Proposed Registration Decision PRD2016-29

Flumethrin

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Overview

Proposed Registration Decision for Flumethrin

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 Flumethrin Technical Insecticide and Bayvarol Beehive Pest Control Strip, containing the technical grade active ingredient flumethrin, to control varroa mites in honeybee hives.

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 Flumethrin Technical Insecticide and Bayvarol Beehive Pest Control Strip.

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. 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 Health Canada's website at healthcanada.gc.ca/pmra.

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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."

Before making a final registration decision on Flumethrin Technical Insecticide and Bayvarol Beehive Pest Control Strip, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on Flumethrin Technical Insecticide and Bayvarol Beehive Pest Control Strip, 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 Flumethrin?

Flumethrin is a pyrethroid that controls mites. The end-use product, Bayvarol Beehive Pest Control Strip, a plastic strip impregnated with flumethrin, is intended to kill varroa mites in honeybee hives.

Health Considerations

Can Approved Uses of Flumethrin Affect Human Health?

Bayvarol Beehive Pest Control Strip, containing flumethrin, is unlikely to affect your health when used according to label directions.

Potential exposure to flumethrin may occur through the diet or when handling and applying Bayvarol Beehive Pest Control Strips. 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 to which humans are normally exposed when pesticide-containing products are used according to label directions.

In laboratory animals, the technical grade active ingredient flumethrin was of high acute toxicity via the oral route of exposure, of slight acute toxicity via the dermal route of exposure, and of moderate acute toxicity via the inhalation route of exposure. Consequently, the signal word and hazard statement "DANGER POISON" are required on the label. Flumethrin was minimally irritating to the eye and non-irritating to the skin, and did not produce an allergic skin reaction.

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

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

Bayvarol Beehive Pest Control Strip is not acutely toxic via the oral and dermal routes of exposure, and is not expected to pose an inhalation hazard. It is not considered irritating to the eyes or skin or to produce an allergic skin reaction. Consequently, no acute hazard labelling is required for this end-use product.

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 flumethrin to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints used for risk assessment were decreased activity and reduced birth weight, as well as impaired growth of the young animal. There is some concern for increased sensitivity of the young exposed to flumethrin. The risk assessment protects against these and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in Food

Dietary risks from food are not of health concern.

Acute and chronic dietary intake estimates for the general population and all population subgroups are not of health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Germany and the United Kingdom using flumethrin in beehives are acceptable. The MRL for this active ingredient can be found in the Science Evaluation of this Proposed Registration Decision.

Occupational Risks From Handling Bayvarol Beehive Pest Control Strip

Risks from commercial use of Bayvarol Beehive Pest Control Strip are not of health concern when used according to label precautions and directions.

Beekeepers, who set Bayvarol Beehive Pest Control Strips, as well as retrieve the strips from beehives, can come in direct contact with residues on the skin. Therefore, the label specifies that anyone handling Bayvarol Beehive Pest Control Strips must wear a long-sleeved shirt, long pants, chemical-resistant gloves (for example, disposable nitrile gloves), socks and shoes. Leather beekeeping gloves must not be worn when handing this product. Taking into consideration these label statements, the use pattern, and the duration of exposure for beekeepers, health risks to these individuals are not a concern.

For bystanders, exposure is considered negligible because they are not expected to handle any strips. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Flumethrin Is Introduced Into the Environment?

Flumethrin is used in the formulation for Bayvarol Beehive Pest Control Strip for the control of varroa mites on honeybees. Since the end-use product will be used in beehives, the risk to non-target organisms is considered to be negligible, when used according to the label directions. Because of the use pattern, flumethrin is unlikely to be introduced to the environment.

Value Considerations

What Is the Value of Bayvarol Beehive Pest Control Strip?

Bayvarol Beehive Pest Control Strip has value as it provides 95 to 100% control of varroa mites, the most important pest of honeybees, and offers users a new active ingredient for use against this pest.

Varroa mites are the most important parasitic pest of honeybees, and have a severe economic impact on the Canadian beekeeping industry. Significant varroa mite infestations in a honeybee colony will cause the loss of the infested colonies. Varroa mites are an important cause of honeybee colony loss in Canada.

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 Bayvarol Beehive Pest Control Strip to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Beekeepers can come in direct contact with residues on the skin during placing and removing the Bayvarol Beehive Pest Control Strips. Therefore, the label specifies the required personal protective equipment for anyone handling Bayvarol Beehive Pest Control Strips. Leather beekeeping gloves must not be worn when handing this product.

Environment

Standard disposal statements to the Bayvarol Beehive Pest Control Strip label have been added to stop any release of the product to the environment from waste product and packaging.

Next Steps

Before making a final registration decision on Flumethrin Technical Insecticide and Bayvarol Beehive Pest Control Strip, the PMRA will consider any 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 note that, to comply with Canada's international trade obligations, consultation on the proposed MRL will also be conducted internationally via a notification to the World Trade Organization. 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

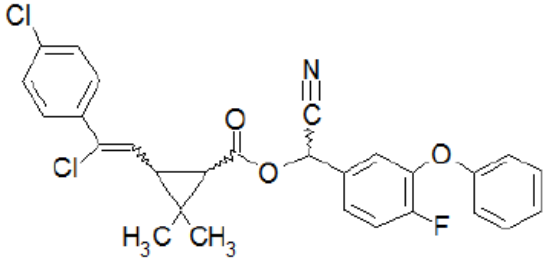
When the PMRA makes its registration decision, it will publish a Registration Decision on Flumethrin Technical Insecticide and Bayvarol Beehive Pest Control Strip (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Flumethrin

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Flumethrin
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(*RS*)-α-cyano-4-fluoro-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-(*EZ*)-3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate or (*RS*)-α-cyano-4-fluoro-3-phenoxybenzyl (1*RS*)-*cis*-*trans*-(*EZ*)-3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate
2. Chemical Abstracts Service (CAS)	Cyano(4-fluoro-3-phenoxyphenyl)methyl 3-[2-chloro-2-(4-chlorophenyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate
CAS number	69770-45-2
Molecular formula	$C_{28}H_{22}Cl_2FNO_3$
Molecular weight	510.3836
Structural formula	
Purity of the active ingredient	96.2%

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

Technical Product—Flumethrin Technical Insecticide

Property	Result
Colour and physical state	Amber solid
Odour	No distinguishable odour
Melting range	156.4°C
Boiling point or range	> 250°C
Density at 20°C	1.383 g/cm^3
Vapour pressure at 20°C	< 2.442×10^{-5} Pa at 24.8°C
Ultraviolet (UV)-visible spectrum	λ_{max} = 268 nm, independent of pH

Property	Result
Solubility in water at 31°C	Water = 0.067 mg/L pH 4 = 0.046 mg/L pH 7 = 0.47 mg/L pH 9 = 0.33 mg/L
Solubility in organic solvents at 21°C	Solvent — Solubility (g/L) Acetone — 199 Acetonitrile — >200 Dichloromethane — >200 Dimethyl sulfoxide — 44 Ethanol — 44 Ethyl acetate — >200 Hexanes — 22 Toluene — >200
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 7.52
Dissociation constant (pK_a)	No dissociation
Stability (temperature, metal)	Stable in the presence of iron, iron acetate, aluminum and aluminum acetate at ambient and elevated temperatures.

End-Use Product—Bayvarol Beehive Pest Control Strip

Property	Bayvarol Beehive Pest Control Strip
Colour	Milky white
Odour	Odourless
Physical state	Solid
Formulation type	Impregnated product
Guarantee	Flumethrin at 3.5 mg per strip
Container material and description	Aluminum foil pouch (primary packaging) in cardboard box (secondary packaging)
Density	0.900-0.930 g/cm^3
pH of 1% dispersion in water	N/A; not soluble in water
Oxidizing or reducing action	Not an oxidizing or reducing agent
Storage stability	Stable over 60 months at ambient temperature.
Corrosion characteristics	Not expected to be corrosive to its commercial packaging
Explodability	Not explosive

1.3 Directions for Use

Strips are suspended into the spaces between combs in the central brood rearing area in such a way that they can be occupied by bees on both sides. Normally developed colonies receive four strips. Nuclei and young colonies and newly collected swarms receive two strips. Large colonies occupying several brood chambers receive four strips per chamber, which are distributed over the central bee space in each brood chamber. For most effective control, Bayvarol Beehive Pest Control Strips are recommended for use in late summer after the honey harvest. Strips should not be used during peak honey flow periods. Bayvarol Beehive Pest Control Strips should be left in the colonies for a maximum of six weeks and then removed.

1.4 Mode of Action

Flumethrin is a pyrethroid insecticide that affects the nervous system of mites, causing paralysis and death. Flumethrin is a Group 3A insecticide. Pyrethroid insecticides delay or prevent the inactivation of the sodium channels, preventing the transmission of nerve signals and ultimately killing the cell. Flumethrin is active as a miticide both by ingestion and contact routes. Bayvarol Beehive Pest Control Strip is a plastic strip impregnated with flumethrin which is placed in beehives and is used as an ectoparasiticide to kill varroa mites. Flumethrin is transferred to the honeybees by direct contact, as they move about the hive and walk on and rub against the strips.

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 the impurities in Flumethrin Technical Insecticide 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 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

A high performance liquid chromatography method with ultraviolet detection (HPLC-UV; Method RA 654/93) was developed for data gathering purposes, and the method was adequately validated based on concurrent recoveries in honey at the limit of quantitation (LOQ). A high performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS; Method 01462 in honey matrix) was developed for enforcement purposes, and the method fulfilled the requirements with regards to specificity, accuracy and precision at the method LOQ. Acceptable recoveries (70-120%) were obtained in honey at fortification levels of 3 ppb, 6 ppb and 30 ppb. The extractability of residues of flumethrin in honey was successfully demonstrated. Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Flumethrin is a synthetic pyrethroid insecticide and is referred to as a Type II pyrethroid due to the presence of an alpha-cyano group. 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 flumethrin typically induce the "CS syndrome" (the "CS" is derived from choreoathetosis and salivation), 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.

A detailed review of the toxicology database for flumethrin was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to flumethrin. Flumethrin has four sites of stereoisomerism (three chiral carbons and one side of geometric isomerism), resulting in 16 isomers. Technical grade flumethrin consists of more than 90% trans-Z1 and trans-Z2 isomers, in a ratio of approximately 60:40 trans-Z1 isomer:trans-Z2 isomer. The majority of the toxicology studies were conducted with a test material of isomeric ratio considered to be representative of that proposed for registration. Certain toxicology studies were conducted with a test diet prepared with a pre-mix of approximately 45% flumethrin with a silica carrier; in these cases, doses were adjusted for the concentration of flumethrin in the test diet.

The absorption, distribution, metabolism, and excretion of flumethrin, uniformly labelled with ^{14}C in the chlorophenyl ring, were investigated in rats following the administration of single or repeated low oral doses, a single high oral dose, or a single low intraduodenal dose. The absorption, distribution, and excretion of flumethrin, uniformly labelled with ^{14}C in the fluorophenyl ring, were also examined in rats following the administration of single low doses via the oral, intravenous, or intraduodenal routes, as well as a single high oral dose. For both radiolabel positions, the administered radioactivity was incompletely absorbed from the intestinal lumen of rats, with absorption estimated to be 50% to 75% of the administered oral dose. A published toxicokinetics study in rabbits demonstrated slow and incomplete absorption of flumethrin following administration of a single oral dose.

In rats, elimination of radioactivity occurred slowly and primarily via the feces. The half-life of elimination of radioactivity from the plasma ranged from 130 to 160 hours. With repeated oral dosing, excretion of radioactivity decreased with each successive dose, indicating an accumulation of radioactivity in tissues.

