Proposed Registration Decision PRD2016-21

Beta-Cyfluthrin

(publié aussi en français)

16 September 2016

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2016-21E (print version)
H113-9/2016-21E-PDF (PDF version)

Table of Contents

Overview 1
Proposed Registration Decision for Beta-Cyfluthrin 1
What Does Health Canada Consider When Making a Registration Decision? 1
What Is Beta-cyfluthrin? 2
Health Considerations 2
Environmental Considerations 4
Value Considerations 4
Measures to Minimize Risk 5
Next Steps 6
Other Information 6
Science Evaluation 7
1.0 The Active Ingredient, Its Properties and Uses 7
1.1 Identity of the Active Ingredient 7
1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product 8
1.3 Directions for Use 10
1.4 Mode of Action 11
2.0 Methods of Analysis 11
2.1 Methods for Analysis of the Active Ingredient 11
2.2 Method for Formulation Analysis 11
2.3 Methods for Residue Analysis 11
3.0 Impact on Human and Animal Health 11
3.1 Toxicology Summary 11
3.1.1 *Pest Control Products Act* Hazard Characterization 17
3.2 Determination of Acute Reference Dose 18
3.3 Determination of Acceptable Daily Intake 18
3.4 Occupational and Residential Risk Assessment 19
3.4.1 Toxicological Endpoints 19
3.4.2 Occupational Exposure and Risk 20
3.4.3 Residential Exposure and Risk Assessment 21
3.5 Aggregate Risk Assessment 23
3.5.1 Toxicology Endpoints 23
3.5.2 Aggregate Exposure and Risk 24
3.6 Cumulative Assessment 24
4.0 Impact on the Environment 25
4.1 Fate and Behaviour in the Environment 25
4.2 Environmental Risk Characterization 25
5.0 Value 25
5.1 Consideration of Benefits 25
5.2 Effectiveness Against Pests 26
5.3 Non-Safety Adverse Effects 26
5.4 Supported Uses 26

6.0 Pest Control Product Policy Considerations 27
6.1 Toxic Substances Management Policy Considerations 27
6.2 Formulants and Contaminants of Health or Environmental Concern 27
7.0 Summary 28
7.1 Human Health and Safety 28
7.2 Environmental Risk 29
7.3 Value 29
8.0 Proposed Regulatory Decision 29
List of Abbreviations 31
Appendix I Tables and Figures 33
Table 1 Residue Analysis 33
Table 2 Toxicology Profile for Cyfluthrin and Beta-cyfluthrin Technical 33
Table 3 Toxicity Profile of Temprid SC Insecticide and Temprid ReadySpray Insecticide Containing Beta-cyfluthrin and Imidacloprid 51
Table 4 Summary of Risk Assessment Endpoints 53
Table 5 PCO Dermal and Inhalation Exposure to Beta-cyfluthrin 54
Table 6 Indoor Inhalation Exposure for Beta-cyfluthrin[1] 54
Table 7 Dermal Exposure to Beta-cyfluthrin from Treated Mattresses[1] 54
Table 8 Dermal Exposure from Hard and Soft Surfaces Treated with Beta-cyfluthrin[1] 55
Table 9 Child (1-2 years) Hand-to-Mouth Exposure to Beta-cyfluthrin 56
Table 10 Child (1 < 2 year) Object-to-Mouth Exposure to Beta-cyfluthrin 56
Table 11 Aggregate Exposure for Beta-cyfluthrin[1] 57
References 59

Overview

Proposed Registration Decision for Beta-Cyfluthrin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Beta-cyfluthrin Technical Insecticide and its end-use products, Temprid SC Insecticide and Temprid ReadySpray Insecticide containing the technical grade active ingredient beta-cyfluthrin. The end-use products are coformulated with the active ingredient, imidacloprid, to kill certain crawling and flying insects found indoors (including on mattresses) and outdoors on the exterior surfaces of structures.

Imidacloprid is an insecticide currently registered for a variety of uses, including against domestic pests such as ants and cockroaches. PMRA is proposing to grant registration for a new use of this insecticide in combination with beta-cyfluthrin.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Beta-cyfluthrin Technical Insecticide and its end-use products, Temprid SC Insecticide and Temprid ReadySpray Insecticide.

What Does Health Canada Consider When Making a Registration Decision?

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

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those

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

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

most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of the Health Canada website at healthcanada.gc.ca/pmra.

Before making a final registration decision on beta-cyfluthrin, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on beta-cyfluthrin, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

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

What Is Beta-cyfluthrin?

Beta-cyfluthrin is an insecticide used to kill insects, sowbugs and spiders. It is combined with another insecticide, imidacloprid, in two commercial class products, Temprid SC Insecticide and Temprid ReadySpray Insecticide. Both products may be used indoors and outdoors on the exterior surfaces of structures. The products may also be applied to sites such as mattresses to control bed bugs and for control of ants, certain beetles, cockroaches, crickets, earwigs, certain flies, firebrats, hornets, Indian meal moth larvae, mosquito adults, sowbugs, spiders, wasps and yellowjackets.

Health Considerations

Can Approved Uses of Beta-cyfluthrin Affect Human Health?

Products containing beta-cyfluthrin are unlikely to affect your health when used according to label directions.

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

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels

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

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

to which humans are normally exposed when pesticide products are used according to label directions. The human health hazard identification for beta-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. Cyfluthrin and beta-cyfluthrin 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 the hazard signal words “DANGER POISON” to appear on the labels of both chemicals.

The end-use product, Temprid SC Insecticide, was of slight acute toxicity via the oral route of exposure, and was of low acute toxicity via the dermal and inhalation routes. It was minimally irritating to the eyes, slightly irritating to the skin, and did not cause an allergic skin reaction.

Temprid ReadySpray Insecticide was of low acute toxicity via the oral and dermal routes of exposure and non-irritating to the eyes. It was considered to be of low acute toxicity by the inhalation route, slightly irritating to the skin and not likely to cause an allergic skin reaction.

Registrant-supplied short, and long term (lifetime) animal toxicity tests, as well as information from the published scientific literature were assessed for the potential of beta-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 bodyweight. There is some concern for increased sensitivity of the young exposed to beta-cyfluthrin. There was no evidence of carcinogenicity in mice after longer-term dosing with beta-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.

Risks in Residential and Other Non-Occupational Environments

Estimated risks from residential exposure are not of concern provided that directions specified on the label are followed.

The exposure assessments conducted for adults, youth and children when contacting indoor and outdoor surfaces treated with Temprid SC Insecticide or Temprid ReadySpray Insecticide did not identify risks of concern when the label directions, which include additional mitigation measures, are followed.

Occupational Risks From Handling Temprid SC Insecticide and Temprid ReadySpray Insecticide

Occupational risks are not of concern when beta-cyfluthrin is used according to the proposed label directions, which include protective measures.

Pest Control Operators (PCOs) mixing, loading and applying Temprid SC Insecticide or applying Temprid ReadySpray Insecticide can come into direct contact with beta-cyfluthrin on the skin or through inhalation. Therefore, the labels will specify that anyone mixing, loading and/or applying beta-cyfluthrin must wear long-sleeves, long pants, chemical-resistant gloves, and shoes plus socks. In overhead areas or confined spaces, goggles and a dust/mist respirator approved for pesticide use are required.

Environmental Considerations

What Happens When Beta-Cyfluthrin Is Introduced Into the Environment?

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

Beta-cyfluthrin is used in the formulation for Temprid SC and Temprid Ready Spray for structural uses limited to indoor and direct application to the outsides of buildings, storage units and other man-made structures. Environmental exposure from this use is expected to be limited. The risk to non-target organisms is considered to be negligible, when used according to the label directions. Because of the use pattern, beta-cyfluthrin is unlikely to be introduced to the environment.

Value Considerations

What Is the Value of Temprid SC Insecticide and Temprid ReadySpray Insecticide?

Temprid SC Insecticide and Temprid ReadySpray Insecticide combine two insecticides, a pyrethroid and neonicotinoid, to kill various crawling and flying insects found indoors and outdoors on the exterior surfaces of structures. The products may also be applied to sites such as mattresses. These products may be used in a pest management program to kill certain pests of public health concern, such as bed bugs and cockroaches.

Temprid SC Insecticide and Temprid ReadySpray Insecticide kill ants, bed bugs, cockroaches, crickets, earwigs, certain flies (for example, house flies), mosquitoes, spiders and stinging insects (for example, yellowjackets) on contact. Temprid ReadySpray Insecticide also kills carpet beetles, confused flour beetles, warehouse beetles, lesser mealworms, firebrats, Indian meal moth larvae and sowbugs on contact. Temprid SC Insecticide and Temprid ReadySpray Insecticide may be an alternative to products being phased out.

