Proposed Registration Decision PRD2018-15

Afidopyropen; Sefina Insecticide; Versys Insecticide

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Overview

Proposed Registration Decision for Afidopyropen

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing registration for the sale and use of Inscalis Technical Insecticide, Sefina Insecticide and Versys Insecticide, containing the technical grade active ingredient afidopyropen, to control aphids and whiteflies on various vegetables and tree fruits, soybeans, hazelnuts, and greenhouse and outdoor ornamentals.

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

This Overview describes the key points of the evaluation, while the Science Evaluation section provides detailed technical information on the human health, environmental and value assessments of Inscalis Technical Insecticide, Sefina Insecticide and Versys Insecticide.

What Does Health Canada Consider When Making a Registration Decision?

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

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 section of Canada.ca.

Before making a final registration decision on afidopyropen, Sefina Insecticide and Versys Insecticide, 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 afidopyropen,

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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."

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

Sefina Insecticide and Versys Insecticide, 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 section of this consultation document.

What Is Afidopyropen?

Afidopyropen affects the nerves of aphids and whiteflies and stops the target insects from feeding on treated plants. It is the active ingredient in two commercial class products, Sefina Insecticide and Versys Insecticide.

Health Considerations

Can Approved Uses of Afidopyropen Affect Human Health?

Sefina Insecticide and Versys Insecticide, containing afidopyropen, are unlikely to affect your health when used according to label directions.

Potential exposure to afidopyropen may occur through the diet (food and water), when handling and applying the end-use products, or through bystander exposure following application. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, the technical grade active ingredient afidopyropen was of low acute toxicity via the oral, dermal and inhalation routes of exposure. It was not irritating to the eyes or skin, and did not cause an allergic skin reaction.

Sefina Insecticide was of low acute toxicity via the oral and dermal routes of exposure. It was slightly acutely toxic via the inhalation route of exposure and mildly irritating to the skin; consequently, the signal word and hazard statements "POISON" and "CAUTION – SKIN IRRITANT" are required on the product label. Sefina Insecticide was minimally irritating to the eye and did not cause an allergic skin reaction.

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

Versys Insecticide was of low acute toxicity via the oral and dermal routes of exposure. It was slightly acutely toxic via the inhalation route of exposure and moderately irritating to the skin; consequently, the signal word and hazard statements "POISON" and "WARNING – SKIN IRRITANT" are required on the product label. Versys Insecticide was minimally irritating to the eye and did not cause an allergic skin reaction.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of afidopyropen to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints used for risk assessment included effects on the brain and an alteration in the sex ratio. There was some evidence suggesting that the young animal may be more sensitive to afidopyropen than the adult animals. There was no evidence that afidopyropen damaged genetic material; however, it did cause uterine tumours in rats. The risk assessment protects against the effects noted above, and other potential effects, by ensuring that the level of human exposure is well below the lowest dose level at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Aggregate dietary intake estimates (food and drinking water) revealed that all population subgroups, including children 1 to 2 years of age, the subpopulation that would ingest the most afidopyropen relative to body weight, are expected to be exposed to less than 3% of the acceptable daily intake. Based on these estimates, the intermediate chronic dietary risk from afidopyropen is not of health concern for all population subgroups.

Chronic non-cancer exposure to the metabolite cyclopropane carboxylic acid (CPCA) from drinking water was estimated to be less than 1% of the acceptable daily intake for all population subgroups, including females 13 to 49 years of age, which is not of health concern.

The lifetime cancer risk from exposure to afidopyropen in food and drinking water was estimated to be 9×10^{-7} to 2×10^{-6} for the general population, which is below the PMRA's level of concern. The lifetime cancer risk from exposure of CPCA in drinking water was estimated to be 1×10^{-6} for the general population, which is below the PMRA's level of concern.

An acute reference dose was not required for the general population. Acute dietary intake (food plus drinking water) estimates for females 13 to 49 years of age were less than 21% of the acute reference dose, and are not of health concern. The acute exposure of CPCA from drinking water for females 13 to 49 years of age was estimated to be less than 3% of the acute reference dose, which is not of health concern.

When combining the exposure estimates from residues of afidopyropen (food and drinking water) with those of CPCA (drinking water) for all population subgroups, the cumulative exposure assessment does not exceed 1% of the afidopyropen or CPCA cumulative reference values.

Occupational Risks From Handling Sefina Insecticide and Versys Insecticide

Occupational risks are not of concern when Sefina Insecticide and Versys Insecticide are used according to the label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Sefina Insecticide and Versys Insecticide as well as field workers re-entering freshly treated fields, nurseries and greenhouses can come in direct contact with afidopyropen residues on the skin. Therefore, the labels specify that a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks must be worn. Additionally, Versys Insecticide requires that chemical handlers wear coveralls over a long-sleeved shirt and long pants and chemical-resistant headgear for airblast application. The labels also require that workers do not enter treated fields for 12 hours after application. Taking into consideration these label statements, the number of applications and the exposure period for handlers and workers, the risks to these individuals are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Afidopyropen Is Introduced Into the Environment?

When afidopyropen is used according to the label directions, the risks to the environment have been determined to be acceptable.

Afidopyropen enters the environment when applied to control insect pests on ornamentals, vegetables, and tree fruit crops. On land, afidopyropen breaks down relatively quickly and its breakdown products are not expected to move through the soil and reach groundwater. In water bodies, afidopyropen and its breakdown products will move to sediments where they may remain over time. Afidopyropen is not expected to be found in the air or to travel long distances from where it was applied. Afidopyropen is not expected to build-up in the tissues of organisms. Afidopyropen is not expected to move inside plants and its residues will remain mostly on the surface of leaves and flowers.

When used according to the label directions, afidopyropen does not present a risk of concern to wild mammals, birds, beneficial insects, earthworms, or terrestrial and aquatic plants. Afidopyropen may pose risks of concern to freshwater and marine invertebrates, freshwater fish, amphibians, and bees; therefore, preventative measures and use restrictions to reduce exposure to animals and insects that are not pests are required.

Value Considerations

What Is the Value of Sefina Insecticide and Versys Insecticide?

Sefina Insecticide controls potato aphid, green peach aphid, sweet potato whitefly and silverleaf whitefly in potato and controls soybean aphid in soybean.

Versys Insecticide controls various aphids and whiteflies in tuberous and corm vegetables, leafy vegetables, brassica head and stem vegetables, fruiting vegetables, cucurbit vegetables, leaf petioles vegetables, pome fruits, stone fruits, hazelnuts, and greenhouse and outdoor ornamentals (except conifers).

Sefina Insecticide and Versys Insecticides are new management tools for control of aphids, which are widespread pests of horticultural crops, and whiteflies, which are prevalent pests in the ornamental greenhouse industry. Both products will aid in resistance management for crops where no other insecticides with the same mode of action are registered, which include hazelnuts, labelled tree fruit crops and most of the vegetable crops.

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 outlined on the labels of Sefina Insecticide and Versys Insecticide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with afidopyropen on the skin or through inhalation of spray mists, anyone mixing, loading and applying afidopyropen must wear a long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks. Additionally, Versys Insecticide requires that all chemical handlers wear coveralls over a long-sleeved shirt and long pants, and chemical-resistant headgear for open cab airblast application. Furthermore, standard label statements to protect against drift during application are present on the label.

Environment

To minimize exposure and reduce risks to bees, aquatic invertebrates, fish and amphibians, use restrictions, vegetative filter strips, spray buffer zones and precautionary label statements are required. Application is restricted to periods when most bees are not actively foraging, for crops that are highly attractive to bees, or when managed bees are used for pollination services.

Next Steps

Before making a final registration decision on afidopyropen, Sefina Insecticide and Versys Insecticide, 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 MRLs 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

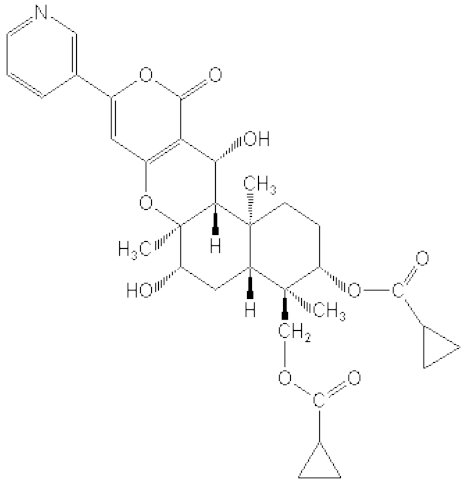
When the PMRA makes its registration decision, it will publish a Registration Decision on afidopyropen, Sefina Insecticide and Versys Insecticide (based on the Science Evaluation section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA’s Reading Room (located in Ottawa).

Science Evaluation

Afidopyropen - Inscalis Technical, Sefina and Versys Insecticides

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Afidopyropen
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	[(3*S*,4*R*,4a*R*,6*S*,6a*S*,12*R*,12a*S*,12b*S*)-3-(cyclopropylcarbonyloxy)-1,2,3,4,4a,5,6,6a,12a,12b-decahydro-6,12-dihydroxy-4,6a,12b-trimethyl-11-oxo-9-(3-pyridyl)-11*H*,12*H*-benzo[*f*]pyrano[4,3-*b*]chromen-4-yl]methyl cyclopropanecarboxylate
2. Chemical Abstracts Service (CAS)	[(3*S*,4*R*,4a*R*,6*S*,6a*S*,12*R*,12a*S*,12b*S*)-3-[(cyclopropylcarbonyl)oxy]-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-6,12-dihydroxy-4,6a,12b-trimethyl-11-oxo-9-(3-pyridinyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-4-yl]methyl cyclopropanecarboxylate
CAS number	915972-17-7
Molecular formula	$C_{33}H_{39}NO_9$
Molecular weight	593.66 g/mol
Structural formula	

Purity of the active ingredient 94.32 %

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

Technical Product – Afidopyropen Technical

Property	Result
Colour and physical state	Fine yellow solid (powder)
Odour	Odourless
Melting range	The melting point was determined to be 150ºC (technical grade)
Boiling point or range	Not applicable
Henry's law constant	2.3×10^{-9} atm·m^3/mol at 25°C
Density	1.291–1.305 g/cm^3 at 20°C (pure active)
Vapour pressure	temperature (°C) — vapour pressure (Pa) 25 — $<9.9 \times 10^{-6}$ 50 — $<1.5 \times 10^{-5}$
Ultraviolet (UV)-visible spectrum	conditions — λ_{max} (nm) — log ε acidic — 231 — 4.28 basic — 231 — 4.33 neutral — 231 — 4.32 ε (L/mol.cm) Smaller peaks were also observed in all media at ~ 320 nm
Solubility in water at 20°C	25.1± 0.79 mg/L at pH=7.2
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) at 20°C n-hexane — 0.00766 toluene — 5.54 dichloromethane — > 500 acetone — > 500 methanol — > 500 ethyl acetate — > 500
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 3.45
Dissociation constant (pK_a)	No significant dissociation in environmentally relevant pH range of 4–9
Stability (temperature, metal)	The technical grade active ingredient is stable in the presence of aluminium, aluminium acetate, iron and iron acetate at 25ºC and 54ºC for 14 days.

End-Use Product – Sefina Insecticide

Property	Result
Colour	Golden yellow
Odour	Odourless
Physical state	Liquid
Formulation type	Emulsifiable concentrate
Guarantee	50.0 g/L
Container material and description	High-density polyethylene (HDPE) jugs or totes.
Density	Density 1.020–1.031 g/cm^3 and relative density 1.0262 – 1.0271.
pH of 1% dispersion in water	7.27–7.65
Oxidizing or reducing action	The product is considered as a moderate reducing agent.
Storage stability	The product was shown to be stable after storage at 54ºC for 14 days in HDPE commercial containers.
Corrosion characteristics	The product did not have any adverse effects on its commercial packaging (HDPE) after storage for 14 days at 54ºC.
Explodability	The product did not react explosively to thermal stress or mechanical stress.

End-Use Product – Versys Insecticide

Property	Result
Colour	Golden yellow
Odour	Odourless
Physical state	Liquid
Formulation type	Emulsifiable concentrate
Guarantee	100.0 g/L
Container material and description	High-density polyethylene (HDPE) jugs or totes.
Density	Density 1.017–1.028 g/cm^3 and the relative density 1.024.
pH of 1% dispersion in water	6.91
Oxidizing or reducing action	The product is considered as a moderate reducing agent.
Storage stability	The product was shown to be stable after storage at 54ºC for 14 days in HDPE commercial containers.
Corrosion characteristics	The product did not have any adverse effects on its commercial packaging (HDPE) after storage for 14 days at 54ºC.
Explodability	The product did not react explosively to thermal stress or mechanical stress.

1.3 Directions for Use

Sefina Insecticide can be applied by ground or air as a foliar application to potato and soybean. In potato, 10 g a.i./ha controls potato aphid and green peach aphid and 35–50 g a.i./ha controls sweet potato whitefly and silverleaf whitefly. Four applications are allowed per year with a maximum of 125 g a.i./ha per year. In soybean, 10 g a.i./ha controls soybean aphid. Two applications are allowed per year with a maximum of 20 g a.i./ha per year. Applications may be repeated every 7 days in both crops if monitoring indicates it is necessary.

Versys Insecticide can be applied by ground as a foliar application to various vegetable, tree fruit and nut crops. Application rates for control of listed species of aphids and whiteflies are 10 g a.i./ha and 35-–50 g a.i./ha, respectively. Labelled crops are tuberous and corm vegetables (Crop Subgroup 1C), leafy vegetables (Crop Group 4-13), brassica head and stem vegetables (Crop Group 5-13), fruiting vegetables (Crop Group 8-09), cucurbit vegetables (Crop Group 9), pome fruits (Crop Group 11-09), stone fruits (Crop Group 12-09), leaf petioles vegetables (Crop Subgroup 22B), hazelnuts, and greenhouse and outdoor ornamentals (except conifers). Applications may be repeated every 7 days if monitoring indicates it is necessary. Four applications are allowed per year on most listed crops with a maximum of 125 g a.i./ha per year. These use directions are for the majority of crops; consult labelled use directions for exceptions to pome fruits, stone fruits, and ornamentals. Aerial applications are allowed only on tuberous and corm vegetables (Crop Subgroup 1C).

1.4 Mode of Action

Afidopyropen is non-systemic, though locally translaminar, and has contact activity on piercing-sucking insects, such as aphids and whiteflies. Thorough and uniform coverage of plant parts is important for the insecticide to be effective. It acts on the nerves and causes immediate cessation of feeding. The Insecticide Resistance Action Committee has classified afidopyropen in Mode of Action (MOA) Group 9D. Pymetrozine (MOA Goup 9B) is the only other active ingredient registered in Canada in MOA Group 9.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

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

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

High-performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes for environmental media. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis in environmental media are summarized in Appendix I, Table 1A.

HPLC-MS/MS methods (Method D1103/01 in plant matrices and Method 1507/01 in animal matrices) were developed and proposed for data gathering and enforcement purposes for plant and animal matrices. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant and animal matrices. The proposed enforcement methods were successfully validated in plant and animal matrices by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled samples (soybean leaf, tomato fruit, cabbage outer leaves) analyzed with the enforcement method. Demonstration of extraction efficiency with radiolabelled animal matrices was not provided for the enforcement method; however, extraction solvents used in the method were similar to those used in the livestock metabolism studies. Methods for residue analysis in plant and animal matrices are summarized in Appendix I, Table 1B.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Afidopyropen is a pyripyropene A derivative and represents a novel class of pesticides. The proposed pesticidal MOA for afidopyropen is gate disruption of transient receptor potential vanilloid (TRPV) channel complexes in insect chordotonal stretch receptor organs. In insects, these organs are critical for hearing, balance, and proprioception, among other functions. Although humans lack these organs, there are human homologues of proteins that make up the TRP channels. These channels play an important role in cilia-dependent function.

A detailed review of the toxicology database for afidopyropen was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Additional studies included repeat-dose dietary toxicity studies in different strains of rats, involving different batches of the test material. A cross-fostering study in rats was also provided, as well as a series of mechanistic studies to support a proposed MOA for uterine tumour formation in rats. In addition, the applicant submitted a position paper that discussed the human relevance of toxicological effects that occurred at dose levels above a proposed kinetically-derived maximum dose (KMD). Finally, acute and repeat-dose oral toxicity studies as well as genotoxicity and toxicokinetic studies were conducted with two metabolites of afidopyropen. The required studies in the afidopyropen database 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 afidopyropen.

Metabolism and toxicokinetic studies were conducted via the oral route in Wistar and Fischer rats, and included testing with different batches of test material. In these studies, afidopyropen was C^{14}- radiolabelled on either the nicotinic acid portion of the molecule or the pyranone ring. Afidopyropen was rapidly and readily absorbed and widely distributed to tissues following single low- (3 mg/kg bw) and high-dose (300 mg/kg bw) gavage administration. The plasma elimination half-life was 0.5 hours and 2–4 hours, for low- and high-dose groups, respectively. Highest levels of radioactivity were observed in the gastrointestinal (GI) tract, liver, adrenal glands and kidney, at 0.5 hours and 2 hours following low- and high-dose administration, respectively. Very low levels of radioactivity were observed in the brain four days post-dosing. No sex differences were noted in the above parameters.

Radioactivity was readily excreted within 96–120 hours with the majority (up to 86% of administered dose) of radioactivity excreted via the feces and lower amounts (up to 21% of administered dose) excreted via the urine. Approximately half of the radioactivity in feces was attributed to biliary excretion based on the findings from studies with bile-duct cannulated rats from both strains of rats. In female Fischer and Wistar and male Fischer rats, levels of radioactivity in urine increased with dose, whereas those in bile and feces decreased with dose. In these studies, bioavailability was not significantly different between the sexes and was not impacted by the dose level administered. Results suggest that biliary excretion is the predominant route of elimination for afidopyropen.

Plasma kinetics were also examined following 14 days of dietary administration of non-radiolabelled afidopyropen followed by a single gavage administration of C^{14}- radiolabelled afidopyropen. Absorption from the GI tract was rapid, and maximum plasma concentrations were reached by one hour post-dosing for the low- (3 mg/kg bw/day) and mid-dose (15 mg/kg bw/day) groups, and by two hours for the high-dose group (50 mg/kg bw/day). The majority of the excretion occurred via the feces, irrespective of dose level.

Afidopyropen was extensively metabolised in the rat with no significant sex differences identified. Most metabolites were structurally similar to the parent compound, with changes in one or two functional groups, and in some cases, loss of one or two CPCA ester moieties. Following single or repeat dosing of Fischer and Wistar rats with 3 or 300 mg/kg bw/day of C^{14}-radiolabelled test material, the main metabolites that were identified included M440I001 (urine, feces), M440I002 (urine, feces), M440I008 (feces), M440I017 (bile), M440I019 (bile), M440I034 (feces), M440I054 (urine), M440I058 (feces), and M440I059 (bile). Significant levels of unchanged afidopyropen were detected only in the feces. The proposed metabolic pathway involves hydrolytic loss of one or both CPCA moieties, N-oxidation at the pyridine ring, hydroxylation of one of the methyl groups, and conjugation of hydroxyl groups of the metabolites. The names of metabolites that were further characterized are presented in Appendix I, Table 2.

The applicant submitted a position paper contending that nonlinear kinetics were observed in the database at dose levels greater than 15 mg/kg bw/day in Fischer rats and greater than 30 mg/kg bw/day in Wistar rats. This, it was argued, would lead to a disproportionate increase in plasma concentration of afidopyropen with increasing dose levels. The applicant reasoned that

toxicological effects that occur at dose levels above a KMD would be of questionable human relevance. The available toxicokinetic data did not allow for the establishment of an inflection point when considering the area-under-the-curve (AUC) data, which could have aided in support to the applicant's contention. The limited number of dose levels utilized in most of the toxicokinetic investigations was considered a key limitation in this regard. Moreover, in the few studies utilizing more than two dose levels, the data suggested linear kinetics. It was concluded that the applicant's position regarding non-linear kinetics and the derivation of a KMD could not be supported.

In acute toxicity testing, afidopyropen was of low acute toxicity to rats via the oral, dermal and inhalation routes of exposure, not irritating to the eyes and skin of rabbits, and negative for skin sensitization in guinea pigs using the Maximization test protocol.

Sefina Insecticide and Versys Insecticide were of low acute toxicity via the oral and dermal routes of exposure in rats. They were slightly acutely toxic via the inhalation route of exposure in rats and minimally irritating to the eyes of rabbits. Sefina Insecticide was mildly irritating to rabbit skin, whereas Versys Insecticide was a moderate skin irritant in rabbits. Both end-use products were negative in dermal sensitization testing inthe guinea pig using the Buehler method. Two genotoxicity studies conducted with Versys Insecticide were also available. This end-use product was negative in a bacterial reverse mutation assay using *S. typhimurium* strains and *E. coli*, and in an in vivo micronucleus test in male mice.

Repeat-dose dietary toxicity studies with afidopyropen were available in mice and rats, and capsule administration studies were available in dogs. In these studies, which involved short-term to longer-term testing, the most sensitive species for toxicity appeared to be the dog, followed by the rat and mouse.

In addition to effects on body weight or body weight gain, the liver was a common target tissue following repeated dosing in these three test species. The liver toxicity was evidenced by increased organ weight, fatty change, and hyaline droplet deposition. In the rat and mouse, hepatocytic vacuolation and hypertrophy were also observed, whereas congestion, hemorrhage, and deposits of brown pigment in Kupffer cells were observed in dogs. Pale colour and accentuated lobular pattern, as well as necrosis and enlargement, were additional findings in mouse livers. In the rat, clinical chemistry alterations suggestive of liver inflammation or damage were also noted, as well as discolouration, slight foci of altered cells, and bile duct hyperplasia.

Another target organ of toxicity following repeated dosing with afidopyropen was the heart, with adverse effects most prominent in rats and mice. In the rat, myocardial vacuolation, as well as incidence and severity of necrosis or fibrosis of the heart, were noted at the higher dose levels. Histopathological examinations of the heart were not conducted at lower dose levels; however, increased serum levels of cardiac troponin I, an indicator of myocardial damage, were observed at these dose levels. Troponin levels were only measured in studies conducted with the rat. In the mouse, heart effects were noted in females only, and included vacuolation and fibrosis of heart muscle. In dogs, heart effects were limited to changes in heart weight that occurred at higher dose levels than those producing liver toxicity.

Adverse effects were observed in the brain in both the mouse and dog following repeated dosing with afidopyropen. These effects, in both species, were observed at dose levels that produced adverse effects on the liver and heart. Vacuolation of the cerebrum was noted in dogs and mice; vacuolation of the glial cell gray matter in the spinal cord was also noted in mice. The brain effects observed in the mouse occurred in females only and at dose levels causing death. In the dog, brain effects included vacuolation of the white matter of the medulla oblongata and the pons, as well as a slight to moderate decrease in myelin density of subcortical white matter. A cyst in the cerebellum was observed in one decedent in the dog one-year toxicity study. In rats, effects in the brain were limited to decreased absolute weight noted in one subchronic study, and in the offspring at the higher dose levels in the range-finding reproductive toxicity study and the cross-fostering study.

Effects on several reproductive organs were also observed following repeated dosing with afidopyropen. In the 90-day dog study, at doses that were clearly toxic, effects included atrophy and hypoplasia of the seminiferous tubules, atrophy of the prostate, and decreased sperm counts, as well as decreased testis, epididymal and prostate weights. In mice and rats, effects included decreased testes and epididymal weights, with rats also displaying decreased seminal vesicle, and prostate weights. In mice and rats, ovary and uterine weights were generally decreased, except for the chronic studies in which ovary weight was increased in the mouse and uterine weight was increased in the rat. Atrophy of the uterus and ovary was also observed in a number of subchronic studies conducted in the rat, and atrophy of the ovary was noted in two 28-day rat studies. Effects on reproductive organs were also observed in the dietary reproductive toxicity studies in the rat, discussed further below, as evidenced by decreased testicular sperm count and lymphoid infiltration of the prostate.

There were several other notable effects observed following repeated oral dosing with afidopyropen. In rats, adrenal weight was increased and was accompanied by hypertrophy, discolouration and vacuolation of the adrenal cortex. In subchronic toxicity studies in Fischer and Wistar rats, effects on adrenal weight were noted exclusively in male Fischer rats. In the reproductive and developmental toxicity studies, conducted in Wistar rats, adrenal weight changes were observed in both sexes; the female adrenal weight changes occurred at lower dose levels than that of males. In mice and rats, effects in the spleen were noted and included congestion, apoptosis of lymphoid tissue, extramedullary hematopoiesis, and atrophy, as well as an increase in organ weight. Vacuolation in the urinary bladder, kidney, and glandular stomach was an additional finding in female mice. Additional findings in rats included hematological changes which included decreased red blood cell, hematocrit and hemoglobin levels.

In a 28-day dermal toxicity study in rats, there was no indication of systemic toxicity up to the limit dose of testing. Multifocal hyperkeratosis of the skin was observed in females at the mid- and high-dose levels. A rationale to waive the requirement for a repeat-dose inhalation toxicity study was submitted. The waiver was supported for the proposed uses on the basis of the low volatility and low acute inhalation toxicity of afidopyropen, as well as the magnitude of the margin of exposure (MOE) obtained for the exposure scenarios when oral endpoints were used in the risk assessment.

In an acute neurotoxicity study in rats conducted via oral gavage, decreased motor activity and clinical signs of toxicity were noted at the limit dose on the day of dosing. There was no indication of neurotoxicity in the rat 90-day dietary neurotoxicity study. Although it is acknowledged that there was a lack of confidence in the results from the high-dose groups due to excessive food spillage, it was possible to establish a no observed adverse effect level (NOAEL) in this study on the basis of the body weight findings at the lower dose levels. Throughout the database, there was some indication of potential effects on the nervous system in the rat, mouse, and dog as evidenced by the brain effects noted previously. The most serious effects were observed in the dog however, and as noted above, included vacuolation of nervous tissue, decreased myelin density of white matter and the corpus callosum, and a cerebellar cyst. Overall, the dog was the most sensitive test species for nervous tissue effects since the findings occurred at much lower dose levels than in the mouse and rat. Since the studies in dogs were performed in adult animals, potential effects on neurodevelopment of the young animal exposed to afidopyropen in utero or during early the post-natal period is not known. Given the relative insensitivity of this test species to the nervous system effects of afidopyropen, there is questionable utility in conducting a developmental neurotoxicity (DNT) study in rats. As a result, there is residual uncertainty regarding potential adverse effects on neurodevelopment. Consequently, an additional factor was applied to the point of departure (POD) for effects on nervous tissue in the one-year dog study when that POD was used in the risk assessment.

A 28-day dietary immunotoxicity study conducted in rats dosed with afidopyropen was submitted. Effects on body weight gain, as well as increases in liver and thymus weights were noted. Although the study was considered to be supplemental due to methodological limitations, no evidence of immune dysregulation was noted in this study, or in the afidopyropen database.

Several dietary reproductive toxicity studies with afidopyropen in rats were provided including two one-generation studies. This consisted of a dose-range finding study, and a study comparing results between testing with a high purity batch and the standard test batch of afidopyropen. Two multi-generation reproductive toxicity studies were also included in the database; the second study employed higher dose levels than the first. A supplemental dietary cross-fostering study in rats was also provided. These studies were considered collectively in determining effect levels for the numerous findings that follow.

The systemic toxicity observed in parental animals in these reproductive toxicity studies was generally consistent with findings reported in other repeat-dose dietary studies in rats, and included increased liver and adrenal weights. Although body weights were decreased throughout the database, body weight was increased in dams during lactation in the reproductive toxicity studies despite a decrease in food consumption. In the initial multi-generation reproductive toxicity study, increased adrenal weight was noted in P and F1 dams at the highest dose level, whereas no adverse effects were noted in males. Adverse effects were noted in males in the second multi-generation reproductive toxicity study, in which the top dose level for both sexes was approximately twice that of the highest dose level in the first study. Effects in males included decreased body weight and body weight gain, increased adrenal weight, and decreases in clinical chemistry parameters. In this second multi-generation reproductive toxicity study, in both mid- and high-dose females, changes in clinical chemistry and hematological parameters were noted in addition to increased adrenal weight. In the high-dose females, adrenal vacuolation

accompanied the adrenal weight changes. Despite the lack of histopathology correlates at the mid-dose level, the increased adrenal weights were considered toxicologically relevant given the consistency of this finding in the database.

Effects on reproductive parameters were observed in several studies. In addition to the weight changes in reproductive organs noted previously, additional findings included decreases in implantation sites, pups born, and litter size, as well as increased lymphoid infiltration of the prostate and observations in dams of "improper nursing of offspring". An altered sex ratio (increased number of males) was observed in all of the reproductive toxicity studies, except the cross-fostering study. When considering the collective results from these studies, the alteration in sex ratio was considered equivocal at doses of 1000 and 1500 ppm due to the inconsistency of the observation at these dose levels. A clear effect on this parameter was noted at 2000 ppm. There was also a decrease in testicular sperm count noted in two of the reproductive toxicity studies, which was deemed to be equivocal when considering the variability in the data, as well as historical control values.

In the reproductive toxicity studies, there was no evidence to suggest sensitivity of the young as effects noted in the offspring occurred at dose levels that were also toxic to the maternal animals. Effects in the young included decreased body weight and body weight gain, as well as decreased thymus and spleen weights. In addition, delayed sexual maturation was observed in both sexes; this finding was observed at a lower dose level in males than in females. A serious effect, increased pup death, was noted at the highest dose levels in the early post-natal period in both studies. Despite some study limitations, results from the supplemental dietary cross-fostering study in rats suggest that in utero exposure was the critical factor leading to pup death.

With respect to developmental toxicity, the database contained a study in rabbits, and two studies in rats, all conducted via oral gavage. In the initial rat study, the study author concluded that there was no clear evidence of overt maternal toxicity at the highest dose level (100 mg/kg bw/day) and conducted a second study with dose levels up to 200 mg/kg bw/day. The PMRA is of the opinion that the change in adrenal weight at the high dose level in the initial study is toxicologically significant, given the consistency of the adrenal findings in the database and the fact that histopathological examination of this organ was not conducted in the developmental toxicity studies. In fetuses, increases in skeletal variations, lumbar (supernumerary) ribs, and metatarsal ossification were observed in this study at the high-dose level. There was also an altered sex ratio at the same dose level, which was considered equivocal. In the second rat developmental toxicity study, clear evidence of effects on maternal animals was observed at the highest dose level and included mortality, as well as decreased body weights and food consumption. At this same dose level, developmental effects included an increased incidence (fetal and litter) of zygomatic bone fused with maxilla and two incidences of a rare malformation, cleft palate, in one litter. At a non-maternally toxic lower dose level, increased incidents of skeletal variations and supernumerary ribs were observed in fetuses, suggesting sensitivity of the young animal.

As noted previously, the heart was a target tissue in the afidopyropen database and the range-finding developmental toxicity study in rats included weight measurements as well as histopathological examination of the heart. Single incidents of slight myocardial degeneration

were observed at the 20 mg/kg bw/day and the 100 mg/kg bw/day dose levels; these were considered equivocal based on the incidence as well as the severity of the response. At higher dose levels in this study, the incidence, as well as the severity grading of this finding, was more pronounced and accompanied by marked maternal toxicity, including death. Although histological examination of the heart was not undertaken in the rat main developmental toxicity studies, the overall maternal NOAEL was considered protective of the heart findings.

In the rabbit developmental toxicity study, clear toxicity to the maternal animal and the fetus was noted at the highest dose level. Effects included a decrease in the number of live fetuses, as well as increases in early resorptions, total litter resorptions and post-implantation loss. A serious effect, an altered sex ratio, was noted at a lower dose level that was not overtly toxic to maternal animals.

Afidopyropen was negative in a genotoxicity testing battery which included bacterial reverse mutation assays in *S. typhimurium* and *E. coli*, an in vitro chromosomal aberration assay in Chinese hamster lung cells, an in vitro forward mutation assay in Chinese hamster ovary cells, and two in vivo micronucleus assays in mice.

There was no evidence of oncogenicity in an 18-month dietary oncogenicity study in mice. Two chronic/oncogenicity studies conducted in Fischer rats were included in the database. These two-year studies were from the same conducting laboratory and were completed consecutively. In the first study, afidopyropen was administered at dose levels up to 1000 ppm (43/51 mg/kg bw/day in males and females, respectively) and the second study included dose levels of 1000, and 3000 ppm (42/50, 128/147 mg/kg bw/day, in males and females respectively). In the first study, there was a non-statistically significant increase in the incidence of uterine adenocarcinoma and combined uterine adenoma/adenocarcinoma at the highest dose level. The incidences of these findings were statistically significantly increased at both dose levels in the second study. A statistically significant linear trend was observed for these tumour findings in both studies.

The applicant submitted a proposed MOA and a human relevance framework analysis for the rat uterine adenocarcinomas. The proposed MOA involved the following key events: agonism of dopamine receptors, decreased serum prolactin levels, decreased corpus luteum support which would lead to decreased production of progesterone and result in estrogen dominance, altered reproductive senescence in aged rats, endometrial hyperproliferation, and promotion of uterine adenocarcinomas. Mechanistic studies submitted by the applicant in support of the proposed MOA included radioligand binding assays for human recombinant dopamine receptors, tissue bioassays using rabbit ear artery, a 28-day dietary toxicity study conducted in female Fischer rats which measured effects on serum prolactin levels, an estrogen-receptor binding assay, and a 14-day dietary study in Fischer rats to measure CYP1A1 and CYP1B1 enzymatic activity and hepatic and uterine mRNA expression.

Studies were submitted to support the first key event (dopamine agonism), and although afidopyropen and one of the tested metabolites (M440I002) induced a concentration-dependent decrease in the twitch contraction amplitude in the rabbit ear artery studies, providing some evidence of dopamine-like effects, the data were not considered to be robust. The 28-day dietary toxicity study submitted to support the second key event provided some evidence that

afidopyropen may decrease prolactin levels under the conditions tested. No study was submitted to support the third key event of decreased corpus luteum support and decreased progesterone production, nor was there was any evidence to support this key event identified from studies within the toxicology database. To support the key event involving altered reproductive senescence in aged rats, the applicant pointed to a decrease in the incidence of mammary gland duct dilation observed in the second rat chronic/oncogenicity study. However, when the data from both chronic/oncogenicity studies were combined, a dose-dependent trend was not observed and thus the evidence was considered to be insufficient to support this key event. To support the key event of endometrial hyperproliferation, the applicant pointed to an increase in the incidence of endometrial hyperplasia observed at the highest dose level in the second chronic study; however, there was no clear dose response observed when the data from both studies were combined.

Although the proposed MOA is biologically plausible, conflicting evidence has been found in the literature regarding the effects of prolactin on uterine carcinogenicity in rats (PMRA #2832324, 2832325, and 2832326). Other MOAs were explored by the applicant, including a mutagenesis MOA, an estrogen receptor-mediated MOA, and a CYP450-mediated MOA. Mutagenesis was not considered to be a likely MOA since the genotoxicity studies for afidopyropen and one of its metabolites (M440I007) were negative. An estrogen receptor transcriptional activation study was submitted which demonstrated that afidopyropen did not alter estrogen receptor transcriptional activation. A study was also submitted that tested the ability of afidopyropen, and metabolites M440I002 and M440I001, to bind to the estrogen receptor. The results for afidopyropen indicated that the assay could not properly assess the interaction of afidopyropen with the estrogen receptor due to experimental limitations. The results for metabolites M440I002 and M440I001 were negative, indicating that estrogen receptor binding was not altered under the tested conditions. The results did not suggest an estrogen receptor-mediated MOA. In a 14-day dietary study with afidopyropen investigating CYP450 enzyme induction, there were increases in hepatic ethoxyresorufin-O-deethylation (EROD), hepatic microsomal estradiol-2-hydroxylation, hepatic CYP1A1 mRNA, hepatic CYP1B1 mRNA, and uterine CYP1A1 mRNA. Although the results suggest that exposure to afidopyropen may increase CYP1A and CYP1B enzyme activity, there were several limitations in the study, including lack of standardization for stage of estrous cycling, and lack of a positive control. The data from this study were not considered adequate to discount the CYP450-mediated MOA.

Within the context of the MOA discussion, it was acknowledged that there was evidence of endocrine perturbation observed throughout the database including delayed sexual maturation, altered sex ratio, altered sperm parameters, sex organ weight changes, and decreased implantation sites as mentioned previously. The interpretation of these findings, however, was complicated by the dynamic nature of female reproductive hormones and the fact that there was a general lack of hormone measurements in the database. Furthermore, the observed endocrine-related effects are not unique to the proposed MOA. Another confounding issue was the fact that many findings were identified in young adult rats, whereas tumours appeared in aged animals that were likely in reproductive senescence. Overall, the data provided were not considered adequate to support the proposed MOA for uterine adenocarcinoma formation in rats. Consequently, a linear low-dose extrapolation approach for cancer risk assessment was undertaken.

Several studies were available for metabolite M440I007, a dimer of afidopyropen, which is a large molecule of high molecular weight that is not likely to be readily absorbed due to its size. M440I007 was not observed in the rat metabolic cascade. This metabolite was of low acute toxicity following oral dosing in the female rat. It was negative in two bacterial reverse mutation assays in *S. typhimurium* and *E. coli*, an in vitro micronucleus test with human lymphocytes, an in vitro forward mutation assay in mouse lymphoma cells, and an in vivo micronucleus assay in mice. An investigation of the metabolic fate of M440I007 in urine and feces following gavage dosing in the rat, although limited to one male, did not suggest that the metabolite biotransforms to the parent compound. In a supplemental 90-day dietary toxicity study in rats with M440I007, minimal necrosis/fibrosis of the heart as well as extramedullary hematopoiesis of the spleen were observed at considerably higher dose levels than those that produced similar findings with afidopyropen. Overall, although the data were limited, they did not suggest that M440I007 was more toxic than afidopyropen.

Afidopyropen contains two CPCA groups at one end of the molecule, which are reportedly cleaved via simple hydrolysis. CPCA and CPCA-related conjugates are of toxicological concern for humans. CPCA toxicity is due in large part to its ability to conjugate to carnitine and fatty acids. Carnitine plays an essential role in the transfer of long-chain fatty acids into mitochondria. The binding of CPCA to carnitine leads to carnitine deficiency, blockage of mitochondrial oxidation of fatty acids, and ultimately lipid accumulation in the cytosol. This lipid accumulation results in impaired organ/tissue function. Since skeletal muscle, and in particular, cardiac muscle, depend on fatty acid oxidation for most of their energy, these tissues are expected to be most severely affected by carnitine deficiency (PMRA #2832327).

An acute oral toxicity study in female rats with CPCA was available and indicated high acute oral toxicity in contrast to the low acute toxicity of afidopyropen. In addition, in a 90-day toxicity study with CPCA in which rats were dosed via gavage, microscopic findings in the liver and thymus of females and the heart and pancreas of both sexes were observed. The toxicity exhibited in this repeat-dose study occurred in females at a nearly 2-fold lower dose in comparison to the rat 90-day dietary study with afidopyropen.

Although CPCA was not measured directly in the rat toxicokinetic studies, there is evidence to suggest that it is a rat metabolite. Exposure to CPCA was estimated by analyzing for CPCA-carnitine as the latter is more readily detected at low concentrations compared to free CPCA. CPCA-carnitine concentrations were measured in rats after 14 days of dietary administration of non-radiolabelled afidopyropen, followed by a single oral gavage administration of C^{14}-radiolabelled afidopyropen. CPCA-carnitine reached a maximum plasma concentration one hour post-gavage dosing in the low-dose group, whereas the high-dose group reached maximum plasma concentration eight hours post-dosing. Plasma levels of CPCA-carnitine declined 72 hours post-dosing; however, CPCA-carnitine was not completely eliminated by that time point. A higher terminal half-life and AUC was noted for CPCA-carnitine as compared to afidopyropen.

Toxicokinetic studies that measured levels of metabolites that had lost one or both of the CPCA ester moieties provide further evidence of exposure of rats to CPCA following dosing with

afidopyropen. Plausible evidence of CPCA-induced toxicity was also observed at high dose levels in afidopyropen subchronic and chronic studies in rats, and in studies conducted in mice and dogs. This evidence included vacuolar change in hepatocytes, the myocardium and brain, fibrosis of the heart, and necrosis of the liver. Though not an effect exclusive to carboxylic acid toxicity, the vacuolation observed in the liver is a known consequence of carboxylic acid-induced mitochondrial dysfunction, and the observed heart vacuolation is also characteristic of defective or reduced carnitine uptake.

Cardiomyopathy and myocardial degeneration were selected as common endpoints in order to compare the relative toxicity of CPCA and afidopyropen. An increased incidence and severity of cardiomyopathy compared to controls was observed in both sexes at ≥ 30 mg/kg bw/day in the CPCA 90-day gavage toxicity study in Sprague-Dawley rats. In afidopyropen 90-day dietary toxicity studies, the lowest dose level at which these heart findings were observed was 181/361 mg/kg bw/day, in male/ female Fischer rats, respectively. Necrosis/fibrosis of the heart was observed at doses of 171/197 mg/kg bw/day (males and females, respectively) in the supplemental 90-day Wistar rat studies in which histopathology was not conducted for the low- or mid-dose groups. In light of these findings, including the limited toxicology data available for CPCA, it was difficult to directly compare the relative toxicity of afidopyropen and CPCA. This was further confounded by the use of different rat strains and routes of administration in the studies, as well as the lack of histopathology examinations in the lower dose groups in the supplemental afidopyropen studies. That being said, the available data suggest that CPCA and afidopyropen may have a similar mechanism of toxicity; the potency for CPCA, however, appears greater. Therefore, separate toxicology reference values were established for CPCA on the basis of a molecular weight (MW) adjustment factor.

Identification of the metabolites of afidopyropen, as well as results of the toxicology studies conducted on laboratory animals with afidopyropen, its metabolites, and end-use products are summarized in Appendix I, Tables 2, 3, 4 and 5, respectively. The toxicology endpoints for use in the human health risk assessment for afidopyropen are summarized in Appendix I, Table 6, and for CPCA in Appendix I, Table 7.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Afidopyropen is a new active ingredient pending registration for use in Canada and the United States, and as of 2 November 2017, no incident reports were submitted to the PMRA. Once products containing afidopyropen are registered, the PMRA will monitor for incident reports.

3.1.1 *Pest Control Products Act* (PCPA) 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 afidopyropen toxicity database as it pertains to the toxicity to infants and children, the database contains the standard complement of required studies including gavage developmental toxicity studies in rats and rabbits, and dietary multi-generation reproductive toxicity studies in rats. A supplemental dietary cross-fostering study in rats was also submitted.

With respect to potential prenatal and postnatal toxicity, there was evidence of increased sensitivity of the fetuses compared to maternal animals in some of the rat and rabbit developmental toxicity studies. In the first rat study, fetal skeletal variations, increased incidence of lumbar (supernumerary ribs) and metatarsal ossification, as well as a serious effect, altered sex ratio, were observed at 100 mg/kg bw/day in the presence of maternal toxicity (increased adrenal gland weights). In the second rat study, which included higher dose levels, increased incidents of skeletal variations and supernumerary ribs occurred in fetuses at the lowest dose level tested (50 mg/kg bw/day), a dose level that was not toxic to the maternal animal. At the highest dose level in this study (200 mg/kg bw/day), developmental effects included an increased fetal and litter incidence of zygomatic bone fused with maxilla relative to controls, and two incidents of cleft palate in one litter. These serious findings were tempered by the fact that this dose level was maternally toxic, as demonstrated by mortality of one dam, and decreases in body weight, body weight gain and food consumption during gestation. In the rabbit developmental toxicity study, a serious effect, altered sex ratio, was observed in fetuses at 16 mg/kg bw/day in the absence of overt maternal toxicity. The NOAEL for this serious effect (8 mg/kg bw/day) represented the lowest NOAEL in the database. At the highest dose level in this rabbit study (32 mg/kg bw/day), there was a decrease in the number of live fetuses, as well as an increase in the number of dead fetuses, early resorptions, total litter resorptions, and post-implantation loss.

In both multi-generation reproductive toxicity studies, effects noted in the offspring (including decreased body weight and body weight gain, decreased thymus and spleen weight, and delayed sexual maturation in both sexes) occurred at dose levels that were also toxic (adrenal effects) to the maternal animals suggesting that the young animal was not more sensitive to afidopyropen toxicity than the adult animal. At higher dose levels, decreased mean litter size was also observed, as well as pup death and an increased number of pups with reduced nutritional condition. The results of the cross-fostering study suggested that in utero exposure appeared to be a critical factor leading to pup death in the early post-natal period.

Due to the observation of an altered sex ratio, which is considered to be a serious endpoint, at a dose that did not produce overt signs of toxicity in the maternal animal, the full 10-fold PCPA factor was retained for exposure scenarios using the POD from the rabbit developmental toxicity study. Selection of this endpoint provides protection for other serious endpoints of concern in the database including pup deaths and malformations.

Evidence of effects on nervous tissue was noted in the database, with the most serious effects being observed in the dog. These effects included vacuolation of nervous tissue, decreased myelin density of subcortical white matter and the corpus callosum, and a cyst in the cerebellum of one decedent observed in the one-year toxicity study. Overall, the dog was the most sensitive test species for effects on the nervous system. Since the studies in dogs were performed in adult

animals, potential effects on neurodevelopment of the young animal exposed in utero or during the early post-natal period is not known. There is questionable utility in conducting a DNT study in rats given the noted relative insensitivity of the rat to the nervous system effects of afidopyropen. As a result, there is residual uncertainty regarding potential adverse effects on neurodevelopment. For exposure scenarios using the POD from the one-year dog study, this residual uncertainty is reflected though a 3-fold PCPA factor to the POD for brain effects in the dog.

For scenarios using a POD based on an effect other than those noted above, the PCPA factor was reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

General Population

An ARfD for the general population was not established as an effect attributable to a single exposure of afidopyropen was not identified in the database.

Females 13-49 Years of Age

To estimate acute dietary risk for females 13–49 years of age, the gavage developmental toxicity study in rabbits with a developmental NOAEL of 8 mg/kg bw/day was selected for risk assessment. At the lowest observed adverse effect level (LOAEL) of 16 mg/kg bw/day, an altered sex ratio was observed in the absence of overt maternal toxicity. The possibility that this effect was a result of a single exposure could not be ruled out; therefore, this endpoint was considered relevant for an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The full PCPA factor of 10-fold was retained for the reasons outlined in the PCPA Hazard Characterization section. The composite assessment factor (CAF) is thus 1000.

The ARfD is calculated according to the following formula:

$$\text{ARfD (females 13–49 yrs)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{8 \text{ mg/kg bw/day}}{1000} = 0.008 \text{ mg/kg bw}$$

3.3 Acceptable Daily Intake (ADI)

General population

To estimate risk of repeated dietary exposure for the general population, the one-year capsule administration study in dogs with a NOAEL of 8 mg/kg bw/day was selected for risk assessment. At the LOAEL of 20 mg/kg bw/day, effects observed included hyaline droplet deposition in hepatocytes, and vacuolation of white matter and neuropil of the cerebrum. Although a NOAEL of 8 mg/kg bw/day was also established for offspring toxicity in one of the reproductive toxicity studies, this was likely attributable to dose spacing. The overall offspring NOAEL was 27 mg/kg bw/day based on the results of both reproductive toxicity studies.

Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, The PCPA factor was reduced to 3-fold for the reasons outlined in the PCPA Hazard Characterization section. The CAF is thus 300.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{8 \text{ mg/kg bw/day}}{300} = 0.03 \text{ mg/kg bw/day}$$

Females 13-49 years of age

To estimate risk of repeated dietary exposure for females 13–49 years of age, the gavage developmental toxicity study in rabbits with a developmental NOAEL of 8 mg/kg bw/day was selected for risk assessment. At the LOAEL of 16 mg/kg bw/day, an altered sex ratio was observed in the absence of overt maternal toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The full PCPA factor of 10-fold was retained for the reasons outlined in the PCPA Hazard Characterization section. The CAF is thus 1000.

The ADI is calculated according to the following formula:

$$\text{ADI (females 13–49 years)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{8 \text{ mg/kg bw/day}}{1000} = 0.008 \text{ mg/kg bw/day}$$

3.4 Occupational Risk Assessment

3.4.1 Toxicology Reference Values

Short-, Intermediate-, and Long-term Dermal

For short- and intermediate-term dermal risk assessments, the rabbit developmental NOAEL of 8 mg/kg bw/day was selected. At the LOAEL of 16 mg/kg bw/day, an altered sex ratio was observed in the absence of overt maternal toxicity. The target MOE is 1000, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a 10-fold factor for a serious effect in the absence of overt maternal toxicity. The selection of this study is protective of all populations, including nursing infants and the unborn children of exposed female workers. Although a 28-day dermal toxicity study in rats was available, it was not chosen for endpoint selection since the design of the study does not allow for the assessment of the relevant endpoint of concern, altered sex ratio.

Short-, Intermediate- and Long-term Inhalation

For short- and intermediate-term inhalation risk assessments, the rabbit developmental NOAEL of 8 mg/kg bw/day was selected. At the LOAEL of 16 mg/kg bw/day, an altered sex ratio was

observed in the absence of overt maternal toxicity. The target MOE is 1000, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a 10-fold factor for a serious effect in the absence of overt maternal toxicity. The selection of this study is protective of all populations, including nursing infants and the unborn children of exposed female workers.

Results from an oral study were used as no repeat-dose inhalation toxicity studies were available; furthermore, the design of a repeat-dose inhalation toxicity study would not allow for the assessment of the relevant endpoint of concern, altered sex ratio.

Cumulative Assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. For the current evaluation, the PMRA did not identify information indicating that afidopyropen shares a common mechanism of toxicity with other pest control products. One of the principal findings in the afidopyropen toxicology database was effects on the heart. This was also observed following toxicity testing with CPCA, a metabolite of afidopyropen. It is acknowledged that CPCA likely contributed to the toxicity observed in the mammalian toxicity studies following dosing with the parent compound, afidopyropen. A comparison of the heart findings in the toxicity studies with afidopyropen and CPCA suggested that CPCA may be more potent, however. Although the key mechanism of action for afidopyropen was not identified, the similarity of the heart findings suggests a similar mechanism of toxicity for these two chemicals. Therefore, there is a requirement for a cumulative risk assessment at this time. The POD selected for cumulative risk assessment are thus based on the heart effects observed with both these chemicals. On the basis of the current use pattern, the cumulative assessment was only conducted for the dietary route of exposure. For afidopyropen, the NOAEL of 18 mg/kg bw/day from the guideline 90-day dietary study in Fischer rats was selected as the POD. For CPCA, the NOAEL of 10 mg/kg bw/day from the 90-day gavage study with CPCA in Sprague-Dawley rats was selected as the POD. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The PCPA factor was reduced to 1-fold for the reasons noted in the PCPA Hazard Characterization section. The CAF for the cumulative risk assessment is thus 100-fold.

Cancer Assessment

Treatment-related increases in the incidences of uterine adenocarcinoma and uterine adenoma/adenocarcinoma combined were observed in both rat oncogenicity studies. Although the proposed MOA was considered to be biologically plausible, the supporting data were not considered adequate due to inconsistent results and a paucity of data to support certain key events. Therefore, a linear low-dose extrapolation approach for the cancer risk assessment was deemed appropriate. The cancer unit risk (q_1*) for the incidence of uterine adenoma/adenocarcinomas combined in female rats is 1.79×10^{-2} $(mg/kg\ bw/day)^{-1}$.

Cyclopropane carboxylic acid (CPCA) Risk Assessment

For the CPCA risk assessment, the afidopyropen reference values were adjusted based on the MW of CPCA. This approach was deemed appropriate since it appeared that both afidopyropen and CPCA have a similar mechanism of toxicity; for example, both produced heart effects in the oral 90-day rat studies. It also takes into consideration other findings in the afidopyropen database; for example, reproductive and developmental toxicity effects and cancer. Data suggest that afidopyropen toxicity is, in part, likely due to CPCA; however, CPCA appears to be more potent. The effects in the 90-day CPCA study were of a greater severity than those observed in the afidopyropen 90-day study. The difference in potency, when comparing effects in the heart, appeared to be between 2- to 7-fold, although there was some uncertainty in this regard since the 90-day studies utilized different methods of administration (diet versus gavage) and animal strains (Wistar versus Sprague-Dawley), and some studies were lacking histopathological examinations at all dose levels. The MW adjustment factor to the afidopyropen reference values was calculated to be 3.5. The uncertainty and PCPA factors applied for the afidopyropen reference values were deemed applicable for CPCA. The toxicology reference values for CPCA can be found in Appendix I, Table 7.

3.4.1.1 Dermal Absorption

A rat in vivo study was submitted. Based on the data presented in the study, a dermal absorption value of 12% was selected for the risk assessment of afidopyropen.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/Loader/Applicator Exposure and Risk Assessment

Individuals have potential for exposure to afidopyropen during mixing, loading and application. Dermal and inhalation exposure estimates for workers mixing, loading and applying were generated from the Agricultural Handlers Exposure Task Force database and Pesticide Handlers Exposure Database (PHED, v1.1).