Seven days after the administration of single or repeated doses of chlorophenyl-labelled flumethrin, up to 20% of the administered dose remained in tissues. The highest levels of radioactivity for all dosing regimens were found in the plasma, lung, erythrocytes, heart, skin, liver, kidney, testis, uterus and ovary. The fat also contained relatively high residues following administration of single high or multiple low oral doses. At ten days after the administration of a single high oral dose of fluorophenyl-labelled flumethrin, less than one percent of the administered dose remained in tissues, with the highest levels in the renal fat, skin, and sciatic nerve. Whole body autoradiographic analysis was also conducted in rats following administration of single high oral doses of flumethrin. At 24 hours following dosing with chlorophenyl-labelled flumethrin, radioactivity was still present in the kidney, liver, intestinal tract contents, blood, bone marrow, fibrous tissues, pineal gland (epiphysis), and pituitary gland (hypophysis). By 48 hours after dosing with fluorophenyl-labelled flumethrin, the stomach wall, the contents of the small and large intestines, and the brown fat were the only tissues with high autoradiographic intensity.

The metabolism of chlorophenyl-labelled flumethrin in rats was limited, with a large proportion of excreted radioactivity identified as unchanged flumethrin. The only metabolite identified was flumethrin acid, which is formed following cleavage of the ester bond. The metabolism of fluorophenyl-labelled flumethrin was not examined.

Results from plasma analysis in the rat gavage reproductive toxicity study demonstrated higher plasma levels of flumethrin in males than females, and suggested that saturation of absorption occurs between doses of 2 and 3 mg/kg bw/day.

In a special study in which rats received flumethrin by intraperitoneal injection for six days, reductions in cytochrome P450 protein content, NADPH-cytochrome c reductase activity, aniline hydroxylase activity, aminopyrine N-demethylase activity, and UDP-GT activity were observed. This response is typical of Type II pyrethroids, as Type II pyrethroids that contain an alpha-cyano group tend to inhibit liver drug-metabolizing enzymes, while Type I pyrethroids that do not contain this group may induce these enzymes.

In acute toxicity testing via the oral route in rats, the trans-Z1 isomer of flumethrin was moderately toxic, and the trans-Z2 isomer was highly toxic. When tested in rats, a mixture of the trans-Z1 isomer:trans-Z2 isomer at a ratio of approximately 60:40 was highly toxic via the oral route, slightly toxic via the dermal route, and moderately toxic via the inhalation route. It was minimally irritating to the eye and non-irritating to the skin of rabbits, and negative for dermal sensitization in guinea pigs using the Maximization method. In a supplemental study, decreased respiratory rate was recorded in rats and mice following one hour of inhalation exposure to flumethrin.

Clinical signs of toxicity following acute oral, dermal and inhalation exposure to flumethrin were consistent with Type II pyrethroids and included salivation, piloerection, decreased activity, hunched posture, spastic gait, shaking movements, body tremors, and increased sensitivity to sound and touch.

In acute toxicity testing, the end-use product, Bayvarol Beehive Pest Control Strip, was of low acute toxicity in rats via the oral and dermal routes of exposure. Based on the low vapour pressure of flumethrin, which is embedded into a plastic carrier in the pest strip, the end-use product is not considered to pose an acute inhalation hazard. Furthermore, Bayvarol Beehive Pest Control Strip is not considered to pose eye or skin irritation or dermal sensitization hazards based on the product design as well as the hazard characteristics of the active ingredient.

Following short-term dietary exposure to flumethrin, clinical signs of toxicity were observed in rats and/or mice and included piloerection, altered gait, impaired mobility, tremors, salivation, lacrimation, and/or laboured breathing. Mortality in mice and rats was observed as well as a grossly visible brain lesion (described as “gyri and sulci filled in”) in rats that died. Of particular interest following both short- and long-term repeated dietary dosing were effects on the skin in rats, mice and dogs. The dermal lesions were severe, manifesting in some studies as wounds, injury, discoloration, encrustation, ulceration, inflammation, and/or missing skin. In several studies, the lesions became severe enough to result in moribundity or mortality. The dose response for skin effects and mortality in the long-term studies in rats and mice was somewhat steep. The dermal lesions sometimes resulted in secondary effects such as plasmacytosis of the draining lymph nodes and extramedullary hematopoiesis, a compensatory reaction to blood loss from the skin wounds. It is possible that these lesions resulted from increased grooming as well as biting and scratching of the skin as a result of paresthesia. This may have resulted from local effects on nerve endings in areas of the body coming in contact with treated diet. However, the toxicokinetic investigations revealed that the skin of rats contained relatively high levels of flumethrin-derived radioactivity seven to ten days after the administration of a single gavage dose. Skin wounds were also observed in maternal animals in the rat and rabbit gavage developmental toxicity studies. Furthermore, dogs exhibited dermal lesions on body surfaces (such as the back) that were less likely to come into direct contact with test diet, which was administered in the form of a mash. An increased sensitivity to being lifted by the scruff of the neck was also recorded for treated dogs. Therefore, the possibility could not be ruled out that the dermal lesions may have resulted from increased grooming as well as scratching and biting of the skin due to paresthesia following systemic absorption of flumethrin via the gastrointestinal tract and subsequent distribution to the skin.

Following repeated dermal exposure to flumethrin for 14, 28, or 90 days, clinical signs of toxicity were observed in rats in the form of gait abnormalities (including high stepping, stilted, and/or uncoordinated gait), reduced mobility, salivation, sunken flanks, hunched backs, and/or laboured breathing. Body weight was also reduced in all three dermal studies. Other effects noted after 90 days of dermal exposure included thymic atrophy, reduced glycogen in the liver, plasmacytosis in the mandibular lymph nodes, and clinical chemistry changes (increased cholesterol and triglycerides; decreased glucose, bilirubin, and creatinine). In contrast to the pronounced skin findings in the repeated-dose dietary studies, only mild effects on the skin, in the form of skin reddening, were observed in the 28-day and 90-day rat dermal toxicity studies, and only at high doses.

Effects noted in a 28-day inhalation toxicity study in rats included clinical signs typical of pyrethroid toxicity, such as salivation and reduced mobility, as well as reductions in cholesterol, triglycerides, and protein levels. The decreased respiratory rate in the supplemental study in rats

and mice following one hour of inhalation exposure was also seen in the rat 28-day inhalation toxicity study. Respiratory symptoms such as bradypnea and laboured breathing were also observed. As was seen in the special study in which rats received flumethrin by intraperitoneal injection for six days, reductions in cytochrome P450 content and N-demethylase activity were also observed in the rat 28-day inhalation toxicity study.

There was evidence in the database suggesting increased toxicity with increasing duration of dosing with flumethrin. Mortality was observed in mice after longer-term dosing at lower dose levels than those resulting in mortality in the short-term studies. Mice also exhibited kidney nephropathy as well as mineralization and glandular hyperplasia of the stomach after longer-term dosing only. In rats, vacuolation of the adrenal cortex and degeneration of muscle and nerve fibers were observed only after chronic exposure.

In long-term dietary studies conducted with flumethrin, there was no evidence of oncogenicity in rats or mice. There was no evidence of genotoxicity when flumethrin was tested in a battery of in vivo and in vitro genotoxicity studies. In a supplemental study conducted with a lower purity of flumethrin, chromosomal aberrations and micronuclei were observed in mice. Overall, flumethrin was not considered to be genotoxic.

In both short-term and long-term rat dietary studies with flumethrin, the reproductive organs were decreased in size, particularly in males. Ovarian weight was decreased in female rats after short-term dosing only, seminal vesicles were reduced in size after short- and long-term dosing, and atrophy of the testes, epididymides, and prostate were noted after chronic dosing.

Two two-generation reproductive toxicity studies in the rat using comparable dose levels were available for flumethrin; one was conducted via dietary administration and the other was conducted via oral gavage. In the dietary study, no treatment-related effects were observed on the reproductive parameters that were examined. In the gavage study, there was no effect on the ability to conceive or carry offspring to parturition; however, there was a decrease in birth weight. Offspring effects noted in the dietary study included cramped or hunched posture, stiff legs held in the caudal position, pigeon chest, and reduced body weight. The offspring in the dietary study were also cool to the touch and squealed frequently. In the gavage study, offspring exhibited reduced body weights, thin appearance, and an absence of milk in the stomach during the postnatal period. An increase in anogenital distance was also noted in males. The effects on birth weight and offspring body observed in the dietary study occurred in the absence of maternal toxicity. At the highest dose level, an increase in pup mortality was observed in both generations of both studies. Pup deaths occurred from postnatal day 0 to 4 in both studies, while in the dietary study, pup loss continued throughout lactation. In the dietary study, the increased pup mortality occurred at a dose at which maternal effects were limited to skin wounds in two P-generation females and reduced food consumption in F1-generation females. In the gavage study, increased pup mortality occurred at a dose at which maternal effects included loss of fur and decreased lactational body weights in P-generation females, and body weight decreases during premating, gestation, and lactation in F1-generation females.

When considering the toxicology database as a whole, the serious endpoint (increased pup mortality) observed in the reproduction studies occurs, in general, at a dose that elicits toxicity in adult animals. Results from a special lactational transfer study confirmed that rat pups were exposed to flumethrin through the milk of maternal animals that were gavage-dosed with flumethrin.

Developmental toxicity studies were conducted with flumethrin in rats and rabbits. In the rat, maternal animals exhibited salivation and reduced body weight gain, while fetuses had reduced body weight and an increased incidence of delayed ossification of several bones. In addition, there were an increased number of fetuses with malformations and a slight increase in the number of fetuses with the malformation microphthalmia. Therefore, in rats, a serious endpoint (malformations) was observed in the presence of maternal toxicity. In rabbits, increases in the incidence of swollen limbs in maternal animals and in the incidence of fused sternebrae in fetuses were apparent. The increased incidence of swollen limbs in maternal animals was considered equivocal due to the low incidence (two dams), while the increased incidence of fused sternebrae in fetuses was considered equivocal when considering the weak dose response and the historical control ranges. At the highest dose, body weight loss and dermal wounds were noted in dams and delayed ossification was observed in fetuses. Abortions and increased resorptions were also observed at the highest dose in the rabbit developmental toxicity study.

The potential for flumethrin to elicit neurotoxic effects was investigated in rats following acute and repeated gavage administration as well as in a gavage developmental neurotoxicity (DNT) study. Following administration of a single dose of flumethrin, reductions in motor and locomotor activity were observed, and at higher doses, staining, abnormal posture, salivation, decreased arousal, reduced body temperature, and lacrimation were also observed. Staining and reduced motor and locomotor activity were also observed following repeated dosing, in addition to decreased body weight, reduced brain weight and ataxia. In the DNT study, body weights were reduced in offspring at the same dose level that caused decreased body weights in maternal animals. Slight increases in motor and locomotor activity were observed in offspring in the early postnatal period only. There was no other treatment-related effect on the neurobehavioural endpoints examined.

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 the 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; gavage dosing results in greater internal doses compared to dietary administration. The pyrethroids are regarded as having a narrow window of time-to-peak-effect. The design of a DNT study does not consider time-to-peak-effect and may miss the window of peak toxicity for the pyrethroids. The current DNT study for flumethrin, 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 a 28-day immunotoxicity study in rats in which flumethrin was administered in the diet, there was indication of dysregulation of the immunologic response in the form of reductions in the number of spleen cells, as well as elevated immunoglobin-A and immunoglobin-M activity and activity of plaque forming cells. There were other indications in the database of perturbations to the immune system, such as thymic atrophy in the 90-day dermal toxicity study in rats, decreased spleen and thymus weights in the 28-day inhalation toxicity study in rats, and lymphocyte depletion in the spleen in the 90-day dietary study in mice.

In several studies, male animals appeared to be more sensitive to flumethrin toxicity than female animals. For example, male mice exhibited mortality and reduced body weights at lower doses than female mice in the long-term dietary study, and reductions in motor activity and body weight occurred at lower doses in males than in females in the 90-day neurotoxicity study. These results are supported by the finding of higher plasma levels of flumethrin in male rats when compared to female rats in the gavage two-generation reproductive toxicity study.

Flumethrin acid, the major metabolite identified in rats and livestock, was of moderate acute toxicity via the oral and inhalation routes in rats, and of low acute toxicity via the dermal route in rats. It was minimally irritating to the eyes and non-irritating to the skin of rabbits. Flumethrin acid was negative for bacterial reverse mutation in the TA98 strain of Salmonella typhimurium. In a 28-day study in which rats were fed a flumethrin acid-treated diet, no adverse effects were noted up to the highest dose tested. Based on these findings, the flumethrin acid metabolite is not considered of greater toxicity than the parent compound flumethrin.

