Proposed Registration Decision PRD2016-01

Fenpyroximate

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Overview

Proposed Registration Decision for Fenpyroximate

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Fenpyroximate Technical and Fenpyroximate 5SC Miticide/Insecticide containing the technical grade active ingredient fenpyroximate, for control of spider mites, broad mite and cyclamen mite and suppression of whiteflies on indoor ornamental plants and greenhouse vegetable crops.

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

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Fenpyroximate Technical and Fenpyroximate 5SC Miticide/Insecticide.

What Does Health Canada Consider When Making a Registration Decision?

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

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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

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

Before making a final registration decision on fenpyroximate, 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 fenpyroximate, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

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

What Is Fenpyroximate?

Fenpyroximate is a new conventional chemical that acts as a miticide and insecticide. It interferes with energy production within cells and may also inhibit development of the target pests. Formulated into the end-use product Fenpyroximate 5SC Miticide/Insecticide, fenpyroximate provides control of spider mites, broad mite and cyclamen mite and suppression of whiteflies on indoor ornamental plants and greenhouse vegetable crops.

Health Considerations

Can Approved Uses of Fenpyroximate Affect Human Health?

Fenpyroximate 5SC Miticide/Insecticide, containing fenpyroximate, is unlikely to affect your health when used according to label directions.

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

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

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

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

In laboratory animals, the technical grade active ingredient fenpyroximate was of high acute toxicity by the oral route. It was of low acute toxicity via the dermal route and of moderate acute toxicity by inhalation exposure. Fenpyroximate was minimally irritating to the eyes and non-irritating to the skin. Fenpyroximate did cause an allergic skin reaction. Based on these findings, the signal word and hazard statements "DANGER – POISON" and "POTENTIAL SKIN SENSITIZER" are required on the label.

The end-use product Fenpyroximate 5SC Miticide/Insecticide was of low acute toxicity by the oral and dermal routes of exposure, and of slight acute toxicity by the inhalation route. It was non-irritating to the skin and did not cause an allergic skin reaction. Fenpyroximate 5SC Miticide/Insecticide was moderately irritating to the eyes. Based on these findings, the signal word and hazard statement "WARNING – EYE IRRITANT" and "POISON" are required on the label.

Registrant-supplied short and long-term (lifetime) animal toxicity tests were assessed for the potential of fenpyroximate to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on body weight, food consumption and the gastro-intestinal tract. In addition, there was an increased incidence of eye effects in the developing fetus, which occurred at a dose that was also toxic to the mothers. Thus, there was no indication that the young were more sensitive than the adult animal.

The risk assessment protects against the effects of fenpyroximate by ensuring that the level of human exposure is well below the lowest dose 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 exposure from food and water was not conducted since there is no likelihood of residue transfer to drinking water from greenhouse use. Dietary intake estimates for food revealed that exposure was <16% of the acceptable daily intake (ADI), with children 1-2 years being the most exposed population subgroup. Females aged 13-49 years have a different ADI than that of the other subgroups and are expected to be exposed to less than 6% of the ADI. Based on these estimates, the chronic dietary risk to food alone from fenpyroximate is not of health concern for all population subgroups.

Fenpyroximate is not carcinogenic; therefore, a cancer dietary risk assessment is not required.

Dietary intake estimates for food indicate that exposure was <15% of the acute reference dose (ARfD), with children 1-2 years being the most exposed population subgroup. Females 13-49 years have a different ARfD than that of the other population subgroups and may be exposed to up to 30% of the ARfD. Based on these estimates, the acute dietary risk to food alone from fenpyroximate is not of health concern for all population subgroups.

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

Residue trials in greenhouses conducted in Canada, in the United States, and the European Union using fenpyroximate on tomatoes, peppers, and cucumbers are acceptable.

Risks in Residential and Other Non-Occupational Environments

Occupants, bystanders and the general public are not expected come into contact with residues of Fenpyroximate 5SC Miticide/Insecticide when it is applied to interior plantscapes, malls and office buildings, since Fenpyroximate 5SC Miticide/Insecticide can only be applied when bystanders are not in the application area and contact with treated plants is not expected to occur until after the residues have dried.

Occupational Risks From Handling Fenpyroximate 5SC Miticide/Insecticide

Occupational risks are not of concern when Fenpyroximate 5SC Miticide/Insecticide is used according to the proposed label directions, which include protective measures.

Workers who mix, load or apply Fenpyroximate 5SC Miticide/Insecticide can come in direct contact with fenpyroximate residues on the skin or through inhaling spray mists during application. Furthermore, workers re-entering freshly treated greenhouses can come in direct contact with Fenpyroximate 5SC Miticide/Insecticide residues on the skin from treated foliage. Therefore, the label specifies that during mixing, loading, application, clean-up and repair when using a backpack sprayer or manually-pressurized handwand, workers must wear a long-sleeved shirt and long pants, chemical-resistant gloves, shoes plus socks and goggles or face shield. The label also specifies that during mixing, loading, application, clean-up and repair using a mechanically-pressurized handwand, workers must wear coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, shoes plus socks and goggles or face shield. The label also requires that nobody can enter treated areas for 12 hours after application.

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 Fenpyroximate Is Used in a Greenhouse?

When used according to label directions, fenpyroximate is not expected to pose an unacceptable risk to the environment.

Fenpyroximate is used in closed greenhouses, and therefore will not be released directly into the environment. Should fenpyroximate enter the environment, it is expected to be only slightly persistent in soil and water because both fenpyroximate and its transformation products break

down quickly in the presence of microbes in both terrestrial and aquatic systems. Fenpyroximate is also not expected to move downward through soil, and therefore is not expected to reach groundwater if it enters the environment. Fenpyroximate is also not likely to accumulate to a significant level in animal tissue.

Fenpyroximate is used as a foliar spray for control of pests on vegetable and ornamental plants, and therefore, beneficial arthropods and bees, which may be used for greenhouse pest management and pollination, could be exposed to spray droplets or residues through contact or oral exposure. Fenpyroximate presents a negligible risk to bees, but could affect certain beneficial insects. Therefore, label statements are required to indicate the potential for risk to beneficial insects that may be used in greenhouse production. Fenpyroximate is toxic to aquatic organisms; therefore, label statements prohibiting release of greenhouse effluent into aquatic systems will be included.

When fenpyroximate is used in accordance with the label and the required risk reduction measures are applied, the resulting environmental risk is considered to be acceptable.

Value Considerations

What Is the Value of Fenpyroximate 5SC Miticide/Insecticide?

Fenpyroximate 5SC Miticide/Insecticide provides a new alternative active ingredient to aid in resistance management and addresses uses identified as priorities by Canadian growers.

Applied as a foliar spray, Fenpyroximate 5SC Miticide/Insecticide provides control of spider mites, broad mite and cyclamen mite and suppression of whiteflies on indoor ornamentals and control of spider mites and suppression of whiteflies on greenhouse tomatoes, peppers, eggplants and cucumbers. Spider mites and whiteflies are key pests for most greenhouse crops and broad mite and cyclamen mite are important pests of ornamentals.

Fenpyroximate 5SC Miticide/Insecticide represents a new mode of action for broad mite and cyclamen mite on ornamentals and whiteflies on greenhouse vegetables. It provides a new alternative for broad mite and cyclamen mite on greenhouse ornamentals and all of the listed pests of indoor plantscapes, for which few other products are registered. Fenpyroximate 5SC Miticide/Insecticide also addresses five priority uses identified by Canadian growers.

Measures to Minimize Risk

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

The key risk-reduction measures being proposed on the label of Fenpyroximate 5SC Miticide/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 Fenpyroximate 5SC Miticide/Insecticide on the skin or through inhalation of spray mists, anyone mixing, loading and applying using a backpack sprayer or manually-pressurized handwand, must wear a long-sleeved shirt and long pants, chemical-resistant gloves, shoes plus socks and goggles or face shield. The label also specifies that during mixing, loading, application, clean-up and repair using a mechanically-pressurized handwand, workers must wear coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, shoes plus socks and goggles or face shield. The label also requires that nobody can enter treated areas for 12 hours after application.

Environment

- *Beneficial arthropods*: Risk-based label statements will be required on the label to inform users that fenpyroximate may affect some species of beneficial arthropods. Environmental statements required on the label include the following:

Toxic to certain beneficial insects. May harm certain beneficial insects, including those used in greenhouse production.

- *Aquatic organisms*: Hazard-based label statements will be required on the label. Environmental statements required on the label include the following:

Toxic to aquatic organisms.

- The following statements are also required to prevent aquatic exposure of fenpyroximate:

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

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

DO NOT allow effluent or runoff from greenhouses containing this product to enter lakes, streams, ponds or other natural waters.

Next Steps

Before making a final registration decision on fenpyroximate, 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

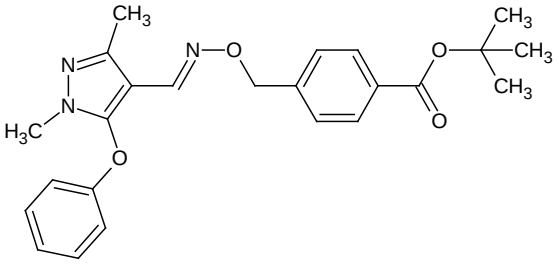
When the PMRA makes its registration decision, it will publish a Registration Decision on fenpyroximate (based on the Science Evaluation section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application,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

Science Evaluation

Fenpyroximate

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Fenpyroximate
Function	Acaricide, Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	*tert*-butyl 4-[({[(*E*)-(1,3-dimethyl-5-phenoxy-1*H*-pyrazol-4-yl)methylidene]amino}oxy)methyl]benzoate
2. Chemical Abstracts Service (CAS)	1,1-dimethylethyl 4-[[[(*E*)-[(1,3-dimethyl-5-phenoxy-1*H*-pyrazol-4-yl)methylene]amino]oxy]methyl]benzoate
CAS number	134098-61-6
Molecular formula	$C_{24}H_{27}N_3O_4$
Molecular weight	421.50
Structural formula	
Purity of the active ingredient	99.5 % nominal

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

Technical Product—Fenpyroximate Technical

Property	Result
Colour and physical state	Pale yellow solid
Odour	No distinctive odour
Melting range	99.3–101.7
Boiling point or range	Not applicable to solids
Density	1.237–1.257 g/cm^3
Vapour pressure at 25°C	7.5×10^{-6} Pa

Property	Result
Ultraviolet (UV)-visible spectrum	Absorption maxima observed at λ = 234.5 and 257.5 nm, negligible absorption above 300 nm.
Solubility in water at 25°C	pH: Solubility (ppb) 5: 21.4 7: 23.1 9: 29.8
Solubility in organic solvents at 25°C	Solvent: Solubility (g/100 mL) dichloromethane: 130.7 chloroform: 119.7 tetrahydrofuran: 73.7 toluene: 26.8 ethyl acetate: 20.1 xylene: 19.3 acetone: 15.0 dimethyl sulfoxide: 2.86 ethanol: 1.65 methanol: 1.53 n-hexane: 0.35
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} 5.01
Dissociation constant (pK_a)	Not provided – expected to be very weakly basic
Stability (temperature, metal)	Stable under labeled packaging conditions

End-Use Product— Fenpyroximate 5SC Miticide / Insecticide

Property	Result
Colour	White
Odour	Odourless
Physical state	Liquid
Formulation type	Suspension
Guarantee	5 % nominal
Container material and description	Plastic jugs
Density	1.03 g/cm^3
pH of 1% dispersion in water	6.69
Oxidizing or reducing action	Not expected to be an oxidizer, expected to react with strong oxidizers
Storage stability	Stable for two years under ambient conditions in pigmented plastic bottles
Corrosion characteristics	Not corrosive to pigmented plastic bottles
Explodability	Not expected to be explosive

1.3 Directions for Use

Crops	Pests	Amount of Product per Application	Application Maximum	Re-application Interval	Pre-harvest Interval
Ornamentals (Greenhouses, Interiorscapes)	Spider mites	1.25 – 1.9 L per 1000 L water	4000 L water per application 7.6 L product per year	21 days	n/a
	Broad mite Cyclamen mite Whiteflies	1.9 L per 1000 L water			
Greenhouse Tomatoes, Peppers and Eggplants	Spider mites Whiteflies	2.5 L/ha	1 application per crop cycle	n/a	1 day
Greenhouse Cucumbers					7 days

1.4 Mode of Action

Fenpyroximate is a mitochondrial Complex I electron transport inhibitor (IRAC Mode of Action Group 21) that also has some moulting inhibitory activity in nymphs. It is not systemic in plants and acts primarily on contact but also through ingestion.

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 formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis in Environmental Media

Methods utilizing high-performance liquid chromatography with ultra-violet spectrometry (HPLC-UV), high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) and gas chromatography with a nitrogen phosphorous detector (GC-NPD) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

2.4 Methods for Residue Analysis in Plants

Liquid and gas chromatography methods with tandem mass spectrometric detection (LC-MS/MS) and nitogen phosphorus detection (GC-NPD) were developed and found to be acceptable for data generation and enforcement purposes for plants. 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 matrices. The proposed enforcement method was successfully validated in plant matrices by an independent laboratory. Extraction solvents used in the method were similar to those used in the metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled crops was not required for the enforcement method. Methods for residue analysis are summarized in Appendix I, Table 1

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Fenpyroximate Technical (hereinafter referred to as fenpyroximate) is an insecticide/acaricide that belongs to the methyl-pyrazole class of pesticides. It is a mitochondrial Complex I electron transport inhibitor.

A detailed review of the toxicological database for fenpyroximate was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of toxic effects that may result from exposure to fenpyroximate.

Toxicokinetic data for fenpyroximate were based on studies in which rats were administered single low or high gavage doses, or repeated low gavage doses of ^{14}C-fenpyroximate, radiolabelled in either the benzyl ring or pyrazole position. There were no significant sex differences in toxicokinetic parameters resulting from position of the radiolabel. The benzyl moiety was eliminated more rapidly in females than males following high-dose administration and in males than females following single low-dose administration. Both absorption and elimination were delayed and half-lives were longer for the high dose when compared to the low dose. The maximum concentration in the blood was reached at 7 to 11 hours following a single low dose compared with 29 to 101 hours after a single high dose administration. The low doses were eliminated from blood within 96 hours, whereas the high dose persisted in the blood through 168 hours. The half-life of elimination from blood was 6.1 to 8.9 hours following the low dose and 35 to 48 hours following the high dose administration.

The majority of the radioactivity following single and repeated low dose administration was excreted in the feces within 24 hours of dosing. In contrast, fecal excretion of the majority of radioactivity following administration of the high dose was delayed until 96 to 144 hours post-dosing, and at 24 hours the majority remained in the stomach contents. After 7 days, 70% to 93% of the administered dose was recovered in feces and 9% to 18% in urine. Biliary excretion showed no significant differences between sexes or the two radiolabels.

Total radioactivity in tissues 7 days after administration of the low dose was negligible, with highest levels detected in fat, liver and portions of the gastro-intestinal tract. In high dose animals, tissue radioactivity accounted for up to 3% of the administered dose, predominantly in gastric and intestinal contents. Administration of a single high dose resulted in delayed excretion, as the majority of the applied radioactivity was still found in the contents of the gastro-intestinal tract 6-12 hours after dosing.

A great number of metabolites were identified, indicating that fenpyroximate was extensively metabolised. The parent was not detected in urine. Metabolism was comparable for all dosing regimens. The relative increase of the parent compound in the feces after administration of the high dose was due to a lowered absorption rate. Metabolite analysis indicated several potential metabolic pathways: cleavage of the benzyl moiety and further oxidation, hydrolysis of the tert-butyl ester before or after ring cleavage, isomerization of the parent or its hydrolysis product, and hydroxylation of the phenoxy ring, oxidation of the butyl ester, and other oxidation reactions. Major metabolites following low dose administration included M8 and M21 (pyrazole) and M18 (benzyl) urinary metabolites, and M3, M4, M5 (both radiolabels), M6, and M18 (benzyl) fecal metabolites. M1 (z-isomer) was the major fecal metabolite at the high dose. (See Appendix I, Table 2 for common metabolite names).

Technical fenpyroximate was of high acute toxicity in rats and mice via the oral route of exposure. In rats, it was of low acute toxicity via the dermal route and of moderate acute toxicity by inhalation exposure. It was minimally irritating to the eyes and non-irritating to the skin of rabbits, and was a skin sensitizer when tested in guinea pigs using the Maximization method.

Fenpyroximate 5SC Miticide/Insecticide is an end-use product that contains fenpyroximate. This product was considered to be of low acute toxicity to rats via the oral and dermal routes of exposure, and of slight acute toxicity to rats via the inhalation route. It was moderately irritating to the eyes and non-irritating to the skin of rabbits, and was not a skin sensitizer when tested in guinea pigs using the Buehler method.

Decreases in body weight, body weight gain and food consumption were the principal effects noted following repeated short- and long-term oral dosing in mice (dietary) and rats (dietary). Alterations in clinical chemistry and hematology parameters, along with effects on the liver, kidneys and adrenals, including organ weight and histopathological changes, were also noted in rats and mice at higher dose levels.

One-year, 90-day and combined 1- and 5-day oral toxicity studies in the dog via capsule administration were available. The effects observed in these studies were similar to those observed in rats and mice (decreased body weight, body weight gain and food consumption); however, emesis was additionally noted in the 90-day study, while excessive salivation and altered thyroid weights were noted in the 1-year study. Bradycardia was observed in both sexes of the 90-day study, but only in males in the 1-year study. Diarrhea was observed in both sexes after a single administration in all dog studies.