Exposure to workers mixing, loading and applying afidopyropen is expected to be of short- to intermediate-term duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixers/loaders/applicators applying afidopyropen to soybeans, tuberous and corm vegetables (including potatoes), leafy vegetables, brassica head and stem vegetables, fruiting vegetables, cucurbit vegetables, leaf petiole vegetables, pome fruit, stone fruit, hazelnut trees and greenhouse and outdoor ornamentals. The exposure estimates are based on mixers/loaders/applicators wearing a single layer plus chemical-resistant gloves.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value. Inhalation exposure was estimated by coupling

the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

For the non-cancer risk assessment, exposure estimates were compared to the toxicological endpoints (NOAELs) to obtain the MOE; the target MOE is 1000 (Appendix I, Table 8).

A cancer risk assessment was conducted for workers mixing, loading and applying afidopyropen. Absorbed daily doses (ADD; equivalent to the exposure estimate for the calculation of non-cancer MOEs) were used as the basis for calculating lifetime average daily dose (LADD) values. LADD values were then calculated by amortizing exposure over the lifetime of the worker. The treatment frequency was assumed to be 30 days per year, with an exposure duration of 40 years. Cancer risk was calculated by multiplying the estimated LADD by a q_1*; the target threshold is < 1.0×10^{-5} (Appendix I, Table 9).

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with Sefina Insecticide and Versys Insecticide to complete tasks such as setting irrigation lines, scouting and hand harvesting. Given the nature of activities performed, exposure should be primarily via the dermal route based on dermal contact with treated foliage. Inhalation exposure is not expected to be of concern as afidopyropen is considered non-volatile with a vapour pressure of < 9.9×10^{-9} kPA (at 25°C), which is less than the North American Free Trade Agreement (NAFTA) criteria for a non-volatile product for outdoor scenarios [1×10^{-4} kPa (7.5×10^{-4} mm Hg) at 20–30° C]. The duration of exposure is considered to be short- to intermediate-term, with the exception of greenhouse uses which are considered long-term.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue (DFR) values with activity-specific transfer coefficients (TCs). Activity TCs are based on data from the Agricultural Reentry Task Force. Chemical-specific DFR data were submitted for cucurbit vegetables, stone fruits and fruiting vegetables, and used in the postapplication risk assessment. Additionally, the DFR data for stone fruits were used as surrogate data for pome fruit, while the DFR data for fruiting vegetables were used as surrogate data in the risk assessment for brassica head and stem vegetables and bok choy. For all other crops, a default DFR value of 25% of the application rate coupled with 10% daily dissipation of residues were used in the exposure assessment, except for greenhouse ornamentals which used a 2.3% daily dissipation rate of residues.

For the non-cancer risk assessment, exposure estimates were compared to the toxicological endpoint to obtain the MOE; the target MOE is 1000. Only exposures and risks to the activities with the highest TCs are presented as MOEs for these activities exceed the target MOE of 1000 (Appendix I, Table 10).

A cancer risk assessment was conducted for workers entering fields treated with afidopyropen. The ADD was used as the basis for calculating LADD values. The exposure frequency was assumed to be equivalent to 30 days per year for agricultural crops and outdoor ornamentals. As greenhouse activities can occur for extended periods, exposure frequencies for cut flowers and

potted flowers were assumed to be 50 days. Career duration of 40 years was assumed for re-entry workers. Cancer risk for workers entering fields and greenhouses treated with afidopyropen was equivalent to or below 1×10^{-5} (Appendix I, Table 11).

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Handler and Postapplication Exposure and Risk

Sefina Insecticide and Versys Insecticide are not domestic class products and are not permitted for use in residential settings; therefore, a residential assessment was not required.

3.4.3.2 Cumulative Risk Assessment

A cumulative risk assessment takes into consideration the combined residential (dermal and inhalation) and dietary (food and drinking water) exposures. However, as there are no residential uses permitted for afidopyropen, the cumulative exposure assessment was only conducted for the dietary exposure.

3.4.3.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.5 Exposure from Drinking Water

3.5.1 Concentrations in Drinking Water

The residue definition (RD) for drinking water includes afidopyropen and 18 structurally-similar transformation products plus the transformation product CPCA. Since CPCA appears to be more potent than afidopyropen and has a separate toxicology reference value, a separate drinking water assessment was required.

There were 18 transformation products included, labelled as M440I0*nn*, where *nn* can be 01, 02, 03, 05, 06, 14, 15, 16, 21, 24, 46, 47, 48, 49, 50, 52, 53, or 57. Since none of the available environmental fate studies assessed all 18 transformation products, estimated environmental concentrations (EECs) were calculated with model inputs using two methods, thereby providing a range of EECs for afidopyropen and all structurally-similar transformation products. In the first method, degradation rates were calculated for afidopyropen and only the structurally-similar transformation products identified in the laboratory studies. In the second calculation method, all extractable residues, including unidentified residues, were included as there was insufficient information to show that these were not structurally-similar to the parent compound, and were greater than 10% of the total radioactivity when considered together. To capture the limitation of the information provided, the PMRA's RD for drinking water was, therefore, defined in two

ways: both with and without considering the unidentified residues. Not including the unidentified residues likely underestimated the EECs, while including the unidentified residues likely overestimated the EECs.

EECs of afidopyropen combined residues, as well as CPCA, were calculated for potential drinking water sources (groundwater and surface water). EECs in groundwater were calculated using the Pesticide in Water Calculator (PWC) model to simulate leaching through a layered soil profile. The concentrations calculated using PWC are average concentrations in the top 1 m of the water table. EECs of afidopyropen in surface water were also calculated using the PWC model, which simulates pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in a vulnerable drinking water source, a small reservoir.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The Level 1 EEC estimates are expected to allow for future use expansion into other crops at application rate(s) equal to or lower than the modelled rate. Table 3.5.1 below lists the application information and main environmental fate characteristics used in the simulations. Twenty-two initial application dates between April and October were modelled. The model was run for 50 years for surface water simulations and 100 years for groundwater simulations. The largest EECs of all selected runs are reported in Table 3.5.2 below. Level 2 EECs were also generated for the use on vegetable crops, which has the highest registered application rate. Brussels sprouts and potatoes were selected as representative crops for vegetable uses.

Table 3.5.1 Major groundwater and surface water model inputs used in the assessment of afidopyropen. The vertical bar separates values calculated without and with unidentified residues.

Parameter	Afidopyropen combined residues	CPCA[a]
Application Information		
Maximum allowable application rate per year (g a.i./ha)	125	(not directly applied to soil)
Maximum rate each application (g a.i./ha)	50	
Maximum number of applications per year	4	
Minimum interval between applications (days)	7	
Method of application	Ground, airblast, or aerial	
Environmental Fate Characteristics[b]		
Hydrolysis half-life at pH 7 (days)	Stable	Stable
Photolysis half-life in water (days)	25 | 136[c]	Stable
Adsorption K_d (mL/g)	6.96[d]	0
Biotransformation half-life in soil (days)	77 | 365[e]	7
Biotransformation half-life in water (days)	202 | 244[f]	Stable
Biotransformation half-life in sediment (days)	618[g]	Stable

Parameter	Afidopyropen combined residues	CPCA[a]
Application Information		

[a] When accounting for the transformation of afidopyropen into CPCA during the modelling of CPCA, half-lives of afidopyropen alone were used (as opposed to combined afidopyropen residues shown in this table): 18 days for soil, 92 days for water and 45.3 days for sediment.
[b] The temperature associated with the derived endpoints was set to match the temperature of the studies.
[c] The average of the environmental half-lives in pH 7 buffer from the two aquatic phototransformation studies.
[d] The 20th percentile of the six soil K_d values for parent afidopyropen.
[e] The 90th percentile confidence bound on the mean of four soil half-lives (averaging the two New Jersey and two Lufa 2.2 soils separately prior to taking the percentile).
[f] The longest whole system representative half-lives from the aerobic aquatic biotransformation study (Ranschgraben).
[g] The longest whole system representative half-life from the anaerobic aquatic biotransformation study was used (Goose River) for both scenarios (with and without unidentified residues).

Table 3.5.2 Level 1 and 2 EECs of afidopyropen combined residues and of CPCA in potential sources of drinking water, given applications of 35, 40, and 50 g a.i./ha at a 7-day interval. The vertical bar separates values calculated without and with unidentified residues.

Chemical	Groundwater (µg/L)		Surface Water (µg/L)	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
Level 1 Afidopyropen + Transformation Products	0.15 | 3.1	0.15 | 3.1	5.0 | 5.3	1.2 | 1.4
Level 2 Afidopyropen + Transformation Products	0.12 | 2.8	0.12 | 2.8	NA	NA
Level 1 CPCA	1.2	1.2	0.41	0.16
Level 2 CPCA	1.04	0.99	NA	NA

1 90th percentile of daily average concentrations
2 90th percentile of 365 day moving average concentrations
3 90th percentile of the peak concentrations from each year
4 90th percentile of yearly average concentrations

3.6 Food Residues Exposure Assessment

3.6.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products and animal commodities is afidopyropen. The data gathering/enforcement analytical methods are valid for the quantitation of afidopyropen residues in crop and livestock matrices. The residues of afidopyropen are stable in representative matrices from five crop categories (high water, high oil, high protein, high starch and high acid content) for up to 24 months when stored at -20°C. Therefore, afidopyropen residues are considered stable in all frozen crop matrices and processed crop fractions for up to 24 months. The raw agricultural commodities (potatoes and soybeans) were processed, but the processed commodities were not further analyzed due to the lack of quantifiable residues. Afidopyropen residues concentrated in the following human food

processed commodities: sundried tomatoes (4.4), orange peel (1.9), and orange oil (4.6). Quantifiable residues are not expected to occur in livestock matrices when exposed to feed items treated according to the current use pattern. Crop field trials conducted throughout Canada and the United States using end-use products containing afidopyropen at approved rates in or on crop subgroup 1C, crop subgroup 4-13A, crop subgroup 4-13B, crop group 5-13, soybeans, crop group 8-09, crop group 9, crop group 10 revised, crop group 11-09, crop group 12-09, crop group 14-11, crop subgroup 20C revised, and crop subgroup 22B are sufficient to support the proposed maximum residue limits (MRLs).

3.6.2 Dietary Risk Assessment

Acute and chronic (cancer and non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID).

3.6.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the intermediate chronic non-cancer analysis for afidopyropen: 100% crop treated, residues of all crops based on supervised trial median residue values, anticipated median residues in processed fractions (where available), and anticipated residues for all animal commodities. The intermediate chronic dietary exposure from all supported afidopyropen food uses (alone), for all representative population subgroups, is 0.4% to 1.4% of the ADI, and 2.0% for females 13 to 49 years of age. Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to afidopyropen from food and drinking water is 0.5% to 2% of the ADI for all population subgroups, except females 13 to 49 years of age, for whom the exposure accounted for 3% of the ADI (0.000214 mg/kg bw/day). The highest exposure and risk estimate is for children 1 to 2 years of age at 1.6% (0.000485 mg/kg bw/day) of the ADI.

The refined chronic cancer risk assessment for afidopyropen was conducted with the same criteria used for the chronic non-cancer assessment, including projected percent crop treated. The lifetime cancer risk from exposure to afidopyropen in food and drinking water was estimated to be 9×10^{-7} to 2×10^{-6} for the general population, which is below the PMRA's level of concern.

The chronic non-cancer exposure to CPCA from drinking water is not of health concern. Specifically, a range from 0.2% to 0.9% of the ADI was obtained for all population subgroups, excluding females 13 to 49 years old, for whom the exposure was 1.0% of the ADI.

The lifetime cancer risk from exposure to CPCA in drinking water was estimated to be 1×10^{-6} for the general population, which is below the PMRA's level of concern.

3.6.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the intermediate acute analysis for afidopyropen: 100% crop treated, highest average residues in/on crops, anticipated highest residues in processed commodities (where available), and anticipated residues in animal commodities. The intermediate acute dietary exposure (food alone) for all supported afidopyropen food

commodities is estimated to be 20% (0.001585 mg/kg bw/day) of the ARfD for females 13 to 49 years old (95th percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable: 21% (0.001654 mg/kg bw/day) of the ARfD for females 13 to 49 years old.

The acute exposure to CPCA from drinking water is not of health concern. Specifically, 3% of the ARfD was obtained for females 13 to 49 years old.

3.6.3 Aggregate Exposure and Risk

The aggregate risk for afidopyropen consists of exposure from food and drinking water sources only; there are no residential uses.

3.6.4 Cumulative Assessment

A cumulative risk assessment takes into consideration the combined residential (dermal and inhalation) and dietary (food and drinking water) exposures. However, as there are no residential uses permitted for afidopyropen, the cumulative exposure assessment was only conducted for the dietary exposure. When combining the exposure estimates from residues of afidopyropen (food and drinking water) with those of CPCA (drinking water), the resultant estimates do not exceed 1% of the afidopyropen or CPCA cumulative reference values.

3.6.5 Maximum Residue Limits

The PMRA recommends that the following MRLs be specified for residues of afidopyropen.

Table 3.6-1 Proposed Maximum Residue Limits

Food Commodity	Recommended MRL (ppm)
Brassica leafy greens (CSG4-13B)	5.0
Leaf petioles vegetables (CSG22B)	3.0
Leafy greens (CSG4-13A)	2.0
Cucurbit vegetables (CG9)	0.7
Brassica head and stem vegetable (CG5-13), dried tomatoes	0.5
Citrus oil	0.4
Fruiting vegetables (CG8-09)	0.2
Citrus fruits (CG10 Revised)	0.15
Cottonseeds (CSG20C Revised)	0.08
Stone fruits (CG12-09)	0.03
Pome fruits (CG11-09)	0.02
Tuberous and corm vegetables (CSG1C), tree nuts (CG14-11), dry soybeans, eggs, fat, meat, and meat by-products of cattle, goats, hogs, horses, poultry, and sheep	0.01

Food Commodity	Recommended MRL (ppm)
Milk	0.001

MRLs are proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides and Pest Management section of Health Canada's website.

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

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, acute and chronic (non-cancer and cancer) dietary risk estimates are summarized in Appendix I, Tables 1B, 12 and 13.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Hydrolysis is not expected to be an important route of dissipation for afidopyropen in the environment. Afidopyropen is effectively stable to hydrolysis at pH 4 and 7, but hydrolyzes gradually at pH 9. Phototransformation is also not expected to be an important route of dissipation for afidopyropen in the environment. Afidopyropen is stable to soil photolysis, and the potential for aqueous photolysis would be minimal based on its propensity to partition to sediment and long half-life in water, making it unavailable to irradiation at the surface of waterbodies. The primary route of dissipation for afidopyropen is biotransformation in terrestrial and aquatic environments.

The transformation pathway consists of three major processes: cleavage of the CPCA esters, oxidation of the alcohols (either present in the parent or formed as a result of ester cleavage), and oxidation of the pyridine ring. In addition, there are several minor transformation pathways, including photodimerization and ring cleavage. These individual processes can occur concurrently to different portions of the molecule while leaving the core ring structure of the molecule intact.

The major transformation products (>10% formed) of afidopyropen in soil and aquatic systems include: M440I001, M440I002, M440I003, M440I024, M440I046, M440I047, M440I057, and nicotinic acid (M440I045). Various minor transformation products were also identified. Only moderate carbon dioxide (CO_2) formation was observed in the aerobic soil biotransformation (up to 28% AR) and aqueous photolysis (up to 20% AR) studies, with the maximum CO_2 formed in all other studies remaining less than 5%. Unextracted residues were formed in large quantities (up to 52% AR) and large amounts of unidentified extractable radioactivity (up to 40% AR) were observed in almost all of the studies.

Based on the structural similarity of most of the transformation products to the core structure of the parent molecule, the transformation products are considered toxicologically equivalent to parent and included in the residue definition. The total unidentified extractable residues are also

included in the residue definition, due to consistency of detection across multiple studies, their potential structural similarity to the parent compound, and were greater than 10% of the total radioactivity when considered together.

Afidopyropen meets three of the eight criteria of Cohen *et al.* (1984) resulting in a non-definitive conclusion regarding leaching; however, the groundwater ubiquity score (GUS) values indicate that parent afidopyropen is a non-leacher. When including all residues, GUS indices encompass the entire range of non-leacher to leacher. Terrestrial field dissipation studies indicate that afidopyropen dissipates rapidly, and no parent or transformation products were detected below 30 cm soil depth, suggesting limited movement to groundwater at the sites evaluated. Overall, taking into consideration results of laboratory studies, assessments using GUS values and criteria of Cohen *et al*. (1984), terrestrial field dissipation studies and conservative water modelling, leaching is not expected to be a significant route of dissipation for afidopyropen and its residues.

The bioaccumulation potential of afidopyropen is low in fish based on a log octanol-water partition coefficient (K_{OW}) of 3.45 and measured bioconcentration factor (BCF) ranging from < 0.43 to 0.74. Afidopyropen is not systemic, but has translaminar movement in plants. As such, afidopyropen applied by foliar spray is expected to mostly remain near leaves and not translocate throughout the plant.

The transformation products of afidopyropen detected in laboratory dissipation studies are summarized in Appendix I, Table 14. The fate and behaviour of afidopyropen and its transformation products in the environment is summarized in Appendix I, Table 15.

4.2 Environmental Risk Characterization

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

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (e.g., direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ=exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC=1 for most species, 0.4 for acute risk to pollinators, and

2 for glass plate studies using the standard beneficial arthropod test species, *Typhlodromus pyri* and *Aphidius rhopalosiphi*). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

A risk assessment for afidopyropen was conducted for terrestrial organisms. For acute toxicity studies, uncertainty factors of 1/2 and 1/10 the EC_{50} (LC_{50}) are typically used in modifying the toxicity values for terrestrial invertebrates, birds and mammals when calculating risk quotients. No uncertainty factors are applied to chronic no observed effect concentration (NOEC) endpoints. A summary of terrestrial toxicity data for afidopyropen, its transformation products (M440I002, M440I003, M440I005, and M440I024), and end-use products (Versys Insecticide and Sefina Insecticide) is presented in Appendix I, Table 16. A summary of Tier II and Tier III studies with honey bees is presented in Appendix I, Table 17. The screening level risk assessment for afidopyropen is presented in Appendix I, Table 18 for terrestrial organisms other than birds and mammals, and in Appendix I, Table 19 for birds and mammals.

Earthworms: Afidopyropen was not toxic to earthworms on an acute or chronic basis at concentrations as high as 1000 mg a.i./kg dw soil. Similarly, its transformation products (M440I002, M440I003, M440I005 and M440I024) and Versys Insecticide were not acutely toxic to earthworms at concentrations as high as 1000 mg/kg dw soil. There were treatment-related effects on earthworm mortality and body weight from Sefina Insecticide; however, the LC_{50} for mortality was still higher than 1000 mg EP/kg dw soil. The risk quotients for earthworms resulting from acute and chronic exposure to afidopyropen do not exceed the level of concern at the screening level. The risk quotient for earthworms resulting from acute exposure to afidopyropen transformation products and the end-use products Versys Insecticide and Sefina Insecticide do not exceed the level of concern at the screening level. The use of afidopyropen is not expected to pose an acute or chronic risk to earthworms.

Other soil-dwelling invertebrates: Chronic exposure to afidopyropen in soil can affect the survival and reproduction of the Collembola, *Folsomia candida*. After 28 days, statistically significant effects on survival and reproduction were observed at a concentration of 277.8 mg a.i./kg dry soil and higher. The risk quotient for Collembola (*Folsomia candida*) resulting from chronic exposure to afidopyropen does not exceed the level of concern at the screening level. The use of afidopyropen is not expected to pose a chronic risk to soil-dwelling invertebrates.

Bees: Afidopyropen, Versys Insecticide and Sefina Insecticide were not considered toxic to honey bees or bumble bees on an acute oral and contact basis, based on mortality endpoints; however, sublethal behavioural effects (such as immobility or impaired locomotion) were

reported in these studies, at times appearing to progress to mortality. Chronic exposure to afidopyropen also resulted in significant sublethal behavioural effects in adult bees at 0.67 µg a.i./bee (10-d LOAEL, sublethal effects on movement), and significantly reduced emergence of larval bees at 7.81 µg a.i./larva (22-d lowest observed effect level, LOEL, emergence). Risk quotients were not exceeded for acute oral and contact exposure to adult bees and larvae (considering both lethal and sublethal endpoints), and no risk was identified for contact exposure based on the contact foliage residue study. However, risk quotients for adult bees exceeded the level of concern at the screening (Tier I) level for chronic oral exposure (based on sublethal endpoints, but not for lethal endpoints). Considering available residue data, risk quotients for bees were not exceeded for the refined Tier I assessment from chronic or acute oral exposure during bloom (presented in Appendix I, Table 20).

In addition, the risk to bees was further characterized using a weight-of-evidence approach considering the proposed uses of afidopyropen on crops and their attractiveness to bees, the fate and behaviour of afidopyropen in plants, as well as results from multiple higher tier (semi-field and field) studies on bee colonies.

The proposed uses of afidopyropen on pome fruits, stone fruits, cucurbits, and ornamentals are expected to result in high exposure to bees, because of the high attractiveness of these crops to bees. Moderate or low exposure to bees is expected for uses on Crop Group 9 Fruiting Vegetables, soybean, hazelnuts, and potato and sweet potato. No exposure is expected for uses that are harvested before bloom, which include Crop Group 1 (excluding potato and sweet potato), Crop Group 4 Leafy Vegetables, Crop Group 5 Brassica, and Crop Group 22 Leaf Petioles Vegetables.

Afidopyropen is not systemic in plants. Bees may be foraging on crops only during the bloom period; therefore, only application during bloom is expected to result in oral and/or contact exposure to bees, depending on the timing of application. Based on residue information as well as higher tier semi-field and field studies, evening applications, when most bees are not foraging, is expected to result in lower exposure and effects compared to application when bees are actively foraging.

Semi-field (Tier II) studies

Six studies were conducted under semi-field conditions to assess the potential effects to honey bee colonies following foliar application of Versys Insecticide to blooming *Phacelia tanacetifolia* (five studies) or canola crops (one study). All studies lasted at least 25 days (covering a full brood cycle) following the application of the test item, with one study conducted over a period of approximately two brood cycles (41 days) and another study over three months (93 days) following application. Five studies involved a single application of Versys Insecticide at 50 g a.i./ha (the maximum proposed Canadian single application rate) while bees were actively foraging, and one study involved an application rate at 10 g a.i./ha, both while bees were foraging and in the evening when bees were not foraging. Bees were typically exposed for 7 days, and then moved to another location (without attractive bee forage) for continued monitoring. Hives were observed for sublethal/behavioural effects, and colony and brood development (including mortality of adults and brood). Control colonies were consistently part

of the study design, and residues were collected in many cases in order to establish exposure to the colonies.

Overall, based on all of the data obtained from the semi-field studies, the weight of evidence indicates that application of Versys Insecticide to blooming crops during bee flight at rates up to 50 g a.i./ha will present a low likelihood of adverse colony level effects on honey bees. In the initial hours (up to 72 hours) after application of Versys Insecticide during the day (applied at either 10 or 50 g a.i./ha), effects such as mortality, foraging activity, and behaviour were observed; however, these effects were transient and ultimately had no delayed or long-term impact on colony and brood development. Application at 10 g a.i./ha in the evening did not result in significant effects compared to the control hives.

Field (Tier III) studies

Two full-field studies were conducted using two formulations, Versys Insecticide and BAS 440 UV I, with the latter being a minor change in the formulation of Versys Insecticide. A single application of 50 g a.i./ha was made to *P. tanacetifolia* at full bloom during active bee flight. For the latter study, residue samples were also taken and analyzed to quantify exposure. One study lasted 25 days (covering a full brood cycle) following the application of the test item whereby the exposure period was 7 days, while the other study was conducted over a period of approximately two brood cycles (43 days), whereby the exposure period was 9 days. Hives were observed for sublethal/behavioural effects, and colony and brood development (including mortality of adults and brood). Control colonies were consistently part of the study design.

Overall, field studies confirm the observations made in the semi-field studies that application of Versys Insecticide to blooming crops during bee flight at a rate of 50 g a.i./ha will present a low likelihood of colony level adverse effects on honey bees. Initialeffects on mortality, foraging activity and behaviour were observed; however, these effects were less pronounced than those observed in the semi-field trials.

Considerations for Mitigation

- There was limited screening level risk. There was only chronic adult oral risk (based on sublethal endpoints). There was no Tier I refined risk identified, considering both lethal and sublethal endpoints and field residues, for acute or chronic adult effects or larvae effects.
- However, there were potential short term effects from applications at the proposed single maximum application rate of 50 g a.i./ha and 10 g a.i./ha, when applied during the day when bees were foraging in semi-field and field studies. The most prominent effects were mortality, and effects on foraging and behaviour; and these effects were transient and did not result in any colony level effects.
- The semi-field and field studies showed that effects on honey bee colonies were transient, and long term colony effects were unlikely. However, because honey bee colonies may have a greater capacity for recovery than other non-*Apis* bees such as bumble bees or solitary bees, there might be a larger effect on non-*Apis* bees.
- Afidopyropen is not systemic in plants. Therefore, only application during bloom is expected to result in oral and contact exposure to bees, depending on the timing of application. Evening

application, when most bees are not foraging, is expected to result in minimal exposure and effects.

In order to mitigate for potential short term effects, when plants are in bloom, application to bee attracting crops will be restricted to evening applications.

Beneficial arthropods: At the screening level, acute exposure on glass plates of the predatory mite, *Typhlodromus pyri*, and the parasitoid wasp, *Aphidius rhopalosiphi*, to Versys Insecticide and Sefina Insecticide resulted in significant effects on survival. The risk quotients for *Typhlodromus pyri* did not exceed the level of concern, but the risk quotients for *Aphidius rhopalosiphi* did exceed the level of concern.

The risk to predatory and parasitic arthropods was further characterized using results from higher tier (extended laboratory and semi-field) toxicity studies with *Aphidius rhopalosiphi* and other terrestrial arthropod species. Risk quotients for higher tier studies with predatory and parasitic arthropods are shown in Appendix I, Table 21.

In extended laboratory/aged residue studies, exposure to fresh residues of Sefina Insecticide on plant leaves affected the survival and fecundity of *Typhlodromus pyri* at 25 g a.i./ha and *Aphidius rhopalosiphi* at 98 g a.i./ha. In extended laboratory/aged residue studies conducted with *Chrysoperla carnea*, no effects on mortality or fecundity were observed. Based on exposure to spray residues of Sefina Insecticide, the risk quotients for survival and reproduction of the parasitic wasp, *Aphidius rhopalosiphi*, and the green lacewing, *Chrysoperla carnea*, did not exceed the level of concern for in-field or off-field exposure. Based on exposure to spray residues of Sefina Insecticide, the risk quotients for survival of the predatory mite, *Typhlodromus pyri*, did not exceed the level of concern for in-field or off-field exposure. The risk quotients for reproductive effects of *Typhlodromus pyri* did not exceed the level of concern for off-field exposures, but did exceed the level of concern for in-field exposure from early season airblast application (RQ=2.8).

Two studies were conducted under semi-field conditions (33 and 36 days) with naturally-occurring populations of the predatory mite, *Typhlodromus pyri*, which were exposed to Sefina Insecticide twice via spray residues on apple trees at a rate of 50 g a.i./ha. In the 33-day study conducted in Germany, there were no statistically significant decreases in mite population density compared to the control at three of the four assessment time points (1st assessment - 3 days before the 1st application; 3rd assessment - 5 days after the 2nd application; and 4th assessment - 26 days after the 2nd application), with the exception of the 2nd assessment performed at 5 days after the 1st application, where there was a 45% reduction in mite population compared to the control. By study termination, the mite population had recovered and was similar in the treated plots as compared to the control plots. In the 36-day study conducted in Southern France, there were no statistically significant decreases in mite population density at any assessment time point.

Overall conclusions about potential risks to beneficial arthropods

Laboratory studies and semi-field studies indicate that application of Sefina Insecticide to crops at the proposed maximum single application rate of 50 g a.i./ha will present a low likelihood of adverse effects to beneficial arthropods. Initial effects on population density are possible; however, these effects are transient and are unlikely to have long-term impact on beneficial arthropod populations.

All higher tier toxicity studies with terrestrial arthropod species were conducted with Sefina Insecticide. The proposed use pattern for Sefina Insecticide is only for potato and soybean whereas the proposed Versys Insecticide use pattern encompasses a wide range of crops (vegetable, orchard and ornamental). As Sefina Insecticide consistently displays higher formulation toxicity than both the active ingredient alone and the Versys Insecticide formulation, the assessment of risk from Sefina Insecticide to beneficial arthropods is considered transferrable to Versys Insecticide as well.

Birds: Afidopyropen was slightly to moderately toxic to birds by dietary consumption or through oral administration, while Versys Insecticide and Sefina Insecticide were practically non-toxic. Significant reproductive effects were observed in duck and quail studies, with the lowest avian reproductive NOEC being 6.7 mg a.i./kg bw/day. The risk quotients for birds resulting from acute oral exposure to afidopyropen did not exceed the level of concern at the screening level. The screening level risk quotients for birds resulting from reproductive exposure slightly exceeded the level of concern for small sized insectivores. The risk to birds was further characterized considering other feeding guilds, on-field and off-field exposures, and maximum and mean residue levels.

Looking at multiple feeding guilds, risk quotients only slightly exceeded the level of concern for small sized insectivorous birds when considering maximum residue levels on the field (RQs of 1.01 and 1.07; Appendix I, Table 22). The assumption that food items all contain maximum residue levels is conservative; levels will likely vary. Risk quotients calculated using mean residues of afidopyropen did not exceed the level of concern for any feeding guild (Appendix I, Table 23).

Risks from off-field exposure were investigated assuming 74% drift from early season airblast applications. No risk quotient for any feeding guild exceeded the level of concern when considering maximum or mean residues off-field (Appendix I, Tables 22 and 23). It should be noted that the other methods of application proposed for use of afidopyropen involve less spray drift than early season airblast application and consequently would result in even lower off-field risk quotients.

Overall conclusion about potential risks to birds

The two risk quotients above the level of concern were all close to 1.0 and involved only one feeding guild (small sized insectivorous birds) and on-field exposure. No risk quotient exceeded the level of concern when considering maximum residues off-field.

Levels on food items are likely variable and thus assuming that 100% of food items contain maximum residue levels is conservative. No risk quotient exceeded the level of concern when considering mean residues on and off-field. Based on these results, the concern for risks of afidopyropen to birds is low.

Mammals: Afidopyropen, Versys Insecticide and Sefina Insecticide were practically non-toxic to rats, with no observed acute toxicity at the highest dose tested. For chronic effects, the two generation rat reproduction study resulted in a NOAEL of 8.4 mg a.i./kg bw/day due to decreases in pre-weaning pup body weights/pup weight gains. The risk quotients for mammals resulting from acute and reproduction exposure to afidopyropen did not exceed the level of concern at the screening level. The use of afidopyropen is not expected to pose a risk to mammals.

Terrestrial vascular plants: In the seedling emergence study with afidopyropen, tomato was the most sensitive species tested, with a no observed adverse effect rate (NOAER) of 62.5 g a.i./ha for survival. No other species tested exhibited significant effects for emergence, survival, length, or dry weight up to the maximum application rate of 125 g a.i./ha. For the vegetative vigour study, no species tested exhibited significant effects for survival, length, or dry weight up to the maximum application rate of 125 g a.i./ha. Based on the seedling emergence and vegetative vigour studies, the calculated risk quotients do not exceed the level of concern for in-field and off-field exposure. The use of afidopyropen is not expected to pose a risk to non-target terrestrial vascular plants.

4.2.2 Risks to Aquatic Organisms

A risk assessment for afidopyropen, the transformation product, M440I024, and end-use products (Versys Insecticide and Sefina Insecticide) was conducted for freshwater and marine aquatic organisms based on available toxicity data. A summary of aquatic toxicity data is presented in Appendix I, Table 24. For acute toxicity studies, uncertainty factors of 1/2 and 1/10 the EC_{50} (LC_{50}) are typically used for aquatic plants, invertebrates, and fish species when calculating risk quotients. No uncertainty factors are applied to chronic NOEC endpoints. For groups where the LOC is exceeded (thus, if RQ≥1), a refined Tier I assessment is conducted to determine risk resulting from spray drift and runoff separately. Risk quotients for afidopyropen and its transformation products were calculated based on the highest maximum seasonal application rate for all uses. The screening level risk quotients for afidopyropen are summarized in Appendix I, Table 25. The risk quotients for the Tier I refined assessment of afidopyropen are presented in Appendix I, Table 26 (spray drift) and Appendix I, Table 27 (runoff).

Invertebrates: Afidopyropen was moderately toxic to freshwater and marine invertebrates on an acute basis, with the lowest EC_{50} = 1.43 mg a.i./L for the marine oyster. Sefina Insecticide and Versys Insecticide were more toxic than the technical grade active ingredient alone, with acute EC_{50} values of 0.09 and 0.12 mg a.i./L, respectively, for *Daphnia magna.* Afidopyropen has a large acute-to-chronic ratio for aquatic invertebrates with chronic NOEC values up to 100 000 times lower than the EC_{50} values.

Several benthic toxicity tests with freshwater and marine invertebrates were conducted with midges (*Chironomus* sp.) and amphipods (*Hyalella azteca* and *Leptocheirus plumulosus*). These tests involve introduction of test substance to the system by spiking the sediment directly and allowing the system to equilibrate with overlying water, or by adding the test substance directly to the overlying water. The former scenario was used to simulate exposure to accumulated pesticide in sediment from runoff and the latter was used to simulate exposure via spray drift. Studies with benthic invertebrates indicate that afidopyropen is substantially less toxic to benthic organisms than free-swimming aquatic invertebrates. Among five acute studies, there were generally no treatment-related effects at the highest concentrations tested, with the exception of one freshwater amphipod study where dry weight was reduced and one marine amphipod study where survival was affected at almost all treatment concentrations. A separate study with the transformation product, M440I024, indicated that it was not acutely toxic to *Chironomus dilutus* at the highest concentration tested. Additionally, for two chronic studies (one with spiked water and another with spiked sediment), no definitive endpoints were established due to a lack of effects at the highest concentration tested.

The screening level risk quotient for acute exposure of *Daphnia magna* to afidopyropen, Versys Insecticide and Sefina Insecticide does not exceed the level of concern at the screening level. The risk quotient for chronic exposure of *Daphnia magna* to afidopyropen exceeds the level of concern (RQ=124.8). The risk quotient for chronic exposure of freshwater invertebrates; *Ceriodaphnia dubia* and *Moina macrocopa* to afidopyropen also exceeds the level of concern (RQs = 84.6 and 18.1, respectively). For marine invertebrates, the risk quotients for acute exposure of the mysid shrimp, *Americamysis bahia* and Eastern oyster, *Crassostrea virginica* to afidopyropen do not exceed the level of concern; however, the risk quotient for chronic exposure of the mysid shrimp, exceeds the level of concern (RQ=3889) by a significant margin. The chronic risks of afidopyropen to freshwater and marine invertebrates from spray drift and runoff was further characterized.

Refined risk assessment (spray drift and runoff)

For freshwater environments, the refined assessment using more realistic environmental exposure estimates indicates that the level of concern from afidopyropen exposure through spray drift is still exceeded for chronic exposure of freshwater aquatic invertebrates (RQs 13.4–62.8). Further characterization of the chronic risk to marine invertebrates from spray drift was conducted assuming only one spray application since tides and dilution are expected to result in negligible residues at the time of subsequent applications. The level of concern from afidopyropen exposure through spray drift is still exceeded for chronic exposure of marine aquatic invertebrates (RQ=1167). Spray buffer zones will be required to mitigate potential effects of afidopyropen drift on aquatic organisms in adjacent freshwater and marine habitats. The spray buffer zones for afidopyropen will be rate-specific for the product labels and will range from 1–75 m for freshwater and up to 800 m for marine waters.

Considering the more refined EECs, risk quotients for freshwater and marine invertebrates from exposure to afidopyropen through runoff continue to exceed the level of concern. The residue definition for runoff includes afidopyropen and all structurally-similar transformation products

(18 in total), and was defined with and without considering the unidentified residues. Not including the unidentified residues likely underestimates the EECs, while including the unidentified residues likely overestimates the EECs. The runoff EECs for both marine and freshwater exposures are based on the yearly cumulative application rate and are modelling without outflow. For the marine exposure scenario, this is a particularly conservative assessment since the EECs do not account for tides/dilution that would be present in the Canadian marine environment.

The primary runoff risk is for chronic exposure of pelagic invertebrates; however, afidopyropen and its residues partition rapidly to sediment; therefore, chronic exposure would be more likely for benthic (sediment-dwelling) invertebrates. Studies show that afidopyropen is less toxic to benthic invertebrates than pelagic invertebrates. There also appears to be a difference in sensitivity between the sexually reproducing marine invertebrate that was tested and the asexually reproducing freshwater invertebrates that were tested.

In order to mitigate potential exposure of afidopyropen to aquatic and marine invertebrates standard label statements to mitigate runoff into aquatic habitats and a mandatory minimum 10-metre wide vegetative filter strip between the treatment area and the edge of a downslope water body are required on the labels of afidopyropen end-use products.

Fish: Afidopyropen was slightly toxic to freshwater and marine fish on an acute basis, while studies with trout indicated that Sefina Insecticide and Versys Insecticide were highly toxic. In chronic early-life stage studies, effects on fish growth were observed, with the most sensitive NOEC value being 0.0818 mg a.i./L. The risk quotients for freshwater fish resulting from acute and early-life stage exposure to afidopyropen do not exceed the level of concern at the screening level. The risk quotient for freshwater fish resulting from acute exposure to Versys Insecticide and Sefina Insecticide exceed the level of concern at the screening level (RQs=1.6 and 3.6, respectively). The risk quotients for marine fish resulting from acute and chronic exposure to afidopyropen do not exceed the level of concern at the screening level.

The refined risk quotients indicate that the level of concern from acute exposure to Sefina Insecticide and Versys Insecticide through spray drift and runoff are still exceeded for freshwater fish. As refined risk quotients for aquatic invertebrates were greater than those for fish, the resulting spray buffer zones, mandatory vegetative filter strips and precautionary label statements to minimize exposure and reduce risks to aquatic invertebrates are also sufficiently protective of fish.

Amphibians: Using an endpoint from an early-life stage study with fish, along with an EEC for afidopyropen in a 15cm-deep body of water, the risk quotients for amphibians resulting from acute and early-life stage exposure to afidopyropen do not exceed the level of concern at the screening level. The risk quotient for amphibians resulting from acute exposure to Versys Insecticide and Sefina Insecticide exceed the level of concern at the screening level (RQs=8.5 and 19.0, respectively).

As refined risk quotients for aquatic invertebrates were greater than those for fish, the resulting spray buffer zones, mandatory vegetative filter strips and precautionary label statements to minimize exposure and reduce risks to aquatic invertebrates are also sufficiently protective of amphibians.

Algae: Afidopyropen, Sefina Insecticide and Versys Insecticide inhibited the growth rate and yield of freshwater and marine algae, with the most sensitive IC_{50} = 2.04 mg a.i./L for the technical grade active, and 0.314 mg a.i./L for the end-use products. The risk quotients for freshwater and marine algae resulting from acute exposure to afidopyropen do not exceed the level of concern at the screening level. The risk quotient for freshwater algae resulting from acute exposure to Versys Insecticide and Sefina Insecticide do not exceed the level of concern at the screening level. The use of afidopyropen is not expected to pose a risk to freshwater and marine algae.

Aquatic vascular plants: Afidopyropen inhibited the growth rate and yield of the aquatic vascular plant, *Lemna gibba*, with a resulting IC_{50} = 8.74 mg a.i./L. The risk quotient for aquatic vascular plants resulting from exposure to afidopyropen does not exceed the level of concern at the screening level. The use of afidopyropen is not expected to pose a risk to aquatic vascular plants.

5.0 Value

Pest claims for aphids and whiteflies were supported by efficacy data from 52 field trials and 13 greenhouse trials, and by scientific rationales. Weight of evidence (including crop and pest grouping principles) supported control of listed pests on labelled crops. Extrapolation among pests was possible in many cases because of similarities in pest biology and feeding damage; extrapolation among crops was possible because of similarities in plant architecture and canopy structure.

Active ingredients in several MOA groups are registered for use against aphids and whiteflies on the labelled crops. Afidopyropen is classified in MOA Group 9D. Pymetrozine (MOA Group 9B) is the only other insecticide in MOA Group 9 registered in Canada. Pymetrozine is registered for use on leafy vegetables, potatoes, and greenhouse and outdoor ornamentals. Consequently, afidopyropen will aid in resistance management for hazelnuts, labelled tree fruit crops, and most of the vegetable crops where no Group 9 insecticides are registered.

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, afidopyropen 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:

- Afidopyropen and its transformation products do not meet all Track 1 criteria, and are not considered Track 1 substances. See Appendix I, Table 28, for comparison with Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette.*[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 afidopyropen and the end-use products, Versys Insecticide and Sefina Insecticide, 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, PMRA Formulants Policy.

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 submitted toxicology database is adequate to identify the majority of the hazards associated with afidopyropen. In short-term and chronic studies on laboratory animals, the targets of toxicity were the liver, heart, adrenal glands, spleen and reproductive organs. There was evidence of carcinogenicity in rats after longer-term dosing, with an increased incidence of uterine adenocarcinoma and uterine adenoma/adenocarcinoma combined. There was evidence of increased sensitivity of the young in developmental toxicity studies, with an altered sex ratio and incidences of skeletal variations and supernumerary ribs observed at dose levels that were not overtly toxic to maternal animals. The evidence provided in an acute and a 90-day neurotoxicity study in rats suggested that afidopyropen was not neurotoxic; however nervous tissue effects were observed in the dog. 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.

Mixer/loader and applicators handling afidopyropen, and workers re-entering treated areas are not expected to be exposed to levels of afidopyropen that will result in an unacceptable risk when afidopyropen is used according to label directions. The personal protective equipment on the product label is long-sleeved shirt, long pants, chemical-resistant gloves, shoes with socks during mixing, loading, application, clean-up and repair. Additionally, on the Versys Insecticide label, coveralls over a long-sleeved shirt and long pants are required for all chemical handlers, while airblast applicators are required to wear chemical-resistant headgear.

The nature of the residues in plants and animals is adequately understood. The residue definition for enforcement is afidopyropen in plant products and in animal matrices. The proposed use of afidopyropen on CSG1C, CSG4-13A, CSG4-13B, CG5-13, soybeans, CG8-09, CG9, CG10R, CG11-09, CG12-09, CG14-11, CSG20C, and CSG22B does not constitute a risk of concern for chronic or acute dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues of afidopyropen.

Food Commodity	Recommended MRL (ppm)
Brassica leafy greens (CSG4-13B)	5.0
Leaf petioles vegetables (CSG22B)	3.0
Leafy greens (CSG4-13A)	2.0
Cucurbit vegetables (CG9)	0.7
Brassica head and stem vegetable (CG5-13), dried tomatoes	0.5

Food Commodity	Recommended MRL (ppm)
Citrus oil	0.4
Fruiting vegetables (CG8-09)	0.2
Citrus fruits (CG10 Revised)	0.15
Cottonseed (CSG20C Revised)	0.08
Stone fruits (CG12-09)	0.03
Pome fruits (CG11-09)	0.02
Tuberous and corm vegetables (CSG1C), tree nuts (CG14-11), dry soybeans, eggs, fat, meat, and meat by-products of cattle, goats, hogs, horses, poultry, and sheep	0.01
Milk	0.001

7.2 Environmental Risk

The use of Sefina Insecticide and Versys Insecticide at the proposed label rates do not pose a risk of concern to wild mammals, birds, beneficial insects, earthworms, or terrestrial and aquatic plants. They may, however, pose a risk to bees, freshwater and marine invertebrates, freshwater fish and amphibians. Risks to these organisms can be mitigated with precautionary label statements, vegetative filter strips, and spray buffer zones to protect sensitive aquatic habitats. Risks to bees can be mitigated by prohibiting application during the day when most bees are foraging for the blooming period of crops that are highly attractive to pollinators, or when managed bees are used for pollination services.

7.3 Value

Value information demonstrated that Sefina Insecticide and Versys Insecticide control various aphids and whiteflies on a wide variety of agricultural and ornamental crops. These products are new management tools for control of aphids, which are widespread pests of horticultural crops, and whiteflies, which are prevalent pests in the ornamental greenhouse industry. Both products will aid in resistance management for crops where no other insecticides with the same mode of action are registered, which include hazelnuts, labelled tree fruit crops, and most of the vegetables.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing registration for the sale and use of Inscalis Technical Insecticide, Sefina Insecticide and Versys Insecticide, containing the technical grade active ingredient afidopyropen, to control aphids and whiteflies on various vegetables and tree fruits, soybeans, hazelnuts, and greenhouse and outdoor ornamentals.

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

Additional Information Being Requested

Since this technical product is manufactured only at pilot scale before registration, five-batch data representing commercial-scale production will be required as post-market information after registration.

List of Abbreviations

♀	female
♂	male
µg	microgram(s)
µL	microlitre(s)
λ	wavelength
^{14}C	Carbon-14 radioactive isotope
°C	Celsius
aa	after application
abs	absolute
a.i.	active ingredient
AD	administered dose
ADD	absorbed daily doses
ADI	acceptable daily intake
ADW	activator/deposition agent/water conditioner
ALP	alanine phosphatase
ALT	alanine aminotransferase
AOPWIN	Atmospheric Oxidation Program for Microsoft Windows
AR	applied radioactivity
ARfD	acute reference dose
AST	aspartate aminotransferase
atm	atmosphere
ATPD	area treated per day
AUC	area under the curve
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
bwg	bodyweight gain
BUN	blood urea nitrogen
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CG	crop group
cm	centimetre(s)
C_{max}	maximum serum concentration
CMC	carboxymethyl cellulose
CO_2	carbon dioxide
COC	crop oil concentrate
Conc.	concentrated spray volume
CPCA	cyclopropane carboxylic acid
CSG	crop subgroup
CYP1A1	cytochrome P4501A1
CYP1B1	cytochrome P4501B1
CYP450	cytochrome P450
d	day(s)
DAA	days after application

DAT	days after treatment
DEEM-FCID	Dietary Exposure Evaluation Model – Food Commodity Intake Database
DFR	dislodgeable foliar residue
DFOP	double first-order in parallel
DNT	developmental neurotoxicity
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
dw	dry weight
EC_{50}	effective concentration on 50% of the population
ED_{50}	effective dose on 50% of the population
EDE	estimated dietary exposure
EEC	estimated environmental concentration
equiv	equivalents
EP	end-use product
ER_{25}	effective rate for 25% of the population
EROD	ethoxyresorufin-O-deethylation
F1	first generation
F2	second generation
fc	food consumption
FIR	food ingestion rate
g	gram(s)
GD	gestation day
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GUS	groundwater ubiquity score
h or hr	hour(s)
ha	hectare(s)
HAFT	highest average field trial
HCT	hematocrit
HDPE:	high-density polyethylene
HEK-293	human embryonic kidney cell line
Hg	mercury
HGB	hemoglobin
HPLC	high performance liquid chromatography
IC_{50}	inhibition concentration on 50% of the population
ILV	independent laboratory validation
IORE	Indeterminate Order Rate Equation
IUPAC	International Union of Pure and Applied Chemistry
IV	intravenous
kg	kilogram(s)
K_d	adsorption quotient
KMD	kinetically-derived maximum dose
K_{oc}	adsorption quotient normalized to organic carbon
K_{ow}	octanol-water partition coefficient
L	litre(s)
LADD	lifetime average daily dose
LAFT	lowest average field trial

LC	liquid chromatography
LC_{50}	lethal concentration 50%
LD	lactation day
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOEC	lowest observed effect concentration
LOEL	lowest observed effect level
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
MAS	maximum average score
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
mg	milligram(s)
MIS	minimum irritation score
mL	millilitre(s)
MOA	mode of action
MOE	margin of exposure
MRL	maximum residue limit
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MS/MS	tandem mass spectrometric detection
MSO	methylated seed oil
MW	molecular weight
N/A, NA	not applicable
N	North
NAFTA	North American Free Trade Agreement
ND	not detected
NER	non-extractable residues
ng	nanogram(s)
NIS	non-ionic surfactant
NMR	nuclear magnetic resonance
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOAER	no observed adverse effect rate
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOER	no observed effect rate
OCSPP	Office of Chemical Safety and Pollution Prevention
OSS	organo-silicone surfactant
P	parental generation
Pa	Pascal
plC_{50}	quantitative activity prediction (=-log(IC_{50}) in molar concentration
PBI	plant-back interval
PCPA	*Pest Control Products Act*
PHED	Pesticide Handlers Exposure Database

PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
POD	point of departure
ppm	parts per million
ppt	parts per trillion
PWC	Pesticide in Water Calculator
q_1*	cancer potency factor
QSAR	quantitative structure activity relationship
RAC	raw agricultural commodity
RBC	red blood cell
RD	residue definition
RQ	risk quotient
RT_{25}	residual time needed to reduce the activity of the test substance and bring bee mortality down to 25%
rel	relative
SC	soluble concentrate
SD	standard deviation
SFO	single first-order
$t_{1/2}$	half-life
t_R	representative half-life
TC	transfer coefficient
TGAI	technical grade active ingredient
T_{max}	time to maximum concentration
TRPV	transient receptor potential vanilloid
TRR	total radioactive residue
TSMP	*Toxic Substances Management Policy*
UER	unidentified extractable residues
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WBC	white blood cell count
w, wk	week(s)
wt	weight
yrs	years

Appendix I Tables and Figures

Table 1A Residue Analysis in Environmental Media

Matrix	Method ID	Analyte	Method Type	LOQ		Reference
Soil and sediment	D1308/02	Afidopyropen	HPLC-MS/MS	0.001 ppm	Loamy sand and Clay loam	PMRA #2627732 PMRA #2627733
		M440I001				
		M440I002				
		M440I003				
		M440I005				
		M440I016				
		M440I024				
		M440I057				
Water	D1505/02	Afidopyropen	HPLC-MS/MS	30 ppt	Drinking and surface water	PMRA #2627734 PMRA #2627735
		M440I001				
		M440I002				
		M440I003				
		M440I005				
		M440I016				
		M440I024				
		M440I057				

Table 1B Residue Analysis in Plant and Animal Matrices

Data Requirement	Matrix	Analytes	Method ID/Type	Limit of Quantitation (ppm)	Reference (PMRA #)
Enforcement and Data Gathering Method – Livestock Commodities	Muscle, fat, liver, milk (bovine), eggs (poultry) –	Afidopyropen	D1507/01 LC-MS/MS	Livestock tissues (muscle, fat, liver) and poultry eggs: 0.01 ppm; Milk: 0.001 ppm	2627727
ILV of Enforcement Method – Livestock Commodities	Muscle, fat, liver, milk (bovine), eggs (poultry)	Afidopyropen	LC-MS/MS	Livestock tissues (muscle, fat, liver) and poultry eggs: 0.01 ppm; Milk: 0.001 ppm	2627726
Radiovalidation of Methods – Livestock Commodities	Not conducted at this time, however similar solvents to the ones used in the livestock metabolism studies				
Enforcement and Data Gathering Method – Plant Commodities	Cotton seed, dry bean, tomato, orange, rice, potatoes	Afidopyropen	D1103/01 LC-MS/MS	0.01 ppm	2627724/ 2627729
ILV of Enforcement Method – Plant Commodities	Lettuce, orange, dry bean, soybean seed, potatoes	Afidopyropen	D1103/01 LC-MS/MS	0.01 ppm	2627725
Radiovalidation of Method – Plant Commodities	Soybean leaf, Tomato fruits, Cabbage outer leaves	Afidopyropen	D1103/01 LC-MS/MS	0.01 ppm	2627723
Multiresidue Method Testing	Orange, apple, potato, kidney bean, canola	Afidopyropen	D1514/01 LC-MS/MS	0.02 ppm	2627728