Results of the toxicology studies conducted on laboratory animals with flumethrin and flumethrin acid as well as the associated end-use product 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

The PMRA has received incident reports involving the active ingredient flumethrin. However, all of these incidents involved the application of a flea and tick collar, containing the active ingredients flumethrin at 4.5% and imidacloprid at 10%, to pets in the United States and are not directly relevant to the use pattern of applying pest strips in beehives. Although the human incidents involved dermal exposure to a product impregnated with flumethrin, which could be considered a situation akin to one that could occur with the application of Bayvarol Beehive Pest Control Strip, the beehive strip contains a much lower concentration of flumethrin (0.05%) and applicators of the beehive strip are required to wear chemical-resistant gloves when handling the strips, thus reducing the likelihood of exposure.

3.1.1 *Pest Control Products Act* Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the standard complement of required studies including developmental toxicity studies in rats and rabbits and reproductive toxicity studies in rats. A developmental neurotoxicity study in rats is also available for flumethrin.

With respect to concerns relevant to the assessment of risk to infants and children, there was no evidence suggestive of increased sensitivity of the young in the rat DNT study since effects in the offspring (decreased body weight and increased activity) occurred in the presence of maternal toxicity (decreased body weight gain). In the rabbit developmental toxicity study, developmental toxicity (an apparent increase in fetal incidence of the variation fused sternebrae) was observed in the presence of maternal toxicity (an apparent increase in the incidence of swollen limbs). In the rat developmental toxicity study, a serious endpoint (malformations) was observed in the presence of maternal toxicity (salivation and decreased body weight gain). In the dietary reproductive toxicity study, clinical signs of toxicity and reduced body weight in offspring were observed at a dose that elicited parental toxicity (dermal lesions). In the gavage reproductive toxicity study, decreases in birth weight and offspring body weight were observed in the absence of maternal toxicity; however, there is a low level of concern for these findings due to the nature of the endpoint. Increased pup mortality (a serious endpoint) occurred in the dietary and gavage reproductive toxicity studies at a dose that elicited toxicity in adult animals.

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. Due to the lack of a comparative oral neurotoxicity study, an adequate assessment of sensitivity of the young is currently not available for flumethrin 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. The endpoints and factors selected for use in risk assessment provide adequate margins to the effects in young animals noted above.

3.2 Acute Reference Dose

To estimate acute dietary risk, the acute oral neurotoxicity study conducted in adult rats with a no observed adverse effect level (NOAEL) of 0.5 mg/kg bw was selected. At the lowest observed adverse effect level (LOAEL) of 1 mg/kg bw, decreased motor and locomotor activity were observed in males. These effects were the result of a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were 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 Acute Reference Dose (ARfD) is calculated according to the following formula:

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

This ARfD provides a margin of 1000 to the NOAEL for malformations observed in rat fetuses in the developmental toxicity study.

3.3 Acceptable Daily Intake

To estimate risk from repeated dietary exposure, the combined results from both the dietary and gavage two-generation reproductive toxicity studies in rats were considered, and the offspring and reproductive NOAEL of 0.5 mg/kg bw/day was selected. At the LOAEL of 1 mg/kg bw/day, decreased birth weight and impaired growth of offspring were observed. The selected NOAEL was the lowest NOAEL in the database, and was considered to provide appropriate protection for all populations. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. A 3-fold database uncertainty factor was applied 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. The CAF is thus 300.

The Acceptable Daily Intake (ADI) is calculated according to the following formula:

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

This ADI provides a margin of 1000 to the NOAEL for malformations observed in rat fetuses in the developmental toxicity study, and a margin of 500 to the NOAEL for pup deaths in the rat gavage reproductive toxicity study.

Cancer Assessment

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

3.4 Occupational and Residential Risk Assessment

Occupational exposures to Bayvarol Beehive Pest Control Strips are characterized as short-term in duration for beekeepers and are predominantly by the dermal route.

3.4.1 Toxicological Endpoints

Short-Term Dermal

For short-term dermal risk assessments, the NOAEL of 0.5 mg/kg bw/day from the combined results of the two-generation reproductive toxicity studies was selected. At the LOAEL of 1 mg/kg bw/day, decreased birth weight and impaired growth of offspring were observed. The selected NOAEL was the lowest NOAEL in the database, and was considered protective of all populations. The target Margin of Exposure (MOE) is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a 3-fold database uncertainty factor for concerns related to potential sensitivity of the young.

3.4.1.1 Dermal Absorption

No dermal absorption studies were submitted for flumethrin and none are available in the literature. Therefore, the physical/chemical properties, observations from toxicity studies of flumethrin, and comparison to other structurally similar pyrethroids for which dermal absorption data are available, are considered in a weight-of-evidence approach, to reduce the dermal absorption of flumethrin from the default of 100%.

Based on the physical-chemical properties (large, strongly hydrophobic compound formulated as a solid), flumethrin fits the profile of a chemical with low dermal absorption potential. Other pyrethroids with similar structural and physical/chemical properties to flumethrin have dermal absorption values in the range of 2-17%, based on in vivo data. The general observations from the dermal and oral toxicology studies indicate that flumethrin is being absorbed but dermal absorption is low.

Using the weight-of-evidence from the physical-chemical properties, dermal and oral toxicity studies of flumethrin, and comparison with other structurally similar pyrethroid compounds, a decreased dermal absorption value from 100% to 50% is supported.

3.4.2 Occupational Exposure and Risk Assessment

3.4.2.1 Applicator Exposure and Risk Assessment

Beekeepers have potential for exposure to Bayvarol Beehive Pest Control Strips during placement of the strips into beehives. Dermal exposure estimates were generated from a chemical-specific worker exposure study which monitored the placement of beehive strips into a beehive. The exposure estimates were based on applicators wearing a long-sleeved shirt, long pants, and chemical-resistant gloves.

Exposures to workers handling Bayvarol Beehive Pest Control Strips are expected to be short-term in duration and to occur primarily by the dermal route. Dermal exposures were estimated by coupling the amount of active ingredient per strip with the number of strips handled per day. Exposures were normalized to mg/kg bw/day by using 80 kg for an adult body weight.

Exposure estimates were compared to the toxicological endpoint (NOAEL) to obtain the MOE; the target MOE is 300 for the dermal route.

Beehive Strip Passive Dosimetry Study

This study was designed to calculate transferable residues when Bayvarol Beehive Pest Control Strips impregnated with flumethrin are hung in beehives. This is a surrogate study conducted in a laboratory while hanging strips in a non-utilized beehive. Transferable residues were sampled from the cotton gloves worn, over nitrile gloves, by workers handling the strips. The hanging of the strips impregnated at a rate of 3.6 mg flumethrin/strip, into an unused beehive are relevant to the proposed use.

The application of Bayvarol Beehive Pest Control Strips into an unused beehive was performed using four groups (1, 10, 30 or 50 sets of 4 strips of eight replicates each). Cotton gloves worn when hanging the strips were analyzed for flumethrin residue to evaluate if multiple applications would lead to increased flumethrin residue, and if glove saturation would occur following handling of multiple strips. The gloves were analyzed using HPLC-MS/MS. The limit of quantitation was 1 µg flumethrin per glove.

Transfer of flumethrin residues to a worker's hands, from hanging impregnated polyethylene strips in beehives, is considered to be low (mean 12.4 µg/pair of gloves (SD = 3.0) when sequentially handling 200 strips) compared to the total amount of flumethrin handled (750 mg). No major limitations were identified in this study; however, minor limitations included incomplete quality control procedures, study not conducted under field use conditions, and only low-end number of strips handled during the study.

This study is considered to be acceptable (generally satisfies the data requirements of OPPTS 875.1600, 875.2400 and OECD Testing and Assessment No. 9 (1997)) for quantifying the amount of flumethrin residue transferable from impregnated strips to worker hands when hanging Bayvarol Beehive Pest Control Strips in beehives. The estimates of exposure and risk of handling Bayvarol Beehive Pest Control Strips are presented in Table 3.4.2.1.

Table 3.4.2.1 Flumethrin residue on gloves from handling Bayvarol Beehive Pest Control Strips.

Scenario	Dermal (hands) unit exposure (µg/pair of gloves)	Exposure [a] (mg/kg bw/day)	MOE [b]
200 strips (50 packages in the study)	12.4	0.0000775	6452
2000 strips (maximum number of strips expected to be used in a day)	12.4 x 10 = 124	0.000775	645

[a] Exposure (mg/kg bw/day) = Dermal unit exposure × dermal absorption (50%) × 0.001 mg/µg / body weight (80 kg)

[b] MOE = NOAEL/Exposure; target MOE = 300

Where, NOAEL = 0.5 mg/kg bw/day

Exposure = $Exposure_{dermal}$ (mg/kg bw/day)

Dermal risks are not of concern for beekeepers wearing the required personal protective equipment when handling Bayvarol Beehive Pest Control Strips. Leather beekeeping gloves must not be worn when handing this product.

3.4.2.2 Postapplication Exposure and Risk Assessment for Workers Removing Beehive Strips

There is potential for exposure to beekeepers removing and disposing of Bayvarol Beehive Pest Control Strips from treated beehives. Given the nature of activities performed, the primary route of exposure for beekeepers removing and disposing of Bayvarol Beehive Pest Control Strips would be through the dermal route. The duration of exposure is considered to be short-term in duration.

No exposure data were submitted to quantify the amount of active ingredient available for transfer from the surface of the strips during removal from a beehive. The removal and disposal of Bayvarol Beehive Pest Control Strips are expected to be similar to placement of the strips into the beehives.

At removal, 42 days (6 weeks) after placement, the amount of flumethrin is expected to have decreased because of the slow, continuous depletion of flumethrin from the strips. Exposure is expected to be less than when first putting the strips into the beehive. Therefore, post-application exposure is not expected to be greater than the exposure from placement of the beehive strips.

3.4.3 Residential Exposure and Risk Assessment

No residential exposures are expected. Occupational bystander dermal exposures are considered to be negligible, taking into consideration that the impregnated strips are handled only by the beekeeper, the low-level release of the active, and that flumethrin is non-volatile.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in honey commodities is flumethrin. The data gathering and enforcement analytical methods are valid for the quantitation of flumethrin residues in honey. The residues of flumethrin were demonstrated to be stable for 9 months in honey when stored at ambient temperature (20-25°C). Beehive field trials, conducted throughout Germany and the United Kingdom, using an end-use product containing flumethrin and conducted at the approved rate are sufficient to support a proposed maximum residue limit on honey.

3.5.2 Dietary Risk Assessment

Acute and chronic (non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™), which incorporates food consumption data from the National Health and Nutritional Examination Survey, What We Eat in America (NHANES/ WWEIA) dietary survey for the years 2005-2010 available through CDC's National Center for Health Statistics (NCHS).

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic non-cancer analysis for flumethrin: 100% of beehives treated and residues of honey based on the proposed MRL for honey. The PMRA estimates that chronic dietary exposure to flumethrin from food is <1% of the ADI for the total population and all population subgroups.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the basic acute analysis for flumethrin: 100% of beehives treated and residues of honey based on the proposed MRL for honey. The basic acute dietary exposure (food alone) from all supported flumethrin registered commodities is estimated to be <1% of the ARfD for the general population and all population subgroups (95^{th} percentile, deterministic).

3.5.3 Maximum Residue Limits

Table 3.5.3.1 Proposed Maximum Residue Limit.

Commodity	Proposed MRL (ppm)
Honey	0.003

For additional information on MRLs in terms of the international situation and trade implications, refer to Appendix II.

The analytical methodology, beehive trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 5 and 6.

4.0 Impact on the Environment

The proposed use pattern as a beehive strip is not expected to result in environmental exposure.

4.1 Beehive Strips

The limited data available for flumethrin indicated that it is to persist in the environment if exposure occurred. However, given the use pattern, no environmental exposure is expected to occur. To facilitate proper disposal of use strips and packaging material, standard disposal statements have been added to the labels.

