (UP TO 15 KG)		
31647			SENTRY HOUSEHOLD FLEA SPRAY	Pressurized product	Pyriproxyfen 0.015% D-phenothrin 0.30% Tetramethrin 0.40%
32546			SERGEANT'S GUARDIAN FLEA, TICK & MOSQUITO CONTROL FOR DOGS (15 TO 30 KG)	Solution	Pyriproxyfen 1.9% Permethrin 45.0%
32547			SERGEANT'S GUARDIAN FLEA CONTROL FOR CATS & KITTENS		Pyriproxyfen 2.2%
32548			SERGEANT'S GUARDIAN FLEA, TICK & MOSQUITO CONTROL FOR DOGS (OVER 30 KG)		Pyriproxyfen 1.9% Permethrin 45.0%
32549			SERGEANT'S GUARDIAN FLEA, TICK & MOSQUITO CONTROL FOR DOGS (UP TO 15 KG)	Liquid	Pyriproxyfen 1.9% Permethrin 45.0%

Table 2 Registered Commercial and Restricted Class Uses of Pyriproxyfen as of 1 May 2019 excluding discontinued products or products with a submission for discontinuation

Site	Pest(s)	Formulation type	Application Method and Equipment	Maximum Single Application Rate	Maximum Cumulative Application Rate per Year	Maximum Number of Applications per year	Minimum Interval Between Applications (Days)
USC 5 – Greenhouse Food Crops							
Greenhouse cucumbers Greenhouse eggplant Greenhouse peppers Greenhouse tomatoes	Silverleaf whitefly, sweet potato whitefly, greenhouse whitefly	Emulsifiable Concentrate	Ground application – foliar spray	4.64 g a.i./100L	18.56 g a.i ./100L	2 per crop Maximum 2 applications per six months (4/year)	14
USC 6 – Greenhouse Non-food Crops							
Greenhouse ornamentals	Silverleaf whitefly, sweet potato whitefly, greenhouse whitefly	Emulsifiable Concentrate	Ground application – foliar spray	4.64 g a.i./100L	18.56 g a.i ./100L	2 per crop Maximum 2 applications per six months (4/year)	14
USC 20 - Structural							
Indoor (Homes, apartment buildings, Office Buildings, Automobiles, Buses, Boats, Ship Cabins and Holds, Trucks, Boxcars and Non-Food Areas of Hotels and Motels)	Fleas (inhibits growth of larvae)	Emulsifiable Concentrate	Broadcast application, spot and crack and crevice application. Any low pressure sprayer typically used for indoor applications	0.48 g a.i./100m^2	0.96 g a.i./100m^2	2	150

Table 3 Registered Domestic Class Uses of Pyriproxyfen as of 1 May 2019, excluding discontinued products or products with a submission for discontinuation[1]

Site	Pest(s)	Formulations	Application Method and Equipment	Maximum Single Application Rate (g a.i./ha)	Maximum Cumulative Application Rate per Year	Maximum Number of Applications per year[1]	Minimum Interval Between Applications[1] (Days)
USC 20 – Structural							
Indoors (Homes, garages, attics and apartments.)	Fleas (larvae) and ticks	Solution	Fine spray applied uniformly to carpets, rugs, pet bedding and all surfaces of upholstered furniture where pests are found.	6.2 mg a.i./m^2	12.4 mg a.i./m^2	[2]	[182]
Indoors (Residential and Commercial uses)	Fleas (Adults and Pre-adult)	Pressurized Product	Spot and crack-and-crevice application only Apply only to localized areas of flea infestation, such as pet bedding	6.56 mg a.i./m^2	13.12 mg a.i./m^2	[2]	[180]
USC 24 – Companion Animals							
Cats (2.3 kg or less) (Do not use on kittens under 8 weeks of age)	Fleas (larvae, adult, egg)	Solution	Place the tip of the applicator tube on the skin and squeeze the tube to completely empty the contents directly on the skin as a single spot.	1.16 mg a.i./application	13.9 mg a.i.	12	30
Cats (2.3–4 kg) (Do not use on kittens under 8 weeks of age)				2.01 mg a.i./application	24.12 mg a.i.		
Cats (over 4 kg) (Do not use on				4.03 mg a.i./application	48.4 mg a.i.		

Site	Pest(s)	Formulations	Application Method and Equipment	Maximum Single Application Rate (g a.i./ha)	Maximum Cumulative Application Rate per Year	Maximum Number of Applications per year[1]	Minimum Interval Between Applications[1] (Days)
kittens under 8 weeks of age)							
Cats (4 kg or less) (Do not use on kitten under 12 weeks of age)	Fleas (eggs)	Solution	Place the tip of the applicator tube on the skin and squeeze the tube to completely empty the contents directly on the skin as a single spot.	34.3 mg a.i./application	137.2 mg a.i.	4	90
Cats (over 4 kg) (Do not use on kitten under 12 weeks of age)					164.6 mg a.i.	4.8	75
Dogs (up to 4.5 kg) (Do not use on puppies under 7 weeks of age)	Fleas (larvae, adult, egg) and lice	Solution	Place the tip of the applicator tube on the skin and squeeze the tube to completely empty the contents directly on the skin as a single spot.	1.84 mg a.i./application	22.08 mg a.i.	12	30
Dogs (4.6 –11 kg) (Do not use on puppies under 7 weeks of age)				5 mg a.i./application	60 mg a.i.		
Dogs (11–25 kg) (Do not use on puppies under 7 weeks of age)				12.6 mg a.i./application	151 mg a.i.		
Dogs (over 25 kg)				20.1 mg a.i./application	241.2 mg a.i.		

Site	Pest(s)	Formulations	Application Method and Equipment	Maximum Single Application Rate (g a.i./ha)	Maximum Cumulative Application Rate per Year	Maximum Number of Applications per year[1]	Minimum Interval Between Applications[1] (Days)
(Do not use on puppies under 7 weeks of age)							
Dogs (4.5 kg or less) (Do not use on puppies under 8 weeks of age)	Fleas (larvae, adult, egg), ticks (adults), mosquitos (adults) and lice (adults)	Solution	Place the tip of the applicator tube on the skin and squeeze the tube to completely empty the contents directly on the skin as a single spot.	2 mg a.i./application	24 mg a.i.	12	30
Dogs (4.6 –11 kg) (Do not use on puppies under 8 weeks of age)				5 mg a.i./application	60 mg a.i.		
Dogs (11–25 kg) (Do not use on puppies under 8 weeks of age)				12.5 mg a.i./application	150 mg a.i.		
Dogs (over 25 kg) (Do not use on puppies under 8 weeks of age)				20.1 mg a.i./application	241.2 mg a.i.		
Dogs (Do not use on puppies under 6 months of age and nursing animals)	Fleas (larvae, egg), ticks (adults)	Emulsifiable Concentrate	Place the tip of the applicator tube on the skin and squeeze the tube to completely empty the contents directly on the skin as a single spot.	1.7 mg a.i./kg body weight./application	88.4 mg a.i./kg body weight	52	7

Site	Pest(s)	Formulations	Application Method and Equipment	Maximum Single Application Rate (g a.i./ha)	Maximum Cumulative Application Rate per Year	Maximum Number of Applications per year[1]	Minimum Interval Between Applications[1] (Days)
Dogs (up to 15 kg) (Do not use on puppies under 3 months)	Fleas, mosquitoes, brown dog ticks, blacklegged (deer) ticks and American dog ticks. Inhibits flea egg development.	Solution	Place the tip of the applicator tube on the skin and squeeze the tube to completely empty the contents directly on the skin as a single spot.	28.5 mg a.i./application	342 mg a.i.	12	30
Dogs (15–30 kg) (Do not use on puppies under 3 months)				57 mg a.i./application	684 mg a.i.		
Dogs (over 30 kg) (Do not use on puppies under 3 months)				85.5 mg a.i./application	1026 mg a.i.		
Dogs (up to 15 kg) (Do not use on puppies under 3 months of age and nursing animals)				32.5 mg a.i./application	390 mg a.i.		
Dogs (15–30 kg) (Do not use on puppies under 3 months of age and nursing animals)				65 mg a.i./application	780 mg a.i.		

Site	Pest(s)	Formulations	Application Method and Equipment	Maximum Single Application Rate (g a.i./ha)	Maximum Cumulative Application Rate per Year	Maximum Number of Applications per year[1]	Minimum Interval Between Applications[1] (Days)
Dogs (over 30 kg) (Do not use on puppies under 3 months of age and nursing animals)				97.6 mg a.i./application	1171.2 mg a.i.		