Table 2 Select Afidopyropen Metabolites

Common Name, BASF Reg. No. (Other names)	Chemical Name (IUPAC)
M440I001 (ME5343-T1)	(3S,4R,4aR,6S,6aS,12R,12aS,12bS)-3,6,12-trihydroxy-4-(hydroxymethyl)-4,6a,12b-trimethyl-9-(pyridin-3-yl)-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2H,11H-benzo[f]pyrano[4,3-b]chromen-11-one
M440I002 (ME5343-T2)	[(3S,4R,4aR,6S,6aS,12R,12aS,12bS)-3,6,12-trihydroxy-4,6a,12b-trimethyl-11-oxo-9-(pyridin-3-yl)-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2H,11H-benzo[f]pyrano[4,3-b]chromen-4-yl]methyl cyclopropanecarboxylate
M440I008 (ME5343-T8)	[(3S,4S\4aR,6S,6aS,l2R, l2aS; l2hS)-3,6, 12-trihydroxy-4-hydroxymethyl-6a,12b-dimethy1-l 1-oxo-9-(pyridin-3-yl)-1,2,3,4,4a,5,6,6a,12a, 12b-decahydro-l lH, l2H-benzo[f]pyrano[4,3-B]chromen-4-yl]methyl cyclopropanecarboxylate
M440I017 (ME5343-T17)	[(3S,4R,4aR,6S,6aS,12R,12aS,12bS)-3-[(cyclopropylcarbonyl)oxy]-6,12-dihydroxy-4,6a,12b-trimethyl-9-(1-oxidopyridin-3-yl)-11-oxo-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2H,11H-benzo[f]pyrano[4,3-b]chromen-4-yl]methyl cyclopropanecarboxylate
M440I019 (ME5343-T19)	[(3S,4aR,6S,6aS,12R,12aS,12bS)-3,6,12-trihydroxy-4,6a,12b-trimethyl-11-oxo-9-(1-oxo-1lambda~5~-pyridin-3-yl)-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2H,11H-naphtho[2,1-b]pyrano[3,4-e]pyran-4-yl]methyl cyclopropanecarboxylate
M440I060 (CPCA-carnitine)	O-(cyclopropylcarbonyl) carnitine
M440I061 (CPCA)	Cyclopropane carboxylic acid

Table 3 Toxicity Profile of Technical Afidopyropen

Note: Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted. Effects above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Study Type/Animal/PMRA #	Study Results
Preliminary absorption, distribution and excretion study, following single gavage doses (low and high) Rat (Fischer) PMRA #2627738	Single gavage dose administration of 3 and 300 mg/kg bw of [^{14}C] afidopyropen (1/sex/group). Excretion: 79–88% of AD excreted in feces, 6–16% of AD excreted in the urine. No significant radioactivity was found in expired air (<0.1%). No significant differences between sexes, or dose levels. Distribution: At 96 hr post-dose, the highest residue level in animals administered the low-dose was found in the liver, followed by adrenal glands, heart and kidneys. At the high-dose, the highest residue level was found in the liver, followed by heart, adrenal glands, and kidneys. Metabolism: Metabolites detected at > 5% AD in the feces (low- and high-dose) were unchanged afidopyropen, M440I001, M440I002, M440I008 and an unidentified metabolite. The only metabolite detected in the urine > 5% AD was M440I001 (high-dose only). Profiles of urinary metabolites were similar to those in feces, except for the presence of unchanged afidopyropen in the feces.
Absorption, distribution and excretion following single oral gavage doses (low and high)	Single gavage dose administration of 3 and 300 mg/kg bw [^{14}C] afidopyropen (4/sex/group). Absorption: Calculated as the sum of radioactivity found in the bile, urine and

Study Type/Animal/PMRA #	Study Results
Rat (Fischer) PMRA #2627741	residual carcass, was determined to be 70 /67% and 71/ 72% in the low- and high-doses, respectively (♂/♀). Absorption did not differ significantly between low and high dose. Excretion: 73–87% of AD excreted in feces, 5–20% of AD excreted in the urine. Approximately 93–95% AD excreted through the urine and feces within 96 hours following single oral administration of radioactive test material. In the biliary excretion experiment, approximately 92–97% AD was excreted within 48 hours following single oral administration of radioactive test material. In low-dose groups 53–53% AD was excreted in the bile, 13–16% AD was excreted in the urine, and 22–27% AD was excreted in the feces. In high-dose groups, 40–41% AD was excreted in the bile, 30% AD was excreted in the urine and 24–26% AD was excreted in the feces. Results indicate that biliary excretion significantly contributes to elimination of the orally administered test material, and shows that the fecal excretion via biliary excretion is the predominant route of elimination. Metabolism: Unchanged afidopyropen was only detected at a significant level in feces (10–39% AD). No significant sex-related differences were noted. Metabolites detected > 5%AD in either urine or feces were M440I001, M440I002, M440I008 and M440I010. In the bile M440I017 was detected as a major metabolite, followed by an unknown metabolite, M440I003 and M440I001. The most notable dose-related difference was in the level of M440I017 measured in the bile (low-dose: 20–32% AD; high-dose: 5–6% AD).
Metabolism, excretion and tissue distribution following single gavage doses (low or high) or repeated gavage doses (high) Rat (Wistar) PMRA #2627737	Single gavage dose administration of 3 and 300 mg/kg bw of [^{14}C] afidopyropen, or repeat gavage dose administration of 300 mg/kg bw/day (non-radiolabelled for 14 days and [^{14}C]-radiolabelled afidopyropen on day 15). Absorption: Radio-labelled afidopyropen was rapidly absorbed from the GI tract and excreted primarily via the urine and feces. Based on bile excretion experiments, 53–66% of the AD was excreted via the bile and urine, and radioactive residues found in the cage wash and carcass. Absorption after a single dose was similar for both low and high-dose levels. Excretion: Excretion via the urine and feces was nearly complete within 96–120 hrs after dosing, with more than two thirds of the administered dose being excreted within 48 hr. 72–86% of AD was excreted via the feces within 7 days, and 5–21% AD was excreted via the urine. Excretion was slower in high-dose groups, and % AD excreted via the urine was higher after administration of the high-dose. In urine, portions of most metabolites (% AD) excreted was increased with increasing dose, except for M440I017 in ♂, which was lower after administration of the high dose. After repeated administration (high-dose only), urinary excretion was slightly lower compared to single high dosing. No significant gender-specific differences were observed, based on route and total rate of excretion. Excretion via the bile was almost complete within 12 hrs in low-dose groups (39–46%), and 33–51 hrs in the high-dose groups (53–66%). Distribution: Levels of radioactive residues were investigated in liver, kidney and plasma of male and female rats 1 hour and 4 hours post-dose, intervals corresponding to maximum plasma levels (Cmax). Portions of radioactive residues in the liver were higher for the low-dose groups (♂ and ♀) and, in the low-dose groups the portion and absolute concentration of radioactive residues in liver, kidney and plasma were higher for the ♂ animals compared to ♀. Metabolism: Unchanged afidopyropen compound was detected in the urine of animals in low portions (0.017–0.116% AD). The main metabolite in rat urine was

Study Type/Animal/PMRA #	Study Results
	metabolite M440I001, followed by metabolite M440I002. Ten metabolites and one characterized component had lost one cyclopropane carboxylic acid (CPCA) ester moiety and four metabolites had lost both CPCA esters. Slight differences were noted in metabolite patterns for both sexes, and in low versus high-dose groups. The total identified metabolites (including unchanged afidopyropen) in urine accounted for 4–5% AD for single low-dose groups, 18–20% AD for high single dose groups, and for 14–15% AD for repeat high-dose groups. Unchanged afidopyropen accounted for 21 –37% AD detected in the feces of low single dose groups, and for 5–10% AD detected in the feces of high single and repeat dose groups. For low-dose groups, the main component was unchanged afidopyropen, followed by M440I001. For high-dose groups and repeat dose groups, metabolite M440I001 was the most abundant component, followed by M440I058. Five metabolites identified in feces had lost one CPCA-ester moiety. Two metabolites and one characterized component had lost both CPCA moieties. The total identified metabolites (including unchanged afidopyropen) in feces accounted for 69–75% AD for the low-dose groups, for 60–64% AD of for the high-dose groups, and for 52–64% AD for the repeat dose groups. Slight differences were noted in metabolite patterns for both sexes. Unchanged afidopyropen was detected in the bile of single low (♂ and ♀) and single high-dose ♀ groups in low portions (0.3–1.4% AD), and was not detectable in the bile of single high-dose ♂. In bile samples the main metabolite was M440I017, followed by M440I019 and M440I059. Eight metabolites and one characterized component had lost one CPCA moiety, and six metabolites and one characterized component had both CPCA esters cleaved. The total identified metabolites (including unchanged afidopyropen) in bile accounted for 37– 43% AD for low-dose groups and for 28–35% AD for the high-dose groups. Metabolite patterns in bile were similar for both sexes.
Toxicokinetic and tissue distribution study following single gavage doses (low and high) Rat (Fischer) PMRA #2627740	Single gavage dose administration of 3 and 300 mg/kg bw of [^{14}C] afidopyropen. **1. <u>Pilot toxicokinetic study</u>** In low-dose groups whole blood and plasma T_{max} was 0.5–1 hr, and RBC T_{max} was 0.25–0.5 hr. T ½ from whole blood was 2.1–5.0 hr, in plasma was 3.2– 4.1 hr, and in RBC was 2.4–3.6 hr. AUC was approximately 1.5 to 2-fold higher in ♂ than ♀. In high-dose groups, whole blood, plasma and RBC T_{max} was 4 hr for each group. T ½ from whole blood was 7.0–7.3 hr, from plasma was 6.0–6.8 hr, and from RBC was 9.6–11.9 hr. AUC was similar for ♂ and ♀. Increases in C_{max} for blood and plasma were slightly less than dose proportional. Increases in C_{max} for RBC were approximately dose proportional. C_{max} was generally similar between ♂ and ♀. Increases in AUC were greater than dose proportional. 2. **<u>Toxicokinetic study</u>** In low-dose groups, mean T_{max} for whole blood, plasma and RBC were 0.5–1.0 hr for ♂ and 0.25–0.5 hr for ♀. AUC was approximately 2.2 to 2.6-fold higher in ♂ than ♀. T ½ from whole blood and 1.0 - 2.5 hr, from plasma was 4.7–4.8 hr and from RBC was 1.2–2.1 hr. In high-dose groups, mean T_{max} whole, plasma and red blood cells were 4.0 h each for ♂ and 2.0 hr each for ♀. T ½ from whole blood was 15–16 hr and from plasma was 7.9–10.2 hr, and in RBC was 31.4–43.6 hr. AUC was similar for ♂ and ♀. For whole blood, plasma, and RBC, increases in C_{max} and AUC were greater than dose proportional. C_{max} was generally similar between ♂ and ♀.

Study Type/Animal/PMRA #	Study Results
	3. **Tissue distribution experiment** In the low-dose group, T_{max} for most tissues was 0.5 hr. T_{max} for bone marrow and GI tract and contents was 8 hrs. Tissues with mean concentrations at T_{max} that exceeded 0.250 µg-equiv/g were GI tract and contents, liver, adrenals, kidney, lung, pancreas, prostate, bone marrow, mesenteric lymph nodes, parathyroid/thyroid, and heart. The mean percent recovery of AD in tissues and carcass was 64% and 70% (♂/♀) at 0.5-hr termination time; 66% and 68% (♂/♀) at 8-hr termination time; and, 0.29% and 0.24% (♂/♀) at 96-hr termination time. Tissues with the highest percent of administered dose at the 0.5 and 8-hr termination times were GI tract and contents, liver, and residual carcass. In the high-dose group, T_{max} for all tissues was 2 hr. Tissues with mean concentrations at T_{max} that exceeded 40 µg-equiv/g were GI tract and contents, liver, adrenals, kidney, urinary bladder (♂ only), pancreas, prostate, uterus, ovaries, spleen (♀ only), pituitary (♀ only), fat, mesenteric lymph nodes, heart, and lung. The mean percent recovery of AD in tissues and carcass was 96% and 104% (♂/♀) at 2-hr termination time; 64% and 49% (♂/♀) at 24-hr termination time; and, 0.80% and 0.79% (♂/♀) at 96-hr termination time. Tissues with the highest percent of AD at the 2- and 24-hr termination times were GI tract and contents, liver, and residual carcass.
Toxicokinetics following single dosing (three dose levels) or multiple (high-dose) gavage dosing or IV dosing (one dose) Rat (Wistar) PMRA #2627742 Results also reported in PMRA #2627737	**Blood/plasma concentration experiments (administration of [^{14}C] afidopyropen in single gavage doses of 3, 30 or 300 mg/kg bw, or single IV dose of 0.5 mg/kg bw):** **Low-dose level**: AUC was comparable for ♂ and ♀ and T_{max} was 1 hr for ♂ and ♀. **Mid- and high-dose levels:** T_{max} was 1 hr in ♂ and 8 hr in ♀. At the high dose level, T_{max} was 4 hr for ♂ and ♀. **IV dose**: internal dose is slightly greater in ♂. **Mass balance/excretion experiments (single gavage dose administration of 3 or 300 mg/kg bw, or repeat gavage dose administration of 300 mg/kg bw/day [non-radiolabelled test material for 14 days and one radiolabelled dose on day 15]):** **Low, single dose level**: total recovery of radioactivity was 92–94% of the AD. Mean total amount of radioactivity excreted in urine was 5.5–5.9% and in feces was 86–87%. **High, single dose level**: total recovery of radioactivity was 94.96 and 96.20 (♂ / ♀). Mean total amount of radioactivity excreted in urine was 20–21% and in feces was 74–75%. **High, repeat dosing**: slightly lower amounts of radioactivity were excreted in the urine in both ♂ and ♀. This indicates that changes in kinetics/metabolism may occur after multiple dosing. Time course evaluations indicate that excretion occurred predominantly within 2 days post-dose. **Tissue distribution experiments (single gavage dose administration of 3 or 300 mg/kg bw):** **Low dose level, 1 hr**: highest concentrations were found in the GI tract/GI tract contents for ♂ and ♀, followed by liver, adrenal glands, kidney, thyroid, pancreas (♂); ovaries, liver, adrenal glands, pancreas, kidney (♀). **High dose level, 4 hr**: highest concentrations were found in the GI tract/GI tract contents for both ♂ and ♀, followed by liver, adrenal gland, thyroid, kidney and pancreas (♂) and adrenal glands, liver, thyroid, pancreas and kidney (♀). For both dose levels, in both ♂ and ♀, radioactive residue concentrations generally

Study Type/Animal/PMRA #	Study Results
	declined in organs and tissues parallel to the radioactive residues in plasma. **Note for Tissue Distribution experiment:** during necropsy, gel-like agglomerations of the test-substance preparation were observed in the stomach of selected animals of the high dose group which were assessed by the study author to be responsible for inconsistent results of plasma levels of this dose group. Therefore, 1% Cremophor (by weight) was added to the carrier (0.5% CMC in tap water) to guarantee the consistency of the test substance preparation when the experiment was repeated. For this reason, the potential impact of the different carrier on the kinetics of radiolabelled afidopyropen could not be determined. **Excretion via the bile (single gavage dose administration of 3 or 300 mg/kg bw)**: **Low dose level**: within 72 hrs, mean excretion was via the bile was 39–46%. Mean total excretion via the urine was 11–17% AD. Based on radioactivity excreted in the bile and urine, and residues in the cage wash and carcass, oral absorption was 57% (♂ and ♀). Higher mean urine excretion was observed in the low dose group in the bile excretion experiment (17% and 11% versus 5.5% and 5.9% for ♂ and ♀, respectively). **High dose level**: within 72 hr, mean excretion via the bile was 36–41% AD. Mean total excretion via the urine was 15–22% AD. Based on radioactivity excreted in the bile and urine, and residues in the cage wash and carcass, oral absorption was 57–60%.
Absorption, distribution, metabolism and excretion following repeat dietary dosing, followed by one single gavage dose of radioactively labelled afidopyropen (low, mid and high doses) Rat (Fischer) PMRA #2627743	**Results from repeat dietary dose administration (14 days) of non-radiolabelled test material, followed by single gavage dose of [^{14}C] afidopyropen. Dose levels of 3, 15 and 50 mg/kg bw/day)**: **Plasma kinetics – Total radioactivity**: For the afidopyropen, when comparing AUC values of the mid or high-dose to the low-dose, AUC values increase with increasing dose in a non-proportional manner. However, when comparing AUC values of mid- to high-dose, the increase is proportional to dose. **3–15 mg/kg bw/day**: AUC ↑ 13.5-fold **3–50 mg/kg bw/day**: AUC ↑ 53-fold **15 – 50 mg/kg bw/day**: AUC ↑ 3.9-fold AUC indicates that exposure to CPCA-carnitine is higher than afidopyropen and metabolites (M440I001 and M440I017). **Plasma kinetics – afidopyropen and its metabolites**: Terminal $t_{1/2}$, 50 mg/kg bw/day dose level: 2.17 hr (afidopyropen); 3.59 (M440I001), 3.78 hr (M440I017); 27.1 hr (CPCA-carnitine; approximation) **Excretion**: After a 72-hr observation period, 0.9, 1.3 and 1.6% of AD was excreted via the urine and 85, 90 and 65% of AD was excreted via the feces from the 3, 15 and 50 mg/kg bw dose groups, respectively. **Tissue distribution** (conducted for 15 and 50 mg/kg bw/day dose groups only; tissues collected and analyzed were blood, plasma, liver and uterus). Time points for sampling were based on the C_{max} values: 1 hr and 1.5 hr for 15 and 50 mg/kg bw, respectively. Direct comparison with plasma kinetic study was not possible as sampling times differed. **15 mg/kg bw/day:** Blood cells: 12.3 ug equiv/g (0.6% AD); Plasma: 3.45 ug equiv/g (0.25%); Uterus: 4.43 ug equiv/g (0.07% AD);

Study Type/Animal/PMRA #	Study Results
	Liver: 42.2 ug equiv /g (8.0% AD) at 1 hr post-dose. **50 mg/kg bw/day**: Blood cells: 8.9 ug equiv /g (0.5% AD); Plasma: 8.62 ug equiv/g (0.18%); Uterus: 12.8 ug equiv/g (0.08% AD); Liver: 92.7 ug equiv/g (5.4% AD) in the liver at 1.5 hr post-dose. **Metabolite profiling** (15 and 50 mg/kg bw/day dose groups only): Nine individual peaks were observed in urine and in feces. Six urine peaks and four feces peaks contained ≥5% of the radioactivity in at least one of the chromatograms. Eight individual peaks were noted in liver samples, of which 4 peaks contained ≥5% of the total radioactivity. Twelve individual peaks were noted in the uterus, of which six contained ≥5% of the radioactivity. A total of 17 peaks were found in different matrices. (**Note:** only M440I001 and M440I017 and afidopyropen were identified.). Afidopyropen was identified in feces, liver and uterus.
Acute oral (gavage) (Acute Toxic Class) Rats (Wistar) PMRA #2627763	Low toxicity. LD_{50} (♀) > 2000 mg/kg bw
Acute dermal Rat (Wistar) PMRA #2627764	Low toxicity. LD_{50} (♂/♀) > 2000 mg/kg bw
Acute inhalation Rat (Wistar) PMRA #2627765	Low toxicity. LC_{50} (♂/♀) > 5.48 mg/L 5.48 mg/L: abnormal respiratory sounds (from termination of exposure to 4 hr post-exposure) (♂/♀)
Skin irritation Rabbit (New Zealand White) PMRA #2627766	MAS = 0 MIS = 0 at 1 hr Non-irritating.
Eye irritation Rabbit (New Zealand White) PMRA #2627767	Non-irrigated eyes: MAS = 0 MIS = 7.3 at 1 hr Irrigated eyes: MAS = 0 MIS = 1.3 at 1 hr Non-irritating.
Skin sensitization (Maximization test) Guinea pigs (Hartley) PMRA #2627768	Non-sensitizing.
28-day oral (dietary)	NOAEL not established

Study Type/Animal/PMRA #	Study Results
Mouse (ICR) PMRA #2627769 to #2627778	Effects at lowest dose tested (49 mg/kg bw/day): ↑ thyroid wt (♀). Effects at 145 mg/kg bw/day: ↑ total bilirubin (♂/♀); ↑ adrenal wt (♂). Supplemental
90-day oral (dietary) Mouse (ICR) PMRA #2627791to #2627801	NOAEL = 69/83 mg/kg bw/day (♂/♀) LOAEL = 285/327 mg/kg bw/day Effects at LOAEL: ↑ bilirubin (♂/♀); ↑ triglycerides, ↑ spleen wt (♀).
28- day oral (dietary) Rat (Fischer) PMRA #2627789	NOAEL not established Effects at 59 mg/kg bw/day: ↑ liver wt (♂). Effects at 128 mg/kg bw/day: ↑ BUN, ↑ AST, ↑ liver wt (♀). Supplemental
90-day oral (dietary) Rat (Fischer) PMRA #2627790	NOAEL = 18/20 mg/kg bw/day (♂/♀) LOAEL = 61/68 mg/kg bw/day Effects at the LOAEL: ↑ rel liver wt (♂/♀); ↑ rel kidney wt, ↑ urobilinogen (urine) (♂); ↓ fc, ↑ BUN, ↑ AST, ↑ ALT, ↑ potassium, ↑ abs liver wt, ↑ rel spleen wt, ↓ abs heart wt, ↑ thymus wt, vacuolar change (fatty change) of hepatocytes and myocardium (♀).
90-day oral (dietary) Rat (Fischer) PMRA #2627749	NOAEL not established Effects at lowest dose tested (19/21 mg/kg bw/day): ↑ cardiac troponin I (1♂ at Day 29, 2 ♂ at Day 92); ↑ urine volume (♀). Effects at 66/79 mg/kg bw/day: ↑ cardiac troponin I (at this dose level: 1 ♂ Day 29, 2 ♂ Day 92 ♂;1♀ at Day 29) (♂/♀); ↑ platelets; ↑ reticulocytes, ↓ triglycerides (♂); ↓ RBC, ↓ HGB, ↓ HCT, ↑ GGT, ↑ urea, ↑ cholesterol, ↑ potassium, ↑ liver wt, ↑ thymus wt, ↓ ovary wt (♀). Supplemental
90-day oral (dietary) Rat (Fischer) PMRA #2627746	NOAEL not established Effects at lowest dose tested (19/20 mg/kg bw/day): ↑ total protein, ↑ albumin, ↑ globulin, ↑ cholesterol, ↑ cardiac troponin I (2♂ affected at 19 mg/kg bw/day: 2 Day 29, 1 Day 92; 3♂ affected at 181 mg/kg bw/day: 1 day 29, 2 day 92) (♂); ↓ HGB, ↓ HCT, ↑ urea, ↑ GGT (♀). Supplemental
90-day oral (dietary) Rat (Wistar) PMRA #2627755	NOAEL not established Effects at lowest dose tested (20 mg/kg bw/day): slight ↓ HGB, slight ↓ HCT (♂). Effects at 98 mg/kg bw/day: ↑ platelets, ↓ motor activity (♀). Supplemental
28-day oral (capsule) Dog (Beagle) PMRA #2627779 to #2627788	NOAEL not established Effects at highest dose tested (90 mg/kg bw/day): vomiting of feed, bw loss, ↑ kidney wt, white mucosa in small intestine (♂/♀); ↑ ALP, ↑ liver wt (♂); ↓ fc (♀). Supplemental
90-day oral (capsule)	NOAEL = 15 mg/kg bw/day (♂/♀) LOAEL = 30 mg/kg bw/day

Study Type/Animal/PMRA #	Study Results
Dog (Beagle) PMRA #2627803 to #2627825	Effects at LOAEL: vomiting of feed, hyaline droplet deposition in hepatocytes (♂/♀); hematuria (♂); ↑ BUN, ↑ albumin (♀).
One-year oral (capsule) Dog (Beagle) PMRA #2627826 to #2627847	NOAEL = 8 mg/kg bw/day (♂/♀) LOAEL = 20 mg/kg bw/day Effects at LOAEL: ↓ neutrophils, hyaline droplet deposition of hepatocytes, ↑ BUN (♂/♀); vacuolation of white matter (1 ♂ at this dose level) and neuropil (2 ♂ at this dose level) of the cerebrum [slight at this dose level] (♂); vomiting of feed (♀).
28-day dermal Rat (Wistar) PMRA #2627850	NOAEL (systemic toxicity) = 1000 mg/kg bw/day (♂/♀) LOAEL: not established <u>Dermal effects:</u> ≥ 300 mg/kg bw/day: ↑ incidence of multifocal hyperkeratosis of the skin (♀). 1000 mg/kg bw/day: ↑ incidence of multifocal hyperkeratosis of the skin (♂).
Repeat-dose inhalation PMRA #2627849	The waiver was supported for the proposed uses on the basis of the low volatility and low acute inhalation toxicity of afidopyropen, as well as the magnitude of the margins of exposure (MOE) obtained for the exposure scenarios when oral endpoints were used in the risk assessment.
One-year chronic (dietary) Rat (Fischer) PMRA #2627860	NOAEL = 15/18 mg/kg bw/day (♂/♀) LOAEL = 48/56 mg/kg bw/day Effects at LOAEL = ↑ platelets, ↓ triglycerides (♂/♀); ↓ ALT (♂); ↓ fc, ↑ ALP, slight vacuolar change (lipid deposition) of hepatocytes and myocardium, ↓ uterine wt (♀).
One-year chronic (dietary) Rat (Fischer) PMRA #2627861	NOAEL not established LOAEL = 48/57 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ platelets, ↓ triglycerides, ↑ liver wt, ↑ spleen wt, ↑ kidney wt (♂/♀); ↑ ALP, ↑ adrenal wt, ↑ thyroid wt, ↑ testes wt, ↑ epididymal wt (♂); ↓ fc, ↑ BUN, ↓ bilirubin, ↓ heart wt, ↑ pituitary wt, ↓ uterine wt, slight vacuolar change (lipid deposition) of hepatocytes and myocardium (slight to moderate at 161 mg/kg bw/day), ↓ zymogen granules of pancreas acinar cells (♀).
Two-year chronic/oncogenicity (dietary) Rat (Fischer) PMRA #2627863	NOAEL = 13/16 mg/kw bw/day (♂/♀) LOAEL = 43/51 mg/kg bw/day Effects at LOAEL: ↑ kidney wt, ↑ liver wt, ↑ adrenal wt (♂); ↓ fc, ↑ uterus wt, ↑ hyperplasia of the bile duct in the liver, ↑ incidence of uterine adenocarcinoma (♀). Evidence of oncogenicity in ♀ based on increased incidence of uterine adenocarcinoma and adenoma/carcinoma combined. Uterine Adenoma: 2/50, 1/50, 2/50, 3/50 Uterine Adenocarcinoma: 4/50 [a], 1/50, 2/50, 10/50 Combined (adenoma and adenocarcinoma): 6/50 [a], 2/50, 4/50, 13/50 [a] denotes a linear trend, $p < 0.01$
Two-year chronic/oncogenicity (dietary) Rat (Fischer)	NOAEL not established LOAEL = 42/50 mg/kg bw/day (♂/♀) Effects at LOAEL = ↑ epididymides wt (♂); ↑ opacity of unilateral lens, ↑ rel liver wt, ↓ abs heart wt, ↓ ovary wt, ↑ adenocarcinoma in the uterus, ↑ hyperplasia of bile

Study Type/Animal/PMRA #	Study Results
PMRA #2627862	ducts in the liver (♀). Evidence of oncogenicity in ♀ based on increased incidence of uterine adenocarcinoma and adenoma/carcinoma combined. Uterine Adenoma : 1/50, 3/50, 4/50 Uterine Adenocarcinoma: 0/50[a], 5/50*, 12/50** Combined (adenoma and adenocarcinoma): 1/50 [a], 8/50, 15/50 * $p < 0.05$ compared to control ** $p < 0.01$ compared to control [a] denotes a linear trend, $p < 0.01$
18-month (dietary) Mouse (ICR) PMRA #2627864	NOAEL = 79/76 mg/kg bw/day (♂/♀) LOAEL = 445/333 mg/kg bw/day Effects at LOAEL: ↓ bw/bwg, ↓ fc (wk 1 only ♂) (♂/♀); ↑ centrilobular hepatocellular hypertrophy, ↑ secreted material depletion in granular ducts of submandibular gland (♂); ↑ mortality (wks 21–25, 41), prone position, bradypnea, ↓ spontaneous motor activity, ↓ fe, ↑ WBC, ↑ lymphocyte count, ↑ large unstained cell count, ↑ spleen wt, ↑ ovary wt, pale-coloured liver, ↓ hematopoiesis in bone marrow (sternum and femur), atrophy of the spleen, fibrosis of cardiac muscle in the heart, apoptosis in lymphocytes in the thymus and lymphoid follicle in the lymph nodes (cervical and mesenteric), vacuolation of the following: heart cardiac muscle, glandular stomach parietal cells, hepatocytes, kidney proximal tubule cells, urinary bladder mucosal epithelial cells, neuropil in the cortex and the choroid plexus epithelium in the cerebrum, glial cell in the gray matter in the spinal cord (cervical, thoracic and lumbar) (♀). No evidence of oncogenicity.
One-generation range-finding study (dietary) Rat (Wistar) PMRA #2627875	NOAELs not established Parental effects at 132 mg/kg bw/day: ↓ bw/bwg, ↓ fc, ↑ adrenal wt, ↑ thymus wt, ↑ liver wt (♀). Parental effects at 192 mg/kg bw/day: ↓ bw/bwg, ↓ fc, ↓ abs pituitary wt, dark brown discolouration of the liver (♂); ↑ thyroid wt (♀). Reproductive effects at 101/132 mg/kg bw/day: ↓ mean number of implantations, ↓ mean number of pups delivered, ↓ seminal vesicle and prostate wt (parental). Offspring effects at lowest dose tested (15 mg/kg bw/day): ↓ bw (8–13%, PND 4 and 7 ♂; 9%, PND 4 ♀). Supplemental
One-generation reproduction (dietary) testing in high purity and standard batches of afidopyropen Rat (Wistar) PMRA #2627876	NOAELs not established (one dose group only) Parental effects at 127/131 mg/kg bw/day (high purity batch): ↓ HGB, ↓ HCT, ↓ ALP, ↓ total bilirubin, ↑ liver wt (♂/♀); ↓ fc (premating wk 0–1), ↑ rel reticulocyte counts, ↑ WBC, ↑ abs neutrophil count, ↑ abs lymphocyte counts, ↓ triglycerides, ↑ kidney wt, ↑ spleen wt, ↑ thyroid wt, extramedullar hematopoiesis of the liver (♂); ↑ bw (LD21), ↑ bwg (lactation), ↓ fc, ↑ platelets, ↑ adrenal wt, periportal fatty change in the liver (♀). Parental effects at 126/132 mg/kg bw/day (standard batch): ↓ HGB, ↑ rel reticulocyte counts, ↓ ALP, ↓ total bilirubin, ↑ cholesterol, ↑ liver wt, ↑ spleen wt, ↑

Study Type/Animal/PMRA #	Study Results
	rel kidney wt (♂/♀); ↓ fc, ↓ triglycerides, extramedullary hematopoiesis of the liver (♂); ↑ bw (pre-mating wks 1–3, LD 21), ↑ bwg (lactation), ↓ fc (premating wk 0–1 and lactation), ↓ HCT, ↓ MCH, ↑ abs neutrophil count, ↓ inorganic phosphate, ↑ adrenal wt, ↑ thyroid wt, ↑ abs kidney wt, enlarged livers, periportal fatty change in the liver (♀). Reproductive effects at 127 mg/kg bw/day (high purity batch): ↓ prostate wt. Reproductive effects at 126/132 mg/kg bw/day (standard batch): ↓ prostate wt, ↓ spermatid counts in the testes, altered sex ratio (↑ % ♂). Offspring effects at 131 mg/kg bw/day (high purity batch): ↓ bw (PND 4 – 21), ↓ bwg (PND 0–21), ↓ spleen wt (♂/♀). Offspring effects at 132 mg/kg bw/day (standard batch): ↑ pup deaths (PND 1–4), ↓ bw (PND 4–21), ↓ bwg (PND 0–21), ↓ spleen wt (♂/♀); altered sex ratio (↑ % ♂) (♂). Supplemental
2-generation reproduction (dietary) Rat (Wistar) PMRA #2627878	Parental ♂ NOAEL = 75 mg/kg bw/day Parental ♀ NOAEL = 27 mg/kg bw/day Parental ♂ LOAEL not established Parental ♀ LOAEL = 85 mg/kg bw/day Effects at ♀ LOAEL: ↑ bwg (F1♂: 8 of 14 wks), ↑ abs liver wt P and F1, ↑ rel liver wt P (♂); ↑ bw [P: LD 21; F1: LD 14–21], ↑ bwg [P: LD 0–21; F1 wks 0–10, LD 0–21], ↓ fc P and F1, ↑ adrenal wt P and F1 (♀). Reproductive NOAEL = 22/27 mg/kg bw/day (♂/♀) Reproductive LOAEL = 75/85 mg/kg Effects at LOAEL: altered sex ratio (↑ % ♂ – equivocal), ↓ prostate wt (F1 parents). Offspring NOAEL = 27 mg/kg bw/day Offspring LOAEL = 85 mg/kg bw/day Effects at LOAEL: ↑ pup death F1 and F2, ↓ bw PND21 P and F1, ↓ spleen wt F1 (♂/♀); delayed sexual maturation (preputial separation) F1 (♂). Serious effects in the presence of maternal toxicity.
2-generation reproduction (dietary) Rat (Wistar) PMRA #2627877	Parental ♂ NOAEL = 39 mg/kg bw/day Parental ♀ NOAEL = 8.4 mg/kg bw/day Parental ♂ LOAEL = 150 mg/kg bw/day Parental ♀ LOAEL = 41 mg/kg bw/day Effects at ♀ LOAEL: ↓ glucose P, ↓ total bilirubin P and F1, ↓ rel basophil counts F1, ↑ abs lymphocyte count F1 ↑ adrenal wt P and F1 (♀). Effects at ♂ LOAEL: ↓ bw/bwg P and F1, ↓fc P and F1, ↓ glucose F1 (♂/♀); ↓ glucose P, ↓ triglycerides P and F1, ↓ total bilirubin P and F1, ↑abs adrenal wt F1, ↑ rel adrenal wt P and F1 (♂);↑ bwg (pre-mating period F1, LD 0– 21 P and F1), ↓ RBC F1, ↓ HGB P and F1, ↓ HCT P and F1, ↑ abs reticulocyte counts P, ↑ rel reticulocyte counts P and F1, ↑ abs lymphocyte count P, ↑cholesterol P and F1, ↓ uterus wt F1,↑ adrenal vacuolation P and F1 (♀). Reproductive NOAEL = 39/41 mg/kg bw/day (♂/♀) Reproductive LOAEL = 150/155 mg/kg bw/day Effects at LOAEL: ↓ implantation sites F1, ↓ mean number of pups /dam F1, ↓ mean litter size (PND 0) F1, “improper nursing of offspring” (P: 3 dams; F1: 6 dams), altered sex ratio (↑ % ♂) P and F1; ↓ abs prostate wt P and F1, ↓ sperm count in the

Study Type/Animal/PMRA #	Study Results
	testes P, ↑ lymphoid infiltration of the prostate F1 (♂); ↓ ovary wt P and F1, and ↓ uterus wt F1 (♀). Offspring NOAEL = 8.4 mg/kg bw/day Offspring LOAEL = 41 mg/kg bw/day F1, effects at LOAEL: ↓ bw (F2: PND 21), ↓ bwg (F1: PND 14 – 21; F2: PND 14–21), ↓ spleen wt F2 (♂/♀); ↓ thymus wt F2, delayed sexual maturation (preputial separation) F1 (♂); ↓ thymus wt F1 (♀). Effects in the presence of maternal toxicity.
Cross-mating (dietary) Rat (Wistar) PMRA #2627914	NOAELs not established; only 1500 ppm (131/132 mg/kg bw/day) dose level tested Parental Effects: Group 1[no dosing of parents premating, mating or gestation; dosing of dams during lactation] 131/132 mg/kg bw/day: ↑ bw (LD 21), ↑ platelets, ↓ HGB, ↓ HCT, ↓ MCHC, ↓ rel neutrophil count, ↓ total bilirubin, ↓ inorganic phosphate, ↑ urea, ↑ cholesterol, ↓ triglycerides, ↑ liver wt, enlarged liver and diffuse hepatocellular hypertrophy (2/20) (♀). Group 2 [dosing of parents premating, mating, gestation and lactation] 131/132 mg/kg bw/day: ↓fc (♂: premating wk 1; ♀: premating, GD 0–14), ↓ HGB, ↓ HCT, ↓ neutrophil counts, ↑ rel lymphocyte counts, ↓ total bilirubin, ↓ inorganic phosphate, ↓ triglycerides, ↑ liver wt (♂/♀); ↑ platelets, ↑ rel reticulocyte counts, ↓ monocyte counts, ↑ kidney wt , ↑ spleen wt (♂); ↓ bwg (GD 0–7), ↑ bw (LD 21), ↓ MCHC, ↑ abs lymphocyte counts, ↑ urea, ↑ cholesterol, ↑ GGT (♀). Group 3 [dosing of parents premating, mating and gestation; delivery of pups via C-section] 131/132 mg/kg bw/day: ↓fc (♂: premating wk 1; ♀: premating, GD 0–14) (♂/♀); ↓ bwg (GD 0–7) (♀). Reproductive Effects: Group 4 [prenatal exposure, born via C-section; no post-natal dosing]: ↑ pup death (PND 0). Offspring Effects: Group 1, 132 mg/kg bw/day [pups exposed only during postnatal period]: ↓ bw (PND 7–21), ↓ bwg (PND 1–21), ↓ spleen wt, ↓ abs heart wt (♂/♀); ↓ abs brain wt, ↓ thymus wt (♂); ↓ abs thymus wt (♀). Group 2, 132 mg/kg bw/day [pups exposed only during postnatal period]: ↓ bw (PND 7–21), ↓ bwg (PND 1–21), ↓ spleen wt, ↓ abs heart wt (♂/♀); ↓ thymus wt (♂); ↓ abs thymus wt (♀). Group 4, 132 mg/kg bw/day [pups exposed only during prenatal period, delivered via C-section]: ↑ pup death (PND 1–4). Supplemental
Range-finding developmental toxicity (gavage) Rabbit (Japanese White) PMRA #2627912	NOAELs not established Maternal LOAEL = 30 mg/kg bw/day Effects at LOAEL: ↓ bw (slight at this dose, 4–6%, GD 24–28), ↓ bwg (overall), ↓ fc, ↑ post-implantation loss. Developmental LOAEL = 30 mg/kg bw/day

Study Type/Animal/PMRA #	Study Results
	Effects at LOAEL: slight ↑ in fetal deaths (on fetal basis only) and post-implantation loss.
Developmental toxicity (gavage) Rabbit (Japanese White) PMRA #2627897 to #2627911	Maternal NOAEL = 8 mg/kg bw/day Maternal LOAEL = 16 mg/kg bw/day Effect at LOAEL: altered sex ratio (↑ % ♂) Developmental NOAEL = 8 mg/kg bw/day Developmental LOAEL = 16 mg/kg bw/day Effect at LOAEL: altered sex ratio (↑ % ♂) Effects at 32 mg/kg bw/day: ↓ live fetuses, ↑ dead fetuses and early resorptions, ↑ total litter resorptions, ↑ post-implantation loss. Evidence of developmental toxicity in the absence of overt maternal toxicity.
Range-finding developmental toxicity (gavage) Rat (Wistar) PMRA #2627880	NOAELs not established Effects at 20 and 100 mg/kg bw/day: single incidents of myocardial degeneration at both dose levels (equivocal). Maternal effects at 500 mg/kg bw/day: mortality (GD 16–18 at 500 mg/kg bw/day; GD 10–17 at 1000 mg/kg bw/day), vaginal hemorrhage, bradypnea, hypothermia, ↓ locomotor activity, soiling of perigenital/perioral fur, ↓ bw, ↓ bwg, ↓ fc, ↓ gravid uterine wt, atrophy of the thymus and spleen (observed grossly), jejunum and glandular stomach mucosa discolouration (multifocal dark red/black patches), adrenal gland hypertrophy (observed grossly), hepatocellular hypertrophy, periportal fatty change in the liver, myocardial degeneration [0/1/1/4/6], ↓ live fetuses and litters, ↑ resorptions and post-implantation loss. Developmental effects at 500 mg/kg bw/day: ↓ live fetuses, litters and viability index, ↑ resorptions and post-implantation loss.
Developmental toxicity (gavage) Rat (Wistar) PMRA #2627882	Maternal NOAEL = 30 mg/kg bw/day Maternal LOAEL = 100 mg/kg bw/day Effects at LOAEL: ↑ adrenal weight, altered sex ratio (↑ % ♂; equivocal). Developmental NOAEL = 30 mg/kg bw/day Developmental LOAEL = 100 mg/kg bw/day Effects at LOAEL: ↑ incidence of fetuses with skeletal variations, ↑ fetal and litter incidence of lumbar (supernumerary) ribs, ↑ metatarsal ossification, altered sex ratio (↑ % ♂; equivocal). Evidence of developmental toxicity in the presence of maternal toxicity.
Developmental toxicity(gavage) Rat (Wistar) PMRA #2627884 to #2627896	Maternal NOAEL = 100 mg/kg bw/day Maternal LOAEL = 200 mg/kg bw/day Effects at LOAEL: mortality (1 ♀, GD 19), ↓ bw (GD 9 only), bwg (GD 6–9 only) and fc (GD 6-15). Developmental NOAEL not established LOAEL = 50 mg/kg bw/day: ↑ fetal incidence of skeletal variations and supernumerary ribs 200 mg/kg bw/day: ↑ fetal and litter incidence of zygomatic bone fused with maxilla, cleft palate [2 (1) versus 0 in controls and none reported in historical control data] Evidence of developmental toxicity in the absence of maternal toxicity.

Study Type/Animal/PMRA #	Study Results
Acute oral neurotoxicity (gavage) Rat (Wistar) PMRA #2627916	NOAEL = 700 mg/kg bw (♂/♀) LOAEL = 2000 mg/kg bw Effects at LOAEL: ↓ motor activity (individual intervals and cumulative total motor activity, day 0) (♂/♀); slight ↑ bwg, slight tremors (1♀, day 0), hypothermia (2♀, day 0) (♀).
90-day neurotoxicity(dietary) Rat (Wistar) PMRA #2627917	NOAEL = 73/92 mg/kg bw/day (♂/♀) LOAEL = 396 mg/kg bw/day Effects at LOAEL: ↓ bw/bwg (♂). Study LOAEL: Excessive food spillage occurred; compound intake was based on a limited number of values. The calculated dietary consumption at this dose level is likely an overestimate based on other rat dietary studies in the database.
28- day immunotoxicity study in ♀ (dietary) Rat (Wistar) PMRA #2627744	NOAEL = 69 mg/kg bw/day LOAEL = 278 mg/kg bw/day Effects at LOAEL: ↓ bwg, ↑ rel liver wt, slight ↑ thymus wt (♀). Study limitations: Unable to measure actual compound intake due to excessive food spillage. Historical control data for food consumption were used to estimate the compound intake for the top two dose groups (69 and 278 mg/kg bw/day). Supplemental
Bacterial reverse mutation assay PMRA #2627851	Negative in *S. typhimurium* strains (TA100, TA1535, TA98, and TA1537) and *E. coli* (WP2 uvrA) strains in the absence and presence of metabolic activation.
Bacterial reverse mutation assay PMRA #2627852	Negative in *S. typhimurium* strains (TA100, TA1535, TA98, and TA1537) and *E. coli* (WP2 uvrA) strains in the absence and presence of metabolic activation.
Bacterial reverse mutation assay PMRA #2627853	Negative in *S. typhimurium* strains (TA100, TA1535, TA98, and TA1537) and *E. coli* (WP2 uvrA) strains in the absence and presence of metabolic activation.
Bacterial reverse mutation assay PMRA #2627854	Negative in *S. typhimurium* strains (TA100, TA1535, TA98, and TA1537) and *E. coli* (WP2 uvrA) strains in the absence and presence of metabolic activation.
In vitro chromosomal aberration assay PMRA #2627855	Negative in Chinese hamster lung cells.
In vitro forward mutation assay in mammalian cells PMRA #2627856	Negative in Chinese hamster ovary cells.
In vivo micronucleus assay (gavage) Mouse (NMRI) PMRA #2627859	Negative, only ♂ tested. 1400 and 2000 mg/kg bw/day: partially closed eyes, ruffled fur, slightly reduced spontaneous activity (♂).

Study Type/Animal/PMRA #	Study Results
In vivo micronucleus assay (gavage) Mouse (NMRI) PMRA #2627858	Negative. Pre-test (♂/♀): 1500 and 2000 mg/kg bw: death of 1 ♀/ group. Main test (only ♂ tested): ≥ 1000 mg/kg bw: abdominal posture, partially closed eyes, ruffled fur, reduced spontaneous activity, tumbling (♂). ≥ 1500 mg/kg bw: hunched posture, apathy, rapid breathing/dyspnea (♂).
In vivo micronucleus assay (gavage) Mouse (ICR) PMRA #2627857	Negative.
Special Study 14-day study investigating CYP1A1 and CYP1B1 induction in ♀ (dietary) Rat (Fischer) PMRA #2627750	197.2 mg/kg bw/day: ↓ bw (days 5 and 8), ↓ bwg, ↓ fc, ↑ liver wt, ↓ uterus wt, ↑ hepatic EROD, ↑ hepatic microsomal estradiol-2-hydroxylation, ↑ hepatic CYP1A1 mRNA, ↑ hepatic CYP1B1 mRNA, ↑ uterine CYP1A1 mRNA (♀). CYP1B1 mRNA not altered in uterine tissue. Supplemental
Special Study Estrogen receptor transcriptional activation assay PMRA #2627753	Negative for estrogen receptor transcriptional activation in stably transfected hERα-HeLa-9903 (human cervical cancer cells) when tested up to insoluble concentrations based on the assay scoring criteria. Supplemental
Special Study Estrogen receptor binding assay PMRA #2627754	Using uterine cytosol from ovariectomized ♀ Sprague-Dawley rats, afidopyropen was classified as equivocal based on the assay scoring criteria. Metabolites M440I002 and M440I001 were classified as non-interacting based on the assay scoring criteria. Supplemental
Special Study Effects on dopamine transporter, receptor, uptake and bioassay (in vitro) PMRA #2627748	Binding assays indicated that the test compounds (afidopyropen, M440I001, M440I002, M440I003 and M440I017) did not show inhibition of the dopamine transporter (isolated from human recombinant Chinese hamster ovary cells). Cellular and nuclear receptor functional assays indicated that the test compounds did not have an agonist or antagonist effect on the dopamine D1 receptor. Enzyme uptake assays indicated that the test compounds did not inhibit dopamine uptake. In the rabbit splenic artery tissue bioassays, test compounds did not show an agonist or antagonist effect on the dopamine D1 receptor. In the rabbit ear artery tissue bioassays, afidopyropen and M4401002 induced a↓ twitch contraction amplitude that was not blocked with sulpiride, indicating an agonist-like effect on the dopamine D2 receptor. Supplemental

Study Type/Animal/PMRA #	Study Results
Special Study Binding assays for dopamine D2S and D2L receptors PMRA #2627751	The test compounds (afidopyropen and M440I002) did not show inhibition of the dopamine D2S and the D2L receptors (isolated from human recombinant HEK-293 cells). Supplemental
Special Study Tissue bioassay for dopamine D2 receptor PMRA #2627752	The test compounds (afidopyropen and M440I002) induced a↓twitch contraction amplitude in a rabbit ear artery indicating an agonist-like effect of the dopamine D2 receptor. Supplemental
Special Study 28-day toxicity study to determine treatment-related effects on prolactin levels in ♀ (dietary) Rat (Fischer) PMRA #2627756	NOAEL = 18 mg/kg bw/day (♀) LOAEL = 81 mg/kg bw/day Effects at LOAEL: ↑ bw/bwg, ↑ fc, ↓ prolactin in metestrus (day 24), ↓ prolactin in proestrus, ↓ prolactin in metestrus (day 28, after stimulation), ↑ abs liver wt, ↓ rel pituitary wt. Effects at 368 mg/kg bw/day: ↓ number of estrous cycles, ↑ length of estrous cycles, ↓ prolactin in proestrus, ↑ liver wt, ↓ adrenal wt, ↓ovary wt, ↓ pituitary wt, ↓ uterus wt, diffuse atrophy of ovaries, uterus, cervix, and vagina, vagina mucification. While in metestrus, ↑ in serum prolactin levels, following stimulation with metoclopramide, were smaller in rats dosed with afidopyropen than in control rats. This result was also observed in rats treated with bromocriptine mesylate. Note: cycle length of control animals was atypically longer than normal. Supplemental
Special Study Activity prediction modelling for the dopamine D2 receptor and dopamine transporter (in silico) PMRA #2627757	The molecular structures of afidopyropen and its metabolites M440I001, M440I002, M440I003 and M440I017 were submitted to in-silico activity prediction models (QSAR) of the human dopamine D2 receptor and dopamine transporter. High inhibition values were predicted regarding the dopamine receptor for the metabolites (except M440I017) and afidopyropen, although these predictions were labelled as borderline due to the high level of uncertainty. Inhibition of the dopamine transporter seemed unlikely given the rather low activity (plC_{50} predictions) for this target. Supplemental

Table 4 Toxicity Profile of Metabolites of Afidopyropen

Note: Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted. Effects above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Study Type / Animal / PMRA #	Study Results
Metabolite M440I007 (dimer)	
Metabolic fate of M440I007-identification of metabolites in urine and feces, single (high, gavage) dose Rat (Fischer) PMRA #2627739	M440I007and a trace of unchanged afidopyropen were detected in the fecal extracts from the treated animal (n = 1♂). The peak area count for the dose formulation was approximately 17,000 and 136–144 for M440I007and afidopyropen, respectively. The relative signal strength could not be used to calculate precise ratios but in comparing relative signal area for M440I007 and afidopyropen, presence of afidopyropen appeared to be lower in the fecal extract than in the dose formulation. No other metabolites were detected. No detectable test substance or metabolites were noted in the urine of the treated animal. M440I007was excreted only through feces (although contribution of the biliary excretion could not be excluded) without extensive transformation to M440I001, M440I002, or M440I003, and its absorption rate or bioavailability is assumed to be very low. Therefore, there was no positive evidence to prove that M440I007 biotransforms to afidopyropen. Afidopyropen was present in the dosing solution as an impurity at levels greater than those seen in the feces, indicating that afidopyropen was not produced though metabolism of the dimer.
Acute (gavage) (Acute Toxic Class) Rat (Wistar) PMRA #2627918	Low toxicity. LD_{50} > 2000 mg/kg bw
90-day oral (dietary) Rat (Wistar) PMRA #2627921	NOAEL = 277/317 mg/kg bw/day (♂/♀) LOAEL = 708/797 mg/kg bw/day Effects at LOAEL: ↑ thymus wt (♂/♀); necrosis/fibrosis (minimal) of the heart (♂); ↑ total bilirubin, extramedullary hematopoiesis of the spleen (♀). Supplemental
Bacterial reverse mutation assay PMRA #2627919	Negative in *S. typhimurium* strains (TA100, TA1535, TA98 and TA1537) and *E. coli* (WP2 uvrA) strains in the absence and presence of metabolic activation.
Bacterial reverse mutation assay PMRA #2627920	Negative in *S. typhimurium* strains (TA100, TA1535, TA98 and TA1537) and *E. coli* (WP2 uvrA) strains in the absence and presence of metabolic activation.
In vivo micronucleus assay (gavage) Mouse (NMRI) PMRA #2627924	Negative. Only ♂ tested.

Study Type / Animal / PMRA #	Study Results
In vitro micronucleus test in human lymphocytes PMRA #2627922	Negative.
In vitro forward mutation assay in mouse lymphoma L5178T cells PMRA #2627923	Negative.
CPCA (cyclopropane carboxylic acid)	
Acute oral (gavage) (Acute Toxic Class) Rat (Wistar) PMRA #2737900	High toxicity. $300 < LD_{50} < 500$ mg/kg bw
90-day (gavage) Rat (Sprague- Dawley) PMRA #2635785 and #2635786	NOAEL = 10 mg/kg bw/day (♂/♀) LOAEL = 30 mg/kg bw/day Effects at LOAEL: ↑ incidence and severity of cardiomyopathy (characterized by one or more areas of myocyte degeneration/necrosis with a mononuclear inflammatory cell infiltrate), ↓ zymogen within acinar cells of the pancreas (♂/♀); ↓ globulin, ↓ total protein (♂); ↑ AST, ↑ total bile acids, ↑ BUN, ↑ inorganic phosphorus, ↓ cholesterol, ↑ liver wt, ↑ kidney wt, discolouration of the liver, myocardial vacuolation, ↑ periportal fatty change in the liver, ↑ mononuclear cell infiltrate in the liver, lymphoid necrosis of the thymus, (♀).

Table 5 Toxicity Profile of End-use Products Versys Insecticide and Sefina Insecticide

Study Type/Animal/PMRA #	Study Results
Versys Insecticide	
Acute oral (gavage) (Acute Toxic Class) Rat (Wistar) PMRA #2627543	Low toxicity. LD_{50} (♀) > 2000 mg/kg bw
Acute dermal Rat (Wistar) PMRA #2627544	Low toxicity. LD_{50} (♂/♀) >5000 mg/kg bw
Acute inhalation Rat (Wistar) PMRA #2627545	Slight toxicity. $0.6 < LC_{50} < 1.13$ mg/L (♂/♀)
Skin irritation Rabbit (New Zealand White) PMRA #2627546	Moderately irritating. MAS = 3.7 MIS = 4 at 24 hr

Study Type/Animal/PMRA #	Study Results
Eye irritation Rabbit (New Zealand White) PMRA #2627547	Minimally irritating. MAS = 1.3 MIS = 6 at 1 hr
Skin sensitization (Buehler) Guinea Pig (Dunkin-Hartley) PMRA #2627548	Non-sensitizing.
Bacterial reverse mutation assay PMRA #2627549	Negative in *S. typhimurium* strains (TA100, TA1535, TA98 and TA1537) and *E. coli* (WP2 uvrA) strains in the absence and presence of metabolic activation.
In vivo micronucleus assay (gavage) Mouse (NMRI) PMRA #2627550	Negative, only ♂ tested. 1000 and 2000 mg/kg bw: piloerection (♂).