A total of three 21-day dermal toxicity studies were available for fenpyroximate. On the basis of a lack of dermal irritation or systemic toxicity at the limit dose of testing in the dose range-finding study, the main study utilized the limit dose of testing. However, decreases in body weight and food consumption, increases in liver weight and acanthosis of the treatment site were observed in the main study, and another study was performed employing additional lower doses. In this additional study, the limit dose produced effects on kidney and liver weights as well as liver necrosis, in addition to reductions in body weight, body weight gain and food consumption.

Effects in rats following 28-days of inhalation exposure were indicative of lung toxicity and included moist and dry rales, laboured breathing, increased lung weight and an increased incidence of squamous metaplasia of the respiratory mucosa. At a higher dose, effects on body weight, body weight gain and food consumption were recorded.

Based on the results of the available studies, the rat appeared to be more sensitive than the mouse or dog to fenpyroximate toxicity. There was no pronounced evidence of increased toxicity with increasing duration of dosing via the oral route. The principal effects seen in the oral studies (reductions in body weight, body weight gain and food consumption) were also recorded following short-term inhalation exposure; however, they were recorded at a higher dose than the lung effects on which the study NOAEC is established. In light of this, and in the absence of an inhalation study of longer duration, there is uncertainty as to the nature of the respiratory tract effects as well as the associated effect levels that would be obtained following a more extended period of exposure via inhalation. This uncertainty has been taken into account in the risk assessment.

A standard genotoxicity battery, consisting of an Ames test, chromosome aberration, mammalian gene mutation and UDS assays, in addition to a DNA Repair assay, were available for fenpyroximate. The results of these tests indicated that fenpyroximate was not genotoxic. In a published literature paper, there was evidence that fenpyroximate induces DNA damage in two human cell lines likely by a mode of action that involves oxidative stress through an increased production of reactive oxygen species (Graillot et al, 2012). No increase in tumour incidence was observed in either the 78-week dietary oncogenicity study in mice or the 104-week dietary carcinogenicity study in rats.

In an oral gavage developmental toxicity study in rats, there was no evidence of sensitivity of the young. There was an increase in the incidence of additional thoracic ribs at the same dose producing marginal decreases in maternal body weight, body weight gain and food consumption. Range-finding oral gavage developmental toxicity studies in rabbits reported marginal reductions in body weight and body weight gains in maternal animals as well as decreased fetal weights at the highest dose level tested. At the same dose level in the main study, although the body weights of treated dams were only marginally decreased, one dam also aborted her litter, suggesting toxicity to the treated animals. An increased fetal incidence of uni- and bilateral slightly folded retina was observed in fetuses at the same dose level. In determining the significance of this finding, it was acknowledged that the scientific literature notes a current movement towards identifying this finding as an artifact caused by routine fixing of the heads in Bouin’s fluid (French et al, 2008), which was the method used in the current study. It was also noted that use of Davidson’s fixative followed by Bouin’s fluid has been reported to markedly

reduce the incidence of slight retinal folding. Additionally, the current version of the IFTS (International Federation of Teratology Societies) international glossary of terms notes that "retinal folds may be due to processing artifact". Although this information is duly noted, the likelihood that the retinal folds were treatment-related could not be discounted as the examination of fetuses from all groups was done, presumably, in a blinded fashion and hence, if this finding was truly an artifact, there should not have been an increase in incidence in treated groups. Further, there were insufficient details in the historical control data to assist in the interpretation (for example, the incidences of combined unilateral and bilateral folded retina were not available). It was concluded that the increased incidence in fetuses could not be dismissed. Accordingly, this finding was considered to represent a serious effect occurring at a dose that produced evidence of maternal toxicity.

Reproductive toxicity was investigated in a dietary 2-generation study in the rat. Decreases in body weight and body weight gain were noted during the pre-mating period in both sexes and in females during gestation for both parental generations, as well as in both generations of offspring at PND 21 and 25 at the high dose. Reproductive effects consisted of increased testes and epididymides weights in F_1 generation high dose males only. There were no effects on any of the reproductive indices. There was no evidence of sensitivity of the young in this study.

Acute delayed neurotoxicity, as well as acute and repeated-dose neurotoxicity, was investigated for fenpyroximate. In an acute delayed neurotoxicity study in hens, there were no clinical signs of toxicity or indication of delayed neurotoxicity. In a rat acute neurotoxicity study conducted via gavage, clinical signs of toxicity consisting of mild dehydration and being cold to the touch were noted along with decreased motor activity, while decreased body weight, body weight gain and food consumption were observed at a higher dose. In the 90-day dietary neurotoxicity study, decreased body weight gain and food consumption were observed at a dose level that also produced clinical signs consisting of dehydration and chromorhinorrhea. There were no neuropathological findings noted in any of the studies.

Fenpyroximate has been grouped with other known Complex I inhibitors, including rotenone and pyridaben, that demonstrate inhibition of glutamate-dependent mitochondrial respiration; specifically NADH:CoQ_1 (otherwise known as NADH-ubiquinone reductase). It was demonstrated that fenpyroximate was of similar potency to rotenone for its ability to inhibit Complex I, while pyridaben's potency was greater than that of rotenone. When compared to pyridaben and rotenone, it was noted that both of these compounds were more toxic to neuroblastoma cells than fenpyroximate. Like rotenone and pyridaben, fenpyroximate is not well absorbed from the gastrointestinal tract following oral exposure and typically affects body weight gain in laboratory animals upon repeated exposure. Despite having a similar mode of action to rotenone and pyridaben, fenpyroximate is structurally dissimilar to these compounds.

Given that brain tissues from humans with Parkinson's disease (PD) exhibit reduced Complex I activity, the potential for neurodegeneration was examined; however, the depth of information available for fenpyroximate is not extensive. To further explore the potential link to PD, fenpyroximate was added to neurons co-cultured with astrocytes from mouse brains that were engineered to suppress or overexpress DJ-1 protein levels. DJ-1 protein serves to protect cells against oxidative stress and cell death; it regulates expression of mitochondrial uncoupling

proteins in dopaminergic neurons of the SNpc (substantia nigra pars compacta) as well as regulates astrocyte inflammatory response among other functions. Genetic DJ-1 deficiency has been linked to familial PD and sporadic PD reactive astrocytes have been shown to over express DJ-1. Results indicated the DJ-1 deficient astrocytes were less neuroprotective for neuronal survival than wild-type astrocytes when exposed, but to a lesser degree than pyridaben and rotenone. Substances that inhibited Complex II, III or IV did not demonstrate this difference, pointing to a selective impairment in neuroprotection with Complex I inhibitors.

Findings in the animal studies that would suggest concern regarding a potential linkage of fenpyroximate to PD (or parkinsonism) are limited to decreased mitochondrial Complex I activity (in vitro). In examining the available in vivo data, it was noted that clinical signs possibly reflective of neurotoxicity (ataxia and coarse tremors) were noted with high dose levels of fenpyroximate in the acute oral toxicity studies in rats and mice. However, these signs were noted in the presence of other clinical signs and may reflect general systemic toxicity, especially considering that death occurred within several days of dosing. Results from the acute gavage neurotoxicity study in rats indicated decreased motor activity and reduced auditory startle response. No similar observations were noted in the rat dietary 90-day neurotoxicity study, however. Moreover, no evidence of neuropathology was recorded in the database, including the acute neurotoxicity study and the 90-day neurotoxicity study, with the latter study employing various staining techniques specific to neurological tissue. All of this information was regarded as supporting a low level of concern for neuronal damage.

A 28-day dietary immunotoxicity study was conducted on rats using a modified Jerne plaque forming cell assay to measure suppression or enhancement of the immune response. There was evidence of disregulation of the immunologic response in females, but not in males.

Results of the toxicology studies conducted on laboratory animals with fenpyroximate and its associated end-use product are summarized in Appendix I, Tables 3 and 4. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 5.

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. Incidents were searched for the active ingredient fenpyroximate. Fenpyroximate is a new active ingredient pending registration for use in Canada. No human or domestic animal incidents involving the active ingredient fenpyroximate have been reported to the PMRA and the applicant did not submit any additional data.

3.1.1 *Pest Control Products Act* Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the standard complement of required studies including gavage developmental toxicity studies in rats and rabbits and a dietary 2-generation reproductive toxicity study in rats was available.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the reproductive toxicity study. Offspring and parental animals were noted to have decreases in body weight and body weight gain at comparable dose levels. In the developmental toxicity study in rats, an increased incidence of additional thoracic ribs was observed in fetuses in the presence of maternal toxicity, as characterized by reductions in body weight, body weight gain and food consumption. In the rabbit developmental toxicity study, an increased incidence of a serious endpoint (slight retinal folding) was observed at a dose that caused a marginal reduction in body weight and an abortion in the mothers. Although there is some indication in the scientific literature that the finding of slight retinal folding may represent an artifact of tissue fixation, the lack of sufficient detail in the historical control data as well as the apparent dose-related increase in incidence led to the conclusion that this finding should be considered possibly linked to treatment with fenpyroximate.

Overall, the database is adequate for determining the sensitivity of the young. There is a low level of concern for sensitivity of the young and effects on the young are well-characterized. The fetal effect in the rabbit developmental toxicity study (slight retinal folding) was considered a serious endpoint although the concern was tempered by the presence of maternal toxicity. Therefore, the *Pest Control Products Act* factor was reduced to 3-fold for scenarios in which this endpoint was used to establish the point of departure for assessing risk to women of reproductive age. For exposure scenarios involving other sub-populations, including children, the risk was considered well-characterized and the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

Females 13-49 Years of Age

For females 13 to 49 years of age, the most appropriate endpoint to estimate acute dietary risk to fenpyroximate was from the gavage rabbit developmental toxicity study. A NOAEL for developmental toxicity of 2.5 mg/kg bw/day, based on the serious endpoint of increased incidence of slightly folded retina, was selected for risk assessment. The LOAEL for this finding was 5 mg/kg bw/day. This effect was considered possibly to result from a single exposure and was therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 3-fold when using this serious endpoint for assessing risk to women of reproductive age. **The composite assessment factor (CAF) is thus 300.**

The ARfD (for females 13 to 49 years of age) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2.5 \text{ mg/kg bw/day}}{300} = 0.008 \text{ mg/kg bw of fenpyroximate}$$

General Population (excluding females 13-49 years of age)

For the general population (excluding females 13 to 49 years of age), the most appropriate endpoint to estimate acute dietary risk to fenpyroximate was from the single-dose phase of the 1- and 5-day oral gavage toxicity study in the dog. A NOAEL of 5 mg/kg bw/day, based on the observation of diarrhea at 20 mg/kg bw/day, was selected for risk assessment. This effect was considered to result from a single exposure and is therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. **The composite assessment factor (CAF) is thus 100.**

The ARfD (for the general population, excluding females 13 to 49 years of age) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{5 \text{ mg/kg bw/day}}{100} = 0.05 \text{ mg/kg bw of fenpyroximate}$$

3.3 Acceptable Daily Intake (ADI)

Females 13-49 Years of Age

To estimate risk from repeated dietary exposure for females 13 to 49 years of age, the rabbit developmental toxicity NOAEL of 2.5 mg/kg bw/day, based on the serious endpoint of increased incidence of slightly folded retina, was selected for risk assessment. The LOAEL for this finding was 5 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 3-fold when using this serious endpoint for assessing risk to women of reproductive age. **The composite assessment factor (CAF) is thus 300.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2.5 \text{ mg/kg bw/day}}{300} = 0.008 \text{ mg/kg bw/day of fenpyroximate}$$

General Population (excluding females 13-49 years of age)

To estimate risk from repeated dietary exposure, the 2-year dietary rat oncogenicity study with a NOAEL of 0.97 mg/kg bw/day was selected for risk assessment. The LOAEL for this study was 3.08 mg/kg bw/day, based on effects on body weight and body weight gain. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. **The composite assessment factor (CAF) is thus 100.**

The ADI is calculated according to the following formula:

$$ADI = \frac{NOAEL}{CAF} = \frac{0.97 \text{ mg/kg bw/day}}{100} = 0.01 \text{ mg/kg bw/day of fenpyroximate}$$

Cancer Assessment

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

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Dermal (all durations)

For short-, intermediate- and long-term occupational exposures via the dermal route, the NOAEL of 2.5 mg/kg bw/day from the oral rabbit developmental toxicity study was selected for risk assessment. The short-term dermal toxicity study did not address the relevant endpoint of concern, *i.e.* developmental toxicity, thus necessitating the use of an oral study for risk assessment. At doses of 5 mg/kg bw/day, an increased fetal incidence of slightly folded retina was observed in the presence of maternal toxicity.

The target Margin of Exposure (MOE) for these scenarios is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a factor of 3-fold for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short-term Inhalation

For short-term occupational exposures via the inhalation route, the NOAEC of 1.8 mg/m^3 (NOAEL of 0.47 mg/kg bw/day) from the 28-day inhalation toxicity study in rats was selected for risk assessment. This study represents the relevant route and appropriate duration of exposure for this scenario. The LOAEC of 10 mg/m^3 (2.61 mg/kg bw/day) was based on an increased incidence of clinical signs of toxicity (moist and dry rales, laboured breathing, soft stool, dried material on facial area), alterations in hematological parameters and increased lung weight in both sexes, with corresponding histopathological findings (squamous metaplasia of the respiratory mucosa) in males.

The target MOE is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Intermediate- and Long-term Inhalation

For intermediate- and long-term occupational exposures via the inhalation route, the NOAEC of 1.8 mg/m^3 (NOAEL of 0.47 mg/kg bw/day) from the 28-day inhalation toxicity study in rats was selected for risk assessment. This study represents the relevant route of exposure for this scenario. The LOAEC of 10 mg/m^3 (2.61 mg/kg bw/day) was based on an increased incidence of clinical signs of toxicity (moist and dry rales, laboured breathing, soft stool, dried material on facial area), alterations in hematological parameters and increased lung weight in both sexes, with corresponding histopathological findings (squamous metaplasia of the respiratory mucosa) in males.

The target MOE is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, and a 3-fold database uncertainty factor to account for the fact that although there was no strong evidence of increased toxicity with increased duration of dosing following oral administration, the effects observed in the inhalation study were different (lung toxicity) from the principal effects seen in the oral studies (changes in body weight, body weight gain and food consumption) and there remains uncertainty as to the effects/effect levels following a more extended dosing period via the inhalation route. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.4.1.1 Dermal Absorption

Although in vitro and in vivo dermal absorption studies were submitted, fenpyroximate did not meet the requirements and minimal standards of the triple-pack approach. The experimental designs and dose levels of each study were very different and a comparison of the study results was impossible. As such, the representativeness of the human in vitro absorption results as an indicator of in vivo absorption could not be validated and the rat in vivo study was chosen to determine a dermal absorption value.

The dermal absorption study was conducted on Sprague-Dawley rats using [pyrazole-3 ^{14}C]-fenpyroximate (purity >97%). The rate and extent of absorption of radioactivity was investigated following topical application of radiolabelled fenpyroximate at a low dose (0.05 g/L or 0.5 µg/cm^2). Only a single dose of fenpyroximate was tested in this study, which is considered to be a major limitation since it is unclear what effect different dose levels may have had on the amount absorbed. Only one exposure duration (6 hours) was tested, which is considered to be a minor limitation of the study since it is unclear if different lengths of exposure could result in different levels of absorption. Recovery of fenpyroximate for individual subjects ranged from 91–101% and no corrections for incomplete recovery were made since total recovery was acceptable. However, given the uncertainty of the amount of skin removed by each tape strip, the PMRA considered all the skin on the tape strips as a uniform layer of stratum corneum. There were residues of fenpyroximate recovered from the excreta throughout the entire monitoring period (10.2%, 2.09% and 6.54% at 6 hours, 24 hours and 120 hours, respectively) and the amount found in the stratum corneum decreased with time (24.86%, 18.47% and 9.96% at 6 hours, 24 hours and 120 hours, respectively), which indicates that the amount found in the stratum corneum does become systemically absorbed with time. Therefore, all the residues on

the tape strips were considered absorbable and the dermal absorption values were 27.68%, 23.42% and 16.81% at 6 hours, 24 hours and 120 hours, respectively. It is determined that the 17% value at the 120 hour interval was the most appropriate dermal absorption value to use for risk assessment purposes.

3.4.2 Occupational and Residential Risk Assessment

Exposure to workers who mix/load and apply Fenpyroximate 5SC Miticide/Insecticide in greenhouses and plantscapes and on interior plants are expected to be exposed for less than 30 days per year (short-term exposure), since the product is applied once or twice only. Workers entering treated greenhouses are expected to have long-term dermal exposure since the product is not expected to dissipate and there is the potential for exposure throughout the entire duration of the crop cycle.

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to Fenpyroximate 5SC Miticide/Insecticide during mixing, loading and application. Dermal and inhalation exposure estimates for workers open mixing & loading and applying using a backpack sprayer, manually-pressurized handwand or mechanically-pressurized handwand, were generated from PHED version 1.1.

Exposure to workers mixing, loading and applying Fenpyroximate 5SC Miticide/Insecticide is expected to be short-term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixers/loaders/applicators applying Fenpyroximate 5SC Miticide/Insecticide to greenhouse cucumbers, fruiting vegetables and potted ornamentals using the above noted equipment. The exposure estimates are based on mixers/loaders/applicators wearing a single layer of clothing plus gloves for backpack and manually-pressurized handwand and a single layer plus coveralls and gloves for mechanically-pressurized handwand application to greenhouse ornamentals.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value from the submitted in vivo dermal absorption study (17%). 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.