[1] Information in Square [ ] brackets is based upon consultation with the registrant

Appendix II Toxicological Information for Health Risk Assessment

Table 1 Chemical Names of Pyriproxyfen and Select Metabolites

Compound Identifier	Chemical Name
pyriproxyfen	4-phenoxyphenyl (RS)-2-(2-pyridyloxy) propyl ether
4'-OH -pyr	4-(4-hydroxyphenoxy)phenyl (RS)-2-(2-pyridyloxy)propyl ether
2'-OH-pyr	4-(2-hydroxyphenoxy)phenyl (RS)-2-(2-pyridyloxy)propyl ether
5",4'-OH-pyr	4-(4'-hydroxyphenoxy)phenyl (RS)-2-(5-hydroxypyridyl-2-oxy)propyl ether
5"-OH-pyr	(RS)-5-hydroxy-2-{1-methyl-2-(4-phenoxyphenoxy)}ethoxy pyridine
DPH-pyr	4-hydroxyphenyl (RS)-2-(2-pyridyloxy)propyl ether
PYPA	(RS)-2-(2-pyridyloxy)propanol
PYPAC	(RS)-2-(2-pyridyloxy)propionic acid
2-OH-py	2-hydroxypyridine
POPA	4-phenoxyphenyl (RS)-2-hydroxypropyl ether
4'-OH-POPA	4-(4-hydroxyphenoxy)phenyl (RS)-2-hydroxypropyl ether
4'-OH-POP	4,4'-oxydiphenol
2,5-OH-py	2,5-hydroxypyridine

Table 2 Summary of Toxicology Studies for Pyriproxyfen

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

Study Type/ Animal/PMRA #	Study Results
Toxicokinetic Studies	
Sprague Dawley Rat PMRA# 1143941, 1143949, 1159016	Sprague Dawley rats were given a single oral dose of 2 mg/kg bw or 1000 mg/kg bw [phenyl-^{14}C] pyriproxyfen, or a single oral dose of 2 mg/kg bw [phenyl-^{14}C] pyriproxyfen following oral administration of 2 mg/kg bw/day unlabelled pyriproxyfen over two weeks; excreta were collected over 7 days. Additionally, Sprague Dawley rats were given a single oral dose of 2 mg/kg bw [phenyl-^{14}C] pyriproxyfen and tissues were sampled at 2, 4, 8, 12, 24, 48 and 72 hrs. **Absorption:** Based on urine concentration data, pyriproxyfen was not well-absorbed. Peak blood levels following a single low dose were noted at 2 hrs (♂) or 2–24 hrs (♀); ♂ showed 4-fold higher ^{14}C concentrations in blood than ♀ until 24 hrs after administration. **Distribution:** In ♂ and ♀ rats, the maximum total tissue ^{14}C residue concentrations were 7.3% and 5.2% of the AD respectively, 8 hrs following a single oral low dose. Maximum tissue concentrations were highest in liver, blood (♂ only), kidneys and adipose tissues. The ^{14}C levels in adipose tissue

Study Type/ Animal/PMRA #	Study Results
	were the highest tissue levels after 7 days. All other non-adipose tissues contained ^{14}C residue concentrations of ≤0.001, ≤0.6, and ≤0.003 ppm for the low, high, and repeated-dose groups, respectively. There were no significant sex or dose-related differences in tissue distribution.
Sprague Dawley Rat PMRA# 2704562	PMRA #2704562 – Sprague Dawley rats were administered [pyridyl-2,6-^{14}C] pyriproxyfen as single oral doses of 2.0 mg/kg bw or 1000 mg/kg bw; urine and feces were collected for 7 days. Additional ♂ rats were orally dosed with [phenyl-^{14}C] pyriproxyfen, from which urine and feces were collected for 2 days. **Absorption:** Based on urine concentration data, pyriproxyfen was not well-absorbed. **Distribution:** Tissues accumulated very little radioactivity; fat contained the greatest amount at 0.024 - 0.042% of the AD 7 days after dosing; no dose or sex difference was noted. **Excretion:** Pyriproxyfen was rapidly eliminated with >85% of the AD eliminated in the first 48 hrs, primarily in the feces. After 7 days, >84% of the AD was in the feces and up to 12% was in the urine. Small amounts of radioactivity were detected in expired air (≤0.5% of the AD). There were no effects of sex, dose or label position on elimination. **Metabolism:** Metabolite analyses were conducted using urine and feces collected during the first 48 hrs after dosing; The major fecal metabolite was 4'-OH-pyr, comprising 23–47% of the AD. Unchanged pyriproxyfen in feces accounted for 21–35% of the AD. Minor fecal metabolites included 2'-OH-, 5"-OH-, and 5", 4'-OH-pyr. Sulfate conjugates of 4'-OH and 5", 4'-OH-pyr and a glucuronide conjugate of the 4'-OH-pyr were detected. 5", 4'-OH-pyr was detected in low-dose ♂ at 7.2% of the AD; all other minor fecal metabolites and conjugates were detected at ≤4% in both sexes at each dose. DPH-pyr, a product of cleavage of the terminal phenyl ring was present in feces at <2% of the AD. Unchanged pyriproxyfen and 4'-OH-pyr were detected in minor amounts in the urine of high-dose rats (1–3% and 1–6% respectively), but were absent in urine of the low-dose rats. PYPAC, a pyridyl metabolite from cleavage of both phenyl rings was present in urine at 1–5%, but was not detected in feces. Minor amounts of the sulfate conjugates were detected in urine. The major pathway of pyriproxyfen metabolism in rats involves hydroxylation at the 4'-position of the terminal phenyl ring. Minor pathways include hydroxylation at the 2'-position of the terminal phenyl ring and at the 5"-pyridyl position, dephenylation, cleavage of ether linkages, and formation of glucuronide and sulfate conjugates. There were no significant effects of sex or dose on the metabolic pattern of pyriproxyfen.
Acute Toxicity Studies	
Acute Oral Sprague Dawley Rat PMRA #1143889, 1159046	Low toxicity LD_{50} > 5000 mg/kg bw (corn oil) No deaths. Clinical signs (↓ spontaneous activity, soft faeces, diarrhea, ↓ bwg at ≥ 2500 mg/kg bw) resolved within 2 days.
Acute Dermal Sprague Dawley Rat	Low toxicity LD_{50} > 2000 mg/kg bw (corn oil)

Study Type/ Animal/PMRA #	Study Results
PMRA #1143893, 1159057	No deaths or clinical signs of toxicity.
Acute Inhalation (4 hr, whole body) Sprague Dawley Rat PMRA #1143894, 1159068, 2704564	Slight toxicity LC_{50} >1.3 mg/L (corn oil) **1.3 mg/L:** Transient clinical signs of toxicity, salivation (2/5 ♂ and 1/5 ♀); urinary incontinence (♀).
Primary Skin Irritation NZW Rabbit PMRA #1143896	Non-irritating. MAS = 4.5 (24, 48 and 72 hrs)
Primary Eye Irritation NZW Rabbit PMRA #1143896	Minimally irritating. MIS = 4.7 (at 1 hr)
Skin Sensitization (Maximization method) Hartley Guinea Pig PMRA #1143897	Not a dermal sensitizer.
Short-Term Toxicity Studies	
21-Day Dermal Sprague Dawley Rat PMRA #1164979	NOAEL = 1000 mg/kg bw/day (corn oil) No compound-related changes were noted.
28-Day Inhalation (whole-body) Sprague Dawley Rat PMRA #1143883	NOAEC = 0.482 mg/L (84 mg/kg bw/day)(♂); 1 mg/L (174 mg/kg bw/day)(♀) **1.00 mg/L (174 mg/kg bw/day):** salivation during initial exposures; ↓ bw, ↑ LDH, ↓ abs lung wt (♂); ↑ wc (♀).
90-Day Oral (dietary) CDBR Rat PMRA #1143899, 1159075	NOAEL = 400 ppm (24/28 mg/kg bw/day in ♂/♀) **≥2000 ppm (118/141 mg/kg bw/day):** cytoplasmic change consisting of ↑ in cytoplasmic content, ↓nucleus/cytoplasm ratio and ↓ sinusoidal space; ↓ RBC, ↓ Hgb, ↓Hct, ↑ cholesterol, ↑ phospholipid, ↑ rel liver wt (♂); ↓MCV (♀). **≥5000 ppm (309/356 mg/kg bw/day):** ↓ bw, ↑ liver wt; ↑ rel kidney wt (♂); ↓ RBC, ↓ Hgb, ↓Hct, ↑ cholesterol (♀). **10 000 ppm (642/784 mg/kg bw/day):** ↑ total protein, ↑ albumin; ↑ phospholipid, ↑ rel kidney wt (♀).
90-Day Oral (dietary)	NOAEL = 1000 ppm (149/197 mg/kg bw/day in ♂/♀)

