Health Canada
Pest Management Regulatory Agency

Santé Canada
Agence de réglementation de la lutte antiparasitaire

PRDD2006-04

PROPOSED REGISTRATION DECISION

Pyriproxyfen

(publié aussi en français)

12 September 2006

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

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ISBN: 0-662-44068-4 (0-662-44069-2)
Catalogue number: H113-9/2006-4E (H113-9/2006-4E-PDF)

FOREWORD

Proposed Decision for Pyriproxyfen

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing full registration for the sale and use of active ingredient pyriproxyfen and the end-use product Distance Insect Growth Regulator to control whiteflies (silver leaf whitefly, sweet potato whitefly and greenhouse whitefly) on greenhouse ornamentals and greenhouse vegetables (tomato, cucumber and pepper).

Current scientific data from the applicant, scientific reports and information from other regulatory agencies were evaluated to determine if, under the proposed conditions of use, the end-use product has value and does not present an unacceptable risk to human health or the environment.

This Proposed Registration Decision is a consultation document[1] that summarizes the science evaluation for pyriproxyfen and the reasons for the decision. It also describes risk reduction measures that will be required to further protect human health and the environment.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health environmental and value assessment of pyriproxyfen.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (please see information on the cover page of this document).

[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act* (http://laws.justice.gc.ca/en/P-9.01/92455.html)

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OVERVIEW

Proposed Registration Decision for Pyriproxyfen

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing full registration for the sale and use of pyriproxyfen technical grade active ingredient and the end-use product Distance Insect Growth Regulator for control of whiteflies (silver leaf whitefly, sweet potato whitefly and greenhouse whitefly) on greenhouse ornamentals and greenhouse vegetables (tomato, cucumber and pepper).

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

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 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 conditions or proposed conditions of registration[2]. The Act also requires that products have value[3] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach a decision, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g., children) as well as organisms in the environment (e.g., those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present 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 PMRA's website at www.pmra-arla.gc.ca.

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2 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act* (http://laws.justice.gc.ca/en/P-9.01/92455.html)

3 "Value" as defined by subsection 2(1) of the *Pest Control Products Act* (http://laws.justice.gc.ca/en/P-9.01/92455.html): "...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 registration decision on pyriproxyfen, the PMRA will consider all comments received from the public in response to this consultation document[4]. The PMRA will then publish a Registration Decision document[5] on pyriproxyfen that will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

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

What is Pyriproxyfen?

Pyriproxyfen is an insecticide for control of whiteflies (silver leaf whitefly, sweet potato whitefly and greenhouse whitefly) on greenhouse ornamentals and greenhouse vegetables (tomato, cucumber and pepper) by foliar application. Pyriproxyfen is an insect growth regulator. It interferes with normal insect development and reproduction.

❖ Health Considerations

♦ Can Approved Uses of Pyriproxyfen Affect Human Health?

Pyriproxyfen is unlikely to affect your health when used according to the proposed label directions.

Potential exposure to pyriproxyfen may occur through diet (food alone) or when handling and applying the product. There is limited potential for pyriproxyfen to migrate to drinking water sources through the proposed greenhouse uses. 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 (e.g., children and nursing mothers). Only uses to which 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 pyriproxyfen products are used according to label directions.

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4 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act* (http://laws.justice.gc.ca/en/P-9.01/92455.html)

5 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act* (http://laws.justice.gc.ca/en/P-9.01/92455.html)

The active ingredient pyriproxyfen caused slight health effects via the inhalation route in animals; consequently, the statement "Caution—Poison" is required on the label. The end-use product, Distance Insect Growth Regulator, caused mild eye and dermal irritation in animals. Because of these effects, the statement "Caution—Skin and Eye Irritant" is required on the label. Pyriproxyfen did not cause cancer in animals and was not genotoxic. There was no indication that pyriproxyfen caused damage to the nervous system, nor did it affect reproduction. There was also no indication that the fetus was more sensitive to pyriproxyfen than the adult animal. The first signs of health effects in animals given daily doses of pyriproxyfen over long periods of time were effects on the liver and kidneys. The risk assessment was conducted to ensure 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 water are not of concern.

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

Dietary intake estimates (food alone) revealed that children, adults and seniors will typically consume less than 14.7% of the acceptable daily intake for pyriproxyfen. Infants, the subpopulation that would ingest the most pyriproxyfen relative to body weight, are expected to eat less than 6.1% of the acceptable daily intake. The dietary intake estimate for females of childbearing age (13 to 50 years old) was about 2.5% of the reference dose, which is not a health concern. Based on these estimates, the chronic dietary risk from pyriproxyfen is not a concern for all population subgroups.

Animal studies revealed no acute health effects. Consequently, a single dose of pyriproxyfen is not likely to cause acute health effects in the general population (including infants and children).

The *Food and Drugs Act* prohibits the sale of food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for the *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Greenhouse residue trials conducted throughout Europe (Italy, France, Spain and Greece) using an end-use product containing pyriproxyfen on greenhouse cucumber, pepper and tomato were sufficient to propose MRLs for cucumbers, bell peppers and tomatoes. The

proposed MRLs for pyriproxyfen can be found in the Science Evaluation section of this consultation document.

♦ Risks in Residential and Other Non-Occupational Environments

Non-occupational risks are not of concern provided that directions specified on the label are observed.

The risk to people who are exposed to pyriproxyfen through diet as well as through the use of pyriproxyfen in and around the home has been assessed and is not of concern.

Bystander exposure is not expected to occur, because Distance Insect Growth Regulator is intended for use in commercial greenhouses only. Therefore, health risks to bystanders are not of concern.

♦ Occupational Risks From Handling Distance Insect Growth Regulator

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

Farmers and pesticide applicators mixing, loading or applying Distance as well as field workers re-entering freshly treated greenhouses, can come in direct contact with pyriproxyfen on the skin or through inhalation of spray mists. Therefore, the label will specify that anyone mixing, loading or applying Distance must wear coveralls or a long-sleeved shirt and long pants, rubber boots, goggles, gloves (rubber, PVC, neoprene or nitrile) and a hat. Taking into consideration the label requirements, that occupational exposure is expected to be brief and that this insecticide is applied up to twice every six months, risk to farmers, applicators or workers is not a concern.

❖ Environmental Considerations

♦ What Happens When Pyriproxyfen is Introduced Into the Environment?