Bed bugs are a difficult pest to control and have substantial impacts on the well-being of Canadians. Cockroaches are known to carry disease and can trigger asthma attacks. The submitted value information demonstrated that combining beta-cyfluthrin and imidacloprid improves efficacy against pyrethroid-resistant bed bugs and against cockroaches. Both products also killed bed bug eggs.

Measures to Minimize Risk

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

The key risk-reduction measures being proposed on the label of Temprid SC Insecticide and Temprid ReadySpray Insecticide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

To reduce direct contact with beta-cyfluthrin, on the skin for adults, youth and children in residential areas, mitigation measures limiting locations of use, application techniques and application rates will be clearly stated on the labels of Temprid SC Insecticide and Temprid ReadySpray Insecticide. These measures will ensure all subpopulations are sufficiently protected.

A re-entry interval is also being established at 8 hours. This was determined based on the data in the public literature, the Incident Reporting Program and the feasibility of restricting access to treated areas.

Based on reports from the Incident Reporting Program, the potential adverse effects will be required to be listed on the product label. Also, as commercial applicators may not always interact with occupants, the label will specify the requirement for an information sheet to be left for the occupants of each treated home/structure. This is to inform occupants of the required re-entry interval, the need to ventilate, and what to do if they experience the potential adverse effects listed on the label and information sheet.

For PCOs mixing, loading and applying Temprid SC Insecticide or applying Temprid ReadySpray, a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks must be worn. When applying to overhead areas or in confined spaces, goggles and a dust/mist respirator approved for pesticide use are required.

Environment

None

Next Steps

Before making a final registration decision on beta-cyfluthrin, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

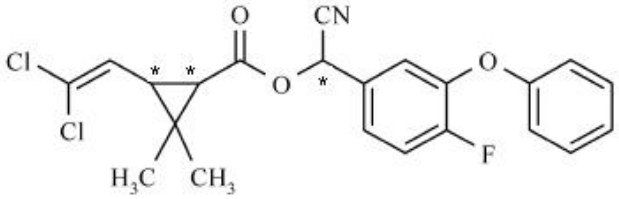
When the PMRA makes its registration decision, it will publish a Registration Decision on beta-cyfluthrin (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Beta-Cyfluthrin

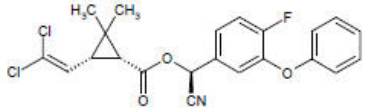
1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Beta-cyfluthrin
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	reaction mixture comprising the enantiomeric pair (R)-α-cyano-4-fluoro-3-phenoxybenzyl (1S,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (S)-α-cyano-4-fluoro-3-phenoxybenzyl (1R,3R)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate in ratio 1:2 with the enantiomeric pair (R)-α-cyano-4-fluoro-3-phenoxybenzyl (1S,3R)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (S)-α-cyano-4-fluoro-3-phenoxybenzyl (1R,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate
2. Chemical Abstracts Service (CAS)	cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
CAS number	68359-37-5 (unstated stereochemistry) 86560-93-2 (enantiomeric pair II) 86560-95-4 (enantiomeric pair IV) Enantiomeric pairs II and IV constitute beta-cyfluthrin
Molecular formula	$C_{22}H_{18}Cl_2FNO_3$
Molecular weight	434.287
Structural formula	

* denotes stereocenter

II



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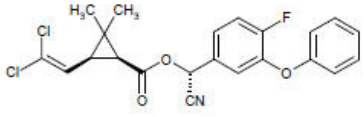
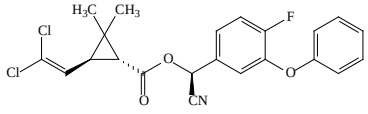


IV



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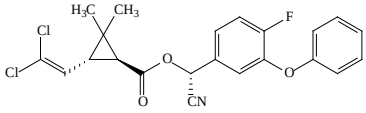

Purity of the active ingredient 97.27%

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

Technical Product – Beta-cyfluthrin Technical Insecticide

Property	Result
Colour and physical state	Colourless to tan solid
Odour	Odourless
Melting range	82–93°C
Boiling point or range	N/A
Relative density	1.35
Vapour pressure at 20°C	mPa Isomer pair II 1.4×10^{-5} Isomer pair IV 8.5×10^{-5}
Ultraviolet (UV)-visible spectrum	Solvent λ_{max}(nm) ε (L/moL × cm) A 268 2023 A = acetonitrile/water (1/1, v/v)
Solubility in water at 20°C	µg/L Isomer II 2.1 Isomer IV 1.2
Solubility in organic solvents at 20°C	Solvent Solubility (g/L) Isomer II / Isomer IV / Technical product n-heptane 3.1 / 1.8 / 4.9 xylene 110 / 110 / 220 dichloromethane - / - / >250 2-propanol 3.5 / 3.2 / 6.7 1-octanol 3.2 / 3.5 / 6.7 polyethylene glycol (PEG) 36 / 20 / 56 acetone - / - / >250 ethyl acetate - / - / >250 acetonitrile 120 / 130 / 250 dimethylsufoxide - / - / > 250
n-Octanol-water partition coefficient (K_{ow})	K_{ow} log K_{ow} Isomer II 1 500 000 6.18 Isomer IV 1 500 000 6.18
Dissociation constant (pK_a)	N/A
Stability (temperature, metal)	At pH 4 – Half life in hours Temp (°C) II IV

Property	Result
	80 | 40 | 45 70 | 59 | 90 60 | 140 | 96 At pH 7 – Half life in hours Temp (°C) | II | IV 80 | 2.39 | 1.95 70 | 7.49 | 4.63 60 | 9.68 | 7.84 40 | 79.5 | 48.7 At pH 9 – Half life in hours Temp (°C) | II | IV 60 | 0.57 | 0.31 50 | 3.65 | 2.71 40 | 5.96 | 4.56 30 | 48.1 | 36.8 Hydrolysis DT_{50} at 22°C II: 117 d (pH 4) / 20 d (pH 7) / 6 d (pH 9) IV: 25 d (pH 4) / 11 d (pH 7) / 5 d (pH 9) Two DSC (Differential Scanning Calorimetry) - measurements in closed glass crucibles showed an endothermic effect in the temperature range of 60 - 105°C and an exothermal decomposition in the temperature range of 200 - 390°C with a mean energy of 470 J/g.

End-Use Product – Temprid SC Insecticide and Temprid ReadySpray Insecticide

Property	Temprid SC Insecticide	Temprid ReadySpray Insecticide
Colour	Opaque beige	Colourless
Odour	Chalky odour	Slight saponaceous odour
Physical state	Liquid	Liquid
Formulation type	Suspension concentrate	Pressurized product
Guarantee	Beta-cylfluthrin…..10.5% Imidacloprid……...21.0%	Beta-cylfluthrin…..0.05% Imidacloprid……...0.025%
Container material and description	Plastic jug/bottle, 240 mL - bulk	Bag-on-valve – a laminated plastic/foil pouch
Density	1.16 g/mL	1 g/mL

Property	Temprid SC Insecticide	Temprid ReadySpray Insecticide
pH of 1% dispersion in water	6.92 at 20°C	5.7 – 6.7
Oxidizing or reducing action	Product contains no oxidizing or reducing agents.	Product contains no oxidizing or reducing agents.
Storage stability	Stable when stored at ambient temperatures for one year in commercial packaging.	Stable when stored at ambient temperatures for one year in commercial packaging.
Corrosion characteristics	Not corrosive to the packaging material	Not corrosive to the packaging material
Explodability	Not explosive	Not explosive

1.3 Directions for Use

Temprid SC Insecticide and Temprid ReadySpray Insecticide are both commercial class products for use indoors and outdoors on the exterior surfaces of certain structures. The products may also be applied to human proximal sites such as mattresses. Both products kill ants, bed bugs, cockroaches, crickets, earwigs, various flies (blue bottle, cluster, flesh, house and stable), hornets, mosquito adults, spiders, wasps and yellowjackets. Temprid ReadySpray Insecticide also kills carpet beetles, confused flour beetles (adults and immature stages), firebrats, Indian meal moth larvae, lesser mealworm (adults and larvae), sowbugs and warehouse beetles (adults and immature stages).

Temprid SC Insecticide is formulated as a suspension concentrate with a guarantee of 21% imidacloprid and 10.5% beta-cyfluthrin. Prior to application, 1 mL of product is diluted in 1L of water for bed bugs or 2 mL of product is diluted in 1 L of water for the remaining pests. When applied indoors, it may be applied as a crack and crevice or void treatment. When applied outdoors on the surfaces of structures, spot or broadcast applications are also permitted. Applications are to be applied as a course spray; however, mist or foam applications are permitted into voids. The maximum application rate is 40 mL of diluted product/m^2.