Study Type/ Animal/PMRA #	Study Results
CD-1 Mouse PMRA #1164978	**≥5000 ppm (838/964 mg/kg bw/day):** hunched posture, few or no feces, ↓Hgb, ↓ Hct, ↑ platelets, ↑ wc, ↑ BUN, ↑ rel liver wt, renal effects (tubular nephrosis, dilation of renal tubules and pelvis, focal mineralization); ↑ mortality, ↓ bw, ↓ bwg, ↑ rel adrenal gland wt, ↓ MCV, ↓ MCH, ↑ AST, ↑ ALT, thymic lymphoid depletion, bone marrow myeloid hyperplasia, ↑ spleen pigmentation (♂); thin appearance, ↓ RBC, ↑ cholesterol, ↑ phospholipids, ↑ abs liver wt (♀). **10,000 ppm (2035/2345 mg/kg bw/day):** myeloid hyperplasia of bone marrow, cardiomyopathy, thymic atrophy; ↓ RBC, mortality, ↓ bw, thymic lymphoid depletion, ↑ spleen pigmentation, extra medullary hematopoiesis (♀).
90-Day Oral (capsule) Beagle Dog PMRA #1143898	NOAEL = 100 mg/kg bw/day (♀); 300 mg/kg bw/day (♂) **≥300 mg/kg bw/day:** ↑ liver wt; hepatocellular enlargement, ↑ cholesterol, ↑ phospholipid (♀). **1000 mg/kg bw/day:** hepatic cytoplasmic changes (eosinophilic bodies, ↑ in smooth endoplasmic reticulum proliferation, dilation of endoplasmic reticulum); hepatocellular enlargement (♂).
52-Week Oral (capsule) Beagle Dog PMRA #1143882, 2704560, 1159076	NOAEL = 30 mg/kg bw/day (♂); 100 mg/kg bw/day (♀) **≥30 mg/kg bw/day:** ↑ rel liver wt (♂). **≥100 mg/kg bw/day:** ↓ bwg, ↑ cholesterol, ↑ liver wt; ↓bw, ↑ triglycerides, ↑ ALK in one animal (♂) **≥300 mg/kg bw/day:** ↑ ALK; thin appearance, ↑ platelets, submucosal fibrosis of the gall bladder (♂); ↓ bw, ↑ triglycerides, ↑ rel kidney wt, ↑ thyroid wt (♀). **1000 mg/kg bw/day:** salivation, diarrhea, emesis, ↑ ALT, centriacinar fibrosis, bile duct hyperplasia, active chronic inflammatory infiltrate, submucosal edema of the gall bladder; 2 mortalities (sacrificed due to toxicity), bw loss, ↑ prothrombin time, ↑ AST, ↑ bilirubin, ↑ urinary volume, ↓ pH, nodular hyperplasia, (♂); ↑ platelets, submucosal fibrosis of the gall bladder (♀).
52-Week Oral (capsule) Beagle Dog PMRA #2704560	NOAEL = 10 mg/kg bw/day ≥3 mg/kg bw/day: slight ↑ platelets (♂). 10 mg/kg bw/day: slight ↑ platelets (♀).
Chronic Toxicity/Oncogenicity Studies	
78-Week Oncogenicity (dietary) CD-1 Mouse PMRA #1143912, 1143930, 1159013, 1169747, 2704561	NOAEL = 120 ppm (16 mg/kg bw/day) (♂); 600 ppm (107 mg/kg bw/day)(♀) **≥120 ppm (16/21 mg/kg bw/day:** hunched posture. **≥600 ppm (79/107 mg/kg bw/day):** ↓ survival after week 64, ↑ severity of amyloidosis in kidneys, thyroid, parathyroid and stomach of decedents (♂). **3000 ppm (413/530 mg/kg bw/day):** ↓ bw, granular/pitted/rough kidneys,

Study Type/ Animal/PMRA #	Study Results
	accelerated development and severity of amyloidosis (multi-tissue), ↑ incidence of chronic progressive nephropathy, ↑ incidence of mineralized renal tubules; ↓ survival after week 60, ↓ motor activity, ↓ bwg up to wk 24, ↓ abs kidney wt at termination (♂); ↓ survival after wk 64, ↓ bwg, erythrocyte changes at wk 52 (↓ Hgb, slight ↓ RBC, slight ↓ Hct, ↑ polychromatic RBC), ↑ liver wt at wk 52, ↑ abs spleen wt at wk 52 (♀). No evidence of carcinogenicity.
2-Year Chronic Toxicity/Oncogenicity (dietary) Sprague Dawley Rat PMRA #1143884, 1143902, 1143903, 2704559, 2704558, 1159077, 1164935	NOAEL = 600 ppm (27/35 mg/kg bw/day) **≥600 ppm (27/35 mg/kg bw/day:** ↓ urinary pH at wk 26 (♀)(non-adverse). **3000 ppm (138/183 mg/kg bw/day):** ↓ bw, ↓bwg, ↑ phospholipid and cholesterol at wk 26; ↑ cholesterol wks 52, 78 (♂); ↑ urinary protein at wk 26, ↑ rel liver wt at interim and terminal sacrifice (♀). No evidence of carcinogenicity.
Developmental/Reproductive Toxicity Studies	
Two-generation Reproductive Toxicity (dietary) Sprague Dawley Rat PMRA #1143904, 1143905	**Parental** NOAEL = 1000 ppm (64/103 mg/kg bw/day) **≥1000 ppm (80 mg/kg bw/day):** ↑ rel liver wt, ↑ rel kidney wt (F_1♂). **5000 ppm (328/531 mg/kg bw/day):** ↓ bw (pre-mating, F_0, F_1), ↓ bwg (pre-mating, F_0, F_1), sporadic ↓ fc, ↑ liver wt (F_1); chronic interstitial nephritis, focal clear cells in liver (F_1 ♂). **Offspring** NOAEL = 1000 ppm (103 mg/kg bw/day) **5000 ppm (531 mg/kg bw/day):** ↓ pup bw PND 14 and 21 (F_1 and F_2). No evidence of increased sensitivity of the young. **Reproductive** NOAEL = 5000 ppm (328/531 mg/kg bw/day) No effect on reproductive parameters.
Reproductive/Developmental Toxicity – non-guideline (gavage) Sprague Dawley Rat PMRA #2704582 Exposure from 9-weeks pre-mating to GD 7 and examination of fetuses at GD 21	**Parental** NOAEL = 100 mg/kg bw/day **≥100 mg/kg bw/day:** transient salivation immediately following dosing; ↑ wc, ↑ rel liver wt, ↑ rel kidney wt, ↑ adrenal wt (♂). **≥300 mg/kg bw/day:** erythema, ↓ bwg; ↓ bw, ↑ fc, ↓ thymus wt, ↑ abs liver wt, ↑ abs kidney wt, enlargement of the liver, dark-red colour of the liver, pitted surface of the kidney, enlargement of the adrenals (♂); diarrhea, swelling of the periproctal region, ↑ wc during gestation (♀). **≥500 mg/kg bw/day:** diarrhea, swelling of the periproctal region, enlargement of the kidney (♂); ↑wc during pre-mating (♀). **1000 mg/kg bw/day:** lacrimation, atrophy of the thymus (♂); mortality in 2

Study Type/ Animal/PMRA #	Study Results
	animals, ↓ bw, ↑fc during gestation, hypoactivity, wasting (♀). **Developmental** NOAEL = 1000 mg/kg bw/day No effects on fetal weight, sex or development. **Reproductive** NOAEL = 500 mg/kg bw/day **1000 mg/kg bw/day:** ↓ number of corpora lutea per dam. No evidence of sensitivity of the young.
Developmental Toxicity (gavage) Sprague Dawley Rat PMRA #1143907, 1159015 Exposure from GD 7-17, examination of fetuses at GD 21 and pups at 3 weeks (general toxicity), 8 weeks (open field test, motor co-ordination test and learning ability) and 11 weeks (reproductive performance)	**Maternal** NOAEL = 100 mg/kg bw/day **100 mg/kg bw/day:** transient ↓ bwg. **≥300 mg/kg bw/day:** ↓ bw, ↓ bwg, ↓ fc, ↑ wc, ↑ rel liver wt, ↑ rel kidney wt. **1000 mg/kg bw/day:** ↑ mortality (all deaths occurring after 4-9 doses), soft stool, erythema, swelling of the periproctal region, bw loss in first few days of dosing, ↑ adrenal wt, ↓ thymus wt, ↓ abs spleen wt, ↓ abs heart wt, ↑ abs kidney wt, adrenal enlargement (GD 21), thymic involution (GD 21), ↑ early resorptions (attributable to 100% resorptions in 2 dams). Dams that died showed hypoactivity, wasting, bloody dirtiness around the nose, blanching of the auricle and extremities, hypothermia, kidney and liver congestion, splenic atrophy, adrenal enlargement, thymic involution, stomach haemorrhage or ulceration. **Developmental/Offspring** NOAEL = 100 mg/kg bw/day **≥300 mg/kg bw/day:** ↑ incidence of opening of the 7th cervical vertebra foramen transversium, ↑ total incidence of skeletal variations in 3-wk-old pups. **1000 mg/kg bw/day:** ↑ total fetal incidence of skeletal variations**,** ↑ incidence of renal pelvis dilatation in 3- and 8-wk-old pups, ↑ rel kidney wt in 8-wk-old ♀ pups. No effects on sensory function, behaviour, motor coordination or learning ability in pups. **Reproductive** NOAEL = 1000 mg/kg bw/day No effects on reproductive performance in pups. No evidence of sensitivity of the young. Not teratogenic.
Reproductive/Developmental Toxicity (gavage)	**Maternal** NOAEL = 100 mg/kg bw/day **≥300 mg/kg bw/day:** diarrhea, salivation, ↓bw (GD 20-22), ↓fc (GD 19-22,

Study Type/ Animal/PMRA #	Study Results
Sprague Dawley Rat PMRA #2704580 Exposure from GD 17-LD20, examination of pups at PND 4 (skeletal anomalies), 3 weeks (general toxicity), 8 weeks (open field test, motor co-ordination test and learning ability) and 11 weeks (reproductive performance)	LD21), ↑liver wt. **500 mg/kg bw/day:** mortality (2 dams after 5 doses), erythema and swelling of the periproctal region, hypoactivity, lacrimation, rough hair, hypothermia, atrophy of the thymus, congestion of liver, atrophy of spleen and adrenals, ulcers of the stomach. **Offspring** NOAEL = 100 mg/kg bw/day **≥300 mg/kg bw/day:** ↓pup weight (PND 0-56), ↑incidence of dilatation of the renal pelvis, equivocal ↓viability index at PND 21. **500 mg/kg bw/day:** ↓viability index at PND 4 and 21 (F_1), slight delay in vaginal opening (F_1). No effects on sensory function, behaviour, motor coordination or learning ability in pups. **Reproductive** NOAEL = 100 mg/kg bw/day **300 mg/kg bw/day:** ↓pup birth wt (F_1) **500 mg/kg bw/day:** ↓ mean implantations (F_1), ↑pre-implantation loss (F_1), ↓livebirth index (F_1), ↓litter size (F_1). No evidence of sensitivity of the young.
14-Day Toxicity (gavage) JW NIBS Rabbit (non-pregnant) PMRA #2704576	Range-finding study - supplemental 1000 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc.
Developmental Toxicity (gavage) JW-NIBS Rabbit PMRA #1143906, 1159014, 1164980	**Maternal** NOAEL = 100 mg/kg bw/day **≥300 mg/kg bw/day:** ↓ bwg, ↓ fc, late abortions/ premature deliveries, in dams that aborted, delivered prematurely or died: soft stool, emaciation, lustreless fur, ↓ activity, bradypnea, abnormally coloured intestinal contents, gall bladder distention, watery/abnormally coloured bile, trace gastro-intestinal haemorrhage and gas retention, and kidney discolouration were observed. **1000 mg/kg bw/day:** ↓ bw, bw loss (GD 6-18), mortality, splenic congestion. **Developmental** NOAEL = 300 mg/kg bw/day **1000 mg/kg bw/day**: ↑ incidence of abnormal location of posterior vena cava.

