Proposed Re-evaluation Decision PRVD2016-17

Cyfluthrin

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Overview

General Introduction

In Canada, pesticides are regulated under the *Pest Control Products Act*, administered by Health Canada's Pest Management Regulatory Agency (PMRA). All pesticides are registered (that is, approved) if a rigorous scientific assessment indicates that the health and environmental risks are acceptable and the products have value. The *Pest Control Products Act* also contains provisions for post-market reviews of registered pesticides namely, re-evaluation and special reviews, to assess whether pesticides continue to meet Health Canada's health and environmental standards, and whether they can continue to be used in Canada.

As part of the decision making process, before making a final decision, the PMRA consults with the members of the public and other interested stakeholders on all proposed major decisions such as new registrations, re-evaluations and special reviews. The PMRA encourages the public and stakeholders to participate in the consultation process. The proposed decisions are made based on the information available at the time, and the PMRA will consider the comments and information received during consultation using a science-based approach before making a final decision. The final decision will be published on the Pesticides and Pest Management portion of Health Canada's website, and it will include a summary of the comments received during the consultation and PMRA's responses to the comments.

The registration status of products and conditions of use of pesticide products on the market are not impacted by proposed re-evaluation or special review decisions. This may be the case only when final decisions are made. However, at any point during the re-evaluation or special review of a pesticide, the *Pest Control Products Act* allows the PMRA to cancel or amend the registration of registered pest control products, if there are reasonable grounds to believe this is necessary to deal with a situation that endangers human health or safety or the environment.

Proposed Re-evaluation Decision for Cyfluthrin

An evaluation of available scientific information has determined that under the currently labelled conditions of use, the human health risks estimated for cyfluthrin meet current standards for most uses. As a requirement for the continued registration of cyfluthrin, new risk-reduction measures are proposed for the commercial-class end-use products registered in Canada. Based on potential risks of concern for residential exposure, all domestic-class products are proposed for cancellation and some residential uses are also proposed to be removed. Consideration of any additional data/information submitted during the consultation period to further refine the health risk assessment may or may not result in a change to this proposal.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for cyfluthrin and presents the reasons for the proposed re-evaluation decision.

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

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

The PMRA will accept written comments on this proposal up to 90 days from the date of publication of this document. Please forward all comments to Publications (please see contact information indicated on the cover page of this document).

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

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

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

What Is Cyfluthrin?

Cyfluthrin is a synthetic pyrethroid insecticide. There are two technical grade active ingredients, three commercial class and four domestic class end-use products registered. The commercial class cyfluthrin products, targeting flying and crawling insects, are applied by pest control applicators to residential and commercial sites using hand pressurized and power operated sprayers. They are also applied by farmers to livestock housing structures. The other commercial products are for use by the cattle industry as a pour on to control horn fly and lice, or as an insecticide impregnated ear tag for horn fly control. The domestic products are available as pressurized spray cans for use indoors to target household pests such as ants, earwigs, cockroaches and spiders.

Health Considerations

Can Approved Uses of Cyfluthrin Affect Human Health?

Products containing cyfluthrin are unlikely to affect human health when used according to the proposed revised label directions.

Potential exposure to cyfluthrin may occur through the diet (food and drinking water), when handling and applying products containing cyfluthrin or during contact with treated surfaces. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose at which no effects are observed. The health effects noted in animals occur at doses which are much higher than levels to which humans are normally exposed when pesticide products are used according to label directions. The human health hazard identification for cyfluthrin was based on data for cyfluthrin and beta-cyfluthrin due to the similarity in chemical structure, mode of toxic action and toxicological findings for these two chemicals.

In laboratory animals, the technical grade active ingredients cyfluthrin and beta-cyfluthrin were of high acute toxicity by the oral route. Both chemicals were of low acute dermal toxicity and were moderately acutely toxic through inhalation exposure. Cyfluthrin was mildly irritating to the eyes and non-irritating to the skin whereas beta-cyfluthrin was slightly irritating to the eyes and mildly irritating to the skin. Neither cyfluthrin nor beta-cyfluthrin caused an allergic skin reaction. The findings of the acute oral toxicity testing trigger the requirement for a hazard signal word to appear on the labels of both chemicals.

Registrant-supplied short, and long term (lifetime) animal toxicity tests, as well as information from the published scientific literature were assessed for the potential of cyfluthrin to cause neurotoxicity, immuno-toxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on the nervous system and body weight. There is some concern for increased sensitivity of the young exposed to cyfluthrin. There was no evidence of carcinogenicity in mice after longer-term dosing with cyfluthrin; however, an equivocal increase in urinary bladder tumours was noted in female rats. The risk assessment protects against the above-noted effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occur in animal tests.

Residues in Food and Drinking Water

Dietary risks from food and drinking water are not of concern when products containing cyfluthrin are used according to the proposed label directions.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose (ARfD) or chronic reference dose (acceptable daily intake or ADI). An acceptable daily intake 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.

Cyfluthrin is a mixture of four diastereoisomers present in somewhat similar ratios. Beta-cyfluthrin contains the same four diastereoisomer pairs as cyfluthrin; however, the two diastereoisomer pairs considered insecticidally active are enriched in beta-cyfluthrin. Cyfluthrin and beta-cyfluthrin are thus structurally identical, differing only in the ratio of the stereoisomers. Analytical methods for current residue monitoring do not distinguish between cyfluthrin and beta-cyfluthrin; therefore, the dietary risk assessments were conducted by combining the uses of both chemicals. Only cyfluthrin is currently registered in Canada; import maximum residue limits (MRLs) are being proposed for beta-cyfluthrin.

Based on the registered uses for cyfluthrin (and the proposed uses for beta-cyfluthrin outlined in PRD2016-21), residues in drinking water are not anticipated. Therefore, risks from exposure to residues in food only were assessed.

Acute and chronic dietary exposures to cyfluthrin were estimated from residues of cyfluthrin and beta-cyfluthrin in treated crops and animal commodities (including imports). Acute dietary exposure is of concern when considering potential residues in milk and dairy food forms. Therefore, as explained below, for the purposes of risk mitigation, potential residues in milk and dairy food forms were excluded from the dietary exposure assessment.

Acute (probabilistic) and chronic dietary exposures were conducted for the general population and different subpopulations, including children and women of reproductive age. For the general population and all subpopulations, the acute dietary exposure estimates from food only range from 18% to 39% of the ARfD, while the chronic dietary exposure estimates range from 1% to 5% of the ADI. Thus, acute and chronic dietary risks are not of concern provided that cyfluthrin is not applied to lactating cattle.

The *Food and Drugs Act* prohibits the sale of adulterated food; that is, food containing a pesticide residue that exceeds the specified MRL. Pesticide MRLs are specified for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. An MRL represents the maximum amount of residues that may remain on food when a pesticide is used according to label directions, and serves as a food safety standard. The Canadian Food Inspection Agency is responsible for monitoring the Canadian food supply for pesticide residues and the determination of compliance with MRLs specified by Health Canada.

Canadian MRLs are currently specified for residues of cyfluthrin on animal commodities. MRLs for the importation of all petitioned beta-cyfluthrin uses have been proposed. Residues for cyfluthrin and beta-cyfluthrin in all other agricultural commodities are regulated under Subsection B.15.002(1) of the *Food and Drugs Regulations*, which requires that residues do not exceed 0.1 ppm. A complete list of MRLs specified in Canada can be found on the PMRA's MRL Database, an online query application that allows users to search for MRLs, regulated under the *Pest Control Products Act*, both for pesticides or food commodities (http://pr-rp.hc-sc.gc.ca/mrl-lrm/index-eng.php).

Risks in Residential and Other Non-Occupational Environments

Risks to residential handlers are not of concern.

Residential handler exposure may occur from applying domestic-class products containing cyfluthrin to indoor environments. Residential handler risks are not of concern.

Residential risks from certain postapplication exposures to children are of concern due to potential for incidental oral exposure of cyfluthrin. Mitigation to limit exposure to children is proposed.

Residential postapplication exposure may occur while performing activities in residential areas treated with cyfluthrin. Treated areas include areas treated by residential handlers using domestic-class products, as well as residential areas treated by commercial applicators. Exposure would be dermal and by inhalation. Incidental oral exposure may also occur for children playing in treated areas.

The following postapplication scenarios were assessed: broadcast application, band and spot application, bedbug application, and crack and crevice application. Risks of concern were identified for children from incidental oral exposure for all scenarios except crack and crevice application of commercial-class products. Label directions are proposed to specify that in residential areas, only crack and crevice applications will be permitted. In addition, after consideration of the incident reports involving cyfluthrin, it is also proposed that entry by residents, workers and others will not be permitted until 8 hours after application.

Residential areas are defined as any use site where bystanders including children could be exposed during or after application. This includes homes, schools, public buildings or any other areas where the general public including children could be exposed.

Crack and crevice application is defined as an application of pesticides with the use of a pin stream nozzle, into cracks and crevices in which pests hide or through which they may enter a building. It does not permit the treatment of surfaces. Such openings commonly occur at expansion joints, between different elements of construction, and between equipment and floors. These openings may lead to voids such as hallow walls, equipment legs and bases, conduits, motor housings, and junction or switch boxes.

Therefore, for the commercial-class product containing cyfluthrin currently registered in Canada for residential use, label amendments are proposed to specify that the product must only be applied using low pressure sprayer equipment with a pin stream nozzle to direct sprays into cracks and crevices. Also, the directions for use are proposed to be modified to provide specific directions for crack and crevice applications. In addition, based on potential risks of concern identified for children for most scenarios, and the fact that domestic-class products cannot be applied as crack and crevice only, all domestic-class products are proposed for cancellation.

Aggregate risks are not of concern when the above-noted proposed mitigation is considered.

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)

Aggregate risks are not of concern when cyfluthrin is applied as a crack and crevice spray only in residential areas.

Occupational Risks

Occupational risks to handlers are not of concern when products containing cyfluthrin are used according to the current label directions.

Risk estimates associated with mixing, loading and applying activities are not of concern when current mitigation measures (personal protective equipment, including chemical-resistant gloves and a respirator) are considered.

Occupational postapplication risks to workers are not of concern when products containing cyfluthrin are used according to the proposed label directions.

Occupational postapplication risk assessments for cyfluthrin consider exposures to workers entering treated sites (for example, food processing plants, warehouses, office buildings) and performing various activities. Current uses of cyfluthrin in indoor commercial areas are crack and crevice applications, band and spot applications, and bedbug application. Broadcast application is limited to livestock housing only.

No risks of concern were identified for workers entering treated sites for the current uses, provided that workers do not enter the treated site until 8 hours after application.

Environmental Considerations

What Happens When Cyfluthrin Is Introduced Into the Environment?

When used according to the proposed label directions cyfluthrin is not expected to pose risks of concern to the environment.

Cyfluthrin is used primarily indoors as a domestic and commercial insecticide. Limited outdoor uses include commercial pour-on and ear tag treatments for livestock. As a result of the limited outdoor use pattern, environmental exposure is expected to be minimal.

If cyfluthrin is released into the environment it can enter soil and surface water. Cyfluthrin is moderately persistent in soil, breaking down in the presence of sunlight and microbes. In water, cyfluthrin is non-persistent, being broken down rapidly by sunlight and microbes. Cyfluthrin is not expected to enter the atmosphere and be transported to areas far from where it was used. Laboratory studies indicate that cyfluthrin binds strongly to soil particles. It is not expected to move downward through the soil and enter ground water.

Cyfluthrin poses negligible risk to birds. At high enough doses it can be toxic to mammals, terrestrial and aquatic invertebrates and fish. The potential for terrestrial and aquatic non-target organisms to be exposed to cyfluthrin is expected to be minimal due to the limited outdoor use pattern. As a result, risk to these organisms is not of concern.

Value Considerations

Cyfluthrin has an important role in Integrated Pest Management (IPM) to help manage pests in structural sites. When pesticide treatments are needed, cyfluthrin can be used alone or in conjunction with another insecticide to target pests in specific locations in structural sites. Cyfluthrin, a synthetic pyrethroid, is important for the purpose of resistance management of insect pests in structural sites (residential and commercial sites). Cyfluthrin domestic products are of benefit to the homeowner to use with other control methods, such as prevention and non-chemical treatments, in the management of pests in the home.

Cyfluthrin has an important role in Integrated Pest Management (IPM) to control horn flies and lice on lactating dairy cattle. Cyfluthrin can be used with non-chemical methods in an IPM approach to control horn flies and lice on lactating dairy cattle. Cyfluthrin is one of the few insecticides registered for use on lactating dairy cattle for control of horn flies and lice.

Proposed Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human health and the environment. These directions must be followed by law. As a result of the re-evaluation of cyfluthrin, the PMRA is proposing further risk-reduction measures for product labels.

Human Health

To protect homeowners, the following requirements are proposed:

- All domestic-class products are proposed for cancellation.
- For the commercial-class products:
    - Application in residential areas to be limited to crack and crevice/void only, and use for bedbug treatment will be cancelled.
    - Application in non-residential areas can be maintained as band, spot, crack and crevice applications, and use for bedbug treatment is allowed.
- As a result of the incident reports, entry to treated sites must occur no sooner than 8 hours after application.

To protect the general population from dietary exposure, the following requirements are proposed:

- Use of cyfluthrin on lactating dairy cattle to be prohibited (both spot-on and ear tag products), and MRLs for cyfluthrin in milk and milk fat to be revoked.

Environment

Due to the limited outdoor use, the risk to terrestrial and aquatic organisms is expected to be minimal. However, precautionary statements are proposed to further protect the environment.

- Toxic to aquatic organisms.
- Toxic to small mammals.

The proposed mitigation measures are outlined in Appendix XI.

What Additional Scientific Information Is Requested?

No additional data are required.

Next Steps

During the consultation period, registrants and stakeholder organizations may submit further data that could be used to refine risk assessments (exposure or use information), which could result in revised risk-reduction measures. Stakeholders who are planning to provide information of this type are advised to contact the PMRA early in the consultation period, for advice on studies or information that could be submitted to help refine the relevant risk assessments.

Before making a final re-evaluation decision on cyfluthrin, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision[2] that will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

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

Science Evaluation

1.0 Introduction

Cyfluthrin is under re-evaluation in Canada as described by the Pest Management Regulatory Agency (PMRA) in the 20 December 2011 Re-evaluation Note REV2011-05, *Re-evaluation of Pyrethroids, Pyrethrins and Related Active Ingredients*. Cyfluthrin is a broad spectrum contact synthetic pyrethroid.

Following the re-evaluation announcement for cyfluthrin, the registrant of the technical grade active ingredient, and primary data provider in Canada indicated continued support for all registered label uses. Currently registered products containing cyfluthrin are listed in Appendix I. All current uses are being supported by the registrant and were, therefore, considered in the re-evaluation of cyfluthrin.

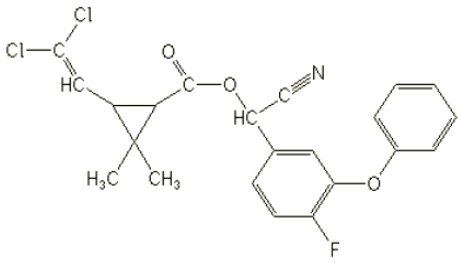
The purpose of this re-evaluation is to review existing information on the active ingredient, cyfluthrin, and the currently registered cyfluthrin technical, commercial and domestic class end-use products, to ensure that risk assessments meet current standards.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient.

Common name		Cyfluthrin
Function		Insecticide
Chemical Family		Pyrethroid
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	(Ξ)-cyano(4-fluoro-3-phenoxyphenyl)methyl (1Ξ,3Ξ)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate
2	**Chemical Abstracts Service (CAS)**	cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
CAS Registry Number		68359-37-5 (for unspecified stereochemistry)
Molecular Formula		$C_{22}H_{18}Cl_2FNO_3$

Structural Formula



Molecular Weight	434.2876
Registration Number	25672
Purity of the Technical Grade Active Ingredient	95.6%

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result		
Vapour pressure at 25°C	**Distereoisomer pair**	**VP (mPa) (20ºC)**	
	I	9.6×10^{-4}	
	II	1.4×10^{-5}	
	III	2.1×10^{-5}	
	IV	8.5×10^{-5}	
Ultraviolet (UV) / visible spectrum	No significant absorption at λ >300 nm		
Solubility in water at 20°C (in µg/L)	**Distereoisomer pair**	**pH 3**	**pH 7**
	I	2.5	2.2
	II	2.1	1.9
	III	3.2	2.2
	IV	4.3	2.9
n-Octanol/water partition coefficient at 20°C	**Disteroisomer pair**	**Log K_{ow}**	
	I	6.0	
	II	5.9	
	III	6.0	
	IV	5.9	
Dissociation constant	Product has no dissociable groups		

2.3 Description of Registered Cyfluthrin Uses

Appendix I list all cyfluthrin products that are registered under the authority of the *Pest Control Products Act*. Appendix IIa lists all commercial-class uses for which cyfluthrin is currently registered, while Appendix IIb lists all domestic-class uses for which cyfluthrin is currently registered.

Uses of cyfluthrin belong to the following use-site categories: human skin and clothing and proximal sites, structural sites and animals for food production.

3.0 Impact on Human And Animal Health

3.1 Toxicology Summary

Cyfluthrin is a synthetic pyrethroid insecticide, and is referred to as a Type II pyrethroid due to the presence of an α-cyano group. It is a racemic mixture of 4 stereoisomers (stereoisomers I and III are in the cis-configuration, stereoisomers II and IV are in the trans-configuration). Beta-cyfluthrin is composed of the same four stereoisomers, but is enriched with stereoisomers II (35%) and IV (62%). Due to the similarity in structure, mode of action and qualitative toxicological findings, the human health risk assessment for cyfluthrin has been based on data for cyfluthrin and beta-cyfluthrin. This approach is further justified by the fact that analytical methods for current residue monitoring cannot distinguish between cyfluthrin stereoisomers. The combined toxicology databases contain the full array of toxicity studies currently required for hazard assessment purposes, as well as some literature studies. 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 define the majority of the toxic effects that may result from exposure to cyfluthrin and beta-cyfluthrin.

Synthetic pyrethroids induce neurotoxic effects primarily by binding to voltage-dependant sodium channels in neurons thereby delaying the closing of sodium channels and causing the depolarization of neurons. This affects action potentials and results in either repetitive activity (Type I pyrethroids) or blockage of nerve conduction (Type II pyrethroids). Type II pyrethroids such as cyfluthrin typically induce the “CS syndrome” which is characterized by choreoathetosis (involuntary excessive movements progressing to sinuous writhing), salivation, sedation, dyspnea, clonic seizures and tremors. Impairment of motor activity and acoustic startle response are also characteristic of Type II pyrethroids.

Available toxicokinetic data for cyfluthrin are based on radiolabel studies in which rats were administered cyfluthrin (a racemic mixture of *cis*- and *trans*-cyfluthrin isomers) either as a single low dose (oral or i.v.), single high dose (oral), repeat low dose (oral), or as a single intraduodenal dose in rats with bile fistulae. In rats treated orally with a single low oral dose of cyfluthrin, absorption from the gastrointestinal tract was rapid and extensive, with blood concentrations reaching peak levels within approximately 2 hours in both sexes. Oral or i.v. dosing resulted in rapid elimination in both sexes, with most of the administered dose being eliminated within 48 hours.

Elimination occurred primarily in urine (70%) and to a lesser extent via feces (30%), with significant biliary contribution. Elimination in exhaled air was negligible. Rate of elimination did not vary with sex, dosage or pre-treatment. The rate of elimination in humans following inhalation exposure to cyfluthrin was rapid, similar to what was observed in the rat.

Twenty-four hours following administration of a single low oral dose or i.v. dose of cyfluthrin in rats, the highest tissue residues were detected in renal fat; levels in brain were low. Radioactivity levels in tissues were higher after i.v. dosing, compared to oral dosing.

Cyfluthrin is metabolized in the liver; in vitro data demonstrate metabolism occurs in rat and human hepatic microsomes via P450 enzymes. Metabolism occurs principally by ester cleavage yielding the 3-phenoxy-4-fluorobenzoic acid. The 3-phenoxy-4-fluorobenzoic acid moiety is then either hydroxylated, conjugated and excreted, or bound first to glycine and then hydroxylated, conjugated and excreted.

Major urinary metabolites consisted of a conjugate of 4-fluoro-3-(4-hydroxyphenoxy) benzoic acid and 3-phenoxy-4-fluorobenzoic acid. Significant amounts (10-20%) of unchanged parent were found only in the feces of rats (both sexes) treated with repeated oral doses or with a single high oral dose. The quantity of 4-fluoro-3-(4-hydroxyphenoxy)-benzoic acid metabolite in feces was sex dependent in all cases, with females having higher amounts than males. Following inhalation exposure, metabolites detected in human excreta included cis or trans-3-(2,2-dichlorovinyl)-2,2-dimethylycyclopropane carboxylic acid (DCCA) and 3-phenoxy-4-fluorobenzoic acid.

When cyfluthrin was administered by gavage in the vehicle Cremophor EL, an increased rate of absorption as well as total absorption was seen, compared to when administered in PEG 400 vehicle, with cyfluthrin residues present in blood as early as 0.5 hours post-dose. Peak blood levels were observed at 1 hour post-dose, and maximum blood levels were 5-fold higher than when administered in PEG 400. When cyfluthrin was administered in PEG 400, peak blood levels occurred at 6-hours post-dose. Differences attributable to the vehicle were also seen in the remainder of the database with studies conducted with the vehicle Cremophor EL often showing lower effect levels.

Acute oral toxicity studies with cyfluthrin in rodents indicated a range of moderate to high acute toxicity depending on the vehicle used, whereas studies with beta-cyfluthrin consistently indicated high acute toxicity. Clinical signs of toxicity following oral exposure to both cyfluthrin and beta-cyfluthrin were characteristic of disruption of the autonomic nervous system and indicative of the “CS syndrome” including choreoathetosis, salivation, excessive grooming, motor incoordination, tremors, pawing and burrowing. Males were more sensitive than females and mice were more sensitive than rats. In acute dermal toxicity studies, cyfluthrin and beta-cyfluthrin were of low toxicity in rats, but beta-cyfluthrin induced clinical signs of neurotoxicity at lower doses than cyfluthrin. Cyfluthrin caused slight to moderate acute inhalation toxicity in rats, whereas beta-cyfluthrin caused moderate acute inhalation toxicity in rats. Cyfluthrin was mildly irritating to the eyes of rabbits, whereas beta-cyfluthrin was slightly irritating.

Cyfluthrin was a non-irritant to skin, and beta-cyfluthrin was mildly irritating to the skin of rabbits. Cyfluthrin was not a dermal sensitizer in guinea pigs in two supplemental studies conducted by the Buehler method. Beta-cyfluthrin was non-sensitizing to the skin of guinea-pigs in a Buehler assay.

In repeat-dose studies conducted by the oral route in rats and dogs, the most sensitive indicators of toxicity were clinical signs of neurotoxicity, with ataxia, tremors and gait abnormalities observed in both species. Additional signs of neurotoxicity observed in rats included apathy, ungroomed coat, dyspnoea, salivation, hyperkinesis, athetotic/choreiform movements, nervousness, emaciation, disturbed behaviour, vocalization and sores/necroses. Emesis, diarrhea, abnormal posture/posture reaction, lying on side with spasms, convulsions/seizures and conjunctival irritation were observed in dogs. In these repeat-dose studies, the dog was the most sensitive species, followed by the rat and mouse. Decreased body weight and food consumption, as well as histological changes in the adrenal gland and stomach observed in a chronic oral rat study with cyfluthrin, indicated a slight increase in toxicity with increasing duration of dosing, since these findings had not been identified in short-term repeat-dose studies. Other notable effects at higher oral doses in repeat-dose studies in rats and mice included effects on the liver, kidney, submaxillary gland and hematopoetic system; spleen effects were observed in mice.

Consistent with oral studies, signs of neurotoxicity were also observed in rats and mice following short-term inhalation exposure to cyfluthrin and beta-cyfluthrin. Decreased body weight and “disturbed non-specific behavior” were the key effects observed at the lowest concentrations following nose-only inhalation exposure to rats, with agitation, erect tail carriage, gait abnormalities and salivation noted at higher concentrations. In a shorter-term (7-day) inhalation study in mice in which dams and their pups received whole-body inhalation exposure, decreased motility, poor general condition, tonic seizures, and temporary scratching were noted in pups at lower concentrations, with a higher concentration resulting in complete pup mortality. No adverse findings were reported in dams in this study. When examining the inhalation studies across the database, the impact of increasing duration of dosing was not easily discernable based on the doses selected.

Short-term dermal toxicity studies in rats and rabbits were available for cyfluthrin. In rats, there was systemic toxicity as evidenced by clinical signs (red nasal discharge, urine staining) at the limit dose. Dermal irritation was evident at the next lowest dose. In rabbits, there was no treatment-related dermal or systemic toxicity up to/including 250 mg/kg bw/day, the highest dose tested.

Cyfluthrin and beta-cyfluthrin were not genotoxic in an extensive battery of in vitro and in vivo tests. There was no evidence of tumorigenicity with cyfluthrin in mice following long-term dietary exposure. A slight increase in the incidence of urinary bladder papillomas was observed in female rats after long-term dietary exposure to cyfluthrin. This finding was considered to provide equivocal evidence for tumorigenicity in view of their low incidence in the study, yet low occurrence within the historical database of the testing laboratory. Given the negative results in the genotoxicity studies, coupled with the lack of tumours observed in mice, the overall weight of evidence suggested a low level of concern for the urinary bladder papilloma findings in rats.

In neurotoxicity studies and repeat-dose toxicity studies, exposure to cyfluthrin and/or beta-cyfluthrin resulted in toxicological effects in rodents, dogs, and hens which were consistent with Type II pyrethroids, including mortality, decreased body weight, salivation, perianal staining, tremors, decreased motor activity, decreased activity in open field, decreased grip strength, splayed/dragging hindlimbs, impaired gait, hypersensitivity, chewing and convulsions. In addition, signs of local paraesthesia (that is, chewing of extremities, burrowing, pawing, excessive grooming) as an acute effect distinct from irritation were noted. Neuropathological changes in the sciatic and femoral nerves (minimal axonal degeneration) were seen in a rat study conducted with cyfluthrin, but only at high dose levels. Decreased motor activity in rats after exposure to beta-cyfluthrin was demonstrated in the published literature. There was no evidence of delayed neurotoxicity in hens. There was evidence of neurological effects in the young in a developmental neurotoxicity (DNT) study in rats treated with beta-cyfluthrin. Offspring had reduced body weights, decreased acoustic startle response and decreased absolute brain weights at a dose level that also elicited reduced food consumption and body weight in maternal animals.

There was some evidence of adverse effects on reproductive capacity in rat multi-generation oral reproductive toxicity studies conducted with cyfluthrin. Decreased fertility, litter size and birth weight were observed in one of two available studies. Effects in parental animals in both studies were similar to those in repeat-dose oral toxicity studies (for example, clinical signs of neurotoxicity, decreased body weight, liver and kidney weight changes) and were evident at comparable dose levels. Effects in the offspring included decreased pup and litter weight, decreased survival and the presence of coarse tremors. Effects in the offspring occurred at dose levels that were not toxic to the maternal animals, suggesting sensitivity of the young.