Study Type/Animal/PMRA #	Study Results
Sefina Insecticide	
Acute oral gavage (Acute Toxic Class) Rat (Wistar) PMRA #2627087	Low toxicity. LD_{50} (♀) > 2000 mg/kg bw
Acute dermal Rat (Wistar) PMRA #2627088	Low toxicity. LD_{50} (♂/♀) > 5000 mg/kg bw
Acute inhalation Rat (Wistar) PMRA #2627089	Slight toxicity. $0.55 < LC_{50} < 1.22$ mg/L
Skin irritation Rabbit (New Zealand White) PMRA #2627090	Mildly irritating. MAS = 2.7 MIS = 3 at 24 hr
Eye irritation Rabbit (New Zealand White) PMRA #2627091	Minimally irritating. MAS = 2.2 MIS = 7.3 at 1 hr

Study Type/Animal/PMRA #	Study Results
Skin sensitization (Buehler) Guinea Pig (Dunkin-Hartley) PMRA #2627092	Non-sensitizing.

Table 6 Toxicology Reference Values for Use in Human Health Risk Assessment for Afidopyropen

Exposure Scenario	Study	Point of Departure and Endpoint	CAF or Target MOE[1]
Acute dietary general population	The acute neurotoxicity study had been considered; however, since the study NOAEL = 700 mg/kg bw (that is, close to a limit dose) it was not considered necessary to establish an ARfD for the general population.		
	ARfD not required		
Acute dietary females 13–49 years of age	Gavage developmental toxicity study in the rabbit	NOAEL = 8 mg/kg bw/day, based on an altered fetal sex ratio.	1000
	ARfD = 0.008 mg/kg bw		
Repeated dietary general population	One-year dietary toxicity study in the dog	NOAEL = 8 mg/kg bw/day, based on pathological changes in the brain observed in males.	300
	ADI = 0.03 mg/kg bw/day		
Repeated dietary females 13–49 years of age	Gavage developmental toxicity study in the rabbit	NOAEL = 8 mg/kg bw/day, based on an altered fetal sex ratio.	1000
	ADI = 0.008 mg/kg bw/day		
Short-, intermediate- and long-term dermal[2]	Gavage developmental toxicity study in the rabbit	NOAEL = 8 mg/kg bw/day, based on an altered fetal sex ratio.	1000
Short-, intermediate-, and long-term inhalation[3]	Gavage developmental toxicity study in the rabbit	NOAEL = 8 mg/kg bw/day, based on an altered fetal sex ratio.	1000
Cancer	Two-year dietary chronic toxicity/oncogenicity study in rats	1.79×10^{-2} (mg/kg bw/day)$^{-1}$, based on the combined incidence of uterine adenoma/ adenocarcinoma.	N/A

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments
[2] Since an oral NOAEL was selected, a dermal absorption factor (12%) was used in a route-to-route extrapolation.
[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to- route extrapolation.

Table 7 Toxicology Reference Values for Use in Human Health Risk Assessment for CPCA[a]

Exposure Scenario	Study	Point of Departure and Endpoint	CAF or Target MOE[1]
Acute dietary general population	The acute neurotoxicity study had been considered; however, since the study NOAEL = 700 mg/kg bw (that is, close to a limit dose) it was not considered necessary to establish an ARfD for the general population.		
	ARfD not required		
Acute dietary females 13–49 years of age	Gavage developmental toxicity study in the rabbit	MW-adjusted NOAEL = 2.3 mg/kg bw/day, based on an altered fetal sex ratio.	1000

Exposure Scenario	Study	Point of Departure and Endpoint	CAF or Target MOE[1]
	ARfD = 0.002 mg/kg bw		
Repeated dietary general population	One-year dietary toxicity study in the dog	MW-adjusted NOAEL = 2.3 mg/kg bw/day, based on pathological changes in the brain observed in males.	300
	ADI = 0.008 mg/kg bw/day		
Repeated dietary females 13–49 years of age	Gavage developmental toxicity study in the rabbit	MW-adjusted NOAEL = 2.3 mg/kg bw/day, based on an altered fetal sex ratio.	1000
	ADI = 0.002 mg/kg bw/day		
Short-, intermediate-, long-term dermal[2]	Gavage developmental toxicity study in the rabbit	MW-adjusted NOAEL = 2.3 mg/kg bw/day, based on an altered fetal sex ratio.	1000
Short-, intermediate-, long-term inhalation[3]	Gavage developmental toxicity study in the rabbit	MW-adjusted NOAEL = 2.3 mg/kg bw/day, based on an altered fetal sex ratio.	1000
Cancer	Two-year dietary chronic toxicity/oncogenicity study in rats	MW-adjusted q_1^* = 6.3 x 10^{-2} (mg/kg bw/day)$^{-1}$, based on the combined incidence of uterine adenoma/ adenocarcinoma.	N/A

[a] NOAELs from afidopyropen studies were adjusted using a molecular weight (MW) factor of 3.5.
The MW adjustment factor is calculated based on the molecular weight of both CPCA (86 g/mol) and afidopyropen (593.7 g/mol), and the number of CPCA molecules per molecule of afidopyropen (2 CPCA / molecule of afidopyropen). Using a NOAEL of 8 mg/kg bw/day, the MW adjustment factor is calculated as follows:
[(NOAEL × MW of CPCA)/ MW of afidopyropen] × 2 CPCA/mol
= [(8 × 86 g/mol)/593.7 g/mol] × 2 CPCA/mol
= 2.3 mg/kg bw/day of CPCA
Thus 8 mg/kg bw/day for afidopyropen would be equivalent to 2.3 mg/kg bw/day of CPCA and the MW adjustment factor to the afidopyropen toxicology reference values would be 3.5 fold.
The q_1^* value was calculated as follows: $(1.79 \times 10^{-2}) \times 3.5$
[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments.
[2] Since an oral NOAEL was selected, a dermal absorption factor (12%) was used in a route-to-route extrapolation.
[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in a route-to- route extrapolation.

Table 8 Mixer/Loader/Applicator Non-Cancer Exposure Estimates and MOE

Crop	Application Method	Total Unit Exposure (µg/kg ai handled)	Rate (kg a.i./ha)	Area Treated per Day (ha/day)	Exposure Estimate (mg a.i./kg bw/day)‡	MOE¶ (Target = 1000)
Sefina Insecticide						
Soybean	Open Mix/Load	7.65	0.01	400	0.0003825	20915
	Aerial	0.33009		400	1.65E-05	484716
	Open Mix/Load + Groundboom, Custom App[1]	12.378		360	0.00055701	14362
Potato	Open Mix/Load	7.65	0.05	400	0.0019125	4183
	Aerial	0.33009		400	8.25E-05	96943
	Open Mix/Load + Groundboom, Custom App[1]	12.378		360	0.00278505	2872

Crop	Application Method	Total Unit Exposure (µg/kg ai handled)	Rate (kg a.i./ha)	Area Treated per Day (ha/day)	Exposure Estimate (mg a.i./kg bw/day)‡	MOE¶ (Target = 1000)
Versys Insecticide						
Tuberous and Corm Vegetables (including potatoes)	Open Mix/Load	7.65	0.05	400	0.0019125	4183
	Aerial	0.33009		400	8.25225E-05	96943
	Open Mix/Load + Groundboom, Custom App[1]	12.378		360	0.00278505	2872
Leafy Vegetables	Open Mix/Load + Groundboom	12.378	0.05	26	0.000201143	39773
Brassica Head and Stem Vegetables	Open Mix/Load + Groundboom	12.378	0.05	26	0.000201143	39773
Fruiting Vegetables	Open Mix/Load + Groundboom	12.378	0.05	26	0.000201143	39773
Cucurbit Vegetables	Open Mix/Load + Groundboom	12.378	0.05	26	0.000201143	39773
Leaf Petiole Vegetables	Open Mix/Load + Groundboom	12.378	0.05	26	0.000201143	39773
Pome Fruit	Open Mix/Load + Airblast	469.05	0.01	20	0.001172615	6822
Stone Fruit	Open Mix/Load + Airblast	469.05	0.01	20	0.001172615	6822
Hazelnut Trees	Open Mix/Load + Airblast	469.05	0.01	20	0.001172615	6822
Greenhouse and Outdoor Ornamentals	Mechanically Pressurized Handgun	821.26	0.00005 kg a.i./L[2]	3800 L/day	0.00195049	4102
	Manually Pressurized Handwand	158.40	0.00005 kg a.i./L[2]	150 L/day	1.48504E-05	538706
	Backpack	715.60	0.0005 kg a.i./L[2]	150 L/day	6.70877E-05	119247

‡Exposure Estimate = ((Dermal Unit Exposure × Dermal Absorption Value + Inhalation Unit Exposure) × ATPD × Rate)/(80 kg bw × 1000 µg/mg)

¶Based on NOAEL = 8 mg/kg bw/day, target MOE = 1000

[1]Groundboom Farmer Application is expected to be covered by Groundboom Custom Application based on lower area treated per day

[2] Maximum Application Rate (kg a.i./L) = (Application Rate (0.5 L/ha)/dilution rate (1000 L/ha) × 100 g a.i./L (guarantee) × 0.001 kg/g

Table 9 Mixer/Loader/Applicator Cancer Exposure Estimates and Risk

Crop	Application Method	Total Unit Exposure (µg/kg ai handled)	Rate (kg a.i./ha)	Area Treated per Day (ha/day)	Absorbed Daily Dose‡ (mg/kg bw/day)	Lifetime Average Daily Dose† (mg/kg bw/day)	Cancer Risk¶
Sefina Insecticide							
Soybean	Open Mix/Load	7.65	0.01	318	0.000304088	1.28E-05	2.29E-07
	Aerial	0.33009		318	1.31E-05	5.53E-07	9.90E-09
	Open Mix/Load + Groundboom, Custom App[1]	12.378		240	0.00037134	1.56E-05	2.80E-07
Potato	Open Mix/Load	7.65	0.05	318	0.001520438	6.41E-05	1.15E-06

Crop	Application Method	Total Unit Exposure (µg/kg ai handled)	Rate (kg a.i./ha)	Area Treated per Day (ha/day)	Absorbed Daily Dose‡ (mg/kg bw/day)	Lifetime Average Daily Dose† (mg/kg bw/day)	Cancer Risk¶
	Aerial	0.33009		318	6.56E-05	2.77E-06	4.95E-08
	Open Mix/Load + Groundboom, Custom App[1]	12.378		240	0.0018567	7.83E-05	1.40E-06
Versys Insecticide							
Tuberous and Corm Vegetables (including potatoes)	Open Mix/Load	7.65	0.05	318	0.001520438	6.41E-05	1.15E-06
	Aerial	0.33009		318	6.56E-05	2.77E-06	4.95E-08
	Open Mix/Load + Groundboom, Custom App[1]	12.378		240	0.001857	7.83E-05	1.40E-06
Leafy Vegetable	Open Mix/Load + Groundboom	12.378	0.05	12	0.000092835	3.91E-06	7.00E-08
Brassica Head and Stem Vegetables	Open Mix/Load + Groundboom	12.378	0.05	12	0.000092835	3.91E-06	7.00E-08
Fruiting Vegetables	Open Mix/Load + Groundboom	12.378	0.05	12	0.000092835	3.91E-06	7.00E-08
Cucurbit Vegetables	Open Mix/Load + Groundboom	12.378	0.05	12	0.000092835	3.91E-06	7.00E-08
Leaf Petiole Vegetables	Open Mix/Load + Groundboom	12.378	0.05	12	0.000092835	3.91E-06	7.00E-08
Pome Fruit	Open Mix/Load + Airblast	469.05	0.01	7	0.000410415	1.73E-05	3.10E-07
Stone Fruit	Open Mix/Load + Airblast	469.05	0.01	7	0.000410415	1.73E-05	3.10E-07
Hazelnut Trees	Open Mix/Load + Airblast	469.05	0.01	7	0.000410415	1.73E-05	3.10E-07
Greenhouse and Outdoor Ornamentals	Mechanically Pressurized Handgun	821.26	0.00005 kg a.i./L[2]	3800 L/day	0.00195	8.22E-05	1.47E-06
	Manually Pressurized Handwand	158.40	0.00005 kg a.i./L[2]	150 L/day	1.49E-05	6.26E-07	1.12E-08
	Backpack	715.60	0.00005 kg a.i./L[2]	150 L/day	6.71E-05	2.83E-06	5.06E-08

‡Absorbed Daily Dose = ((Dermal Unit Exposure × Dermal Absorption Value + Inhalation Unit Exposure) × ATPD × Rate)/(80 kg bw x 1000 µg/mg)

†Lifetime Absorbed Dose = (Absorbed Daily Dose × Treatment Days/Year [30] × Working Duration [40 years])/(365days/year × Life Expectancy [78 years])

¶Based on a cancer endpoint of 1.79×10^{-2} $(mg/kg\ bw/day)^{-1}$

[1]Groundboom Farmer Application is expected to be covered by Groundboom Custom Application based on lower area treated per day

[2] Maximum Application Rate (kg a.i./L) = (Application Rate (0.5 L/ha)/dilution rate (1000 L/ha) × 100 g a.i./L (guarantee) × 0.001 kg/g

Table 10 Postapplication Non-Cancer Exposure Estimates and Margins of Exposure (MOE)

Crop	Peak DFR ($\mu g/cm^2$)*	Activity	Transfer Coefficient (cm^2/hr)	Exposure (mg a.i./kg bw/day) ‡	MOE¶ (Target = 1000)	REI◊ (hours)
Sefina Insecticide						
Soybeans	0.0370	Scouting	1100	0.000488	16399	12
Potato	0.2271†	Irrigation	1750	0.0048	1678	12
Versys Insecticide						
Tuberous & Corm Vegetables (including potatoes)	0.2271†	Irrigation	1750	0.0048	1678	12
Leafy Vegetables	0.2271	Irrigation	1750	0.0048	1678	12
Bok Choy	0.0654φ	Weeding	4400	0.0035	2317	12
Brassica Head & Stem Vegetables	0.0654φ	Hand Harvest	5150	0.0040	1979	12
Fruiting Vegetables	0.0654φ	Irrigation	1750	0.0014	5825	12
Cucurbit Vegetables	0.0750φ	Irrigation	1750	0.0016	5079	12
Leaf Petiole Vegetables	0.2271	Irrigation	1750	0.0048	1678	12
Stone Fruit	0.0310φ	Thinning	3000	0.0011	7168	12
Pome Fruit	0.0310φ	Thinning	3000	0.0011	7168	12
Hazelnut Trees	0.0370	Scouting	580	0.0003	31101	12
Greenhouse Ornamentals *potted flowers*	0.6057	All activities	230	0.0017	4786	12
Greenhouse Ornamentals *cut flowers* (0.05 kg a.i./ha – 1 app. max)[1]	0.125	Hand Harvest/ Disbudding/ Pruning	4000	0.0060	1333	12
Greenhouse Ornamentals *cut flowers* (0.035 kg a.i./ha – 2 app. max)[1]	0.1618	Hand Harvest/ Disbudding/ Pruning	4000	0.0078	1030	12
Greenhouse Ornamentals *cut flowers* (0.01 kg a.i./ha – 35 app.)[1]	0.1658	Hand Harvest/ Disbudding/ Pruning	4000	0.0080	1005	12
Outdoor Ornamentals	0.2389	Irrigation	1750	0.0050	1594	12

†Peak DFR calculated using 4 applications at maximum application rate (0.05 kg a.i./ha), however, the maximum seasonal application rate is 0.125 kg a.i./ha (not expected to underestimate exposure)

* Calculated using the default 25% deposition on the day of application and 10% dissipation per day (2.3% dissipation per day for greenhouse ornamentals)

φ Calculated using chemical-specific DFR data

‡ Exposure = (Peak DFR [$\mu g/cm^2$] × TC [cm^2/hr] × 8 hours × 12% dermal absorption)/(80 kg bw × 1000 µg/mg)

¶ Based on a NOAEL of 8 mg/kg bw/day, target MOE = 1000 (see Table 3)

◊ Minimum REI is 12 hours to allow residues to dry

[1]Based on the specific use pattern for greenhouse cut flowers, postapplication exposure and risk was calculated for each application rate based on the maximum yearly amount of product allowable.

Table 11 Postapplication Cancer Exposure Estimates and Risk

Crop	Activity Scenario	Absorbed Daily Dose‡ (mg/kg bw/day	Activity Days Per Year	Working Duration	Life Expectancy	Lifetime Average Daily Dose† (mg/kg bw/day)	Cancer Risk¶
Sefina Insecticide							
Soybeans	Scouting	0.000488	30	40	78	2.05622E-05	3.68E-07
Potatoes	Irrigation	0.0048	30	40	78	0.000200981	3.60E-06
Versys Insecticide							
Tuberous & Corm Vegetables (including potatoes)	Irrigation	0.0048	30	40	78	0.000200981	3.60E-06
Leafy Vegetables	Irrigation	0.0048	30	40	78	0.000200981	3.60E-06
Leafy Vegetables - Bok Choy	Weeding	0.0035	30	40	78	0.000145548	2.60E-06
Brassica Head & Stem Vegetables	Hand Harvest	0.0040	30	40	78	0.000170357	3.05E-06
Fruiting Vegetables	Irrigation	0.0014	30	40	78	5.78883E-05	1.04E-06
Cucurbits	Irrigation	0.0016	30	40	78	6.63857E-05	1.19E-06
Leaf Petiole Vegetables	Irrigation	0.0048	30	40	78	0.000200981	3.60E-06
Stone Fruit	Thinning	0.0011	30	40	78	4.7039E-05	8.42E-07
Pome Fruit	Thinning	0.0011	30	40	78	4.7039E-05	8.42E-07
Hazelnut	Scouting	0.0003	30	40	78	1.08419E-05	1.94E-07
GH Ornamentals *potted flowers*	All activities except irrigation	0.0017	50	40	78	0.000117433	2.10E-06
GH Ornamentals *cut flowers* (0.05 kg a.i./ha - 1 app. max)	Hand Harvest/Disbudding/Pruning	0.0060	50	40	78	0.000421496	7.54E-06
GH Ornamentals *cut flowers* (0.035 kg a.i./ha - 2 app. max)	Hand Harvest/Disbudding/Pruning	0.0078	50	40	78	0.000545747	9.77E-06
GH Ornamentals *cut flowers* (0.01 kg a.i./ha - 35 app. max)	Hand Harvest/Disbudding/Pruning	0.0080	50	40	78	0.000558971	1.00E-05
Outdoor Ornamentals	Irrigation	0.0050	30	40	78	0.000211499	3.78E-06

‡Absorbed Daily Dose = ((Dermal Unit Exposure × Dermal Absorption Value + Inhalation Unit Exposure) × ATPD × Rate)/(80 kg bw × 1000 µg/mg)
†Lifetime Absorbed Dose = (Absorbed Daily Dose × Treatment Days/Year × Working Duration [40 years])/(365days/year × Life Expectancy [78 years])
¶Based on a cancer endpoint of 1.79×10^{-2} $(mg/kg\ bw/day)^{-1}$

Table 12 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN PLANTS – Tomato, Cabbage, Soybean	**PMRA #2627930, 2627933, 2627934, 2627936, 2627938, 2627939**

All plants were located indoors in a greenhouse with climatic control, with the exception of one of the cabbage study where plants were maintained outside in a netted polytunnel. Afidopyropen was applied to tomato, cabbage, and soybean plants using a 10% water dispersible granular product with different radiolabels (NCA-^{14}C, pyranone-4-^{14}C, and CPCA-^{14}C). Treatments involved one at-transplant soil application followed by late-season foliar applications, or two foliar applications. Storage stability of the samples was demonstrated by re-analysis of samples and comparison of the chromatographic profiles. As needed, post-extraction solids (PES) were hydrolyzed with acid and base solutions or sequentially hydrolyzed with buffered enzyme solutions.

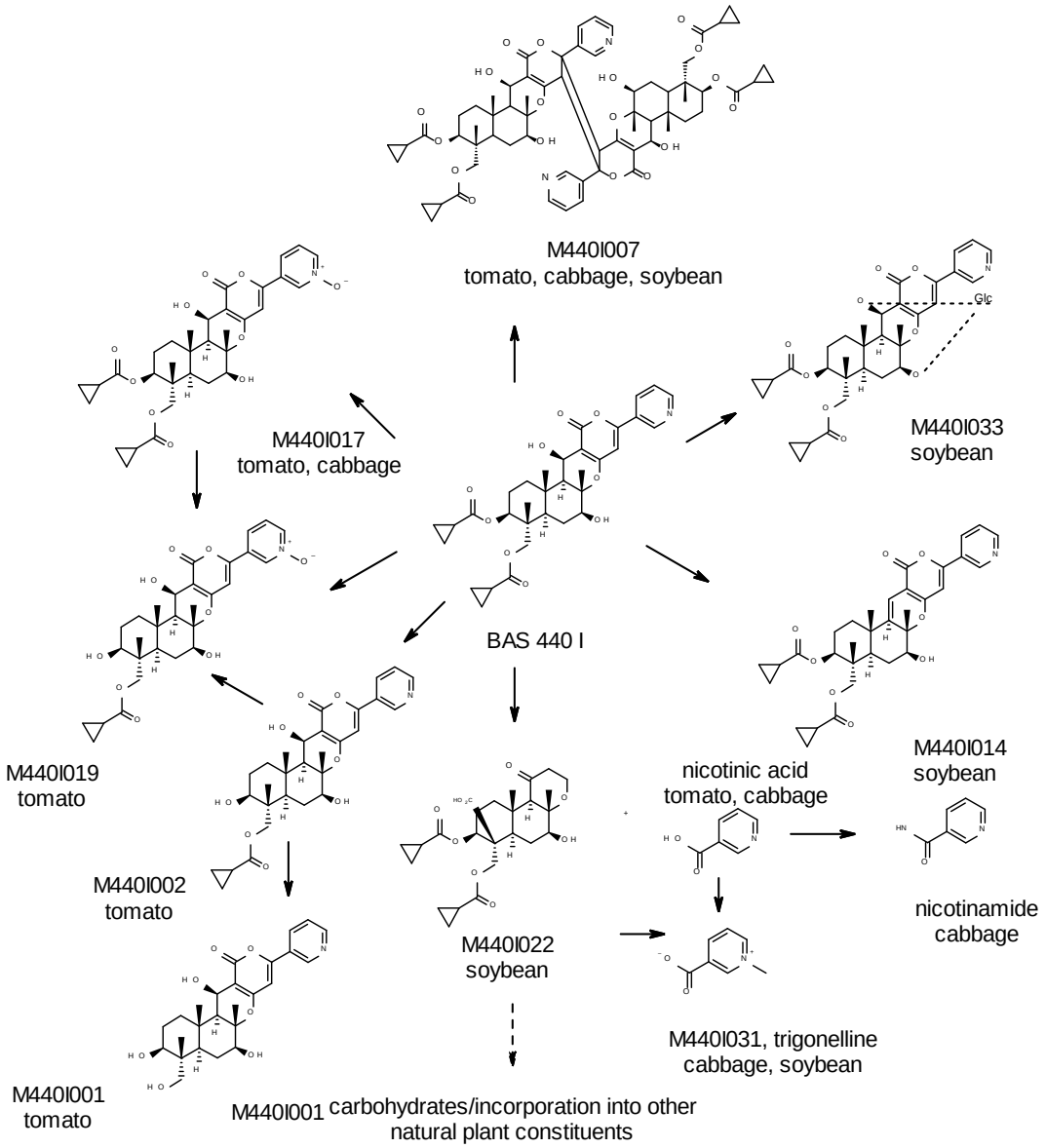
Crop	**Radiolabels**	**Rate (g a.i./ha/season)**	**PHI (days)**
Tomato	[NCA]-^{14}C	707	7; 14
	[Pyranone-4]-^{14}C	125	1
Cabbage	[NCA]-^{14}C	1140	7; 14
	[Pyranone-4]-^{14}C	125	1
Soybean	[NCA]-^{14}C	125	14
	[Pyranone-4]-^{14}C	125	14
	[CPCA]-^{14}C	125	14

Radiolabels		**[NCA]-^{14}C**	**[Pyranone-4]-^{14}C**	**[CPCA]-^{14}C**
Crop	**Fraction**	**Overall TRRs (ppm)**		
Tomato	Leaves	4.3 – PHI=14 d	2.3	-
	Fruits	0.34 – PHI=7 d 0.30 – PHI=14 d	0.05	-
Cabbage	Whole	1.5 – PHI=7 d 1.1 – PHI=14 d	--	-
	Outer leaves	-	1.7	-
	Inner leaves	-	0.4	-
Soybean	Leaves	16.8	20.1	5.0
	Seeds	0.4	0.2	0.01
	Hulls	1.5	1.6	2.6
	Rest of plant	0.4	0.3	0.2 (green pods)

Metabolites Identified		**Major Metabolites (>10% of the TRRs)**			**Minor Metabolites (<10% of the TRRs)**		
Radiolabel Position		**[NCA-^{14}C]**	**[Pyranone-4-^{14}C]**	**[CPCA-^{14}C]**	**[NCA-^{14}C]**	**[Pyranone-4-^{14}C]**	**[CPCA-^{14}C]**
Tomato	Leaves	Afidopyropen M440I007	Afidopyropen	-	-	M440I001, M440I019, M440I002, M440I017, M440I020	-
	Fruits	Afidopyropen M440I007: PHI=7d Afidopyropen: PHI=14d	Afidopyropen M440I007	-	M440I045	M440I020	-
Whole cabbage	-	Afidopyropen M440I007 (PHI=7d); None (PHI=14d)	Afidopyropen M440I007 (Outer leaves and inner leaves); Sugars (inner leaves)	-	Nicotinamide, Nicotinic acid (PHI = 7d, 14d); Afidopyropen M440I007, (PHI = 14d)	M440I017, M440I020 (Outer leaves and inner leaves); Sugars (outer leaves)	-
Soybean	Leaves	Afidopyropen M440I007	Afidopyropen M440I007	Afidopyropen	Trigonelline, M440I033, M440I014	M440I033, sugars, M440I022	M440I033, M440I014, M440I007
	Seeds	Trigonelline	Sugars	M440I007	-	Afidopyropen, M440I007	-

	Hulls	Afidopyropen M440I007	Afidopyropen M440I007	Afidopyropen M440I007	-	Sugars	M440I014
	Rest of plant	M440I007	Afidopyropen M440I007 Sugars	Afidopyropen M440I007 (green pods)	Afidopyropen	-	-

Proposed Metabolic Scheme in Plants



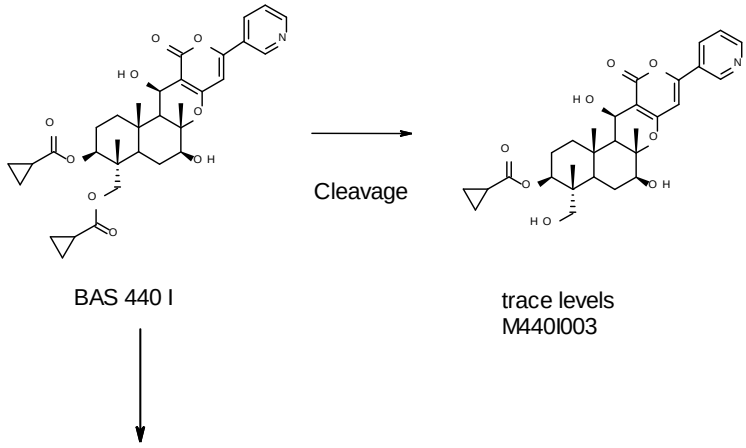
CONFINED ACCUMULATION IN ROTATIONAL CROPS	**PMRA #2627963, 2627964, 2627965**

The metabolism of ^{14}C-Afidopyropen in confined rotational crops was investigated in three separate studies following spray application of a radiolabelled test item to bare sandy loam soil. Three different radiolabels were used for these studies, which included [NCA-^{14}C]- and [Pyranone-4-^{14}C] positions along with the carbonyl labelled on both cyclopropane carboxylic acid groups [CPCA-^{14}C]. For all studies, aging of soil and cultivation of the crops were conducted in a glass-roofed vegetation hall, in phytotrons. Most of the radioactivity in immature/mature spinach and wheat (forage, hay, straw and grain) was characterized with a large fraction remaining as unextractable. Sequential solubilization procedures of the PES in wheat matrices after solvent extraction (Pyranone-^{14}C) was achieved with β-glucosidase and hesperidinase, macerozyme and cellulase, tyrosinase and laccase and amylase and amyloglucosidase, pepsin and pancreatin in order to fully characterize the residues. Due to low levels of radioactivity, solvent

extraction and HPLC were not performed on radish tops and roots.

Radiolabel Position	[Pyranone-^{14}C]	[NCA-^{14}C]	[NCA-^{14}C]	[CPCA-^{14}C]
Study	1	1	2	3
Rate (g a.i./ha)	125 for spinach, wheat and radish	125 for spinach, wheat and radish	20 for winter wheat	20 for wheat; 125 for spinach and radish
PBI (days)	31, 122, 364	29, 119, 365	30, 61, 90	31, 90: spinach, radish 30, 61: wheat
Major metabolites	None	None	None	None
Minor metabolites	None	M440I003 (Wheat straw at 31d PBI)	None	None

Proposed Metabolic Scheme of ^{14}C-BAS 440 I in Rotational Crops



NATURE OF THE RESIDUE IN LAYING HEN	PMRA #2627941

Ten laying hens were dosed orally once daily via gelatin capsule with [CPCA-^{14}C] at 12 ppm for 14 consecutive days. Samples of excreta were collected daily, and eggs twice daily. The hens were sacrificed approximately 10 hours after administration of the final dose. Edible tissues (liver, kidney, composite fat and muscle), GI tract and contents, excreta and cage wash were collected post-mortem. Approximately 98% of the total dose administered was recovered, of which most was in the excreta. Overall TRRs in whole eggs reached a maximum of 0.275 ppm by day 7 after dosing, and were on average 0.225 ppm in the pooled sample (day 10-13).

Matrices	[CPCA-^{14}C]-Afidopyropen	
	Overall TRRs (ppm)	% of Administered Dose
Excreta	-	93.4
Cage Wash	-	1.9
Pooled Egg Yolk (Day 10-13)	0.368	0.2
Pooled Egg White (Day 10-13)	0.138	0.4
Partly Formed Eggs	-	0.1
Liver	0.409	0.1
Kidney	-	0.1
Fat	0.101	< 0.1
Muscle	0.046	< 0.1
GI Tract & Contents	-	1.5

Total Administered Dose	-	97.9
Metabolites identified	**Major Metabolites (> 10% of the TRRs)**	**Minor Metabolites (< 10% of the TRRs)**
Liver	Afidopyropen; M440I017	M440I061 (CPCA)
Muscle	Afidopyropen; M440I060 (CPCA-carnitine)	None
Fat	Afidopyropen	None
Egg white	Afidopyropen	M440I017
Egg yolk	Afidopyropen	None
Excreta	Afidopyropen; M440I017	None

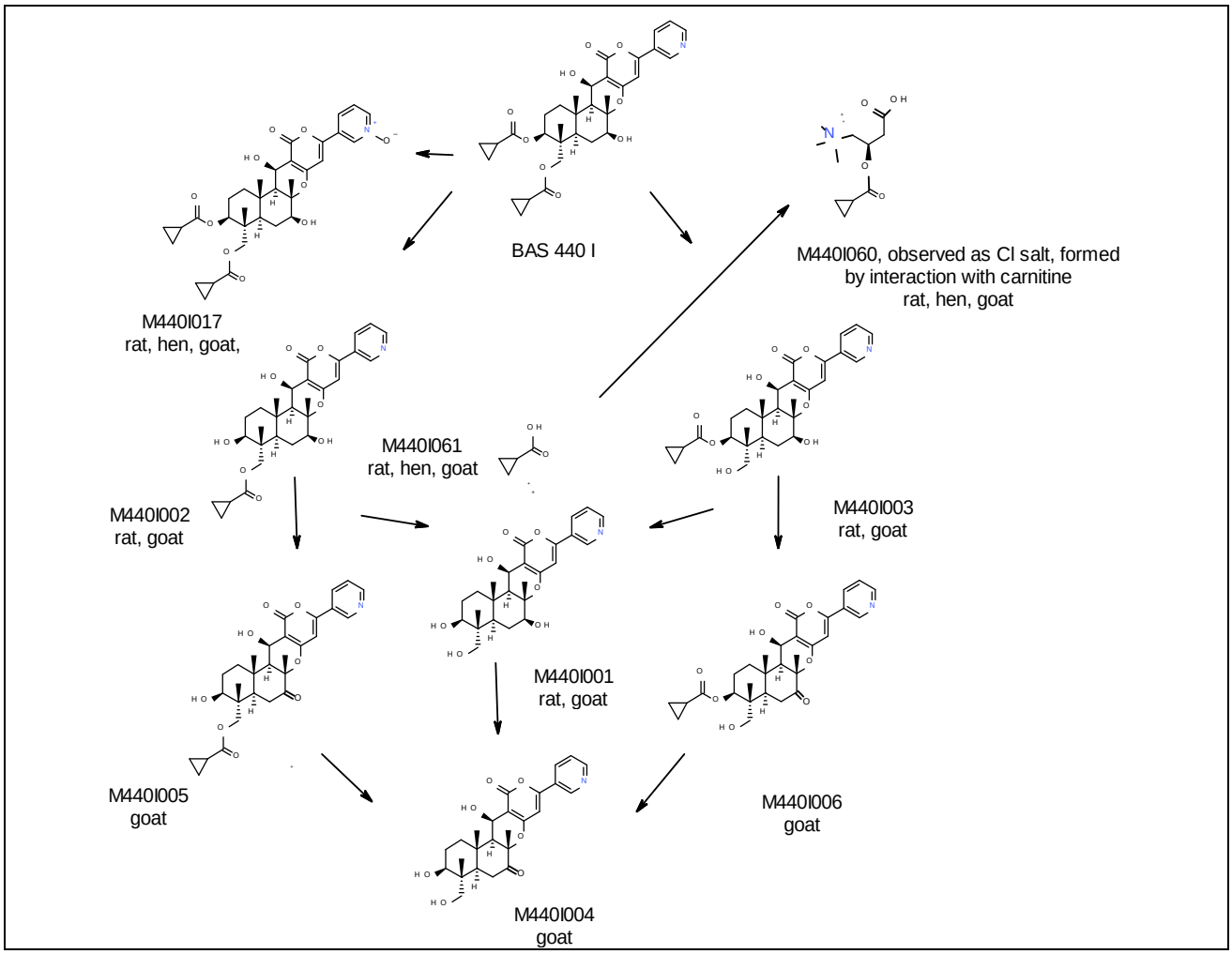
NATURE OF THE RESIDUE IN LACTATING GOAT **PMRA # 2627940, 2627942**

A lactating goat was dosed orally once daily via gelatin capsule with [pyranone-4-^{14}C] at an average of 17 ppm, for 7 consecutive days, and another lactating goat was dosed with [CPCA-^{14}C; 2.70 MBq/mg] at 12 ppm feed for 9 consecutive days. Samples of excreta were collected daily and milk twice daily. The goats were sacrificed 8–10 hours after administration of the final dose. Edible tissues (composite fat and muscle, liver, and kidneys), gastrointestinal tract and contents, excreta, and bile were collected post-mortem. The overall TRRs in whole milk reached a plateau of 0.006 ppm on day 5–6 after dosing for the [pyranone-4-^{14}C]-, and 0.33 ppm at day 7–8 after dosing for the [CPCA-^{14}C]-afidopyropen. Samples were analyzed within 6 months of sampling.

Matrices	**[Pyranone-4-^{14}C]-Afidopyropen**		**[CPCA-^{14}C]-Afidopyropen**	
	Overall TRRs (ppm)	**% of Administered Dose**	**Overall TRRs (ppm)**	**% of Administered Dose**
Urine	0.292	2.5	-	13.2
Feces	5.012	66.5	-	49.9
Cage wash	-	1.4	-	2.3
Blood and plasma	-	-	-	<0.1
Bile	3.223	-	-	0.1
Whole Milk	0.005	< 0.1	0.237	1.9
Cream	-	-	2.007	-
Kidneys	0.037	< 0.1	0.480	0.1
Liver	0.193	0.1	0.207	0.2
GI tract and contents	-	20.7	-	10.1
Composite muscle	0.008	-	0.311	0.5
Composite fat	0.005	-	0.009	<0.1
Total administered dose	-	91	-	78

Metabolites identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel position	**[Pyranone-4-^{14}C]**	**[CPCA-^{14}C]**	**[Pyranone-4-^{14}C]**	**[CPCA-^{14}C]**
Whole Milk	M440I001; M440I005	None	Afidopyropen; M440I003; M440I006	None
Cream	-	None	-	M440I061 (CPCA)
Liver	Afidopyropen; M440I001	Afidopyropen; M440I003; M440I061 (CPCA)	M440I002; M440I003; M440I004	M440I060 (CPCA-carnitine); M440I002 M440I017
Kidney	Afidopyropen; M440I001; M440I003	M440I061(CPCA)	None	M440I060 (CPCA-carnitine); M440I003
Composite Muscle	Afidopyropen; M440I001; M440I003	M440I060 (CPCA-carnitine)	M440I006	M440I061(CPCA); M440I003
Composite Fat	Afidopyropen	Not analyzed as TRRs < 0.01 ppm	M440I001; M440I003; M440I006	Not analyzed as TRRs < 0.01 ppm

Proposed Metabolic Scheme in Livestock



Storage Stability in Plant Matrices				**PMRA #2715858**
This study will cover the maximum storage intervals observed in the relevant crop field trials (8–16 months). Afidopyropen residues were demonstrated to be stable in the five crop commodity categories (high-water, high-starch, high-protein, high-oil, and high-acid) for 24 months at -20ºC.				
Tested Matrices	**Analytes**	**Tested Intervals (months)**	**ºC**	**Category**
Barley grain	Afidopyropen	0, 1, 3, 4, 6, 9, 12, 16, 18, and 24	-20	High-starch
Lettuce				High-water
Navy bean				High-protein
Orange				High-acid
Soybean seed				High-oil
Soybean oil				High-oil
Soybean hay				Other

Storage Stability in Animal Matrices		**PMRA #2627929**
Matrices	**Storage interval for matrices in animal feeding study (months)**	**Interval of demonstrated freezer storage stability data (months)**
Whole milk	2.3	3.3
Liver, kidney	4.0	3.2
Muscle	4.0	3.0

Fat	4.4	2.6-2.8

The storage stability data showed no dissipation of afidopyropen in milk and tissues over the tested intervals of 0, 1 and 3 months. No changes having any significant impact on the measured results would be expected during the additional storage time incurred (0.8 to 1.6 months) during the feeding study.

Crop Field Trials with Afidopyropen

Crop field trials were conducted in North America (2013–2015) with a variety of crops using either a 50 g a.i./L or 100 g a.i./L dispersible concentrate (DC). All trials were conducted at ±25% of GAP. Adjuvants (NIS, ADW, MSO, OSS, COC) were used for all foliar treatment trials. Foliar applications were made using ground equipment with concentrated and dilute spray volumes for pome fruits, stone fruits, citrus fruits and tree nuts. The Canada/US field trial results were generated using an adequate data collection method. Adequate storage stability data are available on diverse crop types to support the storage intervals of the crop field trials. The number and geographic distribution of trials were generally, in accordance with OCSPP harmonized test guideline 860.1500 and Health Canada's DIR2010-05. Independence of trials was assessed for each representative crop from the various crop groups. Residues of afidopyropen generally decreased with increasing PHIs.

Tuberous and corm vegetables: CSG1C — **PMRA #2627949**

GAP: 4 applications (ground or aerial) of 10 to 50 g a.i./ha/application for a total of 125 g a.i./ha/season with RTI of 7 days and a 7-day PHI.

Crop	Total Application Rate [g a.i./ha]	PHI (days)	n	Afidopyropen Residues (ppm)					
				Max.	LAFT	HAFT	Median	Mean	SD
Potato, tuber	119–126	6–7	19	< 0.010	< 0.010	< 0.010	< 0.010	< 0.010	N/A

Leafy greens: CSG4-13A — **PMRA #2627944**

GAP: 4 applications (ground) of 10 to 50 g a.i./ha/application for a total of 125 g a.i./ha/season with RTI of 7 days and a 0-day PHI.

Head lettuce, with wrapper leaves	117–125	0	8	0.287	0.014	0.278	0.164	0.149	0.079
Head lettuce, without wrapper leaves	117–125	0	8	0.275	< 0.010	0.272	0.020	0.051	0.090
Leaf lettuce	117–124	0	8	0.969	0.042	0.944	0.496	0.482	0.312
Spinach	117–124	0	8	1.168	0.042	1.074	0.629	0.651	0.337

***Brassica* leafy greens: CSG4-13B** — **PMRA #2627946**

GAP: 4 applications (ground) of 10 to 50 g a.i./ha/application for a total of 125 g a.i./ha/season with RTI of 7 days and a 0-day PHI.

Mustard greens	117–124	0	8	3.137	< 0.010	2.733	1.196	1.315	0.825

***Brassica* head and stem vegetables: CG5-13** — **PMRA #2627946**

GAP: 4 applications (ground) of 10 to 50 g a.i./ha/application for a total of 125 g a.i./ha/season with RTI of 7 days and a 0-day PHI.

Broccoli	119–121	0	10	0.235	0.043	0.205	0.104	0.112	0.054
Cabbage, with wrapper leaves	117–124	0	10	0.294	< 0.010	0.276	0.042	0.091	0.101
Cabbage, without wrapper leaves	117–124	0	10	0.028	< 0.010	0.024	0.010	0.013	0.006

Dry Soybeans — **PMRA #2627950**

GAP: 2 applications (ground and aerial) of 10 g a.i./ha/application for a total of 20 g a.i./ha/season with RTI of 7 days and a 7-day PHI.

Soybean, forage	19–21	6–8	20	0.075	0.017	0.070	0.034	0.039	0.018
Soybean, hay		6–8	20	0.229	0.045	0.206	0.117	0.121	0.053
Soybean, seed	18–21	6–8	20	< 0.010	< 0.010	< 0.010	< 0.010	< 0.010	N/A
Fruting vegetables: CG8-09								**PMRA # 2627943**	
GAP: 4 applications (ground) of 10 to 50 g a.i./ha/application for a total of 125 g a.i./ha/season with RTI of 7 days and a 0-day PHI.									
Bell pepper	120–130	0	7	0.057	< 0.010	0.046	0.022	0.023	0.012
Non-bell pepper	120–122	0	3	0.061	0.046	0.059	0.055	0.053	0.007
Tomato	116–129	0	19	0.103	< 0.010	0.097	0.019	0.029	0.025
Cucurbit vegetables: CG9								**PMRA #2627945**	
GAP: 4 applications (ground) of 10 to 50 g a.i./ha/application for a total of 125 g a.i./ha/season with RTI of 7 days and a 0-day PHI.									
Cucumber	118–122	0	9	0.443	0.0530	0.406	0.112	0.162	0.120
Cantaloupe	117–123	0	8	0.0255	< 0.010	0.0231	0.018	0.017	0.005
Squash, summer	119–123	0	5	0.0383	< 0.010	0.0334	0.018	0.020	0.010
Squash, winter	119–127	0	5	0.0375	< 0.010	0.0367	0.011	0.018	0.012
Pome fruits: CG11-09								**PMRA #2627948**	
GAP: 4 applications (ground) of 10 g a.i./ha/application for a total of 40 g a.i./ha/season with RTI of 7 days and a 7-day PHI.									
Apple	49–51 (Conc.)	6–7	14	0.011	< 0.010	0.011	0.010	0.010	0.001
	49–51 (Dilute)	6–7	14	< 0.010	< 0.010	< 0.010	< 0.010	< 0.010	N/A
Pear	48–51 (Conc.)	7	8	0.015	< 0.010	0.014	0.010	0.011	0.001
	48–51 (Dilute)	7	8	0.013	< 0.010	0.012	0.010	0.010	0.001
Stone fruits: CG12-09							**PMRA #2627947**		
GAP: 2 applications (ground) of 10 g a.i./ha/application for a total of 20 g a.i./ha/season with RTI of 7 days and a 7-day PHI.									
Cherry	19–21 (Conc.)	7	8	0.017	< 0.010	0.014	0.010	0.011	0.001
	19–21 (Dilute)	7	8	0.021	< 0.010	0.021	0.010	0.012	0.004
Peach	20–21 (Conc.)	7	13	< 0.010	< 0.010	< 0.010	< 0.010	< 0.010	N/A
	20–21 (Dilute)	7	13	0.012	< 0.010	0.011	0.010	0.010	0.001
Plum	20–21 (Conc.)	7	10	< 0.010	< 0.010	< 0.010	< 0.010	< 0.010	N/A
	20–21 (Dilute)	7	10	< 0.010	< 0.010	< 0.010	< 0.010	< 0.010	N/A
Tree nuts: CG14-11						**PMRA #2627955**			
GAP: 2 applications (ground and aerial) of 10 g a.i./ha/application for a total of 20 g a.i./ha/season with RTI of 7 days and a 7-day PHI.									
Almond nutmeat	20 (Conc.)	7	5	< 0.010	< 0.010	< 0.010	< 0.010	< 0.010	N/A
	20 (Dilute)	7	5	< 0.010	< 0.010	< 0.010	< 0.010	< 0.010	N/A
Almond hulls	20 (Conc.)	7	5	0.060	0.019	0.058	0.025	0.030	0.016
	20 (Dilute)	7	5	0.057	0.016	0.056	0.039	0.036	0.015
Pecan nutmeat	20 (Conc.)	6–8	5	< 0.010	< 0.010	< 0.010	< 0.010	< 0.010	N/A
	20 (Dilute)	6–8	5	< 0.010	< 0.010	< 0.010	< 0.010	0.010	N/A
Pistachio nutmeat	20 (Conc.)	7	3	< 0.010	< 0.010	< 0.010	< 0.010	< 0.010	N/A
	20 (Dilute)	7	3	< 0.010	< 0.010	< 0.010	< 0.010	< 0.010	N/A
Citrus fruits: CG10 Revised							**PMRA #2627113**		
GAP: Foliar applications (ground and aerial) of 10 to 50 g a.i./ha/application for a total of 125 g a.i./ha/season with RTI of 7 days and a 0-day PHI.									

Crop	Total Application Rate [g ai/ha]	PHI (days)	n	Afidopyropen Residues (ppm)					
				Max.	Min.	HAFT	Median	Mean	SD
Grapefruit	122–128 (Conc.)	0	6	0.062	< 0.010	0.062	0.025	0.031	0.022
	122–128 (Dilute)	0	6	0.041	< 0.010	0.041	0.026	0.025	0.012
Lemon	123–128 (Conc.)	0	8	0.070	< 0.010	0.070	0.025	0.033	0.025
	123–128 (Dilute)	0	8	0.055	< 0.010	0.055	0.038	0.032	0.016
Orange	122–128 (Conc.)	0	12	0.069	< 0.010	0.069	0.049	0.045	0.021
	122–128 (Dilute)	0	12	0.072	< 0.010	0.072	0.043	0.044	0.020
Cottonseeds: CSG20C Revised							**PMRA #2627112**		
GAP: Foliar applications (ground and aerial) of 10 to 50 g a.i./ha/application for a total of 125 g a.i./ha/season with RTI of 7 days and a 7-day PHI.									
Crop	**Total Application Rate [g ai/ha]**	**PHI (days)**	**n**	**Afidopyropen Residues (ppm)**					
				Max.	**LAFT**	**HAFT**	**Median**	**Mean**	**SD**
Cottonseed	119–124	6–8	12	0.061	< 0.010	0.059	0.010	0.018	0.015
Cotton, gin byproducts	120–121	6–7	3	0.650	0.460	0.600	0.540	0.530	0.073
Leaf petioles vegetables: CSG22B							**PMRA #2627944**		
GAP: 4 applications (ground) of 10 to 50 g a.i./ha/application for a total of 125 g a.i./ha/season with RTI of 7 days and a 0-day PHI.									
Celery	117–125	0	7	1.894	0.027	1.275	0.283	0.434	0.446
Residue Data in Rotational Crops							**PMRA #2627966**		
A request to waive the field accumulation studies was provided since no major metabolites were identified in the confined accumulation in rotational crops studies for all matrices and at all plant-back intervals. Therefore, a 30-day plant-back interval is appropriate for non-labelled crops.									
Processed Food and Feed									
Processing studies were conducted, at 5 to 6-fold GAP, with raw agricultural commodities treated with afidopyropen during the magnitude of the residue trials, while simulating commercial practices as closely as possible. Concurrent recoveries were conducted to validate the analytical method for afidopyropen and the metabolite M440I007 in the various processed commodities. Results of the metabolite M440I007 are not presented herein as it is not part of the residue definition for enforcement and risk assessment purposes. The proposed MRLs are adequate to cover residues of afidopyropen in the processed commodities, with the exception of citrus oil and sundried tomatoes, which will require separate MRLs.									

Raw Agricultural Commodity	Processed Commodity	Processing Factor	PMRA #
Potatoes	Chips, granules/flakes, starch, crisps	< LOQ in RAC; processed fractions not further analyzed	2627958
Tomatoes	Juice	< 0.1	2627959
	Paste	0.6	
	Purée	0.2	
	Sundried tomatoes	4.4	
Soybeans	Crude oil; flour; hulls; meal; miso; pollard; soy milk; soy sauce; meal; tofu	< LOQ in RAC; processed fractions not further analyzed	2627962
	Aspirated grain fractions	> 12.5	
Oranges	Juice	< 0.1	2627114
	Peel	1.9	
	Oil	4.6	

	Marmalade	< 0.1	
Apples	Sauce, fruit syrup, juice, and dried apples	< 0.5	2627961
Plums	Purée, dried prunes, and juice	1.0	2627960
Cottonseed	Refined oil	0.14	2627110

LIVESTOCK FEEDING – Dairy cattle **PMRA #2627957**

Lactating Holstein dairy cows were administered encapsulated afidopyropen via a balling gun at dose levels of 1.54 ppm, 4.61 ppm and 15.34 ppm in the feeds for 29 consecutive days. Animals were sacrificed approximately 18 to 23 hours after the last dose. A depuration study was conducted using the 15.34 ppm dosing group and selected animals were sacrificed 3, 7, and 14 days after withdrawal of the dose. Residues of afidopyropen were less than LOQ in milk and tissues throughout the depuration study, with the exception of liver where residues of afidopyropen declined to < LOQ by day 7.

Commodity	Feeding Level (ppm)	Highest Residues of Afidopyropen (ppm)	MBD (ppm) Beef/Dairy	Anticipated Residues at MBD (ppm)**
Whole milk*	1.54	Not analyzed	0.00003/0.00006	< 0.001
Fat		< 0.01		< 0.01
Liver		0.019		< 0.01
Kidney		< 0.01		< 0.01
Muscle		< 0.01		< 0.01

*At 4.61 and 15.34 ppm feeding levels, residues of afidopyropen were < LOQ (0.001) ppm.
**Given the low dietary burden, anticipated residues are reported as less than LOQ in tissues and milk.

LIVESTOCK FEEDING – Laying hens **PMRA #2627956**

A request to waive the feeding study in poultry was provided based on the low dietary burden. Therefore, the hen metabolism study was used to estimate the anticipated residues in the relevant poultry matrices.

Commodity	Feeding Level (ppm)	Afidopyropen TRRs (ppm)	MBD (ppm)	Anticipated Residue at MBD (ppm)*
Egg Yolk	12	0.355	0.0001	< 0.01
Egg White		0.125		< 0.01
Fat		0.097		< 0.01
Liver		0.241		< 0.01
Muscle		0.021		< 0.01

*Given the low dietary burden, anticipated residues are reported as less than LOQ in eggs and tissues.