Study Type/ Animal/PMRA #	Study Results
	No evidence of increased sensitivity of the young. Not teratogenic. Note: litters available for examination were 13, 12, 11 and 4 at 0, 100, 300, 1000 mg/kg bw/day respectively.
Genotoxicity Studies	
In vitro Bacterial Reverse Mutation Assay *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538; *E. Coli* WP2uvrA PMRA #1143910	Negative with and without activation.
In vitro Mammalian Gene Mutation Assay Chinese hamster V79 lung cells PMRA #1143911	Negative with and without activation.
In vitro Unscheduled DNA Synthesis Assay HeLa S3 cells PMRA #1143909	Negative with and without activation.
In vitro Chromosome Aberration Assay Chinese hamster ovary cells (CHO-K1) PMRA #1143908	Negative with and without activation.
In vivo Micronucleus Assay CD-1 Mouse PMRA #621875	Negative at 5000 mg/kg bw (corn oil).
Neurotoxicity Studies	
Acute Neurotoxicity (gavage) Sprague Dawley Rat PMRA #2704596	Range-finding study - supplemental No treatment-related findings were noted up to and including 2000 mg/kg bw.
Acute Neurotoxicity (gavage) Sprague Dawley Rat PMRA #2704607	NOAEL = 300 mg/kg bw (♂), 1000 mg/kg bw (♀) **≥1000 mg/kg bw:** ↓ motor activity at 8 hrs post-dosing (♂). **2000 mg/kg bw:** unkempt appearance on day 1 post-dosing (♀).

Study Type/ Animal/PMRA #	Study Results
90-Day Neurotoxicity (dietary) Sprague Dawley Rat PMRA #2704606	Range-finding study - supplemental **≥7500 ppm (691/762 mg/kg bw/day):** ↓ bw, ↓ bwg, ↓ fc (♂). **15000 ppm (1359/1468 mg/kg bw/day):** ↓ bw, ↓ bwg (♀).
90-Day Neurotoxicity (dietary) Sprague Dawley Rat PMRA #2704608	NOAEL = 5000 ppm (359/407 mg/kg bw/day) **15000 ppm (1111/1212 mg/kg bw/day):** ↓ bw, ↓ bwg, ↓ fc. No evidence of neurotoxicity.
Special Studies (non-guideline)	
28-Day Immunotoxicity (dietary) CD-1 Mouse PMRA #2704592	Range-finding study **≥4000 ppm (with and without sRBC):** slight bw loss or ↓ bw gain in first four days of dosing, ↓ fc in first wk of dosing, ↑ liver wt. **7000 ppm (with and without sRBC):** hunched posture, dull eyes, piloerection, bw loss, ↓fc, ↑ phospholipid, ↑ cholesterol, ↑ plasma creatinine, ↑ BUN, ↑ kidney wt, enlargement of kidney, pallor, pelvic dilatation, thickened capsule in kidney, granular appearance to the kidney surface, kidney cysts, dilatation of the ureters. **7000 ppm (with sRBC):** ↓ thymus wt.
28-Day Immunotoxicity (dietary) CD-1 Mouse PMRA #2704593	NOAEL = 5000 ppm (1139 mg/kg bw/day) **≥1000 ppm (228 mg/kg bw/day):** ↑ rel liver wt. **≥2000 ppm (449 mg/kg bw/day):** ↑ abs liver wt. **5000 ppm (1139 mg/kg bw/day):** ↓ bwg.
Uterotrophic Assay (gavage for 3 days) Sprague Dawley Juvenile ♀ Rat PMRA #2704584	**≥500 mg/kg bw/day:** rel liver wt. **1000 mg/kg bw/day:** ↓ bw, ↓ bwg, ↑ abs liver wt, ↑ rel kidney wt. No treatment-related effects on uterine wt; positive controls demonstrated expected results.
Hershberger Assay (gavage for 10 days) Sprague Dawley ♂ Rat PMRA #2704597	**1000 mg/kg bw/day:** sporadic occurrences of stained anus and soft stools, ↓ bwg in anti-androgen assay only, ↑ liver wt, ↑ kidney wt. No treatment-related effects on accessory sex organ wts; positive controls demonstrated expected results. Negative for androgenicity and anti-androgenicity.
Pubertal Development and Thyroid Function Assay in ♂ Sprague Dawley Juvenile/Peripubertal ♂ Rat PMRA #2704605	**≥500 mg/kg bw/day:** clear material around mouth post-dosing, ↑ liver wt, ↓ ventral prostate wt, dorsolateral prostate wt , ↑ serum urea nitrogen, ↓ testosterone, hepatocellular hypertrophy, ↑ severity of hepatocellular mitotic figures, renal tubular dilatation and degeneration, ↓ incidence of renal mononuclear infiltrate, ↑ incidence of slight reduction in thyroid colloid area, ↑ slight increase in thyroid follicular cell height.

Study Type/ Animal/PMRA #	Study Results
	1000 mg/kg bw/day: ↓ bw, ↓ bwg, delay for complete preputial separation, two ♂ with small sex organs at necropsy, ↑ kidney wt, ↓ seminal vesicle wt, ↓ LABC wt, ↓ epididymis wt, ↓ testis wt, ↓ incidence of renal basophilic tubules, renal mineralization. No effect on serum T4, TSH.
Pubertal Development and Thyroid Function Assay in ♀ (gavage for 20 days) Sprague Dawley Juvenile/Peripubertal ♀ Rat PMRA #2704602	**≥500 mg/kg bw/day:** one mortality, ↑ liver wt, ↑ kidney wt, hepatocellular hypertrophy and mitotic figures, renal tubular degeneration and/or dilatation, ↓ incidence of renal mononuclear infiltrate. **1000 mg/kg bw/day:** ↓ bw, ↓ bwg, delay for incomplete vaginal opening, ↓ ♀ cycling regularly, ↑ BUN, slight ↑ TSH, ↓ ovary wt, ↓ incidence of renal basophilic tubules. No effect on complete vaginal opening time, day of first estrus, estrous cycle length, number of animals cycling, pathology of ovary, uterus or thyroid, thyroid wt or serum T4.
Testosterone and Thyroid Gland Mechanistic Study (gavage for 30 days) Sprague Dawley Juvenile/Peripubertal ♂ Rat PMRA #2704604	**≥500 mg/kg bw/day:** ↓ bw, ↓ bwg, delay in complete preputial separation, ↑ cholesterol, ↓ triglycerides, ↑ serum urea nitrogen, ↑hepatic enzymes CYP2b, CYP4A, UGT, CYP3A, ↓ testosterone, ↑ rel liver wt, ↑ rel kidney wt, ↓ abs LABC wt, hepatocellular hypertrophy, proliferation of smooth endoplasmic reticulum, ↑ severity of focal basophilic renal tubules, renal tubular degeneration, necrosis and dilatation, renal mineralization, ↓ colloid area in thyroid, ↑ thyroid follicular cell height. **1000 mg/kg bw/day:** one death (enlarged adrenal and testis and small thymus at necropsy), ↓T4, ↓ rel LABC wt, ↓ abs epididymides wt, slight renal papillary edema. No effect on 17β-hydroxysteroid dehydrogenase activity in the testis. Positive controls showed induction of hepatic microsomal enzymes (CYP2B, CYP4A, UGT, CYP3A with phenobarbital, CYP4A with DEHP), ↑ liver wt, hepatocellular hypertrophy, reduced thyroid colloid area, ↑ thyroid follicular cell height; phenobarbital also had ↓T3, ↑TSH and slightly ↓ testosterone. Positive controls did not demonstrate anti-androgenic activity at dose level tested.
In vitro Aromatase Inhibition Assay Human recombinant aromatase (CYP19) microsomes PMRA #2704598	No inhibition of aromatase activity.
In vitro Androgen Receptor Binding Assay Ventral prostate cytosol from Sprague Dawley rat PMRA #2704599	No effect on specific binding of ligand in competitive binding experiment, thus considered a non-binder.
In vitro Steroidogenesis Assay	Precipitation at 100 µM and cytotoxicity at 30 µM No effect on testosterone production up to 10 µM