Exposure estimates were compared to the toxicological endpoints from section 3.4.1 (NOAEL: no observed adverse effects level) to obtain the margin of exposure (MOE) in table 3.4.2.1.1; the target MOE is 300 for dermal exposure and 100 for inhalation exposure. No health risks of concern were identified when workers followed the recommended precautions on the label.

Table 3.4.2.1.1 Mixer/Loader/Applicator Dermal and Inhalation Exposure Estimates and MOE

Exposure scenario	Maximum application rate	Application method	Volume handled per day (litres) †	Area treated per day (based on 1000 L/ha)	Dermal exposure ψ (µg/kg bw/day)	Dermal MOE (target 300)‡	Inhalation exposure ψ (mg/kg bw/day)	Inhalation MOE (target 100)‡
Greenhouse & interiorscapes on ornamentals	386.8 g ai/ha	Backpack	150	0.15 ha/day	0.67	3723	0.05	10436
		Manually-pressurized handwand			0.12	21494	0.03	14337
		Mechanically-pressurized handwand*	3800	3.8 ha/day	7.66	326	2.77	169
Greenhouse vegetables (Cucumbers, tomatoes, peppers, eggplant)	127.25g ai/ha	Backpack	150	0.15 ha/day	0.22	11318	0.01	31721
		Manually-pressurized handwand			0.04	65336	0.01	43581
		Mechanically-pressurized handwand	3800	3.8 ha/day	5.74	436	0.91	515

Ψ Daily exposure = (PHED unit-exposure × 17% dermal absorption × rate × spray (volume/day / dilution rate) × 0.001 kg/g × 0.001mg/µg) / 80 kg bw)
‡ Margin of Exposure (MOE) = $NOAEL_{(route\text{-}specific)}$ / Exposure; toxic effects are different; therefore routes of exposure cannot be combined
* Exposure was estimated for workers wearing a single layer plus gloves with the addition of coveralls. For all other scenarios, exposure was estimated for workers wearing a single layer and gloves.

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 Fenpyroximate 5SC Miticide/Insecticide to perform various activities including hand pruning, hand harvesting and disbudding. Given the nature of activities performed, dermal contact with treated surfaces should occur throughout the season. Inhalation exposure is not expected to occur since workers and bystanders are not allowed to enter until 12 hours after application and the vapour pressure of fenpyroximate is estimated to be 7.73×10^{-9} kPa at 25°C. This vapour pressure is less than the NAFTA waiver for an inhalation study of $< 1 \times 10^{-5}$ kPa at 20-30°C for indoor use. The duration of exposure is considered to be long-term, since residues of fenpyroximate are not expected to dissipate in an indoor environment, with the primary route of exposure for workers re-entering treated areas being dermal exposure.

Dermal exposure to workers entering treated areas is estimated by coupling default dislodgeable foliar residue values with activity-specific transfer coefficients. Activity transfer coefficients are based on generic data Agricultural Reentry Taskforce Data (ARTF). Chemical-specific dislodgeable foliar residue data were not submitted. As such, a default dislodgeable foliar residue value of 25% of the application rate was used in the exposure assessment.

Exposure estimates were compared to the toxicological endpoint to obtain the MOE; the target MOE is 300. No health risks of concern were identified when workers re-enter 12 hours after application.

TABLE 3.4.2.2.1 Postapplication Exposure and Risk Estimate for Fenpyroximate on Day 0 After the Last Application

Crop	Application rate (µg ai/cm^2)	Number of applications per crop cycle	Re-treatment interval (days)	Peak DFR (µg/cm^2) *	Transfer coefficient (cm^2/h)†	Dermal exposure (mg/kg bw/day) ‡	MOE ¶	REI required ◊
Potted plants	3.87	2	14	1.93	230	0.0069	331	12 hours
Greenhouse Vegetables (fruiting vegetables and cucumbers)	1.27	1	N/A	0.318	1400	0.0076	330	12 hours

* Calculated using the default 25% dislodgeable on the day of application and 0% dissipation per day for greenhouses
† Transfer coefficients obtained from ARTF (PMRA Ag TC Table, Nov 26, 2014)
‡ Exposure = (Peak DFR [µg/cm^2] × TC [cm^2/h] × 8 hours × 17% dermal absorption) / (80 kg bw × 1000 µg/mg)
¶ Based on a dermal NOAEL of 2.5 mg/kg bw/day, target MOE = 300
◊ Minimum REI is 12 hours to allow commercial product residues to dry
N/A = Not applicable

3.4.3 Bystander Exposure and Risk

Bystanders are not expected to be inside greenhouses while treatments occur; therefore, exposures are not expected to occur to bystanders. However, applications can occur in interiorscapes/plantscapes (may include 'living walls') during business hours in shopping malls and office buildings, etc. A restriction to prevent the applications when the public or occupants are present is on the label. With this restriction, bystanders are not expected to be in the vicinity during interiorscape spraying events (e.g. inside public areas such as shopping malls and office buildings), but are expected to be in the vicinity postapplication. However, since adults and children do not usually contact interiorscapes and postapplication inhalation exposures are expected to be negligible when compared to worker exposure that are exposed for 8 hours per day, no health risks of concern are expected.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant commodities is fenpyroximate and M-1 (the Z-isomer). The data gathering/enforcement analytical method is valid for the quantitation of fenpyroximate and M-1 residues in crop matrices. The total residues of fenpyroximate are stable in cucumbers for up to 168 days, tomatoes (including some processed fractions) for up to 567 days, and peppers for up to 403 days when stored in a freezer

at -20°C. Total fenpyroximate residues did not concentrate in either tomato paste (0.8X) or tomato puree (0.5X). As greenhouse crops are not typically fed to livestock, transfer of residues to livestock is not expected to occur. Residue trials conducted in the field and in greenhouses in Canada, the United States, and the European Union (EU) using end-use products containing fenpyroximate at approved and at exaggerated rates in or on cucumbers, tomatoes, and peppers are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™), which uses updated food consumption data from the NHANES 2-day food consumption data.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the refined chronic analysis for fenpyroximate: 100% crop treated, default and experimental processing factors (where available), American tolerances, and supervised trial median residue (STMdR) values. The refined chronic dietary exposure from all supported fenpyroximate food uses (alone) for the total population, excluding women 13-49 years, is less than 16% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water were not assessed, as residues are not expected in drinking water from use in greenhouses. The highest exposure and risk estimate is for children 1-2 years at 16% of the ADI (0.01 mg/kg bw/day). For woman 13-49 years, the exposure is 6% of the ADI (0.008 mg/kg bw/day).

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the refined acute analysis for fenpyroximate: 100% crop treated, default and experimental processing factors, American tolerances, and maximum residues in/on crops from supervised trials. The refined acute dietary exposure (food alone) for all supported fenpyroximate treated commodities is estimated to be 30% of the ARfD (0.008 mg/kg bw) for females 13–49 years old, and ≤ 6% of the ARfD (0.05 mg/kg bw) for the general population (95th percentile, deterministic). Aggregate exposure from food and drinking water was not considered as residues in drinking water are considered to be unlikely from greenhouse use.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for fenpyroximate was not conducted since residues in drinking water are unlikely from greenhouse use and there are no residential uses.

3.5.4 Maximum Residue Limits

Table 3.5.4.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Cucumbers	0.4
Fruiting Vegetables, CG 8-09	0.2

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.

The nature of the residues in plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 6 and 7.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Data on the fate and behaviour of fenpyroximate and its major transformation products are summarized in Appendix I, Table 9.

Fenpyroximate will be used in closed greenhouses as a foliar applied insecticide for the control of mites and the suppression of whiteflies in a variety of crops such as indoor fruiting vegetables, ornamentals and cucumbers. As such, fenpyroximate will not be released directly into the environment.

Based on its indoor application in greenhouses, release of fenpyroximate into the terrestrial environment is expected to be negligible. Fenpyroximate is slightly persistent under aerobic soil conditions, and transforms to two major transformation products (M3 and M8). Both of these transformation products reach maximum levels of less than 15%, and then decline to less than 6% by study termination. The high formation of CO_2 (up to 58%) indicates mineralization of fenpyroximate in soil. Fenpyroximate is expected to be immobile in most soils based on very high adsorption coefficients (K_{oc} values ranging from 30243 to 113125 mL/g). In addition to mobility, parameters such as solubility in water, volatility and persistence in soil and water, and the groundwater ubiquity score are considered when determining the potential for a compound to leach through the soil profile and enter groundwater. Overall, considering all information, fenpyroximate is not expected to leach through soil to groundwater.

There may be some potential for aquatic exposure of fenpyroximate if greenhouse effluent is discharged into the aquatic environment. Fenpyroximate is considered insoluble in water. Based on vapour pressure and Henry's Law Constant, fenpyroximate is not expected to volatilize from moist soil or water. In addition, it is not expected to phototransform based on its maximum UV absorbance. Fenpyroximate is expected to biotransform relatively quickly in aquatic systems. Although fenpyroximate is stable to hydrolysis at all pHs, laboratory studies with aerobic aquatic/sediment indicate that fenpyroximate is expected to be slightly persistent (with whole

system half-life values of less than 34 days). Fenpyroximate transforms to three major transformation products, M8, M3 and M11 in the aquatic environment. M8 and M3 are major transformation products formed in water, and are both transient in nature (meaning they decline by study termination). M11 is formed up to 24% in sediment and is increasing up to study termination.

The bioaccumulation studies conducted with rainbow trout show some accumulation in fish tissues. However, given the whole fish bioconcentration factors were below 3000 with rapid depuration rates (<5.5 days), fenpyroximate is unlikely to bioaccumulate significantly under field conditions. The log Kow indicates that the major sediment transformation product, M11, is not expected to bioaccumulate in the environment.

4.2 Environmental Risk and Hazard Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. For greenhouse uses, the estimated environmental exposure concentrations (EECs) are based on the maximum application rates. Relevant ecotoxicology information includes acute and chronic toxicity data for bees and beneficial arthropods used in greenhouse production. For closed greenhouse uses, the primary focus of the risk assessment is for potential effects to bees and beneficial arthropods. In addition, an aquatic hazard assessment is also conducted in order to characterize the inherent toxicity of the chemical. Where applicable, acute toxicity endpoints are 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 specific uses that do not pose a risk to non-target terrestrial 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 (for example, assumed that organisms in greenhouses would be exposed to 100% of the application rate) and sensitive toxicity endpoints.

A risk quotient (RQ) is calculated by dividing the exposure estimate by the toxicity value (i.e. endpoint) which has had the appropriate species uncertainty factor applied (RQ = exposure/toxicity endpoint). The risk quotient is then compared to the level of concern (LOC is 0.4 for acute bee studies; LOC is 2 for screening level beneficial arthropods; LOC is 1 for all other species). A screening level assessment also takes into consideration exposure scenarios from drift, which may occur in non-target habitats. 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 might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, change in fate parameters, and monitoring data.

4.2.1 Risks to Terrestrial Organisms

Risk of fenpyroximate (including end-use products containing 5% fenpyroximate, which is representative of the proposed formulation in Canada for greenhouse use) to terrestrial organisms (see Appendix I, Table 10) was based upon evaluation of toxicity data for the following:

- 1 bee species
- 13 other arthropod species

Terrestrial invertebrates

Honeybees

Two acute studies were conducted with the end-use product formulation (containing 5% TGAI, at concentrations up to 24 µg ai/bee) for contact exposure, and the TGAI (at concentrations up to 118.5 µg ai/bee) for oral exposure. Following 72 hours of exposure, the highest mortality observed was 14% and 6% for the contact and oral tests, respectively.

Bees used in greenhouse production for pollination could be exposed to residues of fenpyroximate as a result of direct application, contact with residues, or ingestion of residues on food sources.

Based on the maximum single application rate, no risk is expected for adult bees exposed through either oral or contact exposure to fenpyroximate (Appendix I, Table 10). Fenpyroximate is not an insect growth regulator, and minimal effects on adult bees were observed. Given the low risk for forager bees, the lack of exposure for larvae (based on destruction of hives as part of greenhouse practice), and the mode of action, a negligible risk to larva is expected.

Predators and parasites (beneficial arthropods)

Laboratory studies were conducted with the adult stages of beneficial arthropods, including the parasitic wasp (*Ephedrus japoicus*) and predatory mite species (*Typhlodromus pyri, Amblyseius longispinosus and Phytoseiulus persimilis*), and other species (e.g. *Harmonia axyridis, Poecilus cupreus, Pardosa* spp*)* whereby insects were exposed to residues of fenpyroximate. Observations of mortality ranged from zero (0) to 90% among the studies, depending on species and rate (Appendix I, Table 10).

Additional studies were also conducted with the juvenile stages of beneficial arthropods, including predacious spiders (*Lycosa pseudoannulata, Misumenops tricuspidatus*), a ladybug (*Harmonia axyridis),* a parasitic wasp (*Apanteles glomeratus*), and a hover fly (*Episyrphus balteatus*). The highest mortality (up to 35%) was exhibited by ladybug larvae following exposure (by dipping larvae in solution) up to 50 g ai/ha (applied as end-use product formulation containing 5% TGAI).

Based on the maximum application rate, a potential risk was identified for the adult predatory mites (*Amblyseius longispinosus* and *Phytoseiulus persimilis*). For most of the other species tested (including larval and adult stages), there was also a potential risk identified, however, this

was the result of the highest maximum rate tested in the studies being below the proposed Canadian rate. In some cases, there was no mortality observed at the highest concentration tested, whereas in other cases, there was mortality observed at the highest concentration tested; therefore, at the higher Canadian label rates it is feasible that effects could occur with some species. Based on the potential risk identified (Appendix I, Table 10) for various beneficial species tested, statements will be required on the label to indicate the potential risk to beneficial arthropods that may be used in greenhouse production.

4.2.2 Hazard Assessment to Non-Target Aquatic Organisms

An aquatic hazard assessment was conducted to assess effects to aquatic organisms, which could be exposed to fenpyroximate if effluent is discharged from greenhouse use. This assessment was based upon the toxicity of fenpyroximate to the following organisms:

- Daphnia (acute study with the TGAI and end-use product)
- Fish (acute study with the TGAI and end-use product)

Two acute daphnia studies were conducted with both the Technical Grade Active Ingredient (TGAI) (at concentrations up to 0.01 mg ai/L) and the end-use product formulation (containing 5% TGAI, at concentrations up to 0.233 mg end use product/L (equivalent to 0.012 mg ai/L)). Following 48 hours of exposure, there was up to 100% mortality observed at the highest concentrations tested. The LC_{50} values were 0.00328 mg ai/L (for daphnids exposed to the technical grade active ingredient), and 0.031 mg end use product/L (equivalent to 0.0016 mg ai/L) (for daphnids exposed to the end-use product) (Appendix I, Table 11). An additional study was conducted that exposed daphnia to the transformation product, M-3, for 48 hours. Based on the LC_{50} value of 14 mg/L, M-3 was less toxic than the parent compound.

Three acute fish studies were also conducted; two studies with the TGAI (at concentrations up to 0.0027 and 0.0033 mg ai/L) and one study with the end-use product formulation [containing 5% TGAI, at concentrations up to 0.16 mg EUP/L) (equivalent to 0.008 mg ai/L)]. Following 96 hours of exposure, there was up to 100% mortality observed at the highest concentrations tested.

The most sensitive LC_{50} values were 0.00064 mg ai/L (for rainbow trout exposed to the technical grade active ingredient) (Appendix I, Table 11). An additional study was conducted which exposed rainbow trout to the transformation product, M-3, for 96 hours. Based on the LC50 value of 8.2 mg/L, M-3 was less toxic than the parent compound.

Based on the results of these studies, fenpyroximate, would be classified as very highly toxic to daphnia and fish in accordance with the classification system of the USEPA. The transformation product, M-3, would be classified as slightly to moderately toxic to aquatic organisms.

In order to assess the potential hazards of M-11, to aquatic organisms, additional information was also considered in the assessment. Since M-3 (which is a precursor to M-11) is orders of magnitude less toxic to both daphnia and fish compared to fenpyroximate (which is the precursor to M3), the assessment for fenpyroximate is expected to be protective of any risk posed by M-11.

The hazard assessment has indicated that fenpyroximate is toxic to aquatic organisms. Therefore, hazard statements will be required on the label. In addition, mitigation will be required to reduce effluent discharge.

4.2.3 Incident reports / additional considerations

Environmental incident reports are obtained from two main sources, the Canadian pesticide incident reporting system (including both mandatory reporting from the registrant and voluntary reporting from the public and other government departments) and the USEPA Ecological Incident Information System (EIIS). Specific information regarding the mandatory reporting system regulations that came into force 26 April 2007 under the *Pest Control Products Act* can be found at http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/incident/index-eng.php.

Fenpyroximate is a new technical grade active ingredient being proposed for Canadian registration. As such, no incidents would be found in Canada. In the United States there are no incident reports for fenpyroximate.

5.0 Value

5.1 Consideration of Benefits

Fenpyroximate is identified in the Canadian Grower Priority Database as a priority for mites on greenhouse tomatoes, peppers, eggplants and cucumbers and for whiteflies on greenhouse tomatoes. Registration of Fenpyroximate 5SC Miticide/Insecticide would provide Canadian growers with access to a product that is already registered in the United States for greenhouse uses, although the U.S. label includes a few additional pests and does not include greenhouse peppers or eggplants.