Table 13 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

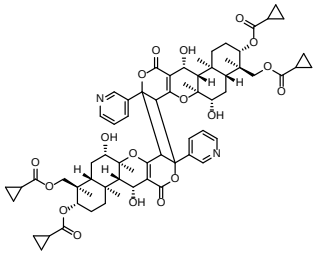
PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT AND RISK ASSESSMENT • **Primary crops (tomato, cabbage, soybean)** • **Rotational crops (spinach, wheat, radish)**	Afidopyropen
METABOLIC PROFILE IN DIVERSE CROPS	The profile in diverse crops is similar.
ANIMAL STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT AND RISK ASSESSMENT • **Ruminant and Poultry**	Afidopyropen
METABOLIC PROFILE IN ANIMALS (goat, hen, rat)	The profile in animals is similar.
FAT SOLUBLE RESIDUE	Yes
RESIDUE DEFINITION FOR RISK ASSESSMENT • **Drinking water**	Afidopyropen + transformation products (identified and unidentified)
	CPCA

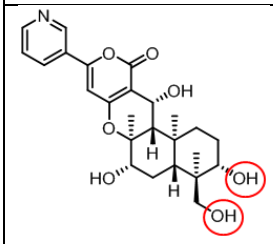
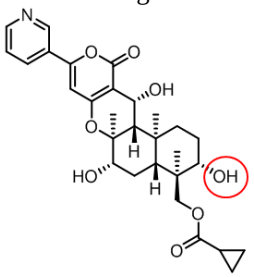
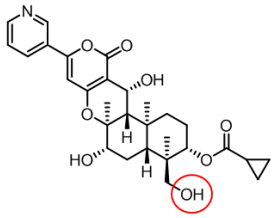
DIETARY RISK FROM FOOD AND WATER			
AFIDOPYROPEN			
Intermediate chronic non-cancer dietary exposure analysis **ADI = 0.03 mg/kg bw/day for general population** **ADI = 0.008 mg/kg bw/day for females 13-49** **Estimated chronic drinking water concentration = 0.0028 ppm**	**POPULATION**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Water**
	All infants < 1 year	0.6	1.3
	Children 1–2 years	1.4	1.6
	Children 3–5 years	1.0	1.2
	Children 6–12 years	0.6	0.8
	Males 13–19 years	0.4	0.5
	Males 20–49 years	0.5	0.7
	Adults 50–99 years	0.6	0.8
	Females 13–49 years	2.0	2.7
Intermediate acute dietary exposure analysis, 95th percentile **ARfD = 0.008 mg/kg bw** **Estimated acute drinking water concentration = 0.0028 ppm**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Alone	**Food and Water**
	Females 13–49 years	20	21
Refined cancer dietary exposure analysis **q_1^* = 0.0179 (mg/kg bw/day)$^{-1}$** **Estimated chronic drinking water concentration = 0.00012-0.0028 ppm**	**Total population**	9×10^{-7}	9×10^{-7} to 2×10^{-6}
CPCA			
Intermediate chronic non-cancer dietary exposure analysis **ADI = 0.008 mg/kg bw/day for general population** **ADI = 0.002 mg/kg bw/day for females 13-49** **Estimated chronic drinking water concentration = 0.00099 ppm**	**POPULATION SUBGROUPS**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Drinking Water	
	All Infants	0.9	
	Children 1–2 years old	0.3	
	Children 3–-5 years old	0.3	
	Children 6–12 years old	0.2	
	Male 13–19 years old	0.2	
	Male 20+ years old	0.2	
	Adults 50–99 years old	0.2	
	Females 13-49 years old	1.0	
Cancer dietary exposure analysis **q_1^* = 0.063 (mg/kg bw/day)$^{-1}$** **Estimated chronic drinking water concentration = 0.00099 ppm**	**Total Population**	$1 - 10^{-6}$	

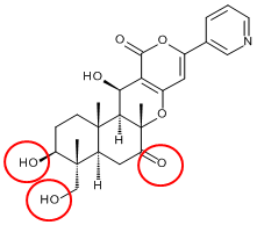
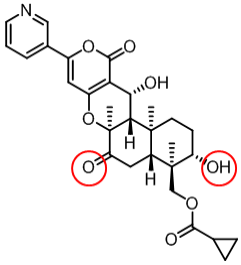
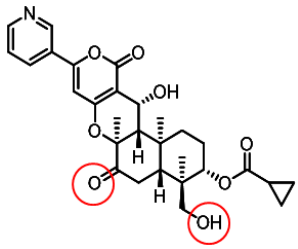
Intermediate acute dietary exposure analysis, 95th percentile ARfD = 0.002 mg/kg bw Estimated acute drinking water concentration = 0.00104 ppm	POPULATION SUBGROUP	ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)
		Drinking Water
	Females 13–49 years old	3

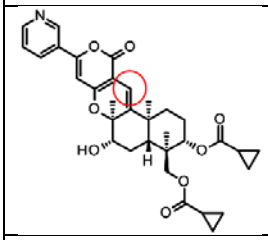
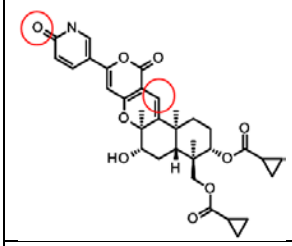
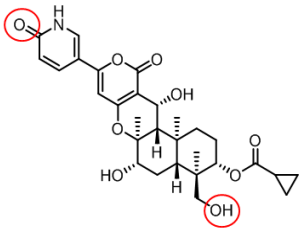
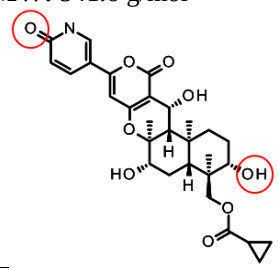
Cumulative Assessment					
Population Subgroup	**Afidopyropen (Food and Water) Exposure Estimates**	**CPCA (Water) Exposure Estimates**	**Total Exposure**	**% Afidopyropen NOAEL (18 mg/kg bw/day; CAF 100)**	**%CPCA NOAEL (10 mg/kg bw/day; CAF 100)**
Male 13–19 years old	0.000108	0.000013	0.000121	0.067	0.121
Male 20+ years old	0.000144	0.000019	0.000163	0.091	0.163
All Infants	0.000191	0.000075	0.000266	0.148	0.266
Children 1–2 years old	0.000407	0.000028	0.000435	0.242	0.435
Children 3–5 years old	0.000308	0.000022	0.00033	0.183	0.330
Children 6–12 years old	0.000185	0.000017	0.000202	0.112	0.202
Adults 50–99 years old	0.000182	0.000019	0.000201	0.112	0.201
Females 13–49 years old	0.000159	0.000020	0.000179	0.099	0.179

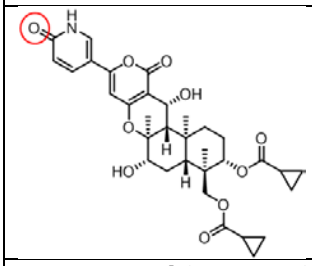
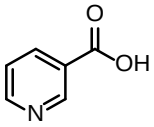
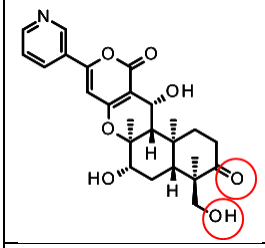
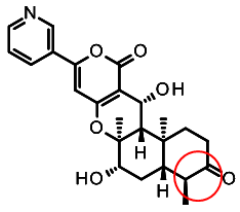
Table 14 Transformation Products of Afidopyropen Detected in Laboratory Dissipation Studies

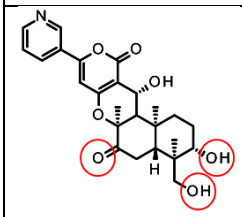
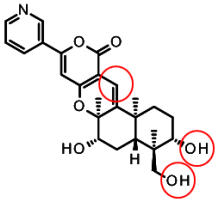
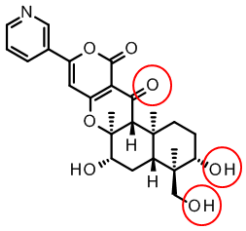
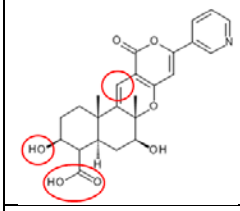
Compound	Study			Maximum %AR (sampling interval in days)	Final %AR (sampling interval in days)
Afidopyropen dimer (M440I007, ME5343-T7) **Formula:** $C_{66}H_{78}N_2O_{18}$ **MW:** 1187.3 g/mol 	Hydrolysis			NA	
	Aqueous photolysis	PMRA #2627711	pH 7 Buffer	2.4 (4)	1.8 (8)
			pH 8.39 River Water	5.4 (1)	0.8 (8)
		PMRA #2627713	pH 7 Buffer	5.75 (1)	3.07 (14)
			pH 7.4 River Water	3.48 (4)	1.75 (14)
	Soil photolysis			ND	
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil	PMRA #2627967		ND	
		PMRA #2627969		ND	
	Anaerobic soil			NA	
M440I001 (ME5343-T1) **Formula:** $C_{25}H_{31}NO_7$ **MW:** 457.5 g/mol	Hydrolysis	PMRA #2627709	pH 9, 10°C	0.9 (7)	0.4 (30)
			pH 9, 25°C	3.7 (30)	3.7 (30)
			pH 9, 50°C	**46.9 (30)**	**46.9 (30)**
	Aqueous photolysis	PMRA #2627711		NA	
		PMRA #2627713		ND	
	Soil photolysis	PMRA #2627973	Sterile Irradiated	ND	
			Sterile Dark	ND	

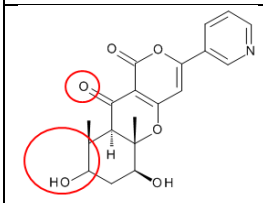
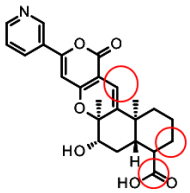
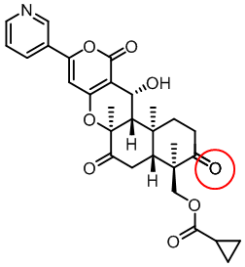
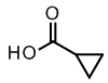
Compound	Study			Maximum %AR (sampling interval in days)	Final %AR (sampling interval in days)
			Nonsterile Irradiated	ND	
			Nonsterile Dark	3.1 (15)	3.1 (15)
	Aerobic aquatic			ND	
	Anaerobic aquatic	PMRA #2627998	Goose River	**15.3 (100)**	**15.3 (100)**
			Golden Lake	**40.4 (100)**	**40.4 (100)**
	Aerobic soil		PMRA# 2627967	ND	
			PMRA# 2627969	ND	
	Anaerobic soil	PMRA #2627971	California	**10.8 (73)**	7.0 (134)
			New Jersey	**14.9 (134)**	**14.9 (134)**
			Lufa 5M	**23.4 (150)**	**23.4 (150)**
			Lufa 2.2	**35.2 (134)**	**35.2 (134)**
M440I002 (ME5343-T2) **Formula:** $C_{29}H_{35}NO_8$ **MW:** 525.6 g/mol 	Hydrolysis	PMRA #2627709	pH 9, 10°C	1.5 (30)	1.5 (30)
			pH 9, 25°C	8.2 (30)	8.2 (30)
			pH 9, 50°C	**13.6 (6)**	5.6 (30)
	Aqueous photolysis	PMRA # 2627711		NA	
		PMRA #2627713	pH 7 Buffer	0.6 (10)	ND
			pH 7.4 River Water	1.79 (10)	0.85 (14)
	Soil photolysis	PMRA #2627973	Sterile Irradiated	ND	
			Sterile Dark	2.4 (15)	2.4 (15)
			Nonsterile Irradiated	2.3 (7)	2.1 (15)
			Nonsterile Dark	8.3 (10)	6.9 (15)
	Aerobic aquatic	PMRA #2627996	Berghäuser Altrhein	5.8 (56)	5.1 (100)
			Ranschgraben	2.9 (14)	1.6 (100)
	Anaerobic aquatic	PMRA #2627998	Goose River	**14.6 (59)**	**13.3 (100)**
			Golden Lake	**15.8 (30)**	8.6 (100)
	Aerobic soil	PMRA #2627967	New Jersey Soil	8.2 (15)	1.2 (120)
			Lufa 2.2 Soil	**11.2 (7)**	2.0 (121)
		PMRA #2627969	Lufa 5M Soil	**10.2 (10)**	3.8 (121)
			Metz Soil	8.6 (2)	0.4 (120)
	Anaerobic soil	PMRA #2627971	California	**18.4 (14)**	1.4 (134)
			New Jersey	**11.2 (21)**	6.2 (134)
			Lufa 5M	**16.9 (59)**	**12.5 (150)**
			Lufa 2.2	**10.1 (15)**	3.6 (134)
M440I003 (ME5343-T3) **Formula:** $C_{29}H_{35}NO_8$ **MW:** 525.6 g/mol 	Hydrolysis	PMRA #2627709	pH 9, 10°C	ND	ND
			pH 9, 25°C	2.1 (30)	2.1 (30)
			pH 9, 50°C	3.7 (6)	1.6 (30)
	Aqueous photolysis	PMRA #2627711		NA	
		PMRA #2627713	pH 7 Buffer	2.47 (4)	1.77 (14)
			pH 7.4 River Water	3.58 (14)	3.58 (14)
	Soil photolysis	PMRA #2627973	Sterile Irradiated	1.4 (15)	1.4 (15)
			Sterile Dark	**12.1 (15)**	**12.1 (15)**
			Nonsterile Irradiated	2.7 (7)	2.5 (15)
			Nonsterile Dark	**13.4 (10)**	**12.8 (15)**
	Aerobic aquatic	PMRA #2627996	Berghäuser Altrhein	3.0 (56)	2.6 (100)
			Ranschgraben	6.4 (78)	5.7 (100)
	Anaerobic aquatic	PMRA #2627998	Goose River	5.5 (77)	4.8 (100)
			Golden Lake	5.7 (30)	1.7 (100)
	Aerobic soil	PMRA #2627967	New Jersey Soil	**14.0 (15)**	3.4 (120)
			Lufa 2.2 Soil	7.7 (7)	1.0 (121)

Compound	Study			Maximum %AR (sampling interval in days)	Final %AR (sampling interval in days)
		PMRA #2627969	Lufa 5M Soil	7.5 (14)	3.2 (121)
			Metz Soil	ND	
	Anaerobic soil	PMRA #2627971	California	4.1 (7)	2.0 (134)
			New Jersey	**15.2 (21)**	4.0 (134)
			Lufa 5M	**10.4 (59)**	4.8 (150)
			Lufa 2.2	**12.0 (15)**	2.4 (134)
M440I004 (ME5343-T4) **Formula:** $C_{25}H_{29}NO_7$ **MW:** 455.5 g/mol 	Hydrolysis			NA	
	Aqueous and soil photolysis			NA	
	Aerobic aquatic			ND	
	Anaerobic aquatic			ND	
	Aerobic soil			ND	
	Anaerobic soil			ND	
M440I005 (ME5343-T5) **Formula:** $C_{29}H_{35}NO_8$ **MW:** 523.6 g/mol 	Hydrolysis			NA	
	Aqueous photolysis			NA	
	Soil photolysis	PMRA #2627973	Sterile Irradiated	ND	
			Sterile Dark	ND	
			Nonsterile Irradiated	ND	
			Nonsterile Dark	2.9 (15)	2.9 (15)
	Aerobic aquatic	PMRA #2627996	Berghäuser Altrhein	5.6 (78)	5.0 (100)
			Ranschgraben	4.4 (56)	2.4 (100)
	Anaerobic aquatic			ND	
	Aerobic soil	PMRA #2627967		ND	
		PMRA #2627969		ND	
	Anaerobic soil			ND	
M440I006 (ME5343-T6) **Formula:** $C_{29}H_{35}NO_8$ **MW:** 523.6 g/mol 	Hydrolysis			NA	
	Aqueous photolysis			NA	
	Soil photolysis			ND	
	Aerobic aquatic	PMRA #2627996	Berghäuser Altrhein	0.3 (100)	0.3 (100)
			Ranschgraben	0.1 (100)	0.1 (100)
	Anaerobic aquatic			ND	
	Aerobic soil	PMRA #2627967		ND	
		PMRA #2627969		ND	
	Anaerobic soil			ND	
M440I014 **Formula:** $C_{33}H_{37}NO_8$ **MW:** 575.7 g/mol	Hydrolysis			NA	
	Aqueous and soil photolysis			NA	
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil	PMRA #2627967	New Jersey Soil	5.4 (7)	4.4 (120)
			Lufa 2.2 Soil	0.4 (10)	0.1 (121)
		PMRA #2627969		NA	
	Anaerobic soil			NA	

Compound	Study			Maximum %AR (sampling interval in days)	Final %AR (sampling interval in days)
					
M440I015 **Formula:** $C_{33}H_{37}NO_9$ **MW:** 591.7 g/mol 	Hydrolysis			NA	
	Aqueous and soil photolysis			NA	
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil	PMRA #2627967	New Jersey Soil	8.9 (10)	6.0 (120)
			Lufa 2.2 Soil	2.8 (1)	0.4 (121)
		PMRA #2627969		NA	
	Anaerobic soil			NA	
M440I016 **Formula:** $C_{29}H_{35}NO_9$ **MW:** 541.6 g/mol 	Hydrolysis			NA	
	Aqueous photolysis			NA	
	Soil photolysis	PMRA #2627973	Sterile Irradiated	ND	
			Sterile Dark	ND	
			Nonsterile Irradiated	ND	
			Nonsterile Dark	8.5 (15)	8.5 (15)
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil	PMRA #2627967	New Jersey Soil	8.0 (57)	4.7 (120)
			Lufa 2.2 Soil	2.5 (15)	1.0 (121)
		PMRA #2627969		NA	
	Anaerobic soil			NA	
M440I021 **Formula:** $C_{29}H_{35}NO_9$ **MW:** 541.6 g/mol 	Hydrolysis			NA	
	Aqueous and soil photolysis			NA	
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil	PMRA #2627967	New Jersey Soil	5.6 (88)	3.0 (120)
			Lufa 2.2 Soil	3.8 (10)	1.4 (121)
		PMRA #2627969		NA	
	Anaerobic soil			NA	
M440I024 **Formula:** $C_{33}H_{39}NO_{10}$ **MW:** 609.7 g/mol	Hydrolysis			NA	
	Aqueous photolysis			NA	
	Soil photolysis	PMRA #2627973	Sterile Irradiated	ND	
			Sterile Dark	ND	
			Nonsterile Irradiated	1.8 (10)	1.2 (15)
			Nonsterile Dark	8.4 (10)	8.3 (15)
	Aerobic aquatic	PMRA #2627996	Berghäuser Altrhein	4.4 (100)	4.4 (100)
			Ranschgraben	9.8 (78)	**10.9 (100)**

Compound	Study			Maximum %AR (sampling interval in days)	Final %AR (sampling interval in days)
	Anaerobic aquatic			NA	
	Aerobic soil	PMRA #2627967	New Jersey Soil	**12.1 (31)**	2.8 (120)
			Lufa 2.2 Soil	6.2 (7)	2.1 (121)
		PMRA #2627969		NA	
	Anaerobic soil			NA	
Nicotinic Acid (M440I045) **CAS#:** 59-67-6 **Formula:** $C_6H_5NO_2$ **MW:** 123.1 g/mol 	Hydrolysis	PMRA #2627709	pH 9, 10°C	ND	ND
			pH 9, 25°C	ND	ND
			pH 9, 50°C	**22.0 (30)**	**22.0 (30)**
	Aqueous photolysis	PMRA #2627711	pH 7 Buffer	5.7 (8)	5.7 (8)
			pH 8.39 River Water	**21.5 (6)**	**20.4 (8)**
		PMRA #2627713		NA	
	Soil photolysis			ND	
	Aerobic aquatic			NA	
	Anaerobic aquatic			ND	
	Aerobic soil	PMRA #2627967		NA	
		PMRA #2627969		ND	
	Anaerobic soil			ND	
M440I046 **Formula:** $C_{25}H_{29}NO_7$ **MW:** 455.5 g/mol 	Hydrolysis			NA	
	Aqueous and soil photolysis			NA	
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil			NA	
	Anaerobic soil	PMRA #2627971	California	**16.6 (105)**	**13.5 (134)**
			New Jersey	**11.8 (105)**	8.8 (134)
			Lufa 5M	**12.3 (150)**	**12.3 (150)**
			Lufa 2.2	6.4 (44)	4.9 (134)
M440I047 **Formula:** $C_{24}H_{27}NO_6$ **MW:** 425.5 g/mol 	Hydrolysis			NA	
	Aqueous and soil photolysis			NA	
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil			NA	
	Anaerobic soil	PMRA #2627971	California	**16.0 (105)**	**17.0 (134)**
			New Jersey	8.4 (105)	4.2 (134)
			Lufa 5M	6.9 (150)	6.9 (150)
			Lufa 2.2	3.2 (29)	1.3 (134)
M440I048 **Formula:** $C_{25}H_{29}NO_7$ **MW:** 455.5 g/mol	Hydrolysis			NA	
	Aqueous and soil photolysis			NA	
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil	PMRA #2627967		NA	
		PMRA #2627969	Lufa 5M Soil	2.2 (62)	1.6 (121)
			Metz Soil	NA	
	Anaerobic soil			NA	

Compound	Study			Maximum %AR (sampling interval in days)	Final %AR (sampling interval in days)
 or isomer					
M440I049 **Formula:** $C_{24}H_{27}NO_6$ **MW:** 425.5 g/mol  or isomer, mixture with M440I053	Hydrolysis			NA	
	Aqueous and soil photolysis			NA	
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil	PMRA #2627967		NA	
		PMRA #2627969	Lufa 5M Soil	NA	
			Metz Soil	7.2 (29)	2.4 (120)
	Anaerobic soil			NA	
M440I050 **Formula:** $C_{24}H_{25}NO_7$ **MW:** 441.5 g/mol  + unidentified contaminant	Hydrolysis			NA	
	Aqueous and soil photolysis			NA	
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil	PMRA #2627967		NA	
		PMRA #2627969	Lufa 5M Soil	NA	
			Metz Soil	8.0 (29)	3.6 (120)
	Anaerobic soil			NA	
M440I051 **Formula:** $C_{24}H_{25}NO_7$ **MW:** 439.5 g/mol 	Hydrolysis			NA	
	Aqueous and soil photolysis			NA	
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil			NA	
	Anaerobic soil			NA	
M440I052 **Formula:** $C_{19}H_{19}NO_6$ **MW:** 357.4 g/mol	Hydrolysis			NA	
	Aqueous and soil photolysis			NA	
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil	PMRA #2627967		NA	
		PMRA #2627969	Lufa 5M Soil	NA	
			Metz Soil	3.9 (62)	3.3 (120)

Compound	Study			Maximum %AR (sampling interval in days)	Final %AR (sampling interval in days)
 or isomer	Anaerobic soil			NA	
M440I053 **Formula:** $C_{24}H_{25}NO_6$ **MW:** 423.5 g/mol  or isomer, mixture with M440I049	Hydrolysis			NA	
	Aqueous and soil photolysis			NA	
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil	PMRA #2627967		NA	
		PMRA #2627969	Lufa 5M Soil	NA	
			Metz Soil	7.2 (29)	2.4 (120)
	Anaerobic soil			NA	
M440I057 **Formula:** $C_{29}H_{33}NO_8$ **MW:** 523.6 g/mol 	Hydrolysis			NA	
	Aqueous and soil photolysis			NA	
	Aerobic aquatic			NA	
	Anaerobic aquatic			NA	
	Aerobic soil	PMRA #2627967	New Jersey Soil	1.6 (15)	0.3 (120)
			Lufa 2.2 Soil	4.4 (10)	1.2 (121)
		PMRA #2627969	Lufa 5M Soil	5.3 (14)	2.6 (121)
			Metz Soil	**36.6 (7)**	4.7 (120)
	Anaerobic soil	PMRA #2627971	California	**37.2 (29)**	**10.6 (134)**
			New Jersey	5.8 (44)	0.8 (134)
			Lufa 5M	3.8 (32)	1.2 (150)
			Lufa 2.2	0.5 (14)	ND (134)
Cyclopropane carboxylic acid (CPCA, M440I061) **CAS#:** 1759-53-1 **Formula:** $C_4H_6O_2$ **MW:** 86.1 g/mol 	*Not analysed for in laboratory studies on the parent compound (CPCA portions of the molecule were not labelled). An aerobic soil biotransformation study using CPCA as the test substance is summarized below.				
	Aerobic soil	PMRA #2627977		Applied directly	**13.6 (28)**
Carbon dioxide **Formula**: CO_2 **MW:** 44.0 g/mol **CAS#**: 124-38-9	Hydrolysis			NA	
	Aqueous photolysis	PMRA #2627711	pH 7 Buffer	-	0.5 (8)
			pH 8.39 River Water	-	0.8 (8)
		PMRA #2627713	pH 7 Buffer	-	**19.36 (14)**
			pH 7.4 River Water	-	**19.02 (14)**
	Soil photolysis	PMRA #2627973	Sterile Irradiated	-	1.9 (15)
			Sterile Dark	-	0.2 (15)
			Nonsterile Irradiated	-	1.3 (15)
			Nonsterile Dark	-	1.1 (15)

Compound	Study			Maximum %AR (sampling interval in days)	Final %AR (sampling interval in days)
	Aerobic aquatic	PMRA #2627996	Berghäuser Altrhein	-	5.1 (100)
			Ranschgraben	-	1.2 (100)
	Anaerobic aquatic	PMRA #2627998	Goose River	-	0.4 (100)
			Golden Lake	-	0.5 (100)
	Aerobic soil	PMRA #2627967	New Jersey Soil	-	6.9 (120)
			Lufa 2.2 Soil	-	**11.9 (120)**
		PMRA #2627969	Lufa 5M Soil	-	**17.8 (121)**
			Metz Soil	-	**28.1 (120)**
	Anaerobic soil	PMRA #2627971	California	-	1.2 (134)
			New Jersey	-	2.6 (134)
			Lufa 5M	-	1.6 (150)
			Lufa 2.2	-	0.8 (134)
Non-extractable Residues (NER)	Hydrolysis			NA	
	Aqueous photolysis			NA	
	Soil photolysis	PMRA #2627973	Sterile Irradiated	11.4 (15)	11.4 (15)
			Sterile Dark	9.2 (15)	9.2 (15)
			Nonsterile Irradiated	**12.6 (15)**	**12.6 (15)**
			Nonsterile Dark	**21.8 (15)**	**21.8 (15)**
	Aerobic aquatic	PMRA #2627996	Berghäuser Altrhein	**25.1 (100)**	**25.1 (100)**
			Ranschgraben	**22.0 (100)**	**22.0 (100)**
	Anaerobic aquatic	PMRA #2627998	Goose River	**38.8 (100)**	**38.8 (100)**
			Golden Lake	**30.2 (100)**	**30.2 (100)**
	Aerobic soil	PMRA #2627967	New Jersey Soil	**51.0 (120)**	**51.0 (120)**
			Lufa 2.2 Soil	**45.0 (120)**	**45.0 (120)**
		PMRA #2627969	Lufa 5M Soil	**29.9 (120)**	**29.9 (120)**
			Metz Soil	**27.8 (120)**	**27.8 (120)**
	Anaerobic soil	PMRA #2627971	California	**17.9 (120)**	**17.9 (120)**
			New Jersey	**52.0 (120)**	**52.0 (120)**
			Lufa 5M	**20.8 (121)**	**20.8 (121)**
			Lufa 2.2	**31.1 (120)**	**31.1 (120)**
Total Unidentified Extractable Residues (UER)	Hydrolysis	PMRA #2627709	pH 9, 10°C	0.5 (30)	0.5 (30)
			pH 9, 25°C	2.3 (15)	1.2 (30)
			pH 9, 50°C	**10.5 (20)**	9.2 (30)
	Aqueous photolysis	PMRA #2627711	pH 7 Buffer	**24.3 (8)**	**24.3 (8)**
			pH 8.39 River Water	**33.0 (8)**	**33.0 (8)**
		PMRA #2627713	pH 7 Buffer	**21.44 (14)**	**21.44 (14)**
			pH 7.4 River Water	**38.56 (14)**	**38.56 (14)**
	Soil photolysis	PMRA #2627973	Sterile Irradiated	7.9 (15)	7.9 (15)
			Sterile Dark	4.1 (15)	4.1 (15)
			Nonsterile Irradiated	6.6 (7)	6.4 (15)
			Nonsterile Dark	**11.2 (10)**	8.5 (15)
	Aerobic aquatic	PMRA #2627996	Berghäuser Altrhein	**11.3 (78)**	9.0 (100)
			Ranschgraben	6.5 (100)	6.5 (100)
	Anaerobic aquatic	PMRA #2627998	Goose River	2.8 (14)	1.0 (100)
			Golden Lake	**11.2 (100)**	**11.2 (100)**
	Aerobic soil	PMRA #2627967	New Jersey Soil	**24.6 (120)**	**24.6 (120)**
			Lufa 2.2 Soil	**29.8 (59)**	**28.8 (120)**
		PMRA #2627969	Lufa 5M Soil	**21.5 (30)**	**16.2 (121)**
			Metz Soil	**25.7 (29)**	**15.2 (120)**

Compound	Study			Maximum %AR (sampling interval in days)	Final %AR (sampling interval in days)
	Anaerobic soil	PMRA #2627971	California	**25.2 (59)**	**13.0 (120)**
			New Jersey	**16.0 (59)**	6.1 (120)
			Lufa 5M	6.4 (7)	4.2 (121)
			Lufa 2.2	8.1 (7)	6.0 (120)

AR – applied radioactivity
NA – not analysed (either no reference standard used or minor non-volatile compounds which were not identified)
ND – not detected
Bolded when appearing at >10%AR

Table 15 Fate and Behaviour of Afidopyropen and Transformation Products in the Environment

Study type	Test material / test system	Value	Transformation products	Comments	PMRA #
Abiotic transformation					
Hydrolysis	Afidopyropen [NCA-^{14}C]-labelled pH 4, 7 and 9 at 10, 25 and 50°C	pH 4 and 7: stable to hydrolysis pH 9, 10°C: DT_{50} = 1259 days (SFO) pH 9, 25°C: DT_{50} = 134 days (SFO) pH 9, 50°C: DT_{50} = 8.2 days (SFO)	Major: M440I001, M440I002, nicotinic acid (M440I045) Minor: M440I001, M440I002, M440I003	Hydrolysis is not expected to be an important route of dissipation for afidopyropen in the environment.	2627709
Phototransformation on soil	Afidopyropen [pyranone-^{14}C]-labelled and [pyranone-6-^{14}C, pyridine-2,6-^{14}C]-labelled	Sterile irradiated: half-life = 44 days Sterile dark: half-life = 41 days Nonsterile irradiated: half-life = 42 days Nonsterile dark: half-life = 10 days * Phototransformation half-life not applicable due to control $t_{1/2} \leq$ irradiated $t_{1/2}$	Major: M440I003 Minor: M440I001, M440I002, M440I003, M440I005, M440I016, M440I024	Phototransformation in soil is not expected to be an important route of dissipation for afidopyropen in the environment.	2627973
Phototransformation in water	Afidopyropen [NCA-^{14}C]-labelled pH 7 buffer and pH 8.39 natural river water	<u>pH 7 buffer:</u> DT_{50} = 32.1 days (SFO – parent) DT_{50} = 230 days (SFO – combined residues) <u>pH 8.39 river water:</u> DT_{50} = 12.9 days (SFO – parent) DT_{50} = 43 days (SFO –	Major: nicotinic acid (M440I045) Minor: M440I007, CO_2 *The majority of transformation products were not characterized	Phototransformation in water is not expected to be an important route of dissipation for afidopyropen in the environment.	2627711

Study type	Test material / test system	Value	Transformation products	Comments	PMRA #
		combined residues)	(total UER up to 34% AR)		
	Afidopyropen [pyranone-^{14}C]-labelled pH 7 buffer and pH 7.4 natural river water	<u>pH 7 buffer:</u> DT_{50} = 17.4 days (SFO – parent) DT_{50} = 43.0 days (SFO – combined residues) <u>pH 7.4 river water:</u> DT_{50} = 10.5 days (SFO – parent) DT_{50} = 51.4 days (SFO – combined residues)	Major: CO_2 Minor: M440I002, M440I003, M440I007 * The majority of transformation products were not characterized (total UER up to 40% AR)		2627713
Phototransformation in air	Afidopyropen is not expected to be volatile under field conditions based on vapour pressure, Henry's law constant and Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) results. Transformation products of afidopyropen are not expected to be volatile under field conditions based on low detection of volatile organics in soil biotransformation studies. A phototransformation study in air is not required.				
Biotransformation					
Biotransformation in aerobic soil	Afidopyropen [pyranone-^{14}C]-labelled and [pyranone-6-^{14}C, pyridine-2,6-^{14}C]-labelled afidopyropen 4 soils: New Jersey loam, New Jersey silt loam, Lufa 2.2 loamy sand (Germany), Lufa 2.2 sandy loam (Germany) Study duration: 120 days	<u>Parent</u> New Jersey loam: DT_{50} = 12.4 days (IORE) t_R = 25.9 days New Jersey silt loam: DT_{50} = 5.6 days (IORE) t_R = 15.6 days Lufa 2.2 loamy sand: DT_{50} = 7.4 days (IORE) t_R = 33.7 days Lufa 2.2 sandy loam: DT_{50} = 7.4 days (IORE) t_R = 25.5 days <u>Combined residues</u> New Jersey loam: DT_{50} = 97.5 days (SFO) New Jersey silt loam: DT_{50} = 77.4 days (DFOP) t_R = 113 days Lufa 2.2 loamy sand: DT_{50} = 64.7 days (IORE) t_R = 375 days Lufa 2.2 sandy loam: DT_{50} = 85.1 days (IORE) t_R = 626 days	Major: **M440I002**, **M440I003**, **M440I024**, CO_2 Minor: **M440I014**, **M440I015**, **M440I016**, **M440I021**, **M440I057** NERs were up to 51% AR and total **UERs** were up to 30% AR. NOTE: Bolded transformation products were included in the residue definition.	Parent afidopyropen is non-persistent, while its combined residues are moderately persistent. Biotransformation in aerobic soil is an important route of dissipation for afidopyropen.	2627967

Study type	Test material / test system	Value	Transformation products	Comments	PMRA #
	Afidopyropen [pyranone-6-^{14}C, pyridine-2,6-^{14}C]-labelled afidopyropen 2 soils: Lufa 5M sandy loam (Germany) and Metz loamy sand (California) Study duration: 120 days	<u>Parent</u> Lufa 5M sandy loam: DT_{50} = 20.5 days (IORE) t_R = 52.5 days Metz loamy sand: DT_{50} = 2.8 days (IORE) t_R = 5.2 days <u>Combined residues</u> Lufa 5M sandy loam: DT_{50} = 90 days (SFO) Metz loamy sand: DT_{50} = 61.5 days (IORE) t_R = 113 days	Major: **M440I002**, **M440I057**, CO_2 Minor: **M440I003**, **M440I048**, **M440I049**, **M440I050**, **M440I052**, **M440I053** NERs were up to 30% AR and total **UERs** were up to 24% AR. NOTE: Bolded transformation products were included in the residue definition.	Parent afidopyropen is non-persistent to slightly persistent, while its combined residues are moderately persistent. Biotransformation in aerobic soil is an important route of dissipation for afidopyropen.	2627969
	Cyclopropane carboxylic acid (CPCA – a transformation product of afidopyropen) [carboxyl-^{14}C]-labelled CPCA 4 soils: California, Indiana, North Carolina, and New Jersey Study duration: 28-31 days	California: DT_{50} = 1.46 days (IORE) t_R = 2.9 days Indiana: DT_{50} = <0.01days (IORE) t_R = 0.7 days North Carolina: DT_{50} = 9.81 days (SFO) New Jersey: DT_{50} = <0.01 days (IORE) t_R = 0.283 days	N/A	CPCA produced substantial volatile residues as CO_2 (up to 42% AR) and non-extractable residues (up to 80% AR). Non-extractable residues were shown to be truly bound through use of multiple extractions including solvents with a wide range of dielectric properties.	2627977
Biotransfor-mation in anaerobic soil	Afidopyropen [pyranone-^{14}C]-labelled and [pyranone-6-^{14}C, pyridine-2,6-^{14}C]-labelled afidopyropen 4 soils: New Jersey silt loam,	<u>Parent</u> New Jersey silt loam: DT_{50} = 26.3 days (DFOP) t_R = 67.6 days California loamy sand: DT_{50} = 23.9 days (DFOP) t_R = 474 days Lufa 2.2 loamy sand: DT_{50} = 55 days (DFOP) t_R = 96 days	Major: **M440I001**, **M440I002**, **M440I003**, **M440I046**, **M440I047**, **M440I057** Minor: CO_2 NERs were up to 55% AR and total	Parent afidopyropen is slightly to moderately persistent, while its combined residues are persistent. Biotransformation in anaerobic soil is not an important route of dissipation	2627971

Study type	Test material / test system	Value	Transformation products	Comments	PMRA #
	California loamy sand, Lufa 2.2 loamy sand (Germany), and Lufa 5M sandy loam (Germany) Study duration: 120 days	Lufa 5M sandy loam: DT_{50} = 60.9 days (DFOP) t_R = 78.4 days <u>Combined residues</u> New Jersey silt loam: DT_{50} = 186 days (IORE) t_R = 1400 days California loamy sand: DT_{50} = 295 days (SFO) Lufa 2.2 loamy sand: DT_{50} = 1009 days (DFOP) t_R = 1470 days Lufa 5M sandy loam: DT_{50} = 633 days (SFO)	UERs were up to 23% AR. NOTE: Bolded transformation products were included in the residue definition.	for afidopyropen.	
Biotransformation in aerobic water systems	Afidopyropen [pyranone-^{14}C]-labelled and [pyranone-6-^{14}C, pyridine-2,6-^{14}C]-labelled 2 test systems: Berghäuser Altrhein and Ranschgraben (Germany) Study duration: 100 days	<u>Parent</u> Berghäuser Altrhein: DT_{50} = 76.2 days (DFOP) t_R = 91.6 days Ranschgraben: DT_{50} = 102 days (DFOP) t_R = 205 days <u>Combined residues</u> Berghäuser Altrhein: DT_{50} = 197 days (SFO) Ranschgraben: DT_{50} = 244 days (SFO) *All values are for the whole system	Major: **M440I024** Minor: **M440I002**, **M440I003**, **M440I005**, **M440I006**, CO_2 NERs were up to 25% AR and total **UERs** were up to 12% AR. NOTE: Bolded transformation products were included in the residue definition.	Parent afidopyropen is moderately persistent, while its combined residues are persistent. Biotransforma-tion in aerobic water systems is an important route of dissipation for afidopyropen.	2627996
Biotransformation in anaerobic water systems	Afidopyropen [pyranone-^{14}C]-labelled and [pyranone-6-^{14}C, pyridine-2,6-^{14}C]-labelled 2 test systems: Golden Lake and Goose River (North Dakota) Study duration:	<u>Parent</u> Golden Lake: DT_{50} = 31.8 days (IORE) t_R = 41.5 days Goose River: DT_{50} = 45.3 days (SFO) <u>Combined residues</u> Golden Lake: DT_{50} = 230 days (DFOP) t_R = 259 days Goose River: DT_{50} = 135 days (IORE) t_R = 475 days	Major: **M440I001**, **M440I002** Minor: **M440I003**, CO_2 NERs were up to 40% AR and total **UERs** were up to 13% AR. NOTE: Bolded transformation products were included in the	Parent afidopyropen is slightly persistent, while its combined residues are moderately persistent to persistent. Biotransformation in anaerobic water systems is an important route of dissipation for afidopyropen.	2627998

Study type	Test material / test system	Value	Transformation products	Comments	PMRA #
	100 days		residue definition.		
Mobility					
Adsorption / desorption in soil	Afidopyropen [pyranone-^{14}C]-labelled afidopyropen Values obtained in 4 American and 2 European soils: California, Indiana, Louisiana, New Jersey, Lufa 5M, and Lufa 2.2.	K_{OC} ranging from 548.45 to 2693.72	N/A	Afidopyropen is classified as having a slight to low potential for mobility in soil.	2627982
	M440I001 [pyranone-^{14}C]-labelled Values obtained in 5 American and 1 European soil: California, Indiana, Louisiana, New Jersey, North Carolina, and Lufa 5M.	K_{OC} ranging from 261.93 to 7452.97	N/A	M440I001 is classified as immobile to having a medium potential for mobility in soil.	2627984
	M440I002 [pyranone-^{14}C]-labelled Values obtained in 5 American and 1 European soil: California, Indiana, Louisiana, New Jersey, North Carolina, and Lufa 5M.	K_{OC} ranging from 450.69 to 5353.13	N/A	M440I002 is classified as immobile to having a medium potential for mobility in soil.	2627986
	M440I003 [pyranone-^{14}C]-labelled Values obtained in 5 American	K_{OC} ranging from 495.43 to 2356.54	N/A	M440I003 is classified as having a slight to medium potential for mobility in soil.	2627988

Study type	Test material / test system	Value	Transformation products	Comments	PMRA #
	and 1 European soil: California, Indiana, Louisiana, New Jersey, North Carolina, and Lufa 5M.				
	M440I005 [pyranone-^{14}C]-labelled Values obtained in 5 American and 1 European soil: California, Indiana, Louisiana, New Jersey, North Carolina, and Lufa 5M.	K_{OC} ranging from 431.41 to 20618.30	N/A	M440I005 is classified as immobile to having a medium potential for mobility in soil.	2627992
	M440I024 [bis-(cyclopropane carboxylic acid-carbonyl-^{14}C)]-labelled Values obtained in 5 American and 1 European soil: California, Indiana, Louisiana, New Jersey, North Carolina, and Lufa 5M.	K_{OC} ranging from 506.72 to 3289.35	N/A	M440I024 is classified as having a slight to low potential for mobility in soil.	2627990
Soil leaching	No soil leaching study with afidopyropen was submitted and none is required.				
Volatilization	Afidopyropen is not expected to be volatile under field conditions based on its vapour pressure ($< 9.9 \times 10^{-6}$ Pa at 25°C) and Henry's law constant (2.3×10^{-9} atm·m^3/mol at 25°C). AOPWIN (v1.92) results indicate that afidopyropen is not persistent in air and is unlikely to be subject to long-range transport. Afidopyropen is predicted to degrade in the atmosphere with a half-life of 0.055 days due to gas phase reactions with hydroxyl radicals and with a half-life of 0.004 days due to gas phase reactions with ozone. Transformation products of afidopyropen are not expected to be volatile under field conditions based on low detection of volatile organics in soil biotransformation studies.				2627690
Field studies					
Field dissipation	Versys end-use product formulation (9.7% afidopyropen)	Parent New York: DT_{50}: 2.04 days (IORE) t_R: 16.3 days Louisiana: DT_{50}: 1.49 days (DFOP)	Major: **M440I002** Minor: **M440I001**, **M440I003**,	Afidopyropen is unlikely to accumulate in soil and carry over to the next growing season.	2627979

Study type	Test material / test system	Value	Transformation products	Comments	PMRA #
	Five bare ground sites (ecoregion) in New York (8.1), Louisiana (8.3), Florida (8.5), Washington (10.1), and California (11.1)	t_R: 22.6 days Florida: DT_{50}: 6.51 days (IORE) t_R: 17.6 days Washington: DT_{50}: 7.9 days (IORE) t_R: 17 days California: DT_{50}: 1.66 days (IORE) t_R: 12.6 days [Average DT_{50} of 3.92 days. t_R 90th percentile upper confidence bound on the mean of 19.7 days.] <u>Combined residues</u> New York: DT_{50}: 3.82 days (DFOP) t_R: 18.6 days Louisiana: DT_{50}: 2.75 days (DFOP) t_R: 61.3 days Florida: DT_{50}: 10 days (IORE) t_R: 35.2 days Washington: DT_{50}: 20.6 days (DFOP) t_R: 31.9 days California: DT_{50}: 1.85 days (DFOP) t_R: 28.1 days [Average DT_{50} of 7.8 days. t_R 90th percentile upper confidence bound on the mean of 46.0 days.] Mean residues of afidopyropen and its transformation products were not detected in soil below the 15-30 cm soil depth at any of the five locations.	**M440I016**, **M440I024**, **M440I057** NOTE: Bolded transformation products were included in the residue definition.	At the sites tested, neither afidopyropen nor it residues appeared to be inherently susceptible to leaching.	
Aquatic field dissipation	No aquatic field dissipation study with afidopyropen was submitted and none is required.				
Bioconcentration / bioaccumulation					
Bioconcentra-tion in fish	Afidopyropen Flow-through bioconcentratio n study	BCF calculated at each measurement time point ranged from <0.43 to 0.74 BCF_{ss} = 0.059	There is some uncertainty with the estimate since the test substance was not radiolabelled,	Afidopyropen does not readily bioconcentrate in fish tissue under the conditions of the study.	2628039

Study type	Test material / test system	Value	Transformation products	Comments	PMRA #
	Carp (*Cyprinus carpio*), were exposed to afidopyropen at nominal concentrations of 0.018 and 0.18 mg a.i./L for an uptake period of 28 days.		transformation products were not measured, and the study design did not include a depuration period.		

SFO – single first-order; DFOP – double first-order in parallel; IORE – indeterminate order rate equation
UER – unidentified extractable residues
NER – non-extractable residues
AR – applied radioactivity

Table 16 Toxicity of Afidopyropen, its Transformation Products and End-use Products to Non-target Terrestrial Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
Invertebrates					
Earthworm, *Eisenia fetida*	14d-Acute	Afidopyropen (TGAI, purity 94.54%)	LC/EC_{50} > 945 mg a.i./kg dw soil NOAEC = 945 mg a.i./kg dw soil	N/A	2628083
	14-d Acute	M440I002 (purity 92.5%)	LC/EC_{50} > 925 mg a.i./kg dw soil NOAEC = 925 mg a.i./kg dw soil	N/A	2628085
	14-d Acute	M440I003 (purity 98.6%)	LC/EC_{50} > 986 mg a.i./kg dw soil NOAEC = 986 mg a.i./kg dw soil	N/A	2628089
	14-d Acute	M440I005 (purity 98.6%)	LC/EC_{50} > 909 mg a.i./kg dw soil NOAEC = 909 mg a.i./kg dw soil	N/A	2628087
	14-d Acute	M440I024 (purity 98.6%)	LC/EC_{50} > 913 mg a.i./kg dw soil NOAEC = 913 mg a.i./kg dw soil	N/A	2628091
	14-d Acute	EP, Versys (9.6% a.i.)	LC/EC_{50} > 97.8 mg a.i./kg dw soil (or > 1000 mg EP/kg dw soil) NOAEC = 97.8 mg a.i./kg dw soil (or > 1000 mg EP/kg dw soil)	N/A	2627523
	14-d Acute	EP, Sefina (4.8% a.i.)	LC_{50} > 48.9 mg a.i./kg dw soil (or > 1000 mg EP/kg dw soil) NOAEC < 3.1 mg a.i./kg dw soil (or 62.5 mg EP/kg dw soil) – due to significant inhibitions in percent body weight change at all treatment levels relative to the negative control, a definitive NOAEC could not be determined.	N/A	2627078

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
	56-d Chronic	Afidopyropen (TGAI, purity 94.54%)	LC/EC_{50} > 473 mg a.i./kg dw soil NOAEC = 473 mg a.i./kg dw soil	N/A	2628093
Collembola, *Folsomia candida*	28-d Chronic	Afidopyropen (TGAI, purity 94.54%)	Mortality: LC_{50} = 386 mg a.i./kg dw soil NOAEC = 154.3 mg a.i./kg dw soil Reproduction: EC_{50} = 426 mg a.i./kg dw soil NOAEC = 154.3 mg a.i./kg dw soil	N/A	2628025
Honey bee, *Apis mellifera*	**ACUTE LABORATORY STUDIES**				
	48-h Oral, adults	Afidopyropen (TGAI, purity 94.54%)	48-h LD_{50} >100 µg a.i./bee 48-h ED_{50} = 15.3 µg a.i./bee NOEL (sublethal endpoints): <4.1 µg a.i./bee LOEL (sublethal endpoints): 4.1 µg a.i./bee Based on sublethal effects (hyperactivity, inactivity/immobility, moribund behaviour and affected locomotion).	Practically non-toxic	2628076
	48-h Contact, adults	Afidopyropen (TGAI, purity 94.54%)	48-h LD_{50} > 200 µg a.i./bee 48-h ED_{50} < 8.2 µg a.i./bee NOEL (sublethal endpoints): < 8.2 µg a.i./bee LOEL (sublethal endpoints): 8.2 µg a.i./bee Based on sublethal effects (hyperactivity, impaired motion and moribund behaviour).	Practically non-toxic	
	96-h Oral, adults	EP, Versys (9.7% a.i.)	96-h LD_{50} > 49.8 µg a.i./bee 96-h ED_{50} based on sublethal effects estimated by PMRA reviewer as > 49.8 µg a.i./bee NOEL (sublethal endpoints) = < 6.6 µg a.i./bee LOEL (sublethal endpoints = 6.6 µg a.i./bee Sublethal behavioural effects (affected coordination and moribund behaviour) occurred at all doses at all assessment time points.	Practically non-toxic	2627486
	96-h Contact, adults	EP, Versys (9.7% a.i.)	96-h LD_{50} 49.4 µg a.i./bee 96-h ED_{50} based on sublethal effects estimated by PMRA reviewer as 9.4	Practically non-toxic	

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
			µg a.i./bee NOEL (sublethal endpoints) = < 4.3 µg a.i./bee LOEL (sublethal endpoints) = 4.3 µg a.i./bee Pronounced sublethal behavioural effects (affected coordination and moribund behaviour) occurred at all doses at all assessment time points. Overall, as mortality increased in later assessments, fewer bees were described as showing sublethal effects, suggesting that sublethal effects progressed to mortality.		
	48-h Oral, adults	EP, Sefina (4.8% a.i.)	48-h LD_{50} 20.8 µg a.i./bee 48-h ED_{50} and NOEL based on sublethal endpoints estimated by PMRA reviewer as < 6.3 µg a.i./bee. LOEL (sublethal endpoints) = 6.3 µg a.i./bee Pronounced sublethal behavioural effects (impaired locomotion and moribund behaviour) occurred at all doses at all assessment time points. Overall, as mortality increased in later assessments, fewer bees were described as showing sublethal effects, suggesting that sublethal effects progressed to mortality.	Practically non-toxic	2627063
	48-h Contact, adults	EP, Sefina (4.8% a.i.)	48-h LD_{50} 20.3 µg a.i./bee 48-h ED_{50} and NOEL estimated by PMRA reviewer as < 6.3 µg a.i./bee. LOEL (sublethal endpoints) = 6.3 µg a.i./bee Pronounced sublethal behavioural effects (impaired locomotion and moribund behaviour) occurred at all doses at all assessment time points. Overall, as mortality increased in later assessments, fewer bees were described as showing sublethal effects, suggesting that sublethal effects progressed to mortality.	Practically non-toxic	
	96-h Oral, larva	EP, Versys (9.7% a.i.)	96-h LD_{50} = 37.57 µg a.i./larva Of the remaining larvae, sublethal effects reportedly occurred in 0.0, 11.6, 3.7 and 33.3% of larvae at 96 h, respectively, in the 11.97, 23.93,	Practically non-toxic	2627501

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
			47.86 and 95.63 µg afidopyropen/larva treatment groups. The ED_{50} (based on live larvae at the end of the test) would be > 95.63 µg a.i./larva. Sublethal effects (reduced food consumption and reduced larval size) noted.		
	CHRONIC LABORATORY STUDIES				
	10-d Chronic, adults	Afidopyropen (TGAI, purity 94.54%)	10-d LD_{50} = > 73.31 µg a.i./bee (mortality) [10-d LC_{50} = > 1883 µg a.i./kg diet] 10-d NOAEL = 73.31 µg a.i./bee (mortality) [10-d NOAEC = 1883 µg a.i./kg diet] 10-d NOAEL = 0.29 µg a.i./bee (sublethal effects) [10-d NOAEC = 8 µg a.i./kg diet] 10-d LOAEL = 0.67 µg a.i./bee (sublethal effects) [10-d LOAEC = 18 µg a.i./kg diet] 10-d ED_{50} = 5.55 µg a.i./bee [10-d EC_{50} = 142.15 µg a.i./kg diet] (behavioural abnormalities such as uncoordinated movement). The occurrence of sublethal effects in test item treatment groups exhibited a dose response, with > 85% of honeybees in the three highest test item treatment levels (13.65, 30.00, and 73.31 µg a.i./bee) exhibiting impaired coordination, immobility, or moribund behaviour. Although > 85% of the bees exhibited sublethal effects in the three highest treatment groups, mortality at the conclusion of the study in these treatment groups was 6.7, 5.0, and 0.0%, respectively.	N/A	2627485
	22-d Chronic, larva	EP, Versys (9.7% a.i.)	22-d NOAEL = 4.04 µg a.i./larva [22-d NOAEL = 26.37 mg a.i./kg diet] 22-d LOAEL = 7.81 µg a.i./larva [22-d LOAEL = 50.97 mg a.i./kg diet]	N/A	2627503