Study Type/ Animal/PMRA #	Study Results
H295R human adrenocortical carcinoma cells PMRA #2704600	↑ estradiol production (1.7-1.8-fold) at 10 μM.
In vitro Estrogen Receptor Binding Assay Uterine cytosol from Sprague Dawley rat PMRA #2704601	No effect on specific binding of ligand in competitive binding experiment, thus considered a non-binder.
ToxCast Studies Cell-free high-throughput assays PMRA #2704603	Inhibition of radio-ligand binding was less than 50% for all concentrations (0.02-50 μM) for bovine and human estrogen receptors, bovine and human progesterone receptors, rat and human androgen receptors and human thyroid receptor-α. Inhibition of human aromatase enzyme activity less than 50% for all concentrations (0.009-20 μM).
ToxCast Studies Cell-based high-throughput assays PMRA #2704603	Inactive for agonist activity at the human AR, human ER-α and the human thyroid hormone receptor-β. Pyriproxyfen did not block (or antagonize) the activity of established ligands at these receptor sites.
In vitro Estrogen Receptor Transcriptional Activation Assay BG1 human ovarian carcinoma cells PMRA #2831625	EC_{10} of 2.9×10^{-5}M Weakly estrogenic.
In vitro Estrogenic Activity mtT/Se rat pituitary tumour cells PMRA #2831627	EC_{10} of 5.5×10^{-5}M Weakly estrogenic.
In vitro Cytotoxic Response (neutral red incorporation assay) Chinese hamster ovary K1 cells PMRA #2831624	Pyriproxyfen showed increased cytotoxicity with time – NRI_{50} values were 377, 83 and 59 μM following 24, 48 and 72 hrs incubation resp. The inclusion of fetal calf serum or bovine serum albumin diminished the cytotoxicity suggesting protein binding. Pre-incubation of pyriproxyfen with 0, 4, 10 or 30% S9 fraction for 24 hrs also diminished the cytotoxicity suggesting that the phase I metabolites were less toxic than pyriproxyfen.
In vitro Hepatotoxic Response (MTT assay) Hepatoma HepG2 cells PMRA #2831626	Pyriproxyfen was cytotoxic at all concentrations (cell viability approximately 50% at 1-10 ppm and <10% at 100 ppm) with both 24 and 48 hr incubation in MTT assay. Intracellular lipids were increased at ≥ 1 ppm (using oil-red-O staining).

Study Type/ Animal/PMRA #	Study Results
Pyriproxyfen Metabolite Studies	
Acute Oral Toxicity 4'-OH-pyr 5"-OH-pyr DPH-pyr POPA PYPAC CD-1 mouse PMRA #2704568	LD_{50} >2000 mg/kg bw (methylcellulose) for all metabolites tested **≥1000 mg/kg bw:** 5"-OH-pyr: ↓ spontaneous activity. **2000 mg/kg bw:** 5"-OH-pyr: death in 1 out of 5 ♂, ataxic gait. DPH-pyr: ↓ spontaneous activity, ataxic gait, prone position. POPA: ↓ spontaneous activity, ataxic gait, prone position, lateral position, irregular respiration. PYPAC: ↓ spontaneous activity. All clinical signs disappeared after 24 hrs.
Acute Oral Toxicity 2,5-OH-py CD-1 mouse PMRA #2704569	LD_{50} = 1150 mg/kg bw (♂), 1000 mg/kg bw (♀) (methyl cellulose) **≥250 mg/kg bw:** ↓ spontaneous activity (♂). **≥500 mg/kg bw:** ataxic gait, mortality in 1 animal after 4 days (♂); ↓ spontaneous activity (♀). **≥1000 mg/kg bw:** prone position, irregular respiration, hypothermia, mortality after 24 hrs (♂); ataxic gait, irregular respiration, mortality within 2-24 hrs (♀). **≥2000 mg/kg bw:** mortality within 2-24 hrs (♂).
Acute Oral Toxicity 2-OH-py CD-1 mouse PMRA #2704570	LD_{50} = 124 mg/kg bw (♂), 166 mg/kg bw (♀) (distilled water) **≥50 mg/kg bw:** ↓ spontaneous activity. **≥140 mg/kg bw:** ataxic gait, irregular respiration; mortality in 4/5 animals within 48 hrs (♂); mortality in 1 animal within 48 hrs (♀). **≥190 mg/kg bw:** mortality in all animals within 24 hrs (♂); mortality in 4/5 animals within 72 hrs (♀). **≥270 mg/kg bw:** mortality in all animals within 24 hrs (♀).
In vitro Bacterial Reverse Mutation Assay 2,5-OH-py *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538; *E. Coli* WP2uvrA PMRA #2704573	Negative with and without metabolic activation.
In vitro Bacterial Reverse	Negative with and without metabolic activation.

Study Type/ Animal/PMRA #	Study Results
Mutation Assay 4'-OH-pyr 5"-OH-pyr DPH-pyr POPA PYPAC *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538; *E. Coli* WP2uvrA PMRA #2704574	
In vitro Bacterial Reverse Mutation Assay 2-OH-py *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538; *E. Coli* WP2uvrA PMRA #2704575	Negative with and without metabolic activation.

Table 3 Reference Values for Use in Human Health Risk Assessment for Pyriproxyfen

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary	Not required as no endpoint of concern attributable to a single exposure was identified.		
Repeated dietary	Mouse oncogenicity	NOAEL = 16 mg/kg bw/day Reduced survival	100
ADI = 0.2 mg/kg bw/day			
Short- and intermediate-term dermal[2] and inhalation[3] (adults)	Rabbit developmental toxicity	NOAEL = 100 mg/kg bw/day Increased abortions/premature deliveries	300
Short- and intermediate-term dermal[2] and inhalation[3] (children)	Rat developmental toxicity	NOAEL = 100 mg/kg bw/day Reduced pup weight and equivocal decrease in pup viability	100
Long-term dermal[2] and inhalation[3]	Mouse oncogenicity	NOAEL = 16 mg/kg bw/day Reduced survival	100
Non-dietary oral ingestion (short-term)	90-Day rat toxicity	NOAEL = 24 mg/kg bw/day Effects on liver and hematology	100
Short- and intermediate term aggregate (adults)	Rabbit developmental toxicity	NOAEL = 100 mg/kg bw/day Increased abortions/premature deliveries	300

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Short- and intermediate term aggregate (children)	Rat developmental toxicity	NOAEL = 100 mg/kg bw/day Reduced pup weight and equivocal decrease in pup viability	100
Long-term aggregate	Mouse oncogenicity	NOAEL = 16 mg/kg bw/day Reduced survival	100
Cancer	No evidence of carcinogenicity in mice or rats. A cancer risk assessment is not required.		

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

[2] Since an oral NOAEL was selected, a dermal absorption factor was used in a route-to-route extrapolation

Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Appendix III Dietary Exposure and Risk Assessments

Summary of Dietary Exposure and Risk from Pyriproxyfen		
Population Subgroup	**Chronic Dietary[1] (Food Only)**	
	Exposure (mg/kg bw/day)	**%ADI**
General Population	0.009679	4.8
All Infants (<1 year old)	0.014614	7.3
Children 1-2 years old	**0.025863**	**12.9**
Children 3-5 years old	0.022463	11.2
Children 6-12 years old	0.014221	7.1
Youth 13-19 years old	0.008737	4.4
Adults 20-49 years old	0.008184	4.1
Adults 50-99 years old	0.007215	3.6
Females 13-49 years old	0.007887	3.9

[1] Acceptable Daily Intake (ADI) of 0.2 mg/kg bw/day applies to the general population and all population subgroups.

Food Residue Chemistry Summary

Currently registered food uses of pyriproxyfen in Canada are greenhouse uses on tomato, pepper, cucumber and eggplant. In addition, some products containing pyriproxyfen (for example, NYLAR®) are registered for space, general surface, spot, and/or crack and crevice treatment, provided that exposed food is covered or removed from the area being treated prior to application.

The first comprehensive dietary risk assessment for pyriproxyfen was conducted in support of the Proposed Registration Decision Document PRDD2006-04, *Pyriproxyfen*, published on 12 September 2006 for greenhouse use on tomato, cucumber and pepper. The assessment was updated in 2011 for the use expansion to greenhouse eggplant. Further updates were conducted in 2013 and 2015 in support of the establishment of MRLs on various imported commodities.

The residue chemistry database for pyriproxyfen is complete and up-to-date for the registered uses. The residue definition in plant and animal commodities was previously determined to be pyriproxyfen per se for enforcement and risk assessment purposes. No change is being proposed as a result of this re-evaluation. This residue definition is aligned with current residue definitions established by the United States Environmental Protection Agency (USEPA), the European Food Safety Authority (EFSA) and JMPR/Codex. It should be noted that, in addition to parent pyriproxyfen, the USEPA has included the free and sulfate forms of the metabolite 4-OH-pyr in its residue definition for animal commodities. However, USEPA concluded that there is no expectation of finite residues in animal commodities and, therefore, waived the necessity of establishing tolerances in animal commodities. There are currently no Canadian registrations on major livestock feed items.

A gas chromatography with nitrogen-phosphorus detection (GC/NPD) method is available for enforcement of pyriproxyfen MRLs. The limit of detection (LOD) and limit of quantitation (LOQ) are 0.01 and 0.02 ppm, respectively. In addition, pyriproxyfen is included in the scopes of multiresidue analytical methods used by the Canadian Food Inspection Agency (CFIA) and the United States Department of Agriculture Pesticide Data Program (USDA PDP).

Appendix IV Occupational Mixer/Loader/Applicator and Postapplication Risk Assessment

Table 1 Occupational Mixer/Loader/Applicator Exposure and Risk Assessment

Scenario[a]	Application Equipment	Application Rate[b]	ATPD[c]	Exposure[d] (mg/kg bw/day)			MOE		
				Dermal	Inhalation	Combined	Dermal[e]	Inhalation[f]	Combined
Mixer/Loader/Applicator: Single Layer, CR gloves									
Indoor Structures (crack & crevice, spot, broadcast) (T = 300)	MPHW	0.16 g a.i./L	40 L	6.9×10^{-3}	2.6×10^{-5}	6.9×10^{-3}	14600	3810000	14500
Greenhouse Ornamentals, Tomatoes, Cucumbers, Peppers, Eggplants (T = 100)	MPHG	0.0464 g a.i./L[g]	3800 L	1.2×10^{-2}	3.3×10^{-4}	1.3×10^{-2}	8100	300500	7900
	MPHW		150 L	8.2×10^{-5}	3.9×10^{-6}	8.6×10^{-5}	1218400	25429800	1162700
	Backpack			4.7×10^{-4}	1.3×10^{-5}	5.4×10^{-6}	211100	18509300	208700

ATPD = Volume treated or handled per day; MOE = Margin of Exposure; Single layer = long-sleeved shirt, long pants; MPHG = Mechanically Pressurized Handgun; MPHW = Manually-Pressurized Hand wand; T = Target MOE; CR = chemical-resistant

[a] The application method or scenario where the application equipment may be used.