The proposed use of pyripoxifen is in greenhouses; consequently, there will be minimal exposure to wild mammals, birds, earthworms, fish, crustaceans, amphibians, algae and aquatic vascular plants. Pyriproxyfen is harmful to some beneficial organisms such as predatory and parasitoid insects.

Pyriproxyfen is non-persistent in soil. No major breakdown products are formed in soil. Pyriproxyfen is not expected to leach through the soil profile beyond 30 cm; therefore, it is not expected to enter groundwater. Furthermore, due to its low volatility, pyriproxyfen is not expected to enter the atmosphere.

Pyriproxyfen presents a minimal risk to wild mammals, birds, earthworms, fish, crustaceans, amphibians, algae and aquatic vascular plants when used in greenhouse. In

order to reduce the harmful effects of pyriproxyfen to beneficial insects during application, label instructions are required.

❖ Value Considerations

♦ What is the Value of Pyriproxyfen?

Pyriproxyfen is an insecticide that controls whiteflies on greenhouse ornamentals and greenhouse vegetables (tomatoes, cucumbers and peppers).

Foliar application of pyriproxyfen controls whiteflies on greenhouse ornamentals and greenhouse vegetables (tomatoes, cucumbers and peppers). It can be integrated with other chemical and cultural control practices and is compatible with current management practices as well as conventional crop production systems. Growers are familiar with monitoring techniques to determine if and when applications are needed.

Pyriproxyfen is a potential alternative to other classes of insecticides currently registered for control of whiteflies on greenhouse ornamentals and greenhouse vegetables (tomatoes, cucumbers and peppers). Alternative chemistries are needed for use against whiteflies in the greenhouse in order to delay the development of resistance.

Measures to Minimize Risk

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions are required by law to be followed.

Next Steps

Before making a registration decision on pyriproxygen, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Registration Decision Document, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and the Agency's response to these comments.

Other Information

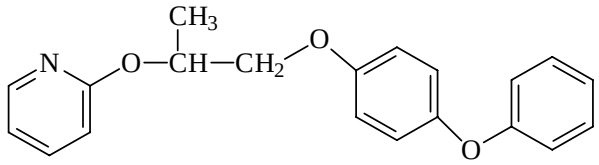
At the time the PMRA makes its registration decision, it will publish an Evaluation Report on pyriproxyfen (based on the Science Evaluation section of this consultation document). In addition, the test data on which the decision is based will also be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

SCIENCE EVALUATION

Pyriproxyfen

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient and Impurities

Active ingredient	Pyriproxyfen
Function	Insecticide
Chemical name	
• International Union of Pure and Applied Chemistry (IUPAC)	4-Phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether
• Chemical Abstracts Service (CAS)	2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine
CAS number	95737-68-1
Molecular formula	$C_{20}H_{19}NO_3$
Molecular weight	321.37
Structural formula	
Nominal purity of the active ingredient	97%
Identity of relevant impurities of toxicological, environmental or other significance	The technical grade pyriproxyfen does not contain any impurities or microcontaminants know to be Toxic Substances Management Policy (TSMP) Track 1 substances.

1.2 Physical and Chemical Properties

Table 1.2.1 Technical Product—Sumilarv Technical Grade

Property	Result	Comment
Colour and physical state	Pale yellow waxy solid	
Odour	Faint characteristic odour	
Melting point or range	47°C	
Boiling point or range	N/A	
Specific gravity	1.56	
Vapour pressure at 23°C	1.33×10^{-7} Pa	Non-volatile under field conditions
Henry's law constant at 20°C	1.1×10^{-7} atm•m^3/mol	Low volatilization potential from water or moist surfaces
Ultraviolet (UV) – visible spectrum	λ_{max} (in water) = 270 nm	No potential for ultraviolet light-induced phototransformation under normal environmental conditions
Solubility in water	0.367 ± 0.004 mg/L at 25°C	Sparingly soluble in water
Solubility in organic solvents (g/kg)	**Solvent** **Solubility** hexane 400 methanol 200 xylene 500	
n-Octanol–water partition coefficient (K_{ow})	log K_{ow} = 5.37	High potential for bioaccumulation
Dissociation constant (pK_a)	Not determined due to solubility problems	
Stability (temperature, metal)	Not provided	

Table 1.2.2 End-Use Product—Distance Insect Growth Regulator

Property	Result
Colour	Clear slightly yellowish
Odour	Not provided
Physical state	Liquid
Formulation type	Emulsifiable concentrate
Nominal guarantee	103 g/L
Formulants	The product does not contain any United States Environmental Protection Agency (USEPA) or PMRA List 1 formulants known to be TSMP Track 1 substances.
Container material and description	High density polyethylene bottles
Density	0.9176 g/cm^3 at 19.5°C
pH of 1% dispersion in water	5.7
Oxidizing or reducing action	N/A
Storage stability	Stable for 12 months when stored at ambient temperature in commercial packaging
Explodability	N/A

1.3 Details of Uses

Valent U.S.A. Corporation has applied for registration of a commercial class end-use product, Distance Insect Growth Regulator, containing the active ingredient pyriproxyfen. This product is for control of whiteflies (silver leaf whitefly, sweet potato whitefly and greenhouse whitefly) on greenhouse ornamentals and greenhouse vegetables (tomato, cucumber and pepper) by foliar application. The application rate is 45 ml product/100 L (4.5 g a.i/100 L). The spray mixture is to be applied uniformly to all plant surfaces and to the point of runoff. Do not apply this product within three days of harvest of tomatoes, peppers and cucumbers. The first application should be made when adult insects begin to appear. If necessary, a second application can be made 14–28 days after the first application. A maximum of two applications per cropping cycle can be applied. If the cropping cycle is less than six months, no more than two applications per six months can be applied.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient as Manufactured

An analytical method was provided for the determination of the active ingredient and structurally-related impurities. The method was shown to be specific, precise and linear.

The method was assessed to be fully validated and acceptable for the analysis of the technical material.

2.2 Method for Formulation Analysis

An analytical method was used for the analysis of the active ingredient in the end-use product. Validation data were provided for linear range, accuracy and precision. The method was shown to be specific, precise and accurate.

The method was assessed to be fully validated and acceptable for use as enforcement analytical method.