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
			22-d ED_{50} = 7.56 µg a.i./larva [22-d EC_{50} = 49.30 mg a.i./kg diet] Endpoints based on effects on adult emergence rate.		
	TOXICITY OF RESIDUES ON FOLIAGE				
	24-h foliar residue test. Alfalfa was treated at 50.0 g a.i./ha and plants were then placed outdoors to weather.	EP, Versys (9.7% a.i.)	Resulting afidopyropen foliar residue levels on alfalfa weathered for 0, 3, 8, and 24 hours, respectively, were 2.89, 1.42, 1.15, and 1.56 mg a.i./kg. Honeybee mortality 24 hours after exposure to the treated foliage was 6.0, 6.7, and 8.7%, respectively, for foliage weathered for 3, 8, and 24 hours. While in most treatment groups no sublethal behavioural effects were reported, in the test item treatment group that was allowed to weather for 24 hours, 2.0% of surviving bees were reported to be lying on their backs, and 1.3% of surviving bees displayed symptoms of lethargy. The time required for weathered residues to cause mortality to 25% of the bees (i.e., the RT_{25} value) was < .3h for adult honeybees under the conditions tested.	N/A	2627488
Bumblebee, *Bombus terrestris* L.	96-h Oral, adults	Afidopyropen (TGAI, purity 94.54%)	96-h LD_{50} > 93.7 µg a.i./bee At 4 hours in the acute oral toxicity test, 0, 93, 73, 75, 50 and 90% of bees exposed to 0, 6.09, 13, 25, 50 and 93.7 µg/bee, respectively, exhibited reduced co-ordination/sublethal effects. At 96 hours, 0, 3, 70, 77, 100 and 100% of bumble bees exhibited effects. Therefore, the lowest dose appeared transient. NOEL (sublethal effects)(4 hours) = < 6.09 µg a.i./bee LOEL (sublethal effects)(4 hours) = 6.09 µg a.i./bee NOEL (sublethal effects)(96 hours) = 6.09 µg a.i./bee LOEL (sublethal effects)(96 hours) = 13 µg a.i./bee Pronounced sublethal behavioural effects (affected coordination,	Practically non-toxic	2628079

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
			apathetic, and moribund behaviour) occurred at all doses at all assessment time points. While data suggest that for lower doses sublethal effects were somewhat transient, at higher doses sublethal effects appeared to be persistent throughout the study.		
	96-h Contact, adults	Afidopyropen (TGAI, purity 94.54%)	96-h LD_{50} > 100 µg a.i./bee At 96 hours in the acute contact toxicity test, 0, 33, 83, 77, 100 and 97% of bumble bees exposed to 0, 6.25, 12.5, 25, 50 and 100 µg/bee, respectively, showed reduced co-ordination. NOEC (sublethal effects) = < 6.25 µg a.i./bee LOEC (sublethal effects) = 6.25 µg a.i./bee ED50 = between 6.25 and 12.5 µg/bee. Pronounced sublethal behavioural effects (affected coordination, apathetic, and moribund behaviour) occurred at all doses at all assessment time points. While data suggest that for lower doses sublethal effects were somewhat transient, at higher doses sublethal effects appeared to be persistent throughout the study.	Practically non-toxic	
Predatory arthropod, *Typhlodromus pyri*	7-d Contact, glass plates	EP, Versys (9.7% a.i.)	LR_{50} > 156 g a.i./ha or 1592 mL EP/ha (mortality) A high percentage of mites (6–37% in the treatment groups) were trapped or escaped. Although this does not necessarily correlate to toxicity, it may be indicative of test substance avoidance.	N/A	2627518
	7-d Contact, glass plates	EP, Sefina (4.9% a.i.)	LR_{50} = 76 g a.i./ha or 1540 mL EP/ha (mortality)	N/A	2627068
	14-d Contact, spray residue on bean leaves	EP, Sefina (4.9% a.i.)	LR_{50} = 141 g a.i./ha or 2870 mL EP/ha (mortality) NOAER = 25 g a.i./ha or 500 mL EP/ha (based on number of eggs/female)	N/A	2627074
	33-d Semi-field, spray residues on apple trees	EP, Sefina (4.9% a.i.)	NOAER < 49 g a.i./ha or < 0.999 mL EP/ha (based on statistically significant reduction (45%) in mite population density 5 days after the first application)	N/A	2627076

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
	2 applications, 7 days apart of 50 g a.i./ha		Mite density was similar between the control and treated plots 5 days after second application and at study termination (26 days after second application).		
	36-d Semi-field, spray residues on apple trees 2 applications, 7 days apart of 50 g a.i./ha	EP, Sefina (4.9% a.i.)	NOAER = 49 g a.i./ha or 0.992 mL EP/ha (based on mite population density) There were no statistically significant decreases in mite population density at any assessment time point.	N/A	2627077
Parasitic arthropod, *Aphidius rhopalosiphi*	48-h Contact, glass plates	EP, Versys (9.6% a.i.)	LR_{50} = 81.5 g a.i./ha or 831 mL EP/ha (mortality)	N/A	2627521
	48-h Contact, glass plates	EP, Sefina (4.9% a.i.)	LR_{50} = 12.3 g a.i./ha or 252 mL EP/ha (mortality) Sublethal effects (still walking, but showing signs of uncoordinated movement) were observed in all treatment groups and were generally dose-responsive, progressing towards mortality.	N/A	2627066
	13-d Contact, spray residue on barley seedlings	EP, Sefina (4.9% a.i.)	LR_{50} > 147 g a.i./ha or > 3000 mL EP/ha (mortality) NOAER < 12 g a.i./ha or < 250 mL EP/ha (based on effects on settling behaviour in all treatment groups) NOAER = 98 g a.i./ha or 2000 mL EP/ha (based on number of mummies/female)	N/A	2627072
Green lacewing, *Chrysoperla carnea*	37-d Contact, spray residue on bean leaves	EP, Sefina (4.9% a.i.)	LR_{50} > 150 g a.i./ha or > 3000 mL EP/ha NOAER = 150 g a.i./ha or 3000 mL EP/ha	N/A	2627070
Birds					
Zebra finch, *Taeniopygia guttata*	14-d Acute oral	Afidopyropen (TGAI, purity 94.54%)	LD_{50} = 341 mg a.i./kg bw Sublethal effects (lethargy, loss of coordination, narcosis, prostration, dyspnea) were observed in all but the two lowest treatment groups and were generally dose-responsive, progressing towards mortality.	Moderately toxic	2628004
Bobwhite quail, *Colinus*	14-d Acute oral	Afidopyropen (TGAI, purity	LD_{50} = 783 mg a.i./kg bw	Slightly toxic	2628000

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
virginianus		95.74%)	Sublethal effects (diarrhea, lethargy, convulsions) were observed in all but the lowest treatment group and were generally dose-responsive, progressing towards mortality.		
	14-d Acute oral	EP, Versys (9.6% a.i.)	LD_{50}/ED_{50} > 188 mg a.i./kg bw (equivalent to > 1962 mg EP/kg bw) No treatment-related effects on mortality, growth (body weight) or food consumption.	Moderately toxic	2627477
	14-d Acute oral	EP, Sefina (4.7% a.i.)	LD_{50}/ED_{50} > 93.6 mg a.i./kg bw (equivalent to > 1992 mg EP/kg bw) No treatment-related effects on mortality, growth (body weight) or food consumption.	Moderately toxic	2627054
	5-d Dietary	Afidopyropen (TGAI, purity 99.9%)	LC_{50} = 532 mg a.i./kg diet LD_{50} = 70.9 mg a.i./kg bw/day LC_{50}/LD_{50} based on mortality. No apparent treatment-related sublethal behavioural effects, effects on growth (body weight) or food consumption.	Moderately toxic	2628006
	21-w reproduction	Afidopyropen (TGAI, purity 94.54%)	NOAEC = 79.6 mg a.i./kg diet NOAEL = 6.7 mg a.i./kg bw/day	N/A	2628010
Mallard duck, *Anas platyrhynchos*	14-d Acute oral	Afidopyropen (TGAI, purity 94.54%)	No mortality, effects on growth (body weight), or substantive sublethal behavioural effects in any treatment group. Due to the occurrence of regurgitation in test organisms, a NOAEL of 989 mg a.i./kg bw was established.	N/A	2628002
	14-d Acute oral	EP, Sefina (4.7% a.i.)	LD_{50}/ED_{50} > 90 mg a.i./kg bw (equivalent to > 1914 mg EP/kg bw) No treatment-related effects on mortality, growth (body weight) or food consumption.	Moderately toxic	2627056
	5-d Dietary	Afidopyropen (TGAI, purity 99.9%)	<u>Mortality:</u> LC_{50}: > 5044 mg a.i./kg diet LD_{50}: > 284 mg a.i./kg bw/day <u>Body weight change:</u> EC_{50}: 1902 mg a.i./kg diet ED_{50}: 254.7 mg a.i./kg bw/day <u>Food consumption change:</u> EC_{50}: 3690 mg a.i./kg diet ED_{50}: 278.4 mg a.i./kg bw/day No treatment-related sublethal behavioural effects.	Slightly toxic	2628008

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
	21-w reproduction	Afidopyropen (TGAI, purity 97.3%)	NOAEC = 161.0 mg a.i./kg diet NOAEL = 21.2 mg a.i./kg bw/day	N/A	2628012
Mammals					
Rat (Wistar)	Acute oral	Afidopyropen (TGAI, purity 95.74%)	LD_{50} > 2000 mg a.i./kg bw	Practically non-toxic	2627763
		EP, Versys (9.6% a.i.)	LD_{50} > 2000 mg/kg bw (>192 mg a.i./ha)	Practically non-toxic	2627543
		EP, Sefina (4.98% a.i.)	LD_{50} > 2000 mg/kg bw (>99.6 mg a.i./ha)	Practically non-toxic	2627087
	2-Generation reproduction	Afidopyropen (TGAI, purity 95.74%)	NOAEC = 100 ppm (8.4 mg a.i./kg bw/day) Based on toxicity in the F1 and F2 offspring (decreased pre-weaning pup body weights/pup weight gains) observed at the next higher dose.	N/A	2627877
			NOAEC = 300 ppm (27 mg a.i./kg bw/day) Based on increased adrenal weight in parental females; and, pup death, decreased body weight and delayed sexual maturation in offspring.	N/A	2627878
Vascular plants					
Monocot and dicot crop species (onion, ryegrass, wheat, corn, sugarbeet, oilseed rape, cabbage, soybean, lettuce and tomato)	21-d Seedling emergence	EP, Versys (9.7% a.i.)	LOAER = 125 g a.i./ha (based on 29% reduction in tomato seedling survival at the highest treatment concentration) ER_{25} > 125 g a.i./ha for all species tested	N/A	2627529
Monocot and dicot crop species (onion, ryegrass, wheat, corn, sugarbeet, oilseed rape, cabbage, soybean, lettuce and tomato)	21-d Vegetative vigour	EP, Versys (9.7% a.i.)	NOAER = 125 g a.i./ha for all species tested ER_{25} > 125 g a.i./ha for all species tested	N/A	2627531

[1] Atkins *et al.*(1981) for bees and USEPA classification for others, where applicable

Table 17 Effects of the End-use Product Versys Insecticide on Honey Bees based on Tier II (Semi-field/Residue) and Tier III (Field) Studies

Study design	Results	PMRA #
RESIDUE STUDIES[1]		
EP, Versys Insecticide (9.7% a.i.) 11-day semi-field test to determine residues in flowers, pollen and nectar. Samples of honey bee-collected pollen (pollen traps), nectar (honey stomach) collected from forager bees and canola flowers were taken 4 times and pollen directly from flowers once until end of flowering. Canola was treated once using a backpack boom-sprayer at 50 g a.i./ha during bloom at a site in North Carolina, United States. NOTE: canola is not included in the Canadian use pattern	Mean residues at 0 DAA (days after application): Flowers: 4.43 ± 0.63 mg/kg (Parent); 0.36 ± 0.035 mg/kg (M4401007) Nectar: 0.052 ± 0.068 mg/kg (Parent); <0.01 mg/kg (M4401007) Pollen: 0.26 ± 0.12 mg/kg (Parent); 0.061 ± 0.034 mg/kg (M4401007) Maximum residues at 0 DAA: Flowers: 4.97 mg/kg (Parent); 0.40 mg/kg (M4401007) Nectar: 0.13 mg/kg (Parent); 0.013 mg/kg (M4401007) Pollen: 0.40 mg/kg (Parent); 0.10 mg/kg (M4401007) Mean residues at 3 DAA: Flowers: 0.11 ± 0.015 mg/kg (Parent); 0.020 ± 0.0049 mg/kg (M4401007) Nectar: < 0.01 (Parent and M4401007) Pollen: 0.023 ± 0.007 mg/kg (Parent); < 0.01 mg/kg (M4401007) Maximum residues at 3 DAA: Flowers: 0.13 mg/kg (Parent); 0.023 mg/kg (M4401007) Nectar: < 0.01 mg/kg (Parent); < 0.01 mg/kg (M4401007) Pollen: 0.031 mg/kg (Parent); 0.018 mg/kg (M4401007) Mean residues at 7 DAA : Flowers: 0.013 ± 0.0021 mg/kg (Parent); < 0.01 mg/kg (M4401007) Nectar: < 0.01 (Parent and M4401007) Pollen: 0.027 ± 0.0091 mg/kg (Parent); < 0.01 mg/kg (M4401007) Maximum residues at 7 DAA: Flowers: 0.015 mg/kg (Parent); < 0.01 mg/kg (M4401007) Nectar: < 0.01 mg/kg (Parent); < 0.01 mg/kg (M4401007) Pollen: 0.037 mg/kg (Parent); < 0.01 mg/kg (M4401007) Mean residues at 10 DAA were < 0.01 (Parent and M4401007) in flowers, nectar and pollen. Weights of pollen samples from treated plots at 0 and 3 DAA were 77–78% lower than controls; however, by 7 and 10 DAA, pollen sample weights from treated plots had increased by 38 and 36%, respectively, relative to controls. These data suggest that bee pollen foraging activity may have been affected in afidopyropen-treated plots from 0 through 3 DAA; however, after this period, bee pollen foraging activity may have increased in the treated group relative to controls. Based on sample sizes of nectar, nectar foraging activity did not appear to be affected.	2627490
EP, Versys Insecticide (9.7% a.i.) 6-day field test to determine residues in nectar, pollen (from flowers), flowers and	Mean residues at 0 DAA: Flowers: 0.773 ± 0.413 mg/kg (Parent); 0.031 ± 0.011 mg/kg (M4401007) Leaves: 1.64 ± 0.416 mg/kg (Parent); 0.250 ± 0.046 mg/kg (M4401007) Nectar: 0.017 ± 0.004 mg/kg (Parent); <0.01 mg/kg (M4401007)	2627492

Study design	Results	PMRA #
leaves. Citrus was treated once using a tractor-mounted airblast sprayer at 50 g a.i./ha during bloom at a site in Florida, USA. NOTE: Citrus is not included in the Canadian use pattern.	Pollen: 2.28 ± 0.343 mg/kg (Parent); 0.040 ± 0.011 mg/kg (M4401007) Maximum residues at 0 DAA: Flowers: 1.25 mg/kg (Parent); 0.043 mg/kg (M4401007) Leaves: 2.12 mg/kg (Parent); 0.28 mg/kg (M4401007) Nectar: 0.022 mg/kg (Parent); < 0.01 mg/kg (M4401007) Pollen: 2.66 mg/kg (Parent); 0.046 mg/kg (M4401007) Mean residues at 3 DAA: Flowers: 0.092 ± 0.019 mg/kg (Parent); 0.030 mg/kg ± 0.003 mg/kg (M4401007) Leaves: 0.58 ± 0.185 mg/kg (Parent); 0.27 ± 0.02 mg/kg (M4401007) Nectar: < 0.01 (Parent and M4401007) Pollen: 0.073 ± 0.020 mg/kg (Parent); 0.024 ± 0.005mg/kg (M4401007) Maximum residues at 3 DAA: Flowers: 0.11 mg/kg (Parent); 0.033 mg/kg (M4401007) Leaves: 0.79 mg/kg (Parent); 0.29 mg/kg (M4401007) Nectar: < 0.01 mg/kg (Parent); < 0.01 mg/kg (M4401007) Pollen: 0.096 mg/kg (Parent); 0.029 mg/kg (M4401007) Mean residues at 5 DAA: Flowers: 0.026 ± 0.003 mg/kg (Parent); < 0.01 mg/kg (M4401007) Leaves: 0.143 ± 0.012 mg/kg (Parent); 0.07 ± 0.006 mg/kg (M4401007) Nectar: < 0.01 (Parent and M4401007) Pollen: 0.038 ± 0.011 mg/kg (Parent); < 0.01 mg/kg (M4401007) Maximum residues at 5 DAA: Flowers: 0.029 mg/kg (Parent); 0.011 mg/kg (M4401007) Leaves: 2.12 mg/kg (Parent); 0.28 mg/kg (M4401007) Nectar: < 0.01 mg/kg (Parent); < 0.01 mg/kg (M4401007) Pollen: 0.049 mg/kg (Parent); 0.01 mg/kg (M4401007)	
EP, Versys Insecticide (9.7% a.i.) 5-day semi-field test to determine residues in leaves, flowers and pollen (collected by bumble bees). Tomato was treated once using a backpack sprayer at 50 g a.i./ha during bloom at a site in Kansas, United States.	Mean residues (maximum values) at 0 DAA: Leaves: 1.93 ± 0.250 (2.13) mg/kg (Parent); 4.55 ± 0.588 (5.10) mg/kg (M4401007) Flowers: 1.417 ± 0.237 (1.67) mg/kg (Parent); 2.07 ± 0.399 (2.41) mg/kg (M4401007) Pollen: Not available Mean residues (maximum values) at 1 DAA: Leaves: 0.843 ± 0.225 (1.06) mg/kg (Parent); 1.52 ± 0.246 (1.78) mg/kg (M4401007) Flowers: 0.837 ± 0.275 (1.01) mg/kg (Parent); 1.187 ± 0.373 (1.49) mg/kg (M4401007) Pollen: 0.067 ± 0.015 (0.08) mg/kg (Parent); 0.107 ± 0.021 (0.13) mg/kg (M4401007) Mean residues (maximum values) at 2 DAA: Leaves: 0.523 ± 0.136 (0.63) mg/kg (Parent); 0.670 ± 0.178 (0.81) mg/kg (M4401007) Flowers: 0.467 ± 0.071 (0.53) mg/kg (Parent); 0.633 ± 0.166 (0.81) mg/kg (M4401007)	2627491

Study design	Results	PMRA #
	Pollen: 0.173 ± 0.031 (0.20) mg/kg (Parent); 0.353 ± 0.090 (0.41) mg/kg (M4401007) Mean residues (maximum values) at 4 DAA: Leaves: 0.263 ± 0.067 (0.34) mg/kg (Parent); 0.390 ± 0.070 (0.47) mg/kg (M4401007) Flowers: 0.270 ± 0.026 (0.30) mg/kg (Parent); 0.260 ± 0.044 (0.31) mg/kg (M4401007) Pollen: 0.177 ± 0.059 (0.22) mg/kg (Parent); 0.213 ± 0.075 (0.29) mg/kg (M4401007) In general, residues of both parent and M440I007 in leaves and flowers declined by > 80% from 0–4 DAA; residues of M440I007 ranged from 1.3 to 2.4-fold higher than those of the parent. In pollen though, afidopyropen residues increased by 2.6-fold from 1–4DAA; residues of M440I007were 1.2 to 2-fold higher than the parent from 1–4DAA. Since residues in pollen were not measured on 0DAA, it is unknown whether afidopyropen and M440I007 may have been higher on the day of application.	
SEMI-FIELD STUDIES		
EP, Versys Insecticide (9.7% a.i.) 27-day semi-field study (Germany) to determine effects on honeybee colonies. Tunnel area: 108 m². Exposure period: 8 days Observation period: 27 days Colony size: 8574 ± 297 bees/colony Replicates: 4 *Phacelia tanacetifolia* in full bloom were exposed by foliar application from a ground-boom sprayer to 50 g a.i./ha, while bees were actively foraging. Hives were covered during treatment to protect them from direct spray.	Afidopyropen treatment resulted in significantly lower foraging activity during the exposure period relative to the control. Afidopyropen treatment also resulted in significantly lower adult worker bee mortality during the exposure and monitoring periods; however, this effect is not considered adverse. Mean mortality of pupae was significantly higher in afidopyropen- and fenoxycarb (reference substance) treated tunnels during the monitoring period. There were no significant differences in brood development indices for afidopyropen-treated colonies, but during the exposure and monitoring periods the mean brood index and brood compensation index for fenoxycarb-treated colonies were significantly lower. While no sublethal behavioural effects were reported in control tunnels, afidopyropen treatments resulted in "coordination problems" for roughly 60 forager bees hours (DAA 00a and DAA 1) after applications were made. Based on statistically significant effects on foraging activity and reduced pupal survival, the NOAEL is < 50 g a.i./ha. NOTE: Study results should be interpreted with caution due to the following issues: adverse weather conditions (high rainfall and temperatures); higher mortality of honeybees in all colonies during the pre-application period (ranging from 71.9 in the control to 75.1 in the afidopyropen treatment hives); lack of analytical verification of treatment levels; etc.	2627508
EP, Versys Insecticide (9.7% a.i.) 26 Day semi-field study (Germany) to determine effects on honeybee colonies.	There were no adverse effects of afidopyropen treatment on honeybee mortality, colony development, colony strength or brood development (brood index, brood compensation index, or brood termination rate). Afidopyropen treatments did however exhibit significant adverse effects on foraging activity during the exposure phase of the study and sublethal behavioural effects (signs of intoxication, loss of coordination, reduced duration of flower	2627505

Study design	Results	PMRA #
Tunnel area: 108 m^2 crop area Exposure period: 7 days Observation period: 26 days Colony size: 8,813 ± 526 bees/colony Replicates: 4 *Phacelia tanacetifolia* in full bloom were exposed by foliar application from a hand-held boom sprayer to 50 g a.i./ha, while bees were actively foraging. Hives were covered during treatment to protect them from direct spray. Note: Food supplies were supplemented 14 DAT with Nektapoll® (commercial pollen substitute/fructose patty) and Apifonda® (commercial sucrose paste).	visitations, and impaired coordination) for roughly 200 bees hours after applications were made, and roughly 100 bees up to 1 DAT. By the conclusion of the study however, there were no significant adverse effects on any of the endpoints measured in afidopyropen-treated colonies relative to negative control colonies. In contrast, compared to the control and the test item group, significant adverse effects were observed in the fenoxycarb-treated groups (reference toxicant) for a number of endpoints, indicating the suitability of the test system to detect effects on honeybee brood development and colony strength. Based on statistically significant effects on foraging activity, the NOAEL is < 50 g a.i./ha. NOTE: As treatment levels were not analytically verified in the study and due to possible effects of weather the day after applications, there is uncertainty regarding actual afidopyropen exposure levels.	
EP, Versys Insecticide (9.7% a.i.) 41-day semi-field study (Germany) to determine effects on honeybee colonies. Tunnel area: 108 m^2 crop area Exposure period: 7 days Observation period: 41 days Colony size: 7627 ± 544 bees/colony Replicates: 4 *Phacelia tanacetifolia* in full bloom were exposed by foliar application from a hand-held boom sprayer to 50 g a.i./ha, while bees were actively foraging. Hives were covered during treatment to protect them	There were no adverse effects of afidopyropen treatment on honeybee pupae mortality, colony strength, condition or food. While there was increased adult worker bee mortality following afidopyropen applications, and decreased foraging activity during the test item exposure phase of the study, at the conclusion of the study there were no significant differences in juvenile survival, or colony strength and condition in afidopyropen-treated colonies relative to control colonies. Therefore, the increased mortality in adult bees and decreased foraging activity following application of afidopyropen appear to be transient effects. Afidopyropen treatments did however exhibit significant adverse effects on overall mean adult bee mortality and foraging activity (during the exposure phase). Afidopyropen treatments also resulted in sublethal behavioural effects (loss of coordination and lethargic behaviour) after application in roughly 50 bees/tunnel. One to four DAT the study author reported that “few” bees (in each tunnel) were observed to fall from flowers while foraging. Significant adverse effects were observed in the dimethoate-treated groups (reference toxicant) for a number of endpoints, indicating the suitability of the test system to detect effects on honeybee brood development and colony strength. Based on statistically significant effects on adult bee mortality and foraging activity, the NOAEL is < 50 g a.i./ha.	2627509

Study design	Results	PMRA #
from direct spray. Note: Food supplies were reportedly supplemented 33 DAT with 500 g Nektapoll (a commercially available protein/fructose [patty] supplement) and 2500 g Apifonda (sucrose paste).	NOTE: As treatment levels were not analytically verified in the study, and due to possible effects of weather the day after applications, there is uncertainty regarding actual afidopyropen exposure levels.	
EP, Versys Insecticide (9.7% a.i.) 93-day semi-field study (Germany) to determine effects on honeybee colonies. Tunnel area: 93.5 m^2 crop area Exposure period: 7 days Observation period: 93 days Colony size: 9802 ± 239 bees/colony Replicates: 4 *Phacelia tanacetifolia* in full bloom were exposed by foliar application from a portable plot sprayer to 10 g a.i./ha, during the day to correspond with active bee flight and during the evening to avoid bee flight.	Following daytime or evening applications, there were no adverse effects on adult mortality, or pupae during the study. Daytime afidopyropen applications resulted in adverse effects on foraging activity (during the exposure phase) and brood development (throughout the study). The mean brood index and brood compensation index were significantly different (i.e., lower by 35–38 and 29–44%, respectively) in colonies that received a daytime application of afidopyropen relative to control colonies, and the mean brood termination rate was significantly different (i.e., higher by 130–169%, respectively) in colonies that received a daytime application of afidopyropen relative to control colonies. Overall effects from evening applications of afidopyropen were similar to effects from daytime applications, though of slightly lower magnitude (i.e., lower brood index and brood compensation index, and higher brood termination rate) but these effects were **not** significantly different from those in control colonies. Daytime afidopyropen treatments also resulted in sublethal behavioural effects within 30 minutes of application: 10–30 bees in each tunnel were motionless, showed reduced ability to respond to stimulation, fell off of crop plants, exhibited impaired locomotion and cramping. Evening applications of afidopyropen did not result in any sublethal effects to bees. Overall, afidopyropen applications during the evening when bees were not actively foraging had relatively minimal adverse effects on honeybee colonies. Significant adverse effects were observed in the fenoxycarb- and dimethoate-treated groups (reference toxicant) for a number of endpoints, indicating the suitability of the test system to detect effects on honeybee brood development and colony strength. Based on statistically significant effects on foraging activity and brood development the NOAEL is < 10 g a.i./ha for applications during active bee flight. NOTE: As treatment levels were not analytically verified in the study, and due to possible effects of weather the day after applications, there is uncertainty regarding actual afidopyropen exposure levels.	2627507
EP, Versys Insecticide (9.7% a.i.)	Although mean bee mortality in afidopyropen-treated tunnels was significantly higher than the negative controls at 1, 2 and 4 DAA during the exposure phase of the study and at 15 DAA during the	2627510

Study design	Results	PMRA #
27-day semi-field study (Germany) to determine effects on honeybee colonies. Tunnel area: 127 m^2 crop area Exposure period: 7 days Observation period: 27 days Colony size: Several bee hives were not in the range of approx. 6000–10 000 bees at the beginning of the study. The 3 smallest hives had 2990 bees (Cd), 4485 (R1a) and 4940 (Tc) bees. The strongest hive had 7930 bees (R1c). average strength within the treatments was very similar (5444, 5379, 6673, 6695 bees/colony in C, T, R1 and R2) Replicates: 4 Flowering oilseed rape were exposed by foliar application from a portable boom sprayer to 50 g a.i./ha, while bees were actively foraging. Hives were covered during treatment to protect them from direct spray.	monitoring phase, the effect was transient and overall colony strength in terms of total number of adult bees appeared to surpass control performance by the end of the monitoring phase. When considered as a combined average across the exposure phase of the study (0–7 DAA), there was no statistical difference in mean (± std dev) bee mortality between afidopyropen-treated tunnels (21.7±5.8) compared to the negative control (16.4±8.2). Apart from a slight reduction of foraging activity immediately after application of the test item, no long-term afidopyropen-related adverse effects were observed relative to the negative control. Overall, adult and honeybee brood development in the afidopyropen treatment group was similar to the negative control. Based on statistically significant effects on mortality the NOAEL is < 50 g a.i./ha NOTE: As treatment levels were not analytically verified in the study, and due to possible effects of weather days after applications, there is uncertainty regarding actual afidopyropen exposure levels.	
EP, Versys Insecticide (9.7% a.i.) 36-day semi-field study (Germany) to determine effects on honeybee colonies. Tunnel area: 93.5 m^2 crop area Exposure period: 7 days Observation period: 26 days Colony size: 6834–7988 bees/colony Replicates: 4	Afidopyropen treatment resulted in significant adverse effects on adult worker bee mortality, foraging activity, and colony strength resulting in a NOAEL of < 50 g a.i./ha. However effects were limited to the first few days of after application. Sublethal effects 1–-2 hours after application were also noted where approx. 50 bees in each tunnel were reported to exhibit impaired locomotion, and in a few cases moribund behaviour. These same sublethal effects were reported to have occurred in several bees per colony through the end of 2 DAT; additionally, over the same time span the study author reported that foraging bees exhibited uncoordinated movements on treated flowers, and fell down to the ground. Adverse treatment effects occurred primarily in the first several days of the exposure phase of the study, after which by almost all measures afidopyropen-treated colonies were roughly similar to negative control colonies. NOTE: As treatment levels were not analytically verified in the study, and due to possible effects of weather days after applications,	2627517

Study design	Results	PMRA #
Phacelia tanacetifolia in full bloom were exposed by foliar application from a hand-held boom sprayer to 50 g a.i./ha, while bees were actively foraging. Hives were covered during treatment to protect them from direct spray.	there is uncertainty regarding actual afidopyropen exposure levels. Study data from fenoxycarb-treated colonies were highly variable, thus there is additional uncertainty as to how consistent applications of the afidopyropen and fenoxycarb items were across tunnels. However, residue monitoring during the study provides some evidence that bees were appropriately exposed to afidopyropen.	
FULL-FIELD STUDIES		
BAS 440 0V I (EP, 9.9% a.i.) 25 Day full-field study (Germany) to determine effects on honeybee colonies. Field size: 13 000 m² for the control and approx. 6000 m² for the treatment. Exposure period: 7 days Observation period: 25 days Colony size: 12 545 ± 2 785 bees/colony in the control and 11 814 ± 1421 bees/colony in the test item group Replicates: 4 bee colonies *Phacelia tanacetifolia* in full bloom were exposed by foliar application from an agricultural boom sprayer to 50 g a.i./ha, while bees were actively foraging. Hives were covered during treatment to protect them from direct spray.	Adult bee mortality, total numbers of adults and brood (eggs, larvae, pupae and males), and food reserves were similar between negative control and afidopyropen groups. Afidopyropen treatment resulted in a statistically significant but transient decrease in bee foraging activity on the day of treatment; however, foraging activity during the remainder of the study was similar to and/or exceeded that of the negative control. After application on the day of treatment (0aa DAT), approximately 100 bees in the afidopyropen-treated dead bee trap were reported as having coordination problems; however, the bees were noted as not showing conspicuous behaviour at the assessment after bee flight was observed. Based on the decrease in adult bee foraging activity, the NOAEC is < 50 g a.i./ha; however, this effect did not appear to have any long-term impact on the colony under the conditions tested. NOTE: There is uncertainty regarding exposure given that treatment solutions were not verified analytically, residue data were not collected, and use of a reference toxicant was not suitable.	2627496
EP, Versys (9.8% a.i.) 43 Day full-field study (Germany) to determine effects on honeybee colonies. Field size: 13 000 m² for the control and approx. 6,000 m² for the treatment. Exposure period: 9 days	Afidopyropen treatment resulted in significant adverse effects on adult worker bee mortality and foraging activity, resulting in a NOAEL of < 50 g a.i./ha. Sublethal behavioural effects on the day of application were also noted, wherein approximately 200 bees were reported as falling from flowers during foraging or inactivity; however, no additional behavioural effects in honeybees in the afidopyropen colonies were noted for the remainder of the assessment period. Adverse effects on worker bee mortality and foraging activity occurred primarily on the day of applications (0 DAT) and on 1 DAT, and by the conclusion of the 43-day study afidopyropen-treated	2627498

Study design	Results	PMRA #
Observation period: 43 days Colony size: 15 083 ± 555 adult bees/colony Replicates: 7 bee colonies *Phacelia tanacetifolia* in full bloom were exposed by foliar application from an portable plot sprayer to 50 g a.i./ha, while bees were actively foraging. Hives were covered during treatment to protect them from direct spray.	colonies were by all measures similar to or exceeded performance of the negative control colonies. NOTE: Treatment levels were not analytically verified, use of a reference toxicant was not suitable, and due to possible effects of weather prior to and immediately following applications, there is some uncertainty regarding actual afidopyropen exposure levels. However, residue data provide some evidence that bees were exposed to afidopyropen in the afidopyropen treatment group.	

DAA - days after application
[1] Note that all means are followed by ± one standard error (SE).

Table 18 Screening Level Risk Assessment of Afidopyropen, its Transformation Products and End-use Products for Non-target Terrestrial Species Other than Birds and Mammals

Organism	Exposure	Endpoint value	EEC[1]	RQ	Level of Concern[2]
Invertebrates					
Earthworm	Acute – a.i.	LC_{50}/2: > 472.5 mg a.i./kg soil	0.055 mg a.i./kg soil	< 0.1	Not exceeded
	Acute – M440I002	LC_{50}/2: > 462.5 mg a.i./kg soil	0.055 mg a.i./kg soil	< 0.1	Not exceeded
	Acute – M440I003	LC_{50}/2: > 493 mg a.i./kg soil	0.055 mg a.i./kg soil	< 0.1	Not exceeded
	Acute – M440I005	LC_{50}/2: > 454.5 mg a.i./kg soil	0.055 mg a.i./kg soil	< 0.1	Not exceeded
	Acute – M440I024	LC_{50}/2: > 456.5 mg a.i./kg soil	0.055 mg a.i./kg soil	< 0.1	Not exceeded
	Acute – Versys Insecticide	LC_{50}/2: > 48.9 mg a.i./kg soil	0.055 mg a.i./kg soil	< 0.1	Not exceeded
	Acute – Sefina Insecticide	LC_{50}/2: > 24.45 mg a.i./kg soil	0.055 mg a.i./kg soil	< 0.1	Not exceeded
	Reproduction – a.i.	NOEC: > 473 mg a.i./kg soil	0.055 mg a.i./kg soil	< 0.1	Not exceeded
Collembola, *Folsomia candida*	Reproduction – a.i.	NOEC: 154.3 mg a.i./kg soil	0.055 mg a.i./kg soil	< 0.1	Not exceeded
Honey bee, *Apis mellifera*	Acute oral, adults – a.i.	LD_{50}: > 100 µg a.i./bee 48-h ED_{50}: 15.3 µg a.i./bee 48-h NOEL: < 4.1 µg a.i./bee	1.45 µg a.i./bee	< 0.014 (LD_{50}) 0.094 (ED_{50} sublethal) > 0.35 (NOEL sublethal)	Not exceeded

Organism	Exposure	Endpoint value	EEC[1]	RQ	Level of Concern[2]
	Acute oral, adults – Versys Insecticide	LD_{50}: > 49.8 µg a.i./bee 96-h ED_{50}: > 49.8 µg a.i./bee 96-h NOEL: < 6.6 µg a.i./bee	1.45 µg a.i./bee	< 0.029 (LD_{50}) < 0.029 (ED_{50} sublethal) > 0.22 (NOEL sublethal)	Not exceeded
	Acute oral, adults – Sefina Insecticide	LD_{50}: 20.8 µg a.i./bee 48-h ED_{50} and NOEL: < 6.3 µg a.i./bee.	1.45 µg a.i./bee	0.07 (LD_{50}) > 0.23 (ED_{50} sublethal) > 0.23 (NOEL sublethal)	Not exceeded
	Acute contact, adults – a.i.	LD_{50}: > 200 µg a.i./bee 48-h ED_{50} and NOAEL: < 8.2 µg a.i./bee	0.12 µg a.i./bee	< 0.0006 (LD_{50}) > 0.015 (ED_{50} sublethal) > 0.015 (NOEL sublethal)	Not exceeded
	Acute contact, adults – Versys Insecticide	LD_{50}: 49.4 µg a.i./bee 96-h ED_{50}: 9.4 µg a.i./bee 96-h NOEL: < 4.3 µg a.i./bee	0.12 µg a.i./bee	0.0024 (LD_{50}) 0.013 (ED_{50} sublethal) > 0.028 (NOEL sublethal)	Not exceeded
	Acute contact, adults – Sefina Insecticide	LD_{50}: 20.3 µg a.i./bee 48-h ED_{50} and NOEL: < 6.3 µg a.i./bee	0.12 µg a.i./bee	0.006 (LD_{50}) > 0.019 (ED_{50} sublethal) > 0.019 (NOEL sublethal)	Not exceeded
	Acute oral, larvae – Versys Insecticide	LD_{50}: 37.57 µg a.i./bee 96-h ED_{50}: > 95.63 µg a.i./larva.	0.6 µg a.i./larva	0.016 (LD_{50}) < 0.006 (ED_{50} sublethal)	Not exceeded
	Chronic oral, adults – a.i.	10-d NOAEL (mortality): 73.31 µg a.i./bee 10-d NOEL (sublethal effects): 0.29 µg a.i./bee 10-d LOAEL (sublethal	1.45 µg a.i./bee	0.02 (NOEL-mortality) **5.0** (NOEL sublethal effects) **2.2** (LOEL sublethal effects)	**Exceeded for sublethal effects**

Organism	Exposure	Endpoint value	EEC[1]	RQ	Level of Concern[2]
		effects): 0.67 µg a.i./bee			
	Chronic oral, larvae – Versys Insecticide	NOED: 4.04 µg a.i./bee	0.6 µg a.i./larva	0.15	Not exceeded
Predatory mite, *Typhlodromus pyri*	Contact, glass plates – Versys Insecticide	LR_{50}: > 156 g a.i./ha	In-field: 87.89 g a.i./ha	0.6	Not exceeded
			Off-field: 65.04 g a.i./ha	0.4	Not exceeded
	Contact, glass plates – Sefina Insecticide	LR_{50}: 76 g a.i./ha	In-field: 87.89 g a.i./ha	1.2	Not exceeded
			Off-field: 65.04 g a.i./ha	0.9	Not exceeded
Parasitoid wasp, *Aphidius rhopalosiphi*	Contact, glass plates – Versys Insecticide	LR_{50}: 81.5 g a.i./ha	In-field: 87.89 g a.i./ha	1.1	Not exceeded
			Off-field: 65.04 g a.i./ha	0.8	Not exceeded
	Contact, glass plates – Sefina Insecticide	LR_{50}: 12.3 g a.i./ha	In-field: 87.89 g a.i./ha	**7.1**	**Exceeded**
			Off-field: 65.04 g a.i./ha	**5.3**	**Exceeded**
Vascular plants					
Vascular plant	Seedling emergence	ER_{25}: > 125 g a.i./ha LOER: 125 g a.i./ha	In-field: 123.55 g a.i./ha	1.0	Not exceeded
			Off-field: 90.93 g a.i./ha	0.7	Not exceeded
	Vegetative vigour	ER_{25}: > 125 g a.i./ha	87.89 g a.i./ha	< 0.7	Not exceeded

[1] Estimated environmental concentrations (EECs) at the screening level were determined using maximum exposure scenarios for afidopyropen to achieve the proposed yearly cumulative rate of 125 g a.i./ha. Off-field EECs were determined based on 74% drift from early season airblast application.
Note: Contact exposure = application rate (kg a.i./ha) × adjustment factor (2.4 µg a.i./bee per kg a.i./ha); adult oral exposure = application rate (kg a.i./ha) × adjustment factor (29 µg a.i./bee per kg a.i./ha); brood exposure = application rate (kg a.i./ha) x adjustment factor (12.15 µg a.i./bee per kg a.i./ha).

[2] Level of concern = 1 for most species; 0.4 for acute risk to pollinators; 1 for chronic risk to pollinators; and 2 for glass plate studies using the standard beneficial arthropod test species.
Note: Acute LOC for bees is set at 0.4; Chronic LOC for bees is set at 1.0.

Table 19 Screening Level Risk Assessment of Afidopyropen for Birds and Mammals

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)[1]	RQ	Level of Concern[2]
Small Bird (0.02 kg)					
Acute	> 9.00	Insectivore	7.15	< 0.79	Not exceeded
Reproduction	6.70	Insectivore	7.15	**1.07**	**Exceeded**
Medium Sized Bird (0.1 kg)					
Acute	> 9.00	Insectivore	5.58	< 0.62	Not exceeded
Reproduction	6.70	Insectivore	5.58	0.83	Not exceeded
Large Sized Bird (1 kg)					
Acute	> 9.00	Herbivore (short grass)	3.61	< 0.40	Not exceeded
Reproduction	6.70	Herbivore (short grass)	3.61	0.54	Not exceeded

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)[1]	RQ	Level of Concern[2]
Small Mammal (0.015 kg)					
Acute	> 9.96	Insectivore	4.11	0.41	Not exceeded
Reproduction	8.4	Insectivore	4.11	0.49	Not exceeded
Medium Sized Mammal (0.035 kg)					
Acute	> 9.96	Herbivore (short grass)	7.98	0.80	Not exceeded
Reproduction	8.4	Herbivore (short grass)	7.98	0.95	Not exceeded
Large Sized Mammal (1 kg)					
Acute	> 9.96	Herbivore (short grass)	4.26	0.43	Not exceeded
Reproduction	8.4	Herbivore (short grass)	4.26	0.51	Not exceeded

[1] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987).
For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) = 0.398 (BW in g) $^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648 (BW in g) $^{0.651}$.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(BW in g) $^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher *et al*. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

[2] Level of concern = 1 for birds and mammals

Table 20 Refined Risk To Pollinators Using Field Residues and Laboratory Endpoints

Sampled Crop	EEC - maximum residue value (ppb)		Did the Acute RQ exceed LOC (0.4)? (RQ)			EEC - mean residue value (ppb)		Did the Chronic RQ exceed LOC (1.0)? (RQ)			Risk Character-ization	Residue Data is Related to Proposed Crop Group
	Pollen	Nectar	Nectar forager	Nurse bees	Bee larvae	Pollen	Nectar	Nectar forager	Nurse bees	Bee larvae		
Canola Applied at 1 × 50 g a.i./ha, during-bloom under semi-field conditions. Samples of honey bee-collected pollen (pollen traps), nectar (honey stomach) collected from forager bees and canola flowers were taken 4 times and pollen directly from flowers once until end of flowering. Flowers generally had higher residues than pollen and nectar. Residues of M440I007 were lower than parent.	Day 0 400 pollen from bees (HB)	Day 0 130 nectar from bees (HB)	No (0.00) *Most sensitive lethal endpoint* No (>0.01) *Most sensitive sublethal endpoint*	No (0.00) *Most sensitive lethal endpoint* No (>0.00) *Most sensitive sublethal endpoint*	No (0.00) *Most sensitive lethal endpoint* No (0.00) *Most sensitive sublethal endpoint*	Day 0 260 pollen from bees (HB)	Day 0 52 nectar from bees (HB)	No (0.00) *Most sensitive lethal endpoint* No (>0.05) *Most sensitive sublethal endpoint*	No (0.00) *Most sensitive lethal endpoint* No (>0.03) *Most sensitive sublethal endpoint*	No (0.00) *Most sensitive lethal endpoint* No (0.00) *Most sensitive sublethal endpoint*	No risk based on lethal or sublethal effects. Residues were most conservative (on first day of application) and toxicity endpoints were the most sensitive.	Canola is not a proposed crop, but can be considered for other bee attracting crops. The application rates for crops with pollinator exposure potential include: -cucurbits and outdoor ornamentals at 125 g a.i./ha -pome fruit at 40 g a.i./ha, and -stone fruit at 20 g a.i./ha Therefore, the canola study, based on rate, is conservative for stone fruit, similar to pome fruit and may under-estimate residues in cucurbit crops. The canola study may be most representative of perennial crops.
Citrus Applied at 1 × 50 g a.i./ha, during-bloom under field conditions. Samples of pollen and nectar were collected from plants. Other matrices	Day 0 2660 pollen from plants	Day 0 22 nectar from plants	No (0.00) *Most sensitive lethal endpoint* No (>0.01) *Most*	No (0.00) *Most sensitive lethal endpoint* No (>0.00) *Most*	No (0.00) *Most sensitive lethal endpoint* No (0.00) *Most*	Day 0 2280 pollen from plants	Day 0 17 nectar from plants+	No (0.00) *Most sensitive lethal endpoint* No (>0.02) *Most*	No (0.00) *Most sensitive lethal endpoint* No (>0.08) *Most*	No (0.00) *Most sensitive lethal endpoint* No (0.00) *Most*	No risk based on lethal or sublethal effects. Residues were most conservative (on first day of	Citrus is not a crop grown in Canada, but can be considered for other bee attracting crops, particularly orchard crops such as pome fruit or stone fruit. The application rates for crops with pollinator exposure potential

Sampled Crop	EEC - maximum residue value (ppb)		Did the Acute RQ exceed LOC (0.4)? (RQ)			EEC - mean residue value (ppb)		Did the Chronic RQ exceed LOC (1.0)? (RQ)			Risk Character-ization	Residue Data is Related to Proposed Crop Group
	Pollen	Nectar	Nectar forager	Nurse bees	Bee larvae	Pollen	Nectar	Nectar forager	Nurse bees	Bee larvae		
were also sampled (whole flowers and leaves, pollen residues were the highest). The residues are assumed to be from plants, although the study also indicates samples were taken from forager bees. Residues of M440I007 were lower than parent.			*sensitive sublethal endpoint*	*sensitive sublethal endpoint*	*sensitive sublethal endpoint*			*sensitive sublethal endpoint*	*sensitive sublethal endpoint*	*sensitive sublethal endpoint*	application) and toxicity endpoints were the most sensitive.	include: -cucurbits and outdoor ornamentals at 125 g a.i./ha -pome fruit at 40 g a.i./ha, and -stone fruit at 20 g a.i./ha Therefore, the citrus study, based on rate, is conservative for stone fruit, similar to pome fruit and may underest-imate residues in cucurbit crops. The citrus study may be most representative of orchard crops.
Tomato Applied at 1 × 50 g a.i./ha, during-bloom <u>under field conditions</u>. Samples of pollen were collected from bumble bees. Other matrices were also sampled (whole flowers and leaves). Residues of M440I007 were higher than parent in some cases. *total residues is the sum of both actives, and	<u>Day 0</u> 1.42 Whole flower (no pollen collect-ed) <u>Day 1</u> 0.067 Pollen collect	N/A	<u>Day 0</u> No (0.00) *Most sensitive lethal endpoint* No (>0.00) *Most sensitive sublethal endpoint* <u>Day 1</u> No (0.00) *Most sensitive*	<u>Day 0</u> No (0.00) *Most sensitive lethal endpoint* No (>0.00) *Most sensitive sublethal endpoint* <u>Day 1</u> No (0.00) *Most sensitive*	<u>Day 0</u> No (0.00) *Most sensitive lethal endpoint* No (0.00) *Most sensitive sublethal endpoint* <u>Day 1</u> No (0.00) *Most sensitive*	<u>Day 0</u> 1.67 Whole flower (no pollen collect-ed) <u>Day 1</u> 0.08 Pollen collect-ed	N/A	<u>Day 0</u> No (0.00) *Most sensitive lethal endpoint* No (>0.00) *Most sensitive sublethal endpoint* <u>Day 1</u> No (0.00) *Most sensitive*	<u>Day 0</u> No (0.00) *Most sensitive lethal endpoint* No (>0.00) *Most sensitive sublethal endpoint* <u>Day 1</u> No (0.00) *Most sensitive*	<u>Day 0</u> No (0.00) *Most sensitive lethal endpoint* No (0.00) *Most sensitive sublethal endpoint* <u>Day 1</u> No (0.00) *Most sensitive*	No risk based on lethal or sublethal effects. Residues were most conservative (on first day of application) and toxicity endpoints were the most sensitive.	Tomato is a proposed crop group and can be considered for other bee attracting crops.

Sampled Crop	EEC - maximum residue value (ppb)		Did the Acute RQ exceed LOC (0.4)? (RQ)			EEC - mean residue value (ppb)		Did the Chronic RQ exceed LOC (1.0)? (RQ)			Risk Character-ization	Residue Data is Related to Proposed Crop Group
	Pollen	Nectar	Nectar forager	Nurse bees	Bee larvae	Pollen	Nectar	Nectar forager	Nurse bees	Bee larvae		
toxicity of the transformation product is assumed to be equal to the parent.	ed by bees (BB)		*lethal endpoint* No (>0.00) *Most sensitive sublethal endpoint*	*lethal endpoint* No (>0.00) *Most sensitive sublethal endpoint*	*lethal endpoint* No (0.00) *Most sensitive sublethal endpoint*	ed by bees (BB)		*lethal endpoint* No (>0.00) *Most sensitive sublethal endpoint*	*lethal endpoint* No (>0.00) *Most sensitive sublethal endpoint*	*lethal endpoint* No (0.00) *Most sensitive sublethal endpoint*		
	Total residue Day 0 3.5 Whole flower (no pollen collect-ed)		Total residue Day 0 No (0.00) *Most sensitive lethal endpoint* No (>0.00) *Most sensitive sublethal endpoint*	Total residue Day 0 No (0.00) *Most sensitive lethal endpoint* No (>0.01) *Most sensitive sublethal endpoint*	Total residue Day 0 No (0.00) *Most sensitive lethal endpoint* No (0.00) *Most sensitive sublethal endpoint*	Total residue Day 0 4.08 Whole flower (no pollen collect-ed)		Total residue Day 0 No (0.00) *Most sensitive lethal endpoint* No (>0.00) *Most sensitive sublethal endpoint*	Total residue Day 0 No (0.00) *Most sensitive lethal endpoint* No (>0.14) *Most sensitive sublethal endpoint*	Total residue Day 0 No (0.00) *Most sensitive lethal endpoint* No (0.00) *Most sensitive sublethal endpoint*		

NOTES: To derive an **acute EEC value** for use in the refined acute oral risk assessment, the *maximum* residue values in pollen and nectar were selected from relevant residue trials. The maximum value was considered the most relevant for the acute risk assessment as there was considerable spatial and temporal variability in the available residue data. To derive a **chronic EEC value** for use in the refined chronic oral risk assessment, the *highest daily mean* residue values in pollen and nectar were selected from relevant residue trials. The highest daily mean was considered the most relevant for the chronic risk assessment as bees in the Tier I chronic studies are typically exposed to afidopyropen over a prolonged period of time (3–4 days for larvae and 10 days for adults).

Acute and chronic risk estimates were calculated for each crop selected for use in the risk assessment by comparing the residue with the toxicity endpoint. The **estimated daily dose value** for relevant bee castes is based on the refined acute or chronic EEC values and the most conservative estimated food consumption rates for adult bees (i.e., 292 mg/day nectar and 0.041 mg/day pollen for worker bees foraging for nectar (nectar foragers); 140 mg/day nectar and 9.6 mg/day pollen for nurse bees consuming pollen and nectar) and mature bee larvae (i.e., 120 mg/day nectar and 3.6 mg/day pollen). The relative importance of each caste of bee in maintaining hive health was not a factor in the choice of food consumption rates, as adverse effects on any of the castes could potentially affect the hive. The **acute estimated daily dose value** is calculated by adding the daily nectar dose [(nectar consumption rate (mg/day) × maximum nectar residue (µg/kg)/ 1.0×10^6)] with the daily pollen dose [(pollen consumption rate (mg/day) × maximum pollen residue (µg/kg)/1.0×10^6)]. The **chronic estimated daily dose value** is calculated the same way except using the highest daily mean residues in nectar and pollen.

Sampled Crop	EEC - maximum residue value (ppb)		Did the Acute RQ exceed LOC (0.4)? (RQ)			EEC - mean residue value (ppb)		Did the Chronic RQ exceed LOC (1.0)? (RQ)			Risk Character-ization	Residue Data is Related to Proposed Crop Group
	Pollen	Nectar	Nectar forager	Nurse bees	Bee larvae	Pollen	Nectar	Nectar forager	Nurse bees	Bee larvae		

Acute and chronic risk quotients (RQ) were also calculated in accordance with the Guidance for Assessing Pesticide Risks to Bees for each bee caste by dividing the estimated daily dose by the corresponding Tier I toxicity endpoint. The RQ value is compared to the corresponding LOC value for either acute (0.4) or chronic (1.0) risk. If one or more of the RQ values exceeds the LOC, risk to honey bee colonies cannot be excluded and a higher tiered risk assessment may be warranted.