For some uses (spider mites and whiteflies on greenhouse ornamentals and greenhouse vegetables) several alternative active ingredients are available, including conventional chemical pesticides representing several different mode of action (MoA) groups. However, for other uses (broad mite and cyclamen mite on ornamentals and all supported pests of interior plantscapes) there are very few alternatives registered. One of the registered alternatives, endosulfan for use on greenhouse ornamentals, is due to be phased out at the end of 2016. Pyridaben (also MoA Group 21) is registered in Canada for spider mites and whiteflies on greenhouse ornamentals and spider mites on greenhouse ornamentals and greenhouse vegetables, but fenpyroximate provides a new mode of action for broad mite and cyclamen mite on ornamentals and whiteflies on greenhouse vegetables.

The additional mode of action provided by fenpyroximate can aid resistance management through rotation of active ingredients. Because of their short life cycles and numerous annual generations, spider mites are prone to the development of resistance, and resistance to fenpyroximate has been reported in twospotted spider mite (*Tetranychus urticae*) and two other species (*Tetranychus kanzawai* and *Panonychus ulmi*). Use of Fenpyroximate 5SC Miticide/Insecticide is limited to one application per crop cycle on greenhouse vegetables but the directions for use allow for multiple applications on ornamentals (if applied at low enough

concentrations and/or spray volumes). The label for Fenpyroximate 5SC Miticide/Insecticide includes the standard resistance management recommendations as well as additional label statements recommending rotation with other pest control products having different modes of action when used on ornamentals. These recommendations should help to minimize the potential for development of resistance.

Fenpyroximate 5SC Miticide/Insecticide is compatible with current management practices as a conventional chemical alternative to be applied when pests reach economic thresholds and used in rotation with different modes of action in integrated pest management (IPM) programs.

5.2 Effectiveness Against Pests

Efficacy data from a total of eight trials against spider mites, including two species of spider mite (*Tetranychus urticae* and *Tetranychus evansi*) and application on three different ornamentals (marigold, cotoneaster and melampodium) as well as tomato and cucumber, supported label claims for spider mites. In addition, use history information from three different individuals reported satisfactory control of spider mites on ornamentals, tomato, pepper and cucumber.

Efficacy data from two trials against broad mite (*Polyphagotarsonemus latus*) on two different varieties of pepper supported the label claim for control of that pest and, by extrapolation, the related and similar cyclamen mite (*Phytonemus pallidus*).

Efficacy data from a total of twelve trials against whiteflies (identified as either *Bemisia tabaci* or *Bemisia argentifolii*), including application on poinsettia, tomato and pepper, supported a claim of suppression.

5.3 Non-Safety Adverse Effects

Most of the efficacy trial reports specifically noted that no adverse effects on the crops were observed. In addition, use history information included reports of no adverse effects on a wide variety of ornamentals as well as tomato, pepper and cucumber.

5.4 Supported Uses

The use of Fenpyroximate 5SC Miticide/Insecticide was supported for control of spider mites on indoor ornamentals at rates of 1.25–1.9 L product per 1000 L, control of broad mite and cyclamen mite and suppression of whiteflies on indoor ornamentals at the rate of 1.9 L product per 1000 L and control of spider mites and suppression of whiteflies on greenhouse tomatoes, peppers, eggplants and cucumbers at the rate of 2.5 L product per hectare. For additional details of the supported use pattern, please refer to Section 1.3.

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, fenpyroximate was assessed in accordance with the PMRA Regulatory Directive DIR99-03 and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Fenpyroximate does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 12 for comparison with Track 1 criteria.
- Fenpyroximate does not form any transformation products that meet all Track 1 criteria

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*[5] maintained in the Canada Gazette. The list is used as described in the PMRA Notice of Intent NOI2005-01[6]and is based on existing policies and regulations including: DIR99-03;[7] 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 conclusion:

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

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

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

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

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

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

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for fenpyroximate is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of carcinogenicity in rats or mice after longer-term dosing. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies, although there was evidence of a serious endpoint (increased incidence of slightly folded retina) in rabbit fetuses at a maternally toxic dose. There was no effect on reproductive performance or outcome. Fenpyroximate was not genotoxic or neurotoxic, although some alterations of immunologic response were observed. In short-term and chronic studies on laboratory animals, the primary target was body weight, body weight gain, food consumption and the gastro-intestinal tract. 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.

Mixers, loaders and applicators handling Fenpyroximate 5SC Miticide/Insecticide and workers re-entering treated greenhouses are not expected to be exposed to levels of Fenpyroximate 5SC Miticide/Insecticide that will result in health risks of concern when the Fenpyroximate 5SC Miticide/Insecticide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers while applying Fenpyroximate 5SC Miticide/Insecticide using a backpack sprayer, manually-pressurized handwand or mechanically-pressurized handwand to greenhouse ornamentals, greenhouse fruiting vegetables, greenhouse cucumbers and to interior plantscapes.

Bystander exposure in office buildings, shopping malls and other interior plantscape locations is not expected to result in health risks of concern when Fenpyroximate 5SC Miticide/Insecticide is used according to label directions, since applications can only occur when the public is not present and bystanders are not expected to come into direct contact with treated foliage.

The nature of the residues in plants is adequately understood. There is no expectation of transfer of residues to livestock from greenhouse use on tomatoes, peppers, eggplant, and cucumber, as they are not feed items. There is no expectation of transfer of residues to drinking water from this use. The residue definition for enforcement and risk assessment is fenpyroximate and its Z-isomer (M-1) in plant products. The proposed use of fenpyroximate on tomatoes, peppers, eggplant, and cucumber does not constitute a risk of concern for chronic or acute dietary exposure (food) 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 fenpyroximate.

Commodity	Recommended MRL (ppm)
Cucumbers	0.4
Fruiting Vegetables, CG 8-09	0.2

7.2 Environmental Risk

When used according to label directions, fenpyroximate does not pose an unacceptable risk to the environment. Mitigative label statements will be required to protect beneficial arthropods and aquatic organisms.

7.3 Value

Fenpyroximate 5SC Miticide/Insecticide has value for control of spider mites, broad mite and cyclamen mite and suppression of whiteflies on indoor ornamentals and control of spider mites and suppression of whiteflies on greenhouse tomatoes, peppers, eggplants and cucumbers. The supported use pattern of Fenpyroximate 5SC Miticide/Insecticide includes uses new to the use pattern of IRAC MoA Group 21 active ingredients registered in Canada and uses with very few registered alternatives. Registration of Fenpyroximate 5SC Miticide/Insecticide would address five priorities for Canadian growers and provide Canadian growers with access to a product that is registered for use in the United States.

8.0 Proposed Regulatory Decision

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Fenpyroximate Technical and Fenpyroximate 5SC Miticide/Insecticide containing the technical grade active ingredient fenpyroximate, to control spider mites, broad mite and cyclamen mite and suppression of whiteflies on indoor ornamental plants and greenhouse vegetable crops.

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

Human Health

Because there is a concern with users coming into direct contact with Fenpyroximate 5SC Miticide/Insecticide on the skin or through inhalation of spray mists, anyone mixing, loading and applying using a backpack sprayer or manually-pressurized handwand, must wear a long-sleeved shirt and long pants, chemical-resistant gloves, shoes plus socks and goggles or face shield. The label also specifies that during mixing, loading, application, clean-up and repair using a mechanically-pressurized handwand, workers must wear coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, shoes plus socks and goggles or face shield. The label also requires that nobody can enter treated areas for 12 hours after application.

Environment

- *Beneficial arthropods*: Risk-based label statements will be required on the label to inform users that fenpyroximate may affect some species of beneficial arthropods. Environmental statements required on the label include the following:

Toxic to certain beneficial insects. May harm certain beneficial insects, including those used in greenhouse production.

- *Aquatic organisms*: Hazard-based label statements will be required on the label. Environmental statements required on the label include the following:

Toxic to aquatic organisms.

- The following statements are also required to prevent aquatic exposure of fenpyroximate:

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

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

DO NOT allow effluent or runoff from greenhouses containing this product to enter lakes, streams, ponds or other natural waters.

List of Abbreviations

µg	micrograms
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
ADI	acceptable daily intake
ALS	acetolactate synthase
ARfD	acute reference dose
atm	atmosphere
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetres
DF	dry flowable
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
ER_{25}	effective rate for 25% of the population
g	gram
ha	hectare(s)
HDT	highest dose tested
Hg	mercury
HPLC	high performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
km	kilometre
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOEC	low observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
mg	milligram
mL	millilitre
MAS	maximum average score
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable

NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
N/R	not required
NZW	New Zealand white
OC	organic carbon content
OM	organic matter content
PBI	plantback interval
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RSD	relative standard deviation
SC	soluble concentrate
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UAN	urea ammonium nitrate
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		Reference
Plant	DFG S19	Fenpyroximate as M-1, and M-1	GC/NPD	0.01-0.05 ppm		PMRA # 2278966, 2278624
	AWJ/03/1	Fenpyroximate and M-1	LC/MS/MS	0.01-0.05 ppm for each analyte		PMRA # 2278969
Animal	1249W	parent	HPLC-MS/MS	0.01 µg/g	Beef Liver and Kidneys	2278967 2278965
		M3	HPLC-MS/MS	0.01 µg/g	Beef Liver and Kidneys	
Soil	107-90-01	parent	HPLC-UV	0.01 µg/g		2309652
	1026W	M3	GC-NPD			2449147
		M8	GC-NPD			
Water	04-0169	parent	HPLC-UV	00.1 µg/L		2466623

Table 2 Common Name of Fenpyroximate Metabolites

Compound/Metabolite	Chemical Name
Fenpyroximate	*tert*-butyl (E)-4-[(1,3-dimethyl-5-phenoxypyrazol-4-yl)-methyleneaminooxymethyl]benzoate
M1	*tert*-butyl (Z)-4-[(1,3-dimethyl-5-phenoxypyrazol-4-yl)-methyleneaminooxymethyl]benzoate
M2	*tert*-butyl (E)-4-{[(1,3-dimethyl-5-(4-hydroxyphenoxy)pyrazol-4-yl]-methyleneaminooxymethyl}benzoate
M3	(E)-4-[(1,3-dimethyl-5-phenoxypyrazol-4-yl)-methyleneaminooxymethyl]benzoic acid
M4	(Z)-4-[(1,3-dimethyl-5-phenoxypyrazol-4-yl)-methyleneaminooxymethyl]benzoic acid
M5	(E)-4-{[(1,3-dimethyl-5-(4-hydroxyphenoxy)pyrazol-4-yl]-methyleneaminooxymethyl}benzoic acid
M6	1,3-dimethyl-5-phenoxypyrazole-4-carbaldehyde
M7	1,3-dimethyl-5-(4-hydroxyphenoxy)pyrazole-4-carbaldehyde
M8	1,3-dimethyl-5-phenoxypyrazole-4-carboxylic acid

M9	3-methyl-5-phenoxypyrazole-4-carbaldehyde
M10	1,3-dimethyl-5-(4-hydroxyphenoxy)pyrazole-4-carbonitrile
M11	1,3-dimethyl-5-phenoxypyrazole-4-carbonitrile
M12	*tert*-butyl (E)-4-[(3-methyl-5-phenoxypyrazol-4-yl)-methyleneaminooxymethyl]benzoate
M13	(E)-1,3-dimethyl-5-phenoxypyrazole-4-carbaldehyde oxime
M14	3-methyl-5-(4-hydroxyphenoxy)pyrazole-4-carbaldehyde
M15	*tert*-butyl 4-hydroxymethylbenzoate
M16	4-hydroxymethylbenzoic acid
M17	4-formylbenzoic acid
M18	terephthalic acid
M21	4-cyano-1-methyl-5-phenoxypyrazole-3-carboxylic acid
M22	2-methyl-2-{9E)-4-[1,3-dimethyl-(5-phenoxypyrazol-4-yl)methyleneaminooxymethyl] benzoyloxy}propionic acid

Table 3 Toxicity Profile of End-Use Product Containing Fenpyroximate

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

Study Type/Animal/PMRA #	**Study Results**
Acute Oral Toxicity Sprague-Dawley rats PMRA #2278944	LD_{50} ♂ = 7193 mg/kg bw LD_{50} ♀ = 6789 mg/kg bw LD_{50} ♂/♀ = 5277 mg/kg bw Low toxicity
Acute Dermal Toxicity Sprague-Dawley rats PMRA #2278945	LD_{50} > 4000 mg/kg bw Low toxicity
Acute Inhalation Toxicity (whole-body) Sprague-Dawley rats PMRA #2278946	LC_{50} ♂ = 1.9 mg/L LC_{50} ♀ = 2.4 mg/L LC_{50} ♂/♀ = 2.3 mg/L Slight toxicity
Dermal Irritation New Zealand White rabbits PMRA #2278948	MAS (24, 48 and 72 hours) = 0 MIS = 0.17 at 1 hour Non-irritating

Study Type/Animal/PMRA #	Study Results
Eye Irritation New Zealand White rabbits PMRA #2278947	MAS (24, 48 and 72 hours) = 17.2 MIS = 19.7 at 48 hours. Irritation persisted to 7 days in 5 of 6 animals. Moderately irritating
Dermal Sensitization (Buehler test) Hartley guinea pigs PMRA #2278949	Non-sensitizer

Table 4 Toxicity Profile of Technical Fenpyroximate

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

Study Type/Animal/PMRA #	Study Results
Pharmacokinetics following a single oral dose (low and high) Sprague-Dawley rat PMRA#2278890 (Study) and 2278768 (DER)	**Pyrazole label (2 mg/kg bw):** Plasma C_{max} was 0.15-0.18 µg/g, reached at 11 hours. The elimination half-life was 8.9 hours, and the AUC was 3.5/3.8 µg × hour/mL (♂/♀). **Pyrazole label (400 mg/kg bw):** Plasma C_{max} was 4.7 µg/g, reached at 101/90 hours (♂/♀). The elimination half-life was 49/45 hours (♂/♀), and the AUC was 377/411 µg × hour/mL (♂/♀). **Benzyl label (2 mg/kg bw):** Plasma C_{max} was 0.10-0.18 µg/g, reached at 7-8 hours. The elimination half-life was 6.1/7.9 hours (♂/♀), and the AUC was 1.8/3.0 µg × hour/mL (♂/♀). **Benzyl label (400 mg/kg bw):** Plasma C_{max} was 5.1/8.9 µg/g (♂/♀), reached at 29/86 hours (♂/♀). The elimination half-life was 47/35 hours (♂/♀), and the AUC was 425/728 µg × hour/mL (♂/♀).
Metabolism and disposition following single (low and high) and repeated (low) doses Sprague-Dawley rat PMRA# 2278884, 2278886, 2278887, 2278888 (study) and 2278768 (DER)	There were no significant differences between sexes or between single and repeated low doses. The high dose resulted in slowed transit through the GI tract and reduced fecal output (attributed as a toxic effect by study authors). **Excretion:** For all groups, 70-92% of the AD was excreted in feces and 9-18% in urine. At low doses, the majority was excreted within 24 hours. At the high dose, excretion was slower, with the majority of the AD excreted in feces at 96 hours, while levels in urine increased up to 7 days post-dosing.

Study Type/Animal/PMRA #	Study Results
PMRA# 2278892 (study) and 2278768 (DER)	**Distribution:** The benzyl label resulted in higher tissue residues (except liver) and residues in a greater number of tissues. At low doses, the highest residues were detected in fat. At 7 days post-dosing with both radiolabels, low but detectable levels were found in the carcass, large intestine, liver, kidneys, lungs, and pancreas. With the benzyl label, low but detectable levels were also found in adrenals, bone, ovaries, stomach, thymus, urinary bladder and uterus. At the high dose, the highest residues were detected in GI contents/tissues and liver. **Metabolism:** Parent was not detected in urine. The major urinary metabolites were M8 and M21 with the pyrazole label and M18 with the benzyl label. In feces, the parent was detected at 6-9% of the AD following a single low dose, 8-20% of the AD following a repeated low dose, and 50-52% of the AD following a single high dose. At the low doses, the major fecal metabolites were M3, M4, M5, and M22 (both labels); M6 with the pyrazole label; and M18 with the benzyl label. At the high dose, the predominant metabolite was M1 (z-isomer). The metabolic pathway involves cleavage of the benzyl moiety and further oxidation, hydrolysis of the tert-butyl ester before or after ring cleavage, isomerization of the parent or its hydrolysis product, hydroxylation of the phenoxy ring, oxidation of the butyl ester, and other oxidation reactions.
Metabolism and disposition in bile duct-cannulated animals following single oral (low) dose Sprague-Dawley rat PMRA# 2428666 (benzyl label) and 2428667 (pyrazole label)	**Pyrazole label:** 47/55% of the AD was excreted in bile, 5/10% in urine, and 17/28% in feces (♂/♀). In bile, no parent was detected; several metabolites were detected (M3, M4, M5, M6, M7, M8, M9, M10, M13, M14, and M22, as well as conjugates of M3, M4, M5, M8). The metabolic pathway involves cleavage of the ester bond, hydroxylation at the phenoxypyrazole group, oxidation at the tert-butyl group, and conjugation with sulfate and glucuronide. **Benzyl label:** 47/51% of the AD was excreted in bile, 6/8% in urine, and 28/40% in feces (♂/♀). TK parameters were similar to rats without bile duct cannulation.