Temprid ReadySpray Insecticide is a ready-to-use pressurized product that has a guarantee of 0.05% imidacloprid and 0.025% beta-cyfluthrin. When applied indoors, it may be applied as a crack and crevice, void, interior perimeter and/or spot treatment to structures and modes of transportation. When applied outdoors on the surfaces of structures, it may also be applied as broadcast treatment to the surfaces of the structure. The maximum application rate is 40 mL product/m^2.

1.4 Mode of Action

Beta-cyfluthrin is a pyrethroid insecticide belonging to mode of action (MOA) group 3A according to the Insecticide Resistance Action Committee's classification scheme. It kills insects, sowbugs and spiders by interfering with the sodium channels of nerves.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

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

2.2 Method for Formulation Analysis

The methods provided for the analysis of the two active ingredients in the formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

2.3 Methods for Residue Analysis

Gas-Liquid Chromatography (GLC) and Gas Chromatography (GC) methods were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

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 4 stereoisomers, but is enriched with stereoisomers IIand IV. Due to the similarity in structure, mode of action and qualitative toxicological findings, the human health risk assessment for beta-cyfluthrin has been based on data for cyfluthrin and beta-cyfluthrin. This approach is further justified by the fact that analytical methods 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 intravenous (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.

The end-use product, Temprid SC Insecticide, was of slight acute toxicity to rats via the oral route of exposure and was of low acute toxicity via the dermal and inhalation routes. It was minimally irritating to the eyes and slightly irritating to the skin of rabbits. Temprid SC Insecticide was not a dermal sensitizer when tested in guinea pigs using the Buehler method. Temprid ReadySpray Insecticide was of low acute toxicity to rats via the oral and dermal routes of exposure. It was considered to be of low toxicity to rats via the inhalation route. It was non-irritating to the eyes of rabbits, and was considered to be slightly irritating to rabbit skin. Temprid ReadySpray Insecticide was not considered to be a dermal sensitizer.

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 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 (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#2050136). 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 in the form 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. A comparison of potencies in repeat-dose studies was confounded due to differences in testing conditions (for example, choice of vehicle, animal strain).

Results of the toxicology studies conducted on laboratory animals with cyfluthrin and beta-cyfluthrin are summarized in Appendix I, Tables 2 and 3. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 4.

Incident Reports

As of 16 October 2015, 30 human incident reports and 64 domestic animal incidents were associated with the active ingredient beta-cyfluthrin or cyfluthrin. Fourteen human incidents involving 42 individuals had a high degree of association with the active ingredient cyfluthrin or beta-cyfluthrin. Eighty percent (80%) of subjects reported experiencing respiratory effects after re-entering homes or a workplace that had been treated with the pesticide. Similar trends were observed in the California Department of Pesticide Regulation's Pesticide Illness/Injury Query database and the NIOSH Sensor database, in which there was a high frequency of reports involving respiratory effects after entering areas treated with cyfluthin or beta-cyfluthrin. The use pattern reported in these incidents (crack and crevice, baseboard (indoor perimeter), and spot spray around homes and businesses) is also proposed for Temprid SC Insecticide and Temprid ReadySpray Insecticide; therefore, there is the potential for similar incidents to occur in Canada following the use of these products.

In light of the above, the following mitigation measures are required. Firstly, the re-entry interval must be increased to 8 hours after treatment. Secondly, the potential adverse effects will be required to be listed on the product label. Finally, as commercial applicators may not always interact with occupants, the label will specify the requirement for an information sheet to be left for the occupant(s) of each treated home/structure. This is to inform occupants of the required re-entry interval, the need to ventilate, and what to do if they experience the potential adverse effects listed on the label and information sheet.

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 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 no observed adverse effect level (NOAEL) of 0.5 mg/kg bw was selected for risk assessment. At the lowest observed adverse effect level (LOAEL) of 2 mg/kg bw, clinical signs, changes in 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 for the general population is calculated according to the following formula:

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

3.3 Determination of Acceptable Daily Intake

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 composite assessment factor (CAF) is thus 300.**

The ADI is calculated according to the following formula:

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

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.

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.

3.4 Occupational and Residential Risk Assessment

Occupational exposure to beta-cyfluthrin is characterized as intermediate- to long-term in duration and predominantly by dermal and inhalation routes. Residential exposure duration to treated surfaces is characterised as short-term for all scenarios and potentially long-term for bed bugs. The routes of exposure are dermal and inhalation for adults and youths (11 < 16 years) and dermal, inhalation and incidental oral for children (1 < 2 years). 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 year olds. Children (1 < 2 years) are expected to have 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.

3.4.1 Toxicological Endpoints

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 Margin of Exposure (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 no observed adverse effect concentration (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.

Short-term Non-dietary (incidental) Oral

For assessment of short-term non-dietary (incidental) oral exposure, a NOAEL of 0.5 mg/kg bw was selected from the acute neurotoxicity study in rats. At the LOAEL of 2 mg/kg bw, clinical signs, changes in FOB parameters and decreased motor activity were observed. A target MOE of 300 was selected which includes uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and a 3-fold for database uncertainty to reflect residual uncertainty regarding potential susceptibility 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.

3.4.1.1 Dermal Absorption

A dermal absorption value was not established as an endpoint for dermal exposure was chosen based on a 21-day dermal toxicity study in rats.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Exposure to PCOs during mixing, loading, application, clean up and repair is expected to be intermediate- to long-term in duration and to occur primarily by the dermal and inhalation routes

Chemical-specific data for assessing human exposures during pesticide handling activities were not reviewed as the Pesticide Handlers Exposure Database (PHED) data were considered appropriate for these use scenarios. Therefore, dermal and inhalation exposure estimates for mixing, loading, and/or applying beta-cyfluthrin indoors and outdoors using manually pressurized and backpack sprayers and aerosol bag-on-valve containers were generated using PHED version 1.1. The exposure estimates are based on PCOs wearing a single layer, long-sleeved shirt and long pants, plus chemical-resistant gloves.

Dermal exposures were estimated by combining the PHED unit exposure values and the amount of product handled per day. Inhalation exposures were estimated by multiplying the PHED unit exposure values with the amount of product handled per day and 100% inhalation absorption. Exposures were normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological endpoint or NOAEL to obtain the MOE. All calculated MOEs exceeded the target MOE of 300 (Appendix 1, Table 5).

3.4.2.2 Postapplication Worker Exposure and Risk

There is potential for exposure to workers re-entering areas treated with beta-cyfluthrin. However, it is expected to be less than the exposures to a PCO from mixing, loading and/or applying which already exceed the target MOE. It is expected that workers re-entering treated areas will be wearing long sleeves, long pants and shoes plus socks.

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Postapplication Exposure and Risk

Short-term dermal and inhalation risks were calculated for adults and youth (11 < 16 years) and inhalation, dermal and incidental oral (hand-to-mouth (HtM) and object-to-mouth (OtM)) risks for children (1 < 2 years). Children (2 years < 11 years) were not assessed separately because their exposure is expected to be less than that of 1 < 2 year olds. Children (1 < 2 years) are expected to have 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.

Post-application exposure assessments for use in residential areas are considered to be representative of those in some non-residential (office buildings, public spaces, commercial areas, etc.) and outdoor areas. This assumption is based on the duration of contact with treated surfaces, which is assumed to be greater in residential areas. Also, when the end use products are used outdoors, they are limited in application to the surfaces of structures where contact is expected to be minimal.

All exposures are considered short-term in duration; however, the treatment of bed bug can potentially be long-term in duration. Long-term exposures were not calculated separately because the dermal and incidental oral endpoints are the same for both the short- and long-term exposure durations and the route of exposure in the toxicological studies is the same. For the inhalation route of exposure, the endpoints do not differ substantially and the route of exposure in the toxicological studies is the same. Also, exposure parameters for long-term assessments use more conservative values, such as the 50^{th} percentile, in comparison to short-term assessments, which use the arithmetic mean or 90^{th} percentile. As such, short-term risk assessments are representative of any potential long-term risk.

All default values were derived from the 2012 United States Environmental Protection Agency (USEPA) Residential SOP for Indoor Environments (Section 7). The fraction transferred from 6% on soft surfaces and 8% on hard surfaces was refined to 4% and 6%, respectively. This refinement is only applicable to pyrethroids as the 4% and 6% are the arithmetic means based on indoor residue transfer studies of chlorpyrifos, pyrethrins, piperonyl butoxide, permethrin and deltamethrin. As 4 of the 5 chemicals used to derive the arithmetic means are pyethroids, it is expected that all pyrethroids, including beta-cyfluthrin, would exhibit similar transfer properties. The refinement is limited to pyrethroids, only.