[b] Maximum application rates were used for each scenario/application equipment.

[c] Volume treated or handled per day values.

[d] Exposure = Unit Exposure (µg/kg a.i.) × ATPD × Application Rate × dermal absorption (100%) / Body Weight (80 kg). Unit exposure values from PHED or Krolski, 2014.

[e] Dermal MOEs for short-to-intermediate term exposure scenarios are based on a NOAEL of 100 mg/kg bw/day (target MOE is 300) from an oral rabbit developmental toxicity study.

[f] Inhalation MOEs for short-to-intermediate term exposure scenarios are based on a NOAEL of 100 mg/kg bw/day (target MOE is 300) from an oral rabbit developmental toxicity study.

[g] Application rate to greenhouse ornamentals is 29.7 g a.i./ha, but only highest rate to all greenhouse crops (92.8 g a.i./ha) was shown in this risk assessment.

Table 2 Occupational Postapplication Exposure and Risk Assessment

Use(s)	Rate[a] (g/ha)	NAPS	Interval (days)	Activity[b]	TC (cm^2/hr)	DFR[c] Inputs			Day 0 Dermal Estimates[f]		REI (days)
						Peak	Disp	DFR_0[f]	Exposure[d] (µg/kg bw/day)	MOE[e]	
Cut Flowers	29. 7	4	14	Pruning, Disbudding, Hand Harvesting	4000	25%	2.3%	0.19	77.8	200	0.5

Use(s)	Rate[a] (g/ha)	NAPS	Interval (days)	Activity[b]	TC (cm^2/hr)	DFR[c] Inputs			Day 0 Dermal Estimates[f]		REI (days)
						Peak	Disp	DFR_0[f]	Exposure[d] (µg/kg bw/day)	MOE[e]	
GH Ornamentals (Non-cut flowers)				All activities	230				4.47	3580	
GH tomatoes, peppers, cucumbers, eggplants	92.8				1400		0%	0.93	130	120	

NAPS = Number of Applications per Season, TC = Transfer Coefficient, DFR = Dislodgeable Foliar Residue, Peak = Peak DFR as Percent of Application Rate, Disp = Percent Dissipation per Day, DFR_0 = Day 0 DFR (ug/cm^2), MOE = Margin of Exposure, REI = Restricted-Entry Interval, GH = Greenhouse

[a] Maximum application rates were used.

[b] Activity with the highest TC for each crop was included in this table.

[c] The default peak DFR value of 25% of the application rate was assumed and a dissipation rate of 2.3%/day was assumed for greenhouse ornamental scenarios, a dissipation rate of 0%/day was assumed for greenhouse vegetable scenarios

[d] Dermal exposure on Day 0 after application = TC × DFR × 8 hours/day × Dermal Absorption (100%) / Body Weight (80 kg).

[e] Dermal MOEs for long-term exposure scenarios are based on a NOAEL of 16 mg/kg bw/day (target MOE is 100) from an oral mouse oncogenicity study.

[f] Calculated for day 0 after the last application.

Appendix V Residential Applicator and Postapplication Risk Assessment

Table 1 Residential Applicator Exposure and Risk Assessment

Scenario[a]	Application Rate[b]	ATPD/Amount Handled per Day[c]	Absorbed Dose (mg/kg bw/day)[d]		MOE (T = 300)		
			Dermal	Inhalation	Dermal[e]	Inhalation[f]	Combined
Spot, crack and crevice (Pressurized product can)	0.000075 kg a.i./can	0.5 can	0.0003824	0.0000031	260000	32000000	260000
Spot, crack and crevice (trigger spray bottle)	0.000088 kg a.i./can	0.5 bottle	0.0001032	7.15×10^{-8}	1100000	1500000000	1100000
Broadcast (trigger spray bottle)		1 bottle	0.0002063	1.43×10^{-5}	530000	760000000	530000
Treated pets (shampoo)	0.0001995 kg a.i./pet	2 pets	0.0219911	0.0000032	4500	31000000	4500
Treated pets (spot-on)[g]	0.0000976 kg a.i./pet		0.0006455	NA	150000	NA	NA

ATPD = Area Treated Per Day; MOE = Margin of Exposure; T = Target MOE; NA = Not Applicable

[a] The application method or scenario where the application equipment may be used.

[b] Maximum rates were used for each scenario/application equipment.

[c] Volume treated or handled per day values.

[d] Absorbed Dose = Unit Exposure (µg/kg a.i.) × ATPD × Application Rate × Dermal Absorption (100%) / Body Weight (80 kg). Unit exposure values from USEPA, 2012.

[e] Dermal MOEs for short-to-intermediate term exposure scenarios are based on a NOAEL of 100 mg/kg bw/day (target MOE is 300) from an oral rabbit developmental toxicity study.

[f] Inhalation MOEs for short-to-intermediate term exposure scenarios are based on a NOAEL of 100 mg/kg bw/day (target MOE is 300) from an oral rabbit developmental toxicity study.

[g] Applicator was wearing gloves in the study used to determine exposure for this scenario. Inhalation exposure is considered to be negligible for spot-on applications (USEPA, 2012).

Table 2 Residential Postapplication Dermal Exposure and Risk Assessment

Exposure Scenario			Lifestage	TR [a] (µg/cm^2)	TC [b] (cm^2/hr)	ET [c] (hr/day)	Dermal Dose [d] (mg/kg bw/day)	MOE [e]
Applied by commercial applicator								
Indoor Environments	Broadcast	Soft surface	Adult	0.0288	6800	8	0.01958	5100
			Children 1<2		1800	4	0.01885	5300
		Hard surface	Adult	0.0384	6800	2	0.00653	15000
			Children 1<2		1800	2	0.01257	8000
	Perimeter/Spot	Soft surface	Adult	0.0144	6800	8	0.00979	10000
			Children 1<2		1800	4	0.00943	11000
		Hard surface	Adult	0.0192	6800	2	0.00326	31000

Exposure Scenario			Lifestage	TR [a] (µg/cm^2)	TC [b] (cm^2/hr)	ET [c] (hr/day)	Dermal Dose [d] (mg/kg bw/day)	MOE [e]
			Children 1<2		1800	2	0.00628	16000
	Crack and crevice	Soft surface	Adult	0.0029	6800	8	0.00196	51000
			Children 1<2		1800	4	0.00189	53000
		Hard surface	Adult	0.0038	6800	2	0.00065	150000
			Children 1<2		1800	2	0.00126	80000
Applied by residential applicator								
Indoor Environments	Broadcast[f] (Trigger pump sprayer)	Soft surface	Adult	0.0372	6800	8	0.02530	4000
			Children 1<2		1800	4	0.02435	4100
		Hard surface	Adult	0.0496	6800	2	0.00843	12000
			Children 1<2		1800	2	0.01623	6200
	Perimeter/Spot (Pressurized Product)	Soft surface	Adult	0.750	1800	8	0.01338	7500
			Children 1<2		6800	4	0.01288	7800
		Hard surface	Adult	1.000	1800	2	0.00446	22000
			Children 1<2		6800	2	0.00859	12000
Treated Pets	Shampoo (dog)	Small	Adult	0.0013	5200	0.77	0.07	1500
			Children 1<2		1400	1	0.17	590
		Medium	Adult	0.0006	5200	0.77	0.03	3500
			Children 1<2		1400	1	0.07	1400
		Large	Adult	0.0004	5200	0.77	0.02	5500
			Children 1<2		1400	1	0.05	2200
	Spot-on (dog)	Small	Adult	0.0007	5200	0.77	0.03257	3100
			Children 1<2		1400	1	0.08281	1200
		Medium	Adult	0.0003	5200	0.77	0.01396	7200
			Children 1<2		1400	1	0.03549	2800
		Large	Adult	0.0002	5200	0.77	0.00888	11000
			Children 1<2		1400	1	0.02259	4400
	Spot-on (cat)	Small	Adult	0.0005	5200	0.77	0.02289	4400
			Children 1<2		1400	1	0.05821	1700
		Medium	Adult	0.0003	5200	0.77	0.01373	7300
			Children 1<2		1400	1	0.03492	2900
		Large	Adult	0.0002	5200	0.77	0.00858	12000
			Children 1<2		1400	1	0.02183	4600

TR = Transferable residue; TC = Transfer coefficient; ET = Exposure time; MOE = Margin of exposure

[a] Transferable residues calculated based on the application rate and the exposure scenario using default fraction transferred values of 2% for pets, 6% for soft surfaces and 8% for hard surfaces (USEPA, 2012). Maximum application rates were used.

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

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

[d] Dermal dose = TR × TC × ET/BW (kg) Body weights of 80 and 11 kg were used for adults and children (1 <2 years) respectively, as stated in the USEPA Residential SOPs (USEPA, 2012). Dermal absorption was assumed to be 100%.