Lethal endpoints:
adult acute oral LD_{50} = 20.8 µg a.i./bee for TGAI; bee larvae acute LD_{50} = 37.57 µg a.i./larva/day
adult chronic oral NOEC = 73.31 µg a.i./bee for TGAI; bee larvae NOEL: 4.04 µg a.i./larva/day
Sublethal endpoints:
adult acute oral ED_{50} = < 4.1 µg a.i./bee for TGAI; bee larvae acute LD_{50} = 37.57 µg a.i./larva/day
adult chronic oral NOEC = 0.29 µg a.i./bee for TGAI; bee larvae NOEL: 4.04 µg a.i./larva/day

Table 21 Further Characterization of the Risk of the End-use Product Sefina Insecticide to Non-target Predatory and Parasitic Arthropods Using Results from Extended Laboratory Studies

Organism	Exposure	Endpoint Value	EEC[1]	RQ	Level of Concern[1]
Predatory arthropod, *Typhlodromus pyri*	Extended laboratory (14-d Contact; spray residue on bean leaves) Sefina Insecticide	LR_{50}: 141 g a.i./ha	In-field (87.89 g a.i./ha × 0.8 foliar deposition factor): 70.31 g a.i./ha	0.5	Not exceeded
			Off-field (87.89 g a.i./ha × 74% drift[2] × 0.1 vegetation distribution factor): 6.5 g a.i./ha	< 0.1	Not exceeded
			Off-field (87.89 g a.i./ha × 6% drift[3] × 0.1 vegetation distribution factor): 0.53 g a.i./ha	< 0.1	Not exceeded
		NOER: 25 g a.i./ha	In-field (87.89 g a.i./ha × 0.8 foliar deposition factor): 70.31 g a.i./ha	**2.8**	**Exceeded**
			Off-field (87.89 g a.i./ha × 74% drift[2] × 0.1 vegetation distribution factor): 6.5 g a.i./ha	0.3	Not exceeded
			Off-field (87.89 g a.i./ha × 6% drift[3] × 0.1 vegetation distribution factor): 0.53 g a.i./ha	< 0.1	Not exceeded
Parasitoid arthropod, *Aphidius rhopalosiphi*	Extended laboratory (13-d Contact; spray residue on bean leaves) Sefina Insecticide	LR_{50}: > 147 g a.i./ha	In-field (87.89 g a.i./ha × 0.8 foliar deposition factor): 70.31 g a.i./ha	< 0.5	Not exceeded
			Off-field (87.89 g a.i./ha × 74% drift[2] × 0.1 vegetation distribution factor): 6.5 g a.i./ha	< 0.1	Not exceeded
			Off-field (87.89 g a.i./ha × 6% drift[3] × 0.1 vegetation distribution factor): 0.53 g a.i./ha	< 0.1	Not exceeded
		NOER: 98 g a.i./ha	In-field (87.89 g a.i./ha × 0.8 foliar deposition factor): 70.31 g a.i./ha	0.7	Not exceeded
			Off-field (87.89 g a.i./ha × 74% drift[2] × 0.1 vegetation distribution factor): 6.5 g a.i./ha	< 0.1	Not exceeded
			Off-field (87.89 g a.i./ha × 6% drift[3] × 0.1 vegetation distribution factor): 0.53 g a.i./ha	< 0.1	Not exceeded
Green lacewing, *Chrysoperla carnea*	Extended laboratory (37-d Contact; spray residue on bean leaves) Sefina Insecticide	LR_{50}: > 150 g a.i./ha NOER: 150 g a.i./ha	In-field (87.89 g a.i./ha × 0.8 foliar deposition factor): 70.31 g a.i./ha	< 0.5	Not exceeded
			Off-field (87.89 g a.i./ha × 74% drift[2] × 0.1 vegetation distribution factor): 6.5 g a.i./ha	< 0.1	Not exceeded
			Off-field (87.89 g a.i./ha × 6% drift[3] × 0.1 vegetation distribution factor): 0.53 g a.i./ha	< 0.1	Not exceeded

[1] Level of concern = 1

[2] 74% drift from early season airblast application.

[3] 6% drift from field sprayer application using minimum spray droplet size of 'medium'. This method of application with lower drift serves to bracket the risk from drift using all application methods.

Table 22 Risk Assessment of Afidopyropen for Birds Using Maximum Residues Expected Following Multiple Applications on Ornamentals

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	On-field		Off Field[2]	
			EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ
Small Bird (0.02 kg)						
Acute	> 9.00	Insectivore	7.15	0.8	5.29	0.6
	> 9.00	Granivore (grain and seeds)	1.11	0.1	0.82	0.1
	> 9.00	Frugivore (fruit)	2.21	0.2	1.64	0.2
Dietary	7.09	Insectivore	7.15	**1.01**	5.29	0.7
	7.09	Granivore (grain and seeds)	1.11	0.2	0.82	0.1
	7.09	Frugivore (fruit)	2.21	0.3	1.64	0.2
Reproduction	6.70	Insectivore	7.15	**1.07**	5.29	0.8
	6.70	Granivore (grain and seeds)	1.11	0.2	0.82	0.1
	6.70	Frugivore (fruit)	2.21	0.3	1.64	0.2
Medium Sized Bird (0.1 kg)						
Acute	> 9.00	Insectivore	5.58	0.6	4.13	0.5
	> 9.00	Granivore (grain and seeds)	0.86	0.1	0.64	0.1
	> 9.00	Frugivore (fruit)	1.73	0.2	1.28	0.1
Dietary	7.09	Insectivore	5.58	0.8	4.13	0.6
	7.09	Granivore (grain and seeds)	0.86	0.1	0.64	0.1
	7.09	Frugivore (fruit)	1.73	0.2	1.28	0.2
Reproduction	6.70	Insectivore	5.58	0.8	4.13	0.6
	6.70	Granivore (grain and seeds)	0.86	0.1	0.64	0.1
	6.70	Frugivore (fruit)	1.73	0.3	1.28	0.2
Large Sized Bird (1 kg)						
Acute	> 9.00	Insectivore	1.63	0.2	1.21	0.1
	> 9.00	Granivore (grain and seeds)	0.25	0.0	0.19	0.0
	> 9.00	Frugivore (fruit)	0.50	0.1	0.37	0.0
	> 9.00	Herbivore (short grass)	3.61	0.4	2.67	0.3
	> 9.00	Herbivore (long grass)	2.20	0.2	1.63	0.2
	> 9.00	Herbivore (Broadleaf plants)	3.34	0.4	2.47	0.3
Dietary	7.09	Insectivore	1.63	0.2	1.21	0.2
	7.09	Granivore (grain and seeds)	0.25	0.0	0.19	0.0
	7.09	Frugivore (fruit)	0.50	0.1	0.37	0.1
	7.09	Herbivore (short grass)	3.61	0.5	2.67	0.4
	7.09	Herbivore (long grass)	2.20	0.3	1.63	0.2
	7.09	Herbivore (Broadleaf plants)	3.34	0.5	2.47	0.3
Reproduction	6.70	Insectivore	1.63	0.2	1.21	0.2
	6.70	Granivore (grain and seeds)	0.25	0.0	0.19	0.0
	6.70	Frugivore (fruit)	0.50	0.1	0.37	0.1
	6.70	Herbivore (short grass)	3.61	0.5	2.67	0.4
	6.70	Herbivore (long grass)	2.20	0.3	1.63	0.2
	6.70	Herbivore (Broadleaf plants)	3.34	0.5	2.47	0.4

[1] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:

FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) = 0.398(BW in g) $^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) $^{0.651}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher *et al*. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

[2] Off-field drift calculated assuming 74% drift resulting from an early season airblast application.

Table 23 Risk Assessment of Afidopyropen for Birds Using Mean Residues Expected Following Multiple Applications on Ornamentals

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	On-field		Off Field[2]	
			EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ
Small Bird (0.02 kg)						
Acute	> 9.00	Insectivore	4.94	0.55	3.66	0.41
	> 9.00	Granivore (grain and seeds)	0.53	0.06	0.39	0.04
	> 9.00	Frugivore (fruit)	1.06	0.12	0.78	0.09
Dietary	7.09	Insectivore	4.94	0.70	3.66	0.52
	7.09	Granivore (grain and seeds)	0.53	0.07	0.39	0.06
	7.09	Frugivore (fruit)	1.06	0.15	0.78	0.11
Reproduction	6.70	Insectivore	4.94	0.74	3.66	0.55
	6.70	Granivore (grain and seeds)	0.53	0.08	0.39	0.06
	6.70	Frugivore (fruit)	1.06	0.16	0.78	0.12
Medium Sized Bird (0.1 kg)						
Acute	> 9.00	Insectivore	3.85	0.43	2.85	0.32
	> 9.00	Granivore (grain and seeds)	0.41	0.05	0.30	0.03
	> 9.00	Frugivore (fruit)	0.82	0.09	0.61	0.07
Dietary	7.09	Insectivore	3.85	0.54	2.85	0.40
	7.09	Granivore (grain and seeds)	0.41	0.06	0.30	0.04
	7.09	Frugivore (fruit)	0.82	0.12	0.61	0.09
Reproduction	6.70	Insectivore	3.85	0.58	2.85	0.43
	6.70	Granivore (grain and seeds)	0.41	0.06	0.30	0.05
	6.70	Frugivore (fruit)	0.82	0.12	0.61	0.09
Large Sized Bird (1 kg)						
Acute	> 9.00	Insectivore	1.13	0.13	0.83	0.09
	> 9.00	Granivore (grain and seeds)	1.13	0.13	0.09	0.01
	> 9.00	Frugivore (fruit)	0.24	0.03	0.18	0.02
	> 9.00	Herbivore (short grass)	1.28	0.14	0.95	0.11
	> 9.00	Herbivore (long grass)	0.72	0.08	0.53	0.06
	> 9.00	Herbivore (Broadleaf plants)	1.10	0.12	0.82	0.09
Dietary	7.09	Insectivore	1.13	0.16	0.83	0.12
	7.09	Granivore (grain and seeds)	1.13	0.16	0.09	0.01
	7.09	Frugivore (fruit)	0.24	0.03	0.18	0.03

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	On-field		Off Field[2]	
			EDE (mg a.i./kg bw)[1]	RQ	EDE (mg a.i./kg bw)[1]	RQ
	7.09	Herbivore (short grass)	1.28	0.18	0.95	0.13
	7.09	Herbivore (long grass)	0.72	0.10	0.53	0.08
	7.09	Herbivore (Broadleaf plants)	1.10	0.16	0.82	0.12
Reproduction	6.70	Insectivore	1.13	0.17	0.83	0.12
	6.70	Granivore (grain and seeds)	1.13	0.17	0.09	0.01
	6.70	Frugivore (fruit)	0.24	0.04	0.18	0.03
	6.70	Herbivore (short grass)	1.28	0.19	0.95	0.14
	6.70	Herbivore (long grass)	0.72	0.11	0.53	0.08
	6.70	Herbivore (Broadleaf plants)	1.10	0.16	0.82	0.12

[1] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) = 0.398(BW in g) $^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) $^{0.651}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher *et al*. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

[2] Off-field drift calculated assuming 74% drift resulting from an early season airblast application.

Table 24 Toxicity of Afidopyropen, its Transformation Products and End-use Products to Non-target Aquatic Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
Freshwater species					
Daphnia magna	48-h Acute	Afidopyropen (TGAI, 95.74%)	EC_{50} = 8.89 mg a.i./L (immobilization) Sublethal effects were observed in 100% of daphnids in all treatment groups 48 hours after exposure.	Moderately toxic	2628041
	48-h Acute	EP, Sefina Insecticide (4.8% a.i.)	EC_{50} = 0.09 mg a.i./L (immobilization)	Very highly toxic	2627059
	48-h Acute	EP, Versys Insecticide (9.7% a.i.)	EC_{50} = 0.12 mg a.i./L (immobilization)	Highly toxic	2627480
	21-d Chronic	Afidopyropen (TGAI, purity 94.54%)	NOAEC = 123.0 ng a.i./L (adult body weight)	N/A	2628043
Ceriodaphnia dubia	7-d Chronic	Afidopyropen (TGAI, purity 94.54%)	NOAEC = 181.5 ng a.i./L (reproductive endpoints) 50% mortality in the highest treatment group, NOAEC for parental survival = 404.5 ng a.i./L	N/A	2628049
Moina	10-d	Afidopyropen	NOAEC = 849.3 ng a.i./L (no	N/A	2628047

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
macrocopa	Chronic	(TGAI, purity 94.54%)	treatment-related effects at highest concentration tested)		
Amphipod, *Hyalella azteca*	10-d Acute, spiked sediment	Afidopyropen (TGAI, purity 94.54%)	Pore water: NOAEC = 29.9 µg a.i./L LOAEC = 59.0 µg a.i./L IC_{50} > 280 µg a.i./L Endpoints based on treatment-related reductions in dry weight.	N/A	2628061
Midge, *Chironomus dilutus*	10-d Acute, spiked sediment	Afidopyropen (TGAI, purity 94.54%)	Pore water: NOAEC = 265 µg a.i./L LOAEC > 265 µg a.i./L IC_{50} > 265 µg a.i./L No treatment-related effects at highest concentration tested.	N/A	2628063
	10-d Acute, spiked sediment	M440I024, purity 91.3%	Pore water: NOAEC = 6.34 mg a.i./L LOAEC > 6.34 mg a.i./L LC_{50}/IC_{50} > 6.34 mg a.i./L No treatment-related effects at highest concentration tested.	N/A	2628067
	40-d Chronic, spiked sediment	Afidopyropen (TGAI, purity 94.54%)	Pore water: NOAEC = 0.161 µg a.i./L LOAEC > 0.161 µg a.i./L EC_{50} > 0.161 µg a.i./L No treatment-related effects at highest concentration tested.	N/A	2628071
Midge, *Chironomus riparius*	25-d Chronic, spiked water	Afidopyropen (TGAI, purity 94.54%)	Pore water: NOAEC = 3.00 µg a.i./L LOAEC > 3.00 µg a.i./L EC_{50} > 3.00 µg a.i./L Overlying water: NOAEC = 22.01 µg a.i./L LOAEC > 22.01 µg a.i./L EC_{50} > 22.01 µg a.i./L No treatment-related effects at highest concentration tested.	N/A	2628051
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute, static-renewal	Afidopyropen (TGAI, purity 94.54%)	LC_{50} = 19.98 mg a.i./L Sublethal behavioural effects were observed at only the two highest test concentrations (lethargy and loss of coordination).	Slightly toxic	2628027
	96-h Acute, static-renewal	EP, Sefina Insecticide (4.8% a.i.)	LC_{50} = 0.043 mg a.i./L (equivalent to 0.893 mg EP/L) Sublethal behavioural effects were observed in all but the lowest concentration tested (loss of	Very highly toxic	2627057

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
			equilibrium, erratic swimming and abnormal opercular flap movement).		
	96-h Acute, static-renewal	EP, Versys Insecticide (9.7% a.i.)	LC_{50} = 0.096 mg a.i./L (equivalent to 0.987 mg EP/L) Sublethal behavioural effects were observed in all but the lowest concentration tested (erratic swimming and abnormal opercular flap movement).	Very highly toxic	2627478
Fathead minnow, *Pimephales promelas*	96-h Acute, static-renewal	Afidopyropen (TGAI, 94.54% a.i.)	LC_{50} = 19.9 mg a.i./L Sublethal behavioural effects were observed at two intermediate test concentrations (loss of equilibrium and lethargy).	Slightly toxic	2628031
	33-d ELS, flow-through	Afidopyropen (TGAI, purity 94.54%)	NOAEC = 0.297 mg a.i./L LOAEC = 0.937 mg a.i./L (based on reductions in wet weight and length) No treatment-related effects on hatching success or survival.	N/A	2628035
Carp, *Cyprinus carpio*	96-h Acute, static-renewal	Afidopyropen (TGAI, purity 95.74%)	LC_{50} = 17.2 mg a.i./L Sublethal behavioural effects were observed at the three highest test concentrations (loss of equilibrium, lethargy and various other effects).	Slightly toxic	2628033
Diatom, *Navicula pelliculosa*	96-h Acute	Afidopyropen (TGAI, purity 94.54%)	IC_{50} = 14.73 mg a.i./L (AUC) There were significant effects on yield, growth rate, and area under the growth curve (AUC), resulting in a NOAEC of 1.99 mg a.i./L.	N/A	2628057
Green algae, *Pseudokirchneriella subcapitata*	72-h Acute	Afidopyropen (TGAI, purity 95.74%)	IC_{50} = 20.37 mg a.i./L (yield) There were significant effects on yield, growth rate, and area under the growth curve (AUC), resulting in a NOAEC of 6.1 mg a.i./L.	N/A	2628059
	96-h Acute	EP, Sefina Insecticide (4.8% a.i.)	IC_{50} = 0.385 mg a.i./L (AUC) There were significant effects on yield, growth rate, and area under the growth curve (AUC), resulting in a NOAEC of 0.014 mg a.i./L.	N/A	2627062
	96-h Acute	EP, Versys Insecticide (9.7% a.i.)	IC_{50} = 0.314 mg a.i./L (AUC) There were significant effects on yield, growth rate, and area under the growth curve (AUC), resulting in a NOAEC of 0.028 mg a.i./L.	N/A	2627483
Blue-green algae,	96-h Acute	Afidopyropen (TGAI, purity	IC_{50} > 44.20 mg a.i./L (AUC)	N/A	2628053

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
Anabaena flos-aquae		94.54%)	There were minimal effects on yield, growth rate, and area under the growth curve (AUC), resulting in a NOAEC of 21.80 mg a.i./L (second highest concentration tested).		
Vascular plant, duckweed, *Lemna gibba*	7-d Dissolved	Afidopyropen (TGAI, purity 94.54%)	IC_{50} = 8.74 mg a.i./L (for most sensitive endpoint of frond number yield) There were significant effects on frond growth rate and yield, and dry weight growth rate and yield, resulting in a NOAEC of 1.58 mg a.i./L (lowest treatment concentration).	N/A	2628073
Marine species					
Amphipod, *Leptocheirus plumulosus*	10-d Acute, spiked sediment	Afidopyropen (TGAI, purity 94.54%)	Pore water: NOAEC < 9.1 µg a.i./L LOAEC = 9.1 µg a.i./L LC_{50} = 84.7 µg a.i./L (pore water) Endpoints based on survival. Sublethal effects (amphipods leaving sediment or located on sediment surface) increased in severity through the duration of the study, and appeared to progress towards mortality (52% mortality at the highest treatment concentration).	N/A	2628065
	10-d Acute, spiked sediment	Afidopyropen (TGAI, purity 94.54%)	Pore water: NOAEC = 5.0 µg a.i./L LOAEC > 5.0 µg a.i./L LC_{50} > 5.0 µg a.i./L No treatment-related effects at highest concentration tested. Sublethal effects not reported.	N/A	2628069
Crustacean, mysid shrimp, *Americamysis bahia*	96-h Acute	Afidopyropen (TGAI, purity 94.54%)	LC_{50} = 4.49 mg a.i./L (survival) There were behavioural abnormalities (lethargy and erratic swimming) in many surviving mysids across all treatment groups and time points, with the percentage of test animals expressing sublethal effects increasing over time. After 96 hours, all surviving mysids in test substance treatment concentrations greater than 0.28 mg a.i./L were reported as showing sublethal effects.	Moderately toxic	2628023
	28-d Chronic	Afidopyropen (TGAI, purity 94.54%)	NOAEC = 3.96 ng a.i./L (no. offspring/female) There were significant effects on	N/A	2628045

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA #
			post-pairing survival; days to first brood release; no. offspring/surviving female; and offspring survival. Sublethal behavioural effects (lethargy, erratic swimming, and loss of equilibrium) were observed at all treatment levels and appeared dose-responsive for both first and second generation mysids.		
Mollusk, Eastern oyster, *Crassostrea virginica*	96-h Acute	Afidopyropen (TGAI, purity 94.54%)	IC_{50} = 1.43 mg a.i./L (shell deposition) No mortality was observed in any treatment group. At study termination, all oysters in the two highest treatment groups (4.16 and 6.81 mg a.i./L) appeared closed and in the highest treatment group reportedly did not produce fecal matter (suggesting abstinence from feeding).	Moderately toxic	2628021
Marine diatom, *Skeletonema costatum*	96-h Acute	Afidopyropen (TGAI, purity 94.54%)	IC_{50} = 2.04 mg a.i./L (yield) There were significant effects on yield, growth rate, and area under the growth curve (AUC), resulting in a NOAEC of 0.07 mg a.i./L.	N/A	2628055
Sheepshead minnow, *Cyprinodon variegatus*	96-h Acute, static	Afidopyropen (TGAI, purity 94.54%)	LC_{50} > 31.5 mg a.i./L NOAEC: 31.5 mg a.i./L No treatment-related effects at highest concentration tested.	Slightly toxic	2628019
	34-d ELS, flow-through	Afidopyropen (TGAI, purity 94.54%)	NOAEC < 0.0818 mg a.i./L LOAEC = 0.0818 mg a.i./L (based on reductions in wet weight and length) Due to statistically significant inhibitions in length (4.2%) and wet weight (7.9%) at the lowest treatment level (0.0818 mg a.i./L), the study resulted in a non-definitive NOAEC. No treatment-related effects on hatching success or survival.	N/A	2628037

[1] USEPA classification, where applicable

Table 25 Screening Level Risk Assessment of Afidopyropen for Aquatic Species

Organism	Exposure	Endpoint value (mg a.i./L)	EEC[1] (mg a.i./L)	RQ	Level of Concern[2]
Freshwater species					
Invertebrate, *Daphnia magna*	Acute – a.i.	EC_{50}/2: 4.4	0.0154	<0.1	
	Acute – Versys Insecticide	EC_{50}/2: 0.06	0.0154	0.3	

Organism	Exposure	Endpoint value (mg a.i./L)	EEC[1] (mg a.i./L)	RQ	Level of Concern[2]
	Acute – Sefina Insecticide	EC_{50}/2: 0.045	0.0154	0.3	Not exceeded
	Chronic – a.i.	NOEC: 0.000 123	0.0154	**124.8**	**Exceeded**
Ceriodaphnia dubia	Chronic – a.i.	NOEC: 0.000 181 5	0.0154	**84.6**	**Exceeded**
Moina macrocopa	Chronic – a.i.	NOEC: 0.000 849 3	0.0154	**18.1**	**Exceeded**
Carp, *Cyprinus carpio*	Acute – a.i.	LC_{50}/10: 1.789	0.0154	< 0.1	Not exceeded
Rainbow trout, *Oncorhynchus mykiss*	Acute – Versys Insecticide	LC_{50}/10: 0.0096	0.0154	**1.6**	**Exceeded**
	Acute – Sefina Insecticide	LC_{50}/10: 0.0043	0.0154	**3.6**	**Exceeded**
Fathead minnow, *Pimephales promelas*	ELS – a.i.	NOEC: 0.297	0.0154	< 0.1	Not exceeded
Amphibians (using fish data as a surrogate)	Acute – a.i.	LC_{50}/10: 1.789	0.0819	< 0.1	Not exceeded
	Acute – Versys Insecticide	LC_{50}/10: 0.0096	0.0819	**8.5**	**Exceeded**
	Acute – Sefina Insecticide	LC_{50}/10: 0.0043	0.0819	**19.0**	**Exceeded**
	ELS – a.i.	NOEC: 0.297	0.0819	0.3	Not exceeded
Aquatic vascular plants, *Lemna gibba*	Dissolved – a.i.	IC_{50}/2: 4.37	0.0154	< 0.1	Not exceeded
Diatom, *Navicula pelliculosa*	Acute – a.i.	IC_{50}/2: 7.365	0.0154	< 0.1	Not exceeded
Green algae, *Pseudokirchneriella subcapitata*	Acute – a.i.	IC_{50}/2: 10.185	0.0154	< 0.1	Not exceeded
	Acute – Versys Insecticide	IC_{50}/2: 0.157	0.0154	< 0.1	Not exceeded
	Acute – Sefina Insecticide	IC_{50}/2: 0.193	0.0154	< 0.1	Not exceeded
Marine species					
Crustacean, mysid shrimp, *Americamysis bahia*	Acute – a.i.	LC_{50}/2: 2.245	0.0154	< 0.1	Not exceeded
	Chronic – a.i.	NOEC: 0.000 003 96	0.0154	**3889**	**Exceeded**
Mollusk, Eastern oyster, *Crassostrea virginica*	Acute – a.i.	LC_{50}/2: 0.715	0.0154	< 0.1	Not exceeded
Sheepshead minnow, *Cyprinodon variegatus*	Acute – a.i.	LC_{50}/10: > 3.15	0.0154	< 0.1	Not exceeded
	ELS – a.i.	NOEC: < 0.0818	0.0154	> 0.2	Not exceeded
Marine diatom, *Skeletonema costatum*	Acute – a.i.	IC_{50}/2: 1.02	0.0154	< 0.1	Not exceeded

[1] Estimated environmental concentrations (EECs) at the screening level in water bodies 80 cm and 15 cm deep were determined using maximum exposure scenarios for afidopyropen to achieve the proposed yearly cumulative rate of 125 g a.i./ha.

[2] Level of concern = 1

Table 26 Risk Quotients for Aquatic Organisms Determined for Drift of Afidopyropen

Organism (exposure)	Endpoint (mg a.i./L)	Refined EEC (mg a.i./L)[1]	RQ	Level of Concern
Freshwater species				
Daphnia magna (chronic; 21 days; technical afidopyropen)[2]	LOEC: 0.000 190	0.0114	**60.0**	**Exceeded**
Ceriodaphnia dubia (chronic; 7 days; technical afidopyropen)	NOEC: 0.000 181 5	0.0114	**62.8**	**Exceeded**
Moina macrocopa (chronic; 10 days; technical afidopyropen)	NOEC: 0.000 849 3	0.0114	**13.4**	**Exceeded**
Chironomus riparius (chronic spiked water; 25 days; technical afidopyropen)[3]	overlying water NOEC: 0.022	0.0114	0.5	Not exceeded
Oncorhynchus mykiss (acute; 96 hours; Versys)	LC_{50}/10: 0.0096	0.0114	**1.2**	**Exceeded**
Oncorhynchus mykiss (acute; 96 hours; Sefina)	LC_{50}/10: 0.0043	0.0114	**2.6**	**Exceeded**
Amphibians (acute; 96 hours; Versys)[4]	LC_{50}/10: 0.0096	0.0606	**6.3**	**Exceeded**
Amphibians (acute; 96 hours; Sefina)[4]	LC_{50}/10: 0.0043	0.0606	**14.1**	**Exceeded**
Marine species				
Mysid shrimp, *Americamysis bahia* (chronic; 28 days; technical afidopyropen)	NOEC: 0.000 003 96	0.00462	**1167**	**Exceeded**

[1] Refined EECs were calculated using a maximum percent drift deposition at one metre downwind (74% for early airblast) from the point of application for an ASAE 'fine' droplet size and the proposed use on outdoor ornamentals. Freshwater EECs were based on the cumulative yearly maximum application rate. The marine EEC was based on the single maximum application rate, since tides and dilution are expected to result in negligible residues at the time of subsequent applications. It is noted that other methods of application are proposed on other crops with less drift deposition.

[2] In the screening level risk assessment a NOEC of 0.000 123 mg a.i./L was used based on a 13% reduction in adult body weight at the next treatment level (0.000 190 mg a.i./L); however, for the refined aquatic risk assessment the LOEC of 0.000 190 mg a.i./L was more appropriate based on more substantial ecologically relevant effects at the next treatment level of 0.000 295 mg a.i./L (16% reduction in mean number of offspring per adult female, 14% reduction in mean number of offspring per reproductive day and 28% reduction in mean adult body weight compared to the negative control). No statistically significant effects on adult survival, time to first brood, production rate of first brood, and adult body length were reported in this study.

[3] In this spiked water study no treatment-related effects were noted at the highest concentration tested.

[4] Using fish data as a surrogate.

Table 27 Risk Quotients for Aquatic Organisms Determined for Runoff of Afidopyropen

Organism (exposure)	Endpoint (mg a.i./L)	EEC (mg a.i./L; the vertical bar indicates values calculated without and with unidentified residues)	RQ	Level of Concern
Freshwater species				
Daphnia magna (chronic; 21 days; technical afidopyropen)[1]	LOEC: 0.000 190	Atlantic (water column 21-d): 0.0074 | 0.0113	**38.9–59.5**	**Exceeded**
		BC (water column 21-d): 0.001 | 0.0012	**5.3–6.3**	**Exceeded**
Ceriodaphnia dubia (chronic; 7 days; technical afidopyropen)	NOEC: 0.000 181 5	Atlantic (water column 96-h): 0.0076 | 0.0114	**41.9 – 62.8**	**Exceeded**
		BC (water column 96-h): 0.0011 | 0.0013	**6.1–7.2**	**Exceeded**
Moina macrocopa (chronic; 10 days; technical afidopyropen)	NOEC: 0.000 849 3	Atlantic (water column 96-h): 0.0076 | 0.0114	**8.9–13.4**	**Exceeded**
		BC (water column 96-h): 0.0011 | 0.0013	**1.3–1.5**	**Exceeded**
Hyalella azteca (acute; 10 days; technical afidopyropen)[2]	pore water IC_{50}/2: > 0.14	Atlantic (pore water peak): 0.0066 | 0.0102	< 0.1	Not exceeded
		BC (pore water peak): 0.0008 | 0.001	< 0.1	Not exceeded
Chironomus dilutus (acute; 10 days; technical afidopyropen)[3]	pore water IC_{50}/2: > 0.13	Atlantic (pore water peak): 0.0066 | 0.0102	< 0.1	Not exceeded
		BC (pore water peak): 0.0008 | 0.001	< 0.1	Not exceeded
Chironomus dilutus (acute; 10 days; M440I024)[4]	pore water IC_{50}/2: > 3.17	Atlantic (pore water peak): 0.0066 | 0.0102	< 0.1	Not exceeded
		BC (pore water peak): 0.0008 | 0.001	< 0.1	Not exceeded
Chironomus dilutus (chronic; 40 days, technical afidopyropen)[5]	pore water NOEC: 0.000 161	Atlantic (pore water 21-d): 0.0066 | 0.0102	**41.0–63.4**	**Exceeded**
		BC (pore water 21-d): 0.0008 | 0.001	**5.0–6.2**	**Exceeded**
Oncorhynchus mykiss (acute; 96 hours, Versys)	LC_{50}/10: 0.0096	Atlantic (water column 96-h): 0.0076 | 0.0114	**0.8–1.2**	**Exceeded**
		BC (water column 96-h): 0.0011 | 0.0013	< 1.0	Not exceeded
Oncorhynchus mykiss (acute; 96 hours, Sefina)	LC_{50}/10: 0.0043	Atlantic (water column 96-h): 0.0076 | 0.0114	**1.8–2.7**	**Exceeded**
		BC (water column 96-h): 0.0011 | 0.0013	< 1.0	Not exceeded
Amphibians (acute; 96 hours, Versys)[6]	LC_{50}/10: 0.0096	Atlantic (water column 96-h): 0.0214 | 0.0329	**2.2 – 3.4**	**Exceeded**
		BC (water column 96-h): 0.0035 | 0.0043	< 1.0	Not exceeded
Amphibians (acute; 96 hours, Sefina)[6]	LC_{50}/10: 0.0043	Atlantic (water column 96-h): 0.0214 | 0.0329	**5.0–7.7**	**Exceeded**
		BC (water column 96-h): 0.0035 | 0.0043	0.8–**1.0**	**Exceeded**
Marine species				
Leptocheirus plumulosus (acute; 10 days; technical afidopyropen)[7]	pore water LC_{50}/2: 0.042	Atlantic (pore water peak): 0.0066 | 0.0102	< 1.0	Not exceeded
		BC (pore water peak): 0.0008 | 0.001	< 1.0	Not exceeded
Leptocheirus plumulosus (acute; 10 days; technical afidopyropen)[8]	pore water LC_{50}/2: > 0.0025	Atlantic (pore water peak): 0.0066 | 0.0102	**2.6 – 4.1**	**Exceeded**
		BC (pore water peak): 0.0008 | 0.001	< 1.0	Not exceeded
Americamysis bahia (chronic; 28 days; technical afidopyropen)[9]	NOEC: 0.000 003 96	Atlantic (water column 21-d): 0.0074 | 0.0113	**1869–2854**	**Exceeded**
		BC (water column 21-d): 0.001 | 0.0012	**252.5–303.0**	**Exceeded**

Organism (exposure)	Endpoint (mg a.i./L)	EEC (mg a.i./L; the vertical bar indicates values calculated without and with unidentified residues)	RQ	Level of Concern

[1] In the screening level risk assessment, a NOEC of 0.000 123 mg a.i./L was used based on a 13% reduction in adult body weight at the next treatment level (0.000 190 mg a.i./L); however, for the refined aquatic risk assessment the LOEC of 0.000 190 mg a.i./L was more appropriate based on more substantial ecologically relevant effects at the next treatment level of 0.000 295 mg a.i./L (16% reduction in mean number of offspring per adult female, 14% reduction in mean number of offspring per reproductive day and 28% reduction in mean adult body weight compared to the negative control). No statistically significant effects on adult survival, time to first brood, production rate of first brood, and adult body length were reported in this study.

[2] In this acute spiked sediment study, dry weight was significantly reduced in the three highest treatment groups by just under 50%, therefore the resulting LC_{50} value was determined to be greater than the highest treatment concentration.

[3] In this acute spiked sediment study, no treatment-related effects were noted at the highest concentration tested.

[4] In this acute spiked sediment study with the transformation product, M440I024, the water EEC for afidopyropen was used as their molecular weights are comparable. No treatment-related effects were noted at the highest concentration tested.

[5] In this chronic spiked sediment study, no treatment-related effects were noted at the highest concentration tested; therefore, the associated RQs are considered overestimated.

[6] Using fish data as a surrogate.

[7] In this acute spiked sediment study, the endpoint was definitive and based on significant effects on survival.

[8] In this acute spiked sediment study, no treatment-related effects were noted at the highest concentration tested.

[9] In this chronic study with mysid shrimp, a NOAEC of 3.96 ng a.i./L, was established based on a significant reduction (34%) in the mean number of offspring per surviving female at the next treatment level of 7.12 ng a.i./L. The NOAEC for G2 survival was 7.12/8.61 ng a.i./L based on a 42% reduction at the next treatment level of 14.3/11.6 ng a.i./L. The NOAEC for post-pairing G1 survival and day-to-first-brood release was 14.3 ng a.i./L based on significant effects (30% reduction in G1 survival and 37% days later to brood release) at the next treatment level of 29.9 ng a.i./L. Sublethal behavioural effects (lethargy, erratic swimming, and loss of equilibrium) were observed across all treatment levels for both G1 and G2 mysids, and appeared to be dose-responsive.

Table 28 Toxic Substances Management Policy Considerations – Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Afidopyropen Endpoints	Endpoints for Combined residues
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	
Predominantly anthropogenic[2]	Yes		Yes	
Persistence[3]	Soil	Half-life ≥ 182 days	*Laboratory studies*	
			No: Representative half-lives of 5.2-52.5 days.	Yes: Representative half-lives of 90 to 626 days.
			Field dissipation studies	
			No: Representative half-lives of 12.6 to 22.6 days.	No: Representative half-lives of 18.6 to 61.3 days.
	Water	Half-life ≥ 182 days	Yes: Representative half-lives of 7.8 to 13 days in the water phase of aerobic and anaerobic water-sediment systems. Total system representative half-lives range from 41.5 to 205 days in aerobic and anaerobic water sediment systems.	Yes: Total system representative half-lives range from 197 to 475 days in aerobic and anaerobic water sediment systems.
	Sediment	Half-life ≥ 365 days	No: Total system representative half-lives of from 91.6 and 205 days in	No: Total system representative half-lives of from 197 and 244 days in

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Afidopyropen Endpoints	Endpoints for Combined residues
			aerobic water sediment systems.	aerobic water sediment systems.
	Air	Half-life ≥ 2 days or evidence of long range transport	No: AOPWIN (v1.92) predicted half-life < 0.1 days.	Unknown; however unlikely based on properties of parent.
Bioaccumulation[4]	Log K_{OW} ≥ 5		No: 3.45	Not available
	BCF ≥ 5000		No: 0.059	Unknown; however unlikely based on BCF of parent.
	BAF ≥ 5000		Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

[1]All pesticides will be considered toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act* (CEPA) for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4]Field data (e.g., bioaccumulation factors (BAFs)) are preferred over laboratory data (e.g., bioconcentration factors (BCFs)) which, in turn, are preferred over chemical properties (e.g., *n*-octanol–water partition coefficient (log K_{OW})).

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

Afidopyropen is a new active ingredient which is concurrently being registered in Canada and the United States. The MRLs proposed for afidopyropen in Canada are the same as corresponding tolerances to be promulgated in the United States, except for livestock commodities, in accordance with Table 1.

Once established, the American tolerances for afidopyropen will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[9] listed for afidopyropen in or on any commodity on the Codex Alimentarius Pesticide Residues in Food website.

Table 1 Comparison of Canadian MRLs and American Tolerances (where different)

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)
Eggs, fat, meat, and meat by-products of cattle, goats, hogs, horses, poultry, and sheep	0.01	Not required[1]
Milk	0.001	Not required[1]

[1] as per Category 3 of 40 CFR 180.6(a) for livestock

MRLs may vary from one country to another for a number of reasons. For animal commodities, differences in MRLs are due to different legislative framework.

[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
2627596	2016, IIA 1.1 Applicant (name, address, contact, phone and fax numbers), DACO: 12.7,Document M
2627597	2016, IIA 1.2 Manufacturer(s) (name, address, contact, phone and fax numbers), DACO: 12.7,Document M
2627599	2016, IIA 1.4 Chemical name, DACO: 12.7,Document M
2627600	2016, IIA 1.5 Manufacturers codes, names and patent status, DACO: 12.7,Document M
2627601	2016, IIA 1.6 Existing CAS, CIPAC, EINECS and ELINCS numbers, DACO: 12.7,Document M
2627602	2016, IIA 1.7 Molecular formula, molecular mass and structural formula, DACO: 12.7,Document M
2627619	2016, IIA 4.2 Methods for the analysis of the active substance as manufactured, DACO: 12.7,Document M
2627621	2016, IIA 4.4 Description of methods for analysis of soil, DACO: 12.7,Document M
2627622	2016, IIA 4.5 Description of methods of analysis of water, DACO: 12.7,Document M
2627666	2016, IIA 2 Physical and chemical properties of the active substance, DACO: 12.7,8.2.1 (OECD),Document M
2627683	2016, DACO 2.1 to 2.9, DACO: 2.1,2.2,2.3,2.3.1,2.4,2.5,2.6,2.7,2.8,2.9,IIA 1.1,IIA 1.2,IIA 1.3,IIA 1.4,IIA 1.5.1,IIA 1.5.2,IIA 1.6,IIA 1.7
2627684	2016, Characterization of five batches of Technical Grade Active Ingredient Afidopyropen (BAS 440 I, Reg.No.: 5599022), DACO: 2.13.3,IIA 1.11.1 CBI
2627686	2016, Product identity and composition of Afidopyropen (BAS 440 I), DACO: 1.1,2.11.1,2.11.2,2.11.3,2.11.4,2.12.1,2.12.2,2.13.4,2.2,2.3,2.3.1,2.4,2.6,2.7,2.8,2.9,7.8, IIA 1.10.2,IIA 1.2,IIA 1.3,IIA 1.5.1,IIA 1.5.2,IIA 1.6,IIA 1.7,IIA 1.8.1,IIA 1.8.2,IIA 1.9.1.1,IIA 1.9.2,IIA 1.9.3,IIA 6.2.6 CBI
2627687	2011, Determination of melting point of ME5343 pure grade, DACO: 2.14.4,IIA 2.1.1
2627688	2011, Determination of boiling point of ME5343 pure grade, DACO: 2.14.5,IIA 2.1.2
2627689	2011, Thermal stability of ME5343 pure grade, DACO: 2.14.13,IIA 2.1.3
2627692	2015, BAS 440 I (TGAI): Stability to normal and elevated temperature, metal and metal ions, DACO: 2.14.13,IIA 2.17.2
2627693	2011, Determination of density of ME5343 pure grade, DACO: 2.14.6,IIA 2.2
2627694	2011, Vapour pressure of ME5343 pure grade - Final revised report, DACO: 2.14.9,IIA 2.3.1
2627696	2009, Determination of physical state of ME5343 pure grade, DACO: 2.14.1,2.14.2,IIA 2.4.1
2627697	2009, Determination of color of ME5343 pure grade, DACO: 2.14.1,2.14.2,IIA 2.4.1
2627698	2009, Determination of odor of ME5343 pure grade, DACO: 2.14.3,IIA 2.4.2
2627699	2011, Ultraviolet-visible (UV/VIS) absorption spectra of ME5343 pure grade - Final report revised (No. 2), DACO: 2.13.2,2.14.12,IIA 2.5.1.1,IIA 2.5.1.5
2627700	2011, Infrared spectrum of ME5343 pure grade, DACO: 2.13.2,IIA 2.5.1.2
2627701	2011, ME5343: Determination of NMR spectra - Amended report, DACO: 2.13.2,IIA 2.5.1.3
2627702	2011, Mass spectrum of ME5343 pure grade, DACO: 2.13.2,IIA 2.5.1.4

PMRA Document Number	Reference
2627703	2016, Determination of the specific optical rotation of "BAS 440 I (TGAI) - Afidopyropen Reg.No. 5599022" - Study No. 15L00455 (confidential), DACO: 2.12.1,2.12.2,2.13.2,IIA 2.5.1.6
2627704	2016, Determination of the specific optical rotation of "BAS 440 I (PAI - Afidopyropen Reg.No.: 5599022" - Study No. 15L00456 (confidential), DACO: 2.12.1,2.12.2,2.13.2,IIA 2.5.1.6
2627705	2011, Water solubility of ME5343 pure grade - Revised final report (No. 2), DACO: 2.14.7,IIA 2.6
2627706	2011, Solubility of ME5343 pure grade in organic solvents - Revised report No. 2, DACO: 2.14.8,IIA 2.7
2627707	2010, Partition coefficient (n-octanol/water) of ME5343 pure grade, DACO: 2.14.11,IIA 2.8.1
2627715	2010, Dissociation constants of ME5343 pure grade, DACO: 2.14.10,8.2.3.2,IIA 2.9.5
2627717	2014, Validation of the analytical method APL0689/01: Determination of the active ingredient Afidopyropen (BAS 440 I, TGAI), DACO: 2.13.1,7.2.5,IIA 4.2.1,IIA 4.2.7 CBI
2627718	2015, Determination of organic solvents by Headspace-GC in Afidopyropen (BAS 440 I, TGAI), DACO: 2.13.4,IIA 4.2.3 CBI
2627719	2015, Validation of the analytical method APL0691/01: Determination of organic solvents by Headspace-GC in Afidopyropen (BAS 440 I, TGAI), DACO: 2.13.4,IIA 4.2.3 CBI
2627720	2015, Determination of process-related impurities in Afidopyropen (BAS 440 I, TGAI), DACO: 2.13.4,IIA 4.2.3 CBI
2627721	2015, Validation of the analytical method APL0690/01 - Determination of process-related impurities in Afidopyropen (BAS 440 I, TGAI), DACO: 2.13.4,IIA 4.2.3 CBI
2627722	2014, Determination of the active ingredient Afidopyropen (BAS 440 I, TGAI), DACO: 2.13.1,7.2.2,IIA 4.2.5 CBI
2628095	2014, Physical properties of Afidopyropen (BAS 440 I, Reg.No. 5599022) technical active ingredient TC/TGAI, DACO: 2.14.1,2.14.2,2.14.3,2.16,3.5.7,IIA 2.16,IIA 2.4.1,IIA 2.4.2,IIIA 2.4.1
2735469	2017, Product identity and composition of Afidopyropen (BAS 440 I), DACO: 1.1,2.11.1,2.11.2,2.11.3,2.11.4,2.12.1,2.12.2,2.13.4,2.2,2.3,2.3.1,2.4,2.6,2.7,2.8,2.9,7.8, IIA 1.10.2,IIA 1.2,IIA 1.3,IIA 1.5.1,IIA 1.5.2,IIA 1.6,IIA 1.7,IIA 1.8.1,IIA 1.8.2,IIA 1.9.1.1,IIA 1.9.2,IIA 1.9.3,IIA 6.2.6 CBI
2627052	2016, DACO 3.1.1 to 3.4, DACO: 3.1.1,3.1.2,3.1.3,3.1.4,IIIA 1.1,IIIA 1.2.1,IIIA 1.2.2,IIIA 1.3
2627053	2015, BAS 440 01 I - Group A - Product identity, composition, and analysis, DACO: 3.2.2,3.2.3,3.5.4,IIIA 1.4.5.1,IIIA 1.4.5.2,IIIA 1.5 CBI
2627080	2016, DACO 3.5.4, 3.5.5,3.5.11,3.5.12,3.5.13,3.5.15, DACO: 3.5.11,3.5.12,3.5.13,3.5.15,3.5.5,3.7,IIIA 2.11,IIIA 2.12,IIIA 2.14,IIIA 2.15,IIIA 2.2.1,IIIA 2.3.2
2627081	2014, BAS 440 01 I - determination of physico-chemical properties according to Directive 94/37/EC (Regulation (EC) No. 440/2008), DACO: 3.5.11,3.5.12,IIIA 2.2.1,IIIA 2.3.1,IIIA 2.3.2
2627082	2014, BAS 440 00 I, BAS 440 01 I: Determination of oxidation/reduction, DACO: 3.5.8,IIIA 2.2.2

PMRA Document Number	Reference
2627083	2014, Accelerated storage stability report - Physical and chemical properties of BAS 440 01 I: Storage stability and corrosion characteristics in commercial type containers, DACO: 2.14.1,2.14.14,2.14.2,2.14.3,3.5.14,3.5.7,IIA 2.17.1,IIA 2.4.1,IIA 2.4.2,IIIA 2.13,IIIA 2.4.1
2627085	2015, GLP Validation of Analytical Method AFR0114/01: Determination of BAS 440 I in BAS 440 01 I Formulations by Reverse-Phase HPLC Using UV Detection., DACO: 3.4.1,IIIA 5.2.1
2735413	2017, Response to PMRA Product chemisty questions, DACO: 2.12 CBI
2627475	2015, BAS 440 00 I - Group A - Product identity, composition, and analysis, DACO: 3.1.2,3.1.3,3.1.4,3.2.1,3.2.2,3.2.3,3.3.1,3.3.2,IIIA 1.2.1,IIIA 1.2.2,IIIA 1.2.3,IIIA 1.3,IIIA 1.4.1,IIIA 1.4.2,IIIA 1.4.3.1,IIIA 1.4.3.2,IIIA 1.4.3.3,IIIA 1.4.4,IIIA 1.4.5.1,IIIA 1.4.5.2 CBI
2627533	2016, DACO 3.5.4, 3.5.5,3.5.11,3.5.12,3.5.13,3.5.15, DACO: 3.5.11,3.5.12,3.5.13,3.5.15,3.5.5,3.7,IIIA 2.11,IIIA 2.12,IIIA 2.14,IIIA 2.15,IIIA 2.2.1,IIIA 2.3.2
2627534	2014, Accelerated storage stability report - Physical and chemical properties of BAS 440 00 I: Storage stability and corrosion characteristics in commercial type containers, DACO: 2.14.1,2.14.14,2.14.2,2.14.3,3.5.14,IIA 2.17.1,IIA 2.4.1,IIA 2.4.2,IIIA 2.13
2627535	2014, BAS 440 00 I - determination of physico-chemical properties according to Directive 94/37/EC (Regulation (C) No. 440/2008), DACO: 3.5.12,IIIA 2.2.1
2627536	2014, BAS 440 00 I, BAS 440 01 I: Determination of oxidation/reduction, DACO: 3.5.8,IIIA 2.2.2

2.0 Human and Animal Health

PMRA Document Number	Reference
2627737	2011, Excretion and metabolism of 14C- Meiji Reg.No. 5599022 (BAS 440 I) after oral administration in rats, DACO: 4.5.9,IIA 5.1.1
2627738	2012, Metabolic fate of (NCA-14C)ME5343 in rats - Preliminary study, DACO: 4.5.9,IIA 5.1.1
2627739	2013, Metabolic fate of ME5343-T7 pure in rats - Identification of metabolites in urine and faeces, DACO: 4.5.9,IIA 5.1.1
2627740	2015, Single-dose oral pharmacokinetic and tissue distribution study of (NCA-14C)ME5343 in Fischer 344 rats, DACO: 4.5.9,IIA 5.1.1
2627741	2015, Metabolic fate of [NCA-14C]ME5343 in rats - Excretion balance study, DACO: 4.5.9,IIA 5.1.1
2627742	2015, Kinetics of 14C-BAS 440 I in rats after oral and intravenous administration, DACO: 4.5.9,IIA 5.1.3
2627743	2016, 14C-BAS 440 I: Study on absorption, distribution, metabolism and excretion in the F344 rat (Japanese clone) after combined dietary and oral administration, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.5.9,4.8,IIA 5.1.3,IIA 5.10
2627744	2016, BAS 440 I (Afidopyropen) - Immunotoxicity study in female Wistar rats - Administration via the diet for 4 weeks, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
2627746	2016, BAS 440 I (Afidopyropen) - Repeated-dose 90-day oral toxicity study in Fischer F344 rats - Administration via the diet, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
2627748	2015, In vitro pharmacology - Study of several compounds: BASF SE study number 99V0676/09X179, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10

PMRA Document Number	Reference
2627749	2016, BAS 440 I (Afidopyropen) - Repeated-dose 90-day oral toxicity study in Fischer F344 rats - Administration via the diet, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
2627750	2015, 14 day dietary study investigating potential for BAS 440 I (Afidopyropen) to induce CYP1A1 and CYP1B1 in female F344 rats, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
2627751	2015, In vitro pharmacology study of compounds 09/0676-1 and 15/0197-1, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
2627752	2015, In vitro pharmacology study of compounds 09/0676-1 and 15/0197-1, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
2627753	2015, Estrogen receptor transcriptional activation (human cell line (Hela-9903)), DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
2627754	2015, Estrogen receptor binding assay using rat uterine cytosol (ER-RUC), DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
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2627756	2016, BAS 440 I - Repeated-dose 28-day toxicity study in Fischer F344 rats to determine treatment-related effects on prolactin levels in comparison to the positive control Bromocriptine mesylate, 28-day acclimatization period, administration via the diet, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
2627757	2016, BAS 440 I (Afidopyropen) - In-silico off-target predictions for BAS 440 I and its main metabolites, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
2627759	2016, Afidopyropen (BAS 440 I): Cyclopropane Carboxylic Acid (CPCA) Metabolite, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
2627761	2016, Mode-of-action and human relevance framework for analysis of uterine adenocarcinomas associated with Afidopyropen, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10
2627763	2009, Acute oral toxicity study of ME5343 technical in rats, DACO: 4.2.1,IIA 5.2.1
2627764	2009, Acute dermal toxicity study of ME5343 technical in rats, DACO: 4.2.2,IIA 5.2.2
2627765	2010, Acute inhalation toxicity study of ME5343 technical in rats, DACO: 4.2.3,IIA 5.2.3
2627766	2009, Skin irritation study of ME5343 technical in rabbits, DACO: 4.2.5,IIA 5.2.4
2627767	2009, Eye irritation study of ME5343 technical in rabbits, DACO: 4.2.4,IIA 5.2.5
2627768	2009, Skin sensitization study of ME5343 Technical in Guinea pigs - Maximization test, DACO: 4.2.6,IIA 5.2.6
2627769	2009, Repeated dose 28-day oral toxicity study of ME5343 Technical in mice, DACO: 4.3.3,IIA 5.3.1
2627779	2009, Repeated dose 28-day oral toxicity study of ME5343 Technical in dogs, DACO: 4.3.3,IIA 5.3.1
2627789	2010, Repeated dose 28-day oral toxicity study of ME5343 Technical in rats (Including amendment no. 1), DACO: 4.3.3,IIA 5.3.1
2627790	2010, Repeated dose 90-day oral toxicity study of ME5343 technical in rats (Including amendment no. 1), DACO: 4.3.1,IIA 5.3.2
2627791	2010, Repeated dose 90-day oral toxicity study of ME5343 Technical in mice, DACO: 4.3.1,IIA 5.3.2
2627803	2010, Repeated dose 90-day oral toxicity study of ME5343 Technical in dogs, DACO: 4.3.2,IIA 5.3.3
2627826	2011, Repeated dose 1-year oral toxicity study of ME5343 technical in dogs, DACO: 4.3.2,IIA 5.3.4