2.3 Methods for Residue Analysis

2.3.1 Analytical Methodology (parent compound and transformation products)—Soil, Sediment and Water

Two analytical methods were used for the analysis of pyriproxyfen and two of its metabolites in soil, sediment and water. Full validation data and all necessary chromatograms were provided for each matrix. The methods were shown to be linear, specific, precise and accurate.

Based on the validation data and chromatograms, the methods were assessed to be acceptable for use as postregistration monitoring methods.

2.3.2 Multiresidue Methods for Residue Analysis

Pyriproxyfen [4-phenoxyphenyl-(*RS*)-2-(2-pyridyloxy)propyl ether] and the metabolite PYPAC [(*RS*)-2-(2-pyridyloxy)propionic acid] were screened through the United States Food and Drug Administration multiresidue methods. Pyriproxyfen and PYPAC were tested under Protocols A, C, D, E and F. PYPAC was tested under Protocol B. Testing under Protocol G was not conducted.

Recoveries of pyriproxyfen from apples spiked at 0.10 and 0.50 ppm were acceptable for Protocol D (99.3–108%). For protocol E, recoveries from apples spiked at 0.05 ppm (61.2–88.2%) using C1-50% and C2-3 eluants were also acceptable. Recoveries of pyriproxyfen for Protocol F from cottonseed spiked at 0.05 ppm and 0.50 ppm were acceptable at 86.0–98.6% using C2-3 eluants.

The recovery of PYPAC for Protocol B from spiked cotton seed extract by gel permeation chromatography was very low at 2.85%. Because PYPAC could not be recovered through the Florisil clean-up column, further testing through Protocol E and Protocol F was not conducted. Recoveries of PYPAC for Protocol D from apples spiked at 0.10 ppm and 0.50 ppm were unacceptable, ranging from 144% to 162%.

2.3.3 Methods for Residue Analysis of Plants and Plant Products

Based on the cucumber, pepper and tomato metabolism studies, the residue definition is pyriproxyfen for enforcement and risk assessment purposes.

Residues of pyriproxyfen were determined using one of several data gathering methods. The analytical methods were developed prior to the full understanding of the metabolism in plants; therefore, some of the analytical methods determined pyriproxyfen as well as its metabolite(s) or only the metabolites.

The published multiresidue method, DFG Method S 19 (extended revision), determined pesticide residues in commodities with high water content. Residues of pyriproxyfen were determined by gas chromatography with a mass selective detector (GC-MSD). Recoveries of pyriproxyfen in cucumber fruit ranged from 82% to 105%, with acceptable accuracy and precision ranging from 0.01 ppm to 0.1 ppm. The level of quantification (LOQ) and level of detection (LOD) were reported as 0.01 ppm and 0.002 ppm, respectively.

Analytical Method NNA-90-0016 determined residues of pyriproxyfen in tomatoes. Residues of pyriproxyfen were determined by gas-liquid chromatography with a thermoionic detector (GC-TID). Recoveries of pyriproxyfen in tomato ranged from 75 to 97%, with acceptable accuracy and precision ranging from 0.01 ppm to 1.0 ppm. The LOQ for pyriproxyfen was reported as 0.01 ppm.

Analytical Method RM-33P-1 determined residues of pyriproxyfen in oily and high moisture crops. Residues of pyriproxyfen were determined by gas chromatography with a nitrogen-phosphorous detector (GC-NPD). Recoveries of pyriproxyfen in apples and undelinted cotton seed ranged from 80% to 113%, with acceptable accuracy and precision in the range of 0.02 ppm to 0.1 ppm. The LOQ and LOD for pyriproxyfen were reported as 0.02 ppm and 0.01 ppm, respectively.

Analytical Method RM-33P-1-3 determined residues of pyriproxyfen and the metabolite 4′-OH-Pyr [4-(4-hydroxyphenoxy)phenyl (*RS*)-2-(2-pyridyloxy)propyl ether] in fruit (apples, pears and citrus). This method was based on analytical method RM-33P-1, with the addition of preparation steps for residues of 4′-OH-Pyr. Residues of pyriproxyfen were determined by GC-NPD; and residues of 4′-OH-Pyr by high performance liquid chromatography with a fluorescence detector (HPLC-fluorescence). Recoveries of each of pyriproxyfen and 4′–OH-Pyr from apples and oranges ranged from 82.5% to 105%, with acceptable accuracy and precision ranging from 0.02 ppm to 0.1 ppm. The LOQ and LOD for each analyte were reported as 0.02 ppm and 0.01 ppm, respectively.

Analytical Method RM-33P-1-3a for the determination of pyriproxyfen residues in fruit (apples, pears and citrus) was based on Analytical Method RM-33P-1-3. This method did not include the analysis for 4′-OH-Pyr. The amount of fruit extracted for pyriproxyfen analysis was doubled by eliminating the splitting of the sample extract. The LOQ and LOD for pyriproxyfen were reported as 0.02 ppm and 0.01 ppm, respectively.

Analytical Method RM-33M-1 determined residues of the metabolites DPH-Pyr [4-hydroxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether], POPA [(*RS*)-2-hydroxypropyl 4-phenoxyphenyl ether], 4′-OH-Pyr [4-(4-hydroxyphenoxy)phenyl (*RS*)-2-(2-pyridyloxy)propyl ether] and 5″-OH-Pyr [(*RS*)-5-hydroxy-2-{1-methyl-2-(4-phenoxyphenoxy)ethoxyl} pyridine] (and its respective conjugates) in apples and pears. Residues of DPH-Pyr were determined by GC-NPD. Residues of POPA, 4′-OH-Pyr and 5″-OH-Pyr were determined by HPLC-fluorescence. Recoveries of each analyte from apples ranged from 68% to 106%, with acceptable accuracy and precision ranging from 0.10 ppm to 0.50 ppm. The LOQ and LOD for each analyte were reported as 0.1 ppm and 0.05 ppm, respectively.

Analytical Method RM-33P-8, the proposed enforcement method, determined residues of pyriproxyfen and the metabolite PYPA [(*RS*)-2-(2-pyridyloxy)propyl alcohol] (and its conjugates) in tomatoes. Analytical method RM-33P-8 was revised to improve the recovery of PYPA in peppers. This revision was designated RM-33P-9. Residues of pyriproxyfen and PYPA were determined by GC-NPD. Recoveries of pyriproxyfen and PYPA from tomatoes ranged from 77% to 108%, with acceptable accuracy and precision ranging from 0.02 ppm to 0.10 ppm. The LOQ and LOD for each analyte were reported as 0.02 ppm and 0.01 ppm, respectively. A radiovalidation study demonstrated that RM-33P-8 effectively extracted bioincurred residues of pyriproxyfen and PYPA (and its conjugates) from tomato pomace and juice samples generated during the tomato metabolism study.