[e] MOE = NOAEL/ exposure, based on a NOAEL of 100 mg/kg bw/day from an oral rabbit developmental toxicity study and a target MOE of 300 for adults, and a NOAEL of 100 mg/kg bw day from an oral rat developmental toxicity study and a target MOE of 100 for children, applicable to short- to intermediate-term exposure scenarios.

[f] Broadcast application is expected to result in higher exposure relative to perimeter/spot application, therefore only broadcast application of trigger pump sprayer product is presented

Table 3 Residential Postapplication Incidental Oral Exposure and Risk Assessment for Children (1<2 Years old)

Exposure Scenario			Hand Residue (mg/hour) or Object Residue (µg/cm^2)[a]	ET[b] (hr/day)	Oral Dose[c] (mg/kg bw/day)	Incidental Oral MOE[d]
Applied by commercial applicator						
Indoor Environments	HtM Broadcast	Soft surface	0.0039	4	0.00018	140000
		Hard surface	0.0052	2	0.00012	200000
	HtM Perimeter/Spot	Soft surface	0.0019	4	0.00009	270000
		Hard surface	0.0026	2	0.00006	410000
	HtM Crack and Crevice	Soft surface	0.0004	4	0.00002	1400000
		Hard surface	0.0005	2	0.00001	2000000
	OtM Broadcast	Soft surface	0.0288	4	0.00038	64000
		Hard surface	0.0384	2	0.00025	96000
	OtM Perimeter/Spot	Soft surface	0.0144	4	0.00019	130000
		Hard surface	0.0192	2	0.00013	190000
	OtM Crack and Crevice	Soft surface	0.0029	4	0.00004	640000
		Hard surface	0.0038	2	0.00003	960000
Applied by residential applicator						
Indoor Environments	HtM Broadcast (Trigger pump sprayer)	Soft surface	0.0050	4	0.00023	110000
		Hard surface	0.0067	2	0.00015	160000
	HtM Perimeter/Spot (Pressurized Product)	Soft surface	0.1013	4	0.00012	200000
		Hard surface	0.1350	2	0.00008	300000
	OtM Broadcast (Trigger pump sprayer)	Soft surface	0.0372	4	0.00049	49000
		Hard surface	0.0496	2	0.00032	74000
	OtM Perimeter/Spot (Pressurized Product)	Soft surface	0.7500	4	0.00026	93000
		Hard surface	1.0000	2	0.00017	140000
Treated Pets	HtM Shampoo (dog)	Small	0.0372	1	0.00042	57000
		Medium	0.0160	1	0.00018	130000
		Large	0.0102	1	0.00012	210000
	HtM Spot-on (dog)	Small	0.0182	1	0.00021	120000
		Medium	0.0078	1	0.00009	270000
		Large	0.0050	1	0.00006	420000
	HtM Spot-on (cat)	Small	0.0128	1	0.00015	160000
		Medium	0.0077	1	0.00009	270000
		Large	0.0048	1	0.00005	440000

ET = Exposure time; MOE = Margin of exposure; HtM = Hand-to-Mouth; OtM = Object-to-Mouth

[a] Based on the dermal postapplication exposure from indoor applications without the body weight × fraction of a.i. on hands compared to the body (0.15)/(4 hr × 4 intervals/hr).

[b] Exposure time based on default values from the USEPA (USEPA, 2012).

[c] Oral dose = [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)) $^{\text{Number events per hour (20)/Replenishment Intervals (4/hr)}}$)]/ Body Weight (11 kg) or oral dose = Object Residue (µg/cm^2) × Conversion factor (mg/µg) × Surface area of object mouthed (10 cm^2/event) × [Exposure time (hrs) × Number of replenishments per hour (4)] × [1-(1-Saliva Extraction Factor (0.48))$^{\text{Frequency of OtM contacts per hour (14)/Number of replenishments per hour (4)}}$] / Body Weight (11 kg)

[d] MOE = NOAEL / exposure, based on a NOAEL of 24 mg/kg bw/day from a 90-day oral rat toxicity study and a target MOE of 100 for children, applicable to short-term exposure scenarios.

Appendix VI Aggregate Risk Assessment

Table 1 Aggregate Exposure and Risk Assessment

Scenario		Lifestage	Dermal Exposure[a] (mg/kg bw/day)	Inhalation Exposure[b] (mg/kg bw/day)	Incidental Oral Exposure[c,d] (mg/kg bw/day)	Chronic Dietary Exposure[e] (mg/kg bw/day)	Aggregate MOE[f]
Indoor Environments (Commercially applied Broadcast)	Soft surfaces	Adult	0.01958	NA	NA	0.007822	3650
		Children (1< 2 yrs)	0.01885	NA	0.00038	0.025864	2220
	Hard surfaces	Adult	0.00653	NA	NA	0.007822	6970
		Children (1< 2 yrs)	0.01257	NA	0.00025	0.025864	2590
Indoor Environments (Domestically applied Perimeter/Spot with pressurized product)	Soft surfaces	Adult	0.01376	3.10×10^{-6}	NA	0.007822	4630
		Children (1< 2 yrs)	0.01288	NA	0.00026	0.025864	2560
	Hard surfaces	Adult	0.00484	3.10×10^{-6}	NA	0.007822	7890
		Children (1< 2 yrs)	0.00859	NA	0.00017	0.025864	2890
Indoor Environments (Domestically applied Broadcast[g] with trigger pump sprayer)	Soft surfaces	Adult	0.02549	1.00×10^{-7}	NA	0.007822	3000
		Children (1< 2 yrs)	0.02435	NA	0.00049	0.025864	1970
	Hard surfaces	Adult	0.00862	1.00×10^{-7}	NA	0.007822	6080
		Children (1< 2 yrs)	0.01623	NA	0.00032	0.025864	2360
Treated Pets (shampoo)		Adult	0.08856	3.19×10^{-6}	NA	0.007822	1040
		Children (1< 2 yrs)	0.16927	NA	0.00042	0.025864	510
Treated Pets (spot-on)		Adult	0.03321	NA	NA	0.007822	2440
		Children (1< 2 yrs)	0.08281	NA	0.00021	0.025864	920

NA = Not Applicable; MOE = Margin of Exposure; yrs = years

[a] Combined dermal exposure resulting from application (when applicable) and postapplication exposure.

[b] Inhalation exposure resulting from application exposure, when applicable.

[c] Incidental oral exposure reflects either hand-to-mouth exposure for treated pets or object-to-mouth exposure for indoor environments. Incidental oral exposure is only applicable to children 1 <2 years old.

[d] Treated indoor environments may result in both hand-to-mouth and object-to-mouth exposure. Since object-to-mouth exposure is higher, object-to-mouth exposure was aggregated.

[e] Chronic dietary exposure (food only) is based on information provided in the dietary risk assessment.

[f] Aggregate MOE = Aggregate NOAEL/Aggregate Exposure (dermal+inhalation+incidental oral+dietary), based on an aggregate NOAEL of 100 mg/kg bw/day from an oral rabbit developmental toxicity study and a target MOE of 300 for adults, and an aggregate NOAEL of 100 mg/kg bw day from an oral rat developmental toxicity study and a target MOE of 100 for children (1<2 years).

[g] Broadcast application is expected to result in higher exposure relative to perimeter/spot application, therefore only broadcast application of trigger pump sprayer product is presented.

Appendix VII Label Amendments for Products Containing Pyriproxyfen

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

I. For Technical Grade of the Active Ingredient and Manufacturing Concentrate:

The following must appear under a section titled “ENVIRONMENTAL PRECAUTIONS”:

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

II. For Commercial End-Use Products for Greenhouse Uses:

1) **Remove** the following under the "PRECAUTIONS" section:

“This product contains a petroleum distillate which is moderately to highly toxic to aquatic organisms. Avoid contamination of aquatic systems during application. Do not contaminate these systems through direct application, disposal of waste or cleaning of equipment.”

2) Under the section “**ENVIRONMENTAL HAZARDS**”, **remove** the following:

“This pesticide is toxic to fish and aquatic invertebrates. Do not apply directly to water, or to areas where surface water is present.”

And **replace** with the following:

“This product contains an active ingredient and aromatic petroleum distillates which are toxic to aquatic organisms.”

3) Change the heading “ENVIRONMENTAL HAZARDS” to “ENVIRONMENTAL PRECAUTIONS”

4) Under “DIRECTIONS FOR USE: MIXING INSTRUCTIONS (Booklet label)”:

Add:

> "As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests."

"DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes."

III. COMMERCIAL-CLASS PRODUCTS (with specific Registration Numbers)

1) For the label with the greenhouse uses (Registration Number 28414):

- Statements related to the personal protective equipment (PPE) and restricted-entry interval (REI) are proposed to be updated to current wording.

  - For PPE, replace:
    "Wear coveralls or long-sleeved shirt and long pants, rubber boots, goggles, gloves (rubber, PVC, neoprene or nitrile) and hat during mixing, loading, cleanup and application."

    with:
    "Wear a long-sleeved shirt, long pants, chemical-resistant gloves (rubber, PVC, neoprene or nitrile), socks and shoes during mixing, loading, application, clean-up and repair."

  - For REI, replace:
    "DO NOT re-enter treated areas within 12 hours."

    with:
    "**DO NOT** enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours."

- Statements are proposed to prohibit application using handheld mist blower or handheld fogging equipment, as data are not available to assess these uses.

- Add to Directions For Use: "Do not apply greenhouse processing water containing this product to field crops (food and feed)."

2) For the label with directions to control fleas in indoor environments (Registration Number 25490):

- The following PPE as per the occupational risk assessment are proposed to be added to the label:
  "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair."