Cyfluthrin residue transfer data available in the public literature (Williams *et al*., 2003) also supports a lower percentage transferred once residues have dried. Residue transfer was monitored at 3, 7, 12, 23, 47.5 and 407.5 hours after application and from 3 to 7 hours residue transfer reduced from 8.5% to less than 2%. This information supports the refinement of the transfer on soft surfaces from 6% to 4% when an appropriate restricted entry interval (REI) is added to the labels.

Additional information from the Canadian Pest Management Association (CPMA) was also considered as part of the risk assessment. This information provided insight on the deposited residue value of 50% of the broadcast equivalent application rate for a crack and crevice application to bed bugs, as assumed in the 2012 USEPA Residential SOP, and suggested that it may potentially overestimate exposure. The CPMA information also indicated the areas in the home treated for bedbugs are not as extensive as originally assumed by the PMRA (or the USEPA). Even for severe infestations, spot treatments are minimal and crack and crevice treatment is limited to bedrooms, living rooms, closets, furniture, and outlets. The treated furniture includes mattresses, box springs, nightstands, dressers, bed frames, and head boards. Many of the surfaces treated are those where contact is expected to be limited. Based on numbers provided by the CPMA[5], approximately 14% and 7% of the total home footprint plus furniture is treated for early infestations in multi-unit and single detached homes, respectively. For severe infestations, approximately 35% and 13% is treated for multi-unit and single detached homes, respectively.[6] As such, the deposited residue refinement factor has been reduced to 25% for Temprid SC Insecticide and Temprid ReadySpray Insecticide considering the deposited residue is estimated from the label application rate.

Even after considering all the refinements, as described above, exposure to beta-cyfluthrin exceeded the target MOE of 300 for all scenarios except for children (1< 2 years) from hand-to-mouth incidental oral exposure on soft surfaces (carpet, upholstered furniture, etc.) (Appendix I, Tables 6 - 10). While certain scenarios were close to, but still under, the target of MOE of 300, the significant refinements to the exposure parameters reduced the conservatives in the risk assessment to a degree to which it could not be justified to allow the uses.

Hand-to-mouth exposure is not expected when a child is sleeping and therefore was not calculated for treated mattresses.

Risk mitigation measures are required for hand-to-mouth exposure to children (1 < 2 years) due to risks of concern from indoor perimeter and spot applications to soft surfaces (for example, carpet, upholstered furniture). Risks were not of concern for children (1 < 2 years) from a crack

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5 http://www.pestworldcanada.net/sites/pestworldcanada/files/Pyrethroid%20Pyrethrin%20usage%20for%20bed%20bugs_ants_%20roaches_%20and%20fleas%20as%20compiled%20by%20the%20Canadian%20Pest%20Mangement%20Association%20FINAL.pdf Accessed December 11, 2014

6 These values are based on the total areas treated provided by the CMPA and the assumption the single detached three bedroom home is 1900 ft^2.
http://www.chba.ca/uploads/pulse%20survey%20results/main%20report2012.pdf, Accessed December 11, 2014

and crevice treatment when the application rate of Temprid SC Insecticide to kill bed bugs was reduced to 1 mL product/L and remained at 2 mL product/L for all other pests.

As the application rate of Temprid ReadySpray Insecticide cannot be altered, it is being restricted to locations of use where children are not present in order to support the use as an indoor perimeter, spot, and crack and crevice treatment to kill all pests supported by the Agency.

It should be noted that the definitions to the types of application relevant to these end use products (indoor perimeter, spot, and crack and crevice) are currently under review within the Agency and may be revised under re-evaluation of the pyrethroid cluster.

3.4.3.2 Bystander Exposure and Risk

The end-use product labels specifically state that no one is to be present during application and so bystander exposure is expected to be negligible.

3.5 Aggregate Risk Assessment

3.5.1 Toxicology Endpoints

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 0.00025 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.

Intermediate- and Long-term Aggregate

For aggregate risk assessment for the general population (including pregnant women, infants and children) for intermediate- and long-term durations, the selected toxicological endpoints are 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 0.00009 mg/L (0.02 mg/kg bw/day) from the 90-day

inhalation study, where clinical signs were observed at the next highest concentration of 0.00071 mg/L (0.19 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.

3.5.2 Aggregate Exposure and Risk

The chronic dietary exposure to beta-cyfluthrin for a child (1 < 2 years) is 0.001098 mg/kg bw/day. As beta-cyfluthrin is not registered on food crops in Canada, exposure did not include drinking water and so was limited to imported food and domestic cyfluthrin uses. Aggregate exposure was only assessed for children (1< 2 years) because the hand-to-mouth route of exposure is the driver in the residential assessment and the dietary exposure was higher than any other age group. Routes of exposure included oral and inhalation based on clinical signs of neurotoxicity.

The aggregate risk did not exceed the target MOE for hard and soft surfaces for both end-use products when used as a perimeter or spot treatment (Appendix I, Table 11). As such, Temprid SC Insecticide can only be supported as a crack and crevice application when used in locations where children may be present. This will allow this product to be used against bed bugs in residential locations. For Temprid ReadySpray Insecticide, the aggregate exposure for children could not be sufficiently mitigated as a reduction in application rate could not be supported. As such, for Temprid ReadySpray Insecticide, restrictions are required on the location of use (that is, not for use in residential areas where children are or maybe present) in order to support the use pattern (maximum rate and application method) on all pests, including bed bugs.

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. Beta-cyfluthrin belongs to a group of insecticides commonly known as the pyrethroids. Pyrethroids and pyrethrins have a common mechanism of toxicity wherein they possess the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity.

Upon completion of the re-evaluation of the individual chemicals in the pyrethroid group, it will be determined whether a cumulative effects assessment is necessary and if so, this will be performed with all relevant chemicals of the common mechanism group.

4.0 Impact on the Environment

Structural use is limited to indoor and direct application to the outsides of buildings, storage units and other man-made structures. Environmental exposure will be limited to dripping from outdoor structural surfaces and potentially loss via rainfall or irrigation that falls on the treated outdoor surface (which can be mitigated through labelling).

4.1 Fate and Behaviour in the Environment

During hydrolysis, isomerization of the beta-cyfluthrins diastereomers II and IV to diasteromers I and III was found prior to hydrolysing. Beta-cyfluthrin was found to be stable at pH 4, to have a half-life of 180 days at pH 7 and a half-life of ~2 hrs at pH 9. This is in-line with the results of the cyfluthrin hydrolysis study. For cyfluthrin, only the transformation product was found to be major (pH 7 and pH 9 only). Therefore, cyfluthrin data for abiotic processes is expected to represent beta-cyfluthrin.

Any future expansion of this compound to outdoor uses may require additional data to confirm behaviour under other environmental conditions.

4.2 Environmental Risk Characterization

Beta-cyfluthrin is used in the formulation for Temprid SC and Temprid Ready Spray for structural uses limited to indoor and direct application to the outsides of buildings, storage units and other man-made structures. Environmental exposure from this use is expected to be limited. The risk to non-target organisms is considered to be negligible, when used according to the label directions.

5.0 Value

5.1 Consideration of Benefits

The majority of commercial class insecticides registered for the labelled pests in structural pest control are pyrethroids (MOA group 3A). Silicon dioxide present as diatomaceous earth is a non-conventional insecticide that is registered for many of the same uses as well. Other active ingredients are registered for use in structural pest control; however, they are labelled for fewer pests and/or they have limitations on where they can be applied compared to the Temprid products. Conventional active ingredients in commercial class insecticides include carbamates (MOA group 1A), organophosphates (MOA group 1B), neonicotinoids (MOA group 4A), abamectin (MOA group 6), the borates (MOA group 8D), chlorfenapyr (MOA group 13) and hydramethylnon (MOA group 20A).

A few non-conventional insecticides (for example, d-limonene, sodium lauryl sulfate, mixture of thyme oil and wintergreen oil) are registered for some uses, and a microbial insecticide (*Beauvaria bassiana* HF 23) is registered for controlling houseflies in livestock facilities.

Two pests that the Temprid products are effective against, bed bugs and cockroaches, have substantial impacts on the health and well-being of Canadians. The combination of beta-cyfluthrin (MOA 3A) and imidacloprid (MOA 4A) improved the efficacy against pyrethroid resistant bed bugs and cockroaches compared to beta-cyfluthrin or imidacloprid alone. Both products also kill bed bug eggs on contact.

Both Temprid SC Insecticide and Temprid ReadySpray Insecticide can be used with other pest control practices (for example, inspection, sanitation, structural repairs) against labelled pests.