Study Type/Animal/PMRA #	Study Results
Toxicokinetics and metabolism in rats following a single oral administration at 96 mg/kg bw Choudhary et al., 2008 PMRA# 2493886	Non-radiolabelled fenpyroximate and metabolite M16 were administered. **Absorption:** Parent was detected in blood at 0.25 hours (2.6 µg/mL), reaching a maximum at 24 hours (22 µg/mL) and a minimum at 144 hours (not detected at 168 hours). M16 was detected in blood at 0.25 hours (1.25 µg/mL), reaching a maximum at 24 hours (7.8 µg/mL) and minimum at 168 hours. The rate of absorption (0.06 h^{-1}), absorption half-life (12 hours), and half-life of elimination (31 hours) indicate slow absorption and elimination of the parent. **Excretion:** The majority of parent and M16 excreted via the urine were measured at 48 and 96 hours, respectively, while in feces, maximum levels were recorded at 72 hours for the parent and at 48 hours for M16. Excretion of both parent and M16 was higher in feces than in urine. The level of M16 was 7-fold higher than parent in urine; the level of parent was 8-fold higher than M16 in feces. The hepatic clearance rate was 63-fold higher than the renal clearance rate, indicating that the major portion of fenpyroximate was excreted through feces (23%) compared to urine (<1%), and that it is predominantly excreted through the bile duct and undergoes enterohepatic circulation. Total body clearance of M16 (1.6-fold that of the parent) suggested that it would not remain much longer in the body than the parent. **Distribution:** For parent, the Vd_{area} (18 L kg^{-1}) and $t_{1/2\beta}$ (31 h) values indicate a wide distribution and long persistence. For M16, the Vd_{area} (48 L kg^{-1}), and $t_{1/2\beta}$ (48 h) values also suggested a wide distribution and long persistence. Parent was detected in all tissues at 0.25 hours and up to 168 hours. The tissue half-life of parent varied from 24 to 44 hours, and was highest in fat tissue. M16 was detected in all tissues at 0.25 hours (indicating rapid metabolism) but was not detected in skeletal muscle at 96 hours onwards or in the heart, lung, brain, fat, bone and stomach at 168 hours.
Metabolism of fenpyroximate in rats following single oral (low) dose Nishizawa et al. (1993) PMRA# 2493912	**Absorption:** C_{max} = 0.18, 0.16, 0.18 µg/mL at 12, 12, or 9 hours for the pyrazole, phenyl or benzyl labels. **Excretion:** Half-life of 11.3, 10.6, 6.2 hours for the pyrazole, phenyl or benzyl labels. In urine, 26, 26, and 6% of the AD detected for the pyrazole, phenyl or benzyl labels. In feces, 66, 64, 87% of the AD detected for the pyrazole, phenyl or benzyl labels.

Study Type/Animal/PMRA #	Study Results
	Metabolism: Major urinary metabolites after dosing with the pyrazole label were M8 (7% of the AD) and M21 (3% of the AD). The conjugates of M10 and M14 were also detected in urine. More than 20 fecal metabolites were detected with the pyrazole label. Parent accounted for 19% of the AD. Major fecal metabolites were M22 (4%), M3 (4%), M5 (3%), M11 (2%), and M6 (2%). Metabolites M1, M2, M4, M7, M9, and M14 were excreted into the feces in small amounts. The main urinary metabolite with the benzyl label was M18 (4%). In feces, parent accounted for 13% of the AD. Fecal metabolites included M15 (0.5%), M16 (8%), M2 (1%), M22 (4%), M3 (11%), M4 (1%), and M5 (4%). Metabolism occurred via oxidation of the tert-butyl group and methyl group at the 3-position in the pyrazole ring, p-hydroxylation in the phenoxy moiety, N-demethylation hydrolysis of the tert-butyl ester, cleavage of the oxime ether bond, and/or E/Z isomerization. There was no evidence of cleavage of the phenoxy linkage or fission of the pyrazole ring. **In vitro metabolism (liver):** Four metabolites were identified (M1, M3, M12, M13). During the incubation, the amount of M3 gradually increased while M12 and M13 were detected at 15 minutes and decreased to be almost negligible at 120 minutes.
Species-specific detoxification Investigation of mode of selective toxicity between spider mites and mammals Motoba et al. (2000) PMRA# 2493892	Fenpyroximate is known to inhibit mitochondrial NADH-ubiquinone oxidoreductase. **Inhibitory activity on rat liver mitochondrial respiration** In rat liver, fenpyroximate and M1 exhibited almost identical inhibition of mitochondrial NADH-ubiquinone oxidoreductase (IC_{50} = 0.4 µM) using NADH-linked substrate (α-ketoglutarate). Lower inhibitor activity was demonstrated for M12 (IC_{50} = 3 µM) and M22 (IC_{50} = 30 µM) using the same substrate. Similar to fenpyroximate, these same two metabolites did not inhibit the electron transfer from succinate to oxygen at high concentrations. This suggests that the site of inhibition of these metabolites is identical to that of fenpyroximate. Metabolites lacking the ester part or benzyl ring (eg. M3, M5, M6) did not exhibit inhibition at all when using the α-ketoglutarate substrate. This suggests that tertiary butyl ester hydrolysis was a critical pathway in the detoxification of fenpyroximate. **In vivo metabolism by rat and spider mites**

Study Type/Animal/PMRA #	Study Results
	In the rat, metabolites M3, M22, A and B detected in plasma 1 hour post-dosing, at levels >12-fold higher than the parent. Metabolites M3, M5, M22, A and B were found in liver at high concentrations at 1 hour, with parent being non-detectable by 12 hours. These data suggest that metabolic dissipation of fenpyroximate in rats would be rapid and that metabolites A and B would be the primary metabolites. *[Note – Metabolites A and B (labile intermediates) were not detected in guideline metabolism studies.]* In spider mites, 93% of AD recovered as parent, metabolites M1 and M12 each recovered at 3% of AD. Ester hydrolyzed metabolites such as M3 and M5 were not detected. Qualitatively, different metabolites were generated in rats and spider mites. **In vitro ester hydrolytic and monooxygenase activity of rat liver and spider mite S9 fraction** In rat liver S9 fraction, the relative rate of tertiary butyl ester hydrolysis to methyl ester hydrolysis was 1/300. S9 fraction from spider mites could hydrolyze only primary and secondary alcohol esters; the hydrolysis of tertiary butyl ester was not detectable. Rat liver S9 degraded fenpyroximate mainly to metabolite A and B, M12, M2 and M20 at rates of 159, 41, 29, and 4 nmol/min/mg protein, respectively. This indicates that production of metabolite A was predominant to other oxidative metabolic pathways. Spider mite S9 fraction exhibited M12 and M20 forming activity at rates of 0.14 and 0.19 nmol/min/mg protein, respectively. As in the in vivo study, metabolite A was not detected. The most notable difference in primary metabolism between the rat and spider mite was the production of metabolites A and B. **Distribution of tert-butyl oxidation activity among various organisms** Mouse liver S9 fraction degraded fenpyroximate mainly to M12, metabolite A, and M20 (77, 13, 8 nmol/min/mg protein). Metabolite A was also observed with S9 fraction prepared from rabbit liver, monkey liver, quail liver, carp liver, and larval moth mid gut (7, 33, 2, 5, 5 nmol/min/mg protein).

Study Type/Animal/PMRA #	Study Results
	In vitro metabolism by S9 from all organisms showed that M12 and metabolite A (N-demethylation and tertiary butyl oxidation) were the predominant metabolites. Every human recombinant CYP isoform tested except 1A2 converted fenpyroximate to metabolite A; metabolism of fenpyroximate to metabolite A occurred in every organism except spider mites.
Acute Oral Toxicity CD mouse PMRA# 2278828	LD_{50} ♂ = 520 mg/kg bw LD_{50} ♀ = 440 mg/kg bw LD_{50} ♂/♀ = 500 mg/kg bw High toxicity. All mortality occurred within 6 days of dosing. Clinical signs included: ataxia, hypopnea, hypoactivity, prostration, urinary staining, abdominal gripping, hyperpnea, dyspnea, hypothermia, hyperactivity, coarse tremors.
Acute Oral Toxicity Sprague-Dawley rat PMRA# 2278829 (study) and 2278736 (DER)	LD_{50} ♂ = 480 mg/kg bw LD_{50} ♀ = 245 mg/kg bw LD_{50} ♂/♀ = 350 mg/kg bw High toxicity. All mortality occurred within 5 days of dosing. Clinical signs included: urinary and fecal staining, soft stool, partially closed eyes, hypoactivity, hypopnea, prostration, dry rales, dry oral discharge, unthrifty coat, alopecia, hypothermia, abdominal gripping, emaciation, dyspnea, ataxia, decreased food consumption.
Acute Dermal Toxicity Sprague-Dawley rat PMRA# 2278831 (study) and 2278737 (DER)	No deaths. LD_{50} > 2000 mg/kg bw Low toxicity. Clinical signs included: decreased food consumption (all animals), dry red nasal discharge (1 ♀)
Acute Inhalation Toxicity (nose-only) Sprague-Dawley rat PMRA# 2278832 (study) and 2278738 (DER)	LC_{50} ♂ = 0.24 mg/L LC_{50} ♀ = 0.37 mg/L LC_{50} ♂/♀ = 0.35 mg/L Moderate toxicity. All mortalities occurred within 1 day of exposure. Clinical signs included: mucoid/red nasal discharge, decreased activity, cool to the touch, matted coat, dried red/brown and/or red/black material on facial area, gasping, rales, tremors, chromodacryorrhea, salivation, soft stool.

Study Type/Animal/PMRA #	Study Results
Acute Inhalation Toxicity (nose-only) Sprague-Dawley rat PMRA# 2278833	LC_{50} ♂ = 0.33 mg/L LC_{50} ♀ = 0.36 mg/L LC_{50} ♂/♀ = 0.36 mg/L Moderate toxicity. Clinical signs included: rales, decreased activity, white material on fur, ano-genital staining, soft stool.
Eye Irritation New Zealand White rabbit PMRA# 2278834 (study) and 2278739 (DER)	MAS (24, 48 and 72 hours) = 1.1 MIS = 7.3 (3 hours) Minimally irritating.
Dermal Irritation New Zealand White rabbit PMRA# 2278836 (study) and 2278740 (DER)	MAS (24, 48 and 72 hours) = 0 MIS = 0 Non-irritating.
Dermal Sensitization (Buehler Method) Dunkin-Hartley guinea pig PMRA# 2278839 (study) and 2278741 (DER)	Supplemental. Negative at 50%, but should have tested at a higher concentration (100%).
Dermal Sensitization (Maximization Test) Hartley guinea pig PMRA# 2278837 (study) and 2278742 (DER)	Positive. Slightly delayed onset of symptoms. Potential dermal sensitizer.
1- and 5-day Oral Toxicity (gavage) Beagle dog PMRA# 2432974	NOAEL = 5 mg/kg bw/day LOAEL = 20 mg/kg bw/day: ↑ incidence of diarrhea

Study Type/Animal/PMRA #	Study Results
90-day Oral Toxicity (diet) CD rat PMRA# 2278840 (study), 2278744 (DER) and 2278745 (Amended DER)	NOAEL = 1.30/1.65 mg/kg bw/day LOAEL = 6.57/8.29 mg/kg bw/day: ↓ bw/bwg, ↓ fc; ↓ WBC (♂)
90-day Oral Toxicity (capsule) Beagle dog PMRA# 2278845 (study), 2278846 (add'l info) and 2278774 (DER)	NOAEL not established LOAEL = 2 mg/kg bw/day: diarrhea; ↓ bw/bwg, ↓ fc, emaciation, lethargy (♀)
1-year Oral Toxicity (capsule) Beagle dog PMRA# 2278843 (study), 2278848 (add'l info) and 2278746 (DER)	NOAEL (♂) = 1.5 mg/kg bw/day LOAEL (♂) = 5 mg/kg bw/day: diarrhea NOAEL (♀) = 5 mg/kg bw/day LOAEL (♀) = 15 mg/kg bw/day: diarrhea, excessive salivation, ↓ cholesterol, ↓ thyroid wt
21-day Dermal Toxicity (range-finding) Sprague-Dawley rat PMRA# 2278853 (study) and 2278747 (DER)	A NOAEL and LOAEL were not established as this study was considered to be supplemental. There were no effects noted at the limit dose of 1000 mg/kg bw/day.
21-day Dermal Toxicity (limit test) Sprague-Dawley rat PMRA# 2278850 (study) and 2278747 (DER)	A NOAEL was not established as only one dose level was tested. LOAEL = 1000 mg/kg bw/day: ↓ bw/bwg, ↓ fc, acanthosis of application site; ↑ liver wt (♀)

Study Type/Animal/PMRA #	Study Results
21-day Dermal Toxicity Sprague-Dawley rat PMRA# 2278850 (study) and 2278748 (DER)	NOAEL = 300 mg/kg bw/day LOAEL = 1000 mg/kg bw/day: ↓ bw/bwg, ↓ fc; ↓ kidney wt (abs), ♀ BUN, ↑ potassium (♂); red nose/mouth/nasal discharge, ↑ liver wt, ↑ hepatocellular necrosis (♀)
28-day Inhalation Toxicity (nose-only) Sprague-Dawley rat PMRA# 2278854	NOAEC = 1.8 mg/m^3 (0.47 mg/kg bw/day) LOAEC = 10 mg/m^3 (2.61 mg/kg bw/day): moist and dry rales, laboured breathing, soft stool, dried material on facial area, ↑ lung wt; ↑ RBC, ↑ incidence of squamous metaplasia of the respiratory mucosa (♂); ↑ total WBC (♀)
Oncogenicity (diet) CD mouse PMRA# 2278857 (study) and 2278749 (DER)	NOAEL = 2.4/2.5 mg/kg bw/day (25 ppm) LOAEL = 9.5/10 mg/kg bw/day (100 ppm): ↓ bw/bwg, ↓ fc, ↓ fe No evidence of carcinogenicity.
Chronic Toxicity/ Carcinogenicity (diet) Sprague-Dawley rat PMRA# 2278858, 2278859, 2278862, 2278863, 2278864 (study 5 vols.) and 2278753 (DER)	NOAEL = 0.97/1.16 mg/kg bw/day (25 ppm) LOAEL = 3.08/3.79 mg/kg bw/day (75 ppm): ↓ bw/bwg, ↓ fc, ↓ β-globulin (week 24), ↓ thyroid wt (week 52); ↓ α1-globulin (week 24), ↓ plasma ChE activity (week 102), ↑ rel. testes wt (week 52), ↓ abs. thyroid wt (week 104)(♂); ↓ fe, ↓ liver wt (week 104)(♀)
Preliminary Developmental Toxicity (gavage) Sprague-Dawley rat PMRA# 2278869	A NOAEL and LOAEL were not established as this study was considered to be supplemental. Maternal toxicity Effects at 25 mg/kg bw/day included: ↓ bw/bwg, ↓ fc Developmental toxicity No treatment-related effects noted.

Study Type/Animal/PMRA #	Study Results
Developmental Toxicity (gavage) Sprague-Dawley rat PMRA#2278871 (study), 2278870 (add'l info), 2278755 (DER) and 2278756 (DER)	Maternal NOAEL = 5 mg/kg bw/day LOAEL = 25 mg/kg bw/day: ↓bw/bwg, ↓ fc Developmental NOAEL = 5 mg/kg bw/day LOAEL = 25 mg/kg bw/day: ↑ incidence of additional thoracic ribs Fetal variations at a marginal maternally toxic dose.
Preliminary Developmental Toxicity (gavage) New Zealand White rabbit PMRA# 2278872 (study) 2278750 (DER)	A NOAEL and LOAEL were not established as this study was considered to be supplemental. Maternal Effects at 5 mg/kg bw/day included: ↓ bw/bwg, ↓ fc/wc, ↑ post-implantation loss, ↓ fecal output Developmental Effects at 5 mg/kg bw/day included: ↓ fetal wt, ↑ number of fetuses with multiple anomalies.
Developmental Toxicity (gavage) New Zealand White rabbit PMRA# 2278874 (study), 2278875 (add'l info), 2278750 (DER)	Maternal NOAEL = 2.5 mg/kg bw/day LOAEL = 5 mg/kg bw/day: ↓bw, ↓ fc/wc, ↓ fecal output, abortion Developmental NOAEL = 2.5 mg/kg bw/day LOAEL = 5 mg/kg bw/day: equivocal ↑ fetal incidence of uni- and bi-lateral slightly folded retina. No evidence of sensitivity of the young.
Reproductive Toxicity (diet) Sprague-Dawley rat PMRA# 2278865 (study) and 2278754 (DER)	Parental Toxicity NOAEL = 1.99/2.44 mg/kg bw/day LOAEL = 6.59/8.60 mg/kg bw/day: ↓ bw/bwg (P, F_1: pre-mating); ↓ bw/bwg (P, F_1: gestation)(♀) Offspring Toxicity NOAEL = 2.44 mg/kg bw/day LOAEL = 8.60 mg/kg bw/day: ↓ bw/bwg (F_1, F_2: PND 21 and 25) Reproductive Toxicity NOAEL (♀) ≥ 9.9 mg/kg bw/day LOAEL (♀) not established. NOAEL (♂) = 2.33 mg/kg bw/day

Study Type/Animal/PMRA #	Study Results
	LOAEL (♂) = 8.45 mg/kg bw/day: ↑ testes wt, ↑ epididymides wt (F_1) No evidence of sensitivity of the young.
Bacterial Reverse Mutation Assay S. typhimurium strains TA98, TA100, TA1535, TA1537, TA1538 and E. coli strain WP2uvrA PMRA# 2278877 (study) and 2278758 (DER)	Negative.
In vitro Mammalian Gene Mutation Assay Chinese hamster V79 cells PMRA# 2278879 (study) and 2278759 (DER)	Negative.
In vitro Chromosome Aberration Assay Human lymphocyte cells PMRA# 2278880 (study) and 2278760 (DER)	Negative.
Mouse Micronucleus Assay (gavage) CD-1 mouse PMRA# 2278881 (study) and 2278761 (DER)	Negative.
In vitro UDS Assay Fischer 344 rat hepatocytes PMRA# 2278882 (study) and 2278766 (DER)	Negative.