5.0 Value

Varroa mites are the most economically important parasitic pest of honeybees in Canada, and have a severe economic impact on the Canadian beekeeping industry. A significant varroa mite infestation will cause the loss of the infested colony, and varroa mites are therefore an important cause of honeybee colony loss in Canada. Without effective control of this pest, beekeeping would not be an economically viable activity in many regions of Canada. Bayvarol Beehive Pest Control Strip has value as it provides 95 to 100% control of varroa mites, and offers users a new active ingredient for use against this pest.

Data from 12 field trials were submitted to support the claim that Bayvarol Beehive Pest Control Strips control varroa mite in honeybee hives. The level of mite control provided by flumethrin treatments was >95%. Data from 5 trials were submitted to demonstrate tolerance of honeybees to Bayvarol applications. In addition to these five trials, four of the submitted efficacy trials also included observations on tolerance, for a total of 9 trials in support of honeybee tolerance. Applications of Bayvarol Beehive Pest Control Strips according to the label directions did not result in increased bee death during the summer or after the winter, did not hinder normal colony development, and was not seen to alter bee behaviour.

Active ingredients currently registered in Canada for control of varroa mites include formic acid, oxalic acid, fluvalinate-tau, amitraz, coumaphos, and thymol. Varroa mites are known to readily develop resistance to conventional control products. Both flumethrin and fluvalinate-tau are pyrethroid insecticides (Group 3A). Widespread resistance to fluvalinate-tau developed across Canada around 2002, following its first registration in 1993. This resistance has been seen to revert if the product is not applied for several years; unfortunately this reversion is reported to be temporary, only allowing for one or two successful applications before resistance to the chemical is once again an issue. Since both flumethrin and fluvalinate-tau are Group 3A insecticides, it is therefore probable that cross-resistance to flumethrin is present, and could limit the performance and utility of Bayvarol Beehive Pest Control Strips. However the potential for reversion of resistance suggests that despite the probability of cross-resistance to fluvalinate-tau, flumethrin may be successfully used in areas with pyrethroid-resistant varro mite populations when used in rotation with non-Group 3A insecticides.

5.1 Supported Uses

The submitted data supports use of Bayvarol Beehive Pest Control Strips to control varroa mites in honeybee hives with an application of four Bayvarol Beehive Pest Control Strips per brood chamber for standard colonies and two Bayvarol Beehive Pest Control Strips per nucleus colony, applied for a treatment duration of 6 weeks (42 days).

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, i.e. 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, flumethrin and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Flumethrin does not meet the exposure criteria and is not *Canadian Environmental Protection Act* (CEPA) toxic. Therefore, it does not meet TSMP criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[8] 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 flumethrin and the end-use product Bayvarol Beehive Pest Control Strip do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

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

6 *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.*

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

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

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

7.0 Summary

7.1 Human Health and Safety

The toxicology database for flumethrin is adequate to define the majority of toxic effects that may result from exposure. In short-term and long-term studies on laboratory animals, the primary target was the nervous system. Dermal lesions were observed following oral exposure to flumethrin and were likely caused by increased grooming as well as biting and scratching of the skin due to paresthesia following systemic absorption of flumethrin via the gastrointestinal tract and subsequent distribution to the skin. Flumethrin demonstrated potential to interact with the immune system. There was no evidence of carcinogenicity in rats or mice after longer-term dosing. Flumethrin did not damage genetic material. Malformations and mortality occurred in the young, although at doses that were toxic to the maternal animal. There is some concern for increased susceptibility of the young exposed to pyrethroids, such as flumethrin. 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.

Beekeepers placing, removing, and disposing of beehive strips are not expected to be exposed to levels of flumethrin that will result in an unacceptable risk when Bayvarol Beehive Pest Control Strips are used according to the label precautions and directions. The personal protective equipment on the product label is adequate to protect beekeepers. The public is not expected to be exposed, as only beekeepers handle the product.

The residue definition for enforcement and risk assessment purposes is flumethrin in honey. The proposed use of flumethrin in beehives does not constitute a risk of concern for chronic or acute dietary exposure (food only) to any segment of the population, including infants, children, adults and seniors. The PMRA recommends that the MRL at LOQ be specified for residues of flumethrin.

Commodity	Proposed MRL (ppm)
Honey	0.003

7.2 Environmental Risk

The proposed use pattern as a beehive strip is not expected to result in environmental exposure.

7.3 Value

Bayvarol Beehive Pest Control Strip has value as it provides 95 to 100% control of varroa mites, the most important pest of honeybees, and offers users a new active ingredient for use against this pest. Applications of Bayvarol Beehive Pest Control Strips according to the label directions did not result in increased bee death, did not hinder normal colony development, and was not observed to alter bee behaviour. The submitted data supports use of Bayvarol Beehive Pest

Control Strips to control varroa mites in honeybee hives with an application of four Bayvarol Beehive Pest Control Strips strips per brood chamber for standard colonies and two Bayvarol Beehive Pest Control Strips strips per nucleus colony, applied for a treatment duration of 6 weeks (42 days).

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 Flumethrin Technical Insecticide and Bayvarol Beehive Pest Control Strip, containing the technical grade active ingredient flumethrin, to control varroa mites in honeybee hives.

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

µg	microgram(s)
ai	active ingredient
AD	administered dose
ADI	acceptable daily intake
ARfD	acute reference dose
AUC	area under the curve
bw	body weight
bwg	bodyweight gain
ºC	degrees centrigrade
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention
CEPA	*Canadian Environmental Protection Act*
cm	centimetre(s)
CS	choreoathetosis and salivation
d	day(s)
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
EPA	Environmental Protection Agency
FDA	*Food and Drugs Act*
F1	first filial generation
F2	second filial generation
fc	food consumption
g	gram(s)
GD	gestation day
ha	hectare(s)
HAFT	highest average field trial
HPLC	high performance liquid chromatography
i.p.	intraperitoneal
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
km	kilometre(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LAFT	lowest average field trial
LC_{50}	lethal concentration to 50%
LD	lactation day
LD_{50}	lethal dose to 50%
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
MAS	maximum average score for 24, 48 and 72 hours
mg	milligram(s)

MIS	maximum irritation score
mL	millilitre(s)
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
MS/MS	tandem mass spectrometry
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NAFTA	North American Free Trade Agreement
NCHS	National Center for Health Statistics
NHANES/WWEIA	National Health and Nutritional Examination Survey/What We Eat in America
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NZW	New Zealand white
OECD	Organization for Economic Cooperation and Development
OPPTS	The Office of Prevention, Pesticides and Toxic Substances
P	parental generation
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
ppb	parts per billion
ppm	parts per million
RD_{50}	concentration producing a 50% decrease in respiratory rate
SD	standard deviation
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
UDP-GT	uridine diphospho-glucuronosyl transferase
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Honey	RA 654/93	Flumethrin	Data-gathering: HPLC-UV	0.003 ppm	PMRA # 2282587; 2282588
Honey	01462	Flumethrin	Enforcement: HPLC-MS/MS	0.003 ppm	PMRA # 2592833

Table 2 Toxicity Profile of Bayvarol Beehive Pest Control Strip

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

Study Type/Animal/PMRA #	Study Results
Acute oral Rat (Wistar) PMRA 2282577	LD_{50} > 2000 mg/kg bw Low Toxicity No clinical signs of toxicity.
Acute dermal Rat (Wistar) PMRA 2282579	LD_{50} > 5000 mg/kg bw Low Toxicity No clinical signs of toxicity. Scab formation was observed at the site of application in four rats.
Acute inhalation Waiver request PMRA 2282580	Waiver request granted. The potential for significant exposure via the inhalation route is low given that the active ingredient has a very low vapour pressure and is embedded into a plastic carrier. Consequently, the product is not considered to pose an acute hazard via the inhalation route.
Eye irritation Waiver request PMRA 2282580	Waiver request granted. The product design prevents ocular exposure. Consequently, the product is not considered to pose an eye irritation hazard.
Dermal irritation Waiver request PMRA 2282580	Waiver request granted. The active ingredient is incorporated into inert polyethylene strips, and the potential for dermal irritation from the end-use product is no greater than for the active ingredient alone, which was non-irritating to the skin of rabbits. Consequently, the product is considered to be non-irritating to the skin.
Dermal sensitization Waiver request PMRA 2282580	Waiver request granted. The active ingredient is incorporated into inert polyethylene strips, and the potential for dermal sensitization from the end-use product is no greater than for the active ingredient alone, which was negative for dermal sensitization. Consequently, the product is not considered to pose a dermal sensitization hazard.

Table 3 Toxicity Profile of Technical Flumethrin and the Metabolite Flumethrin Acid

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

Study Type/Animal/PMRA #	Study Results
Acute oral Rat (Wistar) PMRA 2282259	Old batch (87.9% purity; isomeric ratio unknown) LD_{50} (♂) > 100 mg/kg bw LD_{50} (♀) > 100 mg/kg bw High Toxicity Clinical signs included piloerection, laboured breathing, reduced reactivity, poor reflexes, spasmodic state, spastic gait, increased and/or red salivation, narrowed palpebral fissure, red encrustation on the snout and/or orbital margin, and soft feces. New batch (95.1% purity; 53% trans-Z1 isomer:43% trans-Z2 isomer) LD_{50} (♂) >100 mg/kg bw LD_{50} (♀) = 100 mg/kg bw High Toxicity Clinical signs included piloerection, laboured breathing, breathing sounds, dyspnea, reduced reactivity, spasmodic state, spastic gait, increased and/or red salivation, narrowed palpebral fissure, red encrustation on the snout, and soft feces.
Acute oral Rat (Wistar) PMRA 2282260	trans-Z1 isomer LD_{50} (♂) > 5000 mg/kg bw LD_{50} (♀) > 500 mg/kg bw Moderate Toxicity Clinical signs included diarrhea, uncoordinated gait, digging, preening, and reduced reactivity. trans-Z2 isomer LD_{50} (♂) = 10 to 50 mg/kg bw LD_{50} (♀) = 10 to 50 mg/kg bw High Toxicity Clinical signs included decreased mobility and reactivity, spastic and uncoordinated gait, narrowed palpebral fissure, piloerection, erected tail, sternal recumbency, laboured breathing, dyspnea, breathing sounds, increased salivation, temporary digging, chewing, and convulsions.
Acute oral Rat (Sprague Dawley) PMRA 2282258	LD_{50} (♀) = 175 mg/kg bw High Toxicity Clinical signs included salivation, piloerection, decreased activity, polyuria, crusting

	and/or swelling around the eyes, diarrhea, hunched posture, and crusts on the chest/abdomen.
Acute dermal Rat (Wistar) PMRA 2282261	<u>Old batch (87.9% purity; isomeric ratio unknown)</u> LD_{50} (♂) > 2000 mg/kg bw LD_{50} (♀) > 2000 mg/kg bw Low Toxicity Clinical signs included piloerection, decreased mobility, decreased reactivity, poor reflexes, spastic gait, laboured breathing, increased salivation, narrowed palpebral fissure, transient shaking movements, transient digging behaviour, and red-coloured snout. <u>New batch (95.1% purity; 53% trans-Z1 isomer:43% trans-Z2 isomer)</u> LD_{50} (♂) > 2000 mg/kg bw LD_{50} (♀) > 2000 mg/kg bw Low Toxicity Clinical signs included piloerection, decreased mobility, decreased reactivity, poor reflexes, spastic gait, laboured breathing, increased salivation, narrowed palpebral fissure, transient shaking movements, transient digging behaviour, red-coloured snout, and red encrustation at the orbital margin.
Acute dermal Rat (Sprague Dawley) PMRA 2282266	LD_{50} (♂) = 1998 mg/kg bw LD_{50} (♀) = 1436 mg/kg bw Slight Toxicity Clinical signs of toxicity included polyuria, salivation, decreased activity, piloerection, body tremors, sensitivity to touch and sound, hunched posture, red nasal discharge, diarrhea, emaciation, lateral recumbency, stained fur, spots around the eyes, and crusted eyes.
Acute inhalation Rat (Wistar) PMRA 2282270	LC_{50} (♂) = 0.585 to 0.812 mg/L LC_{50} (♀) = 0.277 to 0.585 mg/L LC_{50} (♂&♀) = 0.572 mg/L Moderate Toxicity Clinical signs included piloerection, bradypnea, dyspnea, laboured breathing pattern, reduced mobility, cyanosis, tremor, red encrustations on the muzzle, sluggishness, ungroomed haircoat, salivation, rales, uncoordinated gait, serous discharge from the nose, pallor, prostration and emaciation. Some animals also exhibited decreased grip strength, decreased and impaired righting response, decreased response to auditory stimuli, and reduced tonus.
Eye irritation Waiver request PMRA 2282273	Waiver request granted. Flumethrin is a glass-like, resinous solid at 20^0C and, in order to weigh out and transfer small quantities of the material, it must be heated to 60-70^0C to yield a viscous liquid. This makes it impossible to accurately remove a 0.1 mL or 100 mg sample for placement in the conjunctival sac. A cryogenic grinding experiment demonstrated that flumethrin can be ground to a fine powder while it is frozen but returns to an amorphous, glass-like solid state immediately upon returning to room temperature.
Eye irritation	MAS = 1.78 MIS = 3.33 (at 1 & 24 hours)