5.2 Effectiveness Against Pests

Temprid SC Insecticide:
Based on efficacy data from 20 studies, a claim of "kills on contact" was supported for ants, bed bugs (eggs, nymphs and adults), blue bottle flies, cockroaches, crickets, flesh flies, house flies, spiders and stable flies. Some species of spider (for example, cellar spiders) were less susceptible to Temprid SC Insecticide which is reflected in the label statements. Cluster flies were supported based on extrapolation from the efficacy data submitted on other flies. Based on the registered use pattern for cyfluthrin, a claim of "kills on contact" was supported for earwigs, hornets, mosquito adults, wasps and yellowjackets.

Temprid ReadySpray Insecticide:
Based on extrapolation of the value information assessed for Temprid SC Insecticide, a claim of "kills on contact" was supported for ants, bed bugs (eggs, nymphs and adults), blue bottle flies, carpet beetles, cluster flies, cockroaches, confused flour beetle (adults and immature stages), crickets, earwigs, flesh flies, firebrats, house flies, hornets, Indian meal moth (larvae only), lesser mealworm (adults and larvae), mosquito adults, spiders, stable flies, sowbugs, warehouse beetles (adults and immature stages), wasps and yellowjackets.

5.3 Non-Safety Adverse Effects

The following cautionary statement is located on the labels of Temprid SC Insecticide and Temprid ReadySpray Insecticide: "Users should test a small, inconspicuous area first to ensure there are no adverse effects such as staining, discolouration or corrosion prior to treating an entire area."

5.4 Supported Uses

Temprid SC Insecticide diluted to 1 mL product per L of water kills bed bugs (eggs, nymphs and adults) on contact and 2 mL product per L of water kills ants, blue bottle flies, cockroaches, cluster flies, crickets, earwigs, flesh flies, house flies, hornets, mosquito adults, spiders, stable flies, wasps and yellowjackets on contact.

Temprid ReadySpray Insecticide kills ants, bed bugs (eggs, nymphs and adults), blue bottle flies, carpet beetles, cluster flies, cockroaches, confused flour beetles (adults and immature stages), crickets, earwigs, flesh flies, firebrats, house flies, hornets, Indian meal moth larvae, lesser mealworm (adults and larvae), mosquito adults, spiders, stable flies, sowbugs, warehouse beetles (adults and immature stages), wasps, and yellowjackets on contact.

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

During the review process, beta-cyfluthrin was assessed in accordance with the PMRA Regulatory Directive DIR99-03[7] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Since environmental exposure from this use is expected to be limited, beta-cyfluthrin is not expected to meet the toxic equivalent criterion of the *Canadian Environmental Protection Act*.

Based on the current information submitted and reviewed for beta-cyfluthrin, it is unlikely to meet all TSMP Track-1 criteria. This assessment will be revisited for any expansion of use resulting in higher environmental exposure.

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*[8]. The list is used as described in the PMRA Notice of Intent NOI2005-01[9] and is based on existing policies

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

[8] *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.*

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

and regulations including DIR99-03 and DIR2006-02[10], 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 beta-cyfluthrin and the end-use product Temprid SC Insecticide and Temprid Ready Spray 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 Summary

7.1 Human Health and Safety

The toxicology databases for cyfluthrin and beta-cyfluthrin were adequate to define the majority of toxic effects which may result from exposure. In short-term and chronic studies on laboratory animals, the primary target of toxicity was the neurological system. There was no evidence of carcinogenicity in mice after longer-term dosing; an equivocal increase in urinary bladder tumors was seen in female rats however. Neither cyfluthrin nor beta-cyfluthrin damaged genetic material. An increase in malformations (microphthalmia) was noted in inhalation, but not oral, developmental toxicity studies, but this occurred only at maternally-toxic levels. There is some concern for increased susceptibility of the young exposed to cyfluthrin based on increased sensitivity observed in reproduction toxicity and inhalation toxicity studies. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

PCOs handling Temprid SC Insecticide or Temprid ReadySpray Insecticide are not expected to be exposed to levels of beta-cyfluthrin that will result in risks of concern when the products are used according to label directions, which includes additional, protective measures. The personal protective equipment of long sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks, along with goggles and a respirator when applying in confined or to overhead areas, are adequate to protect PCOs.

Exposures to individuals contacting surfaces treated with beta-cyfluthrin are not expected to result in risks of concern when the products are used according to label directions. Additional mitigation measures limiting locations of use, application techniques, and application rates will be clearly stated on the labels to ensure high-risk groups are sufficiently protected.

A re-entry interval of 8 hours is also being established. This was determined based on the data presented in Williams *et al.* (2003), the Incident Reporting Program and the feasibility of restricting access to treated areas.

[10] DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

Based on incident reports, it is required that potential adverse effects be listed on the product label. In addition, as commercial applicators may not always interact with occupants, the label will specify the requirement for an information sheet to be left for the occupant(s) of each treated home/structure. This is to inform occupants of the required re-entry interval, the need to ventilate, and what to do if they experience the potential adverse effects listed on the label and information sheet.

7.2 Environmental Risk

When beta-cyfluthrin is used for structural uses, environmental exposure is expected to be limited. When used according to label directions, beta-cyfluthrin is not expected to pose risks of concern to the environment.

7.3 Value

Temprid SC Insecticide and Temprid ReadySpray Insecticide combine two insecticides, a pyrethroid and neonicotinoid, to kill various crawling and flying insects indoors and outdoors on the exterior surfaces of structures. The products may also be applied to sites such as mattresses.

The submitted value information demonstrated that combining these two insecticides improves the efficacy against pyrethroid-resistant bed bugs and cockroaches. It also kills bed bug eggs.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Beta-cyfluthrin Technical Insecticide and its end-use products, Temprid SC Insecticide and Temprid ReadySpray Insecticide containing the technical grade active ingredient beta-cyfluthrin. The end-use products are coformulated with the active ingredient imidacloprid to kill certain crawling and flying insects found indoors (including sites such as mattresses) and outdoors on the exterior surfaces of structures.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

↑	increased
↓	decreased
µg	microgram(s)
µL	microlitre
µM	micromolar
♀	females
♂	males
a.i.	active ingredient
ADI	allowable daily intake level
ALP	alkaline phosphatase
ALT	alanine transaminase
ARfD	acute reference dose
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BAF	bioaccumulation factor
BCF	bioconcentration factor
BMD	benchmark dose
BMDL	benchmark dose lower confidence limits
BUN	blood urea nitrogen
bw	body weight
bwg	body weight gain
CAF	Composite Assessment Factor
CHO	Chinese Hamster Ovary
CPMA	Canadian Pest Management of Association
CXB	beta-cyfluthrin
d	day(s)
DE	diatomaceous earth
DepR	Deposited Residue
DMSO	dimethyl sulfoxide
DNT	developmental neurotoxicity
F0	parental generation
F1	first filial generation
F2	second filial generation
F3	third filial generation
fc	food consumption
FOB	functional observational battery
g	gram
GC-ECD	gas chromatography-electron capture detection
GD	gestation day
GLC	gas liquid chromatography
GPT	glutamate pyruvate transaminase
HB	hemoglobin
HCT	hematocrit
HED	Health Evaluation Directorate
HGPRT	hypoxanthine-guanine phosphoribosyltransferase

i.v.	intravenous
ILV	intralobular vein
IRAC	Insecticide Resistance Action Committee
kg	kilogram(s)
kg bw	kilograms of bodyweight
Koc	adsorption quotient normalized to organic carbon
Kow	octanol water partition coefficient
L	litre(s)
LC50	median lethal concentration
LD	lactation day
LD50	median lethal dose
LDH	lactate dehydrogenase
LDT	lowest dose tested
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
M/L/A	Mixer/loader/applicator
MAS	maximum average score
mg	milligram(s)
mg/kg bw/day	Milligrams per kilogram of bodyweight per day
min	minute(s)
MIS	maximum irritation score
mL	millilitre(s)
mm	millimetre(s)
MOA	Mode of action
MOE	margin of exposure
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
PCO	Pest Control Operator
PEG	polyethylene glycol
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PND	post-natal day
PPE	personal protective equipment
ppm	parts per million
REI	restricted entry interval
S9	mammalian metabolic activation system
TC	transfer coefficient
TGAI	technical grade active ingredient
TSMP	toxic substances management policy
USC	use-site category
USEPA	US Environmental Protection Agency
WBC	white blood cell
WC	water consumption
wt	weight(s)
µg/kg ai	micrograms per kilogram of active ingredient

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ/LOD	Matrix	PMRA #
Soil	Not stated	Cyfluthrin FPBacid Permethric acid	GLC	0.01 ppm (LOQ)	Various types of soil: sandy clay loam, loam, sandy loam, silt loam, loamy sand, silty clay loam and sand	2073014
Water	Not stated	Cyfluthrin	GC-ECD	2 ng/L (LOD)	Pond water	2073015, 2073046 and 2073017

Table 2 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 either hydroxylated, conjugated and excreted,or bound first to glycine and then hydroxylated and conjugated.
Human dose-excretion studies (inhalation) Cyfluthrin Human	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.