Analytical Method RM-33P-2-2 determined residues of pyriproxyfen and PYPAC in cottonseed. Residues of pyriproxyfen and PYPAC were determined by GC-NPD. The LOQ and LOD for each analyte were reported as 0.02 ppm and 0.01 ppm, respectively. Analytical Method RM-33P-2-2 was successfully validated by an independent laboratory. Recoveries of each analyte from cottonseed ranged from 72% to 95% , with acceptable accuracy and precision ranging from 0.02 ppm to 0.1 ppm.

In summary, analytical methods DFG Method S 19 (extended revision) (GC-MSD), NNA-90-0016 (GC-TID), RM-33P-1 (GC-NPD), RM-33P-1-3 (GC-NPD), RM-33P-1-3a (GC-NPD), RM-33P-8 (GC-NPD), RM-33P-9 (GC-NPD) and RM-33P-2-2 (GC-NPD) were deemed adequate as data gathering methods for residues of pyriproxyfen (residue definition) in plant matrices. Analytical methods RM-33P-8 and RM-33P-9 included an acid reflux step of the extract prior to clean-up for pyriproxyfen and PYPA (and its conjugates) residues separately. Analytical method RM-33P-8 was deemed adequate as an enforcement method as it was able to effectively extract bioincurred residues of pyriproxyfen from tomato pomace and tomato juice. A similar analytical method, RM-33P-2-2, was successfully validated by an independent laboratory using cottonseed. The United States Food and Drug Administration multiresidue methods were also deemed adequate as an enforcement method for residues of pyriproxyfen in plant matrices.

2.3.4 Methods for Residue Analysis of Food of Animal Origin

Based on the goat metabolism study, the residue definition in animal commodities (ruminant only) is pyriproxyfen for enforcement and risk assessment purposes.

Residues of pyriproxyfen and/or its metabolite(s) were determined using one of several data gathering methods.

Analytical Method RM-33G-2 determined residues of pyriproxyfen and the metabolites POP (4-phenoxyphenol) and its conjugates and 4′-OH-Pyr and its conjugates in milk. Residues of pyriproxyfen were determined by GC-NPD. Residues of POP and 4′-OH-Pyr were determined by HPLC with an UV detector (λ = 275 nm). Recoveries of each analyte (pyriproxyfen, POP as the sulfate conjugate POP-SO_3K and 4′-OH-Pyr) in milk ranged from 75–108% with acceptable accuracy and precision in the range of 0.020–0.10 ppm. For each analyte, the LOQ and LOD were reported as 0.02 ppm and 0.01 ppm, respectively.

Analytical Method RM-33G-3 determined residues of 2,5-OH-Py (2,5-dihydroxypyridine) and its conjugates in milk. Residues of 2,5-OH-Py were determined by HPLC-fluorescence ($\lambda_{excitation}$ = 320 nm and $\lambda_{emission}$ = 395 nm). Recoveries of 2,5-OH-Py in milk ranged from 78.1–115% with acceptable accuracy and precision in the range of 0.020–0.10 ppm. The LOQ and LOD were reported as 0.02 ppm and 0.01 ppm, respectively.

Analytical Method RM-33T-1 determined residues of pyriproxyfen in bovine tissue. Residues of pyriproxyfen were determined by GC-NPD. Recoveries of pyriproxyfen in bovine liver ranged from 94.5–102.9% with acceptable accuracy and precision in the range of 0.020–0.10 ppm. The LOQ and LOD were reported as 0.02 ppm and 0.01 ppm, respectively.

Analytical Method RM-33T-2 determined residues of 4′-OH-Pyr and its conjugates in bovine tissue. Residues of 4′-OH-Pyr were determined by HPLC with an UV detector (λ = 275 nm). Recoveries of 4′-OH-Pyr in bovine liver ranged from 74.9–93.0% with acceptable accuracy and precision in the range of 0.020–0.10 ppm. The LOQ and LOD were reported as 0.02 ppm and 0.01 ppm, respectively.

Analytical Method RM-33T-3 determined residues of POP and its conjugates in bovine tissue. Residues of POP were determined by HPLC-fluorescence ($\lambda_{excitation}$ = 235 nm and $\lambda_{emission}$ = 327 nm). Recoveries of POP in bovine liver ranged from 74.3–97.5% with acceptable accuracy and precision in the range of 0.020–0.10 ppm. The LOQ and LOD were reported as 0.02 ppm and 0.01 ppm, respectively.

Analytical Method RM-33T-4 determined residues of 2,5-OH-Py and its conjugates in bovine liver. Residues of 2,5-OH-Py were determined by HPLC-fluorescence ($\lambda_{excitation}$ = 320 nm and $\lambda_{emission}$ = 395 nm). Recoveries of 2,5-OH-Py in bovine liver ranged from 77.1–102.5% with acceptable accuracy and precision in the range of 0.020–0.10 ppm. The LOQ and LOD were reported as 0.02 ppm and 0.01 ppm, respectively.

In summary, analytical methods RM-33G-2 (GC-NPD) and RM-33T-1 (GC-NPD) were deemed adequate as data gathering methods for residues of pyriproxyfen (residue definition) in milk and bovine tissue, respectively. The enforcement analytical methodology was not proposed and an independent laboratory validation (ILV) was not submitted. As the proposed crops (greenhouse cucumber, pepper and tomato) are not considered livestock feed items, these methods are not relevant to the uses under consideration.

3.0 Impact on Human and Animal Health

3.1 Effects Having Relevance to Human and Animal Health Arising from Exposure to the Active Ingredient or to Impurities in the Active Ingredient or to Their Transformation Products

In 1998, the PMRA conducted a detailed review of the toxicological database for pyriproxyfen. For the current submission, one new study was submitted under DACO 4.5.7—Genotoxicity: In vivo chromosomal aberrations. The database is complete, consisting of the full array of toxicity studies currently required for regulatory purposes. The database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical.