Rabbit (New Zealand White) PMRA 2282274	Minimally Irritating Supplemental: The manner in which the test material was applied (diluted in olive oil) did not conform to guideline requirements.
Dermal irritation Rabbit (New Zealand White) PMRA 2282274	MAS = 0 MIS = 0 Non-irritating Supplemental: The manner in which the test material was applied (diluted in olive oil) did not conform to guideline requirements.
Dermal irritation Rabbit (New Zealand White) PMRA 2282275	MAS = 0 MIS = 1 (at 1 hour) Non-irritating
Dermal sensitization (Maximization) Guinea pig (Dunkin Hartley) PMRA 2282276, 2282277	Negative
90-day oral (dietary) 45.6% (BAY Vq 1950) (administered as a 50% pre-mix with silica carrier) Rat (Wistar) PMRA 2300058	NOAEL and LOAEL not established as study was considered supplemental. Effects at 1.8/2.1 mg/kg bw/day (♂/♀): ulcerative dermatitis, slight ↑ aspartate aminotransferase (week 4 only); ↓ absolute ovary weight (♀).
90-day oral (dietary) Rat (Wistar) PMRA 2282282	NOAEL = 0.7/0.8 mg/kg bw/day (♂/♀) LOAEL = 2.9/3.4 mg/kg bw/day (♂/♀) Effects at the LOAEL: wounds on shoulder, ulcers on skin; laboured breathing, increased salivation, ↓ water intake, ↑ adrenal weight (♀).
90-day oral (dietary) Mouse (CD-1) PMRA 2282283	NOAEL = 0.9/1.4 mg/kg bw/day (♂/♀) LOAEL = 1.9/2.5 mg/kg bw/day (♂/♀) Effects at the LOAEL: skin lesions (reddening), ↑ piloerection, ↑ fc (♂); ↓ fc, dermal lesions with mild hyperkeratosis and acanthosis next to lesions (1 animal) (♀).
90-day oral (dietary) 45.3% (BAY Vq 1950) (administered as a 50% pre-mix with silica carrier) Dog (Beagle) PMRA 2300059	NOAEL not established as effects occurred down to the lowest dose tested. LOAEL = 2.3/2.8 mg/kg bw/day (♂/♀) Effects at the LOAEL: vomiting, localized skin reactions (thinning, 'moth-eaten' patches, weeping, scabbed wounds - mainly confined to the limbs, ears, tail, neck, and back, and mainly observed in the second half of the treatment period), ↑ sensitivity to being lifted by the scruff of the neck.
90-day oral (dietary) 45.3% (BAY Vq 1950)	NOAEL = 1.0/1.1 mg/kg bw/day (♂/♀) (highest dose tested) LOAEL not established as no treatment-related effects were observed in the study.

(administered as a 50% pre-mix with silica carrier) Dog (Beagle) PMRA 2300062	
14-day dermal (dose range-finding study) Rat (Wistar) PMRA 2282286	NOAEL and LOAEL not established as study was considered supplemental. Effects at 30 mg/kg bw/day: ↓ bw week 1. Effects at 100 mg/kg bw/day included bloody muzzle, reduced mobility, hunched back, uncoordinated gait, high stepping gait, laboured breathing, increased salivation, bleeding on nose, narrowed eyelids (most signs resolved by study termination), ↓ overall bw.
28-day dermal (dose range-finding study) Rat (Wistar) PMRA 2282287	NOAEL and LOAEL not established as study was considered supplemental. Effects at 100 mg/kg bw/day included bloody muzzle, reduced mobility, uncoordinated gait, increased salivation, ↓ bw; diarrhea (♂); sunken flanks, high-stepping gait (♀).
90-day dermal Rat (Wistar) PMRA 2282285	NOAEL = 10 mg/kg bw/day LOAEL = 30 mg/kg bw/day Effects at the LOAEL: ↓ bw & bwg, ↑ water intake; high stepping/stilted gait, skin reddening, thymic atrophy (♀).
28-day inhalation Rat (Wistar) PMRA 2282288	NOAEC = 0.00012 mg/L (0.03 mg/kg bw/day) LOAEC = 0.00133 mg/L (0.36 mg/kg bw/day) Effects at the LOAEC: hypothermia, piloerection, ungroomed haircoat, bradypnea, laboured breathing pattern, red discharge/encrustrations in the nostrils and perinasal area; borderline effects on apnea time, ↓ tidal volume, ↑ adrenal weight (♂); reduced mobility, atony, salivation, ↓ grip strength, ↓ cytochrome P450 activity, ↓ protein, ↓ albumin, ↓ cholesterol (♀).
18-month oncogenicity (dietary) Mouse (CD-1) PMRA 2282289	NOAEL = 0.39/0.52 mg/kg bw/day (♂/♀) LOAEL = 2.0/2.5 mg/kg bw/day (♂/♀) Effects at the LOAEL: skin changes (discolouration, encrustations, sores, missing skin or ears, and/or deformed ears), auricle missing, high stepping gait, skin lesions (epidermal hyperplasia, inflammation, ulceration), lymphoid hyperplasia in the mandibular lymph nodes; mortality, loss of hair, eye reduced in size, wound on hairless area, enlarged/swollen spleen, plasmacytosis in the mandibular lymph nodes, hematopoiesis (mesenteric lymph nodes and all affected organs), ↓ glycogen content in the liver, hepatic atrophy (♂); glandular hyperplasia of the stomach (♀). No evidence of oncogenicity.
Two-year combined chronic toxicity/oncogenicity (dietary) Rat (Wistar) PMRA 2282291	NOAEL = 0.7 mg/kg bw/day LOAEL = 2 mg/kg bw/day Effects at the LOAEL: skin changes, loss of hair; vacuolation of adrenal cortex (interim sacrifice) (♂). No evidence of oncogenicity.
Two-generation reproduction (dietary)	Parental NOAEL = 0.23/0.28 mg/kg bw/day (♂/♀) Parental LOAEL = 2.4/2.9 mg/kg bw/day (♂/♀)

45.6% (BAY Vq 1950) (administered as a 50% pre-mix with silica carrier) Rat (Wistar) PMRA 2282295	Effects at the parental LOAEL: skin wounds; ↓ bwg (P), ↓ premating fc (P&F1) (♂); ↓ fc during gestation (P) & lactation (P&F1) (♀). Reproductive NOAEL = 2.4/2.9 mg/kg bw/day (highest dose tested) Reproductive LOAEL not established as no treatment-related effects were noted in the reproductive parameters evaluated. Offspring NOAEL = 0.28 mg/kg bw/day Offspring LOAEL = 2.9 mg/kg bw/day Effects at the offspring LOAEL: cramped/hunched posture, stiff legs held in caudal position, pectus carinatum [pigeon chest], pups cool to the touch and squealed more frequently (F1), ↓ bw throughout lactation period (F1&F2), ↑ postnatal loss PND 0-4 & 5-21 (F1&F2). Several parameters were not evaluated (for example, estrous cycle duration or periodicity; sperm counts, motility and morphology). However, the study is considered acceptable when the results of this study are considered in conjunction with those of the second two-generation reproduction study conducted via gavage (PMRA 2282294). Serious endpoint (reduced pup survival) in the absence of maternal toxicity in this study (loss of F2 pups while the only effect in F1 maternal animals was reduced food consumption during lactation).
Reproduction dose range-finding study – 28-day oral (gavage) Rat (Wistar) PMRA 2282284	NOAEL and LOAEL not established as study was considered supplemental. Effects at 5.0 mg/kg bw/day: ↓ spleen weight, ↓ thymus weight (♂).
Reproduction dose range-finding study – 19-week oral (gavage) PMRA 2282297	NOAELs and LOAELs not established as study was considered supplemental. Parental effects at 3 mg/kg bw/day: ↓ bw & bwg during gestation (♀). Reproductive effects at 3 mg/kg bw/day: ↓ birth weight, ↓ litter size at birth (considered equivocal). Offspring effects at 3 mg/kg bw/day: ↓ pup bw PND 4. <u>Toxicokinetics</u> At 0.08 mg/kg bw/day, flumethrin was not detected in plasma. At the higher dose levels, the maximum plasma levels of flumethrin were measured 2 or 4 hours post-dosing. A clear increase in plasma levels with dose was noted between 0.4 and 2 mg/kg bw/day. A similar increase was not seen in the dose range of 3 to 5 mg/kg bw/day.
Lactational transfer study (gavage) Rat (Wistar) Summary provided in PMRA	NOAELs and LOAELs not established as study was considered supplemental. Maternal effects at 2 mg/kg bw/day: ↓ bw during gestation and lactation, ↓ bwg during gestation, lacrimation (during gestation), nasal stain (during gestation and lactation), salivation (during gestation and lactation), and oral stain (during gestation and lactation).

2550258	Maternal effects at 4 mg/kg bw/day: group was terminated on GD 16 due to excessive toxicity including clinical signs (hunched posture, ataxia, ↓ activity, salivation, lacrimation, and lacrimal/nasal/perianal/oral staining) and marked ↓ bw and fc, one animal euthanized in moribund condition on GD 10. Reproductive effects at 2 mg/kg bw/day: ↓ birth weight. Offspring effects at 2 mg/kg bw/day: ↓ bw PND 4-21. Flumethrin was detected in pups on PND 11 confirming that pups were exposed to flumethrin during lactation.
Two-generation reproduction (gavage) Rat (Wistar) PMRA 2282294 PMRA 2282312	Parental NOAEL = 1 mg/kg bw/day Parental LOAEL = 3 mg/kg bw/day Effects at the parental LOAEL: ↓ premating bw & bwg (P&F1) (♂); loss of fur (P), ↓ premating bw (F1), ↓ bw GD 0-20 (F1), ↓ bwg GD 0-20 (P&F1), ↓ bw LD 0-21 (F1), ↓ bwg LD 0-4 (P&F1), ↑ bwg LD 0-20 (P), ↓ fc LD 0-7 (P), ↓ fc LD 0-4 F1 (♀). Reproductive NOAEL = 0.5 mg/kg bw/day Reproductive LOAEL = 1 mg/kg bw/day Effects at the reproductive LOAEL: ↓ birth weight (F1). Effects at the next higher dose of 3 mg/kg bw/day: pup deaths PND 0 (F1&F2), ↓ birth weight (F2). Offspring NOAEL = 0.5 mg/kg bw/day Offspring LOAEL = 1 mg/kg bw/day Effects at the offspring LOAEL: ↓ bw PND 4-7 (F1), ↓ bwg PND 0-4 (F1). Effects at the next higher dose of 3 mg/kg bw/day: ↓ bw starting PND 4 (F1&F2), ↓ bwg PND 0-7 (F1&F2), pup deaths PND 1-4 (F1&F2), ↓ mean litter size PND 4 (F1&F2), ↓ number of litters surviving to PND 4 (F1&F2), absence of milk in stomach (F1), thin appearance (F1); ↑ anogenital distance (F2) (♂). Evidence of increased sensitivity of the young. <u>Toxicokinetics</u> The concentration of flumethrin in the plasma collected from P-generation rats during the pre-mating phase followed a clear dose response. However, the increase between 1 mg/kg bw/day and 3 mg/kg bw/day was not dose-proportional. The plasma levels of flumethrin peaked at 4 hours post-dosing and were below the limit of quantitation at 24 hours post-dosing. The concentration of flumethrin in the plasma of ♂ was significantly higher than in ♀.
Developmental toxicity (gavage) Rat (Wistar) PMRA 2282299	Maternal NOAEL = 0.75 mg/kg bw/day Maternal LOAEL = 2 mg/kg bw/day Effects at the maternal LOAEL: salivation, ↓ corrected bw, ↓ bwg GD 6-19, ↓ bwg GD 0-20, ↓ corrected bwg GD 0-20, ↓ fc. Developmental NOAEL = 2 mg/kg bw/day Developmental LOAEL = 5 mg/kg bw/day Effects at the developmental LOAEL: ↓ fetal weight, ↑ incidence of malformed