In a pubertal development and thyroid function study, delayed vaginal opening was observed in female rats as well as transient decreased body weight gains. There was no evidence of effects of cyfluthrin on preputial separation of male rats.

In developmental toxicity studies with orally administered cyfluthrin and beta-cyfluthrin, developmental effects were observed in rats and rabbits in the presence of maternal toxicity. Abortions were noted in rabbits treated with cyfluthrin, although the interpretation of this finding was confounded by the potential stress incurred as a result of construction noise in the animal treatment room. With beta-cyfluthrin, incomplete ossification, reduced fetal weight and enlarged anterior fontanelle were observed in rat fetuses at doses where maternal toxicity (including mortality) was observed. The most notable signs of toxicity in rat dams treated with cyfluthrin were clinical signs of neurotoxicity including high stepping gait, ataxia and decreased motility. Rat dams treated with beta-cyfluthrin demonstrated increased mortality and clinical signs of neurotoxicity (hypoactivity, locomotor incoordination and salivation). Mortality of rat dams treated with beta-cyfluthrin was observed at doses comparable to those at which ataxia and decreased motility were observed with cyfluthrin, indicating a possible higher oral toxicity of beta-cyfluthrin in this subpopulation.

In a developmental toxicity study conducted in rats exposed to cyfluthrin via the inhalation route, increased numbers of runts and skeletal anomalies of the sternum were observed at doses where maternal toxicity was not observed, suggesting susceptibility of the young. At a higher dose, an increased incidence of microphthalmia was observed. In a second inhalation developmental toxicity study in rats with cyfluthrin, in which an additional group of high dose animals received

oxygen supplementation, decreased placental and fetal weights and delayed ossification were observed at doses where maternal toxicity (clinical signs and decreased body weight, body weight gain and food consumption) was observed. At the highest dose, with and without oxygen supplementation, an increased incidence of malformations (microphthalmia) was observed in the presence of additional signs of maternal toxicity (respiratory distress, hypoactivity, high-stepping gait, salivation).

Studies from the published literature indicate that pharmacodynamic and pharmacokinetic factors, notably age-dependent maturation of key metabolic processes, may lead to increased susceptibility of the young to pyrethroid toxicity. Young animals have incomplete maturation of the enzyme systems that detoxify pyrethroids, particularly the carboxylesterases and cytochrome P450s. Consequently, pyrethroid concentrations in target tissues (for example, brain) may be higher in young animals than in adults given the same dose. In general, pyrethroid neurotoxicity is correlated to peak concentrations of the compound, with gavage dosing patterns resulting in greater internal doses compared to dietary administration. The pyrethroids are regarded as having a narrow window of time-to-peak-effect. The design of a DNT study does not consider time-to-peak-effect and may miss the window of peak toxicity for the pyrethroids (PMRA# 2394767, 2428095). The current DNT study for beta-cyfluthrin, therefore, is of limited value in addressing residual concern for the young. A comparative oral gavage neurotoxicity study conducted in pups, weanlings and adults, which considers the time of peak effect, could address this uncertainty. The PMRA is aware that there is currently work underway by a consortium of pyrethroid registrants to develop data to help address issues of comparative sensitivity of young and adult animals to pyrethroid neurotoxicity. The PMRA will consider this information when the studies become available. In the interim, this uncertainty has been reflected through the application of a database uncertainty factor.

In general, beta-cyfluthrin appears to be 2-4-fold more acutely toxic via the oral route, slightly more acutely toxic via the dermal and inhalation routes and more irritating to the eye and skin, when compared to cyfluthrin. In repeated-dose toxicity studies, there was no significant difference in toxicity between the two chemicals.

Results of the toxicology studies conducted on laboratory animals with cyfluthrin and beta-cyfluthrin are summarized in Table 1 of Appendix III. The toxicology endpoints for use in the human health risk assessment are summarized in Table 2 of Appendix III.

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, extensive data were available for cyfluthrin and beta-cyfluthrin. The database contains the full complement of required studies including developmental toxicity studies in rats (oral and inhalation routes) and rabbits and multigeneration studies in rats. A pubertal assay in rats and a developmental neurotoxicity study in rats were available. Additionally, a 7-day dam and pup whole-body inhalation study in rats was performed.

With respect to concerns relevant to the assessment of risk to infants and children, developmental toxicity observed in oral developmental toxicity studies occurred in the presence of maternal toxicity and included abortion (cyfluthrin rabbit study) and reduced fetal weight and delayed ossification (beta-cyfluthrin rat study). No evidence of treatment-related malformations was noted in the oral studies. In one of two developmental toxicity studies conducted via inhalation, effects on fetuses (increased runts and skeletal anomalies of the sternum) were observed at levels that were not toxic to the mother, suggesting sensitivity of the young. Malformations (microphthalmia) observed in both inhalation studies at maternally toxic levels, were considered serious endpoints. Evidence of increased susceptibility of the young was also present in rat oral reproductive toxicity studies in which tremors and decreased pup survival and body weight were seen at non-maternally toxic levels. A 7-day inhalation study in mice confirmed sensitivity, with clinical signs and mortality seen in offspring but not mothers. Neurological effects were noted in offspring in a guideline DNT study conducted in rats with beta-cyfluthrin, characterized by decreased response amplitude for acoustic startle and decreased brain weights at a dose which produced reduced maternal body weights and food consumption only.

Young animals have incomplete maturation of enzyme systems which detoxify pyrethroids and thus may be more susceptible due to higher and prolonged brain concentrations, compared to adults (PMRA# 2007551). Due to the lack of a comparative oral neurotoxicity study, an adequate assessment of sensitivity of the young is currently not available and residual uncertainty remains concerning susceptibility of the young to potential neurotoxic effects. This concern was reflected through the use of a database uncertainty factor of 3-fold in the risk assessment. Since these concerns were addressed with a database uncertainty factor, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Dietary Exposure and Risk Assessment

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

The PMRA considers limiting use of a pesticide when exposure exceeds 100% of the reference dose or the lifetime cancer risk estimate exceeds 1×10^{-6} (one-in-a-million). PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute, chronic and cancer risk assessment procedures.

Residue estimates used in the dietary risk assessment may be based conservatively (using upper bound estimates) on the maximum residue limits (MRLs) or 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's (USDA) Pesticide Data Program (PDP). Theoretical and experimental processing factors as well as specific information regarding percent of crops treated may also be incorporated to the greatest extent possible.

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

Sufficient information was available to adequately assess the dietary exposure and risk to cyfluthrin. Acute and chronic dietary (food only) 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) 2005-2010 available through the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS). As noted previously (Section 3.1), cyfluthrin and beta-cyfluthrin are structurally identical, differing only in the ratio of the stereoisomers. Analytical methods for current residue monitoring do not distinguish between cyfluthrin and beta-cyfluthrin; therefore, the dietary risk assessments were conducted by combining the uses of both chemicals. Only cyfluthrin is currently registered in Canada; import MRLs are being proposed for beta-cyfluthrin.

Based on the registered uses for cyfluthrin (and the proposed uses for beta-cyfluthrin that can be supported), residues in drinking water are not anticipated. Therefore, acute and chronic dietary exposures to cyfluthrin were estimated from residues of cyfluthrin and beta-cyfluthrin in treated crops and animal commodities (including imports).

The acute and chronic exposure estimates are considered to be highly refined (more precise) as monitoring residues, percent crop treated, experimental processing factors and domestic/import data were used to the extent possible. For more information on dietary risk estimates or residue chemistry information used in the dietary assessment, see Appendices IV and V.

3.2.1 Determination of Acute Reference Dose

General Population (including pregnant women, infants and children):

To estimate acute dietary risk, the acute neurotoxicity study conducted with beta-cyfluthrin in adult rats with a NOAEL of 0.5 mg/kg bw was selected for risk assessment. At the LOAEL of 2 mg/kg bw, clinical signs, changes in the functional observational battery (FOB) parameters and decreased motor activity were observed. These effects were the result of a single exposure and are therefore relevant to an acute risk assessment. The selection of this NOAEL was supported by a $BMDL_{20}$ of 1.4 mg/kg bw generated from motor activity data in a published non-guideline acute neurotoxicity study. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. A 3-fold database uncertainty factor was applied to reflect residual uncertainty regarding potential susceptibility of the young. Consequently, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section. The composite assessment factor (CAF) is thus 300. The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.5 \text{ mg/kg bw}}{300} = 0.002 \text{ mg/kg bw of cyfluthrin or beta-cyfluthrin}$$

3.2.2 Acute Dietary Exposure and Risk Assessment

The acute dietary risk from food only was calculated considering the highest ingestion of cyfluthrin that would be likely on any one day, and using food consumption and food residue values. The expected intake of residues is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARfD, then acute dietary exposure is not of concern.

The acute probabilistic risk assessment was conducted for the general population and all subpopulations using available residue monitoring data from the CFIA and the USDA's PDP. The general MRL of 0.1 ppm or the LOQ value from field trial residue data were used for a few commodities for which no monitoring data were available. In addition, the following inputs were incorporated where available: percentage of crops treated (PCT) information in Canada and in the United States; 100% crop treated for commodities for which no PCT information was available; available information on domestic production and import supply; and available experimental processing factors. Theoretical processing factors from DEEM were used when experimental processing factors were not available.

The acute exposure estimates at the 99.9^{th} percentile for the general population and all subpopulations range from 38% to 214% of the ARfD. Milk is the major risk driver for the most highly exposed subpopulation of children aged 1 2 years old, contributing 81% to the exposure.

When milk and dairy food forms are removed from the exposure assessment, the acute dietary risk estimates from cyfluthrin and beta-cyfluthrin through food only for all subpopulations range from 18% to 39% of the ARfD, and therefore are not of concern. Consequently, the application of cyfluthrin to lactating dairy cattle as a pour-on or as ear tags is proposed to be prohibited (see Section 9.1.1).

3.2.3 Determination of Acceptable Daily Intake (ADI)

General Population (including pregnant women, infants and children):

To estimate risk of repeat dietary exposure, the acute neurotoxicity study conducted with beta-cyfluthrin in adult rats with a NOAEL of 0.5 mg/kg bw was selected for risk assessment. At the LOAEL of 2 mg/kg bw, clinical signs, changes in FOB parameters and decreased motor activity were observed. The selection of this NOAEL was supported by a $BMDL_{20}$ of 1.4 mg/kg bw generated from motor activity data in a published non-guideline acute neurotoxicity study in adult rats. The selected NOAEL was the lowest NOAEL in the database, and was considered to provide appropriate protection to the general population. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. A 3-fold database uncertainty factor was applied to reflect residual uncertainty regarding potential susceptibility of the young. Consequently, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section. The CAF is thus 300. The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.5 \text{ mg/kg bw/day}}{300} = 0.002 \text{ mg/kg bw/day of cyfluthrin or beta-cyfluthrin}$$

The ADI provides a margin of 12750 to the dose at which urinary bladder tumours were observed in female rats in a dietary chronic toxicity/oncogenicity study.

The ADI provides a margin of 2700 to the NOAEL for decreased pup survival in the rat reproduction study.

3.2.4 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk from food only was calculated using the average consumption of different foods and the average residue values on those foods. This estimated exposure was then compared to the ADI. When the estimated exposure is less than the ADI, the chronic dietary exposure is not of concern.

The chronic assessment was conducted for the general population and all subpopulations using average residues from the same CFIA and PDP monitoring data used in the acute assessment, adjusted with percent crop treated data and domestic/import statistics; the general MRL of 0.1 ppm or the LOQ value from field trial residue data for commodities for which no monitoring data were available; and experimental processing factors when available (otherwise DEEM default processing factors were used).

To account for the use of cyfluthrin in food handling establishments, all the remaining commodities listed in DEEM were included in the chronic analysis using a point estimate of 0.025 ppm, corresponding to ½ LOQ of the analytical method used to assess residues resulting from food handling establishments (residues were all < LOQ of 0.05 ppm) and a percent crop treated value of 4.65%.

The chronic exposure estimates for the general population and all subpopulations range from 5% to 48% of the ADI. When milk and dairy food forms are removed from the exposure assessment (see Section 3.2.2), the chronic dietary risk estimates from cyfluthrin and beta-cyfluthrin through food only for all subpopulations range from 1% to 5% of the ADI, and therefore are not of concern.

3.2.5 Cancer Assessment

As previously discussed, a slight increase in the incidence of urinary bladder tumours in females in the rat chronic toxicity/oncogenicity study with cyfluthrin was considered equivocal based on the weight of evidence. Overall, the endpoints selected for the non-cancer risk assessment are protective of these equivocal findings.

3.3 Exposure from Drinking Water

Based on the registered uses for cyfluthrin (and the proposed uses for beta-cyfluthrin outlined in PRD2016-21), residues in drinking water are not anticipated. As such, a drinking water risk assessment is not required at this time.

3.4 Occupational and Non-Occupational Exposure and Risk Assessment

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

3.4.1 Toxicology Endpoint Selection for Occupational and Non-Occupational Risk Assessment

Short-, Intermediate- and Long-Term Dermal Exposure:

For short-, intermediate- and long-term dermal risk assessments for all populations, a NOAEL of 376 mg/kg bw/day was selected from the 21-day dermal toxicity study in adult rats. At a dose of 1077 mg/kg bw/day, clinical signs (nasal discharge, urine staining) and decreased food consumption were observed. The target MOE is 300. This includes uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and a 3-fold database uncertainty factor for concerns related to potential sensitivity of the young. For residential scenarios, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section.

Short-Term Inhalation Exposure:

For short-term inhalation risk assessments for all populations, a NOAEC of 0.0002 mg/L (0.07 mg/kg bw/day) was selected based on the 28-day inhalation toxicity study with beta-cyfluthrin in adult rats. At the next highest concentration of 0.0027 mg/L (0.9 mg/kg bw/day), decreased body weight and body weight gain were observed. The target MOE is 300 and includes uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and a 3-fold database uncertainty factor for concerns related to potential sensitivity of the young. For residential scenarios, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section. Selection of this endpoint provides a margin > 5000 to the NOAEL for malformations that occurred in the presence of maternal toxicity in inhalation developmental toxicity studies in the rat.

Intermediate- and Long-Term Inhalation:

For intermediate- and long-term inhalation risk assessments for all populations, a NOAEC of 0.00009 mg/L (0.02 mg/kg bw/day) was selected based on the 90-day inhalation toxicity study in rats. At the next highest concentration of 0.00071 mg/L (0.19 mg/kg bw/day), decreased body weight and clinical signs (disturbed non-specific behaviour) were observed. The target MOE is 300 and includes uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and a 3-fold database uncertainty factor for concerns related to potential sensitivity of the young. For residential scenarios, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section.

Cancer Assessment:

See Section 3.2.5 above.

Dermal Absorption:

A dermal absorption value was not required as the toxicological endpoint selected for the dermal risk assessment is based on a dermal study.

3.4.2 Non-Occupational Exposure and Risk Assessment

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

The United States Environmental Protection Agency (USEPA) has generated standard default assumptions for developing residential exposure assessments for both applicator and postapplication exposures when chemical- and/or site-specific field data are limited. The assumptions and algorithms 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. The assumptions and algorithms relevant to the cyfluthrin re-evaluation are outlined in the Standard Operating Procedures (SOPs) for Residential Pesticide Exposure Assessments 2012 under “Section 7: Indoor Environments”

Residential Applicator Exposure and Risk Assessment

A residential applicator refers to an adult (≥ 16 years old) who applies a domestic-class product in or around the home. For cyfluthrin, the residential applicator would apply the product using a ready-to-use aerosol can. Residential applicators are assumed to be wearing shorts, a short-sleeved shirt, shoes and socks. The residential applicator has the potential for short-term exposure (1 to 30 days) when applying products containing cyfluthrin.

Calculated MOEs exceeded the target MOE for both dermal and inhalation exposures, and therefore risks are not of concern. The two exposure routes were not combined since the endpoints were based on different toxicological effects (see Appendix VII, Table 1).

Residential Postapplication Exposure and Risk Assessment

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

The following postapplication scenarios were assessed: broadcast application, band and spot application, bedbug application including to mattresses, and crack and crevice application. Multiple applications were not assessed, since exposure on the day of application without any dissipation was assumed for the entire duration of exposure (for several months). This is considered to be a conservative assumption, combined with the other inputs and algorithms from the residential SOPs for dermal exposure.

While exposure may occur for people of all ages, adults (≥16 years old), youth (11 < 16 years old), and children (1 < 2 years old) have been chosen as the index lifestages to assess, based on behavioural characteristics and the quality of the available data. Children 2 years old to < 11 years old are not assessed separately because their exposure is expected to be less than that of 1 < 2 years old. Children (1 < 2 years) are expected to have a greater exposure because of additional routes of exposure (incidental oral) as well as a greater body surface area (cm^2) to body-weight (kg) ratio.

Postapplication residential exposure to cyfluthrin is expected to be intermittent short-term (1 to 30 days) in duration, with the exception of bedbug treatment which is assumed to result in intermittent short- to long-term (1 to 180 days) exposure. Adults and youth have the potential for dermal and inhalation exposures, while children have the potential for dermal, inhalation and incidental oral exposures (both hand-to-mouth and object-to-mouth).

For all indoor postapplication scenarios, the calculated dermal MOEs exceeded the target MOE for all age groups, and therefore risks are not of concern (see Appendix VII, Tables 2-3).

The calculated inhalation MOEs exceeded the target MOE for all scenarios (see Appendix VII, Tables 4-5). However, to mitigate inhalation concerns identified by the PMRA's Incident Reporting Program (see Section 7.0), entry to treated sites must occur no sooner than eight hours after application.

Assessment of incidental oral exposure assumes that pesticide residues are transferred to the skin of children playing on treated indoor surfaces and are subsequently ingested as a result of hand-to-mouth transfer. Residues can also be transferred to a child's toy and subsequently ingested as a result of object-to-mouth transfer. Incidental oral exposures from indoor hard surface or carpet applications are considered to be protective of mattress applications.

For incidental oral exposure, target MOEs were met only for crack and crevice applications. For other scenarios, target MOEs were not met, and therefore, there are potential risks of concern for children (see Appendix VII, Tables 6-9).

Combined exposures and risk from incidental oral exposure and inhalation exposure was conducted for crack and crevice application. Target MOEs were met and therefore, risk is not of concern (see Appendix VII, Tables 10-11). Exposures for the dermal and inhalation routes were not combined for cyfluthrin as the toxicological endpoints for these routes were not similar.

To ensure crack and crevice application only in residential areas, the following measures are proposed:

- Cancellation of all domestic-class products.
- Label directions on commercial-class products to include definition of residential areas.
- Label directions to include definition of crack and crevice application.
- Label directions to prohibit broadcast application, band and spot application and bedbug application in residential areas.
- Label directions to specify that the product must only be applied using a low pressure sprayer equipped with a pin stream nozzle to direct sprays into cracks and crevices. Also, the directions for use must be modified to provide specific use directions for crack and crevice application.
- A requirement that products be marketed with separate labels for agricultural uses versus non-agricultural uses. This is to clarify for farmers to not apply the product intended for agricultural use inside their homes (broadcast, band, spot and bedbug application is permitted in animal housing).

  Note: Many commercial sites would be considered residential areas, since there is potential for children to enter treated sites. These sites also need to be limited to crack and crevice application. These sites include but are not limited to:

- Public areas of hotels and motels.
- Nursing homes and hospitals.
- Schools.
- Public areas of stores.
- Seating areas of aircraft, buses, railcars, ships and trucks.
- Public areas of restaurants.

3.4.3 Occupational Exposure and Risk Assessment

There is a potential for exposure to cyfluthrin in occupational scenarios from workers handling cyfluthrin products during the application process and a potential for postapplication exposure from workers entering into areas previously treated with cyfluthrin. Current uses of cyfluthrin in indoor commercial areas are crack and crevice applications, band and spot applications and bedbug applications. Broadcast application is limited to livestock housing only.

Handler Exposure and Risk Assessment

For commercial-class products, there are potential exposures to mixers, loaders and applicators (M/L/A). The following scenarios were assessed:

- Mixing, loading and applying a wettable powder formulation using a low pressure handwand sprayer.
- Mixing, loading and applying a wettable powder formulation using a backpack sprayer.
- Applying a pour-on formulation to beef and dairy cattle.
- Applying ear tags to beef and dairy cattle.

Mixer, loader and applicator exposure was estimated based on current label personal protective equipment: long-pants, long-sleeved short, chemical-resistant gloves and respirator. Commercial applicators would apply cyfluthrin to many different types of use sites to control a variety of pests. Therefore, their exposure would be long-term (≥ 6 months) and intermittent. Farmers would have intermittent short-term exposure (≤ 30 days) from application to livestock housing.

No appropriate chemical-specific handler exposure data were available for cyfluthrin at the initiation of the re-evaluation. Therefore, dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database (PHED) Version 1.1. The PHED is a compilation of generic mixer/loader/applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of personal protective equipment. In most cases, PHED did not contain appropriate data sets to estimate exposure to workers wearing a respirator. This was estimated by incorporating a 90% protection factor for a respirator into the unit exposure values, where applicable. Inhalation exposures were based on light inhalation rates (17 L/min) except for backpack applicator scenarios, which were based on moderate inhalation rates (27 L/min). For amount handled per day, information was provided by the registrant. The highest amount handled per day with the highest application rates were used for the exposure assessment.

It should be noted that an observational study to determine dermal and inhalation exposure to commercial applicators applying deltamethrin and/or beta-cyfluthrin using hand-held equipment in a crack and crevice application was submitted by the applicant for the registration of beta-cyfluthrin. This study was submitted after the risk assessment for cyfluthrin was completed and it will be reviewed for relevance to the current risk assessment prior to issuing a final decision on the re-evaluation of cyfluthrin.

For commercial application of ear tags to cattle, measured exposure data are not available and existing database models are not appropriate to estimate worker exposure during handling (in other words, application and removal) of ear tags. Herd treatment is anticipated; however, considering the low frequency of application, design of the product as a slow release of cyfluthrin over time, and the current label requirement to wear chemical-resistant gloves during application or when otherwise handling the tag, potential applicator exposure is not expected to be of concern. Mixer, loader and applicator exposure estimates are based on the best available data at this time.

Calculated dermal MOEs for M/L/A exceeded the target MOE, and therefore are not of concern. The current label requirement is to wear non-absorbent gloves when applying pour-on to cattle while chemical-resistant gloves are specified for all other commercial uses. As such, no additional mitigation measures are required.

For intermediate- and long-term inhalation exposure, the calculated MOEs exceeded the target MOE for most scenarios, and therefore risks are not of concern. For commercial applicators, since the inhalation MOE of 278 is close to the target MOE of 300, it is considered that risks would not be of concern due to conservatisms in the exposure assessment.

Exposures for the dermal and inhalation routes were not combined for cyfluthrin as the toxicological endpoints for these routes were not similar.

The results of the mixer/loader and applicator assessment are presented in Appendix VI, Tables 1-2.

Postapplication Worker Exposure and Risk Assessment

Potential occupational postapplication worker scenarios include:

Dermal Exposure:

- Commercial applicators returning to treated sites for scouting.
- Workers entering treated areas in the following sites:
  - Hotels and motels
  - Nursing homes and hospitals
  - Factories, laboratories, mausoleums, non-commercial greenhouses, schools, stores and warehouses
  - Aircraft, buses, rail cars, ships and trucks
  - Food/feed handling establishments such as bakeries, bottling plants, canneries, dairies, frozen food plants, grain mills, kitchens, meat packing plants, poultry and egg processing plants and restaurants
  - Pet kennels
  - Livestock housing, including poultry houses

Data were not available to assess indoor postapplication exposures to workers. However, postapplication exposure assessments for residential areas are considered to be representative for non-residential areas. This assumption is based on the duration and degree of contact with treated surfaces which is assumed to be greater in residential areas.

Although there is potential dermal exposure to workers handling treated livestock following ear-tag or pour-on applications, these activities are expected to be limited.

No risks of concern were identified for workers entering treated sites for the current uses provided that workers do not enter the treated site sooner than eight hours after application in order to mitigate inhalation concerns identified as a result of the PMRA's Incident Reporting Program (see Section 7.0).

Note: For some sites, although risks of concern were not identified for workers, applications must be limited to crack and crevice if there is potential for children to enter the treated site (for example, hotel rooms, eating areas of restaurants). See Section 3.4.2.

3.5 Aggregate Exposure and Risk Assessment

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

3.5.1 Toxicology Endpoint Selection for Aggregate Risk Assessment

Short-term Aggregate:

For aggregate risk assessment for the general population (including pregnant women, infants and children) for short-term duration, the selected toxicological endpoint is clinical signs of neurotoxicity. For oral exposure, the NOAEL of 0.5 mg/kg bw from an acute neurotoxicity study conducted with beta-cyfluthrin in adult rats was selected; clinical signs were seen at the LOAEL of 2 mg/kg bw. For inhalation aggregate risk assessment, it was considered appropriate to consider the NOAEC of 0.0002 mg/L (0.07 mg/kg bw/day) from the 5-day inhalation study with beta-cyfluthrin, where clinical signs were observed at the next highest concentration of 0.0038 mg/L (1.07 mg/kg bw/day). It was not considered necessary to include the dermal route in the aggregate risk assessment as clinical signs of neurotoxicity were not evident following dermal dosing in rats. For both the oral and inhalation routes of exposure, a target MOE of 300 was selected. This target MOE includes a 10-fold uncertainty factor for interspecies extrapolation, a 10-fold uncertainty factor for intraspecies variability and a 3-fold database uncertainty factor for concerns related to potential sensitivity of the young. The *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section.

Cancer Assessment:

See Section 3.2.5 above.

3.5.2 Residential, Non-Occupational 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. Additionally, only exposures from routes that share common toxicological endpoints can be aggregated. As such for cyfluthrin, only exposures from inhalation and oral routes were aggregated for the crack and crevice application.

Children (1 < 2 years old) were selected for the aggregate exposure scenarios since they would have both incidental oral exposure and inhalation exposure following crack and crevice application in residential areas, as well as dietary exposure.

The following scenarios were aggregated:

- Short-term hand-to-mouth exposure from hard surfaces, short-term inhalation exposure and chronic food exposure for children (1 < 2 years old).
- Short-term hand-to-mouth exposure from soft surfaces, short-term inhalation exposure and chronic food exposure for children (1 < 2 years old).

These scenarios were assessed for crack and crevice application only as all other scenarios did not meet the target MOE and are proposed to be removed.

Calculated aggregate MOEs exceeded the target MOE, and therefore are not of concern (see Appendix VIII, Tables 1-2).

3.5.3 Human Biomonitoring Data

Biological monitoring or biomonitoring is a method of assessing exposure to a pesticide by measuring the pesticide or its metabolites in biological media, such as urine or blood. Compared to ambient monitoring, biological monitoring has the advantage that it provides an integrated estimate of exposure through all relevant routes (respiratory, dermal and oral) and by all possible pathways (for example, food, drinking water and indoor uses) and reflects behavioural and physical sources of variability. It differs from the standard approach for aggregate human health risk assessments, in which exposure models and algorithms are used to estimate route-specific exposures using measurements of pesticide concentrations in the environment or what is deposited on the skin, inhaled, and/or consumed for specific scenarios.

Human biomonitoring (HBM) data can be used to establish baseline levels of chemicals, to compare exposures, assess the effectiveness of exposure management strategies and to identify priorities. HBM data are considered to be refined since they are reflective of the ‘real-life’ use of chemicals and, in the case of population biomonitoring surveys, would represent aggregate risk for the general population. Therefore, HBM data may be used when evaluating aggregate exposure to a pesticide to support risk estimates generated using PMRA’s standard approach for human health risk assessments.