Study Type/ Animal/ PMRA #	Study Results
PMRA# 2429024	
Acute Toxicity Studies	
Acute oral toxicity (gavage) Cyfluthrin NMRI mouse PMRA# 1216160	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 and apathy. **Highly toxic**
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 and 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) Beta-cyfluthrin Wistar rat PMRA# 2072874	LD_{50} (fasted) = 380 mg/kg bw (♂); 651 mg/kg bw (♀) (PEG E 400) 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)**

Study Type/ Animal/ PMRA #	Study 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 and 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 were also observed.
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	LD_{50} (♂, ♀) > 5000 mg/kg bw (PEG 400) Clinical signs at 5000 mg/kg bw included apathy and ataxia.

Study Type/ Animal/ PMRA #	Study Results
Cyfluthrin Wistar rat PMRA# 1216160	**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 PMRA# 2072884	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**
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 and 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 and 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	<u>Aerosol:</u> LC50 = 0.082 mg/L (♂); 0.081 mg/L (♀) (PEG 400)

Study Type/ Animal/ PMRA #	Study Results
only) Beta-cyfluthrin Rat PMRA# 2072890	<u>Dust:</u> LC50 = 0.532 mg/L (♂); 0.212 mg/L (♀) **Moderately toxic**
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 PMRA# 1216167, 1227054	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 **Mildly irritating**
Primary eye irritation Beta-cyfluthrin	MAS = 3.78 MIS = 11.33 at 1 hr **Slightly irritating**

Study Type/ Animal/ PMRA #	Study Results
NZW rabbit PMRA# 2072894	
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 PMRA# 1216168	**Supplemental due to study deficiencies (lack of positive controls, dose selection rationale, dosing regimen, purity information)** **No evidence of sensitization**
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, and 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, and↓ 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)	**NOAEL = 24.7 mg/kg bw/day (♂); 25.2 mg/kg bw/day (♀)** 24.7 mg/kg bw/day: ↓ glucose (♂)

Study Type/ Animal/ PMRA #	Study Results
Cyfluthrin Rat (Strain N/S) PMRA# 1216141	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 (♀) 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 Beagle dog PMRA# 2072914	**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 present at the next feeding); ↓ bw, ↓ bwg (♀) No difference in bone/teeth fluoride levels of treated animals compared to controls.
6-month toxicity (diet)	**Supplemental due to poor animal health**

Study Type/ Animal/ PMRA #	Study Results
Cyfluthrin Beagle dog PMRA# 1216146	≥ 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 Sprague Dawley rat PMRA# 2429023	**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 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)	<u>Phase I (PEG 400/ethanol):</u> **No NOAEC established** ≥0.0023 mg/L (0.6 mg.kg bw/day): ↓ bw (♂)

Study Type/ Animal/ PMRA #	Study Results
Cyfluthrin Wistar rat PMRA# 1216144	≥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) Cyfluthrin Wistar rat PMRA# 1207821, 1227058, 1216144	**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) (♂) ≥ 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.

Study Type/ Animal/ PMRA #	Study Results
	Equivocal increase in bladder tumours (♀)
Developmental/Reproductive Toxicity Studies	
7-day inhalation toxicity (whole body) (non-guideline) Cyfluthrin NMRI mouse PMRA# 2429023	Maternal Toxicity: **NOAEC = 0.058 mg/L (23.7 mg/kg bw/day)** No treatment-related toxicity in dams. Offspring Toxicity: **NOAEC = 0.006 mg/L (2.45 mg/kg bw/day)** 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** No effects on reproductive parameters or function. Offspring Toxicity **NOAEL = 4 mg/kg bw/day**

Study Type/ Animal/ PMRA #	Study Results
	≥ 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) Cyfluthrin Himalayan rabbit PMRA# 1216151	Maternal Toxicity **NOAEL = 5 mg/kg bw/day** (Cremophor EL) 15 mg/kg bw/day: ↑ soft feces 45 mg/kg bw/day: 2 abortions, 1 total litter loss Developmental Toxicity **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	Maternal Toxicity **NOAEL = 20 mg/kg bw/day** (corn oil) ≥ 60 mg/kg bw/day: ↓ bw, ↓ fc Developmental Toxicity **NOAEL > 180 mg/kg bw/day** (corn oil) **No evidence of sensitivity of the young or malformations**

Study Type/ Animal/ PMRA #	Study Results
Developmental toxicity (inhalation) Cyfluthrin Wistar rat PMRA# 2429023	Maternal Toxicity **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 Developmental Toxicity **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 (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	Maternal Toxicity **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 Developmental Toxicity **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.

Study Type/ Animal/ PMRA #	Study Results
Genotoxicity Studies	
Sister chromatid exchange assay Cyfluthrin Chinese Hamster Ovary (CHO) Cells PMRA# 1124950, 1207823,	Negative
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) Cyfluthrin Escheria coli pol A+	Negative

Study Type/ Animal/ PMRA #	Study Results
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
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	Negative

Study Type/ Animal/ PMRA #	Study Results
PMRA# 2072980	
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 synthesis Rat primary hepatocytes Beta-cyfluthrin PMRA# 2072985	Negative
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.

Study Type/ Animal/ PMRA #	Study Results
Delayed neurotoxicity (gavage) Cyfluthrin White leghorn chicken PMRA# 1216161	**Supplemental** <u>Single Dose:</u> 2500 mg/kg bw: clinical signs (behavioral disorders and signs of excitation observed days 1-3 only). 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) Cyfluthrin Wistar rat PMRA# 1207832,	**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
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) Cyfluthrin Wistar rat PMRA# 2072961	**NOAEL = 49.1/59.6 mg/kg bw/day** 49.1/59.6: ↓ bw, ↓ bwg and ↓ fc (attributed to decreased diet palatability in both sexes as well as a possible slight effect of treatment in ♀)
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) Cyfluthrin Wistar rat PMRA# 1207833	**Supplemental due to lack of individual data** (Cremophor EL) ≥ 0.03 mg/kg bw/day: impaired ability of rats to maintain stationary position (♂)
Developmental neurotoxicity (diet) Beta-cyfluthrin	<u>Maternal Toxicity</u> **NOAEL = 11.0 mg/kg bw/day** 17.8 mg/kg bw/day: ↓ bw during gestation and lactation, ↓ fc during lactation

Study Type/ Animal/ PMRA #	Study Results
Wistar rat PMRA# 2072967	<u>Offspring Toxicity</u> **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 leukocyte membrane assessment Cyfluthrin Synaptosomal and leukocyte membranes (Wistar rat, ♂) PMRA# 2359598	10 µM: ↓ ATPase activity, not statistically significant ≥ 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	Metabolism occurs in rat hepatic microsomes: CYP1A1, CYP2C6, CYP2D, CYP2C12, CYP2D1, CYP3A1and CYP3A2 Metabolism occurs in human hepatic microsomes: CYP1A1, CYP1A2, CYP2C8, CYP2C91,

Study Type/ Animal/ PMRA #	Study Results
Rat and human hepatic microsomes, Cytochrome P450 isoforms PMRA# 2428095	CYP2C19 and CYP3A4
Functional observational battery study (gavage) Beta-cyfluthrin Sprague Dawley rat PMRA# 2428089	≥ 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. 45 mg/kg bw/day: 1 death, lacrimation

Table 3 Toxicity Profile of Temprid SC Insecticide and Temprid ReadySpray Insecticide Containing Beta-cyfluthrin and Imidacloprid

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.