Study Type/Animal/PMRA #	Study Results
DNA Repair Test (REC-Assay) B. subtilis H17 (rec^+) and M45 (rec^-) PMRA# 2278883 (study) and 2278763 (DER)	Negative.
Acute Oral Delayed Neurotoxicity (gavage) Sterling Ranger hybrid hen PMRA# 2278867 (study) and 2278771 (DER)	NOAEL ≥ 5000 mg/kg bw 5000 mg/kg bw: No treatment-related effects. No evidence of delayed neurotoxicity.
Acute Oral Neurotoxicity (gavage) Sprague-Dawley rat PMRA# 2278867 (study) and 2278772 (DER)	NOAEL = 37.5 mg/kg bw/day LOAEL = 150 mg/kg bw/day: ↓ motor activity; mild dehydration (♂); ↓ auditory startle response (♀) No neuropathological findings observed.
90-day Oral Neurotoxicity (diet) Sprague-Dawley rat PMRA# 2278868 (study) and 2278773 (DER)	NOAEL = 1.8/2.2 mg/kg bw/day LOAEL = 6.1/6.6 mg/kg bw/day: chromorhinorrhea, dehydration, ↓ bwg, ↓ fc/ fe No neuropathological findings observed.
Immunotoxicity (diet) (28-day) Modified Jerne Plaque forming cell assay Sprague-Dawley rat PMRA# 2278856	NOAEL = 2.2/2.6 mg/kg bw/day LOAEL = 7.1/7.9 mg/kg bw/day: ↓ bwg, ↓ fc; altered specific activity of spleen cells and total spleen activity (♀) Evidence of disregulation of the immunologic response at ≥ 7.9 mg/kg bw/day in females. No evidence of immunotoxicity in males.

Study Type/Animal/PMRA #	Study Results
Journal of Neurochemistry (2007) (100: 1469-1479) Sherer, T.B., et al PMRA# 2356217	Mechanism of toxicity of pesticides acting at Complex I: relevance to environmental etiologies of Parkinson's disease. Several commercially used pesticides directly inhibit complex I via oxidative damage. Rank order of toxicity to neuroblastoma cells: pyridaben>rotenone> fenpyroximate>tebufenpyrad, with a similar order of potency for reduction of ATP levels (except pyridaben)
Clinical Toxicology (Nov. 2012) (vol 50, iss 9:858-861) Lee, H.Y., et al. PMRA# 2493888	Case report of intentional poisoning Adult female taken to hospital with reduced level of consciousness, hypotension and severe lactic acidosis following deliberate ingestion of 5% fenpyroximate solution. Acidosis progressed and cardiac arrest required resuscitation. The patient was successfully treated with percutaneous cardiopulmonary support, therapeutic hypothermia and intravenous acteylcysteine. Blood gas measurements revealed decreased arteriovenous oxygen difference. Impaired oxygen utilization at the tissue level believed to be the major mechanism underlying Complex I inhibitor poisoning.
Pesticide Biochemistry and Physiology (1992) (43: 37-44) Motoba, K., et al. PMRA# 2493884	Effect of a New Acaricide, Fenpyroximate, on Energy Metabolism and Mitochondrial Morphology in Adult Female *Tetranychus urticae* (Two-Spotted Spider Mite) Oxygen consumption rates of rat liver mitochondria utilizing NADH-linked substrates such as isocitrate and α-ketoglutarate as the electron donor were significantly inhibited by fenpyroximate, but not when succinate was used as a substrate. It is suggested that the site of inhibition on the electron transport chain is the NADH-Co Q reductase, more specifically the Co-Q reducing part (the oxygen side). Following exposure to fenpyroximate, the ultrastructure of peripheral nerves in *T. urticae* showed that only mitochondria exhibited morphological changes such as swelling, irregular cristae arrangement and low matrix electron density; other intracellular organelles in peripheral nerves did not show changes. In muscles, mitochondria retained their usual morphology (parallel-aligned cristae and high matrix electron density).
Biochimica et Biophysica Acta (1998) (1364:222-235) Esposti, M. D. PMRA# 2356207	Inhibitors of NADH-ubiquinone reductase: an overview. NADH-ubiquinone reductase is the energy-conserving enzyme complex that is commonly known as Complex I. Fenpyroximate displaces dihydro-rotenone, but appears to act differently from the classic Complex I inhibitor rotenone as fenpyroximate inhibits bacterial glucose dehydrogenase.

Study Type/Animal/PMRA #	Study Results
Journal of Neurochemistry (2011) (117:375-387) Mullett, S.J. and D.A. Hinkle PMRA# 2356215	DJ-1 deficiency in astrocytes selectively enhances mitochondrial Complex I inhibitor-induced neurotoxicity. DJ-1 is abundantly expressed in reactive astrocytes, but not in neurons. Both astrocytes and DJ-1 can promote neuronal survival. Impaired astrocytes were less protective of neuronal survival in the presence of fenpyroximate and other Complex I inhibitors, but not with agents that inhibit Complexes II-V. Bioassays with fenpyroximate also detected modest, but significant, augmentation of astrocyte-mediated neuroprotection induced by astrocytic DJ-1 over-expression.
Mutation Research/ Genetic Toxicology and Environmental Mutagenesis (2012) (748:8-16) Graillot, V., et. al PMRA# 2493889	Evidence of the in vitro genotoxicity of methyl-pyrazole pesticides in human cells. Fenpyroximate and several other methyl pyrazole-containing pesticides were assessed for genotoxicity to human cell lines using a new and sensitive in vitro genotoxicity assay. Genotoxic activity was assessed in the human SH-SY5Y neuroblastoma cell line at nanomolar concentrations. Complementary experiments assessed these same compounds in the Jurkat human T-cell leukemia cell line also indicated genotoxicity. These assays demonstrate that fenpyroximate induces DNA damage in human cell lines, very likely by a mode of action that involves oxidative stress by increased production of reactive oxygen species.
Biochemistry (2012) (51:1953-1963) Shiraishi, Y., et. al PMRA# 2493881	Fenpyroximate binds to the interface between PSST and 49 kDa subunits on mitochondrial NADH-ubiquinone oxidoreductase. Using a photoaffinity labelling technique, it was concluded that fenpyroximate does not bind to the distal end of the membrane domain on Complex I, but rather at the interface between the hydrophilic and membrane domains, sharing a common binding pocket with other inhibitors. Chemically diverse inhibitors bind to the cavity, but in considerably different manners depending upon their chemical properties. A study of fenpyroximate derivatives showed that the heterocyclic pyrazole ring including the 5-phenoxy group was critical to the core of the inhibitor, but the side chain had no specific function and contributed solely to an increase in the overall hydrophobicity of the molecule.

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population (excluding females 13-49 years of age)	Dog acute toxicity (1-day/5-day)	NOAEL = 2 mg/kg bw Diarrhea observed after single exposure	100
	ARfD = 0.01 mg/kg bw		
Acute dietary females 13-49 years of age	Rabbit developmental toxicity	NOAEL(developmental) = 2.5 mg/kg bw/day Increased incidence of slightly folded retina in fetuses	300
	ARfD = 0.008 mg/kg bw		
Repeated dietary general population (excluding females13-49 years of age)	2-year rat chronic toxicity /oncogenicity	NOAEL = 0.97 mg/kg bw/day Effects on body weight/body weight gain, food consumption, and organ weights	100
	ADI = 0.01 mg/kg bw/day		
Repeated dietary females 13-49 years of age	Rabbit developmental toxicity	NOAEL (developmental)= 2.5 mg/kg bw/day Increased incidence of slightly folded retina in fetuses	300
	ADI = 0.008 mg/kg bw/day		
Dermal (all durations)[2]	Rabbit developmental toxicity	NOAEL(developmental) = 2.5 mg/kg bw/day Increased incidence of slightly folded retina in fetuses	300
Short-term inhalation	Rat 28-day inhalation	NOAEL = 0.47 mg/kg bw/day Respiratory clinical signs, changes in hematological parameters, effects on the lungs	100
Intermediate- and long- term inhalation	Rat 28-day inhalation	NOAEL = 0.47 mg/kg bw/day Respiratory clinical signs, changes in hematological parameters, effects on the lungs	300
Cancer	Not required as there was no evidence of oncogenic potential.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments

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

Table 6 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN Cotton			**PMRA # 2278907**
Radiolabel Position	[Pyrazole-3-^{14}C]-Fenpyroximate		
Test Site	Field		
Treatment	Foliar treatment		
Total Rate	167 g a.i./ha		
Formulation	Emulsifaible concentrate (EC) formulation		
Preharvest interval	Immature Cotton Plants: 7 d PHI; Undelinted Cottonseed and Gin Trash: 30 d PHI		
Matrices	**PHI (days)**	**[Pyrazole-3-^{14}C]-Fenpyroximate TRRs (ppm)**	
Kernel of cottonseed	30	0.008	
Lint and Hulls	30	0.021	
Dried Leaves	30	14.63	
Immature Forage	7	3.60	
Field Gin Trash	30	8.38	
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**
Radiolabel Position	**[Pyrazole-3-^{14}C]-Fenpyroximate**		
Kernel of cottonseed	Fenpyroximate + M-1		-
Immature Forage	Fenpyroximate + M-1		M-8
Field Gin Trash	Fenpyroximate + M-1		M-8
Dried Leaves	Fenpyroximate + M-1		M-8
NATURE OF THE RESIDUE IN Grapes			**PMRA # 2278906, 2278905**
Radiolabel Position	**[U-^{14}C-Benzyl]-Fenpyroximate**		
Test Site	Field		
Treatment	Foliar treatment		
Total Rate	58.2 g a.i./ha		
Formulation	Suspension concentrate (SC) formulation		
Preharvest interval	Grapes and Leaves at 0, 7, 14, 28, and 57 day PHI; Mature grapes at 57 d PHI		
Matrices	**PHI (days)**	**[U-^{14}C-Benzyl]-Fenpyroximate TRRs (ppm)**	
Leaves	0 7 14 28 57	7.49 4.08 2.87 2.47 1.16	

Grapes	0 7 14 28 57	0.086 0.144 0.073 0.087 0.060			
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**		
Radiolabel Position	**[U-^{14}C-Benzyl]-Fenpyroximate**				
Leaves	Fenpyroximate + M-1		M-2, M-3, M-4, M-18, M-19		
Grapes	Fenpyroximate + M-1		M-3, M-4, M-17, M-20, M-18, M-22		
NATURE OF THE RESIDUE IN Apples			**PMRA # 2278902, 2278901, 2278900**		
Radiolabel Position	**[Pyrazole-3-^{14}C]-Fenpyroximate** and **[U-^{14}C-Benzyl]-Fenpyroximate**				
Test Site	Field				
Treatment	Foliar treatment				
Total Rate	58 g a.i./ha for both radiolabels				
Formulation	Suspension concentrate (SC) formulation				
Preharvest interval	Fruit and leaves at 0, 7, 14, and 28 d PHI; Mature fruit and leaves at 57 days				
Matrices	**PHI (days)**	**[Pyrazole-3-^{14}C]-Fenpyroximate**	**[U-^{14}C-Benzyl]-Fenpyroximate**		
		TRRs (ppm)	**TRRs (ppm)**		
Leaves	0 7 14 28 57	10.33 5.22 1.81 2.63 0.51	12.21 6.72 2.58 2.41 0.63		
Apples	0 7 14 28 57	0.128 0.108 0.081 0.061 0.032	0.120 0.140 0.110 0.075 0.036		
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**		
Radiolabel Position	**[Pyrazole-3-^{14}C]-Fenpyroximate**	**[U-^{14}C-Benzyl]-Fenpyroximate**	**[Pyrazole-3-^{14}C]-Fenpyroximate**	**[U-^{14}C-Benzyl]-Fenpyroximate**	
Leaves	Fenpyroximate + M-1	Fenpyroximate + M-1	M-3, M-4, M-11	M-3, M-4, M-16, M-18	
Apples	Fenpyroximate + M-1	Fenpyroximate + M-1	M-3, M-4, M-8	M-3, M-4, M-18	

NATURE OF THE RESIDUE IN Citrus			**PMRA # 2278897, 2278898, 2278899, 2278910**
Radiolabel Position	**[Pyrazole-3-^{14}C]-Fenpyroximate** and [**U-^{14}C-Benzyl]-Fenpyroximate**		
Test Site	In individual pots in greenhouse, and field		
Treatment	Foliar treatment		
Total Rate	288-550 g ai/ha, 20 mg ai/tree		
Formulation	Suspension concentrate (SC) formulation		
Preharvest interval	0-137 days, depending on study		
Matrices	**PHI (days)**	**[Pyrazole-3-^{14}C]-Fenpyroximate**	[**U-^{14}C-Benzyl]-Fenpyroximate**
		TRRs (ppm)	**TRRs (ppm)**
Mandarin Pulp (288 g ai/ha benzyl label)	0 3 7 14 28 98	na na na na na na	<0.01 <0.01 <0.01 <0.01 <0.01 <0.01
Mandarine Leaves (590 g ai/ha pyrazole label; 288 g ai/ha benzyl label)	0 3 7 14 28 98 137	5.33 5.54 3.37 2.27 1.78 - 1.37	9.80 9.17 6.40 4.23 2.47 0.86 -
Mandarine Rind (590 g ai/ha pyrazole label; 288 g ai/ha benzyl label)	0 3 7 14 28 137	0.49 0.63 0.52 0.48 0.49 0.36	1.13 1.25 1.02 1.13 0.87 0.21
Tangerine Leaves (20 mg ai/tree)	0 7 14 28 65	13.76 12.07 13.24 11.24 14.26	na na na na na
Tangerine Rind (20 mg ai/tree)	0 7 14 28 65	0.96 1.04 1.36 1.10 1.03	na na na na na

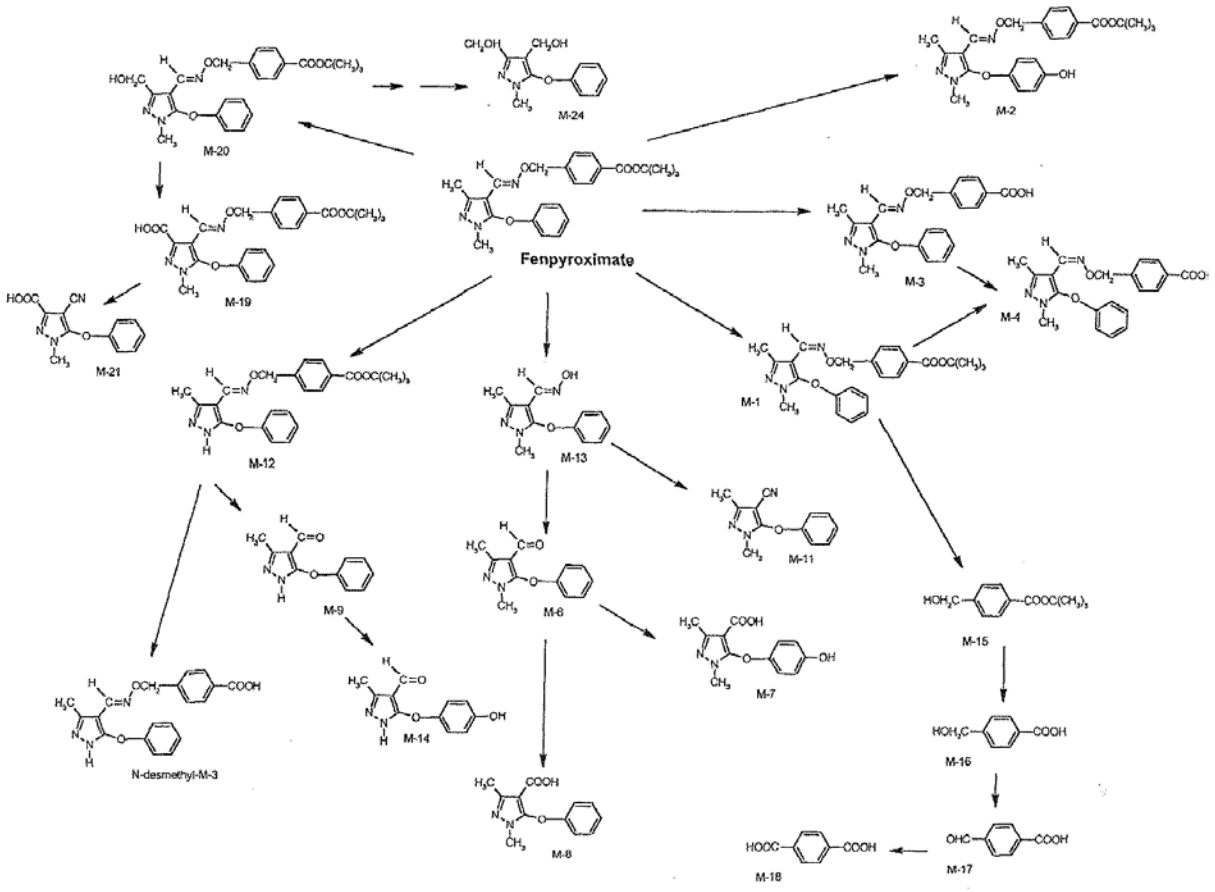
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[Pyrazole-3-^{14}C]-Fenpyroximate**	**[U-^{14}C-Benzyl]-Fenpyroximate**	**[Pyrazole-3-^{14}C]-Fenpyroximate**	**[U-^{14}C-Benzyl]-Fenpyroximate**
Mandarin Leaves	Fenpyroximate + M-1	Fenpyroximate + M-1	M-2, M-3, M-6, M-8, M-9, M-11, M-12, M-13, M-14, M-19, M-20	M-2, M-3, M-12, M-15, M-17, M-19, M-20
Mandarin Rind	Fenpyroximate + M-1	Fenpyroximate + M-1, M-12	M-3, M-6, M-8, M-9, M-11, M-12, M-13, M-14, M-19, M-20	M-2, M-3, M-12, M-15, M-17, M-19, M-20
Tangerine Leaves	Fenpyroximate + M-1	na	M-3, M-6, M-8, M-9, M-11, M-12, M-13, M-19	na
Tangerine Rind	Fenpyroximate + M-1	na	M-3, M-6, M-8, M-9, M-11, M-12, M-13, M-19	na