HBM data from the Canadian Health Measures Survey (CHMS; cycles 1 & 2; 2007-2011) and the Maternal-Infant Research on Environmental Chemicals – Child Development Plus (MIREC-CD Plus; 2013-2014[3]) were considered in the cyfluthrin re-evaluation.

The CHMS is an on-going, nationally representative health measures survey that has been conducted by Statistics Canada, in partnership with Health Canada and the Public Health Agency of Canada, since 2007. The cross-sectional survey collects information from Canadians such as physical measures (for example, height and weight) and general health (for example, blood pressure and fitness), as well as a biomonitoring component. It follows a similar study design to the United States National Health and Nutritional Examination Survey (NHANES) biomonitoring component. In Cycle 1 of the CHMS (2007-2009), blood and spot urine samples were collected from approximately 5,600 Canadians, 6-79 years old. In Cycle 2 (2009-2011), children as young as 3 years old were included. Pyrethroid metabolites, including a specific metabolite for cyfluthrin, were included in the suite of compounds measured.

The MIREC study was a national-level multi-year study that recruited approximately 2,000 women in the first trimester of pregnancy from 10 cities across Canada [Arbuckle *et al*., 2013]. Women were followed over the course of their pregnancy to measure their exposure to environmental chemicals and examine potential health risks associated with these exposures. The MIREC-CD Plus study, an off shoot of the MIREC study, recruited children between the ages of 15 months and 5 years of age from six of the most populous recruitment sites for the MIREC pregnancy cohort study. In addition to measuring their growth and neurodevelopment, blood and spot urine samples were collected from participating children. Approximately 200 urine samples from children under 3 years of age were analyzed. Data from the MIREC study were analysed at the request of PMRA under the Chemical Management Plan. Although the MIREC-CD Plus study aimed to collect urine from children that were 15 months to 3 years of age, there were no samples in the pyrethroid data set for children younger than 23 months.

Pyrethroid pesticides are rapidly metabolized and eliminated from the body through hydrolysis, oxidation, and conjugation. Following oral ingestion, inhalation or dermal exposure, pyrethroids are metabolized into carboxylic and phenoxybenzoic acids and excreted with urine. Pyrethroids and their metabolites can be measured in blood and urine, and are reflective of recent exposure to the parent compound or the metabolite in the environment.

For the cyfluthrin re-evaluation, the 95th percentile values from CHMS and MIREC-CD Plus data were used to conduct the aggregate risk assessment using two approaches: forward dosimetry and reverse dosimetry.

Forward Dosimetry:

Forward dosimetry is an approach that can be used to understand the quantitative relationship between pesticide exposures and observed concentrations of the parent or metabolite. An example of forward dosimetry is biological equivalents (BEs). A BE is defined as the

[3] Unpublished data from the populations Studies Division, Healthy Environments and Consumer Safety Branch, Health Canada (received December 2014).

concentration or range of concentrations of a chemical or its metabolites in a biologic medium (blood, urine or other medium) that is consistent with an existing health-based exposure guidance value such as a Reference Dose or Acceptable Daily Intake (ADI). In other words, the BE is the toxicological reference dose translated into a blood or urinary value using pharmacokinetic data. BEs are intended to be used as screening tools to provide an assessment of whether a chemical biomarker is present at levels well below, near, at, or above concentrations that are consistent with existing risk assessments and exposure guidance values.

A BE for the specific cyfluthrin metabolite, 4-fluoro-3-phenoxybenzoic acid (4-F-3-PBA), in urine was derived by Hays *et al.* (2009) based on exposure guidance values, pharmacokinetic data, daily urinary volume or creatinine excretion, and body weight. Using the same methodology as Hayes *et al.* (2009), a BE was derived for cyfluthrin based on the ADI established by PMRA (see Section 3.2.3) The levels of the cyfluthrin metabolite for both adults and children above 6 years old as measured in CHMS were lower than the derived BE, indicating that the aggregate risk is not of concern for these age groups, and supporting the conclusions of PMRA's aggregate assessment (see Appendix IX, Table 1).

Reverse Dosimetry:

Reverse dosimetry (in other words, exposure reconstruction) is an approach used to work backwards from metabolite measurements to estimates of human pesticide exposure. In this approach, human biomonitoring data are back-transformed into systemic exposure estimates (µg/kg bw/day) using human pharmacokinetic data in combination with information regarding the nature of the potential exposures. The resulting systemic exposure estimates are then compared to hazard endpoints to estimate risk.

In addition to the biomonitoring data, two human pharmacokinetic studies were available for cyfluthrin (Leng *et al.*, 1997a-b) and were used to determine the amount of 4-F-3-PBA metabolite excreted following administration of the parent compound, cyfluthrin. The studies were conducted in volunteers, followed informed consent procedures and were approved by an independent ethics committee.

Equations for estimating daily urinary creatinine excretion were used to calculate daily exposure estimates. As such, a urinary excretion fraction value of 10% was selected for 4-F-3-PBA. This was determined by multiplying the urinary excretion fraction of 4-F-3-PBA with its relative urinary concentration as measured in the CHMS and MIREC-CD Plus biomonitoring studies. The CHMS and MIREC-CD Plus metabolite data have been normalized by each individual's body weight and extrapolated to a full day value using daily creatinine excretion values (determined for each individual based on their height and weight) using the equations from Mage *et al.* (2008).

The results of the reverse dosimetry calculations for cyfluthrin are summarized in Appendix IX, Table 2. The calculated aggregate MOEs based on HBM data exceeded the target MOE for the populations measured. This indicates that aggregate risk is not of concern for these age groups, and supports the conclusions of PMRA's aggregate assessment.

The available HBM data are unlikely to capture incidental oral exposure in children (1 to < 2 years old) since children younger than 23 months were not included in the surveys.

3.6 Cumulative Assessment

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

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Cyfluthrin is used in homes as a domestic and commercial insecticide and outdoors on livestock as commercial pour-on and ear tags. Due to this limited outdoor use pattern, environmental exposure is expected to be minimal.

Data on the fate and behaviour of cyfluthrin are summarized in Table 1 of Appendix X

In soil, cyfluthrin transforms through photolysis and biotransformation and is moderately persistent with a half-life of 53.1- 56.8 days. It transforms mainly to FPBacid, DCVA, CO_2 and bound residues. DCVA is slightly to moderately persistent in aerobic soil (DT_{50} 12-62 d). Cyfluthrin is expected to be immobile in soil based on high adsorption coefficients (Koc: 45471-180000) and is not expected to leach and enter groundwater. The transformation product DCVA is expected to be highly mobile (Koc: 53.4).

If cyfluthrin enters the aquatic environment, it is non-persistent and forms 3 major transformation products: DCVA, FPBacid and FPBald, all of which partition predominantly into the sediment phase.

Cyfluthrin is insoluble in water and is non-volatile. The log octanol/water partitioning coefficient (Kow = 5.97) suggests cyfluthrin has the potential to bioaccumulate in the food chain. However, based on its limited outdoor use pattern, environmental exposure is expected to be limited.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. Available toxicity data for cyfluthrin is presented in Table 2, Appendix X.

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

4.2.1 Risks to Terrestrial Organisms

Due to the limited outdoor use, the potential exposure of terrestrial non-target organisms is not expected to be significant. Therefore, risk of concern to terrestrial organisms are not expected.

4.2.2 Risks to Aquatic Organisms

Due to the limited outdoor use, exposure to aquatic habitats is expected to be minimal. Therefore, risk of concern to aquatic organisms are not expected .

5.0 Value

5.1 Value of Cyfluthrin

Cyfluthrin has an important role in Integrated Pest Management to help manage pests in structural sites.

Cyfluthrin is compatible with Integrated Pest Management practices to help manage labelled pests in structural sites. Many of the pests on the cyfluthrin use pattern, including ants, cockroaches and bedbugs, are challenging to control and sometimes require repeated pest control treatments. Multiple control strategies are typically required to manage these pests, including non-chemical approaches such as sanitation, structural repairs, and exclusion, and pesticide treatments using insecticides from the same or different resistance management group or using different application methods such as insecticides applied as dusts, gel baits, pressurized products. When pesticide treatments are needed in a pest management strategy, cyfluthrin can be used alone or in conjunction with another insecticide (for example, pyrethrins applied as a dust, pyrethroids applied as an aerosol, cockroach gel baits) to target pests in specific locations in residential sites.

Cyfluthrin is important for the purpose of resistance management of structural insect pests.

Cyfluthrin is a synthetic pyrethroid (resistance mode of action (MoA) group 3 insecticides) which is registered for use in residential sites targeting pests such as ants, bedbugs, cockroaches and earwigs. Cyfluthrin is important as a rotational product for resistance management in residential sites. In recent years, the registrations of several carbamate and organophosphate insecticides (MoA group 1A and 1B insecticides, respectively) that were used within structures have been discontinued (for example, bendiocarb, diazinon), or their use patterns have been amended, limiting their use to specific sites or to specific application methods (for example dichlorvos, propoxur and chlorpyrifos). This limits the availability of active ingredients from MoA groups 1A and 1B to rotate with the synthetic pyrethroids (MoA group 3 insecticides) leading to the potential for limited resistance management options. Other pyrethroid active

ingredients currently registered for use in residential sites includes lambda-cyhalothrin, permethrin, d-phenothrin, and tetramethrin are also under re-evaluation. Their registration status as alternatives to cyfluthrin may change as a result of the re-evaluation decisions.

Cyfluthrin has an important role in Integrated Pest Management to control horn flies and lice on lactating dairy cattle.

Multiple pest management practices, including chemical and non-chemical methods, are needed to help control horn flies and lice on lactating dairy cattle. Cyfluthrin is one of the few insecticides registered for use on lactating dairy cattle. It can be used with non-chemical methods in an integrated pest management approach to control horn flies and lice on lactating dairy cattle. Chemical methods for horn fly control typically involves monitoring of pest, applying insecticides only when horn fly numbers exceed the treatment threshold, treating only when fly populations warrant them late in the season, rotating with an insecticide with a different mode of action than the one used during peak periods, and removing insecticide impregnated ear tags in the fall. Non-chemical practices include mechanical fly control (fly traps and screens), manure management in pastures, rotating pastures, and encouraging beneficial organisms such as predators, parasites and natural competitors.

Cyfluthrin is important as a rotational product for resistance management in lactating dairy cattle because few effective horn fly control chemicals are registered. In Canada, horn fly populations resistant to organophosphate and pyrethroid insecticides are documented. Pesticides registered for use on lactating dairy cattle include a limited number of organophosphates, pyrethroids, pyrethrins, and one carbamate. These active ingredients can be applied the following ways: insecticide impregnated ear tags (diazinon, diazinon/cypermethrin, permethrin and tetrachlovinphos), animal sprays or backrubber treatments (permethrin), pour on (permethrin, pyrethrins, dichlorvos/pyrethrins), dusts applications (carbaryl) and fogs and sprays applications in dairy buildings (for example, pyrethrins). Eprinomectin, a veterinary drug of the macrocyclic lactones group, is also registered for horn fly control. However, it is recommended that the reliance of pour on macrocylic lactones as a horn fly control should be limited so to lessen internal parasite resistance which it also controls. The majority of the pesticides identified above are also under re-evaluation. Their registration status as alternatives to cyfluthrin may change as a result of the re-evaluation decisions.

Cyfluthrin is one of a limited number of active ingredients for control of lice on lactating dairy cattle.

A small number of lice on cattle may be common and cause no problems, but a severe infestation can be more serious and require chemical control. Good herd health and daily checks to monitor lice, and use of pesticides only when needed to target the correct pest species helps reduce the reliance on chemical treatments.

Permethrin, pyrethrins, carbaryl, and pour on veterinary drugs (eprinomectin and moxidectin), are registered for use on lactating cattle to control biting and sucking lice. All pesticides for use on lactating cattle are also under re-evaluation. Their registration status as alternatives to cyfluthrin may change as a result of the re-evaluation decisions.

Cyfluthrin is of benefit to the homeowner in the management of pests in and around the home

Domestic products containing cyfluthrin are registered for use on a broad spectrum of pests, such as ants, cockroaches, silverfish, spiders and crickets. Cyfluthrin products are of benefit to the homeowner to use with other control methods, such as prevention and non-chemical treatments, in the management of pests in homes.

5.2 Domestic Class Products

5.2.1 Alternatives to Domestic Class Products

The cyfluthrin domestic products are co-formulated with pyrethrins and piperonyl butoxide, and are available as pressurized spray cans for use indoors to target household pests such as ants, earwigs, cockroaches and spiders. The majority of the products registered against the same insect and spider pests on the cyfluthrin use pattern are also pyrethroids and currently under re-evaluation. Ants and crawling insects, such as earwigs, are the most prevalent types of insects in residential homes. Insecticide baits are a popular method of insect control against ants and crawling insects, while sprays/aerosols are typically used as a last resort when insect populations get too large to ignore. Active ingredients registered for ants and cockroaches include spinosad, abamectin, chlorpyrifos, borates, diatomaceous earth/silicon dioxide and soybean oil, d-limonene and German cockroach extract (cockroaches only). Domestic products to target earwigs in residential sites include boric acid, chlorpyrifos in baits, pressurized products containing resmethrin, pyrethrins, permethrin, tetramethrin/ d-phenothrin, dusts (diatomaceous earth), and ready to use sprays (soybean oil).

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bioaccumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*.

During the review process, cyfluthrin and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[4] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Cyfluthrin does not meet Track 1 criteria, and is not considered a Track 1 substance. See Appendix X, Table 3 for comparison with Track 1 criteria.
- Cyfluthrin does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[5] The list is used as described in the PMRA Notice of Intent NOI2005-01[6] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[7] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

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

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

7.0 Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA. Information on the reporting of incidents can be found on the PMRA website.

As of 16 October 2015, there have been 30 human and 64 domestic animal incidents reported for the active ingredients cyfluthrin and beta-cyfluthrin. Fourteen human incident reports and 33 domestic animal incidents were associated with the active ingredient cyfluthrin. One domestic

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

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

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

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

animal incident was associated with the active ingredient beta-cyfluthrin. The 14 human incidents involved 42 individuals. Thirty-four individuals reported experiencing respiratory effects after re-entering homes or a workplace that had been treated with cyfluthrin. Similar trends were observed in the United States, in which there was a high frequency of reports involving respiratory effects after entering areas treated with cyfluthrin or beta-cyfluthrin.

The following are recommendations that could help to prevent adverse effects from occurring following product application:

1) Based on the incident data, it is proposed that a longer re-entry interval appear on the commercial-class product label in order to reduce the likelihood of effects.
2) Adverse effects should be listed on the commercial-class product label.
3) Because commercial applicators may not always interact with occupants, it is recommended that for the commercial-class product, an information sheet be left in each treated home/structure, so that all users are aware of re-entry intervals, the need to ventilate, and potential adverse effects.

Mitigation to address this concern is summarized in Section 9.1.1 – *Proposed Regulatory Action Related to Human Health* and Appendices XI and XII.

There have been no environmental incidents involving cyfluthrin reported to the PMRA.

8.0 Organisation for Economic Co-operation and Development Status of cyfluthrin

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

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

Cyfluthrin is currently acceptable for use in other OECD member countries, including Australia, Japan, and the United States. As of 18 March 2016, no decision by an OECD member country to prohibit all uses of cyfluthrin for health or environmental reasons has been identified.

9.0 Proposed Re-evaluation Decision

The PMRA is proposing that most products containing cyfluthrin for use and sale in Canada are acceptable for continued registration. Based on the evaluation of currently available scientific information, mitigation measures are proposed to further protect human health, including cancellation of domestic-class products. In addition, due to the limited outdoor use, the risk to terrestrial and aquatic organisms is expected to be minimal. However, precautionary statements are proposed to further protect the environment.

The labels of Canadian end-use product must be amended to include the label statements listed in Appendix XI. No additional data are being requested at this time.

9.1 Proposed Regulatory Action Related to Human Health

9.1.1 Proposed Mitigation Related to Toxicology

Label statements are required (see Appendix XI) as well as an information sheet for occupants of areas treated with the commercial-class product (see Appendix XII).

9.1.2 Proposed Mitigation Related to Dietary Exposure

- Use of cyfluthrin on lactating dairy cattle is proposed to be prohibited.
- Maximum residue limits (MRLs) for cyfluthrin in milk and milk fat are proposed to be revoked.

9.1.3 Proposed Mitigation Related to Occupational and Residential Exposure

Label directions must be added to specify that entry to treated sites must not occur sooner than eight hours after application, to mitigate inhalation concerns.

To ensure crack and crevice application only, in residential areas, the following measures are proposed:

- Cancellation of all domestic-class products.
- Label directions to include definition of residential areas.

  Residential areas are defined as any use site where bystanders including children could be exposed during or after application. This includes homes, schools, public buildings or any other areas where the general public, including children, could be exposed.

- Label directions to include definition of crack and crevice application.

  Crack and crevice is defined as an application of pesticides with the use of a pin stream nozzle, into cracks and crevices in which pests hide or through which they may enter a building. It does not permit the treatment of surfaces. Such openings commonly occur at expansion joints, between different elements of construction, and between equipment and floors. These openings may lead to voids such as hallow walls, equipment legs and bases, conduits, motor housings, and junction or switch boxes.

- Label directions must be added to prohibit broadcast application, band and spot application and bedbug application in residential areas.
- Label directions must be added to specify that the product must only be applied using a low pressure sprayer equipped with a pin stream nozzle to direct sprays into cracks and crevices. Also, the directions for use must be modified to provide specific use directions for crack and crevice application.

- A requirement that separate labels for products be marketed for agricultural uses versus non-agricultural uses. This is to ensure that farmers do not apply the product inside their homes (broadcast, band, spot, and bedbug application is permitted in animal housing).
- A requirement that an information sheet be left in each treated home/structure, so that all users are aware that entry is not permitted by residents, workers and others until 8 hours after application, the need to ventilate, and potential adverse effects.

  Note: Many commercial sites would be considered residential areas since there is potential for children to enter treated sites. These sites also need to be limited to crack and crevice application. These sites include but are not limited to:

  - Public areas of hotels and motels.
  - Nursing homes and hospitals.
  - Schools.
  - Public areas of stores.
  - Seating areas of aircraft, buses, railcars, ships and trucks.
  - Public areas of restaurants.

9.1.4 Residue Definition for Risk Assessment and Enforcement

Currently, the residue definition for cyfluthrin in Canada is cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate. No change is proposed to this residue definition per se as a result of the re-evaluation. However, the residue definition for MRL enforcement will be revised to indicate residues are to be measured as **cyfluthrin** (cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate) **(sum of isomers)**.

9.2 Proposed Regulatory Action Related to the Environment

Due to the limited outdoor use, the risk to terrestrial and aquatic organisms is expected to be minimal. However, the following precautionary statements are proposed to further protect the environment:

- Toxic to aquatic organisms.
- Toxic to small mammals.

10.0 Supporting Documentation

PMRA documents, such as Regulatory Directive DIR2012-02, *Re-evaluation Program Cyclical Re-evaluation*, and DACO tables can be found on the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra. PMRA documents are also available through the Pest Management Information Service. Phone: 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); fax: 613-736-3798; e-mail: pmra.infoserv@hc-sc.gc.ca.

The federal Toxic Substances Management Policy is available through Environment Canada's website at www.ec.gc.ca/toxics.

List of Abbreviations

↑	Increased
↓	Decreased
µg	Microgram(s)
µM	Micromolar
♀	Females
♂	Males
ADI	acceptable daily intake
a.i.	active ingredient
AHETF	Agricultural Handlers Exposure Task Force
ALP	alkaline phosphatase
ALT	Alanine transaminase
ARfD	acute reference dose
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ATPD	area treated per day
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
BE	Biomonitoring equivalent
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limits
BUN	blood urea nitrogen
bw	body weight
bwg	Body weight gain
CAF	composite assessment factor
CAS	chemical abstracts service
CDC	Centers for disease control and prevention
CFIA	Canadian food inspection agency
CHMS:	Canadian Health Measures Survey
CHO	Chinese Hamster Ovary
cm	centimetres
cm^2	Centimetres squared
cm^2/hr	Centimetres squared per hour
DA	dermal absorption
DACO:	data code
DEEM-FCID	Dietary exposure evaluation model - food commodity intake database
DMSO	Dimethyl sulfoxide
DNA	deoxyribonucleic acid
DU	dust or powder formulation
EPA	Environmental protection agency
et al.	and others
F_1	first generation
F_2	second generation
fc	food consumption
g	gram(s)
GC-ECD	A Gas Chromatography – Electron Capture Detector

GC-MSD	Gas Chromatography with Mass Selective Detection
GD	gestation day
GPT	Glutamate pyruvate transaminase
ha	hectare(s)
HB	Hemoglobin
HBM	Human biomonitoring
HCT	Hematocrit
HGPRT	Hypoxanthine-guanine phosphoribosyltransferase
i.v.	Intravenous
ILV	Intralobular vein
kg	kilogram(s)
kg bw	Kilograms of body weight
K_{oc}	organic-carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50%
LD	Lactation day
LD_{50}	lethal dose to 50%
LDH	lactate dehydrogenase
LDT	Lowest dose tested
LOAEL	lowest observed adverse effect level
LOD	Limit of detection
LOQ	Limit of quantitation
m	metre(s)
m^3	metres cubed
MAS	maximum average score for 24, 48 and 72 hours
mg	milligram(s)
mg/kg bw	Milligrams per kilogram of body weight
mg/kg bw/day	Milligrams per kilogram of body weight per day
min	Minute(s)
MIREC	Maternal infant research on environmental chemical
MIREC CD-Plus	Maternal infant research on environmental chemicals-child development plus
MIS	maximum irritation score
mL	Millilitre(s)
mm	Millimetre(s)
MOE	margin of exposure
MRL	Maximum residue limit
MRM	Multi-residue analytical method
MTD	maximum tolerated dose
MW	Molecular weight
NCHS	National center for health statistics
NHANES	National health and nutrition examination survey
NOAEC	No observed adverse effect concentration
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
ORETF	Outdoor Residential Exposure Task Force
P	parental generation

PCO	Pest Control Operator
PCP	pest control product
PDP	Pesticide data program
PEG	Polyethylene glycol
PHED	pesticide handlers exposure database
PMRA	Pest Management Regulatory Agency
PND	Post-natal day
ppm	parts per million
S9	Mammalian metabolic activation system
SOP	standard operating procedure
USEPA	United States Environmental Protection Agency
WBC	white blood cells
WC	Water consumption
wt(s)	weight(s)

Appendix I Registered Cyfluthrin Products as of 18 March 2016[1]

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
23939	Technical	Bayer Cropscience Inc.	Cylathrin Technical Insecticide	Not applicable	95.6% cyfluthrin
25672	Technical	Bayer Cropscience Inc.	Cyfluthrin Technical	Not applicable	95.6% cyfluthrin
25673	Commercial	Bayer Cropscience Inc.	Tempo 20 Wp Insecticide	Wettable powder	20.0% cyfluthrin
25674	Commercial	Bayer Inc.	Cylence Pour-On Insecticide	Solution	1.0% cyfluthrin
26880	Commercial	Bayer Inc	Cylent Gold Insecticide Cattle Ear Tag	Slow Release Generator	10.0% cyfluthrin
30355	Domestic	S.C. Johnson And Son Ltd	Raid® Ant Roach & Earwig Bug Killer 19	Pressurized product	0.05% cyfluthrin, 0.2% pyrethrins, 0.48% piperonyl butoxide
30356	Domestic	S.C. Johnson And Son Ltd	Raid® Spider Blaster Bug Killer 4	Pressurized product	0.05% cyfluthrin, 0.2% pyrethrins, 0.48% piperonyl butoxide
30357	Domestic	S.C. Johnson And Son Ltd	Raid Max® Crawling Insect Bug Killer 3	Pressurized product	0.05% cyfluthrin, 0.2% pyrethrins, 0.48% piperonyl butoxide
30640	Domestic	S.C. Johnson And Son Ltd	Raid® Max Spider Blaster Bug Killer	Pressurized product	0.05% cyfluthrin, 0.2% pyrethrins, 0.48% piperonyl butoxide

[1] Discontinued products and products with a submission for discontinuation have not been included

Appendix IIa Registered Commercial-Class Uses of Cyfluthrin in Canada as of 18 March 2016

Site	Pests	Maximum Container Size	Formulation Type (% a.i.)	Application Method	Maximum active ingredient application rate
Indoor sites: Dwellings; institutions; modes of transport; food/feed establishments; pet kennels	Crawling Pests: Ants (except Pharaoh); Bedbug; Carpet beetles; Cockroaches; Crickets; Lesser Mealworm (adults & larvae); Earwigs Firebrat; Sowbugs; Spiders Flying Pests: Flies; Mosquitoes; Wasps Pantry & Stored Product Pests: Beetles (exposed adults & immature stages): Confused flour beetles; Warehouse beetle Moths: Indian meal moth (larvae only)	420 g	Wettable powder (20%)	Spot, crack and crevice spray	1.01 g/L
	Wood Infesting Pests: Carpenter ants			Spot, crack and crevice spray and void (spray application)	1.01 g/L (Do not exceed 0.03 to 0.05 g per m^2 of treated surface)
Indoor sites: Livestock housing structures, including poultry houses	Crawling Pests: Ants (except Pharaoh); Carpet beetles; Cockroaches; Crickets; Lesser Mealworm (adults & larvae); Earwigs; Firebrat; Sowbugs; Spiders			Crack and crevice and/or General surface spray	1.01 g/L 3.8 g/100 m^2
	Flying Pests: Flies; Mosquitoes; Wasps			General surface spray	3.8 g/100 m^2
Beef cattle and dairy cattle (including lactating)	Horn Flies, Chewing Lice (Mallophaga) and Sucking Lice (Anoplura)	3 L	Solution (1%)	Pour directly on animal	0.01896 g a.i./45 kg to 90 kg of animal weight [Max seasonal rate =0.06 g a.i./45 kg to 90 kg of animal weight]
	Horn Flies	20 tags (13.7 grams per tag)	Slow release generator (10%)	Allflex Tagging System	2.74 g a.i./animal (one tag per ear)

Appendix IIb Registered Domestic-Class uses of Cyfluthrin in Canada as of 18 March 2016

Site	**Pests**	**Maximum Container Size**	**Formulation Type** (Maximum % a.i.)	**Application Method**	**Application Rate**
Residential Indoor (homes, apartments, kitchen)	Spiders, ants, cockroaches, earwigs, multi-coloured Asian ladybird beetles, centipedes, silverfish and crickets	500 g	Pressurized product (0.05%)	Crack, crevice, and spot treatment	Not stated