Pyriproxyfen was rapidly excreted in urine and feces of rats following oral dosing. The major route of excretion was fecal. The rate of elimination did not vary with sex or dosage. The highest residue levels were in liver, blood (males only), kidney and adipose tissue. Blood residue concentrations were considerably lower in females than in males. Residues were more slowly eliminated from adipose tissue than other tissues. The major metabolic reaction was oxidation at the 4' position of the terminal phenyl group. No qualitative differences were found in the metabolite profile between sexes or dosing regimens, but quantitative differences were observed.

In acute testing, technical grade pyriproxyfen was of low toxicity to rats via the oral, dermal and inhalation routes. It was minimally irritating to the eyes, non-irritating to the skin and not considered a potential dermal sensitizer. The end-use product Distance Insect Growth Regulator was of low toxicity via oral, dermal and inhalation routes. It was mildly irritating to the eyes and skin and is not considered to be a potential dermal sensitizer.

The principal target organ of toxicity following oral administration was the liver. Liver effects were recorded in all species tested (rats, mice and dogs). In short- and/or long-term studies in rats and mice, liver effects included increases in organ weights and increased plasma lipid levels (plasma cholesterol and phospholipid or triglyceride). In short-term studies in mice and dogs, plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) levels were increased. The rat and dog exhibited cytoplasmic changes in the liver in short-term studies. The data are suggestive of an adaptive response in the liver.

Kidneys were also adversely affected with oral pyriproxyfen administration in rats, mice and dogs. All species exhibited increased kidney weights. In short- and long-term studies, mice showed kidney pathology (tubular nephrosis, tubular dilation, mineralization and chronic

progressive nephropathy). Chronic interstitial nephritis was also recorded in parental rats in the reproduction study.

Other findings included decreased weight gain, food consumption and red blood cells parameters (rodents), as well as increased platelets (dogs and mice), water consumption (rodents) and adrenal weights (rodents). In general, males were more sensitive than females to toxic effects.

Pyriproxyfen was not oncogenic in mice or rats at the doses tested and no evidence of mutagenic potential was observed in a battery of tests.

In a multigeneration reproductive toxicity study in rats, pyriproxyfen had no effect on reproductive indices, but did cause depressed pup body weights at days 14 and 21 of lactation. In developmental toxicity studies in rats and rabbits, mortality was observed in pregnant animals at the highest dose tested (1000 mg/kg bw/day). Increased resorptions were noted at 1000 mg/kg bw/day in rats and increased abortions/premature deliveries were observed at 300 mg/kg bw/day and above in rabbits. In offspring, an increased incidence of skeletal and visceral variations was observed in rats and rabbits, respectively. These effects were apparent at a dose level that also caused overt toxicity in the dams, and overall, pyriproxyfen was not considered to be teratogenic. There was no evidence of enhanced susceptibility of the young.

A modified functional observation battery (which included behavioural, motor coordination and learning ability tests) was conducted on offspring in the rat developmental toxicity study. These tests did not reveal any evidence of neurotoxicity. Other than salivation noted in the inhalation studies, no evidence suggesting neurotoxic potential was observed throughout the pyriproxyfen toxicology database.

3.2 Toxicological Endpoint for Assessment of Risk Following Long-Term Dietary Exposure—Acceptable Daily Intake

The 78-week mouse study was chosen as the most appropriate study for assessment of risk following dietary exposure. The no observed adverse effect level (NOAEL) in the 78-week mouse study was 16.0 mg/kg bw/day based on decreased survival associated with systemic amyloidosis. This NOAEL represents the lowest NOAEL for repeat dosing studies.

The standard 100-fold uncertainty factor (10-fold for interspecies extrapolation and 10-fold for intraspecies variation) was applied to the risk assessment.

The calculation of the acceptable daily intake (ADI) is:

$$\text{ADI} = \frac{16 \text{ mg/kg bw/day}}{100} = 0.16 \text{ mg/kg bw/day}$$

3.3 Toxicological Endpoint for Assessment of Risk Following Acute Dietary Exposure—Acute Reference Dose

Pyriproxyfen showed very low acute toxicity. Because no acute effects were apparent, Pyriproxyfen is unlikely to present an acute hazard. It is not necessary to set an acute reference dose.

3.4 Toxicological Endpoint for Assessment of Occupational, Residential and Bystander Risks

Exposure to the end-use product Distance Insect Growth Regulator is expected to be intermittent over a short-term duration for mixer/loader and applicators. There is potential for short- to intermediate- to long-term exposure to workers involved in cultivation of greenhouse ornamentals and vegetables. Dermal and inhalation exposures are the predominant routes of exposure.

Short-term dermal exposure: The NOAEL of 1000 mg/kg bw/day from the rat 21-day dermal study was selected for short-term dermal exposure. No compound related changes were noted at this dose.

Short-term inhalation exposure: The NOAEL of 0.482 mg/L (equivalent to 84 mg/kg bw) from the 28-day rat inhalation study was selected for short-term inhalation exposure. The NOAEL was based on salivation, increased lactate dehydrogenase (LDH) as well as decreased absolute lung weight in males and increased water consumption in females noted at the lowest observed adverse effect level (LOAEL).

Intermediate to long-term dermal and inhalation exposure: The chronic 78-week dietary study in mouse provided the lowest NOAEL of the database and was considered the most appropriate study to assess the intermediate and chronic dermal and inhalation scenarios. The NOAEL was 16 mg/kg bw/day in males, based on decreased survival in both sexes after week 60.

Short-term oral aggregate exposure: Short-term aggregate exposure to pyriproxyfen has been considered to address food and residential (incidental oral) exposures. The 90-day rat dietary study was considered the most appropriate study to assess the short-term duration of exposure by the oral route. The NOAEL of 24 mg/kg bw/day in this study was based on increased cholesterol and phospholipid and decreased red blood cell parameters.

The standard uncertainty factor (10-fold for interspecies extrapolation and 10-fold for intraspecies variation) was applied to establish a target margin of exposure (MOE) of 100 for all endpoints.

3.5 Impact on Human and Animal Health Arising from Exposure to the Active Ingredient or to Its Impurities

3.5.1 Operator Exposure Assessment

3.5.1.1 Handler Exposure and Risk

Individuals have potential for exposure to pyriproxyfen during mixing, loading and application to greenhouse vegetables and greenhouse ornamentals. Only ground application is proposed (backpack, low-pressure and high-pressure handwand). Distance Insecticide Growth Regulator is applied at a rate of 45 ml product/100 L of water (0.0463 g a.i./L). The typical area treated per day is approximately one hectare per day. Individuals may be exposed intermittently over a short-term duration.