	fetuses, slight↑ fetal incidence of microphthalmia, ↑ incidence of delayed ossification of phalangeal, metacarpal, metatarsal, vertebral (arches and/or bodies), sternal, cranial bones, ↑ number of fetuses with wavy ribs. Serious endpoint (malformations) in the presence of maternal toxicity.
Developmental toxicity (gavage) Rabbit (Himalayan) PMRA 2282300	Maternal NOAEL = 0.5 mg/kg bw/day Maternal LOAEL = 1.5 mg/kg bw/day Effects at the maternal LOAEL: ↑ incidence of swelling of limbs (considered equivocal). Developmental NOAEL = 0.5 mg/kg bw/day Developmental LOAEL = 1.5 mg/kg bw/day Effects at the developmental LOAEL: ↑ incidence of fused sternebrae (considered equivocal). Developmental effects in the presence of maternal toxicity.
28-day immunotoxicity (dietary) Rat (Wistar) PMRA 2282322, 2538481, 2538482	NOAEL = 3.0/3.5 mg/kg bw/day (♂/♀) LOAEL = 12 mg/kg bw/day Effects at the LOAEL: ↓ bwg, ↓ fc, clinical signs near the end of the study (injury on head and/or shoulder in 1 rat/sex, bloody muzzle and high-stepping gait in 1 ♀); ↓ bw, ↓ number of spleen cells, ↑ immunoglobin A (♂); bw loss, ↑ specific activity of plaque forming cells, ↑ immunoglobin M (♀). Indication of perturbation/dysregulation of the immunologic response.
Acute oral neurotoxicity (gavage) Rat (Wistar) PMRA 2282318	NOAEL (♂) = 0.5 mg/kg bw LOAEL (♂) = 1 mg/kg bw Effects at the ♂ LOAEL: ↓ motor and locomotor activity on day of dosing (♂). NOAEL (♀) = 1 mg/kg bw LOAEL (♀) = 5 mg/kg bw Effects at the ♀ LOAEL: urine stains; ↓ motor and locomotor activity on day of dosing (♀).
90-day oral neurotoxicity (gavage) Rat (Wistar) PMRA 2282320	NOAEL = 1 mg/kg bw/day LOAEL = 2.5 mg/kg bw/day Effects at the LOAEL: urine stains, ↓ motor and locomotor activity week 2; ↓ bw, ↓ bwg, ↓ fc (♂); red oral stain (♀).
Developmental neurotoxicity (gavage) Rat (Wistar) PMRA 2282321	Maternal NOAEL = 1 mg/kg bw/day Maternal LOAEL = 2 mg/kg bw/day Effects at the LOAEL: ↓ bwg (GD 0-20), ↓ fc (GD 13-20). Developmental NOAEL = 1 mg/kg bw/day Developmental LOAEL = 2 mg/kg bw/day Effects at the LOAEL: ↓ bw (PND 11-21), ↓ bwg (PND 0-21); ↓ bw (PND 28-70), ↓ terminal perfused and non-perfused bw (♂); ↑ motor activity PND 13 & 17, ↑ locomotor activity PND 17, ↓ perfused bw PND 21 (♀).

	No evidence of increased sensitivity of the young.
Bacterial reverse mutation S. typhimurium TA98, TA100, TA102, TA1535, TA1537 PMRA 2282301	Negative Tested up to the limit concentration.
Bacterial reverse mutation S. typhimurium TA98, TA100, TA1535, TA1537 PMRA 2282303	Negative Tested up to the limit concentration.
In vitro forward mutation assay in mammalian cells Chinese hamster V79 lung cells PMRA 2282306	Negative Tested up to the limit of solubility.
In vitro forward mutation assay in mammalian cells Chinese hamster V79 lung cells PMRA 2282307	Negative Tested up to the limit of solubility.
In vitro chromosomal aberration assay Chinese hamster V79 lung cells PMRA 2282304	Negative Tested up to the limit of solubility.
In vitro chromosomal aberration assay Chinese hamster V79 lung cells PMRA 2282305	Negative Tested up to the limit of solubility.
In vitro unscheduled DNA synthesis Primary rat hepatocytes PMRA 2282310	Negative Tested up to cytotoxic concentrations.
In vivo micronucleus assay (i.p. injection) Mouse (NMRI) PMRA 2282309	Negative Effects at 1000 mg/kg bw: apathy, roughened fur, spasm, difficulty breathing, eyelids stuck together, and death of one animal.

In vivo micronucleus assay (i.p. injection) Mouse (NMRI) PMRA 2282308	Negative Effects at 125 mg/kg bw: apathy, roughened fur, loss of weight, spasm, periodic stretching of body, difficulty breathing, diarrhea, reduced body temperature. Effects at 500 mg/kg bw: death of two animals.
In vivo chromosomal aberration / micronucleus assay (dermal application or i.p. injection) Mouse (Swiss Webster) PMRA 2563697	<u>Dermal Application</u> Effects at 5000 mg/kg bw: ↓ mitotic index at all time points, ↑ frequency of gaps at 24-hour sacrifice only. No induction of micronuclei. <u>Single I.P. Injection</u> Effects at 694 mg/kg bw: ↓ mitotic index. Effects at 2083 mg/kg bw: ↑ frequency of breaks, ↑ frequency of micronucleated polychromatic erythrocytes. <u>Multiple I.P. Injections</u> Effects at 128 mg/kg bw: ↑ frequency of micronucleated polychromatic erythrocytes, ↓ number of polychromatic erythrocytes. No increase in chromosomal aberrations. Study was considered supplemental as it was a non-guideline study; the purity of the test material was stated to be 60%.
Inhalation RD_{50} Rat (Wistar) PMRA 2282267	RD_{50} = 0.0194 mg/L The RD_{50} value was based on a decrease in respiratory minute volume rather than respiratory rate which appeared to be less sensitive when compared to minute volume. Study was considered supplemental as it was a non-guideline study.
Inhalation RD_{50} Mouse (ICO:OF1) PMRA 2282271	RD_{50} = 0.048 mg/L The RD_{50} value was based on a decrease in respiratory minute volume rather than respiratory rate which appeared to be less sensitive when compared to minute volume. Study was considered supplemental as it was a non-guideline study.
Effects on hepatic drug-metabolizing enzymes and antipyrine disposition in rats (i.p. injection and/or gavage) Rat (Wistar) PMRA 2563696	Rats were administered either six daily i.p. injections of 40 mg/kg bw/day of flumethrin; six daily i.p. injections of 40 mg/kg bw/day of flumethrin followed by a single oral dose of 20 mg/kg bw antipyrine; or a single oral dose of 20 mg/kg bw of antipyrine followed by six daily i.p. injections of 40 mg/kg bw/day of flumethrin followed by another single oral dose of 20 mg/kg bw antipyrine. All flumethrin-treated rats exhibited salivation and choreoathetoid movements within 4 hours of each dose, which resolved by 24 hours post-dose. Prolonged dosing did not increase severity or duration of these effects. There was no effect on liver weight or microsomal protein content of liver in flumethrin-treated rats. Flumethrin exposure resulted in ↓ cytochrome P450, NADPH-cytochrome c reductase, aniline hydroxylase, aminopyrine-N-demethylase, and UDP-GT. There was no effect on level of cytochrome b5. Exposure to flumethrin altered the plasma kinetics of antipyrine (slower plasma elimination, ↑ AUC, ↑ mean residence time). The urinary recovery of antipyrine, norantipyrine, 4-hydroxyantipyrine, and 3-

	hydroxymethylantipyrine accounted for 90% of the dose when antipyrine was administered before flumethrin treatment but only 55% when it was given after flumethrin treatment. The formation of all three metabolites of antipyrine decreased after flumethrin administration, demonstrating that flumethrin diminishes oxidative metabolism of antipyrine. Study was considered supplemental as it was a non-guideline study; the purity of the test material was not stated.
Toxicokinetics Rat (Wistar) PMRA 2282315	Rats were administered a single oral dose of 1 mg/kg bw (low dose) or 5 mg/kg bw (high dose), repeated oral doses of 1 mg/kg bw, or a single intraduodenal dose of 1 mg/kg bw (bile duct cannulated rats) of chlorophenyl-labelled flumethrin. Absorption was approximately 75% of the AD following a single low oral dose, when considering the radioactivity in urine, bile, and tissues in bile duct-cannulated rats. Peak plasma levels following a single oral dose were observed 8 hours post-dosing in low dose and high dose ♂, and at 24 hours post-dosing in low dose ♀. The plasma concentration of radioactivity increased 10-fold during the 7 days of repeated oral dosing. Elimination of radioactivity was slow, with plasma elimination half-lives of 130 hours for single low dose ♂, and 160 hours for single high dose ♂ and single low dose ♀. The plasma elimination half-life of the post-dosing phase of the repeated-dosing scenario was 155 hours. Excretion occurred primarily via the feces (≥77% of the AD), with only 2-3% of the AD eliminated via the urine. In bile duct-cannulated rats, 44% of the AD was eliminated in the bile and approximately 20% of the AD was in the feces. Minimal radioactivity was eliminated via expired air. In the repeated-dose group, excretion of radioactivity decreased with each successive dose, indicating an accumulation of radioactivity in the tissues. At sacrifice, 9-20% of the AD remained in tissues. The highest concentrations of radioactivity for all dosing regimens were found in the plasma, lung, erythrocytes, heart, skin, liver, kidney, testis, uterus and ovary. For the single high dose and multiple low dose groups, the fat also contained high residues. The distribution volume under steady state conditions varied between 25% and 44% of the body volume, indicating that the radioactivity was slowly and to a limited extent distributed from plasma into peripheral compartments. Compounds identified in feces following a single dose include unchanged parent compound (~50% of the AD in ♂; 25% of the AD in ♀) and the ester cleavage product flumethrin acid (15-18% of the AD in ♂; ~30% of the AD in ♀).
Toxicokinetics Rat (Sprague Dawley) PMRA 2550260	Rats were administered a single oral dose of 1 mg/kg bw (low dose) or 10 mg/kg bw (high dose), a single intravenous dose of 1 mg/kg bw, or a single intraduodenal dose of 1 mg/kg bw of fluorophenyl-labelled flumethrin. Absorption was approximately 50% of the AD following oral dosing. Peak plasma levels following a single oral low dose were observed at approximately 3 hours (2.5 to 3.3 hours) following a single oral low and a single oral high dose. The absorption appeared to be proportional to dose.