Appendix III Toxicology Assessment for Cyfluthrin

Table 1 Toxicology Profile for Cyfluthrin and Beta-cyfluthrin Technical

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	
Toxicokinetics and metabolism (gavage or i.v.) Cyfluthrin Sprague Dawley rat PMRA# 1215480, 1215483	Cyfluthrin was rapidly and nearly completely absorbed. Following oral administration, peak plasma levels of radioactivity were observed at about 2 hours. Following i.v. dosing, a 2-phase plasma elimination pattern was noted with half-lives of 2.1 and 20 hours. Following i.v. or oral dosing, cyfluthrin was rapidly eliminated in the urine and feces with urine being the predominant route of elimination (approximately 70% in urine vs 30% in feces). Males excreted slightly more than females via the urine. At least half of the fecally-excreted radioactivity resulted from biliary excretion. Most radioactivity was eliminated within 48 hours of dosing and rate of elimination did not vary significantly with sex, dosage, route of administration or pretreatment. Data indicated that radioactivity levels in tissues were higher after i.v. dosing compared to oral dosing. Following oral dosing, concentration of radioactivity in tissues was not increased by dosage or pretreatment. In all cases, renal fat appeared to have the highest radioactivity level and brain had the lowest. Major urinary metabolites were a conjugate of 4-fluoro-3-(4-hydroxyphenoxy) benzoic acid, and 3-phenoxy-4-fluorobenzoic acid. Significant amounts (10-20%) of unchanged parent compound were found only in the feces of animals (both sexes) treated with repeated oral doses or with a single high oral dose. The quantity of 4-fluoro-3-(4-hydroxyphenoxy) benzoic acid metabolite in feces was sex dependent in all cases with females having the higher amounts. Metabolism occurs via cleavage of the ester bond and oxidation to yield 3-phenoxy-4-fluorobenzoic acid. This is then either hydroxylated, conjugated and excreted,or bound first to glycine and then hydroxylated and conjugated**.**
Human dose-excretion studies (inhalation) Cyfluthrin Human PMRA# 2429024	40 µg/m^3: urinary metabolites < LOD in first 2 hours post-dose 160 µg/m^3: 93% of metabolites were excreted within 24 h with peak excretion rates between 0.5 and 3 hours. The mean half-lives were 6.9 for cis-3-(2,2-dichlorovinyl)-2,2-dimethylycyclopropane carboxylic acid (DCCA), 6.2h for trans-DCCA and 5.3h for 4-fluoro-3-phenoxybenzoic acid.
Acute Toxicity Studies	
Acute oral toxicity (gavage) Cyfluthrin	LD_{50} = 291 mg/kg bw (♂); 609 mg/kg bw (♀) (PEG 400) Clinical signs at ≥ 50 mg/kg bw included restlessness, hypermotility, dyspnea, uncoordinated and ataxic movement, apathy. **Highly toxic**

Study Type/ Animal/ PMRA #	Study Results
NMRI mouse PMRA# 1216160	
Acute oral toxicity (gavage) Beta-cyfluthrin NMRI mouse PMRA# 2072879	LD_{50} (fasted) = 91 mg/kg bw (♂); 165 mg/kg bw (♀) (PEG E 400) Clinical signs at ≥ 25 mg/kg bw included lethargy, uncoordinated gait, splayed gait, increased activity, digging and preening movements, salivation, difficult breathing and rolling. Mortality was observed within 1 hour to 2 days post-treatment. **High toxicity**
Acute oral toxicity (gavage) Cyfluthrin Wistar rat, NMRI mouse PMRA# 1216133, 1124945	<u>Rat ♂:</u> LD_{50} = 16.2 mg/kg bw (Cremophor EL in distilled water) LD_{50} = 254 mg/kg bw (acetone, oil) LD_{50} = 396 mg/kg bw (DMSO) LD_{50} = 500-1000 mg/kg bw (n-methyl pyrrolidone) <u>Mouse, ♀:</u> LD_{50} < 100 mg/kg bw (Cremophor EL in distilled water) **Highly toxic**
Acute oral toxicity (gavage) Cyfluthrin Wistar rat PMRA# 1216160	LD_{50} = 590 mg/kg bw (♂) ; LD_{50} = 1189 mg/kg bw (♀)(PEG 400) Clinical signs at ≥ 50 mg/kg bw included restlessness, salivation, hypermotility, reduced breathing rate, ataxia **Moderately toxic**
Acute oral toxicity (gavage) Beta-cyfluthrin Wistar rat PMRA# 2072873	LD_{50} (fasted) = 84 mg/kg bw (♂); 77 mg/kg bw (♀) (acetone/peanut oil) Clinical signs at ≥ 10 mg/kg bw included lethargy, cramped posture, digging and preening movements, uncoordinated gait, splayed gait, salivation, rolling, increased activity, soft feces, difficult breathing and piloerection. Mortality was observed 1-2 days post-treatment in fasted animals and 1-3 days post-treatment in unfasted animals **High toxicity**
Acute oral toxicity (gavage)	LD_{50} (fasted) = 380 mg/kg bw (♂); 651 mg/kg bw (♀) (PEG E 400)

Study Type/ Animal/ PMRA #	Study Results
Beta-cyfluthrin Wistar rat PMRA# 2072874	Clinical signs at ≥ 100 mg/kg bw included increased activity, digging and preening movements, lethargy, salivation, uncoordinated gait, splayed gait, labored breathing, rolling, piloerection and soft feces. Mortality was observed <24 hours to 7 days post-treatment in fasted animals and <24 hours to 12 days post-treatment in unfasted animals. **High toxicity (based on ♂ results)**
Acute oral toxicity (gavage) Beta-cyfluthrin Wistar rat PMRA# 2072878	LD_{50} (fasted) = 211 mg/kg bw (♂); 336 mg/kg bw (♀) (xylene) Clinical signs noted in vehicle control animals and animals receiving 1 mg/kg bw/day included lethargy, reduced activity, difficult breathing. Clinical signs at ≥ 10 mg/kg bw included lethargy, uncoordinated gait, digging and preening movements, cramped posture, splayed gait, rolling, salivation, difficult breathing and piloerection. Mortality was observed 1-3 days post-treatment in fasted rats and < 24 hours to 3 days post-treatment in unfasted rats. **High toxicity**
Acute oral toxicity **Cyfluthrin Metabolite FCR 3191** Wistar rat PMRA# 2072881	LD_{50} (♂, ♀) > 5000 mg/kg bw (PEG E 400) Clinical signs at 5000 mg/kg bw included apathy, reduced motility, dyspnea, staggering gait and increased urination. There were no mortalities during the study. **Low toxicity**
Acute oral toxicity (gavage) Cyfluthrin NZW rabbit PMRA# 1216160	**Supplemental due to group size** No deaths at ≤ 1000 mg/kg bw Clinical signs at ≥ 250 mg/kg bw included apathy, reduced appetite.
Acute oral toxicity (gavage) Cyfluthrin Beagle dog PMRA# 1216160	**Supplemental due to group size, emesis** No deaths, dogs vomited up test material after dosing with 50 or 100 mg/kg bw. Apathy and reduced appetite also observed.

Study Type/ Animal/ PMRA #	Study Results
Acute oral toxicity (gavage) Cyfluthrin Beagle dog PMRA# 1215545	**Supplemental** 20 mg/kg bw: immediately post treatment: slight salivation, nausea (♂) and emesis (♂). 2 hrs post treatment: emesis. 100 mg/kg bw: immediately post treatment: salivation. 20-120 minutes post treatment: emesis, increased water consumption (♂). During post treatment observation period, ↓fc and bw (♀).
Acute oral toxicity (gavage) Beta-cyfluthrin Beagle dog PMRA# 2072915	**Supplemental** <u>Oral administration:</u> Dogs vomited after oral administration of 2500 and 5000 mg/kg bw. The quantity of substance vomited could not be estimated. No mortality. <u>i.v. administration:</u> Both dogs exhibited convulsive twitching, impaired respiration, and vocalization after administration of 3-5 mg/kg bw. The female died about 40 minutes after administration.
Acute dermal toxicity Cyfluthrin Wistar rat PMRA# 1216160	LD_{50} (♂, ♀) > 5000 mg/kg bw (PEG 400) Clinical signs at 5000 mg/kg bw included apathy and ataxia. **Low toxicity**
Acute dermal toxicity Cyfluthrin Wistar rat PMRA# 1216133	LD_{50} > 5000 mg/kg bw (Cremophor EL in distilled water) **Low toxicity**
Acute dermal toxicity Beta-cyfluthrin Wistar rat	LD_{50} (♂, ♀) > 5000 mg/kg bw (PEG E 400) Clinical signs at ≥ 1000mg/kg bw included lethargy, uncoordinated gait, splayed gait, difficult breathing, soft feces. Mortality was observed in one ♀ exposed to 5000 mg/kg bw, 3 days post-treatment. **Low toxicity**

Study Type/ Animal/ PMRA #	Study Results
PMRA# 2072884	
Acute inhalation toxicity Cyfluthrin Wistar rat PMRA# 1216165	LC_{50} > 0.74 mg/L (♂); 0.2 to 0.74 mg/L (♀) (deionized water) Signs of toxicity included irritation of eyes and nasal mucosa, bleeding at the nose, severe dyspnoea, stomach and side postures, rowing movements, cramps and slightly disturbed behaviour. **Slightly toxic (♂)** **Moderately toxic (♀)** LC_{50} = 0.58 mg/L (♂); 0.49 mg/L (♀) (DMSO/PEG 400) Signs of toxicity included apathy, debilitation, lying on side and stomach, rowing movements, dyspnea, irritation of the eyes and nasal mucosa, muscle tremor, cramps, uncoordinated movement, excitation, hyperkinesis, convulsions, apathy **Slightly toxic (♂)** **Moderately toxic (♀)**
Acute inhalation toxicity (head/nose only) Cyfluthrin Wistar rat PMRA# 1227059	LC_{50} = 0.41 mg/L (♂); LC_{50} = 0.39 mg/L (♀) (PEG 400/ethanol) Clinical signs at ≥ 0.025 mg/L included piloerection, reduced activity, unpreened hair coat, staggering gait, tremors, bloody noses, irregular breathing, sternal recumbancy, convulsions-opisthotonic spasms, choreoathetoid movements, blepharophimosis, behavioral disturbance. <u>Satellite Group 1</u> ≥ 0.025 mg/L: ↓ respiratory rate 0.078 mg/L:↑lung elasticity <u>Satellite Group 2:</u> no effects on blood gases ≤ 0.06 mg/L **Moderately toxic**
Acute inhalation toxicity (head/nose only) Beta-cyfluthrin Rat PMRA# 2072890	<u>Aerosol:</u> LC50 = 0.082 mg/L (♂); 0.081 mg/L (♀) (PEG 400) <u>Dust:</u> LC50 = 0.532 mg/L (♂); 0.212 mg/L (♀) **Moderately toxic**

Study Type/ Animal/ PMRA #	Study Results
Dermal irritation Cyfluthrin NZW rabbit PMRA# 1216160	No sign of erythema or edema. **Non-irritant to skin**
Dermal irritation Cyfluthrin Albino Japanese rabbit PMRA# 1227049, 1216167	Slight erythema seen in one animal at 24 hours only **Non-irritant to skin**
Dermal irritation Beta-cyfluthrin NZW rabbit PMRA# 2072894	MAS = 0.67 MIS = 1, at 24 and 48 hrs All scores 0 by Day 7 **Mildly irritating**
Primary eye irritation Cyfluthrin NZW rabbit PMRA# 1216160, 1227049	5 minute exposure: MAS = 2.67, MIS = 7.6 24 hour exposure: MAS = 2.89, MIS = 8.67 **Mildly irritating**
Primary eye irritation Cyfluthrin Albino Japanese rabbit	Immediately after treatment, animals severely rubbed their eyes for up to 30 minutes. Effects mostly resolved by Day 7 MAS (24, 48, 72 hr) = 5.03 (unwashed) MIS = 13 at 1 hour

Study Type/ Animal/ PMRA #	Study Results
PMRA# 1216167, 1227054	**Mildly irritating**
Primary eye irritation Beta-cyfluthrin NZW rabbit PMRA# 2072894	MAS = 3.78 MIS = 11.33 at 1 hr **Slightly irritating**
Primary eye irritation Beta-cyfluthrin NZW rabbit PMRA# 2072894	MAS = 3.78 MIS = 11.33 at 1 hr **Slightly irritating**
Dermal sensitization (Maximization assay) Cyfluthrin Pirbright guinea pig PMRA# 1216128	**Supplemental due to study deficiencies (lack of positive controls, dose selection, purity information)** **No evidence of sensitization**
Dermal sensitization (Draize test) Cyfluthrin Pirbright guinea pig	**Supplemental due to study deficiencies (lack of positive controls, dose selection rationale, dosing regimen, purity information)** **No evidence of sensitization**

Study Type/ Animal/ PMRA #	Study Results
PMRA# 1216168	
Dermal sensitization (Maximization method) Beta-cyfluthrin Guinea pig PMRA# 2072897	**Negative**
Short-Term Toxicity Studies	
28-day oral toxicity (diet) Cyfluthrin Mouse PMRA# 1216142	**NOAEL = 43.1 mg/kg bw/day (♂); 50.4 mg/kg bw/day (♀)** ≥136/165 mg/kg bw/day: ↑ cytoplasmic swelling of glandular epithelium in submaxillary glands; ↓bwg , ↑rel liver wt , slight ↑chromatin nuclei of hepatocytes (♂) 407/433 mg/kg bw/day: Clinical signs (salivation, ataxia, emaciation), ↓bw, ↓bwg, ↓WC, slight ↓WBC, ↑ALP, ↑BUN, dark liver, ↑rel submaxillary gland wt, ↑ rel kidney wt , ↓ spleen wt, ↑cytoplasmic swelling of glandular epithelium in submaxillary glands ; ↑abs liver wt (♂); mortality (1/18), ↓abs adrenal wt ↓rel adrenal wt, ↓abs ovary wt (♀) ↑ relative kidney weight and ↑ BUN (♂) had not resolved by the end of the 4-week recovery period.
28-day oral toxicity (gavage) Cyfluthrin Wistar rat PMRA# 1216139	**NOAEL = 20 mg/kg bw/day** (PEG 400) 80/40 mg/kg bw/day: ↑mortality, clinical signs (apathy, ungroomed coat, dyspnoea, salivation, hyperkinesis, ataxia, athetotic and choreiform movements), ↑ plasma GPT, ↑ adrenal wt; ↓ bw (♂); ↑ liver wt (♀) During the recovery period, bw of high dose ♂ had recovered within one week.
28-day oral toxicity (diet) Cyfluthrin Rat (Strain N/S) PMRA# 1216141	**NOAEL = 24.7 mg/kg bw/day (♂); 25.2 mg/kg bw/day (♀)** 24.7 mg/kg bw/day: ↓glucose (♂) 79/78 mg/kg bw/day: abnormal gait, salivation, nervousness, ↓bw, ↓bwg, ↓WC, ↑urobilinogen, ↑ketone body , ↓HCT, ↓HB, ↓glucose , ↑submaxillary gland wt, cytoplasmic swelling of glandular epithelium in submaxillary glands, minimal single fibre degeneration of sciatic nerve; ↑ rel liver wt , ↑ rel kidney wt (♂); ↓protein (♀)

Study Type/ Animal/ PMRA #	Study Results
	All findings (with the exception of clinical chemistry parameters) were no longer present at the end of the recovery period.
28-day oral (gavage) Beta-cyfluthrin Wistar rat PMRA# 2072918	**NOAEL = 1 mg/kg bw/day** (Cremophor EL in distilled water) *≥1 mg/kg bw/day: ↑ liver wt (♀) –non-adverse* ≥ 4 mg/kg bw/day: increased mobility, digging, and grooming movements, excess salivation; ↑ lung wt (♀) 16 mg/kg bw/day: mortality, uncoordinated/spread/spastic gait, dyspnea, rolling, dacryohemorrhea, respiratory distress; ↓bw, ↓bwg, ↑adrenal wt Clinical signs of toxicity observed during the treatment period were no longer present after 1 week of recovery. bw effects noted in ♂ had recovered by the end of the observation period.
90-day oral toxicity (diet) Cyfluthrin Wistar rat PMRA# 1216140	**NOAEL > 22.5/28 mg/kg bw/day** ≥ 7.4/8.8 mg/kg bw/day: ↑ lipid accumulation in liver (♂)
90-day dietary Beta-cyfluthrin Wistar rat PMRA# 2072909	**NOAEL = 9.5/10.9 mg/kg bw/day** 38.9/42.4 mg/kg bw/day: uncoordinated gait and impaired general condition during Wks 2-5 of dosing, ↓bw; ↓bwg (Wks 1-5), ↓ fc (Wk1), ↓ WC (Wks 1-5), ↓ cholesterol; mortality (2♂, 1 main study, 1 recovery group), sores & necroses, non-adverse kidney & lung findings bw and cholesterol effects not recovered by the end of observation period.
28-day dietary (range-finding) Beta-cyfluthrin Beagle dog PMRA# 2072916	**Supplemental** (Necropsies were not performed. Food consumption was not measured.) 16/8 mg/kg bw/day (640/320 ppm): After 2 weeks dosing with 640 ppm the following were noted: ↓ bw, impaired movement, vomiting, conjunctival irritation, one animal (♀) found prone on its side with spasms, one animal (♂) found dead on day 15. After administration of 320 ppm for the remainder of the study (2 weeks), impaired movement, vomiting (♂/♀) and conjunctival irritation were noted.
90-day dietary Beta-cyfluthrin	**NOAEL = 2.38/2.46 mg/kg bw/day** 13.8/15.3 mg/kg bw/day: ↑vomiting, diarrhea, pasty feces, motor disturbances in the hind limb region (uncertain, awkward, or staggering gait and occasional buckling); motor disturbances were present for about 6-8 hrs after feeding and were no longer

Study Type/ Animal/ PMRA #	Study Results
Beagle dog PMRA# 2072914	present at the next feeding); ↓ bw, ↓ bwg (♀) No difference in bone/teeth fluoride levels of treated animals compared to controls.
6-month toxicity (diet) Cyfluthrin Beagle dog PMRA# 1216146	**Supplemental due to poor animal health** ≥ 7.5 mg/kg bw/day: ↓ thymus wt (♂); non-adverse ↓WBC (♀) 22.3 mg/kg bw/day: ↓fc, clinical signs (ataxia, emesis, diarrhea); ↓ WBC (♂); ↓ bwg, ↓ thymus wt (♀)
12-month oral toxicity (diet) Cyfluthrin Beagle dog PMRA# 1216147	**Supplemental due to low purity, poor animal health** 25.6 mg/kg bw/day: hind limb weakness, emesis, liquid feces; ↓ bwg (♂) ; ↑ spleen wt (♀)
12-month oral toxicity (diet) Cyfluthrin Beagle dog PMRA# 2429023	**NOAEL = 2.4/3.6 mg/kg bw/day** ≥10.6/10.7 mg/kg bw/day: clinical signs (abnormal posture, vomiting, gait abnormalities, abnormal postural reaction) 15.5/18.0 mg/kg bw/day: clinical signs (seizures, convulsions, tremors, diarrhea), ↓ bw, ↓ bwg, ↑hepatic N-demethylase (♂)
21-day dermal toxicity Cyfluthrin NZW rabbit PMRA# 1216143	**NOAEL = 250 mg/kg bw/day** No treatment-related dermal or systemic toxicity
21-day dermal toxicity Cyfluthrin	**NOAEL = 113 mg/kg bw/day for dermal toxicity** **NOAEL = 376 mg/kg bw/day for systemic toxicity** 376 mg/kg bw/day: ulceration with adjacent epidermis thickened by acanthosis and hyperkeratosis; scabbing at the application

Study Type/ Animal/ PMRA #	Study Results
Sprague Dawley rat PMRA# 2429023	site (♀) 1077 mg/kg bw/day: ↓fc during week 1; scabbing at the application site, red nasal discharge (♂); urine staining (♀)
5-day inhalation (range-finding) Beta-cyfluthrin Wistar rat PMRA# 2072928	**Supplemental** (PEG 400/ethanol) NOAEC = 0.00025 mg/L (0.07 mg/kg bw/day) ≥ 0.0038 mg/L (1.01/1.07 mg/kg bw/day): unpreened hair coat and piloerection after dosing Day 3-5, but were no longer present the following morning prior to the next exposure. ↓ bw (marginal at 0.0038 mg/L) 0.028 mg/L (7.4/7.9 mg/kg bw/day): reduced activity after each exposure, unpreened hair coat and piloerection still noted prior to subsequent exposures No clinical signs related to treatment were evident during the recovery phase. ↓ bw at 0.028 mg/L had recovered by the third day of the recovery phase.
21-day inhalation toxicity (head/nose only) Cyfluthrin Wistar rat PMRA# 1216144	<u>Phase I (PEG 400/ethanol):</u> **No NOAEC established** ≥0.0023 mg/L (0.6 mg.kg bw/day): ↓ bw (♂) ≥0.0115 mg/L (3.12 mg/kg bw/day): ungroomed coat, stiff/unsteady gait, salivation, ↓ bw (♂) <u>Phase II (PEG 400/ethanol):</u> **NOAEC = 0.0014 mg/L (0.38 mg/kg bw/day)** ≥ 0.0014 mg/L (0.38 mg/kg bw/day): non-adverse ↓ bw (♂) 0.0105 mg/L (2.85 mg/kg bw/day): clinical signs (behavioural disorders), ↓ bw (♂)
28-day inhalation Beta-cyfluthrin Wistar rat PMRA# 2072927	**NOAEC = 0.0002 mg/L (0.07 mg/kg bw/day)** (PEG E 400/ethanol) ≥ 0.0027 mg/L (0.9 mg/kg bw/day): ↓ bwg; ↓ bw (♂) 0.0235 mg/L (8 mg/kg bw/day): ungroomed fur, piloerection, slightly reduced motility, ↑ activity, ↓ thymus and spleen wt; slight ↓ leukocytes and lymphocytes, slight changes in clinical chemistry (alkaline phosphatase, cholesterol, protein, potassium, calcium, phosphate) No treatment-related changes in lung function
90-day inhalation toxicity (head/ nose only)	**NOAEC = 0.00009 mg/L (0.02 mg/kg bw/day)** ≥0.00009 mg/L (0.02 mg/kg bw/day): non-adverse ↓ bw (6-13 weeks) (♂)

Study Type/ Animal/ PMRA #	Study Results
Cyfluthrin Wistar rat PMRA# 1207821, 1227058, 1216144	≥ 0.00071 mg/L (0.19 mg/kg bw/day): ↓ bw; clinical signs (disturbed non-specific behavior) (♀) 0.0045 mg/L (1.2 mg/kg bw/day): clinical signs (disturbed non-specific behavior, agitation, erect tail carriage)
Chronic Toxicity/Oncogenicity Studies	
23-month oncogenicity (diet) Cyfluthrin CF1/W74 mouse PMRA# 1216036	**NOAEL = 45.8/63 mg/kg bw/day** 194/260 mg/kg bw/day: ↓ bwg , ↓ bw, ↑ hemorrhagic lesions of the stomach;↑ ALP (♂) Fluoride levels not increased in bones/teeth **No evidence of oncogenicity**
2-year oral toxicity and oncogenicity (diet) Cyfluthrin Wistar rat PMRA# 1215546, 1216145, 1216127, 1130066	**NOAEL = 6.19/8.15 mg/kg bw/day** ≥ 6.19/8.15 mg/kg bw/day: ↓ bw , ↓ abs liver wt, ↓ abs kidney wts, ↑ fluoride levels in bones at 2 years; ↓serum protein (♂);↓ serum calcium (♀) (all effects minimal and considered non-adverse) 19.2/25.5 mg/kg bw/day: ↓fc, ↑ fluoride levels in teeth at 1 and 2 years; ↑ medullary hyperplasia of the adrenal, glandular ectasia of the stomach (♂); ↑cortical hyperplastic nodules in the adrenal, bladder papillomas (0, 0, 0, 6%), bladder hyperplasia (0, , 4%, 4%, 8%)(♀) Historical controls for bladder papillomas:1 incidence in 11 studies. Historical control for bladder hyperplasia up to 23%. 2 animals in high dose that had bladder papillomas also had bladder hyperplasia **Equivocal increase in bladder tumours (♀)**
Developmental/Reproductive Toxicity Studies	
7-day inhalation toxicity (whole body) (non-guideline) Cyfluthrin NMRI mouse	<u>Maternal Toxicity:</u> **NOAEC = 0.058 mg/L (23.7 mg/kg bw/day)** No treatment-related toxicity in dams. <u>Offspring Toxicity:</u> **NOAEC = 0.006 mg/L (2.45 mg/kg bw/day)**

Study Type/ Animal/ PMRA #	Study Results
PMRA# 2429023	0.015 mg/L (6.12 mg/kg bw/day): clinical signs (decreased motility, poor general condition, tonic seizures, temporary scratching); ↑ motor activity 4-months post-exposure (♀) 0.058 mg/L (23.7 mg/kg bw/day): mortality in all animals No treatment-related effects on hematology, clinical chemistry, pathology or muscarinic acetylcholine receptors in cortex of adult mice.
Multigeneration study (diet) Cyfluthrin Wistar rat PMRA# 1215505, 1216148, 1130065,	Parental Toxicity **LOAEL = 3.83 mg/kg bw/day (♂); NOAEL = 48.5 mg/kg bw/day (♀)** ≥ 3.83 mg/kg bw/day: ↓ bw (F1♂) ≥ 12.3/15.1 mg/kg bw/day: ↓bw, ↓fc (F2♂); ↓ abs liver wt (F2 ♀), ↓abs kidney wt (F2 ♀) 37.2/48.5 mg/kg bw/day: ↓ bw (F0♂, F1♀, F2♂); ↓ fc, ↓ abs liver wt (F2 ♂), Reproductive Toxicity **NOAEL = 12.3/15.1 mg/kg bw/day** 37.3/48.5 mg/kg bw/day: ↓ fertility index (2nd mating F1b – 65% vs 85%), ↓ litter size (F3a, F3b), ↓ birth weight (F1a, F2a, F3a) Offspring Toxicity **NOAEL not established** **LOAEL = 5.4 mg/kg bw/day** ≥ 5.4 mg/kg bw/day: ↓ pup weight (F2a, F2b, F3a, F3b) ≥ 15.1 mg/kg bw/day: ↓lactation index (F2b), ↓viability index (F3a), ↓pup weight (F1a, F1b) 48.5 mg/kg bw/day: ↓viability index (F2a, F3b), ↓lactation index (F1a, F1b, F2a, F3b) **Evidence of sensitivity of the young**
Multigeneration study (diet) Cyfluthrin Sprague Dawley rat PMRA# 2429023	Parental Toxicity **NOAEL 3 mg/kg bw/day (♂); 10 mg/kg bw/day (♀)** ≥9/10 mg/kg bw/day: ↓bw (F1♂); ↓fc (lactation, F1 ♀) 29/33 mg/kg bw/day: ↓bw terminal (F1); ↑ splayed hind limbs during lactation (P, F1), ↓ bw (lactation, P1, F1), ↓fc (lactation, P1(♀) Reproductive Toxicity **NOAEL = 33 mg/kg bw/day**