Exposure estimates for mixers, loaders and applicators (M/L/A) are based on data from the Pesticide Handlers Exposure Database (PHED) Version 1.1. The PHED is a compilation of generic mixer/loader/applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates. Appropriate subsets of A, B and C grade data (low–high confidence) were created from the PHED database files for liquid mixer/loader and either backpack, low-pressure and high-pressure handwand application. All data were normalized for kg of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency such as mean, median or geometric mean, i.e., summing the measure of central tendency for each body part.

The exposure estimates are based on mixer/loaders/applicators wearing a single layer of clothing (long pants and a long-sleeved shirt) as well as gloves.

For the handler risk assessments, route-specific estimates were generated based on either a dermal NOAEL of 1000 mg/kg bw/day from a rat 21-day dermal study or on a inhalation NOAEL of 0.482 mg/L (equivalent to 84 mg/kg bw) from the 28-day rat inhalation study. All MOEs exceed the target of 100 and are considered acceptable.

3.5.1.2 Postapplication Exposure and Risk

There is potential for intermediate to long-term exposure to workers scouting, pruning, de-leafing, irrigating, hand harvesting and thinning greenhouse vegetables and greenhouse ornamentals treated with pyriproxyfen. Exposure estimates were generated by coupling default dislodgeable foliar residue (DFR) values (20% of the application rate available for dislodging on day of application) with activity-specific transfer coefficients (TCs). Standard defaults were also used to estimate exposure, including an 8-hour work day and a body weight of 70 kg. Because the applicant is a member of the Agricultural Re-entry Task Force (ARTF), the transfer coefficients, based on ARTF data were used. In addition, in the absence of a dermal absorption study, a default dermal absorption value of 100% was used to estimate system exposure.

A summary of postapplication exposure estimates for Distance Insect Growth Regulator on the day of the last application are presented in Table 3.5.1.2.1.

Table 3.5.1.2.1 Occupational Postapplication Exposure Estimates and Margins of Exposure for Pyriproxyfen

Scenario	TC (cm^2/hr)[a]	DFR Value ($\mu g/cm^2$)[b]	Exposure Estimate After Two Applications (mg/kg bw/day)[c,d]	MOE After Two Applications[e]
Potted plants, greenhouse lettuce	400	0.1924	0.01759	**910**
Cut flowers	2500	0.1924	0.10994	**146**
Greenhouse vegetables (tomato, cucumber, pepper)	1800	0.1924	0.07916	**202**

[a] TCs, based on the ARTF data. The applicant, Syngenta Crop Protection Canada, is a member of the ARTF.

[b] Based on a default of 20% of the application rate (20% × 0.962 $\mu g/cm^2$ = 0.1924 $\mu g/cm^2$)

[c] Exposure estimates were calculated using the following formula:

$$\frac{\text{DFR value } (\mu g/cm^2) \times \text{TC } (cm^2/\text{hour}) \times 8 \text{ hours worked per day (hour)} \times \text{conversion factor (1mg/1000 } \mu g)}{\text{body weight (70 kg)}}$$

[d] Based on a dermal absorption value of 100%

[e] Based on a NOAEL of 16 mg/kg bw/day from a chronic 78-week dietary study on mice and compared to the target MOE of 100.

Postapplication exposure was compared to the NOAEL of 16 mg/kg bw/day from chronic 78-week dietary study on mice. MOEs for all activities exceed the target MOE and are considered acceptable.

3.5.2 Residential Exposure and Risk

3.5.2.1 Handler Exposure and Risk

There are no domestic products; therefore, a residential handler assessment was not required.

3.5.2.2 Postapplication Exposure and Risk

There is no residential postapplication exposure associated with the use of this product; therefore, a residential postapplication assessment was not required.

Table 3.5.2.2.1 Summary of Daily Exposure Estimates and Margins of Exposure for Pyriproxyfen

Exposure Pattern	Scenario	Daily Exposure (µg-a.i./kg-bw/day)[a]		Dermal MOE[c]	Inhalation MOE[d]
		Dermal Deposition[b]	Inhalation		
Backpack	M/L/A[e]	7.21	0.08	138659	1021424
Low-pressure handwand		1.25	0.06	800454	1403328
High-pressure handwand		7.40	0.20	135194	420069

[a] Calculated as PHED unit exposure values (µg a.i./kg-a.i. handled) × application rate (92.7 g a.i./ha) × area treated per day (1 ha) / body weight (70 kg)

[b] No dermal absorption study required because a dermal endpoint was used.

[c] Based on a NOAEL of 1000 mg/kg bw/day from a rat 21-day dermal study, target MOE of 100

[d] Based on a NOAEL of 0.482 mg/L (equivalent to 84 mg/kg bw) from the 28-day rat inhalation study, target MOE of 10.

[e] Personal protective equipment for mixer/loader/applicator: long pants, a long-sleeved shirt and gloves

4.0 Residues

4.1 Residue Summary

Using either [phenoxyphenyl-^{14}C]-pyriproxyfen or [2,6-pyridyl-^{14}C]-pyriproxyfen, the metabolism of pyriproxyfen was investigated in plants following three foliar spray applications to apple and tomato; and following a single foliar application to cucumber fruit or leaves. The metabolism of pyriproxyfen was similar in apple, cucumber and tomato. The major residue observed was pyriproxyfen. The major metabolic pathways were the hydroxylation and cleavage of the ether linkages. Primary metabolites were further metabolized to more polar products by oxidation or conjugation reactions. The residue definition in plants is pyriproxyfen, both for enforcement and risk assessment purposes. In rotational crops, neither pyriproxyfen nor its metabolites were identified. The HPLC analyses of the water soluble residues in wheat straw and wheat chaff indicated several unidentified components, each at ≤ 0.01 ppm. The residue definition in rotational crops is pyriproxyfen, both for enforcement and risk assessment purposes. The metabolic pathway for pyriproxyfen in ruminants was evaluated following oral administration to lactating goats of either [phenoxyphenyl-^{14}C]-pyriproxyfen or [2,6-pyridyl-^{14}C]-pyriproxyfen for 5 consecutive days. Pyriproxyfen was identified as a major residue in muscle, fat and milk but not in kidney or liver. Additional major metabolites, primarily in the

conjugate form, identified included 4′-OH-Pyr-sulfate (muscle, kidney, liver and milk), 4′-OH-Pyr (muscle and fat), 5″-OH-Pyr-sulfate (kidney), POP-sulfate (kidney), POPA (liver), PYPA-conjugate (kidney), 2-OH-Py (muscle) and 2,5-OH-Py-conjugate (milk). The metabolism of [phenoxyphenyl-^{14}C]-pyriproxyfen and [2,6-pyridyl-^{14}C]-pyriproxyfen in the lactating goat was similar including hydroxylation of the 4′ position of the phenoxyphenyl ring, hydroxylation of the 5″ position of the pyridyl ring, cleavage of the ether linkage, sulfation of the 4′-OH-phenoxyphenyl moiety and oxidation of the -CH_2 group of the side chain (pyridyl label only). The residue definition in animals (ruminant only) is pyriproxyfen, both for risk assessment and enforcement purposes.