Study Type/ Animal/ PMRA #	Study Results
ACUTE STUDIES – Temprid SC Insecticide (end-use product containing 21% imidacloprid and 10.5% beta-cyfluthrin)	
Oral (Up and Down Procedure) Sprague Dawley rat PMRA# 2073801	LD_{50} (&) = 1044 mg/kg bw There were no clinical signs of toxicity or abnormal findings at necropsy. **SLIGHT TOXICITY**
Dermal Sprague Dawley rat PMRA# 2073804	LD_{50} (%/&) > 2000 mg/kg bw There were no clinical signs of toxicity or abnormal findings at necropsy. **LOW TOXICITY**
Inhalation (nose-only) Sprague Dawley rat PMRA# 2073807	LC_{50} (%/&) > 2.03 mg/L Following exposure all animals were hypoactive; however all animals recovered by Day 2. No abnormal findings at necropsy. **LOW TOXICITY**

Eye Irritation NZW rabbit PMRA# 2073808	MAS = 6 MIS = 21.3 at 1 hr **Minimally irritating**
Dermal Irritation NZW rabbit PMRA# 2073809	MAS = 1.33 MIS = 3.0 at 1 and 24 hrs **Slightly irritating**
Skin Sensitization-(Buehler) Hartley Guinea pig PMRA# 2073810	**Not a dermal sensitizer**
ACUTE STUDIES – Temprid ReadySpray Insecticide (end-use product containing 0.05% imidacloprid and 0.025% beta-cyfluthrin)	
Oral (Up and Down Procedure) Sprague Dawley rat PMRA# 2257258	LD_{50} (♀)>5000 mg/kg bw There were no clinical signs of toxicity or abnormal findings at necropsy **LOW TOXICITY**
Dermal Sprague Dawley rat PMRA# 2257259	LD_{50} (♂/♀) >5000 mg/kg bw There were no clinical signs of toxicity or abnormal findings at necropsy **LOW TOXICITY**
Inhalation	Bridged to Temprid SC Insecticide **LOW TOXICITY**
Eye Irritation NZW rabbit PMRA# 2257260	MAS = 0 MIS = 1.3 at 1 hr. **Non-irritating**

Dermal Irritation	Bridged to Temprid SC Insecticide **Slightly irritating**
Skin Sensitization	Bridged to Temprid SC Insecticide **Not a dermal sensitizer**

Table 4 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
Non-dietary incidental oral (short-term)	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
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
Intermediate- and Long-term Aggregate - Inhalation	90-day inhalation toxicity study	NOAEC = 0.00009 mg/L (0.02 mg/kg bw/day)	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.

[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

Table 5 PCO Dermal and Inhalation Exposure to Beta-cyfluthrin

Application Equipment	Amount Handled Per Day[1]	Unit Exposure (µg/ kg ai handled)[2]		Dermal Exposure (mg/kg bw/day)[3]	Dermal MOE[4]	Inhalation Exposure (mg/kg bw/day)[3]	Inhalation MOE[4]
		Dermal	Inhalation				
Temprid SC Insecticide							
Manually pressurized handwand	150 L /day	943.37	45.20	4.31×10^{-5}	873000	2.06×10^{-5}	969
Backpack	150 L /day	5445.85	62.1	2.49×10^{-4}	151000	2.84×10^{-5}	705
Temprid ReadySpray Insecticide							
Aerosol	14 cans per day	146598.1	1646	2.85×10^{-4}	132000	3.19×10^{-5}	626

[1] Based on Agency default Amount Handled Per Day values and USEPA (2006).
[2] PHED single layer with chemical resistant gloves. Light inhalation except for backpack which is moderate.
[3] Exposure (mg/kg bw/day) = [(Amount Handled Per Day (L/day) × Dilution Rate (2.0 mL product/L) × Density for Temprid SC) **OR** (Amount Handled Per Day (cans/day) × Net Contents (mL/can) × Density for Temprid ReadySpray Insecticide)] × Guarantee (%) × Unit Exposure (µg/ kg ai handled) × Absorption Value (%) × Unit Conversion (mg/ 1000 µg)
[4] MOE = Intermediate-to long-term NOAEL (mg/kg bw/day) ÷ Exposure (mg/kg bw/day); Target MOE = 300

Table 6 Indoor Inhalation Exposure for Beta-cyfluthrin[1]

Lifestage	Application Rate (kg a.i./L)[2]	Amount Handled (L/day)[3]	Mass of ai (mg; either M_{label} or M_{Csat})	Exposure Time (hr)	Inhalation Exposure (mg/kg/day)[4]	Inhalation MOE[5]
Adults	2.56×10^{-4}	1.89	483	16	3.13×10^{-8}	2230000
Youths 11 < 16 years				15	4.02×10^{-8}	1740000
Children 1 < 2 years				18	1.35×10^{-7}	520000

[1] For a full review of calculations, refer to USEPA Section 7 Indoor Environments SOP
[2] Application Rate = 2.0 mL/L dilution × Guarantee (10.5%) × Density × Conversion Factor (kg/1000g) = 0.0002558 kg a.i./L
[3] The amount handled is based on the 2012 USEPA SOP for Indoor Environments, which states that 0.5 gallons (1.89 L) would be used per day.
[4] Beta-cyfluthrin inhalation exposure was based on information from the Chemistry Exposure Section.
[5] MOE = NOAEL of 0.07 mg/kg bw/day ÷ Inhalation Exposure (mg/kg bw/day); target MOE = 300

Table 7 Dermal Exposure to Beta-cyfluthrin from Treated Mattresses[1]

Lifestage	Deposited Residue (µg/cm^2)	Surface area/ Body weight Ratio (cm^2/kg)	Fraction of skin in contact with surface	Fraction transferred	Protection factor	Dermal Exposure (mg/kg/day)	Dermal MOE
Adults	1	280	0.5	0.04	0.5	0.00286	131000
Youth 11 < 16 years	0.49	280				0.00137	275000
Children 1 < 2 years		640				0.00312	120000

[1] For a full review of calculations, refer to the USEPA Section 7 Indoor Environments SOP.

Table 8 Dermal Exposure from Hard and Soft Surfaces Treated with Beta-cyfluthrin[1]

Exposure Scenario		Lifestage (years)	DepR (µg/cm^2)[2]	Fraction Transferred	Transferable Residue (µg/cm^2)	TC (cm^2/hr)	ET (hr/day)	Exposure (mg/kg/day)	Dermal MOE[3]	Dermal MOE (Floor + Mattress)
Perimeter/ Spot (Coarse & Pin Stream, all pests excluding bed bugs)	Soft Surfaces	Adults	0.49	0.04	0.0195	6800	8	0.0136	28400	23300
		Youth (11 < 16)				5600	5	0.00982	39300	34400
		Children (1 < 2)				1800	4	0.01309	29500	23700
	Hard surfaces	Adults		0.06	0.0292	6800	2	0.0051	75700	48000
		Youth (11 < 16)				5600	1	0.00295	131000	88700
		Children (1 < 2)				1800	2	0.00982	39300	29600
Bed bugs (Perimeter/ Spot)	Soft Surfaces	Adults	0.24	0.04	0.00974	6800	8	0.00662	56770	39600
		Youth (11 < 16)				5600	5	0.00478	78586	61100
		Children (1 < 2)				1800	4	0.00638	58978	39600
	Hard surfaces	Adults		0.06	0.0146	6800	2	0.00248	151387	70100
		Youth (11 < 16)				5600	1	0.00144	261954	134000
		Children (1 < 2)				1800	2	0.00478	78637	47500
Bed bugs (crack and crevice)	Soft Surfaces	Adults	0.12	0.04	0.0049	6800	8	0.02408	15600	13900
		Youth (11 < 16)				5600	5	0.01240	30300	27300
		Children (1 < 2)				1800	4	0.00319	118000	59500
	Hard surfaces	Adults		0.06	0.0073	6800	2	0.00903	41600	31600
		Youth (11 < 16)				5600	1	0.00372	101000	73900
		Children (1 < 2)				1800	2	0.00239	157000	68000
Crack and crevice (excluding bed bugs)	Soft Surfaces	Adults	0.097	0.04	0.00390	6800	8	0.00272	142000	68100
		Youth (11 < 16)				5600	5	0.00196	196000	114000
		Children (1 < 2)				1800	4	0.00262	147000	66100
	Hard surfaces	Adults		0.06	0.00584	6800	2	0.00102	378000	97300
		Youth (11 < 16)				5600	1	0.000589	655000	194000
		Children (1 < 2)				1800	2	0.00196	197000	74600

[1] For a full review of calculations, refer to the USEPA Section 7 Indoor Environments SOP.
[2] DepR = Deposited Residue.
[3] Exposure for people under 16 years was calculated using the dilution rate for Temprid SC Insecticide at 2 mL product/L for hard and soft surfaces and the dilution rate of 1 mL product/L for bed bugs and mattresses. For adults, the dermal exposure to mattresses treated with Temprid ReadySpray Insecticide (Table 7) was used because it has a higher deposited residue for bed bugs.