Study Type/ Animal/ PMRA #	Study Results
	No effects on reproductive parameters or function Offspring Toxicity **NOAEL = 4 mg/kg bw/day** ≥ 10 mg/kg bw/day: coarse tremors during PND 5-17 (F1, F2), ↓ bw (PND 4-21, F1 and F2) 33 mg/kg bw/day: ↓mean litter weight (PND 0-21, F1, F2) **Evidence of sensitivity of the young**
Developmental toxicity study (gavage) Cyfluthrin Wistar rat PMRA# 1216150	Maternal Toxicity **NOAEL = 3 mg/kg bw/day**(PEG 400) ≥ 10 mg/kg bw/day: high stepping gait noted on occasion 30 mg/kg bw/day: ataxia/decreased motility noted on occasion Developmental Toxicity **NOAEL = 30 mg/kg bw/day(**PEG 400) **No evidence of sensitivity of the young or malformations**
Developmental toxicity (gavage) Beta-cyfluthrin Wistar rat PMRA# 2072970	Maternal Toxicity **NOAEL = 10 mg/kg bw/day** (Cremophor) 40 mg/kg bw/day: mortality , hypoactivity, locomotor incoordination, salivation, bw loss GD 6-8, ↓bwg over dosing period, ↓fc Developmental Toxicity **NOAEL = 10 mg/kg bw/day** (Cremophor) 40 mg/kg bw/day: ↓fetal bw, incompletely ossified frontal bones, sacral arches, metacarpals and 2nd sternebrae; unossified caudal arches, 5th sternebrae and xiphoid; enlarged anterior fontanelle (all considered to be secondary to the severe maternal toxicity and resultant retardation in fetal development observed at this dose) **No evidence of sensitivity of the young or malformations**
Developmental toxicity study (gavage)	Maternal Toxicity **NOAEL = 5 mg/kg bw/day** (Cremophor EL) 15 mg/kg bw/day: ↑ soft feces

Study Type/ Animal/ PMRA #	Study Results
Cyfluthrin Himalayan rabbit PMRA# 1216151	45 mg/kg bw/day: 2 abortions, 1 total litter loss <u>Developmental Toxicity</u> **NOAEL = 15 mg/kg bw/day** (Cremophor EL) 45 mg/kg bw/day: 2 abortions, 1 total resorption **Note: construction noise impact undetermined**
Developmental toxicity (gavage) Cyfluthrin Chinchilla rabbit PMRA# 2396904	<u>Maternal Toxicity</u> **NOAEL = 20 mg/kg bw/day** (corn oil) ≥ 60 mg/kg bw/day: ↓ bw, ↓ fc <u>Developmental Toxicity</u> **NOAEL > 180 mg/kg bw/day** (corn oil) **No evidence of sensitivity of the young or malformations**
Developmental toxicity (inhalation) Cyfluthrin Wistar rat PMRA# 2429023	<u>Maternal Toxicity</u> **NOAEL not established; LOAEL = 0.0005 mg/L (0.13 mg/kg bw/day)** (PEG 400/ethanol) ≥0.0005 mg/L (0.13 mg/kg bw/day): bradypnea, hypothermia, ↓ bw, ↓ bwg, ↓ fc ≥0.0026 mg/L (0.69 mg/kg bw/day): bloody snouts, ungroomed fur, piloerection 0.012 mg/L (3.18 mg/kg bw/day): respiratory distress, hypoactivity, high-stepping gait, salivation, plasma level = 19 pmol/ml 0.013 mg/L + O_2 (3.45 mg/kg bw/day): respiratory distress, hypoactivity, plasma level 15 pmol/ml <u>Developmental Toxicity</u> **NOAEL = 0.0005 mg/L (0.13 mg/kg bw/day)** (PEG 400/ethanol) ≥0.0026 mg/L (0.69 mg/kg bw/day): ↓ placental and fetal weight, ↑ delayed ossification 0.012 mg/L (3.18 mg/kg bw/day): ↑ % fetuses and litters with malformations, ↑% fetuses and litters with microphthalmia (5.4%/35%) compared to control (0.6%/9%) or upper range of historical controls (1.95%/13.6%) 0.013 mg/L + O_2 (3.45 mg/kg bw/day): ↑ % fetuses and litters with malformations, ↑% fetuses and litters with microphthalmia

Study Type/ Animal/ PMRA #	Study Results
	(2.9%/21.7%) **No evidence of sensitivity of the young; evidence of malformations at maternally-toxic levels**
Developmental toxicity (inhalation) Cyfluthrin Wistar rat PMRA# 2429023 2 studies	<u>Maternal Toxicity</u> **NOAEL = 0.0011 mg/L (0.29 mg/kg bw/day)** (PEG 400/ethanol) ≥ 0.0047 mg/L (1.24 mg/kg bw/day): ↓motility, dyspnea, piloerection, ungroomed coats, eye irritation <u>Developmental Toxicity</u> **NOAEL = 0.00059 mg/L (0.16 mg/kg bw/day)** (PEG 400/ethanol) ≥ 0.0011 mg/L (0.29 mg/kg bw/day): ↑ runts, ↑skeletal anomalies of the sternum ≥ 0.0047 mg/L (1.24 mg/kg bw/day): ↓ pup weight 0.0237 mg/L (6.3 mg/kg bw/day): ↑ post-implantation loss, ↑ late embryonic death, ↑ skeletal anomalies of extremities, ↑microphthalmia, (# fetuses: 1,2,1,8; # litters 1,2,1,5) **Evidence of sensitivity of the young and malformations at maternally-toxic levels** **Note: limited detail on reporting of skeletal abnormalities**
Pubertal development and thyroid function (gavage) Cyfluthrin Sprague Dawley rat PMRA# 2272340	**NOAEL = 10 mg/kg bw/day** (corn oil) 20 mg/kg bw/day: ↓bwg (Days 1-2), salivation; ↓ bwg (Days 1-7), piloerection, lack of grooming, wasted appearance, uncoordination, tremors, (♂); delay in vaginal opening, slight ↑ age at first estrus , ↑ mean cycle length , ↓cycling (♀) No evidence of an effect on preputial separation in ♂ rats.
Genotoxicity Studies	
Sister chromatid exchange assay Cyfluthrin Chinese Hamster Ovary (CHO) Cells PMRA# 1124950, 1207823,	Negative

Study Type/ Animal/ PMRA #	Study Results
CHO/HGPRT Mutation Assay Cyfluthrin Chinese Hamster Ovary (CHO) Cells PMRA# 1207824,	Negative
Unscheduled DNA Synthesis Cyfluthrin Rat Primary Hepatocytes PMRA# 1207827	Negative
In vitro Microsome test Cyfluthrin Salmonella Typhimurium PMRA# 1216152	Negative Precipitate formed at ≥ 2500 µg/plate
Dominant lethal assay (gavage) Cyfluthrin NMRI/ORIG Kisslegg mouse PMRA# 1216154	Negative 60 mg/kg bw (PEG 400): mortality
DNA damage test (non-guideline)	Negative

Study Type/ Animal/ PMRA #	Study Results
Cyfluthrin Escheria coli pol A+ and pol A_1- PMRA# 1216155	
Reverse mutation assay Cyfluthrin E. coli B/r WP2; S. typhimurium TA 1535, 1537, 1538, 98 and 100 Rec assay Bacillus subtilis NIG 45 and NIG 17 PMRA# 1216156	Negative
Reverse mutation assay Cyfluthrin E. coli WP2 her, S. typhimurium TA 1535, TA 1538, TA 100, TA98 Rec assay B. subtilis E17 (rec+) and M45 (rec-); PMRA# 1216157	Negative

Study Type/ Animal/ PMRA #	Study Results
Reverse mutation assay Cyfluthrin S. cerevisiae S138, S211, D7 PMRA# 1216158, 1216159	Negative
Bacterial mutation assay (Ames) Beta-cyfluthrin S. typhimurium TA 1535, TA 1537, TA 100, TA98 PMRA# 2072980	Negative
In vivo micronucleus (gavage) Cyfluthrin NMRI/ORIG Kisslegg mouse PMRA# 1216153	Negative 15 mg/kg bw (PEG 400): mortality
In vitro CHO-HGPRT Forward Mutation Assay Beta-cyfluthrin PMRA# 2072983	Negative
In vitro unscheduled DNA	Negative

Study Type/ Animal/ PMRA #	Study Results
synthesis Rat primary hepatocytes Beta-cyfluthrin PMRA# 2072985	
In vitro mammalian clastogenicity Human lymphocytes Beta-cyfluthrin PMRA# 2072989	Negative
In vivo cytogenetics – micronucleus assay Beta-cyfluthrin Bor:NMRI Mouse PMRA# 2072992	Negative 80 mg/kg bw (Cremophor):clinical signs of toxicity for up to 24 hours (apathy, digging and grooming movements, uncoordinated movement, staggering gait, rolling over, retching movement and salivation). No increase in micronucleated polychromatic erythrocytes was observed in treated animals.
Neurotoxicity Studies	
Delayed neurotoxicity (gavage) Cyfluthrin Hen PMRA# 1216161	Negative for delayed neurotoxicity (no effect on NTE or pathology) Treated hens showed mortality, ↓ bw, clinical signs (aggression or somnolence) but no ataxic behavior
Delayed neurotoxicity (gavage)	**Supplemental** <u>Single Dose:</u> 2500 mg/kg bw: clinical signs (behavioral disorders and signs of excitation observed days 1-3 only)

Study Type/ Animal/ PMRA #	Study Results
Cyfluthrin White leghorn chicken PMRA# 1216161	5000 mg/kg bw: mortality, clinical signs of neurotoxicity (behavioral disorders and signs of excitation observed days 1-5) with histopathological findings (axon fragmentation, swelling and eosinophilia) <u>Two doses, 21 days apart:</u> 5000 mg/kg bw/day: mortality (4 after 2nd dose on day 14, 20, 36 and 40 post-treatment), clinical signs of neurotoxicity (behavioral disorders, signs of excitation and/or uncoordinated leg movements were observed up to 3 days after first dose, and 2 days following second dose), signs of paralysis were observed, ↓ bw, gross pathology findings (pale lungs, pale kidneys, clay-coloured livers) with histopathological findings (fibre degeneration, distended, optically void or granularly disintegrated myelin sheaths, swollen or fragmented axons, activated or proliferated Schwann's cells, macrophages containing granular material). <u>Five daily doses:</u> 5000 mg/kg bw/day: mortality (1 after 3rd dose, 2 after 5th dose), clinical signs of neurotoxicity (behavioural disorders, drowsiness, cramped gait), ↓ bw, gross pathology findings (emaciation, mottled kidneys, brittle liver) and histopathological findings (fibre degeneration, distended or granular disintegration of medullary sheaths, swollen or fragmented axis cylinders, proliferated Schwann's cells) within nervi ischiadici, with similar alterations noted in cervical marrow of one animal.
Acute neurotoxicity (gavage) Beta-cyfluthrin Fischer rat PMRA# 2072957	**NOAEL = 0.5 mg/kg bw** (Cremophor EL in deionized water) ≥ 2 mg/kg bw: perianal staining; ↓approach response, oral stains (♂); ↓motor and locomotor activity in figure-eight maze, ↓activity in the open field, ptosis(♀) 10 mg/kg bw: oral and urine staining, gait incoordination, ↓activity, flattened posture in home cage, repetitive pawing motion, diminished approach and touch responses, impaired aerial righting, salivation; ↓body temperature, writhing behaviour, flattened posture in open field, diminished tail-pinch response and prolapsed penis, ↓motor and locomotor activity in figure-eight maze, ptosis (♂); slight muscle fasciculation (♀)
Motor activity assessment (non-guideline) Beta-cyfluthrin Long Evans rat PMRA# 2429021	≥ 0.5 mg/kg bw: ↓ motor activity (corn oil) $BMD_{20}/BMDL_{20}$ = 1.56/1.436 mg/kg bw
14-day neurotoxicity (gavage) (non-guideline)	**Supplemental** (PEG 400) ≥50 mg/kg bw/day: disturbed behaviour, rolling, tremor, stretched gait, uncoordinated gait, salivation; ↓bwg (♂) 60 mg/kg bw/day: mortality, vocalization (♂)

Study Type/ Animal/ PMRA #	Study Results
Cyfluthrin Wistar rat PMRA# 1207832, 1227056	
Nervous system morphology study (gavage) (non-guideline) Cyfluthrin Sprague Dawley rat PMRA# 1183308	80 mg/kg bw/day in PEG 400 for 5 days, reduced to 40 mg/kg bw/day for 9 days abnormal gait, salivation and chromodacryorrhea for several hours post-dosing, ↓bw during treatment, minimal axonal degeneration in the sciatic and femoral nerves up to 2 months post-dosing, however full recovery by 3 months.
90-day neurotoxicity (diet) Beta-cyfluthrin Fischer 344 rat PMRA# 2072963	**NOAEL = 2.02/2.34 mg/kg bw/day** ≥ 7.99/9.40 mg/kg bw/day: self-induced dermal lesions from scratching (likely due to paresthesia following absorption of test material through the skin and stimulation of nerve endings in areas of the body coming in contact with treated diet) (♂); ↓ bw and fc(♀) 26.8/30.8 mg/kg bw/day: ataxia, ↓forelimb and hindlimb grip strength, repetitive chewing movements; ↓ bw and fc (♂); repetitive pawing, ↑ reactivity, ↑activity, slightly exaggerated auditory response, slight ↓ body temperature, uncoordinated righting response, red nasal stain, dermal lesions (♀)
5-month neurotoxicity study (gavage) (non-guideline) Cyfluthrin Wistar rat PMRA# 1216145, 1227053	**Supplemental** (PEG 400) 30-80 mg/kg bw/day: signs of toxicity included apathy, lack of grooming, laboured breathing, tremors, uncoordinated gait, salivation, ↓ bwg. No indication of paralysis or damage to the nervous tissues.
Tilting plane test (gavage) (non-guideline)	**Supplemental due to lack of individual data** (Cremophor EL) ≥ 0.03 mg/kg bw/day: impaired ability of rats to maintain stationary position (♂)

Study Type/ Animal/ PMRA #	Study Results
Cyfluthrin Wistar rat PMRA# 1207833	
Developmental neurotoxicity (diet) Beta-cyfluthrin Wistar rat PMRA# 2072967	Maternal Toxicity **NOAEL = 11.0 mg/kg bw/day** 17.8 mg/kg bw/day: ↓ bw during gestation and lactation, ↓ fc during lactation Offspring Toxicity **NOAEL = 11.0 mg/kg bw/day** 17.8 mg/kg bw/day: ↓ bw and bwg from PND 4-21; ↓ response amplitude for acoustic startle response on PND22 (♂); ↓ absolute brain wt on PND 21(♀) Brain concentrations: PND 4 and 21 pups had comparable or lower brain concentrations of cyfluthrin compared to dams at LD 21.
Special Studies (non-guideline)	
Effect of vehicle on absorption (gavage) Cyfluthrin Wistar rat PMRA# 1216132	10 mg/kg bw in Cremophor EL or PEG 400 Cremophor EL: ↑ rate and total absorption with enantiomers of cyfluthrin present in blood as early as 0.5 hours post dose. Peak blood levels at 1 hour post-dose. Maximum blood levels 5-fold higher than with PEG 400 PEG 400: Peak blood levels at 6 hours post-dose. Concentrations of isomers in stomach were considerably higher during the first four hours in PEG 400 group compared to Cremophor EL.
Gene expression Cyfluthrin Primary human fetal astrocytes PMRA# 2359599	Cyfluthrin induced damage to molecular chaperones, signal transducers, transcriptional regulators, transporters, including those involved in behavior and development. Further analyses showed upregulation of targets of interferon-γ and insulin-signaling pathways as well as increased protein levels of activated extracellular signal regulated kinase 1/2.
Rat brain synaptosome and	10 µM: ↓ ATPase activity, not statistically significant

Study Type/ Animal/ PMRA #	Study Results
leukocyte membrane assessment Cyfluthrin Synaptosomal and leukocyte membranes (Wistar rat, ♂) PMRA# 2359598	≥ 2 µM (plus piperonyl butoxide): ↓ ATPase activity Results suggest synergistic inhibitory interaction
Biochemical and Histological Changes in Rat Liver Beta-cyfluthrin Wistar rat PMRA# 2358830	35 mg/kg bw (single dose) or 1-5 mg/kg bw/day for 7-28 days All groups showed ↑AST, ALT, LDH, total lipid, cholesterol, phospholipid and free fatty acids and ↓ ALP, glycogen, total protein. Histological changes were seen in liver of all groups and included intralobular vein membrane dilation, presence of hepatocytes in ILV, cytoplasmic vacuolisation, multinuclear cells, nuclear polymorphisms, nuclear vacuolisation, hepatocyte membrane damage, nuclear division, nuclear eccentricity, pyknosis, necrosis and karyorrhexis.
In vitro metabolism study Beta-cyfluthrin Rat and human hepatic microsomes, Cytochrome P450 isoforms PMRA# 2428095	Metabolism occurs in rat hepatic microsomes: CYP1A1, CYP2C6, CYP2D, CYP2C12, CYP2D1, CYP3A1and CYP3A2 Metabolism occurs in human hepatic microsomes: CYP1A1, CYP1A2, CYP2C8, CYP2C91, CYP2C19 and CYP3A4
Functional observational battery study (gavage)	≥ 12.5 mg/kg bw/day: clonic convulsions, tremors (not dose-related) ≥ 25 mg/kg bw/day: ↓ bw on day 2, sitting with head held low, prostration, salivation, ventral wetness, ataxia, impaired mobility, gait impairment, clonic convulsions, low arousal level, head flick, ↓ sensory responses, ↓ body temperature, ↓ forelimb grip strength.

Study Type/ Animal/ PMRA #	Study Results
Beta-cyfluthrin Sprague Dawley rat PMRA# 2428089	45 mg/kg bw/day: 1 death, lacrimation

Table 2 Summary of Risk Assessment Endpoints

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary (All populations)	Acute neurotoxicity study in rats	NOAEL = 0.5 mg/kg bw; based on clinical signs of toxicity, changes in FOB parameters and decreased motor activity.	300
	ARfD = 0.002 mg/kg bw		
Repeated dietary (All populations)	Acute neurotoxicity study in rats	NOAEL = 0.5 mg/kg bw; based on clinical signs of toxicity, changes in FOB parameters and decreased motor activity.	300
	ADI = 0.002 mg/kg bw/day		
Short-, intermediate- and long-term dermal (All populations)	21-day dermal toxicity study in rats	NOAEL = 376 mg/kg bw/day; based on clinical signs of toxicity, decreased food consumption.	300
Short-term inhalation (All populations)	28-day inhalation toxicity study in rats	NOAEC = 0.0002 mg/L (0.07 mg/kg bw/day); based on decreased body weight and body weight gain.	300
Intermediate- and long-term inhalation (All populations)	90-day inhalation toxicity study in rats	NOAEC = 0.00009 mg/L (0.02 mg/kg bw/day); based on clinical signs of toxicity and decreased body weight.	300
Cancer	Equivocal increase in the incidence of urinary bladder tumours in females in the rat chronic toxicity/oncogenicity study with cyfluthrin. Endpoints selected for the non-cancer risk assessment are protective of these equivocal findings.		

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Aggregate Exposure: Based on clinical signs of neurotoxicity			
All Durations Aggregate - Oral (All populations)	Acute neurotoxicity study in rats	NOAEL = 0.5 mg/kg bw	300
Short-term Aggregate - Inhalation (All populations)	5-day inhalation toxicity study	NOAEC=0.00025 mg/L (0.07 mg/kg bw/day)	300

[1] CAF (Composite assessment factor) refers to the total of uncertainty and *Pest Control Products Act* factors for dietary risk assessments, MOE refers to target MOE for occupational assessments

Appendix IV Dietary Exposure and Risk Estimates for Cyfluthrin

Table 1 Summary of Acute Dietary Exposure and Risk from Cyfluthrin

Population Subgroup	Food Only – 99.9th Percentile			
	All uses included		All uses included except milk and dairy food forms	
	Exposure (mg/kg bw)	**%ARfD**[1]	**Exposure** (mg/kg bw)	**%ARfD**[1]
All Population	0.002350	118	0.000486	24
All Infants (< 1 year old)	0.003093	155	0.000511	26
Children 1-2 years old	**0.004283**	**214**	**0.000779**	**39**
Children 3-5 years old	0.002388	119	0.000730	37
Children 6-12 years old	0.001650	82	0.000513	26
Youth 13-19 years old	0.000939	47	0.000352	18
Adults 20-49 years old	0.000755	38	0.000447	22
Adults 50+ years old	0.000751	38	0.000445	22
Females 13-49 years old	0.000785	39	0.000448	22

[1]Acute Reference Dose (ARfD) of 0.002 mg/kg bw.

Shaded cells indicate risks exceeding 100% of the ARfD.

Table 2 Summary of Chronic Dietary Exposure and Risk from Cyfluthrin

Population Subgroup	Food Only			
	All uses included		All uses included except milk and dairy food forms	
	Exposure (mg/kg bw)	**%ADI**[1]	**Exposure** (mg/kg bw)	**%ADI**[1]
All Population	0.000167	8	0.000039	2
All Infants (< 1 year old)	0.000304	15	0.000081	4
Children 1-2 years old	**0.000959**	**48**	**0.000093**	**5**
Children 3-5 years old	0.000549	27	0.000087	4
Children 6-12 years old	0.000304	15	0.000059	3
Youth 13-19 years old	0.000146	7	0.000040	2
Adults 20-49 years old	0.000101	5	0.000034	2
Adults 50+ years old	0.000093	5	0.000027	1
Females 13-49 years old	0.000105	5	0.000032	2

[1]Acceptable Daily Intake (ADI) of 0.002 mg/kg bw/day.

Based on the registered uses for cyfluthrin and the supported uses for beta-cyfluthrin, residues in drinking water are not anticipated. Therefore, a drinking water risk assessment is not required.

Appendix V Food Residue Chemistry Summary

The pyrethroid, cyfluthrin, is a synthetic non-systemic insecticide that causes rapid knockdown and has long residual activity. It is a mixture of four diastereoisomers present in somewhat similar ratios. Beta-cyfluthrin contains the same four diastereoisomer pairs as cyfluthrin; however, the two diastereoisomer pairs considered insecticidally active are enriched for beta-cyfluthrin. Cyfluthrin and beta-cyfluthrin are thus structurally identical, differing only in the ratio of the stereoisomers.

In Canada, cyfluthrin is registered for use as a direct application to beef and lactating cattle as well as in various indoor areas, including food handling establishments and livestock housing. Beta-cyfluthrin is currently being reviewed by the PMRA for registration and Canadian MRLs are being proposed for import purposes at the limit of quantification of the field trials.

The nature of the residue of cyfluthrin in livestock and plant commodities is adequately understood based on acceptable metabolism studies in laying hens, cows, potato, soybean, cotton and tomato. The residue definition in plant and animal commodities is currently expressed as "*cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate*" (in other words, the parent compound, cyfluthrin).

Gas chromatography methods were developed for data generation in plant matrices (GC-ECD; method 85823) and animal matrices (GC-MS; method 85883). Gas chromatography methods were developed for enforcement in plant matrices (GC-MS; method 108139) and animal matrices (GC-MS; DFG S19). Multi-residue analytical methods (MRMs) for cyfluthrin/beta-cyfluthrin for both plant and animal matrices are available from the US Food and Drug Administration and the Canadian Food Inspection Agency's National Chemical Residue Monitoring Program. These MRMs have been validated by independent laboratories, and therefore fulfill the requirements for enforcement purposes. As such, they are currently used for enforcement by Canada and for both enforcement and risk assessment by the US. Since all currently available analytical methods, including MRMs, do not distinguish between cyfluthrin and beta-cyfluthrin, residues are reported as cyfluthrin *per se*.

As cyfluthrin and beta-cyfluthrin are structurally identical (differing only in the ratio of the stereoisomers) and the available analytical methods cannot distinguish between cyfluthrin and beta-cyfluthrin, the residue definition for risk assessment and enforcement in plant and animal commodities is cyfluthrin *per se* for both chemicals.

The *Food and Drugs Act* prohibits the sale of adulterated food; that is, food containing a pesticide residue that exceeds the specified maximum residue limit (MRL). Pesticide MRLs are specified for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. An MRL represents the maximum amount of residues that may remain on food when a pesticide is used according to label directions, and serves as a food safety standard. The Canadian Food Inspection Agency is responsible for monitoring the Canadian food supply for pesticide residues and the determination of compliance with MRLs specified by Health Canada.

MRLs are specified in Canada for residues of cyfluthrin on animal commodities: milk (0.5 ppm); milk fat (15 ppm); fat of cattle, goats, hogs, horses, poultry and sheep (5 ppm); meat by-products of cattle, goats, hogs, horses, poultry and sheep (0.4 ppm); meat of cattle, goats, hogs, horses, poultry and sheep (0.4 ppm); and eggs (0.01 ppm). MRLs for the proposed importation of all petitioned beta-cyfluthrin uses are being proposed at the relevant LOQ from the reviewed crop field trials for each imported petitioned commodity. The exception is succulent shelled southern peas, where the LOQ value (0.25 ppm) is greater than 0.1 ppm; therefore, the cyfluthrin MRL is being proposed at the general MRL of 0.1 ppm to be more protective for the Canadian population. The proposed MRLs for beta-cyfluthrin are listed in Table 1 below. Residues of cyfluthrin and beta-cyfluthrin in all other agricultural commodities are regulated under Subsection B.15.002(1) of the *Food and Drugs Regulations*, which requires that residues do not exceed 0.1 ppm. A complete list of MRLs specified in Canada can be found on the PMRA's MRL Database, an online query application that allows users to search for specified MRLs, regulated under the *Pest Control Products Act*, both for pesticides or food commodities (http://pr-rp.hc-sc.gc.ca/mrl-lrm/index-eng.php).

Based on the registered uses for cyfluthrin (and the proposed uses for beta-cyfluthrin that can be supported), residue chemistry data for confined crop rotational studies and field accumulation in rotational crops are not required.

Available residue data support the specified MRLs for cyfluthrin (and the proposed uses for beta-cyfluthrin that can be supported), and therefore are deemed adequate.

Overall, no major data gaps were identified. Therefore, no residue chemistry data are required as a result of cyfluthrin re-evaluation.

Table 1 Canadian Proposed MRLs for Beta-Cyfluthrin

RAC and/or Processed Commodity	MRL (ppm)
Crop Group 1 – Root and Tuber Vegetables	0.01
Crop Group 4-13: Leafy Vegetables	0.01
Crop Subgroup 5-13: Brassica Head and Stem Vegetable Group	0.01
Dried field peas	0.05
Dried beans	0.01
Succulent shelled southern peas	0.10
Dry soybeans	0.01
Crop Group 8-09: Fruiting Vegetables	0.05
Crop Group 9: Cucurbit Vegetables	0.01
Crop Group 10: Citrus Fruit (Revised)	0.01
Crop Group 11-09: Pome Fruit	0.01
Crop Group 12-09: Stone Fruits	0.01
Grapes	0.01
Crop Group 14-11: Tree Nuts	0.01
Field corn	0.01
Sweet corn kernels plus cob with husks removed	0.01
Sorghum	0.01
Wheat	0.05

RAC and/or Processed Commodity	MRL (ppm)
Sunflower seeds	0.01
Undelinted cotton seeds	0.1
Crop Subgroup 22B: Leaf Petioles Vegetables	0.01
Sugarcane cane	0.01
Hops (dried)	0.01
Peanuts	0.01

Appendix VI Commercial Mixer/Loader/Applicator Risk Assessment

Table 1 Short-Term Commercial Applicator Exposure and Risk Assessment*

MLA Scenarios	Application Method	Equipment	PHED Unit Exposure (µg/kg a.i. handled)			Application Rate (kg a.i./L unless specified)	ATPD[a]	Amount Handled[b] (kg a.i./day)	Dermal Exposure[c] (mg/kg bw/day)	Dermal MOE[d]	Inhalation Exposure[e] (mg/kg bw/day)	Inhalation MOE[f]	Inhalation Exposure[e] (mg/kg bw/day)	Inhalation MOE[f]
			Dermal	Inhalation							No Resp.		With Resp.	
				No Resp.	With Resp.									
Professional applicator	Bedbug	MPHW	19745	1423	142.3	0.00101	6	0.00606	0.001496	251392	0.000108	649	0.000011	6494
		Backpack	5977	118	11.8	0.00101	6	0.00606	0.000453	830434	0.000009	7811	0.000001	78114
	Residential indoor band, spot, crack and crevice	MPHW	19745	1423	142.3	0.00101	10	0.0101	0.002493	150835	0.000180	390	0.000018	3896
		Backpack	5977	118	11.8	0.00101	10	0.0101	0.000755	498261	0.000015	4687	0.000001	46869
	Commercial indoor band, spot, crack and crevice	MPHW	19745	1423	142.3	0.00101	40	0.0404	0.009971	37709	0.000719	97	0.000072	974
		Backpack	5977	118	11.8	0.00101	40	0.0404	0.003019	124565	0.000060	1172	0.000006	11717
Professional applicator and farmer	Livestock housing general surface spray (broadcast)	MPHW	19745	1423	142.3	0.00004[g]	1600	0.0608	0.015006	25056	0.001081	65	0.000108	647
		Backpack	5977	118	11.8	0.00004[g]	1600	0.0608	0.004543	82770	0.000090	779	0.000009	7786
Farmer	Pour-on application to livestock	MPHW	943	45.2	4.52	0.000114[h]	470	0.0535	0.000630	596594	0.000030	2317	0.000003	23172

MPHW = manually pressurized handwand.