European greenhouse trials (eight trials each for cucumber and pepper; six trials for tomato) were submitted and were sufficient to support the proposed use pattern for Distance Insect Growth Regulator on greenhouse cucumber, pepper and tomato in Canada. Residues of pyriproxyfen at harvest (preharvest interval of 3–4 days) ranged from < 0.01 ppm to 0.02 ppm in cucumber, 0.08 ppm to 0.49 ppm in pepper and from 0.05 ppm to 0.17 ppm in tomato. The proposed maximum residue limits (MRLs) are as follows: cucumbers (0.02 ppm); bell peppers (0.80 ppm); and tomatoes (0.25 ppm). Processing data indicated the potential of pyriproxyfen residues to concentrate in tomato purée. Use of the North American Free Trade Agreement MRL calculator on the submitted residue data indicated that residues of pyriproxyfen in the processed fraction will be covered by the proposed MRL for tomato. An adequate dairy cattle feeding study with pyriproxyfen has been submitted. However, MRLs are not needed because the proposed crops (cucumber, pepper and tomato) are not fed to livestock. Storage stability data indicated that the stability of pyriproxyfen was matrix dependent. Based on the interval of storage of samples from the magnitude of residue studies, corrections due to in-storage dissipation of pyriproxyfen residues were required only for samples from the greenhouse pepper trials. Storage stability data were not provided for the tomato and pepper processed fractions. However, the bulk of tomato processed commodities produced in Canada are generated from field tomatoes and canned peppers are not a major feed item in Canada; consequently, additional data demonstrating the storage stability of pyriproxyfen residues in tomato and pepper processed fractions will not be required.

The proposed domestic use of pyriproxyfen on greenhouse cucumber, pepper and tomato does not pose an unacceptable chronic (food alone) risk to any segment of the population, including infants, children, adults and seniors. An expected environmental concentration (EEC) value was not estimated for pyriproxyfen because there is little potential for its migration to drinking water sources through the proposed greenhouse uses.

4.2 Residues Relevant to Consumer Safety

Aggregate Exposure and Risk Assessment

There is potential for dietary as well as residential exposures to pyriproxyfen because this active ingredient is registered for control of fleas (e.g., treatment of companion animals, broadcast application to indoor surfaces such as carpets). It was considered that there was a significant likelihood of co-occurrence of companion animal treatment and indoor surface (e.g., carpet) application. Therefore, the residential exposure assessment sums previously derived estimates for these exposure scenarios. The aggregate exposure assessment was conducted for the most

highly exposed subpopulation (children 1–2 years old) and the predominant route of exposure (oral) and is summarized in Table 4.2.

The refined chronic dietary exposure from food for the same subpopulation (children 1–2 years old) was 0.022550 mg/kg bw/day. (Water was not included in the assessment because residues of pyriproxyfen in drinking water resulting from the proposed greenhouse uses were considered unlikely.).

Aggregate exposure and risk are presented in Table 4.2.1.

Table 4.2.1 Postapplication Exposure and MOEs for Pyriproxyfen

Population	Companion Animal Uses (oral exposure)	Carpet Treatments (oral exposure)	Chronic Dietary (food alone)	Aggregate[a]	MOE[b]
Children 1–2 years old	0.20 mg/kg bw/day	0.02 mg/kg bw/day	0.02 mg/kg bw/day	0.24 mg/kg bw/day	100

[a] Aggregate exposure is the sum of oral exposure from companion animal and carpet sprays as well as chronic dietary intake.

[b] MOE = NOAEL (24 mg/kg bw/day) / aggregate Exposure, target MOE of 100.

The target MOE is achieved and aggregate exposure and risk is considered acceptable. It is recognized that the residential component of the assessment is an overestimate as conservative approaches were used to derive the exposure estimates.

5.0 Fate and Behaviour in the Environment

5.1 Physical and Chemical Properties Relevant to the Environment

Pyriproxyfen is sparingly soluble in water (0.367 mg /L) at 25°C. The vapour pressure ($1.33 \times 10^{-}$ Pa at 23°C) indicates pyriproxyfen is non-volatile. The log K_{ow} is 5.37, indicating a high potential for bioaccumulation. The physicochemical properties of pyriproxyfen relevant to the environment are summarized in Table 1.2.1.

5.2 Abiotic Transformation

Pyriproxyfen is hydrolytically stable in acidic, alkaline and neutral pH conditions. Two unidentified minor transformation products were collectively formed at less than 2.5% (of the applied parent compound) by 30 days. Therefore, hydrolysis is not expected to be an important route of transformation in the environment.

5.3 Biotransformation

The biotransformation of pyriproxyfen was fairly rapid in aerobic soils. Its pattern of transformation was characterized by a rapid declination within the first 30 days, followed by a gradual decrease. In sandy loam soil, pyriproxyfen biotransformed with a disappearance time for 50% of the highest amount (DT_{50}) value of 6–10 days, indicating pyriproxyfen to be non-persistent in aerobic soils (Goring et al. 1975). The following three minor transformation products of pyriproxyfen were detected in aerobic soils:

- 4'-OH-Pyr or 4-(4-hydroxyphenoxy) (*RS*)-2-(2-pyridyloxy)propyl ether;
- DPH-Pyr or 4-hydroxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether; and
- PYPAC or (*RS*)-2-(2-pyridyloxy)propionic acid.