NATURE OF THE RESIDUE IN Snap Beans	**PMRA # 2278909**

Radiolabel Position	**[Pyrazole-3-^{14}C]-Fenpyroximate** and [**U-^{14}C-Benzyl]-Fenpyroximate**		
Test Site	Field		
Treatment	Foliar treatment		
Total Rate	104 g a.i./ha for both radiolabels		
Formulation	Suspension concentrate (SC) formulation		
Preharvest interval	Pods and leaves at 7 d PHI (leaves not analyzed)		
Matrices	**PHI (days)**	**[Pyrazole-3-^{14}C]-Fenpyroximate**	**[U-^{14}C-Benzyl]-Fenpyroximate**
		TRRs (ppm)	**TRRs (ppm)**
Pods	7	0.124	0.107

Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[Pyrazole-3-^{14}C]-Fenpyroximate**	**[U-^{14}C-Benzyl]-Fenpyroximate**	**[Pyrazole-3-^{14}C]-Fenpyroximate**	**[U-^{14}C-Benzyl]-Fenpyroximate**
Pods	Fenpyroximate + M-1	Fenpyroximate + M-1	-	-

Proposed Metabolic Scheme in Plants



FREEZER STORAGE STABILITY	**PMRA # 2278646, 2278676, 2278649**

Plant matrices: Cucumber, tomato, pepper, tomato paste, and tomato puree

The freezer storage stability data indicate that residues of Fenpyroximate and M-1 are stable at -20°C for 168 days (cucumber), 567 days (tomato), 403 days (peppers), and ~530 days (tomato paste and puree).

CROP FIELD TRIALS ON Greenhouse Tomatoes										**PMRA # 2278676**
Greenhouse trials were conducted in 2005 in the United States. Trials were conducted in NAFTA Growing Regions 3(1 trial), 6 (1 trial) and 9 (1 trial) for a total of 3 trials. Fujimite 5EC was applied twice at a rate of 112 g a.i./ha/application for a total application rate of 224 g a.i./ha. The applications were made at 13-day intervals with the last application occurring approximately 1 day before harvest.										
Commodity	**Total Application Rate (g a.i./ha)**	**PHI (days)**	**Residue Levels (ppm)**							
			n	Min. [#]	Max. [#]	LAFT [*]	HAFT [*]	Median [*]	Mean [*]	SD [*]
Fenpyroximate + M-1										
Greenhouse Tomato	218-233	1	6	0.098	0.174	0.105	0.140	0.107	0.117	0.028
[#] Values based on total number of samples. [*] Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ. n = number of field trials.										
CROP FIELD TRIALS & RESIDUE DECLINE ON Field Tomatoes										**PMRA # 2278676**
Field trials were conducted in 2005 in the United States. Trials were conducted in NAFTA Growing Regions 1(1 trial), 2 (1 trial), 3 (2 trials), 5 (1 trial), and 10 (11 trials) for a total of 16 trials. Fujimite 5EC was applied twice as foliar broadcast sprays at a rate of 112 g a.i./ha/application for a seasonal application rate of 224 g a.i./ha. The applications were made at 13-day intervals with the last application occurring approximately 1 days before harvest. One field trial received a third application due to delayed crop maturity. Residue decline data show that residues of fenpyroximate decreased in field tomatoes with increasing preharvest intervals (PHIs).										
Commodity	**Total Application Rate (g a.i./ha)**	**PHI (days)**	**Residue Levels (ppm)**							
			n	Min. [#]	Max. [#]	LAFT [*]	HAFT [*]	Median [*]	Mean [*]	SD [*]
Fenpyroximate + M-1										
Field Tomato	222-278	1	30	<0.055	0.185	<0.055	0.170	0.084	0.092	0.029
[#] Values based on total number of samples. [*] Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ. n = number of field trials.										

CROP FIELD TRIALS ON Greenhouse Peppers										PMRA # 2278649
Greenhouse trials were conducted in 2005 in the United States. Trials were conducted in NAFTA Growing Regions 2(1 trial), 6 (1 trial), and 9 (1 trial) for a total of 3 trials. Fujimite 5ECwas applied twice as foliar broadcast sprays at a rate of 112 g a.i./ha/application for a total application rate of 224 g a.i./ha. The applications were made at 13-14-day intervals with the last application occurring approximately 1 day before harvest. One trial was conducted with non-bell peppers, and two trials with bell peppers.										
Commodity	**Total Application Rate (g a.i./ha)**	**PHI (days)**	**Residue Levels (ppm)**							
			n	Min. [#]	Max. [#]	LAFT [*]	HAFT [*]	Median [*]	Mean [*]	SD [*]
Fenpyroximate + M-1										
Greenhouse Bell Peppers	226-231	1	4	<0.05	0.069	<0.05	0.069	0.059	0.059	0.01
Greenhouse Non-bell Peppers	229	1	2	0.052	0.056	0.054	0.054	-	0.056	-
[#] Values based on total number of samples. [*] Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ. n = number of field trials.										

CROP FIELD TRIALS & RESIDUE DECLINE ON Field Peppers	PMRA # 2278649
Field trials were conducted in 2005 in the United States. Trials were conducted in NAFTA Growing Regions 2(3 trials), 3 (3 trials), 5 (2 trials), 6 (2 trials), and 10 (3 trials) for a total of 13 trials. Fujimite 5EC was applied twice as foliar broadcast sprays at a rate of 112 g a.i./ha/application for a seasonal application rate of 224 g a.i./ha. The applications were made at 13-16-day intervals with the last application occurring approximately 1 day before harvest. Five trials involved non-bell peppers, and 8 trials bell peppers. Residue decline data show that residues of fenpyroximate decreased in field peppers with increasing preharvest intervals (PHIs).	

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)							
			n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
Fenpyroximate + M-1										
Field Bell Peppers	225-351	1	16	<0.05	0.133	<0.05	0.127	0.050	0.050	0.03
Field Non-bell Peppers	224-231	1	10	<0.05	0.120	<0.05	0.115	0.050	0.064	0.03

Values based on total number of samples.
* Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of field trials.

CROP FIELD TRIALS & RESIDUE DECLINE ON Greenhouse Cucumbers	PMRA # 2278663, 2278972

Greenhouse trials were conducted in 2001-2003 in the EU. Trials were conducted in North EU (3 trials) and the South EU (6 trials) for a total of 9 trials. Fenpyroximate 5SC formulation was applied once at a rate of 102.5 g a.i./ha. The application was made 7 days before harvest.

Residue decline data show that residues of fenpyroximate decreased in greenhouse grown cucumbers with increasing preharvest intervals (PHIs).

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)							
			n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
Fenpyroximate + M-1										
Greenhouse Cucumber	100-112	7	9	<0.02	<0.03	<0.02	<0.03	0.02	0.02	0.005

Values based on total number of samples.
* Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of field trials.

CROP FIELD TRIALS ON Field Cucumbers	PMRA # 2278646

Field trials were conducted in 2008-2009 in the United States. Trials were conducted in NAFTA Growing Regions 2(3 trial), 3 (2 trials), 5 (2 trials), 6 (1 trial), and 10 (1 trial) for a total of 9 trials. Fujimite 5EC formulation was applied twice as foliar broadcast sprays at a rate of 112 g a.i./ha/application for a nominal seasonal application rate of 224 g a.i./ha. The applications were made at a14-day interval with the last application occurring approximately 1 day before harvest.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)							
			n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
Fenpyrioximate + M-1										
Field Cucumber	218-226	1	18	0.100	0.240	0.100	0.220	0.115	0.129	0.039
# Values based on total number of samples. * Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ. n = number of field trials.										

PROCESSED FOOD AND FEED - Tomato	**PMRA # 2278676**
Test Site	Two trials in NAFTA Growing Region 10.
Treatment	Broadcast foliar applications
Rate	448-451 g ai/ha
End-use product/formulation	Fujimite 5EC
Preharvest interval	1 day
Processed Commodity	**Average Processing Factor**
Tomato paste	0.8x
Tomato puree	0.5x
M-1 residues were all <LOQ (<0.05 ppm) in RAC and processed fractions. Therefore, the above processing factors are for fenpyroximate *per se*.	

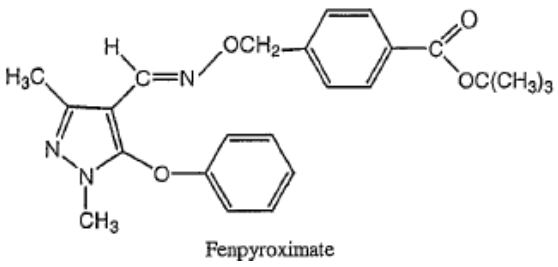
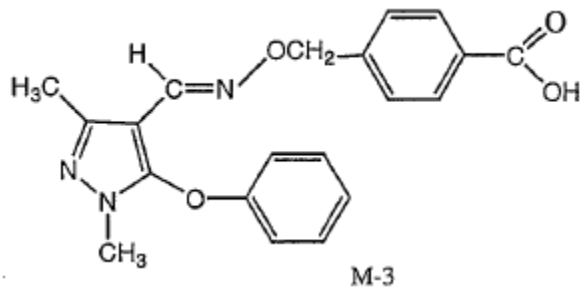
Table 7 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES		
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (list crops; corn)** **Rotational crops**		Fenpyroximate and M-1 (Z-isomer) Not applicable
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops** **Rotational crops**		Fenpyroximate and M-1 (Z-isomer) Not applicable
METABOLIC PROFILE IN DIVERSE CROPS		The profile in cotton, apples, citrus, and snap peas is similar.
DIETARY RISK FROM FOOD AND WATER		
POPULATION	**ADI (mg/kg bw/day)**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**
		Food Alone
All infants < 1 year	0.01	8.1
Children 1–2 years		15.3

Children 3 to 5 years		11.9
Children 6–12 years		7.0
Males 13–19 years		4.4
Males 20–49 years		4.9
Adults 50+ years		5.4
Females 13-49 years	0.008	6.0
POPULATION	**ARfD (mg/kg bw)**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**
		Food Alone
All infants < 1 year	0.05	9.9
Children 1–2 years		14.1
Children 3 to 5 years		11.3
Children 6–12 years		7.2
Males 13–19 years		4.1
Males 20–49 years		4.4
Adults 50+ years		4.9
Females 13-49 years	0.008	30

Table 8 Environmental exposure

Chemical structures of parent and major transformation products

Chemical name	Formation	Structure
Parent, [14C]Fenpyroximate, tert-Butyl €-α-(1, 3-dimethyl-5-phenoxypyrazol-4-ylmethyleneamino-oxy)-p-toluate	Not applicable.	 Fenpyroximate
(*E*)-4-[(1,3-dimethyl-5- phenoxypyrazole-4-yl)-methyleneaminooxy-methyl]benzoic acid (M3)	**Aerobic soil:** Pyrazole label system: Maximum of 15% at day 60 declined to 4% by study termination. Benzyl label system: Maximum of 13.7% at day 61 declined to 5.8% by study termination.	 M-3

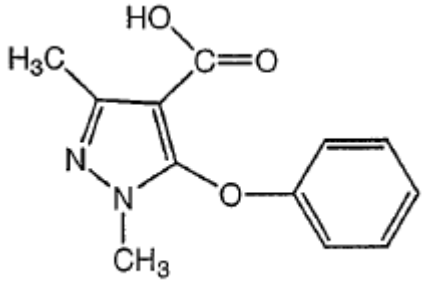
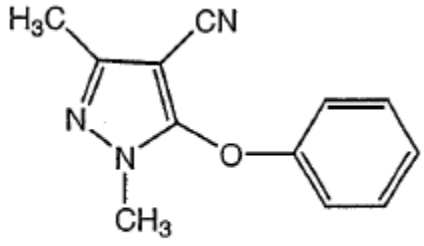
	Aerobic aquatic/sediment: Silt loam pond: 20.8% in water at 14 days. Rhine river, sandy loam: 13% in water at 14 days.	
1,3-dimethyl-5-phenoxypyrazole- 4-carboxylic acid (M8)	**Aerobic soil:** Pyrazole label system: Maximum of 12% by day 90 then declining to 2% by study termination **Aerobic aquatic/sediment:** Rhine river, sandy loam: 16% in water at 30 days and 61 days. Silt loam pond: 27.7% in water at 61 days.	 M-8
1,3-dimethyl-5-phenoxypyrazole- 4-carbonitrile (M11)	**Aerobic aquatic/sediment:** Rhine river, sandy loam: 16.8% in sediment at 61 days. Silt loam pond: 24.3% in sediment at 105 days.	 M-11

Table 9 Fate and behaviour in the terrestrial and aquatic environment

Property	Test substance	PMRA Value	Comments	Major TPs formed	References (PMRA study #)
Terrestrial					
Abiotic transformation					
Hydrolysis pH 5, pH 7, and pH 9 for 30 days	Fenpyroximate	DT50 values (25ºC)(SFO) pH 4: 180 days (stable) **pH 7: 226 days (stable)** pH 9: 221 days (stable)	Not an important route of transformation. Stable at all pH values.	None	2309646
Biotic transformation					

Property	Test substance	PMRA Value	Comments	Major TPs formed	References (PMRA study #)
Aerobic soil Moist sandy loam soil for 365 days with two labels (pyrazole and benzyl)	Fenpyroximate	DT50 values Pyrazole label: 37.1 days (SFO) Benzyl label: 36.2 days (IORE)	EPA classification (Goring et al. 1975): Slightly persistent [a]	Pyrazole label system: **M3** = maximum of 15% at day 60 declined to 4% by study termination. **M8** = maximum of 12% by day 90 then declining to 2% by study termination **CO_2** = 29% at study termination Benzyl label system: **M3** = maximum of 13.7% at day 61 declined to 5.8% by study termination. **CO_2** = 57.8% at study termination	2309658

Property	Test substance	PMRA Value	Comments	Major TPs formed	References (PMRA study #)
Mobility					
Adsorption / desorption in soil (mL/g)	Fenpyroximate	Texas sand Kd=57.46, Koc=30243.9 Ohio sandy loam Kd=279.4, Koc=34490.5 California clay loam Kd=397.2, Koc=33099.7 Texas loam Kd=281.2, Koc=34718.2	EPA classification (McCall et al. 1981): Immobile [c]	Not applicable	2309659
Adsorption / desorption in soil (mL/g)	Fenpyroximate	Commerce silt Kd=726, Koc=103733 Cajon loamy sand Kd=262, Koc=87399 Washington loamy sand Kd=566, Koc=113125 ND Karl Boeren clay loam Kd=1673, Koc=53962 ND Randy Casey sand	EPA classification (McCall et al. 1981): Immobile [c]	Not applicable	2309661

Property	Test substance	PMRA Value	Comments	Major TPs formed	References (PMRA study #)
		Kd=448, Koc=40765			
Aquatic					
Water sediment systems					
Aerobic aquatic biotransformation Two systems (Rhine river and silty loam pond) for 105 days.	Fenpryroximate	<u>System A (Rhine river, sandy loam):</u> water DT50= 2.8 days water DT90 = 9.2 days **whole system DT50 = 34.1 days** whole system DT90 = 113.1 days <u>System B (silt loam pond):</u> water DT50= 3.1 days water DT90 = 24.3 days **whole system DT50 = 23.4 days** whole system DT90 = 77.8 days	EPA classification (McEwen and Stephenson 1979): Slightly persistent in whole system [b]	<u>System A (Rhine river, sandy loam):</u> **M8** = 16% in water at 30 days and 61 days. **M3** = 13% in water at 14 days. **M11** = 16.8% in sediment at 61 days. <u>System B (silt loam pond):</u> **M8** = 27.7% in water at 61 days. **M3** = 20.8% in water at 14 days. **M11** = 24.3% in sediment at 105 days.	Not submitted to PMRA. Based on EFSA report.