Table 9 Child (1-2 years) Hand-to-Mouth Exposure to Beta-cyfluthrin

(shaded cells indicate the target MOE is not exceeded)

Exposure Scenario	Deposited Residue (µg a.i./cm^2)	Dermal Exposure (mg)	Surface area of 1 hand (cm^2)	Hand residue loading (mg/cm^2)	Fraction of hand mouthed	Exposure Time (hours/day)	Incidental Oral Exposure (mg/kg/day)	Incidental Oral MOE
Temprid ReadySpray Insecticide								
Indoor Perimeter/Spot (Coarse & Pin Stream) / Bed Bugs								
Soft Surfaces	0.5	0.14	150	0.000072	0.13	4	0.00196	255
Hard Surfaces		0.11		0.000054		2	0.000737	679
Bed bugs (crack and crevice)								
Soft Surfaces	0.25	0.072	150	0.000036	0.13	4	0.000982	509
Hard Surfaces		0.054		0.000027		2	0.000368	1360
Crack and crevice								
Soft Surfaces	0.1	0.029	150	0.000014	0.13	4	0.000393	1270
Hard Surfaces		0.022		0.000011		2	0.000147	3390
Temprid SC Insecticide								
Indoor Perimeter/Spot (Coarse & Pin Stream) (All pests excluding bed bugs)								
Soft Surfaces	0.49	0.14	150	0.000070	0.13	4	0.00191	260
Hard Surfaces		0.11		0.000053		2	0.000718	697
Bed Bugs (indoor perimeter/spot)								
Soft Surfaces	0.24	0.070	150	0.000035	0.13	4	0.000957	523
Hard Surfaces		0.053		0.000026		2	0.000359	1390
Bed Bugs (crack and crevice)								
Soft Surfaces	0.12	0.035	150	0.000018	0.13	4	0.000478	1050
Hard Surfaces		0.026		0.000013		2	0.000179	2790
Crack and crevice (All pests, excluding bed bugs)								
Soft Surfaces	0.1	0.028	150	0.000014	0.13	4	0.000383	1310
Hard Surfaces		0.021		0.000011		2	0.000144	3480

[1] For a full review of calculations, refer to the USEPA Section 7 Indoor Environments SOP.

Table 10 Child (1 < 2 year) Object-to-Mouth Exposure to Beta-cyfluthrin

Exposure Scenario	Deposited Residue (µg/cm^2)	Fraction of residue transferred to object	Object Residue (µg/cm^2)	Exposure Time (hours/day)	Extraction by Saliva	Incidental Oral Exposure (mg/kg/day)	Incidental Oral MOE
Indoor Perimeter/Spot (Coarse & Pin Stream) (All pests excluding bed bugs)							
Soft Surfaces	0.49	0.04	0.019	4	0.48	0.000255	1960
Hard Surfaces		0.06	0.029	2		0.000191	2620
Bed Bugs (indoor perimeter/spot)							
Soft Surfaces	0.24	0.04	0.010	4	0.48	0.000127	3930
Hard Surfaces		0.06	0.015	2		0.000095	5240

Bed bug (crack and crevice)							
Soft Surfaces	0.12	0.04	0.005	4	0.48	0.000064	7850
Hard Surfaces		0.06	0.007	2		0.000048	10500
Crack and crevice (All pests, excluding bed bugs)							
Soft Surfaces	0.1	0.04	0.004	4	0.48	0.000051	9820
Hard Surfaces		0.06	0.006	2		0.000038	13100

[1] For a full review of calculations, refer to the USEPA Section 7 Indoor Environments SOP.

Table 11 Aggregate Exposure for Beta-cyfluthrin[1]

(shading indicates the target MOE is not exceeded)

Temprid ReadySpray Insecticide								
	Hard Surface MOEs				Soft Surface MOEs			
	HtM	Inhalation	Dietary	Aggregate	HtM	Inhalation	Dietary	Aggregate
Perimeter/Spot (Coarse & Pin Stream)/Bed Bug	679	520000	455	272	255	520000	455	163
Bed bugs (crack and crevice)	1360	520000	455	341	509	520000	455	240
Crack and crevice (excluding bed bugs)	3390	520000	455	401	1270	520000	455	335
Temprid SC Insecticide								
	Hard Surface MOEs				Soft Surface MOEs			
	HtM	Inhalation	Dietary	Aggregate	HtM	Inhalation	Dietary	Aggregate
Perimeter/Spot (Coarse & Pin Stream) (All pests, excluding bed bugs)	697	520000	455	275	260	520000	455	166
Bed Bug (perimeter and spot)	1390	520000	455	343	523	520000	455	243
Bed Bug (crack and crevice)	2790	520000	455	391	1050	520000	455	317
Crack and crevice (All pests, excluding bed bugs)	3480	520000	455	402	1310	520000	455	337

[1] The aggregate NOAEL of 0.5 mg/kg bw/day for oral exposure and 0.07 for short-term inhalation exposure; target MOE = 300
The aggregate MOE was calculated by, $\frac{1}{[(1/MOE_{HtM}) + (1/MOE_{Inhalation}) + (1/MOE_{Dietary})]}$

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2072856	2008, Product chemistry of Baythroid technical insecticide (CBI), DACO: 2.1, 2.11.1, 2.11.2, 2.11.3, 2.11.4, 2.12.1, 2.13.1, 2.13.2, 2.13.3, 2.13.4, 2.2, 2.3.1, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 CBI
2072857	1988, Product chemistry of BAY FCR 4545 technical, DACO: 2.14.1, 2.14.10, 2.14.11, 2.14.12, 2.14.13, 2.14.14, 2.14.15, 2.14.2, 2.14.3, 2.14.6, 2.14.7, 2.14.8, 2.14.9, 2.16, 8.2.1 CBI
2072860	2010, Tier 2 summary identity, physical and chemical properties, data on application and further information on the plant protection products - DACO Part 3 - Baythroid XL, DACO: 2.16
2072861	2010, Tier 2 summary identity, physical and chemical properties, data on application and further information on the plant protection products - DACO Part 3 - Poncho Beta - BCS DER for product chemistry of Poncho Beta, DACO: 2.16
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2124889	2011, Clarification response letter, DACO: 2.2 CBI
2147185	2007, Final Report beta-cyfluthrin (FCR4545 / AE 1430672), technical substance Melting Point A.1. (OECD 102) Boiling Point A.2. (OECD 103) Thermal Stability (OECD 113), DACO: 2.14, 2.14.13, 2.14.4, 2.14.5 CBI
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2147194	2007, Determination of the pH-value of beta-cyfluthrin (AE 1430672), pure substance, DACO: 2.14 CBI
2147195	2007, Determination of the pH-value of beta-cyfluthrin (AE 1430672), technical substance, DACO: 2.14 CBI
2147197	1988, Octanol/Water Partition Coefficient Of Cyfluthrin K+L, DACO: 2.14, 2.14.11 CBI
2147198	1995, Determination of Safety-Relevant Parameters of FCR 4545 (Bulldock Techn.), DACO: 2.14 CBI
2147199	2001, Spectral Data Set of 6-Cyfluthrin, DACO: 2.14 CBI
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PMRA Document Number	Reference
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2257124	2012, Beta-cyfluthrin (AE 1430672) Description of the Manufacturing Process of the Technical Grade Active Substance, DACO: 2.11.1, 2.11.2, 2.11.3 CBI
2257125	2012, Beta-cyfluthrin (AE 1430672) Description of the Impurities, Formation and Justification (Certified Limits) in the Technical Grade Active Substance, DACO: 2.11.4 CBI
2411024	2014, Material Accountability of Technical beta-cyfluthrin (AE 1430671/FCR4545), DACO: 2.13.1 CBI
2413512	2008, Product chemistry of Baythroid technical insecticide (CBI), DACO: 2.13.1 CBI
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2413521	2014, Validation of the analytical method AM038613FP1: Determination of (CBI) in technical beta-Cyfluthrin (AE 1430672 / FCR4545) by gas chromatography, DACO: 2.13.1 CBI
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2073015	1986, Gas chromatographic determination of cyfluthrin (FCR 1272) in pond water [Tox/Ecotox method], DACO: 8.2.2.3
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2073799	2010, Storage Stability and/or Corrosion Characteristics of Temprid SC, DACO: 3.5.10, 3.5.14 CBI
2240172	2012, HPLC Determination of Beta-cyfluthrin, DACO: 3.4.1 CBI
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2413048	2014, Precision and Accuracy for Method AM007307KF1, DACO: 3.4.1 CBI
2073799	2010, Storage Stability and/or Corrosion Characteristics of Temprid SC, DACO: 3.5.10, 3.5.14 CBI
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2632696	2016, Packaging Storage Stability and Corrosion Characteristics of Temprid ReadySpray, DACO: 3.5.10,3.5.14 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
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1215546 1216127	Chronic Toxicity Study On Rats, DACO: 4.4.1
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3.0 Environment

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4.0 Value

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PMRA Document Number	Reference
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3.0 Environment

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2407575	Pyrethroid Photochemistry: Decamethrin, DACO: 8.2.3.2
2407577	Beta-Cyfluthrin, DACO: 8.2.3.2
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4.0 Value

na

ii) Unpublished Information

1.0 Chemistry

na

2.0 Human and Animal Health

na

3.0 Environment

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4.0 Value

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1156558	Efficacy Trial Summaries On The Control Of European Earwig (Tempo 20WP)(106519), DACO: 10.1
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