	Approximately 37% to 48% of the AD was eliminated via the urine and 40% to 60% of the AD via the feces following the administration of a single oral dose (low and high). The elimination curves suggested biphasic elimination via the urine and bile. At 2 hours post-dosing, the highest relative concentrations in tissues were observed in the liver, plasma, and adrenal gland. By 10 days post-dosing the highest relative tissue concentrations were observed in the renal fat, skin, and sciatic nerve. Less than 1% of the administered dose of radioactivity was detected in the whole body by 10 days post-dosing. This study was considered supplemental due to limitations in reporting.
Whole-body autoradiography Rat (Wistar) PMRA 2550259	Rats were administered a single oral dose of 5 mg/kg bw of chlorophenyl-labelled flumethrin. At 1 hour: The level of radioactivity was highest in the lumen of the intestinal tract, followed by the liver. Small amounts of radioactivity were detectable in the spleen, kidney, adrenal cortex, lung, cartilage, bone marrow, subcutaneous fat layer, and some glandular tissues in the head and throat area. At 4 hours: The pattern of radioactivity was similar to that at 1 hour. A higher concentration of radioactivity was seen in the blood and in highly perfused organs and tissues (for example, the testis). More radioactivity was also seen in the intestines (indicating the onset of fecal elimination), and radioactivity was still present in the stomach (indicating a delay in absorption). The renal cortex contained more radioactivity than the renal medulla (indicating that more radioactivity is transported to the kidneys than can be filtered or the radioactivity is reabsorbed by the nephrons). Radioactivity was also evident in the adrenal cortex, fibrous tissues (muscle, diaphragm), epiphysis (pineal gland), hypophysis (pituitary gland), and cisterna chyli. At 8 hours: Increased radioactivity was seen in the gonads, cartilage, kidney, connective tissue fibers, bone marrow, epiphysis, hypophysis, and other glandular tissues. Radioactivity was also present in the fur. At 24 hours: Radioactivity was still present in the kidney, liver, contents of the intestinal tract, blood, bone marrow, fibrous tissues, epiphysis and hypophysis.
90-day oral (dietary) with pharmacokinetic investigations Bayticol P (93.1%) and Bayticol P Granulate (51.4%) Rat (Wistar) PMRA 2282313	Effects at ~4 mg/kg bw/day: skin lesions (exuding or bleeding) on head and neck (excessive scratching), loss of hair, piloerection. Effects at ~12 mg/kg bw/day: early sacrifice (day 70) due to excessive skin lesions; ↓ bw (♂). The plasma levels of flumethrin were comparable in female rats fed diets with Bayticol P or Bayticol P Granulate. Data were not provided for male rats. The results demonstrate that the bioavailability of Bayticol P was not different from that of Bayticol P Granulate. This study was considered supplemental as it was a non-guideline study.
Toxicokinetics Rabbit (New Zealand white) PMRA 2563698	Rabbits were administered unlabelled flumethrin administered as a single oral or single intravenous dose at 10 mg/kg bw. Flumethrin levels in blood determined using gas chromatography. <u>Oral administration</u>: Absorption half-life of 1.9 hours; half-lives of elimination (alpha and beta) of 4.8 and

	43 hours; mean residence time of 60 hours; maximum plasma concentration of 0.54 µg/mL at 5.4 hours; area under the curve (0-72 hours) of 16 mg/h/L. Intravenous administration: Half-lives of elimination (alpha and beta) of 0.18 and 34 hours; mean residence time of 48 hours; area under the curve (0-72 hours) of 28 mg/h/L. Comparing the results from oral and intravenous administration suggests that absorption of flumethrin from the gastrointestinal tract is incomplete and relatively slow, and that the bioavailability of flumethrin is approximately 61%. The study authors concluded that flumethrin is a compound for which absorption is not as fast as the other pyrethroid pesticides such as permethrin, deltamethrin, and lambda-cyhalothrin; the half-life and mean residence time are longer than those for other pyrethroids.
Studies with flumethrin acid, a metabolite of flumethrin	
Acute oral – Flumethrin acid Rat (Wistar) PMRA 2590666	LD_{50} (♀) > 10 mg/kg bw An acute toxicity classification would not be determined as the doses used were not sufficient. No clinical signs were observed. There were no dose-related effects on the results of the inclined plane test. Supplemental
Acute oral – Flumethrin acid Rat (Wistar) PMRA 2590663	LD_{50} (♂) = 935 mg/kg bw LD_{50} (♀) = 620 mg/kg bw Moderate Toxicity Clinical signs included ruffled fur, apathy, decreased mobility, staggering gait, prone position, drowsiness, and slow or labored breathing. Supplemental
Acute dermal – Flumethrin acid Rat (Wistar) PMRA 2590663	LD_{50} > 5000 mg/kg bw Low Toxicity Clinical signs included lethargy and reduced motor activity. Small lesions and hyperaemia were observed at the application site. Supplemental
Acute inhalation – Flumethrin acid Rat (Wistar) PMRA 2590663	LC_{50} > 0.34 mg/L (highest attainable concentration) Moderate Toxicity No clinical signs were observed. Supplemental
Eye irritation – Flumethrin acid Rabbit (NZW)	MAS (24, 48, 72 hours) = 2.22 MIS = 4.67 at 1 hour Minimally Irritating

PMRA 2590663	Supplemental
Dermal irritation – Flumethrin acid Rabbit (NZW) PMRA 2590663	All scores were zero. Non-irritating Supplemental
Bacterial reverse mutation – Flumethrin acid S. typhimurium TA98 PMRA 2590664	Negative Tested up to cytotoxic concentrations. Supplemental
28-day oral (dietary) – Flumethrin acid Rat (Wistar) PMRA 2590668	NOAEL = 27/28 mg/kg bw/day (♂/♀) (highest dose tested) LOAEL not established as no adverse effects were observed in the study.

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Flumethrin

Exposure Scenario	Study	Point of Departure and Endpoint	CAF or Target MOE[1]
Acute dietary	Acute oral neurotoxicity study in the rat	NOAEL = 0.5 mg/kg bw Decreased motor activity in males	300
	ARfD = 0.002 mg/kg bw		
Chronic dietary	Combined results from two oral (dietary and gavage) two-generation reproductive toxicity studies in rats	Reproductive and offspring NOAEL = 0.5 mg/kg bw/day Decreased birth weight and impaired growth of offspring	300
	ADI = 0.002 mg/kg bw/day		
Short-term dermal[2]	Combined results from two oral (dietary and gavage) two-generation reproductive toxicity studies in rats	Reproductive and offspring NOAEL = 0.5 mg/kg bw/day Decreased birth weight and impaired growth of offspring	300
Cancer	A cancer risk assessment was not required		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments.
[2] Since an oral NOAEL was selected, a dermal absorption factor was used in a route-to-route extrapolation.

Table 5 Integrated Food Residue Chemistry Summary

FREEZER STORAGE STABILITY	PMRA # 2579337
Honey matrix: The storage stability for residues of flumethrin was demonstrated in honey at ambient temperatures (20-25°C) for up to 9 months.	

BEEHIVE TRIALS	PMRA # 2282591, 2282592, 2282593, 2282594, 2282596, 2282597

A total of seven beehive trials were conducted in Germany and the United Kingdom. Four strips (3.6 mg ai/strip) per brood chamber, for a total rate of 14.4 mg ai/brood chamber, were used inside the beehives for treatments lasting 6-21 weeks, starting in the Fall or Spring. Samples of honey were collected during treatment or up to 33 weeks after removal of strips. In one German trial, the beehive was treated for two consecutive years at a rate of four strips (3.6 mg ai/strip) per brood chamber per year, for a total of 14.4 mg ai/brood chamber/year, for 6 consecutive weeks for each treatment. Samples of honey were collected 8 months after the second treatment.

Commodity	Total Application Rate (mg ai/brood chamber)	PHI (days)	Residue Levels (ppm)					
			n	LAFT*	HAFT*	Median*	Mean*	SD*
Flumethrin								
Honey	14.4 × 1 year	N/A	22	<0.003	<0.003	<0.003	<0.003	0
	14.4 × 2 consecutive years	N/A	4	<0.003	<0.003	<0.003	<0.003	0

* Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of independent honey samples. In some trials, one sample was taken per colony, while in other trials, samples were combined resulting in a number of honey samples less than the number of tested colonies.

Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

OTHER STUDIES		
HONEY MATRIX		
RESIDUE DEFINITION FOR ENFORCEMENT Honey		Flumethrin
RESIDUE DEFINITION FOR RISK ASSESSMENT Honey		Flumethrin
FAT SOLUBLE RESIDUE		Yes
DIETARY RISK FROM FOOD ALONE		
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**
		Food Alone
Basic chronic non-cancer dietary exposure analysis **ADI = 0.002 mg/kg bw/day**	**All infants < 1 year**	<1
	Children 1–2 years	<1
	Children 3–5 years	<1
	Children 6–12 years	<1
	Youth 13–19 years	<1
	Adults 20–49 years	<1
	Adults 50–99 years	<1
	Total population	<1
	POPULATION	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**
		Food Alone
Basic acute dietary exposure analysis, 95th percentile (deterministic) **ARfD = 0.002 mg/kg bw**	**All infants < 1 year**	<1
	Children 1–2 years	<1
	Children 3–5 years	<1
	Children 6–12 years	<1

	Youth 13–19 years	<1
	Adults 20–49 years	<1
	Adults 50–99 years	<1
	Total population	<1

Table 7 Use (label) Claims Proposed by Applicant and Accepted

Proposed label claim	VRD supported use claim
Control of varroa mites in honeybee colonies: Apply 4 strips per brood chamber. For Nuclei colonies, young colonies, and newly collected swarms, apply 2 strips. Duration of treatment is 6 weeks. Strips should not be used during peak honey flow periods.	Accepted as proposed.

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Flumethrin is a new active ingredient which is being registered in Canada.

Table 1 compares the MRLs proposed for flumethrin in Canada with corresponding American tolerances and Codex MRLs.[9] American tolerances are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide. A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Residues in Food website, by pesticide or commodity.

Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)	Codex MRL (ppm)
Honey	0.003[1]	None	None

[1] LOQ = 0.003 ppm.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

[9] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2282251	2011, Flumethrin technical insecticide - Tier 2 summary of part 2 chemistry requirements for the registration of a technicalgrade of active ingredient (TGAI) or an integrated system product (ISP), DACO: 2.1,2.16 CBI
2282252	2009, Product chemistry of flumethrin technical, DACO: 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
2282254	2009, Product chemistry of flumethrin technical, DACO: 2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.14,2.14.15,2.14.2,2.14.3,2.14.6,2.14.7,2.14.8,2.14.9,2.3.1,8.2.1 CBI
2418958	2011, Flumethrin Product Chemistry - EPA DER, DACO: 2.12.1 CBI
2418959	2004, US EPA 40 CFR 158.175, DACO: 2.12.1
2418960	2005, AE 0172747 Determination of [CBI REMOVED] Validation of Method 2201-0225603-96, DACO: 2.13.1 CBI
2418961	2005, Validation of HPLC method 2201-0347301-05 Flimethrin AI, By-Products, HPLC method, DACO: 2.13.1 CBI
2418962	2014, Characterization of reference substances, DACO: 2.13.2 CBI
2437986	2014, Flumethrin Technical Insecticide Clarification response, DACO: 2.11.4,2.15 CBI
2282581	2011, Bayvarol strips - Dossier Part II, DACO: 3.1.2,3.1.3,3.1.4,3.2.1,3.2.2,3.2.3,3.3.1,3.4.1,3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.2,3.5.3,3.5.4,3.5.5,3.5.6,3.5.7,3.5.8 CBI
2282582	2008, Bayvarol strips (Flumethrin) - Tabular formats - Appendix 1 to the pharmaceutical expert report, DACO: 3.2.1,3.7
2282583	2011, Bayvarol Bee-Hive Strips - Part 3 chemistry requirements for the registration of a manufacturing concentrate (MA) or an end use-product (EP), DACO: 3.7
2416090	2013, Bayvarol Strip Stability Data if the Drug Product, DACO: 3.5.10 CBI
2438069	2009, Flumethrin AI Stability data under accelerated test conditions of the active drug substance, DACO: 3.4.1 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
2282585	1986, Liquid chromatographic method to determine the content of Bayvarol (FCR-1622) in honey and beeswax, DACO: 7.2.1
2282587	1993, Analytical method for the determination of Bayvarol (active ingredient flumethrin) in honey and wax, DACO: 7.2.1
2282588	1993, Method for determining the residue of flumethrin in bees honey and wax, DACO: 7.2.1