Property	Test substance	PMRA Value	Comments	Major TPs formed	References (PMRA study #)
Bioaccumulation					
Bluegill sunfish were exposed to one nominal test concentration (0.10 ug/L) and a dimethylformamide (DMF) solvent control 0.1 mL/L) for a period of 14 days. Thereafter, fish were transferred to clean tanks containing dilution water only for a depuration period of 22 days.	Fenpyroximate	The BCF_{ss} (steady state) value in whole fish was 1465. The kinetic BCF_k value for whole fish was 1131.	Does not meet TSMP criteria of 5000 for bioaccumulation		2309709
Bluegill sunfish were exposed to one nominal test concentration (0.19 ug/L) and a dimethylformamide (DMF) solvent control 0.1 mL/L) for a period of 25 days. Thereafter, fish were transferred to clean tanks containing dilution water only for a depuration period of 24 days.		The BCF_{ss} (steady state) values in whole fish was 1999. The kinetic BCF_k value for whole fish was 2109.	Does not meet TSMP criteria of 5000 for bioaccumulation		2309708

[a] Persistence of pesticide in soil (Goring et al. 1975)
[b] Persistence in water (McEwen and Stephenson 1979)
[c] Adsorption/Desorption and Mobility (McCall et al. 1981)

Table 10 Risk estimation for terrestrial organisms

Organism	Exposure	Endpoint value	EEC	RQ (EEC/ toxicity)	Risk [c]
Invertebrates					
Honeybees[a, b]	Fenpyroximate EUP (5% TGAI) 72 hour CONTACT Exposure = 0 (control), 239.9 and 479.8 µg EUP/bee (= 12 and 24 µg a.i./bee)	LC50 > 479.8 µg EUP/bee (>24 µg a.i./bee) 14% mortality at 479.8 µg EUP/bee	0.928 µg a.i./bee	<0.039	No
	Fenpyroximate (TGAI) 72 hour ORAL Exposure = 0 (control), 1, 5, 10, 50 and 100 µg a.i. per bee	The LD50 > 118.5 µg a.i./bee <6% mortality across control and treatment groups	11.22 µg a.i./bee	<0.095	No
Laboratory studies (predatory mite and parasitic wasp)					
Adult Predatory mite (*Typhlodromus pyri)*	Fenpyroximate EUP (5% TGAI) 0.25, 0.75, 2.5 g ai/ha – sprayed on glass plates	The LC50 >2.5 g ai/ha (with mortality up to 43% (or 34.6% corrected for control) in the highest test group) after 14 days of exposure. NOEC for reproductive effects was <0.25 g ai/ha.	387 g ai/ha	<155	Potential risk. Test was not conducted at maximum label rate.

Organism	Exposure	Endpoint value	EEC	RQ (EEC/ toxicity)	Risk [c]
Adult Predatory mite (*Amblyseius longispinosus* and *Phytoseiulus persimilis)*	Fenpyroximate EUP (5% TGAI) 25, 50 100 and 200 ppm (=g ai/ha) on kidney bean infested by two spotted spider mites	2 day LC50 = 29 ppm (g ai/ha) (95% confidence interval of 6.7 to 43.5 ppm) for *Phytoseiulus persimilis* 2 day LC50 = 178 ppm (g ai/ha) (95% confidence interval of 99 to 214868 ppm) for *Amblyseius longispinosus*.	387 g ai/ha	13 2	Yes Yes
Adult Parasitic wasp (*Ephedrus japonicus)*	Fenpyroximate EUP (5% TGAI) 25, 50 or 100 ppm (=g ai/ha). Mummies were dipped in test solution.	LD50 >100 ppm (g ai/ha) At the end of the 6 day period, 14% mortality in the highest test concentration.	387 g ai/ha	<4	Potential risk. Test was not conducted at maximum label rate.

Organism	Exposure	Endpoint value	EEC	RQ (EEC/ toxicity)	Risk [c]
Tier I studies (laboratory screening tests – non-screening level species)					
Larvae and adults of Green lacewing (*C. niponensis)*	Fenpyroximate TGAI 25 and 50 ppm (=g ai/ha) for larvae (sprayed with test solution) 25, 50 or 100 ppm (=g ai/ha) for adults (sprayed with test solution)	The LD50 values would be >100 g ai/ha for adult green lacewing and >50 g ai/ha for larvae of green lacewing. After 48 hours of exposure ≤10% mortality for both larvae and adults throughout study.	387 g ai/ha	<7 (for larvae) <4 (for adults)	Potential risk. Test was not conducted at maximum label rate.
Larvae and adults of Ladybug (*Harmonia axyridis*)	Fenpyroximate (5%) 25 and 50 ppm (g ai/ha) contact exposure. Adults and larvae were soaked in solution.	Larvae of *C. niponensis* the acute contact LD50 value would be >50 ppm (g ai/ha). After 72 hours there was 0% mortality for adult exposure and 35% mortality for larvae exposure. *Adult control mortality was high (up to 40%) for contact and oral portion of study and will not be considered in the risk assessment)*	387 g ai/ha	<7	Potential risk. Test was not conducted at maximum label rate.

Organism	Exposure	Endpoint value	EEC	RQ (EEC/ toxicity)	Risk [c]
Adult predacious thrips (*Scolothrips sp..)*	Fenpyroximate (5%) 50 ppm (g ai/ha) Contact exposure of adults to dried residues on soybean leaves (with mites provided as food).	LD50 is >50 ppm (g ai/ha) After 4 days there was 0% mortality.	387 g ai/ha	<7	Potential risk. Test was not conducted at maximum label rate.
Adults and pupae of parasitic wasp (*Apanteles glomeratus*)	Fenpyroximate TGAI 25 and 50 ppm (g ai/ha). Pupa and adults were dipped in solution.	Adult LD50 >25 ppm (g ai/ha) and <50 ppm (g ai/ha). After 48 hours, percent mortality was 10, 45 and 90% for adult *Apanteles glomeratusi* exposed to 25 and 50 ppm of fenpyroximate, respectively. Larvae LD50> 50 ppm (g ai/ha)(>94% emergence of pupae) **NOTE**: The results of this study (for adults) will be considered supplemental to the other predator and parasite studies since there is no reliable endpoint and no replication.	387 g ai/ha	For larvae (<7)	For larvae, potential risk. Test was not conducted at maximum label rate.

Organism	Exposure	Endpoint value	EEC	RQ (EEC/ toxicity)	Risk [c]
Juvenile spider (*Lycosa pseudoannulata)*	Fenpyroximate TGAI 25 and 50 ppm (g ai/ha) Spiders were dipped in solution.	LD50> 50 ppm (g ai/ha) After 7 days ≤15% mortality during study.	387 g ai/ha	<7	Potential risk. Test was not conducted at maximum label rate.
Juvenile spider (*Misumenops tricuspidatus*)	Fenpyroximate TGAI 25, 50 and 100 ppm (g ai/ha) Spiders were dipped in solution.	LD50> 100 ppm (g ai/ha) After 7 days there was 0% mortality during study.	387 g ai/ha	<4	Potential risk. Test was not conducted at maximum label rate.
Adult spider *Pardosa* spp.	Fenpyroximate (AE F094552 OO SC05 A107, 5% TGAI) 3.2 and 80 g ai/ha Contact exposure (spiders were sprayed)	LD50 would be > 80 g ai/ha. After 14 days of exposure, mortality was 6.7% in the highest test concentration.	387 g ai/ha	<5	Potential risk. Test was not conducted at maximum label rate.

Organism	Exposure	Endpoint value	EEC	RQ (EEC/ toxicity)	Risk [c]
Rove beetle (*Aleochara bilineata)*	Fenpyroximate (5%) 150 g ai/ha Contact exposure. Sand with rove beetles was sprayed. Therefore, rove beetles were directly sprayed.	At study termination (8 weeks) the average parasitization efficiency was 69% in the treatment group (150 g ai/ha) compared to 58% in the water control group. Therefore, there does not appear to be an effect from fenpyroximate on parasitization. NOTE: The validity criteria for parasitization in the control group are unknown. It is also unknown if 69% is considered "effective parasitization".	387 g ai/ha	Not calculated for this study.	NA
Adult Carabidae (*Poecilus cupreus*)	Fenpyroximate (5%) 3.2 and 80 g ai/ha Contact exposure. Sand was sprayed with test material.	LD50 would be > 80 g ai/ha. After 14 days of exposure, 0% mortality was observed and feeding behavior was not affected.	387 g ai/ha	<5	Potential risk. Test was not conducted at maximum label rate.

Organism	Exposure	Endpoint value	EEC	RQ (EEC/ toxicity)	Risk [c]
Larvae of Hover fly (*Episyrphus balteatus*)	Fenpyroximate (5%) 500 g ai/ha Petri dishes were sprayed and larvae were added. Fecundity of surviving flies	LD50 would be > 500 g ai/ha. The mean pre-imaginal mortality of the hover fly larvae from exposure to 500 g ai/ha was 21.4%. Note: A fertility test could not be carried out on the control or test substance since no eggs hatched. Therefore, the reproductive assessment of the study will not be considered in the risk assessment.	387 g ai/ha	0.77	No

Note: (example calculation of conversion for rates from ppm to g/ha): ppm = mg/kg; 29 mg/kg × 0.0015 kg/cm^3 (bulk density of soil) = 0.0435 mg/cm^3 × 5 cm depth = 0.2175 mg/cm^2 converted to m^2 = 0.2175 mg/m^2 × 10 000 m^2/ha = 2175 mg/ha/1000 (convert mg to g) = 2.175 g/ha).
Honeybee hazard classification based on Atkins (1981)
[a] EECs for bees for contact exposure is calculated as follows: 0.387 kg a.i./ha × 2.4 µg a.i./bee
[b] EECs for bees for oral exposure is calculated as follows: 0.387 kg a.i./ha × 29 µg a.i./bee
[c] LOC is 0.4 for acute bee studies; LOC is 2 for screening level beneficial arthropods; LOC is 1 for all other species.
Note: Studies which dipped organisms in solution containing fenpyroximate are expected to be a conservative estimate of exposure.

Table 11 Effects on aquatic organisms

Organism	Exposure	Endpoint value	Degree of Toxicity [a]	Reference
Freshwater invertebrates				
Daphnia	Fenpyroximate TGAI (static test)	48 hour LC50 = 0.00328 mg/L	Very highly toxic	PMRA 2309693
	EUP (Fenpyroximate 5%EC) (static renewal every 24 hours)	48 hour LC50 = 0.031 mg EUP/L (equivalent to 0.00155 mg a.i./L)	Very highly toxic	PMRA 2309697
	M-3 (transformation product)	48 hour LC50 = 14 mg TP/L	Slightly toxic	PMRA 2309694
Freshwater fish				
Rainbow trout (*Oncorhynchus mykiss*)	Fenpyroximate TGAI (flow-through)	96 hour LC50 = 0.00105 mg/L Note: Recovery of the test material was low in the study by study termination (38 to 57%). Results are based on mean measured concentrations.	Very highly toxic	PMRA 2309702
	Fenpyroximate TGAI (static renewal – at 48 hours)	96 hour LC_{50} = 0.00064 mg a.i./L Note: Recovery was between 68 and 90%. Results are based on mean measured concentrations.	Very highly toxic	PMRA 2309707
	EUP (Fenpyroximate	LC_{50} = 0.041 mg	Very highly toxic	PMRA

	Flowable-R 5%)	formulation/L (equivalent to 0.0021 mg a.i./L) Results account for low recovery.		2309705
	M-3 (transformation product)	48 hour LC50 = 8.2 mg TP/L	Moderately toxic	PMRA 2309706

[a] According to US EPA toxicity classification

Table 12 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	**In soil,** fenpyroximate does not meet the TSMP critieria (DT50 values (Pyrazole label: 37.1 days (SFO) and Benzyl label: 36.2 days (IORE)). **In water**, the whole system (biotic) half-life of fenpyroximate in aerobic water/sediment (from the EFSA review), the TSMP criteria was not met (water half-life: 3.1 days and whole system half-life: 34.1 days). It is expected that fenpyroximate would biotransform quickly in the environment, if exposure occurred.
	Water	Half-life ≥ 182 days	
	Sediment	Half-life ≥ 365 days	
	Air	Half-life ≥ 2 days or evidence of long range transport	Based on the vapour pressure (2.6 × 10-8 mm Hg at 25 °C) and Henry's Law Constant ((1/H) 3.85×10^4) and the half-life estimated of 0.22 days in air (AOP v.1.92), long-range atmospheric transport is unlikely.
Bioaccumulation[4]	Log $K_{OW} \geq 5$		**Bioaccumulation** based on the results of two bioaccumulation studies, the BCF trigger is not met (Maximum BCF_{ss} value of 2746 for edible tissue).
	BCF ≥ 5000		
	BAF ≥ 5000		
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			**No**, does not meet TSMP Track 1 criteria.

[1]All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (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 (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

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2309708 2010, Fenpyroximate: A Bioconcentration Test with the Bluegill (Lepomis macrochirus), DACO: 9.5.6

2309709 1997, Bioaccumulation of [14C]-Fenpyroximate in Bluegill Sunfish (Lepomis macrochirus), DACO: 9.5.6

2309687 1991, Acute Toxicity Study of Fenpyroximate in Green Lacewing, DACO: 9.2.5

2309690 1991, Acute Toxicity Study of Fenpyroximate in Ladybug, DACO: 9.2.5

2309691 1992, Acute Toxicity Study of Fenpyroximate in Predacious Thrips, Scolothrips SP., DACO: 9.2.5

2309684 2002, Fenpyroximate and Fenpyroximate 5% SC: Acute Toxicity Study to Beneficial Arthropods, DACO: 9.2.5,9.2.6

2309692 2013, Non-Target Fresh Water Invertebrate Summary of Fenpyroximate Technical, DACO: 9.3.1

2309693 1992, A Study of the Acute Toxicity to the Freshwater Aquatic Invertebrate (daphnia magna) of Fenpyroximate, DACO: 9.3.2

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2309697 2006, Fenpyroximate 5EC: A 48 Hour Static Renewal Acute Toxicity Test with the Cladoceran (daphnia magna), DACO: 9.3.2

2309698 2013, Non-Target Fish Summary for Fenpyroximate Technical, DACO: 9.5.1

2309702 1992, A Study of the Acute Toxicity to Fish (oncorhynchus mykiss) of Fenpyroximate under Flow Through Conditions, DACO: 9.5.2.1

2309703 2001, A Study of the Acute Toxicity to Fish (oncorhynchus mykiss) of Fenpyroximate under Flow Through Conditions; Addendum 1, DACO: 9.5.2.1

2309704 2004, A Study of the Acute Toxicity to Fish (oncorhynchus mykiss) of Fenpyroximate under Flow Through Conditions; Addendum 2, DACO: 9.5.2.1

2309705 1992, A Study of the Acute Toxicity to Fish (oncorhynchus mykiss) of Fenpyroximate Flowable-R 5% Under Flow Through Conditions, DACO: 9.5.2.1

2309706 2005, Acute Toxicity of M-3, A Fenpyroximate Metabolite, to Rainbow Trout (oncorhynchus mykiss) in a 96 Hour Static Test, DACO: 9.5.2.1

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2309709 1997, Bioaccumulation of [14C]-Fenpyroximate in Bluegill Sunfish (Lepomis macrochirus), DACO: 9.5.6

4.0 Value

2278981 2013, Value Summary for Fenpyroximate Miticide/Insecticide, DACO: 10.1, 10.2, 10.2.1, 10.2.2, 10.2.3, 10.2.3.1, 10.2.3.2, 10.2.3.3, 10.3.1, 10.3.2, 10.3.3, 10.4, 10.5, 10.5.1, 10.5.2, 10.5.3, 10.5.4

2358243 2013, Addendum to Value Summary for Fenpyroximate Miticide/Insecticide, DACO: 10.2.3.1, 10.2.3.3(D), 10.2.4

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

2490660	J. French, et. al., retinal folding in the term rabbit fetus – Developmental abnormality or fixation artifact DACO: 4.8
2493881	Y. Shiraishi, et. al., Fenpyroximate Binds to the Interface between PSST and 49 kDa Subunits in Mitochondrial NADH-Ubiquinone Oxidoreductase, DACO: 4.8
2493884	K. Motoba et. al., Effect of a New Acaricide, Fenpyroximate, on Energy Metabolism and Mitochondrial Morphology in Adult Female Tetranychus urticae (Two-Spotted Spider Mite), DACO: 4.8
2493886	G.K. Choudhary, et. al., Toxicokinetics and metabolism of fenpyroximate in rats following a single oral administration, DACO: 4.5.9
2493888	H.Y. Lee, et. al., A case of near-fatal fenpyroximate intoxication: The role of percutaneous cardiopulmonary support and theraputic hypothermia, DACO: 4.8
2493889	V. Graillot, et. al., Evidence of the in vitro genotoxicity of methyl-pyrazole pesticides in human cells, DACO: 4.5.8
2493892	K. Motoba, et. al., Species-Specific detoxification Metabolism of Fenpyroximate, a Potent Acaricide, DACO: 4.5.9
2493912	H. Nishizawa, et. al., Metabolism of Fenpyroximate in Rats, DACO: 4.5.9

2.0 Value

2394683 Arthropod Pesticide Resistance Database: fenpyroximate, DACO: 10.5.3