***** Assessment based on current label personal protective equipment: Long-sleeved shirt, long pants and gloves (the labels require non-absorbent gloves for application to livestock and chemical-resistant gloves for all other scenarios) and respirator.

[a] ATPD = Area Treated Per Day. Values were provided by the registrant, except for application to livestock. Based upon the 2011 Census, the 95th percentile for cattle farm size in Canada was 470 head (including cows, heifers, bulls, steer, *etc.*)

[b] Amount Handled (kg a.i./day) = Application Rate (kg a.i./L or kg a.i./m^2 or kg a.i./animal) × ATPD (litres for residential and commercial indoors; m^2 for livestock housing; number of animals for application to livestock)

[c] Dermal Exposure (mg/kg bw/day) = Dermal Unit Exposure (µg/ kg a.i. handled) × Amount Handled (kg a.i./day) × Unit Conversion (0.001 mg/µg) ÷ 80 kg bw. Dermal absorption is not required since the dermal NOAEL is based on a dermal toxicity study.

[d] MOE = margin of exposure; Dermal MOE = Dermal NOAEL (mg/kg bw/day) ÷ Dermal Exposure (mg/kg bw/day), based on a dermal NOAEL of 376 mg/kg bw/day and a target MOE of 300.

[e] Inhalation Exposure (mg/kg bw/day) = Inhalation Unit Exposure (µg/ kg a.i. handled) × Amount Handled (kg a.i./day) × Unit Conversion (0.001 mg/µg) ÷ 80 kg bw; Unit Exposures are based on light inhalation rate.

[f] MOE = margin of exposure; Inhalation MOE = Inhalation NOAEL÷ Inhalation Exposure (mg/kg bw/day), based on a inhalation NOAEL of 0.07 mg/kg bw/day with a target MOE of 300. Shaded cells indicate MOEs that are less than the target MOE.
[g] Unit in kg a.i./m^2.
[h] Unit in kg a.i./animal.

Table 2 Intermediate- to Long-Term Commercial Applicator Exposure and Risk Assessment*

MLA Scenarios	Application Method		PHED Unit Exposure (µg/kg a.i. handled)			Application Rate (kg a.i./L)	ATPD[a]	Amount Handled[b] (kg a.i./day)	Dermal Exposure[c] (mg/kg bw/day)	Dermal MOE[d]	Inhalation Exposure[e] (mg/kg bw/day)	Inhalation MOE[f]	Inhalation Exposure[e] (mg/kg bw/day)	Inhalation MOE[f]
			Dermal	Inhalation							No Resp.		With Resp.	
				No Resp.	With Resp.									
Professional applicator	Bedbug	MPHW	19745	1423	142.3	0.00101	6	0.00606	0.001496	251392	0.000108	186	0.000011	1855
		Backpack	5977	118	11.8	0.00101	6	0.00606	0.000453	830434	0.000009	2232	0.000001	22318
	Residential indoor band, spot, crack and crevice	MPHW	19745	1423	142.3	0.00101	10	0.0101	0.002493	150835	0.000180	111	0.000018	1113
		Backpack	5977	118	11.8	0.00101	10	0.0101	0.000755	498261	0.000015	1339	0.000001	13391
	Commercial indoor band, spot, crack and crevice	MPHW	19745	1423	142.3	0.00101	40	0.0404	0.009971	37709	0.000719	28	0.000072	278
		Backpack	5977	118	11.8	0.00101	40	0.0404	0.003019	124565	0.000060	335	0.000006	3348

MPHW = manually pressurized handwand.
* Assessment based on baseline personal protective equipment: Long-sleeved shirt, long pants and gloves (the labels require non-absorbent gloves for application to livestock and chemical-resistant gloves for all other scenarios)
[a] ATPD = Area Treated Per Day. Values were provided by the registrant, except for application to livestock. Based upon the 2011 Census, the 95th percentile for cattle farm size in Canada was 470 head (including cows, heifers, bulls, steer, etc.)
[b] Amount Handled (kg a.i./day) = Application Rate (kg a.i./L or kg a.i./m^2 or kg a.i./animal) × ATPD (litres)
[c] Dermal Exposure (mg/kg bw/day) = Dermal Unit Exposure (µg/ kg a.i. handled) × Amount Handled (kg a.i./day) × Unit Conversion (0.001 mg/µg) ÷ 80 kg bw. Dermal absorption is not required since the dermal NOAEL is based on a dermal toxicity study.
[d] MOE = margin of exposure; Dermal MOE = Dermal NOAEL (mg/kg bw/day) ÷ Dermal Exposure (mg/kg bw/day), based on a dermal NOAEL of 376 mg/kg bw/day and a target MOE of 300.
[e] Inhalation Exposure (mg/kg bw/day) = Inhalation Unit Exposure (µg/ kg a.i. handled) × Amount Handled (kg a.i./day) × Unit Conversion (0.001 mg/µg) ÷ 80 kg bw; Unit Exposures are based on light inhalation rate.
[f] MOE = margin of exposure; Inhalation MOE = Inhalation NOAEL÷ Inhalation Exposure (mg/kg bw/day), based on a inhalation NOAEL of 0.02 mg/kg bw/day with a target MOE of 300. Shaded cells indicate MOEs that are less than the target MOE.

Appendix VII Non-Occupational Risk Assessment

Table 1 Short-Term Residential Applicator Exposure Risk Assessment – Indoor Environment

Formulation[a]	Application Equipment /Method[b]	Type	PHED Unit Exposure (µg/kg a.i. handled)		Amount Handled Daily[c] (can/day)	Application Rate (kg a.i./day)	Dermal Exposure[d] (mg/kg bw/day)	Dermal MOE[e]	Inhalation Exposure[f] (mg/kg bw/day)	Inhalation MOE[g]
			Dermal	Inhalation						
PP	Aerosol can	Indoor band, spot, crack and crevice	816000	6610	0.5	0.000125	0.001275	294902	0.000010	6778

[a] PP = pressurized product.
[b] Based on percent guarantee, and size of product. The maximum application rate was used for each scenario.
[c] Based on U.S. EPA Residential SOPs (2012) measured in containers for PP formulations.
[d] Dermal Exposure (mg/kg bw/day) = (Unit Exposure × Application Rate × Amount Handled Daily) ÷ 80 kg. Dermal absorption is not required since the dermal NOAEL is based on a dermal toxicity study.
[e] MOE = Margin of Exposure; MOE = Dermal NOAEL (mg/kg bw/day) ÷ Dermal Exposure (mg/kg bw/day), based on a dermal NOAEL of 376 mg/kg bw/day and a target MOE of 300.
[f] Inhalation Exposure (mg/kg bw/day) = (Unit Exposure × Application Rate × Amount Handled Daily) ÷ 80 kg.
[g] MOE = Inhalation NOAEL (mg/kg bw/day) ÷ Inhalation Exposure (mg/kg bw/day), based on a inhalation NOAEL of 0.07 mg/kg bw/day and a target MOE of 300.

Table 2 Short- to Long-Term Postapplication Dermal Exposure from Carpets and Hard Surfaces – Domestic- and Commercial-Class Products

Exposure Scenario		Life Stage	Transferable Residue ($\mu g/cm^2$)[a]	Transfer Coefficient (cm^2/hr)[b]	Exposure Time (hr/day)[c]	Dermal Dose (mg/kg bw/day)[d]	MOE[e]
Indoor band, spot and bedbug (coarse)	Carpet	Adults	0.180	6800	8	0.12240	3100
		Youth		5600	5	0.08842	4300
		Children		1800	4	0.11782	3200
	Hard surface	Adults	0.270	6800	2	0.04590	8200
		Youth		5600	1	0.02653	14000
		Children		1800	2	0.08836	4300
Indoor band, spot and bedbug (pin stream)	Carpet	Adults	0.044	6800	8	0.02992	13000
		Youth		5600	5	0.02161	17000
		Children		1800	4	0.02880	13000
	Hard surface	Adults	0.066	6800	2	0.01122	34000
		Youth		5600	1	0.00648	58000
		Children		1800	2	0.02160	17000

Exposure Scenario		Life Stage	Transferable Residue ($\mu g/cm^2$)[a]	Transfer Coefficient (cm^2/hr)[b]	Exposure Time (hr/day)[c]	Dermal Dose (mg/kg bw/day)[d]	MOE[e]
Crack and crevice	Carpet	Adults	0.012	6800	8	0.00816	46000
		Youth		5600	5	0.00589	64000
		Children		1800	4	0.00785	48000
	Hard surface	Adults	0.018	6800	2	0.00306	120000
		Youth		5600	1	0.00177	210000
		Children		1800	2	0.00589	64000

[a] Transferable Residue ($\mu g/cm^2$) = Residue ($\mu g/cm^2$) × Fraction Transferred (%). Deposited residues were calculated based on default residue values derived from the USEPA Residential SOPs [USEPA, 2012] as no application rates were provided in their labels [USEPA, 2012]. See Section 5.2.1 for more information.
[b] Transfer Coefficient (cm^2/hr) default values obtained from the USEPA Residential SOPs [USEPA, 2012].
[c] Exposure Time (hr/day) default values obtained from the USEPA Residential SOPs [USEPA, 2012].
[d] Dermal Dose (mg/kg bw/day) = (Transferable Residue ($\mu g/cm^2$) × 0.001 mg/µg × Transfer Coefficient (cm^2/hr) × Exposure Time (hr/day))/Body Weight (kg). Body weights of 80, 57 and 11 kg were used for adults, youths (11 <16 years), and children (1 <2 years) respectively [USEPA, 2012]. Dermal absorption not required because the dermal NOAEL is based on a dermal toxicity study.
[e] MOE = margin of exposure; Dermal MOE = Dermal NOAEL (mg/kg bw/day) ÷ Dermal Exposure (mg/kg bw/day), based on a dermal NOAEL of 376 mg/kg bw/day and a target MOE of 300 applicable to short-, intermediate- and long-term scenarios.

Table 3 Short- to Long-Term Postapplication Dermal Exposure from Mattresses – Commercial-Class Product

Exposure Scenario	Life Stage	Deposited Residue ($\mu g/cm^2$)[a]	Surface Area/Body Weight Ratio (cm^2/kg)[b]	Dermal Dose (mg/kg bw/day)[c]	MOE[d]
Application to mattress	Adults	20.2	280	0.057	6600
	Youth	20.2	280	0.057	6600
	Children	20.2	640	0.13	2900

[a] Deposited residue was calculated based on the maximum label application rate using the USEPA Residential SOPs [USEPA, 2012] algorithms for all scenarios. See Section 5.2.1 for more information.
[b] Values were obtained from the USEPA Residential SOPs [USEPA, 2012] based on body weights of 80 kg for adults, 57 kg for youth, and 11 kg for children (1<2 years).
[c] Dermal Dose (mg/kg bw/day) = Deposited Residue ($\mu g/cm^2$) × 0.001 mg/µg × Surface Area/Body Weight Ratio (cm^2/kg) × Fraction of skin in contact with mattress (0.5) × Fraction transferred (0.04) × Protection Factor (0.5). Dermal absorption not required because the dermal NOAEL is based on a dermal toxicity study.
[d] MOE = margin of exposure; Dermal MOE = Dermal NOAEL (mg/kg bw/day) ÷ Dermal Exposure (mg/kg bw/day), based on a dermal NOAEL of 376 mg/kg bw/day and a target MOE of 300 applicable to short-, intermediate- and long-term scenarios.

Table 4 Short-Term Postapplication Inhalation Exposure from Indoor Surface Directed Sprays – Domestic-Class Products

Exposure Scenario	Life Stage	Mass of a.i. (mg; Mlabel)[a]	Exposure Time (hour)[b]	Inhalation Dose (mg/kg bw/day)[c]	MOE[d]
Surface directed spray	Adults	125	16	0.0000008	91000
	Youths 11 <16 years	125	15	0.0000010	71000
	Children 1 to <2 years	125	18	0.0000033	21000

[a] Mass of a.i. = The mass of a.i. applied based on the product label (M_{label}) was used in the calculations as it was less than the mass of a.i. that would result in an air concentration equal to the saturation constant for cyfluthrin (M_{csat}). Refer to the USEPA Residential SOPs and spreadsheets for more information [USEPA, 2012]

[b] Exposure Time (hr/day) default values obtained from the USEPA Residential SOPs [USEPA, 2012].

[c] Inhalation exposure (mg/kg bw/day) = $\frac{IR \times M}{ACH \times V} \times \left[1 - \left(\frac{(ACH \times e^{-k \times ET}) - (k \times e^{-ACH \times ET})}{ACH - k}\right)\right] \times \frac{1}{BW}$.

The equation assumes 100% absorption through inhalation; air exchanges (ACH) = 0.45 hr^{-1}; volume of a room (V) = 33 m^3; decay rate (k) = First order decay rate (hr^{-1}), refer to the USEPA Residential SOPs [USEPA, 2012] for the equations used to calculate k; M = mass of a.i., ET = exposure time. Inhalation rates (IR) of 0.64, 0.63 and 0.33 m^3/hr and body weights (BW) of 80, 57 and 11 kg were used for adults, youth and children (1<2 years old) respectively.

[d] MOE = margin of exposure; Inhalation MOE = Inhalation NOAEL÷ Inhalation Exposure (mg/kg bw/day), based on a inhalation NOAEL of 0.07 mg/kg bw/day with a target MOE of 300.

Table 5 Short- to Long-Term Postapplication Inhalation Exposure from Indoor Surface Directed Sprays – Commercial-Class Product

Exposure Scenario	Life Stage	Mass of a.i. (mg; Mlabel)[a]	Exposure Time (hour)[b]	Inhalation Dose (mg/kg bw/day)[c]	Short-Term MOE[d]	Long-Term MOE[d]
Surface directed spray	Adults	1,909	16	0.00001	6000	1700
	Youths 11 <16 years	1,909	15	0.00002	4700	1300
	Children 1 to <2 years	1,909	18	0.00005	1400	400

[a] Mass of a.i. = The mass of a.i. applied based on the product label (M_{label}) was used in the calculations as it was less than the mass of a.i. that would result in an air concentration equal to the saturation constant for cyfluthrin (M_{csat}). Refer to the USEPA Residential SOPs and spreadsheets for more information [USEPA, 2012]

[b] Exposure Time (hr/day) default values obtained from the USEPA Residential SOPs [USEPA, 2012].

[c] Inhalation exposure (mg/kg bw/day) = $\frac{IR \times M}{ACH \times V} \times \left[1 - \left(\frac{(ACH \times e^{-k \times ET}) - (k \times e^{-ACH \times ET})}{ACH - k}\right)\right] \times \frac{1}{BW}$.

The equation assumes 100% absorption through inhalation; air exchanges (ACH) = 0.45 hr^{-1}; volume of a room (V) = 33 m^3; decay rate (k) = First order decay rate (hr^{-1}), refer to the USEPA Residential SOPs [USEPA, 2012] for the equations used to calculate k; M = mass of a.i., ET = exposure time. Inhalation rates (IR) of 0.64, 0.63 and 0.33 m^3/hr and body weights (BW) of 80, 57 and 11 kg were used for adults, youth and children (1<2 years old) respectively.

[d] MOE = margin of exposure; Inhalation MOE = Inhalation NOAEL÷ Inhalation Exposure (mg/kg bw/day), based on inhalation NOAELs of 0.07 and 0.02 mg/kg bw/day applicable to short- and long-term scenarios, respectively, with a target MOE of 300.

Table 6 Short-Term Postapplication Hand-to-Mouth Exposure to Children from Indoor Environments – Domestic-Class Products

Exposure Scenario		Hand Residue Loading (mg/cm^2)[a]	Oral Dose (mg/kg bw/day)[b]	MOE[c]
Indoor band and spot (coarse)	Carpet	0.00065	0.01768	28
	Hard surface	0.00049	0.00663	75
Indoor band and spot (pin stream)	Carpet	0.00016	0.00432	120
	Hard surface	0.00012	0.00162	310

[a] Based on the dermal postapplication exposure from indoor applications without the body weight × fraction of a.i. on hands compared to total body surface residue (0.15).
[b] Oral Dose (mg/kg bw/day) = [Hand Residue (mg/cm^2) × (Fraction of hand mouthed/event (0.13) × Surface Area of one hand (150 cm^2)) × (Exposure Time (hrs/day) × 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). Exposure times for carpets and hard surfaces were 4 and 2 hrs, respectively, as stated in the USEPA Residential SOPs [USEPA, 2012].
[c] MOE = margin of exposure; Oral MOE = oral NOAEL/Oral exposure, based on an oral NOAEL of 0.5 mg/kg bw/day and a target MOE of 300. Shaded cells indicate MOEs that are less than the target MOE.

Table 7 Short- to Long-Term Postapplication Hand-to-Mouth Exposure to Children from Indoor Environments – Commercial-Class Product

Exposure Scenario		Hand Residue Loading (mg/cm^2)[a]	Oral Dose (mg/kg bw/day)[b]	MOE[c]
Broadcast	Carpet	0.00043	0.01099	45
	Hard surface	0.00032	0.00412	120
Indoor band, spot and bedbug (coarse)	Carpet	0.00065	0.01768	28
	Hard surface	0.00049	0.00663	75
Indoor band, spot and bedbug (pin stream)	Carpet	0.00016	0.00432	120
	Hard surface	0.00012	0.00162	310
Crack and crevice	Carpet	0.00004	0.00118	420
	Hard surface	0.00003	0.00044	1100

[a] Based on the dermal postapplication exposure from indoor applications without the body weight × fraction of a.i. on hands compared to total body surface residue (0.15).
[b] Oral Dose (mg/kg bw/day) = [Hand Residue (mg/cm^2) × (Fraction of hand mouthed/event (0.13) × Surface Area of one hand (150 cm^2)) × (Exposure Time (hrs/day) × 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). Exposure times for carpets and hard surfaces were 4 and 2 hrs, respectively, as stated in the USEPA Residential SOPs [USEPA, 2012].
[c] MOE = margin of exposure; Oral MOE = oral NOAEL/Oral exposure, based on an oral NOAEL of 0.5 mg/kg bw/day and a target MOE of 300. Shaded cells indicate MOEs that are less than the target MOE.

Table 8 Short-Term Postapplication Object-to-Mouth Exposure to Children from Indoor Environments – Domestic-Class Products

Exposure Scenario		Object Residue ($\mu g/cm^2$)[a]	Oral Dose (mg/kg bw/day)[b]	MOE[c]
Indoor band and spot (coarse)	Carpet	0.180	0.00235	210
	Hard surface	0.270	0.00176	280
Indoor band and spot (pin stream)	Carpet	0.044	0.00058	870
	Hard surface	0.066	0.00043	1200

[a] Object Residue = Deposited Residue ($\mu g/cm^2$) × Fraction of residue transferred (4% for carpets and 6% for hard surfaces). Deposited residues were derived from the USEPA Residential SOPs [USEPA, 2012]. See Section 5.2.1 for more information.

[b] Oral Dose (mg/kg bw/day) = [Object Residue ($\mu g/cm^2$) × 0.001 mg/µg × Surface Area of object mouthed (10 cm^2/event) × (Exposure Time (hr) × Replenishment Intervals (4/hr)) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (14)/Replenishment Intervals (4/hr)}}$)]/ Body Weight (11 kg). Exposure times for carpets and hard surfaces were 4 and 2 hrs, respectively, as stated in the USEPA Residential SOPs [USEPA, 2012].

[c] MOE = margin of exposure; Oral MOE = oral NOAEL/Oral exposure, based on an oral NOAEL of 0.5 mg/kg bw/day and a target MOE of 300. Shaded cells indicate MOEs that are less than the target MOE.

Table 9 Short- to Long-Term Postapplication Object-to-Mouth Exposure to Children from Indoor Environments – Commercial-Class Product

Exposure Scenario		Object Residue ($\mu g/cm^2$)[a]	Oral Dose (mg/kg bw/day)[b]	MOE[c]
Broadcast	Carpet	0.120	0.00157	320
	Hard surface	0.180	0.00118	430
Indoor band, spot and bedbug (coarse)	Carpet	0.180	0.00235	210
	Hard surface	0.270	0.00176	280
Indoor band, spot and bedbug (pin stream)	Carpet	0.044	0.00058	870
	Hard surface	0.066	0.00043	1200
Crack and crevice	Carpet	0.012	0.00016	3200
	Hard surface	0.018	0.00012	4300

[a] Object Residue = Deposited Residue ($\mu g/cm^2$) × Fraction of residue transferred (4% for carpets and 6% for hard surfaces). Deposited residues were derived from the USEPA Residential SOPs [USEPA, 2012]. See Section 5.2.1 for more information.

[b] Oral Dose (mg/kg bw/day) = [Object Residue ($\mu g/cm^2$) × 0.001 mg/µg × Surface Area of object mouthed (10 cm^2/event) × (Exposure Time (hr) × Replenishment Intervals (4/hr)) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (14)/Replenishment Intervals (4/hr)}}$)]/ Body Weight (11 kg). Exposure times for carpets and hard surfaces were 4 and 2 hrs, respectively, as stated in the USEPA Residential SOPs [USEPA, 2012].

[c] MOE = margin of exposure; Oral MOE = oral NOAEL/Oral exposure, based on an oral NOAEL of 0.5 mg/kg bw/day and a target MOE of 300. Shaded cells indicate MOEs that are less than the target MOE.

Table 10 Short-Term Postapplication Combined Hand-to-Mouth from Hard Surfaces and Inhalation Exposure– Commercial-Class Product

Scenarios	Life Stage	Hand-to-Mouth Hard Surfaces MOE[a]	Inhalation MOE[b]	Combined MOE[c]
Crack and crevice	Children 1 to <2 years	1100	1400	616

[a] MOE = margin of exposure; short-term estimates were extracted for children from the postapplication hand-to-mouth exposure from hard surfaces (see Appendix 9, Table 9.2)
[b] MOE = margin of exposure; short-term estimates were extracted for children from the postapplication inhalation exposure (see Appendix 8, Table 8.2)
[c] MOE = margin of exposure; Combined MOE = $\frac{1}{[(1/MOE_{Hand\text{-}to\text{-}Mouth}) + (1/MOE_{Inhalation})]}$

Table 11 Short-Term Postapplication Combined Hand-to-Mouth from Soft Surfaces and Inhalation Exposure– Commercial-Class Product

Scenarios	Life Stage	Hand-to-Mouth Soft Surfaces MOE[a]	Inhalation MOE[b]	Combined MOE[c]
Crack and crevice	Children 1 to <2 years	420	1400	323

[a] MOE = margin of exposure; short-term estimates were extracted for children from the postapplication hand-to-mouth exposure from carpet (see Appendix 9, Table 9.2)
[b] MOE = margin of exposure; short-term estimates were extracted for children from the postapplication inhalation exposure (see Appendix 8, Table 8.2)
[c] MOE = margin of exposure; Combined MOE = $\frac{1}{[(1/MOE_{Hand\text{-}to\text{-}Mouth}) + (1/MOE_{Inhalation})]}$

Appendix VIII Aggregate Risk Assessment

Table 1 Short-Term Postapplication Aggregate Hand-to-Mouth from Crack and Crevice Application to Hard Surfaces, Inhalation and Chronic Food Exposure – Commercial-Class Product

Scenarios	Life Stage	Hand-to-Mouth Hard Surfaces MOE[a]	Inhalation MOE[b]	Dietary Exposure (mg/kg bw/day)	Dietary MOE	Aggregate MOE[c]
Crack and crevice	Children 1 to <2 years	1100	1400	0.000087	5747	556

[a] MOE = margin of exposure; short-term estimates were extracted for children from the postapplication hand-to-mouth exposure from hard surfaces (see Appendix 9, Table 9.2)
[b] MOE = margin of exposure; short-term estimates were extracted for children from the postapplication inhalation exposure (see Appendix 8, Table 8.2)
[c] MOE = margin of exposure; Aggregate MOE = $\frac{1}{[(1/MOE_{Hand\text{-}to\text{-}Mouth}) + (1/MOE_{Inhalation}) + (1/MOE_{Food})]}$

Table 2 Short-Term Postapplication Aggregate Hand-to-Mouth from Crack and Crevice Application to Soft Surfaces, Inhalation and Chronic Food Exposure – Commercial-Class Product

Scenarios	Life Stage	Hand-to-Mouth Soft Surfaces MOE[a]	Inhalation MOE[b]	Dietary Exposure (mg/kg bw/day)	Dietary MOE	Aggregate MOE[c]
Crack and crevice	Children 1 to <2 years	420	1400	0.000087	5747	306

[a] MOE = margin of exposure; short-term estimates were extracted for children from the postapplication hand-to-mouth exposure from carpet (see Appendix 9, Table 9.2)
[b] MOE = margin of exposure; short-term estimates were extracted for children from the postapplication inhalation exposure (see Appendix 8, Table 8.2)
[c] MOE = margin of exposure; Aggregate MOE = $\frac{1}{[(1/MOE_{Hand\text{-}to\text{-}Mouth}) + (1/MOE_{Inhalation}) + (1/MOE_{Food})]}$

Appendix IX Biomonitoring Data

Table 1 Comparison of Biomonitoring Data and BE for Cyfluthrin Metabolite

		4-F-3-PBA[a]	
BE[b,c]		16 µg/L	21 µg/g creatinine
CHMS (95th percentile)	General population (6-79 yrs)	0.102 µg/L	0.075 µg/g creatinine
	Children (6-10 yrs)	0.056 µg/L	0.072 µg/g creatinine
	Youth (11-15 yrs)	0.051 µg/L	0.043 µg/g creatinine
	Adults (16-79 yrs)	0.109 µg/L	0.079 µg/g creatinine

BE = Biomonitoring equivalent; CHMS = Canadian Health Measures Survey.
[a] Specific metabolite of cyfluthrin.
[b] BE based on the acceptable daily intake (ADI) established by PMRA (see Section 3.2.3) was used for cyfluthrin (4-F-3-PBA).
[c] Biomonitoring data for persons aged >6 years old were compared to the BE. As the BE was not developed for younger sub-populations (<6 years old), it is not appropriate to compare them with the BE.