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2627850	2012, BAS 440 I (Reg.No. 5599022, ME5343 technical) - Repeated dose 28-day dermal toxicity study in Wistar rats, DACO: 4.3.5,IIA 5.3.7
2627851	2009, Bacterial reverse mutation test on ME5343 technical, DACO: 4.5.4,IIA 5.4.1
2627852	2015, BAS 440 I (Afidopyropen) - Salmonella typhimurium / Escherichia coli - Reverse mutation assay, DACO: 4.5.4,IIA 5.4.1
2627853	2015, BAS 440 I (Afidopyropen) - Salmonella typhimurium / Escherichia coli - Reverse mutation assay, DACO: 4.5.4,IIA 5.4.1
2627854	2015, BAS 440 I (Afidopyropen) - Salmonella typhimurium / Escherichia coli reverse mutation assay, DACO: 4.5.4,IIA 5.4.1
2627855	2009, Chromosome aberration test in cultured mammalian cells with ME5343 technical, DACO: 4.5.6,IIA 5.4.2
2627856	2015, BAS 440 I (Afidopyropen) - In vitro gene mutation test in CHO cells (HPRT locus assay), DACO: 4.5.5,IIA 5.4.3
2627857	2009, Micronucleus test in mice with ME5343 technical, DACO: 4.5.7,IIA 5.4.4
2627858	2015, BAS 440 I (Afidopyropen): Micronucleus Assay in bone marrow cells of the mouse (Including the Analytical Report), DACO: 4.5.7,IIA 5.4.4
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2627860	2011, Repeated dose 1-year oral toxicity study of ME5343 technical in rats, DACO: 4.4.1,4.4.4,IIA 5.5.1
2627861	2015, Repeated dose 1-year oral toxicity study of BAS 440 I (Reg.No. 5599022, ME5343 technical) in rats administration via the diet, DACO: 4.4.1,4.4.4,IIA 5.5.1
2627862	2015, Carcinogenicity study of BAS 440 I (Reg.No. 5599022, ME5343 technical) in rats - Administration via the diet, DACO: 4.4.2,4.4.4,IIA 5.5.2
2627863	2014, Carcinogenicity study of ME5343 Technical in rats, DACO: 4.4.2,4.4.4,IIA 5.5.2
2627864	2012, Carcinogenicity study of ME5343 technical in mice, DACO: 4.4.3,IIA 5.5.3
2627875	2009, Two-generation reproductive toxicity study of ME5343 technical in rats, dose-range finding study (Including amendment no.1), DACO: 4.5.1,IIA 5.6.1
2627876	2016, BAS 440 I (Afidopyropen) - One-Generation reproduction toxicity study in Wistar rats - Administration via the diet, DACO: 4.5.1,IIA 5.6.1
2627877	2016, BAS 440 I (Afidopyropen) - Two-Generation reproduction toxicity study in Wistar rats - Administration via the diet, DACO: 4.5.1,IIA 5.6.1
2627878	2013, Two-generation reproductive toxicity study of ME5343 Technical in rats, DACO: 4.5.1,IIA 5.6.1
2627880	2013, Teratogenicity study of ME5343 Technical in rats - Dose-Range Finding Study, DACO: 4.5.2,IIA 5.6.10
2627882	2013, Teratogenicity study of ME5343 Technical in rats, DACO: 4.5.2,IIA 5.6.10
2627884	2014, Teratogenicity study of ME5343 Technical in rats, DACO: 4.5.2,IIA 5.6.10
2627897	2011, Teratogenicity study of ME5343 Technical in rabbits, DACO: 4.5.3,IIA 5.6.11
2627912	2009, Teratogenicity study of ME5343 Technical in rabbits - Dose range-finding study, DACO: 4.5.3,IIA 5.6.11
2627914	2016, BAS 440 I (Afidopyropen) - Cross fostering study to detect prenatal and postnatal developmental toxicity in Wistar rats - Oral administration via the diet, DACO: 4.8,IIA 5.6.5
2627916	2012, BAS 440 I (Reg.No. 5599022, ME5343 technical) - Acute oral neurotoxicity study in Wistar rats - Administration via gavage, DACO: 4.5.12,IIA 5.7.1

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2627917	2016, BAS 440 I (Afidopyropen) - Repeated dose 90-day oral neurotoxicity study in Wistar rats - Administration via the diet, DACO: 4.5.12,IIA 5.7.1
2627918	2012, Acute oral toxicity study of ME5343-T7 in rats, DACO: 4.8,IIA 5.8
2627919	2012, Bacterial reverse mutation test on ME5343-T7, DACO: 4.8,IIA 5.8
2627920	2014, Reg.No. 5824749 (metabolite of BAS 440 I, Afidopyropen) - Salmonella typhimurium / Escherichia coli reverse mutation assay, DACO: 4.8,IIA 5.8
2627921	2016, Reg.No. 5824749 (metabolite of BAS 440 I, Afidopyropen) - Repeated dose 90-day oral toxicity study in Wistar rats - Administration via the diet, DACO: 4.8,IIA 5.8
2627922	2015, Reg.No. 5824749 (metabolite of BAS 440 I, Afidopyropen): Micronucleus test in human lymphocytes in vitro, DACO: 4.8,IIA 5.8
2627923	2015, Reg.No. 5824749 (metabolite of BAS 440 I, Afidopyropen) - In vitro gene mutation test in L5178Y mouse lymphoma cells (TK+/- locus assay, microwell version), DACO: 4.8,IIA 5.8
2627924	2015, Reg.No. 5824749 (metabolite of BAS 440 I, Afidopyropen) - Micronucleus test in bone marrow cells of the mouse, DACO: 4.8,IIA 5.8
2635785	2012, IN-V0977: Subchronic Toxicity 90-Day Gavage Study in Rats, DACO: 4.3.1
2635786	2012, IN-V0977: Subchronic Toxicity 90-Day Gavage Study in Rats, DACO: 4.3.1
2737900	2017, Reg.No. 53128 (metabolite of BAS 440 I, Afidopyropen) - Acute oral toxicity study in rats, DACO: 4.8,IIA 5.8
2760761	2017, BrlHanWIST@Jcl(GALAS) historical control data for fetal abnormalities (SR10180), DACO: 4.5.2,IIA 5.6.10
2760762	2017, PMRA comment 3_revised historical control data Wistar Han 2009-2012 IET 13-0049., DACO: 4.5.2,IIA 5.6.10
2760763	2017, Reply to PMRA comment 4_ historical control data, JW RB 2001-2015 (20170427)., DACO: 4.5.2,IIA 5.6.10
2760766	2017, HCD_09R65_Wurfdaten_Ratte_Gen_with_live_males_fr_Kanada, DACO: 4.5.2,IIA 5.6.10
2760767	2017, HCD_ 09R105_Wurfdaten_Ratte_Gen_with_live_males_fr_Kanada, DACO: 4.5.2,IIA 5.6.10
2776084	2009, Stability study of ME5343 technical in the diet for rodents (IET 08-5039), DACO: 4.5.1
2776086	2017, Report Amendment 1- 14 Day Dietary Study investigating potential for BAS 440 I (Afidopyropen) to induce CYP1A1 and CYP1B1 in Female F344 Rats, DACO: 4.8
2776087	2009, Stability study of ME5343 technical in 1% sodium carboxymethyl cellulose solution, DACO: 4.8
2784120	2017, Incidence of neoplastic lesions in control rates (24 month study), DACO: 4.5.1,IIA 5.6.1
2796732	2017, BASF Response to PMRA request for Historical Control data Prostate Inflammation, DACO: 4.8,IIA 5.8
2627543	2014, BAS 440 00 I - Acute oral toxicity study in rats, DACO: 4.6.1,IIIA 7.1.1
2627544	2014, BAS 440 00 I - Acute dermal toxicity study in rats, DACO: 4.6.2,IIIA 7.1.2
2627545	2014, Acute (4-hour) inhalation toxicity study with BAS 440 00 I in rats, DACO: 4.6.3,IIIA 7.1.3
2627546	2014, BAS 440 00 I - Acute dermal irritation / corrosion in rabbits, DACO: 4.6.5,IIIA 7.1.4
2627547	2014, BAS 440 00 I - Acute eye irritation in rabbits, DACO: 4.6.4,IIIA 7.1.5
2627548	2014, BAS 440 00 I - Assessment of sensitizing properties on albino guinea pig by repeated applications BUEHLER test with 3 applications (Including analytical report), DACO: 4.6.6,IIIA 7.1.6

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2627550	2015, BAS 440 00 I - Micronucleus test in bone marrow cells of the mouse, DACO: 4.6.8,4.7.7,4.8,5.14,IIIA 7.11
2627087	2014, BAS 440 01 I - Acute oral toxicity study in rats, DACO: 4.6.1,IIIA 7.1.1
2627088	2014, BAS 440 01 I - Acute dermal toxicity study in rats, DACO: 4.6.2,IIIA 7.1.2
2627089	2014, Acute (4-hour) inhalation toxicity study with BAS 440 01 I in rats, DACO: 4.6.3,IIIA 7.1.3
2627090	2014, BAS 440 01 I - Acute dermal irritation / corrosion in rabbits, DACO: 4.6.5,IIIA 7.1.4
2627091	2015, BAS 440 01 I - Acute eye irritation in rabbits (Including amendment no. 1), DACO: 4.6.4,IIIA 7.1.5
2627092	2014, BAS 440 01 I - Assessment of sensitizing properties on albino guinea pig by repeated applications - BUEHLER test with 3 applications (including the analytical report), DACO: 4.6.6,IIIA 7.1.6
2784120	2017, Incidence of neoplastic lesions in control rates (24 month study), DACO: 4.5.1,IIA 5.6.1
2627925	2015, ^{14}C-BAS 440 I in BAS 440 01 I - Study of the dermal penetration in rats, DACO: 5.8,IIA 5.9.9
2627552	2016, Dissipation of dislodgeable foliar residues of the insecticide BAS 440 I from melons following broadcast applications of BAS 440 00 I (DC), DACO: 5.9,IIIA 7.7.1
2627553	2016, Dissipation of dislodgeable foliar residues of the insecticide BAS 440 I from peaches following braodcast applications of BAS 440 00 I (DC), DACO: 5.9,IIIA 7.7.1
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2115788	2008, Data Submitted by the Agricultural Rentry Task Force (ARTF) to Support Revision of Agricultural Transfer Coefficients., DACO: 5.6
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2572743	2014, Agricultural Handler Exposure Scenario Monograph: Open Cab Airblast Application of Liquid Sprays, DACO: 5.3,5.4
2572745	2015, Agricultural Handler Exposure Scenario Monograph: Open Pour Mixing and Loading of Liquid Formulations, DACO: 5.3,5.4
2627723	2015, Investigation of the extractability of BAS 440 I and its metabolite M440I007 in samples from ^{14}C plant metabolism studies, DACO: 7.2.1,7.2.4,IIA 4.3
2627724	2015, Validation of BASF Method D1103 in cotton seed (seed), beans (seed), tomato (whole fruit), citrus (whole fruit) and potato (tuber): Determination of Residues of BAS 440 I and its Metabolite M440I007 in Plant Matrices using LC-MS/MS, DACO: 7.2.1,7.2.4,IIA 4.3
2627725	2015, Independent laboratory validation of BASF analytical method D1103/01: Determination of residues of BAS 440 I and its metabolite M440I007 in plant matrices using LC-MS/MS, DACO: 7.2.1,7.2.4,IIA 4.3
2627726	2016, Independent laboratory validation of residue method D1507/01: Method for the determination of residues of Afidopyropen (BAS 440 I Reg No. 5599022) and its metabolites M440I001 (Reg No. 5741530), M440I003 (Reg No. 5741533), M440I005 (Reg No. 5824382) and CPCA Carnatine (Reg No. 6009307) in animal matrices by

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	LC-MS/MS, DACO: 7.2.1,7.2.4,IIA 4.3
2627727	2016, Validation of BASF analytical method D1507/01: Method for the determination of residues of Afidopyropen (BAS 440 I - Reg No. 5599022) and its metabolites M440I001 (Reg No. 5741530), M440I003 (Reg No. 5741533), M440I005 (Reg No. 5824382) and CPCA Carnatine (Reg No. 6009307) in animal matrices by LC-MS/MS, DACO: 7.2.1,7.2.4,IIA 4.3
2627728	2016, Validation of BASF method D1514/01: Multi-residue method using AOAC official method 2007.01 for the determination of residues of Afidopyropen (BAS 440 I, Reg no. 5599022) and its metabolite M440I007 (Reg no. 5824749) in plant matrices using LC-MS/MS, DACO: 7.2.1,7.2.4,IIA 4.3
2627729	2016, Validation of BASF Method Number D1103/01 for the determination of residues of BAS 440 I and its metabolite M440I007 in cotton (seed), dry bean (seed), tomato (whole fruit), citrus (whole fruit) and rice (grain with hulls) using LC-MS/MS (Including amendment no. 1), DACO: 7.2.1,7.2.4,IIA 4.3
2627929	2016, Afidopyropen (BAS 440 I): Request to waive requirement for additional freezer storage stability data for Afidopyropen and metabolites in animal matrices, DACO: 7.3,IIA 6.1.1
2627930	2015, Metabolism of ^{14}C-BAS 440 I in soybean, DACO: 6.3,IIA 6.2.1
2627931	2015, Metabolism of ^{14}C-BAS 440 I in soybean, DACO: 6.3,IIA 6.2.1 CBI
2627932	2015, Metabolism of ^{14}C BAS 440 I in cabbage, DACO: 6.3,IIA 6.2.1
2627933	2015, Metabolism of ^{14}C BAS 440 I in cabbage, DACO: 6.3,IIA 6.2.1 CBI
2627934	2015, Metabolism of ^{14}C BAS 440 I in tomato, DACO: 6.3,IIA 6.2.1
2627935	2015, Metabolism of ^{14}C BAS 440 I in tomato, DACO: 6.3,IIA 6.2.1 CBI
2627936	2015, Metabolism of ^{14}C BAS 440 I in soybean, DACO: 6.3,IIA 6.2.1
2627937	2016, Investigation of BAS M440I031 (Trigonelline) in [^{14}C]-BAS 440 I treated cabbage, DACO: 6.3,IIA 6.2.1
2627938	2015, (NCA-^{14}C)ME5343 - Metabolic fate in tomato, DACO: 6.3,IIA 6.2.1
2627939	2015, Amended report - (NCA-^{14}C)ME5343 - Metabolism in cabbages, DACO: 6.3,IIA 6.2.1
2627940	2013, The metabolism of ^{14}C-BAS 440 I (Reg.No. 5599022) in the lactating goat, DACO: 6.2,IIA 6.2.2
2627941	2016, The metabolism of ^{14}C-CPCA-BAS 440 I in the laying hen, DACO: 6.2,IIA 6.2.2
2627942	2016, The metabolism of [^{14}C-CPCA]-BAS 440 I in the lactating goat including Amendment No 1., DACO: 6.2,IIA 6.2.2
2627943	2016, Magnitude of the residues of BAS 440 I in fruiting vegetables following applications of BAS 440 00 I, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
2627944	2015, Magnitude of the residues of BAS 440 I in/on leafy vegetables following applications of BAS 440 00 I, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
2627945	2015, Magnitude of the residues of BAS 440 I in/on cucurbit vegetables following applications of BAS 440 00 I, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
2627946	2016, Residue in brassica BAS 440 I, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
2627947	2016, Residue in BAS 440 00 I Stone Fruit (Crop Group 12), DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
2627948	2016, Residue in BAS 440 00 I pomefruit, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
2627949	2016, Magnitude of BAS 440 I and metabolite residues in potato following applications of BAS 440 00 I DC in North America, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1

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2627950	2016, Magnitude of BAS 440 I and metabolite residues in soybean following applications of BAS 440 01 I in North America, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
2627951	2015, Determination of residues of BAS 440 00 I in potatoes following four (4) applications of BAS 440 00 I, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
2627952	2015, Determination of residues of BAS 440 00 I in fruiting vegetables following four (4) applications of BAS 440 00 I, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
2627953	2015, Determination of residues of BAS 440 00 I in brassicas and leafy vegetables following four (4) applications of BAS 440 00 I, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
2627955	2016, Magnitude of the residues of BAS 440 I in tree nut raw agricultural commodities, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
2627956	2016, Afidopryopen (BAS 440 I): Request for waiver of a feeding study in poultry, DACO: 7.5,7.6,IIA 6.4.1
2627957	2016, A Meat and Milk Magnitude of the Residue Study with BAS 440 I in Lactating Dairy Cows, DACO: 7.5,7.6,IIA 6.4.2
2627958	2016, Magnitude of the residues of BAS 440 I in potato processed fractions following applications of BAS 440 00I DC, DACO: 7.4.5,IIA 6.5.3
2627959	2015, Magnitude of the residues of BAS 440 I in tomato processing fractions following applications of BAS 440 00 I to tomatoes, DACO: 7.4.5,IIA 6.5.3
2627960	2016, BAS 440 I Plum Process fraction, DACO: 7.4.5,IIA 6.5.3
2627961	2016, Residue in BAS 440 00 I apple process fraction, DACO: 7.4.5,IIA 6.5.3
2627962	2016, Magnitude of the residue of BAS 440 I in soybean processed fractions, DACO: 7.4.5,IIA 6.5.3
2627963	2015, Confined rotational crop study with ^{14}C-BAS 440 I, DACO: 7.4.4,IIA 6.6.2
2627964	2016, Confined rotational crop study with ^{14}C-BAS 440 I, DACO: 7.4.4,IIA 6.6.2
2627965	2016, Confined rotational crop study with ^{14}C-BAS 440 I, DACO: 7.4.4,IIA 6.6.2
2627966	2016, Afidopyropen (BAS 440 I): Request to waive requirement for field accumulation in rotational crops, DACO: 7.4.4,IIA 6.6.3
2715858	2016, 24 month freezer stability report - Determination of residues of Afidopyropen (BAS 440 I) and its metabolite M440I007 in plant matrices using LC-MS/MS, DACO: 7.3,IIA 6.1.1

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2627054	2015, BAS 440 01 F - Acute toxicity in the bobwhite quail (*Colinus virginianus*) after single oral administration (LD50), DACO: 9.6.4,IIIA 10.1.6
2627055	2015, BAS 440 01 F - Acute toxicity in the bobwhite quail (*Colinus virginianus*) after single oral administration (LD50), DACO: 9.6.4,IIIA 10.1.6
2627056	2015, BAS 440 01 I - Acute toxicity in the mallard duck (*Anas platyrhynchos*) after single oral administration (LD50), DACO: 9.6.4,IIIA 10.1.6
2627057	2014, BAS 440 01 I - Rainbow trout, acute toxicity test, DACO: 9.5.4,IIIA 10.2.2.1
2627058	2014, BAS 440 01 I - Rainbow trout, acute toxicity test, DACO: 9.5.4,IIIA 10.2.2.1
2627059	2014, BAS 440 01 I - *Daphnia magna*, acute immobilization test, DACO: 9.3.2,IIIA 10.2.2.2
2627061	2014, BAS 440 01 I - *Daphnia magna*, acute immobilization test, DACO: 9.3.2,IIIA 10.2.2.2
2627062	2014, BAS 440 01 I - *Pseudokirchneriella subcapitata* SAG 61.81 - Growth inhibition test, DACO: 9.8.2,9.8.3,IIIA 10.2.2.3

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2627063	2015, Acute toxicity of BAS 440 01 I to the honeybee *Apis mellifera L.* under laboratory conditions, DACO: 9.2.8,IIIA 10.4.1.1,IIIA 10.4.2.2
2627064	2015, Acute toxicity of BAS 440 01 I to the honeybee *Apis mellifera L.* under laboratory conditions, DACO: 9.2.8,IIIA 10.4.1.1,IIIA 10.4.2.2
2627065	2015, Acute toxicity of BAS 440 01 I to the honeybee *Apis mellifera L.* under laboratory conditions, DACO: 9.2.8,IIIA 10.4.1.1,IIIA 10.4.2.2
2627066	2012, Effects of EXP 5599022 AA I on the parasitic wasp *Aphidius rhopalosiphi* (DESTEPHANI-PEREZ) (Hymenoptera: Braconidae) in a laboratory trial - Dose response design, DACO: 9.2.8,IIIA 10.5.1
2627067	2012, Effects of EXP 5599022 AA I on the parasitic wasp *Aphidius rhopalosiphi* (DESTEPHANI-PEREZ) (Hymenoptera: Braconidae) in a laboratory trial - Dose response design, DACO: 9.2.8,IIIA 10.5.1
2627068	2012, Effects of EXP 5599022 AA I on the predatory mite *Typhlodromus pyri* (Acari: Phytoseiidae) in a laboratory trial - Dose response design, DACO: 9.2.8,IIIA 10.5.1
2627069	2012, Effects of EXP 5599022 AA I on the predatory mite *Typhlodromus pyri* (Acari: Phytoseiidae) in a laboratory trial - Dose response design, DACO: 9.2.8,IIIA 10.5.1
2627070	2015, EXP 5599022 AA I: Toxicity to the green lacewing *Chrysoperla carnea Steph.* (Neuroptera, Chrysopidae) after exposure to freshly applied spray deposits under extended laboratory conditions, DACO: 9.2.8,IIIA 10.5.1
2627071	2015, EXP 5599022 AA I: Toxicity to the green lacewing *Chrysoperla carnea Steph.* (Neuroptera, Chrysopidae) after exposure to freshly applied spray deposits under extended laboratory conditions, DACO: 9.2.8,IIIA 10.5.1
2627072	2012, Effects of EXP 5599022 AA I on the parasitic wasp *Aphidius rhopalosiphi* (DESTEPHANI-PEREZ) (Hymenoptera: Braconidae) in an extended laboratory trial - Dose response design, DACO: 9.2.8,IIIA 10.5.2
2627073	2012, Effects of EXP 5599022 AA I on the parasitic wasp *Aphidius rhopalosiphi* (DESTEPHANI-PEREZ) (Hymenoptera: Braconidae) in an extended laboratory trial - Dose response design, DACO: 9.2.8,IIIA 10.5.2
2627074	2012, Effects of EXP 5599022 AA I on the predatory mite *Typhlodromus pyri* (Acari: Phytoseiidae) in an extended laboratory trial - Dose response design, DACO: 9.2.8,IIIA 10.5.2
2627075	2012, Effects of EXP 5599022 AA I on the predatory mite *Typhlodromus pyri* (Acari: Phytoseiidae) in an extended laboratory trial - Dose response design, DACO: 9.2.8,IIIA 10.5.2
2627076	2012, A field study to evaluate the effects of EXP 5599022 AA I on predatory mites (Acari: Phytoseiidae) in an apple orchard in Germany - Two late applications, DACO: 9.2.9,IIIA 10.5.4
2627077	2012, A field study to evaluate the effects of EXP 5599022 AA I on predatory mites (Acari: Phytoseiidae) in an apple orchard in Southern France - Two late applications, DACO: 9.2.9,IIIA 10.5.4
2627078	2015, Acute toxicity of BAS 440 01 I to the earthworm *Eisenia fetida* in artificial soil with 10 % peat, DACO: 9.2.8,IIIA 10.6.2
2627079	2015, Acute toxicity of BAS 440 01 I to the earthworm *Eisenia fetida* in artificial soil with 10 % peat, DACO: 9.2.8,IIIA 10.6.2
2627476	2015, BAS 440 00 I - Acute toxicity in the bobwhite quail (*Colinus virginianus*) after single oral administration (LD50), DACO: 9.6.4,IIIA 10.1.6
2627477	2015, BAS 440 00 I - Acute toxicity in the bobwhite quail (*Colinus virginianus*) after single oral administration (LD50), DACO: 9.6.4,IIIA 10.1.6
2627478	2014, BAS 440 00 I - Rainbow trout, acute toxicity test, DACO: 9.5.4,IIIA 10.2.2.1

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2627479	2014, BAS 440 00 I - Rainbow trout, acute toxicity test, DACO: 9.5.4,IIIA 10.2.2.1
2627480	2014, BAS 440 00 I - *Daphnia magna*, acute immobilization test, DACO: 9.3.2,IIIA 10.2.2.2
2627481	2014, BAS 440 00 I - i, acute immobilization test, DACO: 9.3.2,IIIA 10.2.2.2
2627482	2014, BAS 440 I - *Pseudokirchneriella subcapitata* SAG 61.81, growth inhibition test, DACO: 9.4.6,9.5.4,IIIA 10.2.2.4
2627483	2014, BAS 440 I - *Pseudokirchneriella subcapitata* SAG 61.81, growth inhibition test, DACO: 9.4.6,9.5.4,IIIA 10.2.2.4
2627484	2014, Chronic toxicity of BAS 440 I (Reg.No. 5599022) to the honeybee *Apis mellifera L.* under laboratory conditions, DACO: 9.2.8,IIIA 10.4.1.2
2627485	2014, Chronic toxicity of BAS 440 I (Reg.No. 5599022) to the honeybee *Apis mellifera L.* under laboratory conditions, DACO: 9.2.8,IIIA 10.4.1.2
2627486	2013, BAS 440 00 I - Acute oral and contact toxicity to the honeybee, *Apis mellifera L.* under laboratory conditions (Including amendment no. 1), DACO: 9.2.8,IIIA 10.4.2.1,IIIA 10.4.2.2
2627487	2013, BAS 440 00 I - Acute oral and contact toxicity to the honeybee, *Apis mellifera L.* under laboratory conditions (Including amendment no. 1), DACO: 9.2.8,IIIA 10.4.2.1,IIIA 10.4.2.2
2627488	2015, BAS 440 00 I (a.i. name/reg. no. Afidopyropen/5599022): Toxicity of residues on foliage to the Honey bee, *Apis mellifera*, DACO: 9.2.8,IIIA 10.4.3
2627489	2015, BAS 440 00 I (a.i. name/reg. no. Afidopyropen/5599022): Toxicity of residues on foliage to the Honey bee, *Apis mellifera*, DACO: 9.2.8,IIIA 10.4.3
2627490	2015, Determination of residues of BAS 440 00 I (Afidopyropen) in bee-relevant matrices in a semi-field honey bee (*Apis mellifera L.*) study in canola (Brassica sp.) after one application during flowering, DACO: 9.2.8,IIIA 10.4.3
2627491	2015, Determination of the residues of BAS 440 00 I in bee relevant matrices collected from tomatoes following a full bloom foliar application of BAS 440 00 I, DACO: 9.2.8,IIIA 10.4.3
2627492	2015, Determination of residues of BAS 440 00 I (Afidopyropen and its metabolite M440I007) in bee-relevant matrices in a field study in citrus after one application during flowering, DACO: 9.2.8,IIIA 10.4.3
2627493	2015, Determination of residues of BAS 440 00 I (Afidopyropen) in bee-relevant matrices in a semi-field honey bee (*Apis mellifera L.*) study in canola (Brassica sp.) after one application during flowering, DACO: 9.2.8,IIIA 10.4.3
2627494	2015, Determination of the residues of BAS 440 00 I in bee relevant matrices collected from tomatoes following a full bloom foliar application of BAS 440 00 I, DACO: 9.2.8,IIIA 10.4.3
2627495	2015, Determination of residues of BAS 440 00 I (Afidopyropen and its metabolite M440I007) in bee-relevant matrices in a field study in citrus after one application during flowering, DACO: 9.2.8,IIIA 10.4.3
2627496	2013, Field study to evaluate potential side effects of BAS 440 UV I on honeybees (*Apis mellifera L.*) (Including amendment no. 1), DACO: 9.2.9,IIIA 10.4.5
2627497	2013, Field study to evaluate potential side effects of BAS 440 UV I on honeybees (*Apis mellifera L.*) (Including amendment no. 1), DACO: 9.2.9,IIIA 10.4.5
2627498	2014, Effects of BAS 440 00 I on the honeybee Apis mellifera L. under field conditions with additional assessments on colony and brood development, DACO: 9.2.9,IIIA 10.4.5

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2627499	2014, Effects of BAS 440 00 I on the honeybee *Apis mellifera L.* under field conditions with additional assessments on colony and brood development, DACO: 9.2.9,IIIA 10.4.5
2627500	2015, Acute toxicity of BAS 440 00 I to honeybee larvae (*Apis mellifera L.*) under laboratory conditions (in vitro) (Including amendment no. 1), DACO: 9.2.9,IIIA 10.4.6.1
2627501	2015, Acute toxicity of BAS 440 00 I to honeybee larvae (*Apis mellifera L.*) under laboratory conditions (in vitro) (Including amendment no. 1), DACO: 9.2.9,IIIA 10.4.6.1
2627503	2015, Chronic toxicity of BAS 440 00 I to honeybee larvae *Apis mellifera L.* under laboratory conditions (in vitro), DACO: 9.2.9,IIIA 10.4.6.1
2627504	2015, Chronic toxicity of BAS 440 00 I to honeybee larvae *Apis mellifera L.* under laboratory conditions (in vitro), DACO: 9.2.9,IIIA 10.4.6.1
2627505	2014, Semi-field brood study to evaluate potential effects of BAS 440 00 I on brood development of honeybees (*Apis mellifera L.*), DACO: 9.2.8,IIIA 10.4.7
2627506	2014, Semi-field brood study to evaluate potential effects of BAS 440 00 I on brood development of honeybees (*Apis mellifera L.*), DACO: 9.2.8,IIIA 10.4.7
2627507	2015, Effects of BAS 440 00 I on the honeybee *Apis mellifera L.* under semi-field conditions (tunnel test) with additional assessments on colony and brood development, DACO: 9.2.8,IIIA 10.4.7
2627508	2015, Semi-field brood study to evaluate potential effects of BAS 440 00 I on brood development of honeybees (*Apis mellifera L.*), DACO: 9.2.8,IIIA 10.4.7
2627509	2015, Semi-field study to evaluate potential effects of BAS 440 00 I on the development of honeybee colonies (*Apis mellifera L.*), DACO: 9.2.8,IIIA 10.4.7
2627510	2015, Determination of side-effects of BAS 440 00 I (Afidopyropen) on honey bees (*Apis mellifera L.*) in a semi-field (tunnel) study after application in flowering winter oil seed rape (*Brassica napus*), DACO: 9.2.8,IIIA 10.4.7
2627511	2015, Effects of BAS 440 00 I on the honeybee *Apis mellifera L.* under semi-field conditions (tunnel test) with additional assessments on colony and brood development, DACO: 9.2.8,IIIA 10.4.7
2627512	2015, Semi-field brood study to evaluate potential effects of BAS 440 00 I on brood development of honeybees (*Apis mellifera L.*), DACO: 9.2.8,IIIA 10.4.7
2627513	2015, Semi-field study to evaluate potential effects of BAS 440 00 I on the development of honeybee colonies (*Apis mellifera L.*), DACO: 9.2.8,IIIA 10.4.7
2627514	2015, Determination of side-effects of BAS 440 00 I (Afidopyropen) on honey bees (*Apis mellifera L.*) in a semi-field (tunnel) study after application in flowering winter oil seed rape (*Brassica napus*), DACO: 9.2.8,IIIA 10.4.7
2627516	2015, Effects of BAS 440 00 I on the honeybee *Apis mellifera L.* under semi-field conditions (tunnel test) with additional assessments on colony and brood development, DACO: 9.2.8,IIIA 10.4.7
2627517	2015, Effects of BAS 440 00 I on the honeybee *Apis mellifera L.* under semi-field conditions (tunnel test) with additional assessments on colony and brood development, DACO: 9.2.8,IIIA 10.4.7
2627518	2014, Effects of BAS 440 00 I on the predatory mite *Typhlodromus pyri* SCHEUTEN in a laboratory test - Rate-response test, DACO: 9.2.8,IIIA 10.5.1
2627519	2014, Effects of BAS 440 00 I on the parasitic wasp *Aphidius rhopalosiphi* (DeStefani-Perez) in a laboratory test - Rate-Response-Test (LR50), DACO: 9.2.8,IIIA 10.5.1
2627521	2014, Effects of BAS 440 00 I on the parasitic wasp *Aphidius rhopalosiphi* (DeStefani-Perez) in a laboratory test - Rate-Response-Test (LR50), DACO: 9.2.8,IIIA 10.5.1

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2627522	2014, Effects of BAS 440 00 I on the predatory mite *Typhlodromus pyri* SCHEUTEN in a laboratory test - Rate-response test, DACO: 9.2.8,IIIA 10.5.1
2627523	2014, Acute toxicity of BAS 440 00 I to the earthworm *Eisenia fetida* in artificial soil with 10 % peat, DACO: 9.2.8,IIIA 10.6.2
2627524	2014, Acute toxicity of BAS 440 00 I to the earthworm *Eisenia fetida* in artificial soil with 10 % peat, DACO: 9.2.8,IIIA 10.6.2
2627525	2014, Effects of BAS 440 00 I on the activity of soil microflora (Carbon transformation test), DACO: 9.2.8,IIIA 10.7.1
2627526	2014, Effects of BAS 440 00 I on the activity of soil microflora (Nitrogen transformation test), DACO: 9.2.8,IIIA 10.7.1
2627527	2014, Effects of BAS 440 00 I on the activity of soil microflora (Carbon transformation test), DACO: 9.2.8,IIIA 10.7.1
2627528	2014, Effects of BAS 440 00 I on the activity of soil microflora (Nitrogen transformation test), DACO: 9.2.8,IIIA 10.7.1
2627529	2015, BAS 440 00I: A toxicity test to determine the effects on seedling emergence of ten species of plants, DACO: 9.8.6,IIIA 10.8.1.1
2627530	2015, BAS 440 00I: A toxicity test to determine the effects on seedling emergence of ten species of plants, DACO: 9.8.6,IIIA 10.8.1.1
2627531	2015, BAS 440 00I: A toxicity test to determine the effects on vegetative vigor of ten species of plants, DACO: 9.8.6,IIIA 10.8.1.2
2627532	2015, BAS 440 00I: A toxicity test to determine the effects on vegetative vigor of ten species of plants, DACO: 9.8.6,IIIA 10.8.1.2
2628000	2012, BAS 440 I (Reg.No. 5599022, ME5343 technical) - Acute toxicity in the Bobwhite quail (*Colinus virginianus*) after single oral administration (LD50), DACO: 9.6.2.1,9.6.2.2,9.6.2.3,IIA 8.1.1
2628001	2012, BAS 440 I (Reg.No. 5599022, ME5343 technical) - Acute toxicity in the Bobwhite quail (*Colinus virginianus*) after single oral administration (LD50), DACO: 9.6.2.1,9.6.2.2,9.6.2.3,IIA 8.1.1
2628002	2012, BAS 440 I (Reg.No. 5599022, ME5343 technical) - Acute toxicity in the Mallard duck (*Anas platyrhynchos*) after single oral administration (LD50), DACO: 9.6.2.1,9.6.2.2,9.6.2.3,IIA 8.1.1
2628003	2012, BAS 440 I (Reg.No. 5599022, ME5343 technical) - Acute toxicity in the Mallard duck (*Anas platyrhynchos*) after single oral administration (LD50), DACO: 9.6.2.1,9.6.2.2,9.6.2.3,IIA 8.1.1
2628004	2013, BAS 440 I (Afidopyropen) - Acute toxicity in the Zebra finch (*Taeniopygia guttata*) after single oral administration (LD50), DACO: 9.6.2.1,9.6.2.2,9.6.2.3,IIA 8.1.1
2628005	2013, BAS 440 I (Afidopyropen) - Acute toxicity in the Zebra finch (*Taeniopygia guttata*) after single oral administration (LD50), DACO: 9.6.2.1,9.6.2.2,9.6.2.3,IIA 8.1.1
2628006	2012, BAS 440 I (Reg.No. 5599022, ME5343 technical) - Avian dietary LC50 test in chicks of the Bobwhite quail (*Colinus virginianus*), DACO: 9.6.2.4,9.6.2.5,IIA 8.1.2
2628007	2012, BAS 440 I (Reg.No. 5599022, ME5343 technical) - Avian dietary LC50 test in chicks of the Bobwhite quail (*Colinus virginianus*), DACO: 9.6.2.4,9.6.2.5,IIA 8.1.2
2628008	2012, BAS 440 I (Reg.No. 5599022, ME5343 technical) - Avian dietary LC50 test in ducklings of the mallard duck (*Anas platyrhynchos*), DACO: 9.6.2.4,9.6.2.5,IIA 8.1.2
2628009	2012, BAS 440 I (Reg.No. 5599022, ME5343 technical) - Avian dietary LC50 test in ducklings of the mallard duck (*Anas platyrhynchos*), DACO: 9.6.2.4,9.6.2.5,IIA 8.1.2

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2628010	2014, BAS 440 I - A reproduction study with the Northern Bobwhite, DACO: 9.6.3.1,9.6.3.2,9.6.3.3,IIA 8.1.4
2628011	2014, BAS 440 I - A reproduction study with the Northern Bobwhite, DACO: 9.6.3.1,9.6.3.2,9.6.3.3,IIA 8.1.4
2628012	2015, BAS 440 I: A Reproduction Study with the Mallard, DACO: 9.6.3.1,9.6.3.2,9.6.3.3,IIA 8.1.4
2628013	2015, BAS 440 I: A Reproduction Study with the Mallard, DACO: 9.6.3.1,9.6.3.2,9.6.3.3,IIA 8.1.4
2628014	2015, Effects of BAS 440 I (Reg.No. 5599022, ME 5343 technical) on the activity of soil microflora (Nitrogen transformation test), DACO: 9.2.8,9.2.9,IIA 8.10.1
2628015	2015, Effects of BAS 440 I (Reg.No. 5599022, ME 5343 technical) on the activity of soil microflora (Nitrogen transformation test), DACO: 9.2.8,9.2.9,IIA 8.10.1
2628016	2015, Effects of BAS 440 I (Reg.No. 5599022, ME 5343 technical) on the activity of soil microflora (Carbon transformation test), DACO: 9.2.8,9.2.9,IIA 8.10.2
2628017	2015, Effects of BAS 440 I (Reg.No. 5599022, ME 5343 technical) on the activity of soil microflora (Carbon transformation test), DACO: 9.2.8,9.2.9,IIA 8.10.2
2628018	2015, Effects of BAS 440 I (Reg.No. 5599022, ME 5343 technical) on the activity of soil microflora (Carbon transformation test), DACO: 9.2.8,9.2.9,IIA 8.10.2
2628019	2012, BAS 440 I: A 96-hour static acute toxicity test with the sheepshead minnow (*Cyprinodon variegatus*), DACO: 9.4.2,9.4.3,9.4.4,IIA 8.11.1
2628020	2012, BAS 440 I: A 96-hour static acute toxicity test with the sheepshead minnow (*Cyprinodon variegatus*), DACO: 9.4.2,9.4.3,9.4.4,IIA 8.11.1
2628021	2012, BAS 440 I: A 96-hour shell deposition test with the eastern oyster (*Crassostrea virginica*), DACO: 9.4.2,9.4.3,9.4.4,IIA 8.11.1
2628022	2012, BAS 440 I: A 96-hour shell deposition test with the eastern oyster (*Crassostrea virginica*), DACO: 9.4.2,9.4.3,9.4.4,IIA 8.11.1
2628023	2015, BAS 440 I: A 96-hour static acute toxicity test with the saltwater mysid (*Americamysis bahia*), DACO: 9.4.2,9.4.3,9.4.4,IIA 8.11.1
2628024	2016, BAS 440 I (Afidopyropen): Detailed review of metabolites of relevance for ecotoxicology, DACO: 9.9,IIA 8.14.2
2628025	2015, Effects of BAS 440 I (Reg.No. 5599022, ME5343 technical) on the reproduction of the collembolan *Folsomia candida*, DACO: 9.3.4,9.6.6,9.9,IIA 8.16.1
2628027	2015, BAS 440 I (Afidopyropen) - Acute toxicity study in the rainbow trout (*Oncorhynchus mykiss*), DACO: 9.5.2.1,9.5.2.3,IIA 8.2.1.1
2628029	2015, BAS 440 I (Afidopyropen) - Acute toxicity study in the rainbow trout (*Oncorhynchus mykiss*), DACO: 9.5.2.1,9.5.2.3,IIA 8.2.1.1
2628031	2013, BAS 440 I (Reg.No. 5599022, ME5343 technical) - Acute toxicity study in the fathead minnow (*Pimephales promelas*), DACO: 9.5.2.2,9.5.2.3,IIA 8.2.1.2
2628032	2013, BAS 440 I (Reg.No. 5599022, ME5343 technical) - Acute toxicity study in the fathead minnow (*Pimephales promelas*), DACO: 9.5.2.2,9.5.2.3,IIA 8.2.1.2
2628033	2011, Acute toxicity Study of ME5343 in Carp, DACO: 9.5.2.2,9.5.2.3,IIA 8.2.1.2
2628034	2011, Acute toxicity Study of ME5343 in Carp, DACO: 9.5.2.2,9.5.2.3,IIA 8.2.1.2
2628035	2013, BAS 440 I (Afidopyropen) - Early life-stage toxicity test on the fathead minnow (*Pimephales promelas*) in a flow through system, DACO: 9.5.3.1,IIA 8.2.4
2628036	2013, BAS 440 I (Afidopyropen) - Early life-stage toxicity test on the fathead minnow (*Pimephales promelas*) in a flow through system, DACO: 9.5.3.1,IIA 8.2.4
2628037	2015, BAS 440I: An early life-stage toxicity test with the sheepshead minnow (*Cyprinodon variegatus*), DACO: 9.5.3.1,IIA 8.2.4

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2628038	2015, BAS 440I: An early life-stage toxicity test with the sheepshead minnow (*Cyprinodon variegatus*), DACO: 9.5.3.1,IIA 8.2.4
2628039	2013, Bioconcentration study of ME5343 in carp, DACO: 9.5.6,IIA 8.2.6.1
2628040	2013, Bioconcentration study of ME5343 in carp, DACO: 9.5.6,IIA 8.2.6.1
2628041	2011, Acute immobilization study of ME5343 with *Daphnia magna*, DACO: 9.3.2,IIA 8.3.1.1
2628042	2011, Acute immobilization study of ME5343 with *Daphnia magna*, DACO: 9.3.2,IIA 8.3.1.1
2628043	2014, Chronic toxicity of BAS 440 I (Reg.No.5599022, ME5343 technical) to *Daphnia magna* Straus in a 21 day semi-static test, DACO: 9.3.3,IIA 8.3.2.1
2628044	2014, Chronic toxicity of BAS 440 I (Reg.No.5599022, ME5343 technical) to *Daphnia magna* Straus in a 21 day semi-static test, DACO: 9.3.3,IIA 8.3.2.1
2628045	2013, BAS 440 I: A flow-through life-cycle toxicity test with the saltwater mysid (*Americamysis bahia*), DACO: 9.3.3,IIA 8.3.2.1
2628046	2013, BAS 440 I: A flow-through life-cycle toxicity test with the saltwater mysid (*Americamysis bahia*), DACO: 9.3.3,IIA 8.3.2.1
2628047	2014, Chronic toxicity of the BAS 440 I (Reg.No.5599022; ME5343 technical) to Moina macrocopa in a 10 day semi-static test, DACO: 9.3.3,IIA 8.3.2.1
2628048	2014, Chronic toxicity of the BAS 440 I (Reg.No.5599022; ME5343 technical) to Moina macrocopa in a 10 day semi-static test, DACO: 9.3.3,IIA 8.3.2.1
2628049	2014, BAS 440 I: Chronic toxicity to the Cladoceran, *Ceriodaphnia dubia*, under flow-through test conditions, DACO: 9.3.3,IIA 8.3.2.1
2628050	2014, BAS 440 I: Chronic toxicity to the Cladoceran, *Ceriodaphnia dubia*, under flow-through test conditions, DACO: 9.3.3,IIA 8.3.2.1
2628051	2013, Chronic toxicity of BAS 440 I (Reg.No. 5599022, ME5343) to the non-biting midge *Chironomus riparius* - A spiked water study, DACO: 9.3.4,9.9,IIA 8.3.2.2,IIA 8.5.2
2628052	2013, Chronic toxicity of BAS 440 I (Reg.No. 5599022, ME5343) to the non-biting midge *Chironomus riparius* - A spiked water study, DACO: 9.3.4,9.9,IIA 8.3.2.2,IIA 8.5.2
2628053	2014, Effect of BAS 440 I (ME5343, Reg.No. 5599022) on the growth of the blue-green alga *Anabaena flos-aquae*, DACO: 9.8.2,9.8.3,IIA 8.4
2628054	2014, Effect of BAS 440 I (ME5343, Reg.No. 5599022) on the growth of the blue-green alga *Anabaena flos-aquae*, DACO: 9.8.2,9.8.3,IIA 8.4
2628055	2014, BAS 440 I (Reg. No. 5599022) - *Skeletonema costatum* UTEX LB 2308 growth inhibition test, DACO: 9.8.2,9.8.3,IIA 8.4
2628056	2014, BAS 440 I (Reg. No. 5599022) - *Skeletonema costatum* UTEX LB 2308 growth inhibition test, DACO: 9.8.2,9.8.3,IIA 8.4
2628057	2014, BAS 440 I (Reg. No. 5599022) - *Navicula pelliculosa* SAG 1050-3 - Growth inhibition test, DACO: 9.8.2,9.8.3,IIA 8.4
2628058	2014, BAS 440 I (Reg. No. 5599022) - *Navicula pelliculosa* SAG 1050-3 - Growth inhibition test, DACO: 9.8.2,9.8.3,IIA 8.4
2628059	2011, Algae growth inhibition study of ME5343, DACO: 9.8.2,9.8.3,IIA 8.4
2628060	2011, Algae growth inhibition study of ME5343, DACO: 9.8.2,9.8.3,IIA 8.4
2628061	2014, BAS 440 I: A 10-day acute toxicity test with the freshwater amphipod (*Hyalella azteca*) using spiked sediment, DACO: 9.9,IIA 8.5.1
2628062	2014, BAS 440 I: A 10-day acute toxicity test with the freshwater amphipod (*Hyalella azteca*) using spiked sediment, DACO: 9.9,IIA 8.5.1

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2628063	2014, BAS 440 I: A 10-day acute toxicity test with the chironomid midge (*Chironomus dilutus*) using spiked sediment, DACO: 9.9,IIA 8.5.1
2628064	2014, BAS 440 I: A 10-day acute toxicity test with the chironomid midge (*Chironomus dilutus*) using spiked sediment, DACO: 9.9,IIA 8.5.1
2628065	2014, BAS 440 I: A 10-day acute toxicity test with the marine amphipod (*Leptocheirus plumulosus*) using spiked sediment, DACO: 9.9,IIA 8.5.1
2628066	2014, BAS 440 I: A 10-day acute toxicity test with the marine amphipod (*Leptocheirus plumulosus*) using spiked sediment, DACO: 9.9,IIA 8.5.1
2628067	2015, M440I024: A 10-day acute toxicity test with the midge (*Chironomus dilutus*) using spiked sediment, DACO: 9.9,IIA 8.5.1
2628068	2015, M440I024: A 10-day acute toxicity test with the midge (*Chironomus dilutus*) using spiked sediment, DACO: 9.9,IIA 8.5.1
2628069	2015, BAS 440 I - 10-Day toxicity test exposing estuarine amphipods (*Leptocheirus plumulosus*) to a test substance applied to sediment under static conditions, DACO: 9.9,IIA 8.5.1
2628070	2015, BAS 440 I - 10-Day toxicity test exposing estuarine amphipods (*Leptocheirus plumulosus*) to a test substance applied to sediment under static conditions, DACO: 9.9,IIA 8.5.1
2628071	2015, BAS 440 I: A Life cycle toxicity test with the midge (*Chironomus dilutus*) Using Spiked Sediment, DACO: 9.9,IIA 8.5.2
2628072	2015, BAS 440 I: A Life cycle toxicity test with the midge (*Chironomus dilutus*) Using Spiked Sediment, DACO: 9.9,IIA 8.5.2
2628073	2014, BAS 440 I (Reg. No. 5599022) - *Lemna gibba* CPCC 310 growth inhibition test, DACO: 9.8.5,IIA 8.6
2628074	2014, BAS 440 I (Reg. No. 5599022) - *Lemna gibba* CPCC 310 growth inhibition test, DACO: 9.8.5,IIA 8.6
2628075	2016, BAS 440 I (Afidopyropen): Pollinator Screening Level Ecological Risk Assessment Including Higher Tiered Steps for Proposed Applications in Several Crops of the United States and Canada, DACO: 9.2.4.2,IIA 8.7.1
2628076	2013, Acute toxicity of BAS 440 I (Reg.No. 5599022) to the honeybee *Apis mellifera L.* under laboratory conditions, DACO: 9.2.4.1,9.2.4.2,IIA 8.7.1,IIA 8.7.2
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2628078	2013, Acute toxicity of BAS 440 I (Reg.No. 5599022) to the honeybee *Apis mellifera L.* under laboratory conditions, DACO: 9.2.4.1,9.2.4.2,IIA 8.7.1,IIA 8.7.2
2628079	2014, Acute oral and contact toxicity of BAS 440 I (Reg.No. 5599022) to the bumblebee (*Bombus terrestris L.*) in the laboratory, DACO: 9.2.4.1,9.2.4.2,IIA 8.7.1,IIA 8.7.2
2628080	2014, Acute oral and contact toxicity of BAS 440 I (Reg.No. 5599022) to the bumblebee (*Bombus terrestris L.*) in the laboratory, DACO: 9.2.4.1,9.2.4.2,IIA 8.7.1,IIA 8.7.2
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2628083	2012, Acute toxicity (14 days) of BAS 440 I (Reg.No. 5599022, ME5343 technical) to the earthworm *Eisenia fetida* in artificial soil with 5% peat, DACO: 9.2.3.1,IIA 8.9.1

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2628085	2014, Acute toxicity of Reg.No. 5741532 (metabolite of BAS 440 I), M440I002) to the earthworm - *Eisenia fetida* in artificial soil with 10% peat, DACO: 9.2.3.1,IIA 8.9.1
2628086	2014, Acute toxicity of Reg.No. 5741532 (metabolite of BAS 440 I), M440I002) to the earthworm - *Eisenia fetida* in artificial soil with 10% peat, DACO: 9.2.3.1,IIA 8.9.1
2628087	2014, Acute toxicity of Reg.No. 5824382 (metabolite of BAS 440 I, M440Ioo5) to the earthworm *Eisenia fetida* in artificial soil with 10% peat, DACO: 9.2.3.1,IIA 8.9.1
2628088	2014, Acute toxicity of Reg.No. 5824382 (metabolite of BAS 440 I, M440Ioo5) to the earthworm *Eisenia fetida* in artificial soil with 10% peat, DACO: 9.2.3.1,IIA 8.9.1
2628089	2014, Reg.No. 5741533 (metabolite of BAS 440 I): Acute toxicity to the earthworm *Eisenia fetida* in artificial soil with 10% peat, DACO: 9.2.3.1,IIA 8.9.1
2628090	2014, Reg.No. 5741533 (metabolite of BAS 440 I): Acute toxicity to the earthworm *Eisenia fetida* in artificial soil with 10% peat, DACO: 9.2.3.1,IIA 8.9.1
2628091	2015, Reg.No. 5886215 (metabolite of BAS 440 I, M440I024): Acute toxicity to the earthworm *Eisenia fetida* in artificial soil with 10% peat, DACO: 9.2.3.1,IIA 8.9.1
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2627709	2014, (NCA-14C)ME5343 - Hydrolysis in water, DACO: 8.2.3.2,IIA 2.9.1,IIA 7.5
2627710	2014, (NCA-14C)ME5343 - Hydrolysis in water, DACO: 8.2.3.2,IIA 2.9.1,IIA 7.5
2627711	2014, (NCA-14C)ME5343 - Photodegradation in water and determination of the quantum yield, DACO: 8.2.3.3,8.2.3.3.2,IIA 2.9.2,IIA 2.9.3,IIA 2.9.4,IIA 7.6
2627712	2014, (NCA-14C)ME5343 - Photodegradation in water and determination of the quantum yield, DACO: 8.2.3.3,8.2.3.3.2,IIA 2.9.2,IIA 2.9.3,IIA 2.9.4,IIA 7.6
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2627714	2015, (Pyranon-14C)ME5343: Photolytic fate in water, DACO: 8.2.3.3.2,IIA 2.9.2,IIA 7.6
2627730	2015, Extractability evaluation of BAS 440 I residues in soil using procedures from the aerobic soil metabolism and the residue analytical method, DACO: 8.2.2.1,IIA 4.4
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PMRA Document Number	Reference
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2627968	2015, Aerobic soil metabolism of BAS 440 I, DACO: 8.2.3.4.2,IIA 7.1.1,IIA 7.2.3
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2627970	2015, Degradation of BAS 440 I in aerobic soils, DACO: 8.2.3.4.2,IIA 7.1.1,IIA 7.2.3
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2627975	2015, USDA taxonomic information for soils used in the environmental fate studies of Afidopyropen (BAS 440 I), DACO: 8.2.3.6,8.2.4.6,8.5.1,8.6,IIA 7.13
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2627983	2015, Adsorption / desorption behavior of 14C-BAS 440 I in US and European soils, DACO: 8.2.4.2,IIA 7.4.1
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2627986	2015, Adsorption / desorption behavior of M440I002 (metabolite of BAS 440 I) on different US and European soils, DACO: 8.2.4.2,IIA 7.4.2
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2627991	2015, Adsorption / desorption behavior of M440I024 (metabolite of BAS 440 I) on US and European soils, DACO: 8.2.4.2,IIA 7.4.2
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4.0 Value

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2627539	2016, Value 10 Summary, DACO: 10.2.3.1, 10.2.3.2, 10.2.3.3, 10.2.3.4, 10.3.1, 10.3.2, 10.3.3, 10.4, 10.5.1, 10.5.2, 10.5.3, 10.5.4, 10.6, IIIA 6.1.1, IIIA 6.1.2, IIIA 6.1.3, IIIA 6.1.4.1, IIIA 6.1.4.2, IIIA 6.1.4.3, IIIA 6.2.1, IIIA 6.2.2, IIIA 6.2.3, IIIA 6.2.4, IIIA 6.2.5, IIIA 6.2.6, IIIA 6.2.7, IIIA 6.2.8, IIIA 6.3, IIIA 6.4.1, IIIA 6.4.2, IIIA 6.4.3, IIIA 6.5, IIIA 6.6, IIIA 6.7
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B. Additional Information Considered

i) Published Information

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