PMRA Document Number	Reference
2592833	2015, Analytical method for the determination of flumethrin in bees honey and wax by LC-MS/MS, DACO: 7.2.1
2579337	E. Korta, A. Bakkali, L. A. Berrueta, B. Gallo, F. Vicente, V. Kilchenmann, and S. Bogdanov, 2001, Study of Acaricide Stability in Honey. Characterization of Amitraz Degradation Products in Honey and Beeswax, J. Agric. Food Chem, DACO: 7.3
2282591	1990, Residues of flumethrin in honey following the use of Bayvarol strips during the winter, DACO: 7.5
2282592	1990, Residues of flumethrin in honey following the use of Bayvarol strips during the pre-winter storage period, DACO: 7.5
2282593	1994, Residues of flumethrin in honey after administration of Bayvarol strips to honeybee colonies in Great Britain, DACO: 7.5
2282594	1990, Residues of flumethrin in honey following the use of Bayvarol strips during in spring, DACO: 7.5
2282596	1990, Residues of flumethrin in honey following the use of Bayvarol strips during nectar flow period, DACO: 7.5
2282597	1994, Residues of flumethrin in honey after administration of Bayvarol strips to honeybee colonies in Germany, DACO: 7.5
2282602	2012, Bayvarol beehive pest control strips - Tier 2 summaries of part 5 occupational exposure, DACO: 5.1
2282604	2012, Occupational exposure assessment for Bayvarol Beehive Pest Control Strips, DACO: 5.2,5.3
2474507	2014, Determination of the exposure of beekeepers to Flumethrin (Bayvarol Strips) by hanging up strips into beehives, DACO: 5.11
2579447	2015, Extract of raw data and example calculation from study V14-001, DACO: 5.14
2579448	2010, Method for the LC-MS/MS determination of imidacloprid and flumethrin in cotton gloves, DACO: 5.14
2282258	2007, Acute oral toxicity (UDP) in rats (flumethrin technical), DACO: 4.2.1
2282259	1994, Bayticol P (c.n. flumethrin) - Study for acute oral toxicity in rats, DACO: 4.2.1
2282260	1997, trans-Z1- and trans-Z2 isomers of flumethrin (c.n. flumethrin) - Study for acute oral toxicity in rats, DACO: 4.2.1
2282261	1994, Bayticol P (c.n. flumethrin) - Study for acute dermal toxicity in rats, DACO: 4.2.2
2282266	2008, Acute dermal toxicity in rats (flumethrin technical), DACO: 4.2.2
2282267	1997, Bayticol P - Pilot study on the RD50-determination on rats, DACO: 4.2.3
2282270	1996, Flumethrin - Study on acute inhalation toxicity in rats according to OECD no. 403, DACO: 4.2.3
2282271	1997, Bayticol P - Pilot study on the RD50-determination on mice, DACO: 4.2.3
2282273	2010, Request for waiver from the requirement of primary eye irritation study - flumethrin technical, DACO: 4.2.4
2282274	1994, BAY Vq 1950 (c. n. : flumethrin) - Study for skin and eye irritation/corrosion in rabbits, DACO: 4.2.4,4.2.5
2282275	2007, Acute dermal irritation study in rabbits (flumethrin technical), DACO: 4.2.5
2282276	1994, Bayticol P - Investigations of skin sensitization in guinea pigs (Magnusson and Kligman maximization test), DACO: 4.2.6

PMRA Document Number	Reference
2282277	1993, Verification of the Magnusson and Kligman maximization test in the DHPW guinea strain used in Bayer AG's toxicology department using 2-mercaptobenzothiazole, DACO: 4.2.6
2282282	1995, Bayticol P - Investigations of subchronic toxicity in Wistar rats (feeding study over 15 weeks), DACO: 4.3.1
2282283	1998, Bayticol P - Report on two dose-range-finding studies in CD-1 mice (administration in the food over 3 months), DACO: 4.3.1
2282284	2006, Flumethrin (project: PNR 1395) - Exploratory subacute oral toxicity study in rats (pilot study for a two-generation study with a 4-weeks administration via gavage), DACO: 4.3.3
2282285	2008, Flumethrin - Subchronic toxicity study in Wistar rats (13 weeks dermal administration), DACO: 4.3.4
2282286	2007, Flumethrin active substance - Pilot toxicity study in Wistar rats (2 weeks dermal administration), DACO: 4.3.5
2282287	2007, Flumethrin (project PNR 1395) - Pilot toxicity study in Wistar rats (4 weeks dermal administration), DACO: 4.3.5
2282288	1997, Bayticol P (flumethrin) - Subacute inhalation toxicity in rats (exposure: 5 x 6 hr/week for 4 weeks), DACO: 4.3.7
2282289	1999, Bayticol P - Oncogenicity study in CD-1 mice - Dietary administration over 18 months, DACO: 4.4.2
2282291	1999, Bayticol P - Combined study on chronic toxicity and carcinogenicity in Wistar rats - Dietary administration over 2 years with dose-adjustment, DACO: 4.4.4
2282294	2008, Flumethrin - Two-generation reproduction study in wistar rats (administration by gavage), DACO: 4.5.1
2282295	1992, Bay Vq 1950 - Multiple generation study in rats (report part 1), DACO: 4.5.1
2282297	2006, Flumethrin (project: PNR 1395) - Exploratory subchronic oral toxicity study in rats (pilot study for a two-generation study with a 19-weeks administration via gavage), DACO: 4.5.1
2282299	1999, Bayticol P - Developmental toxicity study in rats after oral administration, DACO: 4.5.2
2282300	2009, Flumethrin - Developmental toxicity study in rabbits after oral administration, DACO: 4.5.3
2282301	2006, Flumethrin - Salmonella/microsome test plate incorporation and preincubation method, DACO: 4.5.4
2282303	1993, Flumethrin - Salmonella/microsome test special study, DACO: 4.5.4
2282304	1996, Flumethrin; in vitro mammalian chromosome aberration test with Chinese hamster V79 cells, DACO: 4.5.5
2282305	2007, Flumethrin (project: PNR 1395): In vitro chromosome aberration test with Chinese hamster V79 cells, DACO: 4.5.5
2282306	2007, Flumethrin - V79/HPRT-test in vitro for the detection of induced forward mutations, DACO: 4.5.5
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2282308	2007, Flumethrin - Micronucleus-test on the male mouse, DACO: 4.5.7
2282309	1995, Flumethrin - Micronucleus-test on the mouse, DACO: 4.5.7

PMRA Document Number	Reference
2282310	1994, Flumethrin - Test on unscheduled DNA synthesis in rat liver primary cell cultures in vitro, DACO: 4.5.8
2282312	2007, Determination of flumethrin in rat plasma within the scope of the toxicological study T9073333, DACO: 4.5.9
2282313	2000, Bayticol P and Bayticol P granulate (c.n.: flumethrin) - Study for subchronic oral toxicity in rats (13 week feeding study), DACO: 4.5.9
2282315	1992, [c)-phenyl-u-14c] flumethrin: investigation of the biokinetic behaviour and the metabolism in the rat, DACO: 4.5.9
2282318	2008, An acute oral neurotoxicity screening study with technical grade flumethrin in Wistar rats, DACO: 4.5.12
2282320	2008, A subchronic oral neurotoxicity screening study with technical grade flumethrin in Wistar rats, DACO: 4.5.13
2282321	2008, A developmental neurotoxicity study with technical grade flumethrin in Wistar rats, DACO: 4.5.14
2282322	2009, Flumethrin - Subacute oral immunotoxicity study in Wistar rats (4 weeks administration by diet), DACO: 4.8
2300058	1985, BAY Vq 1950 (BAY V1 6045p). Subchronic toxicological investigations in rats; feeding study over 13 weeks., DACO: 4.3.1
2300059	1984, BAY Vq 1950. Subchronic toxicity study in dogs with oral administration (13-week feeding study), DACO: 4.3.2
2300062	1985, BAY Vq 1950. Subchronic toxicity study in dogs with oral administration supplementary study (13-week feeding study), DACO: 4.3.2
2300063	2013, Flumethrin Technical Insecticide - Waiver for one-year dog study, DACO: 4.3.2
2538481	2009, Confirmation of the function of a plaque forming cell assay in rats with cyclophosphamide, DACO: 4.8
2538482	2009, Facscan analysis and Elisa with cyclophosphamide as positive control, DACO: 4.8
2550258	2015, 2013-1613 Flumethrin Technical Insecticide Clarification response letter, DACO: 4.8
2550259	1992, [Cl-Phenyl-U-14C] Flumethrin: Investigation on the Distribution of the Total Radioactivity in the Rat by Whole-Body Autoradiography, DACO: 4.8
2550260	1983, Pharmacokinetics in Rats, DACO: 4.8
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2282580	2012, Waiver request of acute toxicity studies for Bayvarol Beehive Pest Control Strips, DACO: 4.6.3,4.6.4,4.6.5,4.6.6
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2590664	1984, Bayticol acid - Salmonella microsome test to check for point-mutagenic effects, DACO: 4.8
2590666	1995, Bayticol acid (Bayticolsaure) Study for the Acute Toxicity in Female Rats, DACO: 4.8
2590668	1995, Bayticol P-Saure. Investigations of Subacute Toxicity in Wistar Rats (Feeding Study over 4 Weeks), DACO: 4.8

3.0 Environment

PMRA Document Number	Reference
2282325	2003, Bayticol P (flumethrin) – Hydrolysis in acidic, neutral and basic medium, DACO: 8.2.3.2
2282327	1999, The degradation of [14C]-flumethrin in soil under aerobic conditions, DACO: 8.2.3.4.2
2282328	2000, Adsorption/desorption of [14C]-flumethrin in soil, DACO: 8.2.4.2

4.0 Value

PMRA Document Number	Reference
2282552	2013, Bayvarol beehive pest control strip (flumethrin) for varroa mite control on honeybee, DACO: 10.1,10.2.1,10.2.2,10.2.3.1,10.2.3.3,10.3.1,10.3.2,10.5.1,10.5.2,10.5.3
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2282556	1987, Optimisation of the arrangement and dosage of Bayvarol strips in colonies without brood cells, DACO: 10.2.3.3
2282558	1990, Field experiment to determine the efficacy of Bayvarol strips on Varroa mites in the bee colonies and to determine the effect of the medicament on colony development in the month following application, DACO: 10.2.3.3
2282559	1989, Efficacy of Bayvarol strips when used in autumn, DACO: 10.2.3.3
2282560	1985, To determine the therapeutic range of flumethrin when treating honeybee against mite infestation, DACO: 10.2.3.3
2282561	1988, Optimisation of the arrangement and dosage of Bayvarol strips in colonies containing brood cells, DACO: 10.2.3.3
2282562	1980, Efficacy of Bayvarol strips against bee mites when used in summer, DACO: 10.2.3.3
2282563	1988, Field study using Bayvarol strips with different active substance concentrations on commercial colonies and nuclei / artificial swarms, DACO: 10.2.3.3
2282564	1989, Field study- use of Bayvarol strips during the harvest period, DACO: 10.2.3.3
2282565	1986, Testing of the efficacy of strips containing different levels of active substance, DACO: 10.2.3.3
2282566	1987, long term investigations into the bee tolerability of Bayvarol strips, DACO: 10.3.2
2282570	1989, Field study- use of Bayvarol strips during the winter, DACO: 10.3.2
2282572	1989, Observations on the long-term effects of Bayvarol on colony development, DACO: 10.3.2
2282573	1986, Acute bee tolerance of strips with different concentrations of active substance, DACO: 10.3.2
2282574	1990, Testing of acute tolerability in bees, DACO: 10.3.2

2282607 Koeniger, N.; Fuchs, S., 1988, Control of *varroa jacobsoni* oud. in honeybee colonies containing sealed brood cells, Apidologie, DACO: 10.2.1

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

PMRA Document Number	Reference
2483856	Molan_1992, DACO: 7.1
2483858	Tulloch, DACO: 7.1
2598248	1996, JMPR Evaluation on Flumethrin, DACO: 12.5
2598249	1986, Some Facts about Beeswax Extracted from Propolis, DACO: 12.5
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