Table 2 Aggregate Chronic Exposure and Risk Assessment using CHMS and MIREC-CD Plus Biomonitoring Data

Sub-population	Daily Exposure[a] (mg/kg bw/day)	Aggregate MOE[b] (Target = 300)
General Population (6-79 years)	0.000027	18300
Children (2 <3 years)[c]	0.000087	5800
Children (3-5 years)[d]	0.000027	18000
Children (6-10 years)	0.000024	20000
Youth (11-15 years)	0.000014	35000
Adult (16-79 years)	0.000029	17000

CHMS = Canadian Health Measures Survey; MIREC-CD Plus = Maternal Infant Research on Environmental Chemicals – Child Development Plus.
[a] Daily Exposure was calculated using the following equation: Daily Exposure (mg/kg bw/day) = [(urinary metabolite concentration from CHMS and MIREC-CD Plus × daily excretion (g creatinine/day) × (molecular weight parent/ molecular weight metabolite)] / [urinary excretion fraction from human pharmacokinetic studies × body weight]; CHMS data was used for adults, youth and children older than 3. MIREC-CD Plus data was used for children under 3 years old. The 95th percentile values were used in the risk assessment.
[b] MOE = Margin of Exposure; MOEs were calculated using the following equation: MOE = NOAEL (mg/kg bw/day)/Daily Exposure (mg/kg bw/day); a NOAEL of 0.5 mg/kg bw/day (based on clinical signs of toxicity, changes in FOB parameters and decreased motor activity) and target MOE of 300 were used.
[c] Data from MIREC-CD Plus.
[d] Cycle 2 data only from CHMS.

Appendix X Environmental Exposure and Risk Assessment for Cyfluthrin

Table 1 Fate and Behaviour in the Environment

Property	Test substance	Value	Transformation products	Comments	PMRA#
Abiotic transformation					
Hydrolysis	cyfluthrin	stable @pH5 193 d @pH7 <2 d @pH9	FPBald and DCVA.	Increasingly stable towards neutral and acidic conditions but relatively fast in alkaline conditions (pH 9)	1168277 2073018 1215522
Biotransformation					
Biotransformation in aerobic soil	cyfluthrin	DT_{50} = 53.1-56.8 d	FPBacid, DCVA, CO_2 and bound residues	Moderately persistent	1168279
	DCVA	DT_{50}: 12-62 d		Slightly to moderately persistent	2559846
Biotransformation in aerobic water systems	cyfluthrin	**Water:** DT_{50}: < 1 d DT_{90} : < 1 d **Whole System**: DT_{50}: 0.22 – 0.36 d DT_{90}: 6.1 – 9.9 d	FPBacid	Non-persistent	2601554
Biotransformation in anaerobic soil	cyfluthrin	DT_{50} could not be determined	FPBacid and bound residues		1168279
Mobility					
Adsorption / desorption in soil	cyfluthrin	Kd 633-1793 K_{OC} = 45471 - 180000		Immobile	1216369
	DCVA	K_{OC} = 53.4		Highly mobile in soil	2579990
Soil leaching	cyfluthrin	Residues found in the upper soil layers only		Low potential to leach	1215504 1215524
Bioaccumulation					
Bioconcentration in bluegill sunfish	cyfluthrin	Log Kow =5.97		Cyfluthrin has the potential to bioaccumulate in food chain. Cyfluthrin does not meet all the TSMP criteria for bioaccumulation	1215515

Table 2 Toxicity to Non-Target Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Invertebrates					
Honey bee *Apis mellifera*	24h-Oral	cyfluthrin	0.051 µg a.i./bee	Highly toxic	2558356 2559846 2580000
	24h-Contact	cyfluthrin	0.0098 µg a.i./bee		
	48h-Contact	cyfluthrin	0.037 µg a.i./bee		
	10 d-Residual	2 EC Baythroid	0.037 µg a.i./bee		
Birds					
Birds Bobwhite quail	Acute	cyfluthrin	LD_{50} >2000mg a.i./kg/bw	Non-toxic	2559846
Mammals					
Rat	Acute	cyfluthrin	LD_{50} = 16.2 mg a.i. /kgbw	Highly toxic	2559846
			590 mg a.i./kgbw (♂); 1189 (♀)mg/kgbw (PEG 400)	Slightly toxic	2429210 (HED Review)
	Multi-generational Reproduction	cyfluthrin	NOEC **Parent** 48.5 mg a.i./kg bw/day (♀) **Reproductive** 12.3/15.1 mg a.i./kg bw/day		
			NOEC **Parent** 3 mg a.i./kg bw/day (♂); 10 mg/kg bw/day (♀) **Reproductive** 33 mg a.i.//kg bw/day **Offspring** 4 mg a.i.//kg bw/day		
Freshwater species					
Daphnia magna	48h-Acute static	cyfluthrin	LC_{50} = 0.025 µg a.i.//L NOEC=0.016 µg a.i./i/L	Very highly toxic	1183302
			LC_{50} = 0.14 µg a.i.//L NOEC=0. 01 µg a.i.//L		
			LC_{50} = 0.16 µg a.i.//L NOEC=0.028 µg a.i.//L		
			LC_{50} = 2.7 µg a.i.//L NOEC=0.1 µg a.i.//L		
Rainbow trout	96h-Acute static	cyfluthrin	LC_{50} = 0.68 µg a.i./i/L NOEC=0.25µg a.i.//L	Very highly toxic	1183400 1215532 1207844 1183303
			LC_{50} = 2.9 µg a.i.//L NOEC=2.2 µg a.i.//L		
			LC_{50} = 0.47 µg a.i.//L[1] NOEC=0.09 µg a.i.//L[1]		
		DVCA	LC_{50} = >14700 µg a.i.//L NOEC=14700 µg a.i.//L	Slightly toxic	

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Bluegill sunfish	96h-Acute	cyfluthrin	LC_{50} =1.5 µg a.i.//L NOEC=0.2 µg a.i.//L	Very highly toxic	
			LC_{50} = 0.10 µg a.i.//L NOEC=0.51 µg a.i.//L		

a Atkins et al. (1981) for bees and USEPA classification for others, where applicable

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

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Cyfluthrin Endpoints
Toxic or toxic equivalent according to the *Canadian Environmental Protection Act*[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	DT_{50} of 53.1 and 58.6 days
	Water	Half-life ≥ 182 days	DT_{50} < 1 day
	Sediment	Half-life ≥ 365 days	0.22 to 3.5 days
	Air	Half-life ≥ 2 days or evidence of long range transport	Volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (2.1×10^{-9} mmHg at 20°C). Cyfluthrin may volatilise from water and moist surfaces based on the Henry's Law Constant 5.17 $x10^{-7}$ atm m^3/mole (20°C)
Bioaccumulation[4]	Log $K_{OW} \geq 5$		Log K_{OW} = 5.97
	BCF ≥ 5000		Could not be determined, study not reliable.
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

[1]All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (that is, all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) then the criterion for persistence is considered to be met.
[4]Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).
NA= not available

Appendix XI Label Amendments for End-Use Products Containing Cyfluthrin

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 following label statements.

I) TECHNICAL GRADE ACTIVE INGREDIENTS

The following must be placed on the label under the section entitled **Toxicological Information:**

> "Skin exposure may cause transient sensations (tingling, burning, itching, numbness). Other symptoms of exposure could include respiratory effects (such as cough, sore throat, or shortness of breath), nausea, dizziness. Treat symptomatically."

II) DOMESTIC-CLASS PRODUCTS

Cancellation of all domestic-class products is being proposed

III) COMMERCIAL-CLASS PRODUCTS

For all commercial-class products, the following statements are proposed to be added under **ENVIRONMENTAL PRECAUTIONS**:

"TOXIC to aquatic organisms."

"TOXIC to small mammals"

For pour-on insecticides such as Cylence Pour-On Insecticide (Registration No. 25674)

The following must be placed on the label under the section entitled **Toxicological Information**:

> "Skin exposure may cause transient sensations (tingling, burning, itching, numbness)."

Cover Page:

Remove: "For Control of Horn Flies, Chewing Lice and Sucking Lice on Beef and Dairy (including lactating) Cattle"

Replace with: "For Control of Horn Flies, Chewing Lice and Sucking Lice on Beef and **Non-Lactating** Dairy Cattle"

DIRECTIONS:

Remove: "For control of Horn Flies, Chewing Lice and Sucking Lice on Beef and Dairy (including lactating) Cattle."

Replace with: "For control of Horn Flies, Chewing Lice and Sucking Lice on Beef and **Non-Lactating** Dairy Cattle"

PRECAUTIONS:

Add: "DO NOT USE ON LACTATING DAIRY CATTLE."

For Cattle ear tags such as Cylent Gold Insecticide Cattle Ear Tag (Registration No. 26880)

The following must be placed on the label under the section entitled **Toxicological Information**:

"Skin exposure may cause transient sensations (tingling, burning, itching, numbness)**.**"

Cover Page:

Remove: "FOR USE ON BEEF AND DAIRY CATTLE (INCLUDING LACTATING) TO CONTROL HORN FLIES"

Replace with: "FOR USE ON BEEF AND **NON-LACTATING** DAIRY CATTLE TO CONTROL HORN FLIES"

DIRECTIONS FOR USE:

Remove: "For the control of Horn Flies on Beef and Dairy Cattle (including lactating)."

Replace with: "For the control of Horn Flies on Beef and **Non-Lactating** Dairy Cattle"

PRECAUTIONS:

Add: "DO NOT USE ON LACTATING DAIRY CATTLE."

POUCH LABEL:

Remove: "FOR USE ON BEEF AND DAIRY CATTLE (INCLUDING LACTATING) TO CONTROL HORN FLIES"

Replace with: "FOR USE ON BEEF AND **NON-LACTATING** DAIRY CATTLE TO CONTROL HORN FLIES"

PRECAUTIONS:

Add: "DO NOT USE ON LACTATING DAIRY CATTLE."

For products used for structural pest control such as Tempo 20 WP Insecticide (Registration No. 25673)

The following must be placed on the label under the section entitled **Toxicological Information**:

"Skin exposure may cause transient sensations (tingling, burning, itching, numbness). Other symptoms of exposure could include respiratory effects (such as cough, sore throat, or shortness of breath), nausea, dizziness. Treat symptomatically."

Remove the livestock housing (including poultry houses) uses from the commercial label.

Apply to register a separate AGRICULTURAL label for the livestock housing (including poultry houses) uses.

Restricted-Entry Intervals:

Add: "The re-entry interval is 8 hours after application for the livestock housing (including poultry houses)."

Include the Information Sheet for Occupants of areas treated with the product (see Appendix XII for an example).

For clarity, reorganize the commercial label by creating two distinct sections:

i) RESIDENTIAL AREAS

ii) COMMERCIAL AREAS

See example, including proposed label amendments, below.

i) RESIDENTIAL AREAS

Add: "Residential areas are defined as any use site where bystanders including children could be exposed during or after application. This includes homes, schools, public buildings or any other areas where the general public including children could be exposed."

Add: "Residential areas include, but are not limited to:
- Public areas of hotels and motels.
- Nursing homes and hospitals.
- Schools.
- Public areas of stores.
- Seating areas of aircraft, buses, railcars, ships and trucks.
- Public areas of restaurants."

PESTS CONTROLLED BY Tempo 20 WP Insecticide

Remove: "Bedbug"

DIRECTIONS FOR USE:

Add: "In residential areas, apply as a crack and crevice/void treatment only for all pests."

Add: "Crack and crevice application is defined as an application of pesticides with the use of a pin stream nozzle, into cracks and crevices in which pests hide or through which they may enter a building. It does not permit the treatment of surfaces. Such openings commonly occur at

expansion joints, between different elements of construction, and between equipment and floors. These openings may lead to voids such as hallow walls, equipment legs and bases, conduits, motor housings, and junction or switch boxes."

Add: "For crack and crevice, the product must only be applied using a low-pressure system (do not exceed 345 kPa (50 psi) at nozzle tip) with a pin-point or variable pattern nozzle."

Add: "Do not apply as a broadcast, band or spot treatments."

Add: "Do not apply on the same day as other beta-cyfluthrin or cyfluthrin products."

Add: "Do not apply any product containing beta-cyfluthrin or cyfluthrin more than once every 10 days."

For control of carpenter ants in houses and other structures:

Remove: "Do not exceed 30 to 50 mL of dilute suspension per m^2 of treated surface."
Replace with: "Do not exceed 30 mL of dilute suspension per m^2 of treated surface."

PRECAUTIONS:

Add: "Applicators, workers and residents must not enter the treated areas or rooms until 8 hours after application."

Remove: "Wear a NIOSH-approved respirator when mixing loading and applying Tempo 20 WP Insecticide."

Replace with: "Wear a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides when mixing loading and applying Tempo 20 WP Insecticide."

Remove: "Wear long pants and chemical-resistant gloves when handling the product".

Replace with: "Wear long-sleeved shirt, long pants, chemical resistant gloves and shoes plus socks during mixing, loading and application."

Remove: "Ventilate treated areas."

Replace with: **"**Ventilate treated areas 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."

Add: "If you experience respiratory effects (such as cough, sore throat, or shortness of breath), nausea, dizziness, or eye irritation upon re-entering areas treated with Tempo 20 WP Insecticide, ventilate the area more and vacate the premises."

Add: "If you continue to experience effects after additional ventilation, contact your health care professional."

Add: "**Information Sheet for Occupants must be posted at entry points to treated indoor areas by applicator"**

ii) COMMERCIAL AREAS:

Add: "Commercial areas are locations where children are not present at any time (for example, office buildings, adult-only shelters, food processing plants)."

Use Directions:

Add: "Apply as indoor band, spot and/or crack and crevice/void applications only for all pests, including bedbugs."

Add: "Do not apply as a broadcast treatment."

Add: "Do not apply on the same day as other beta-cyfluthrin or cyfluthrin products."

Add: "Do not apply any product containing beta-cyfluthrin or cyfluthrin more than once every 10 days."

For control of carpenter ants in houses and other structures:

Remove: "Do not exceed 30 to 50 mL of dilute suspension per m^2 of treated surface."

Replace with: "Do not exceed 30 mL of dilute suspension per m^2 of treated surface."

Add: "**Label instructions for mattresses for control of bedbugs:"**

Add: "Do not make general surface sprays (the entire surface area) or spot treatment on furniture or upholstery. Apply to the tufts and seams only."

Add: "For infested mattresses, remove linens. Apply only to tufts, seams, folds, and edges of the mattress until moist using a pin stream nozzle. Do not treat bed linens or pillows. Allow treated area to dry before replacing clean linens on treated mattress."

Add: "Apply using a pin stream nozzle to the cracks and joints of bedsprings and bedframes and the tufts and seams of box springs. If bed bugs are found in upholstery, apply only to the infested tufts, seams, folds and edges."

PRECAUTIONS:

Add: "Applicators, workers and others must not enter the treated areas or rooms until 8 hours after application."

Remove: "Wear a NIOSH-approved respirator when mixing loading and applying Tempo 20 WP Insecticide."

Replace with: "Wear a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides when mixing loading and applying Tempo 20 WP Insecticide."

Remove: "Wear long pants and chemical-resistant gloves when handling the product".

Replace with: "Wear long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks during mixing, loading and application."

Remove:	"Ventilate treated areas."
Replace with:	"Ventilate treated areas 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."
Add:	"If you experience respiratory effects (such as cough, sore throat, or shortness of breath), nausea, dizziness, or eye irritation upon re-entering areas treated with Tempo 20 WP Insecticide, ventilate the area more and vacate the premises"
Add:	"If you continue to experience effects after additional ventilation, contact your health care professional."
Add:	"**Information Sheet for Occupants must be posted at entry points to treated indoor areas by applicator"**

Appendix XII Proposed Information Sheet for areas treated with Tempo 20 WP Insecticide (Reg. No. 25673).

Information Sheet for Occupants of areas treated with Tempo 20 WP Insecticide.

To be posted at points of entry.

This area has been treated with Tempo 20 WP Insecticide (Reg. No. 25673), containing the active ingredient cyfluthrin.

DATE APPLIED:

TIME APPLIED:

- Bystanders and animals must not be present during application.
- Do not re-enter the treated area until at least 8 hours after the product has been applied.
- Ventilate the area after treatment (for example, open your doors and windows for a few hours).

The following adverse effects have been reported following re-entry into areas treated with products containing cyfluthrin:

- respiratory effects such as cough, sore throat, or shortness of breath
- nausea
- dizziness
- eye irritation

If you experience effects, leave the area and ventilate further. If the effects do not resolve rapidly or become worrisome, contact your health care professional.

For more information, contact

BAYER CROPSCIENCE INC.
Suite 200, 160 Quarry Park Blvd. S.E.
Calgary, Alberta T2C 3G3
Telephone: 1 888 283- 6847

References

A. Studies Considered in the Chemistry Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1774240	1984, Samples, Specifications and Analytical Methodology, DACO:2.99.
1774244	1988, Samples, Specifications and Analytical Methodology for Technical, DACO: 2.99
1609634	2004, Product Chemistry, DACO:2.0, 2.11.2, 2.11.3, 2.11.4, 2.12.1, 2.12.2, 2.13.1, 2.13.3, 2.2,2.3, 2.4, 2.5, 2.6 ,2.7,2.8.
1609636	2008, Product Chemistry DACO:2.0, 2.11.2, 2.11.3, 2.11.4, 2.12.1, 2.12.2, 2.13.1, 2.13.3, 2.2,2.3, 2.4,2.5, 2.6,2.7, 2.8
1792491	2006, Material Accountability of Cyfluthrin, DACO:2.13.1, 2.13.3

B. Studies Considered in the Toxicological Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1124945	Comparative Tests For Acute Toxicity With Various Formulation Aids. DACO: 4.2.9
1124950	Sister Chromatid Exchange Assay In Chinese Hamster Ovary (Cho) Cells. DACO: 4.5.4
1130065	Fcr 1272 Cyfluthrin: Multigeneration Study On Rats (85881), DACO: 4.1,4.5.1
1130066	Fcr 1272 Cyfluthrin: Chronic Toxicity Study On Rats (2-Year Feeding Experiment). DACO: 4.4.1
1183308	Baythroid Pyrethroid Insecticide Supplement To Toxicology, Neurotoxicity Studies, Fcr 1272, Special Toxicological Study (Morphological Effects On The Nervous System Of Rats). DACO: 4.5.10
1207821	Study For Subchronic Inhalative Toxicity To The Rat For 13 Weeks. DACO: 4.7
1207823	Sister Chromatid Exchange Assay In Chinese Hamster Ovary Cells. DACO: 4.5.4
1207824	Cho/Hgprt Mutation Assay In The Presence And Absence Of Exogenous Metabolic Activation. DACO: 4.5.4
1207827	Unscheduled DNA Synthesis In Rat Primary Hepatocytes. DACO: 4.5.4
1207832	Study For Neurotoxic Effect On Rats After Subacute Oral Administration. DACO: 4.5.10
1207833	Study For Fcr 1272 On Neuromuscular Dysfunction In The Tilting Plane Test On Rats. DACO: 5.1
1215480	Biokinetic Part Of The General Metabolism Studies In The Rat. DACO: 4.5.9,6.4
1215483	Metabolism Studies In The Rat. DACO:: 4.5.9,6.4
1215505	An Analytical Residue Method For Baythroid And Its Major Metabolites In Soil, Multigeneration Study On Rats. DACO: 4.5.1
1215545	Acute Toxicity To Dogs. DACO: 4.2.1

PMRA Document Number	Reference
1215546	Chronic Toxicity Study On Rats. DACO: 4.4.1
1216036	Chronic Toxicological Study On Mice (Feeding Study Over 23 Months). DACO: 4.4.1
1216127	Chronic Toxicity Study On Rats (Cont'd From 571). DACO: 4.4.1
1216128	Test For Sensitizing Effect On Guinea Pigs. DACO: 4.2.6
1216132	Comparative Study Of Rats On Absorption After Single Oral Administration. DACO: 0
1216133	Comparative Tests For Acute Toxicity With Various Formulation Aids. DACO: 4.2.1
1216139	Subacute Oral Toxicity Study On Rats. DACO: 4.3.1
1216140	Subchronic Toxicity Study On Rats (3 Month Feeding Experiment). DACO: 4.3.1
1216141	Short Term Toxicity Tests On Rats (4 Week Feeding And 4 Week Recovery Tests). DACO: 4.3.1
1216142	Short Term Toxicity Tests On Mice (4 Week Feeding And 4 Week Recovery Tests). DACO: 4.3.1
1216143	Subacute Dermal Toxicity Study On Rabbits. DACO: 4.3.4
1216144	Subacute Inhalation Toxicity Study On Rats. DACO: 4.3.6
1216145	Study For Nerve Damage Effect On The Rat After 5 Months Oral Application. DACO: 4.3.8
1216146	Chronic Toxicity Study On Dogs (6 Month Feeding Experiment). DACO: 4.4.1
1216147	Chronic Toxicity To Dogs On Oral Administration (12 Month Feeding Study). DACO: 4.4.1
1216148	Multigeneration Study On Rats. DACO: 4.5.1
1216150	Evaluation For Embryotxic And Teratogenic Effects On Orally Dosed Rats. DACO: 4.5.2
1216152	Salmonella/Microsome Test For Detection Of Point-Mutagenic Effects. DACO: 4.5.4
1216153	Micronucleus Test On Mouse To Evaluate For Mutagenic Potential. DACO: 4.5.4
1216154	Dominant Lethal Test On Male Mouse To Evaluate For Mutagenic Potential. DACO:: 4.5.4
1216155	Pol A1 Test On E. Coli To Evaluate Effects For Dna Dammage. DACO: 4.5.4
1216156	Mutagenicity Test On Bacterial System. DACO: 4.5.4
1216157	Microbial Mutagenicity Study. DACO: 4.5.4
1216158	Mutagenicity Evaluation In The Reverse Mutation Induction Assay. DACO: 4.5.4
1216159	Evaluation Of The Induced Mitotic Crossing Over, Reverse Mutation And Gene Conversion Assay. DACO: 4.5.4
1216160	Acute Toxicity Studies. DACO: 4.2.1
1216161	Neurotoxic Study On Hens. DACO: 4.5.10
1216165	Study For Acute Inhalation Toxicity. DACO: 4.2.3
1216167	Acute Toxicity - Eye Irritation And Skin Irritation. DACO: 4.2.4,4.2.5
1216168	Intracutaneous Sensitization Test On Guinea Pigs. DACO: 4.2.6
1227049	Test For Eye Irritants. DACO: 4.2.4
1227053	Study For Nerve Damage Effect On The Rat After 5-Months Oral Application. DACO: 4.5.11
1227054	Eye Irritation Study On Rabbits. DACO:: 4.2.4

PMRA Document Number	Reference
1227056	Study For Neurotoxic Effect On Rats After Subacute Oral Administration. DACO: 4.5.11
1227058	Study Of The Subchronic Inhalation Toxicity In Accordance With OECD Guidline No.413. DACO: 4.3.6
1227059	Study Of The Acute Inhalation Toxicity To Rats Using OECD Guideline No.403. DACO: 4.2.3
2072873	1987, FCR 4545 technical - Study of the acute oral toxicity to rats (formulation in Acetone/Peanut Oil). DACO: 4.2.1
2072874	1987, FCR 4545 technical - Study of the acute oral toxicity to rats (formulation in Polyethylene Glycol E 400). DACO: 4.2.1
2072878	1987, FCR 4545 technical - Study of the acute oral toxicity to rats (formulation in Xylene). DACO: 4.2.1
2072879	1987, FCR 4545 technical. - Study of the acute oral toxicity to mice (formulation in polyethylene glycol E 400). DACO: 4.2.1
2072881	1986, FCR 3191 = THS 2997 - Study for acute oral toxicity in rats. DACO:: 4.2.1
2072884	1987, FCR 4545 technical - Study of the acute dermal toxicity to rats (formulation in polyethylene glycol E 400). DACO: 4.2.2
2072894	1985, FCR 4545 (techn.), Study for irritant/corrosive effect on skin and eye (rabbit). DACO: 4.2.4,4.2.5
2072897	1995, FCR 4545 Study for the skin sensitization effect in guinea pigs (maximization test of Magnusson and Kligman). DACO: 4.2.6
2072909	1994, FCR 4545 - Subchronic toxicological study on rats (administration with feed for 13 weeks). DACO: 4.3.1
2072914	1987, FCR 4545 - Study of subchronic oral toxicity to dogs (13-week feeding study). DACO: 4.3.2
2072915	1985, FCR 4545 - Range-Finding test for acute toxicity to the dog. DACO: 4.3.2
2072916	1986, FCR 4545 - Range-finding toxicological study to establish dosage for a subchronic study of toxitcity to beagle dogs. DACO: 4.3.2
2072918	1988, FCR 4545 techn. Subacute study of oral toxicity to rats. DACO: 4.3.3
2072927	1989, FCR 4545 (c.n.: Betacyfluthrin, proposed) Subacute inhalation toxicity study in the rat according to OECD guideline no. 412. DACO: 4.3.7
2072928	1988, FCR 4545 (common name: Cyfluthrin K+L, suggested) Study of the range-finding subacute inhalation toxicity to rats in accordance with OECD guideline no. 403. DACO: 4.3.7
2072957	1997, An acute oral neurotoxicity screening study with technical grade FCR 4545 in Fischer 344 rats. DACO: 4.5.12
2072963	1997, A subchronic dietary neurotoxicity screening study with technical grade FCR 4545 (Beta-Cyfluthrin) in Fischer 344 rats. DACO: 4.5.13
2072967	2003, A developmental neurotoxicity screening study with technical grade beta-cyfluthrin in Wistar rats. DACO: 4.5.14
2072980	1986, FCR 4545 - Salmonella/Microsome test for point-mutagenig effect. DACO: 4.5.4
2072983	1988, FCR 4545 (C.N. cyfluthrine K+L (proposed)) - Mutagenicity study for the detection of induced forward mutations in the CHO-HGPRT assay in vitro. DACO: 4.5.5

PMRA Document Number	Reference
2072985	1987, Mutagenicity test on FCR 4545 technical in the rat primary hepatocyte unscheduled DNA synthesis assay. DACO: 4.5.6
2072989	1988, FCR 4545 In vitro cytogenetic study with human lymphocytes for the detection of induced clastogenic effects. DACO: 4.5.6
2072992	1988, FCR 4545 Micronucleus test on the mouse to evaluate for clastogenic effects. DACO:: 4.5.7
2272340	2011, Assessment of Pubertal Development and Thyroid Function in Juvenile/Peripubertal Male and Female Rats. DACO: 4.8