- Statements related to entry after application are proposed to be updated to current wording as follows:
  "BROADCAST APPLICATION: DO NOT allow people or pets to enter treated areas for 2 hours or until sprays have dried.
  SPOT AND CRACK AND CREVICE APPLICATION: DO NOT allow people or

pets to enter treated areas until sprays have dried."

- Best practice statements to update the precautionary label directions as per PRO2018-04 are proposed:

  Under "**DIRECTIONS FOR USE**":

  "**DO NOT** apply to mattresses, linens, toys or clothing."
  "**DO NOT** apply to overhead areas or in confined spaces without appropriate respiratory and eye protection."
  "**DO NOT** allow spray to drip or allow drift onto non-target surfaces; any spray residue on non-target areas must be removed by the applicator."
  "**DO NOT** apply as a space spray."
  "Use a coarse, low pressure spray not exceeding 345 kPa (50 psi)."

  Under "**PRECAUTIONS**":

  "**DO NOT** apply to surfaces that may come into contact with food/feed."
  "Cover or remove all food/feed. Cover all food/feed processing surfaces, equipment and utensils or thoroughly wash following treatment."
  "Ventilate treated areas after application either by opening windows and doors or through use of air exchange/ventilation systems confirmed to be operational. Use fans where required to aid in the circulation of air."
  "**DO NOT** apply when people or pets are present."

IV. DOMESTIC-CLASS PRODUCTS

End-use products with instructions for indoor applications to control fleas and which are co-formulated with tetramethrin or d-phenothrin have conflicting application directions as a result of label changes required for the re-evaluation of tetramethrin or d-phenothrin. Therefore, label changes are proposed to clarify application directions for specific use sites while ensuring consistency with the evaluations of tetramethrin and d-phenothrin.

These label amendments include:

- Removal of label statements restricting application to crack and crevice and perimeter applications. Directions for spot treatment are proposed to remain for products co-formulated with tetramethrin.
- Application directions, including clarification of rates, are proposed to be added for specific uses on the current labels, that is, for pet bedding, indoor surfaces (rugs, carpets and drapes) and upholstery.

- In addition, best practice statements to update the precautionary label directions as per PRO2018-04 are proposed:

  Under "**DIRECTIONS FOR USE**":

"**DO NOT** apply to mattresses, linens, toys or clothing."
"**DO NOT** apply to overhead areas or in confined spaces without appropriate respiratory and eye protection."
"**DO NOT** allow spray to drip or allow drift onto non-target surfaces; any spray residue on non-target areas must be removed by the applicator."
"**DO NOT** apply as a space spray."
"Use a coarse, low pressure spray not exceeding 345 kPa (50 psi)."

Under "**PRECAUTIONS**":

"**DO NOT** apply to surfaces that may come into contact with food/feed."
"Cover or remove all food/feed. Cover all food/feed processing surfaces, equipment and utensils or thoroughly wash following treatment."
"Ventilate treated areas after application either by opening windows and doors or through use of air exchange/ventilation systems confirmed to be operational. Use fans where required to aid in the circulation of air."
"**DO NOT** apply when people or pets are present."
"**DO NOT** allow people or pets to enter treated areas ["until sprays have dried" or re-entry time currently stated on label]."

- Remove from all domestic-class indoor application labels:
  "[Retreat/Repeat] as necessary."

For spot-on, pyriproxyfen products registered for use on cats and dogs, the following precautionary label directions as per PRO2018-01 are proposed:

- For products used on dogs:

  "Monitor your dog after application. Side effects may include: skin irritation such as redness or scratching; changes in behaviour such as agitation or lethargy; or gastrointestinal effects such as vomiting or loss of appetite. If these or other side effects occur consult your veterinarian or [Registrant at 1-800-number]."

- For products used on cats:

  "Monitor your cat after application. Side effects may include: skin irritation such as scratching or hair loss at the application site, or changes in behaviour such as agitation or lethargy. Gastrointestinal effects such as drooling, vomiting, or loss of appetite may also occur. If these or other side effects occur consult your veterinarian or [Registrant at 1-800-number]."

The following label improvements for spot-on products are proposed:

- Remove label language that allows re-application of the product before the end of the effective control period. For example, products that are labeled as providing four weeks of control, should not have statements such as "Reapply after one week if necessary".

- Add label language to contraindicate use of other flea control products with the same active ingredients as the spot-on (For example: “This product contains [name of active ingredient(s)]. Do not apply another pest control product such as a shampoo, collar, or powder which contains [name of active ingredient(s)] to the treated animal when using [name of spot-on product]”).

References

Information Considered in the Chemistry Assessment

A. Studies/Information Submitted by Registrant

PMRA Document Number	Reference
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1854760	1989, [CBI removed] Sumilarv - Product Identity and Composition, DACO: 2.11.2,2.11.3,2.11.4 CBI
1854801	1989, [CBI removed] Sumilarv - Physical and Chemical Characteristics, DACO: 2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.14,2.14.2,2.14.3,2.14.4,2.14.6,2.14.7, 2.14.9 CBI
1855168	1989, [CBI removed] Sumilarv - Product Identity and Composition (Revised) - Product Identity, Description of Beginning Materials and Manufacturing Process, Impurities, DACO: 2.11,2.14.1,2.14.13,2.14.2,2.14.4,2.3,2.5,2.6,2.7,2.8,2.9 CBI
2704557	2016, Batch Analysis of Pyriproxyfen Technical Grade, DACO: 2.13.3,2.13.4 CBI

Information Considered for the Toxicological Assessment

A. List of Studies/Information Submitted by Registrant

3.0 Human Health

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1143882	1991, S31183: Toxicity Study by Oral (capsule) Administration to Beagle Dogs for 52 weeks., DACO: 4.3.1,4.3.2
1143883	1998, Sumilarv-Subacute Inhalation Toxicity Study of S-31183 in Rats., DACO: 4.3.6
1143884	1991, SUMILARV: COMBINED CHRONIC TOXICITY AND ONCOGENICITY STUDY IN RATS WITH S-31183, DACO: 4.4.1,4.4.2
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1143910	SUMILARV- REVERSE MUTATION TEST OF S-31183 IN BACTERIAL SYSTEMS (153;NNT-80-0034), DACO: 4.5.4
1143911	1990, SUMILARV- IN VITRO GENE MUTATION TEST OF S-31183 IN V79 CHINESE HAMSTER CELLS, DACO: 4.5.4

PMRA Document Number	Reference
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1143930	1991, SUMILARV- ONCOGENICTITY STUDY IN MICE WITH S-31183, DACO: 4.4.2
1143941	SUMILARV- METABOLISM OF S-31183 IN RATS (NNM-80-0001;807;810;811), DACO: 4.5.9
1143949	1998, SUMILARV- METABOLISM OF S-31183 IN RATS (TISSUE DISTRIBUTION STUDY), DACO: 4.5.9
1159013	ONCOGENICITY STUDY IN MICE (343-215,JULY 23,1991)(CRITERIA UTLIZED BY THE PATHOLOGIST IN DETERMINING THE GRADING SYSTEM FOR HISTOPATHOLOGICAL LESIONS)(SUMILARV), DACO: 4.4.2
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1159015	RAT TERATOLOGY STUDY (NNT-80-0029,MARCH 28,1988)(ADDITIONAL DATA AS REQUESTED SEE MICROFILM FOR MORE DETAIL)(SUMILARV), DACO: 4.5.2
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1159046	1987, ACUTE ORAL TOXICITY IN RATS AMENDMENT TO FINAL REPORT NO. NNT-70-0005, FEBRUARY 4, 1987 (INDIVIDUAL TOXIC SIGNS/BODY WEIGHT/GROSS PATHOLOGY FINDINGS)(ACT86033)(SUMILARV), DACO: 4.2.1
1159057	1987, ACUTE DERMAL TOXICITY IN RATS AMENDMENT TO FINAL REPORT NO. NNT-70-0006,FEBRUARY 4,1987 (INDIVIDUAL BODY WEIGHT/GROSS PATHOLOGY FINDINGS)(ACT86034)(SUMILARV), DACO: 4.2.2
1159068	1994, ACUTE INHALATION TOXICITY IN RATS AMENDMENT TO FINAL REPORT NO. NNT-70-0022,DECEMBER 3,1989 (PARTICLE SIZE,INDIVIDUAL TOXIC SIGNS/BODY WEIGHT/GROSS PATHOLOGY FINDINGS/INDIVIDUAL HISTOPATHOLOGICAL EXAMINATION)(636)(SUMILARV), DACO: 4.2.3

PMRA Document Number	Reference
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1164979	1993, SUMILARV- 21 DAY DERMAL TOXICITY STUDY IN RATS WITH S-31183., DACO: 4.3.4
1164980	1996, RESPONSE TO HEALTH CANADA QUESTIONS REGARDING THE EVALUATION CRITERIA IN THE TERATOGENICITY/DEVELOPMENTAL TOXICITY STUDY OF SUMILARV (S-31183) IN RABBITS. DATE COMPLETED: FEBRUARY 12,1996.(VOLUME 43;NNT-80-0033).(PYRIPROXYFEN), DACO: 4.5.2
1169747	1994, SUPPLEMENTAL DATA AND REVIEW OF ONCOGENICITY STUDY WITH S-31183 (SUMILARV) IN MICE., DACO: 4.4.2
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2704562	1993, METABOLISM OF [PYRIDYL-2,6-14C] PYRIPROXYFEN IN RATS, DACO: 4.5.9
2704564	1992, SUMILARV - ACUTE INHALATION TOXICITY OF S-31183 IN RATS SUPPLEMENTAL DATA SUPPLEMENT TO MRID # 42178304, DACO: 4.2.3
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