Additional Information Considered

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PMRA Document Number	Reference
2007551	Kim, Kyu-Bong et al, 2009, Age, Dose, and Time-Dependency of Plasma and Tissue Distribution of Deltamethrin in Immature Rats - Toxicological Sciences, Volume 115, Number 2, Pages 354 to 368, DACO: 4.5.9
2358830	Bhushan, Brijender, Prabhu N. Saxena, and Nishi Saxena, 2013, Biochemical and Histological Changes in Rat Liver Caused by Cypermethrin and Beta-Cyflutherin - Archives of Industrial Hygiene and Toxicology, Volume 64, Pages 57 to 67, DACO: 4.8
2359598	Grosman, Nina, and Friedhelm Diel, 2004, Influence of Pyrethroids and Piperonyl Butoxide on the Ca2+-ATPase Activity of Rat Brain Synaptosomes and Leukocyte Membranes - International Immunopharmacology, Volume 5, Pages 263 to 270, DACO: 4.8
2359599	Mense, Sarah M. et al, 2006, The Common Insecticides Cyfluthrin and Chlorpyrifos Alter the Expression of a Subset of Genes with Diverse Functions in Primary Human Astrocytes - Toxicological Sciences, Volume 93, Number 1, Pages 125 to 135, DACO: 4.8
2394767	2010, Cyfluthrins Summary Document Registration Review: Initial Docket September, 2010, DACO: 4.8
2396904	2001, Data Evaluation Record: Supplement to DER for MRID No.: 42675401 Cyflutherin: [Developmental Toxicology Study in the Rabbit], DACO: 4.5.3
2428089	Weiner, Myra L. et al, 2009, Comparative functional observational battery study of twelve commercial pyrethroid insecticides in male rats following acute oral exposure - NeuroToxicology Volume 30S, Pages S1 to S16, DACO: 4.8
2428095	Scollon, Edward J. et al, 2008, In Vitro Metabolism of Pyrethroid Pesticides by Rat and Human Hepatic Microsomes and Cytochrome P450 Isoforms - Drug Metabolism and Disposition, Volume 37, Number 1, Pages 221 to 228, DACO: 4.8
2429021	Wolansky, M.J., 2007, Neurobehavioral toxicology of pyrethroid insecticides in adult animals: A critical review - Neurotoxicology and Teratology, Volume 30, Pages 55 to 78, DACO:: 4.8

PMRA Document Number	Reference
2429023	United States Environmental Protection Agency, 1993, Beta-Cyflutherin: Requested Review of Data Package, DACO: 12.5
2429024	Leng, G et al, 1997, Human dose-excretion studies with the pyrethroid insecticide cyfluthrin : urinary metabolite profile following inhalation (Abstract) - Xenobiotica, Volume 27, Number 12, Pages 1273 to 1283, DACO: 4.8

C. Information Considered in the Dietary Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1033642	1989. Residue Chemistry of Cutter Gold Insecticide Cattle Ear Tag. Magnitude of the Residue: Meat and Milk.
1033646	Part 6 Metabolism/Toxicokinetic Studies Cutter Gold Insecticide Ear Tag. Metabolism/Toxicokinetics Studies, Summaries, Livestock and Plants.
1033647	Part 7 Food, Feed and Tobacco Residue Studies: Cutter Gold Insecticide Ear Tag. Summaries, Residue Trial Analytical Methodology, and Crop Residue Data.
1156548	1986. A Gas Chromatographic Method for Cyflurthirn Residue in Various Foods and Processed Food Products,
1156549	1986. Recovery of Tempo from Food or Food Products,
1156551	1986. Cyflurthrin Residue in Foods or Food Products Following Application of Tempo 2 in A Simulated Food Handling,
1156552	1986. Residue of Tempo in Food or Food Products,
1166118	Summaries - Metabolism (Cylene Pour-On Insecticide),
1166119	1993. Predicting the Metabolic fate of Cyfluthrin Following Dermal Application to Cattle,
1166121	Summaries - Food, Feed and Tobacco Residue Studies (Cylence Pour-On Insecticide),
1166123	1990. Cyfluthrin - Magnitude of The Residue Dermal Application to Lactating Dairy Cattle,
1166124	Cyfluthrin - Magnitude of the Residue Dermal Application to Beef Cattle (Cylence Pour-On Insecticide),
1174616	1993. Residue Levels of Cyfluthrin in Tissues Resulting from Treatment of Swine Premises with Cyfluthrin Premise Spray; Analytical Part,
1174618	1991. Validation of an Analytical Residue Method for Determining Levels of Cyfluthrin in Swine Tissue.
1174619	1991. Validation of an Analytical Residue Method for Determining Levels of Cyfluthrin in Chicken Tissue.
1174620	1993. Residue Levels of Cyfluthrin in Chicken Tissues and Eggs Resulting from Premise Treatment of Laying Hen House Facilities; Analytical Portion.
1174621	1993 Residue Levels of Cyfluthrin in Tissues Resulting from Treatment of Swine Premises with Cyfluthrin Premise Spray; Animal Part.

PMRA Document Number	Reference
1174622	1993. Residue Levels of Cyfluthrin in Chicken Tissues and Eggs Resulting from Premise Treatment of Laying Hen House Facilities; Animal Part
1212488	In Bovine and Poultry Tissues, Milk and Eggs,
1212490	Milk Residues - Cattle,
1212491	1986. Tissue Residues – Cattle,
1215475	Residues of Baythroid in Canola,
1215477	Synopsis of Baythroid Residue Chemistry on Cereal Crops
1215478	Summary Tables, Apparent Baythroid Residues in Barley,
1215479	1983. Metabolism of Baythroid in Cotton and Soybeans,
1215518	
1215480	1983. Biokinetic Part of The General Metabolism Studies in the Rat,
1215481	1983. Metabolism of Baythroid in a Dairy Cow,
1215482	1983. The Distribution and Metabolism of Baythroid in Laying Hens,
1215483	1983. Metabolism Studies in The Rat,
1215484	Recovery of Baythroid from Wheat and Barley,
1215486	A Gas Chromatographic Method for Baythroid Residues in Crops (85823),
1215487	1983. The Effect of Frozen Storage at 0 deg. F to -10 deg. F on Baythroid in
1215547	Cotton and Soybeans,
1215488	Residues of Baythroid in Barley.
1215489	Residues of Baythroid in Wheat,
1215490	1983. A 28-Day Baythroid Bovine Feeding Study,
1215491	1983. A 28-Day Baythroid Poultry Feeding Study,
1215493	1984. Synopsis of Baythroid Residue Chemistry on Alfalfa,
1215494	Summary Tables, Apparent Baythroid Residues in Alfalfa Controls.
1215495	Recovery of Baythroid from Green Forage and Hay,
1215496	Synopsis of Baythroid Residue Chemistry on Canola (Rapeseed),
1215497	A Gas Chromatographic Method for Baythroid Residues in Crops,
1215498	An Interference Study for the Baythroid Residue Method for Cotton, Peanuts and
1215548	Soybeans,
1215499	Residues of Baythroid in Alfalfa,
1215507	Summary Tables, Apparent Baythroid Residues in Canola Controls.
1215525	1983. Radioactive Residues of Baythroid in Rotational Crops.
1215529	Recovery of Baythroid from Cotton,
1215540	A Gas Chromatograph Method for Baythroid Residues in Crops,
2072999	Tier II summary document,
2073001	1984. Baythroid Metabolites in Chicken Tissues (Muscle, Fat, Skin, Liver and Gizzard).
2073002	1993. Distribution of Radioactive Residue in Milk following Oral Dosing of a Dairy Cow for 5 Consecutive Days with [Phenoxy-UL-14C] Cyfluthrin,
2073004	1983. Metabolism of BAYTHROID in a Dairy Cow,
2073006	2000. [Nitroimino-14C]TI-435 Sugarbeet Metabolism Seed Treatment,
2073007	1983. Metabolism of Baythroid TM in cotton
2073008	1983. Metabolism of Baythroid TM in potatoes
2073009	1983. Metabolism of Baythroid TM of soybeans
2073010	1985. Metabolism of (14C) R Baythroid in apples

PMRA Document Number	Reference
2073011	1985. Metabolism of Baythroid in wheat
2073012	1986. Studies on metabolism of cyfluthrin (FCR 1272) in tomatoes
2073213	2004. Substitution of cyfluthrin by beta-cyfluthrin in products for food-use,
2073435	1983. A gas chromatographic method for Baythroid residue in crops
2073436	1983. A gas chromatographic method for the determination of Baythroid FPB metabolite residues in crops
2073437	2002. A modified analytical method for the determination of cyfluthrin residues in various plant matrices by chemical ionization - GC/MS
2073438	1988. Baythroid - Gas chromatographic interference study plant and animal tissue methods
2073439	1984. An interference study for total residues of Baythroid in animal tissues and products,
2073440	1983. An Analytical Method for BAYTHROID in Bovine and Poultry Tissues, Milk and Eggs,
2073441	1983. An analytical method for Baythroid in bovine and poultry tissues, milk and eggs; Additional recovery reports,
2073442	1998. An analytical method for determination of Cyfluthrin and Beta-Cyfluthrin residues in various crops,
2073442	1998. An analytical method for determination of Cyfluthrin and Beta-Cyfluthrin residues in various crops
2073443	2002. Independent laboratory validation of DFG method S19 (extended revision) for the determination of residues of cyfluthrin in materials of animal origin,
2073444	1998. Independent laboratory validation for the determination of residues of cyfluthrin in com grain,
2073445	1987. Baythroid, Multiresidue Method Trial.
2073447	1995. Freezer storage stability of cyfluthrin in corn green forage, head lettuce, and wheat green forage
2073448	1989. Freezer storage stability of cyfluthrin in apples, cotton, potatoes and soybeans
2073449	1989. Freezer storage stability of cyfluthrin in hops
2073450	1988. Baythroid - Storage stability of residues in various frozen crops
2073451	1996. Addendum 3 - Storage stability of cyfluthrin in crops and processed products
2073452	1994. Storage stability of cyfluthrin in crops and processed products
2073453	1994. Storage stability of cyfluthrin in crops and processed products
2073454	1985. Baythroid freezer storage stability on soybeans
2073455	1992. Storage stability of cyfluthrin in crops and processing fractions
2073458	1988. Baythroid - Magnitude of the residue on sunflowers
2073459	1997. Baythroid 2 EC/125 SC - Magnitude of the residue in field treated cotton
2073460	1999. Cyfluthrin: Magnitude of the residue on dry pea
2073461	2002. Baythroid 20 WP and Baythroid 2 - Magnitude of the residue in apples and pears (crop group 11 - pome fruit)
2073462	2000. Cyfluthrin: Magnitude of the residue on pea (Southern)
2073463	1992. Cyfluthrin: Recoveries from green (fresh) and dried hops
2073466	2009. Proposed maximum residue levels for Baythroid XL in/on soybeans after foliar applications

PMRA Document Number	Reference
2073467	1992. Cyfluthrin: Magnitude of residue on hops
2073468	1999. Baythroid - Magnitude of the residue on sugarcane
2073469	1999. Baythroid 2 - Magnitude of the residue in lettuce
2073471	1988. Baythroid - Magnitude of residues on spinach
2073472	1989. Baythroid - Magnitude of the residue on hops
2073473	1988. Baythroid - Magnitude of the residue on sorghum
2073474	1999. Baythroid 2 - Magnitude of the residue in head and stem brassica (broccoli / cabbage - crop subgroup 5A)
2073477	2001. Baythroid 20 WP and Baythroid 2 EC - Magnitude of the residue in almonds and pecans (crop group 14 - tree nuts)
2073478	1988. Baythroid - Magnitude of the residues on lettuce
2073479	2002. Baythroid 2 EC and Baythroid 20 WP - Magnitude of the residue on mustard greens (crop subgroup 5B) - leafy brassica greens)
2073480	2002. Baythroid 2 EC and Baythroid 20 WP - Magnitude of the residue on broccoli and cabbage (crop subgroup 5A) - head and stem brassica)
2073481	2002. Baythroid 2 EC and Baythroid 20 WP - Magnitude of the residue in dried peas and dried beans (crop subgroup 6C - dried, shelled pea and bean - except soybean)
2073483	2002. Baythroid 2 EC and Baythroid 20 WP - Magnitude of the residue on peppers and tomatoes (bridging trials)
2073484	2002. Baythroid 20 WP and Baythroid 2 EC - Magnitude of the residue in celery and spinach and crop group 4
2073486	2002. Baythroid 2 EC and Baythroid 20 WP - Magnitude of the residue on cantaloupe, cucumber, and summer squash (crop group 9 - cucurbit vegetables)
2073487	2002. Baythroid 2 EC and Baythroid 20 WP - Magnitude of the residue on sweet and tart cherries, peaches, and plums (crop group 12 - stone fruits)
2073488	2002. Baythroid 2 - Magnitude of the residue in wheat
2073489	2002. Baythroid 2 EC and Baythroid 20 WP - Magnitude of the residue in potatoes (bridging trials)
2073490	2002. Baythroid 2 EC and Baythroid 20 WP - Magnitude of the residue in carrots and radishes (bridging trials)
2073491	2002. Baythroid 2 EC and Baythroid 20 WP - Magnitude of the residue on grapefruits, lemons, and oranges (crop group 10 - citrus fruits, bridging trials)
2073492	2002. Baythroid 2 EC and Baythroid 20 WP - Magnitude of the residue on grapes
2073494	2002. Baythroid 2 EC - Magnitude of the residues in/on peanuts
2073495	2001. Baythroid 20 WP and Baythroid 2 EC - Magnitude of the residue in leaf lettuce and head lettuce (bridging trials)
2073496	1999. Baythroid 2 - Magnitude of the residue in field corn
2073497	1988. Baythroid - Magnitude of the residue on radishes
2073498	1999. Baythroid 2 - Magnitude of the residue in mustard greens
2073499	2006. Baythroid 2 EC - Magnitude of the residue in/on grass
2073500	1988. Baythroid - Magnitude of the residue on carrots
2073501	1999. Baythroid - Magnitude of the residue on green peppers
2073502	1992. Cyfluthrin (2 EC) - Magnitude of the residue on soybean
2073503	1988. Baythroid - Magnitude of residue on celery

PMRA Document Number	Reference
2073504	1988. Baythroid - Magnitude of the residue on tomatoes
2073505	1999. Baythroid 2 EC - Magnitude of the residue in field-treated citrus
2073506	1994. Baythroid 2 EC - Magnitude of the residue on field treated pears
2073507	1988. Baythroid - Magnitude of the residue on potatoes
2073508	2002. Baythroid 2 - Magnitude of the residue in wheat grain, wheat aspirated grain fractions, and wheat processed commodities
2073509	1999. Baythroid - Magnitude of the residue on unprocessed whole corn and corn processed products
2073510	1992. Cyfluthrin (2EC) - Magnitude of the residue on field treated citrus/processed orange commodities
2073511	1990. Cyfluthrin (2 EC formulation) - Magnitude of the residue on sweet corn and sweet corn processed product
2073514	1989. Baythroid R - residues in field rotational Cereal crops - addendum no. 1,
2073515	1988. Baythroid R - residues in field rotational crops,
2073516	1992. Cyfluthrin (2EC) - Magnitude of the residue on processed soybean commodities
2073517	1988. Baythroid - Magnitude of the residue on soybean processed products
2073518	1988. Baythroid - Magnitude of the residue on sunflower processed products
2073519	1989. Baythroid - Magnitude of the residue on hops processed products
2073520	1991. Cyfluthrin (2EC formulation) - Magnitude of the residue on sorghum processed products
2073521	1990. Cyfluthrin (2 EC formulation) - Magnitude of the residue in potato processed products
2073522	2002. Baythroid 20 WP - Magnitude of the residue in apple processed commodities
2073523	2002. Baythroid 20 WP - Magnitude of the residue in grape processed commodities
2073524	2002. Baythroid 2 EC - Magnitude of the residue in peanut processed commodities
2073526	1992. Cyfluthrin (2 EC) - Magnitude of the residue on processed sunflower commodities
2073528	1988. Baythroid - Magnitude of the residue on tomato processed products
2073529	1995. Cyfluthrin (2EC formulation) - Magnitude of the residue in sugar cane processed products
2073530	2006. Clothianidin + cyfluthrin 600 SE - Magnitude of the residue in/on sugar beet processed commodities,
2073531	2009. Baythroid XL - Magnitude of the residue in/on soybean aspirated grain fractions and soybean processed commodities
2073532	1998. Baythroid 2 - Magnitude of the residue in aspirated grain fractions and corn processed commodities
2073535	1983. Revised 1984. A 28 Day BAYTHROID™ Poultry Feeding Study,
2073536	1994. Cyfluthrin – A 28-Day Dairy Cattle Feeding Study.
2073537	1983. Revised 1984. Baythroid™ 28 Day Bovine Feeding Study,
2073538	1983. The Effect of Frozen Storage at 0 to -10°F on Baythroid in Bovine Tissues and Milk.
2073539	1983. Recovery Report of Baythroid Metabolites from Chicken Tissues.

PMRA Document Number	Reference
2073540	1995. Potential for secondary residues of cyfluthrin in tissues, milk and eggs from animal fed livestock feed items from cyfluthrin-treated crops,
2073915	2002. A modified analytical method for the determination of cyfluthrin residues in various plant matrices by chemical ionization - GC/MS,
2073922	1996. Addendum 3 - Storage stability of cyfluthrin in crops and processed products
2073923	1994. Storage stability of cyfluthrin in crops and processed products
2073924	1994. Storage stability of cyfluthrin in crops and processed products
2073925	1992, Storage stability of cyfluthrin in crops and processing fractions
2146602	Assessment of the Non-Dietary Exposure to Tempo® 20 WP Insecticide
2240044	1998. Independent Laboratory Validation for the Determination of Residues of
2073444	Cyfluthrin in Corn,
2240046	2002. Enforcement method 00086/M045 for the Determination of Residues of Cyfluthrin in Materials of Animal Origin – Validation of DFG Method S19 (Extended Revision).
2240048	1984. Poultry Tissue/Eggs Effect of Frozen Storage at 0 To -10 Degrees Fahrenheit on Residues.
2240049	1983. The Effect of Frozen Storage at 0 to -10F on BAYTHROID in Poultry Tissues and Eggs.
2240050	1999. Determination of the Storage Stability of Cyfluthrin in Tissues of Cattle,
2240050	1999. Determination of the Stability of Cyfluthrin in Liver, Kidney, Musculature and Fat of Cattle during Frozen Storage at - 18 °C or below for 2 Months.

Published Information

PMRA Document Number	Reference
2073446	1998. Multi-residue method for analysis of pesticides in fruit and vegetables using ethyl acetate extraction, GPC clean-up and GC determination. Pages 9-41. Report no. 17/1998. Published Report by the National Food Administration, Sweden. DACO: 7.2.4

D. Information Considered in the Occupational and Non-Occupational Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2146601	User Safety Assessment – Bayofly Pour-on. DACO: 5.14, 5.2, 5.3
2146602	Assessment of the Non-Dietary Exposure to Tempo® 20 WP Insecticide. DACO: 5.14, 5.2, 5.3

PMRA Document Number	Reference
2146603	Observational Study to Determine Dermal and Inhalation Exposure to Pest Control Operator (PCO) Workers Applying Deltamethrin and/or β-Cyfluthrin Using Hand-held Equipment in a Crack and Crevice Application. DACO: 5.14, 5.2, 5.3
2073813	Assessment of the Non-Dietary Exposure to Temprid™ SC Insecticide. Exposure (Occupational and/or Bystander) Parts 5.1 through 5.8. DACO: 5.0
2292820	2001. Analysis of the National Pest Management Association Pest Control Operators (PCO) Product Use and Usage Information Survey. DACO: 5.2

Additional Information Considered

Published Information

PMRA Document Number	Reference
2409268	USEPA (2012). Standard Operating Procedures for Residential Pesticide Exposure Assessment. EPA: Washington, DC. Revised October 2012. USEPA, 1997. USEPA RED for propoxur. USEPA, 2011. Exposure Factors Handbook 2011 Edition (Final). US Environmental Protection Agency, Washington, DC, EPA/600/R-09/052F. Health Canada. 2010. Report on Human Biomonitoring of Environmental Chemicals in Canada. Results of the Canadian Health Measures Survey Cycle 1 (2007-2009). August 2010. Health Canada. 2013. Second Report on Human Biomonitoring of Environmental Chemicals in Canada. Results of the Canadian Health Measures Survey Cycle 2 (2009-2011). April 2013. Arbuckle TE, Fraser WD, Fisher M, Davis K, Liang CL, Lupien N, Bastien S, et al.. 2013. Cohort profile: the maternal-infant research on environmental chemicals research platform. Paediatr Perinat Epidemiol. 2013 Jul;27(4):415-25. doi: 10.1111/ppe.12061. Sobus, J.R., Morgan, M.K., Pleil, J.D., Barr, D.B. 2010. Chapter 45: Biomonitoring: Uses and Considerations for Assessing Nonoccupational Human Exposure to Pesticides. In: Hayes' Handbook of Pesticide Toxicology. 3rd Edition. Krieger, R. (editor). Elsevier Inc. ISBN: 978-0-12-374367-1 Hays, S.M., Aylward, L. L., Gagne, M., Krishnan, K. 2009. Derivation of Biomonitoring Equivalents for Cyfluthrin. Reg. Tox. Pharm. 55:268-275. Leng, G., Kuhn, K.H., Idel, H. 1997a. Biological Monitoring of Pyrethroids in Blood and Pyrethroid Metabolites in Urine: Applications and Limitations. Sci. Total. Environ. 199:173-181. Leng. G, Leng, A., Kuhn, K.H., Lewalter, J., Pauluhn, J. 1997b. Human Dose-Excretion Studies with the Pyrethroid Insecticide Cyfluthrin: Urinary Metabolite Profile Following Inhalation. Xenobiotica. 27 (12):1273-1283

PMRA Document Number	Reference
	Mage. D.T., Allen, R.H. Kodali, A. 2008. Creatinine Corrections for Estimating Children's and Adult's Pesticide Intake Doses in Equilbrium with Urinary Pesticide and Creatinine Concentrations. J. Exp. Sci. Env. Epi. 18: 360-368. Aylward, L.L., Krishnan, K., Kirman, C.R., Nong, A. Hays, S.M. 2011. Biomonitoring Equivalents for Deltamethrin. Reg. Tox. Pharmaco. 60:189-199.

Unpublished Information

USEPA Residential SOPs Task Force Information [Section 7: Indoor Environments]

PMRA Document Number	Reference
1414011 1160386	King, C.; Prince, P. (1995). Chlorothalonil Worker Exposure during Application of Daconil 2787 Flowable Funigicide in Greenhouses: Lab Project Number: 5968-94-0104-CR-001: 94-0104: SDS-2787. Unpublished study prepared by Ricerca, Inc. AHETF AH605. EPA MRID # 43623202
1560575	Merricks, D.L. (1997a). Carbaryl Mixer/Loader/Applicator Exposure Study during Application of RP-2 Liquid (21%), Sevin Ready to Use Insect Spray or Sevin 10 Dust to Home Garden Vegetables. ORETF OMA006. EPA MRID # 44459801
1826528	Selim, S. (2000a) Measurement of Transfer of Pyrethrin and Piperonyl Butoxide Residues from Vinyl Flooring Treated with a Fogger Formulation. Unpublished study prepared by Non-Dietary Exposure Task Force. (MRID 46188605). NDETF
1826520	Selim, S. (2000b) Post-Application Deposition Measurements for Pyrethrins and Piperonyl Butoxide Following Use of a Total Release Indoor Fogger. Unpublished study prepared by Non-Dietary Exposure Task Force. (MRID 46188602). NDETF
1826575	Selim, S. (2000c) Post Application Measurements for Deltamethrin Following Use of a Total Release Fogger. Unpublished study prepared by Non-Dietary Exposure Task Force. (MRID 46609901). NDETF
1826539	Selim, S. (2002a) Determination of Pyrethrin (PY) and Piperonyl Butoxide (PBO) Residue on the Hand from Treated Vinyl Flooring Sections Following Hand Press on Untreated Surfaces. Unpublished study prepared by Non-Dietary Exposure Task Force. (MRID 46188614). NDETF
1826546	Selim, S. (2002b) Determination of Pyrethrin (PY) and Piperonyl Butoxide (PBO) Residue on the Hand following Hand Press on Treated and Untreated Carpet. Unpublished study prepared by Non-Dietary Exposure Task Force. (MRID 46188620). NDETF
1826551	Selim, S. (2003a) Measurement of Transfer of Permethrin and Piperonyl Butoxide Residues from Vinyl and Carpet Flooring Treated with a Fogger Formulation Following a Single Hand Press. Unpublished study prepared by Non-Dietary Exposure Task Force. (MRID 46188625). NDETF

USEPA Residential SOPs Task Force Information [Section 7: Indoor Environments]

PMRA Document Number	Reference
1826554	Selim, S. (2003b) Determination of Permethrin (PER) and Piperonyl Butoxide (PBO) Residue on the Hand Following Hand Press on Treated and Untreated Vinyl and Carpet. Unpublished study prepared by Non-Dietary Exposure Task Force. (MRID 46188628). NDETF
1826549	Selim, S. (2003c) Post-Application Deposition Measurements For Permethrin and Piperonyl Butoxide Following Use of a Total Release Indoor Fogger. Unpublished study prepared by Non-Dietary Exposure Task Force. (MRID 46188623). NDETF
1826562	Selim, S. (2004) Measurement of Transfer of Deltamethrin Residues from Vinyl and Carpet flooring Treated with a Fogger Formulation Following a Single Hand Press. Unpublished study prepared by Non-Dietary Exposure Task Force. (MRID 46297602). NDETF

E. Information Considered in the Environmental Risk Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1168277	1983, Hydrolysis Of Baythroid In Sterile, Aqueous Buffered Solutions, DACO:8.2.3.2
1168279	1983, Decomposition Of Baythroid In Soil Under Aerobic And Anaerobic Conditions, DACO:8.2.3.4.2, 8.2.3.4.4
1215504	1983, Soil Thin-Layer Mobility Of Aged Extracts Of Soil Treated With Baytroid, DACO:8.2.4.1
1215522	1983, Hydrolysis Of Baythroid In Sterile, Aqueous Buffered Solutions, DACO:8.2.1
1215524	1982, Soil Thin-Layer Mobility Of Bay FCR 1272, Bay Sir 8514, And Bay Ssh 0860, DACO:8.2.4.1
1216369	1987, Adsorption Of Baythroid To Sandy Loam, DACO:8.2.1
2073018	1983, Hydrolysis Of Baythroid Tm In Sterile, Aqueous Buffered Solutions, DACO:8.2.3.2
1183302	1983, Acute Toxicity Of Technical Cyfluthrin (Baythroid) To *Daphnia Magna*, DACO:9.3.2
1183303	1983, Acute Toxicity Of Cyfluthrin Technical To Bluegill Sunfish, DACO:9.5.2.2
1183400	1983, Acute Toxicity Of Cyfluthrin Technical To Rainbow Trout, DACO:9.5.2.1
1207844	1984, Acute Toxicity Of Dichlorovinylcarboxylic Acid To Rainbow Trout, DACO: 9.5.2.1
1215515	1984, Bioconcentration Of Cyfluthrin By Bluegill Sunfish, DACO:9.5.5
1215532	1984, Acute Toxicity Of Cyfluthrin To Rainbow Trout, DACO:9.5.2.1

2558356 1985, Report On A Laboratory Investigation Into The Toxicity Of Cyfluthrin (Baytroid) To Honey Bees (*Apis Mellifera*), DACO:9.2.4.1

Additional Information Considered

Published Information

PMRA Document Number	Reference
2559846	USEPA, 2013, Risks Of Cyfluthrin And Beta-Cyfluthrin Use. Epa Assessment, DACO: 12.5.8
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