5.4 Mobility

The adsorption/desorption characteristics of pyriproxyfen were studied in clay loam, sand, silty loam and silty clay loam soils. Mean simple adsorption constants normalized to organic carbon (K_{oc}) were 11 000–34 200 for the five soils tested, indicating pyriproxyfen to be immobile (McCall et al. 1981).

5.5 Dissipation and Accumulation Under Field Conditions

Soil dissipation/accumulation of pyriproxyfen under field conditions in northern United States (Ecoregions 8.1 and 10.1) resulted in DT_{50} values ranging from 9 to 10 days, indicating that pyriproxyfen is non-persistent.

5.6 Bioaccumulation

In a study reviewed by the USEPA (Master Record Identification Number 4902002), ^{14}C pyriproxyfen residues accumulated in Bluegill sunfish continuously exposed to pyriproxyfen at 20 µg/l for 28 days under flow-through conditions. Mean bioconcentration factors were 465–478× for edible tissues, 2390–2482× for non-edible tissues and 1379–1495× for whole fish. After a two-week depuration period, 93% of accumulated residues had been eliminated. Therefore, pyriproxyfen is not expected to bioconcentrate in fish under environmentally relevant conditions due to the rapid depuration of the parent compound from fish.

5.7 Summary of Fate and Behaviour in the Terrestrial Environment

Pyriproxyfen is non-persistent in the terrestrial environment, with biotransformation in soil being the principal route of dissipation. Pyriproxyfen is hydrolytically stable and is not expected to volatilize from dry or moist surfaces under field conditions. Aerobic soil biotransformation studies indicated pyriproxyfen is non-persistent (DT_{50} = 6–10 days). Field dissipation studies indicated that pyriproxyfen was non-persistent (DT_{50} = 9–10 days). Based on an adsorption/desorption study, pyriproxyfen is immobile in soils (K_{oc} > 11 000). Considering its immobility in soil combined with its low water solubility and its non-persistence in soil, pyriproxyfen is not expected to leach into groundwater.

5.8 Summary of Fate and Behaviour in the Aquatic Environment

Based on the proposed use, pyriproxyfen is not expected to reach the aquatic environment.

5.9 Expected environmental Concentrations

5.9.1 Soil

Although the proposed use is for greenhouse crops, the expected environmental concentration of pyriproxyfen in soil is calculated based on the most conservative scenario (direct overspray). Assuming a soil bulk density of 1.5 g/cm^3, a 15-cm soil depth, a scenario in which the maximum Canadian label rate (92.6 g a.i./ha) is applied twice per season at a 14-day interval, to bare soil by direct overspray and assuming no dissipation, the EEC of residue of pyriproxyfen in soil due to application of Distance Insect Growth Regulator would be 0.06066 mg a.i./kg soil.

5.9.2 Aquatic Systems

Not applicable, based on the proposed use.

5.9.3 Vegetation and Other Food Sources

Not applicable, based on the proposed use.

6.0 Effects on Non-Target Species

6.1 Effects on Terrestrial Organisms

There is no potential exposure to birds, mammals and vascular plants. There may be exposure to beneficial organisms. Published information gathered by the reviewer indicates some harmful effects on predators and parasites. Significant declines in *Encarsia formosa* parasitoid emergence, *Phytoseilus persimilis* predatory mite and *Hyposoter didymator* (Ichneumonidae) adult emergence were observed after foliar application of Admiral 100 EC (0.025 g a.i./L) or topical application of Juvinal 10 EC (1 mg a.i./L) (Sterk et al. 2003; Schneider et al. 2003). Because the maximum allowed application rate of pyriproxyfen on greenhouse vegetables and ornamentals (0.0463 g a.i./L) is higher than that of the study rates and applied twice at 14-day intervals, resident populations of both *E. formosa, H. didymator* parasitoid and *P. persimilis* predatory mite may be depressed beyond that of the field study. Further suppression of other non-target arthropod populations cannot be ruled out given the higher pyriproxyfen application rate and frequency of application.

6.2 Effects on Aquatic Organisms

Based on the proposed use, there is no potential exposure to aquatic organisms such as invertebrates, fish, algae and vascular plants. However, submitted information indicates that pyriproxyfen was highly toxic to *Daphnia magna* (48-hour effective concentration at 50% = 400 ppb). Results from the daphnid life-cycle study indicated that pyriproxyfen reduces adult growth (length) and reproduction (number of young). The most sensitive endpoints (lowest observed effect concentration [LOEC] = 0.02 ppb) were the number of young female / reproductive day. Acute toxicity study of the technical grade active ingredient pyriproxyfen using freshwater fish was qualified as supplemental because of a solubility problem. However, two studies using the end-use product indicated that pyriproxyfen was highly toxic to Rainbow trout, *Onchorhynchus mykiss*, (96-hour lethal concentration to 50% [LC_{50}] = 450 ppb) and Bluegill sunfish, *Lepomis macrochirus*, (96-hour LC_{50} = 590 ppb) on an acute basis. A freshwater fish early life-stage test using the technical grade active ingredient indicated that pyriproxyfen reduces body length (NOEL = 4.3 ppb; LOEC = 6.7 ppb) in Rainbow trout at 61-day posthatch. Acute toxicity with estuarine/marine fish indicated that pyriproxyfen is highly toxic to Sheephead minnow, *Cyprinodon variegatus*, (no observed effect concentration [NOEC] = 50 ppb; 96-hour LC_{50} > 350 ppb). Another acute toxicity study with estuarine/marine invertevrate found pyriproxyfen to be very highly toxic to the mysid, *Americamysis bahia*, on an acute basis (LC_{50} = 67 ppb). The mysid reproduction study indicated reduction in number of young per female reproduction day (NOEC $\leq$ 0.81 ppb; LOEC $\leq$ 1.6 ppb).

6.3 Effects on Biological Methods of Sewage Treatment

The PMRA did not require the data.

6.4 Risk Characterization

6.4.1 Environmental Behaviour

In the terrestrial environment, pyriproxyfen is not expected to volatilize under field conditions (i.e., from dry and wet or moist surfaces). Pyriproxyfen, however, is not expected to be mobile and persistent in the terrestrial environment (DT_{50} = 9–10 days). Considering its immobility in soil combined with its low water solubility and its non-persistence in soil, pyriproxyfen is not expected to leach into groundwater. Only minor transformation products (PYPAC and 4'-OH pyriproxyfen) were detected in soil. The aquatic behaviour of pyriproxyfen was not assessed because there is no potential exposure to aquatic organisms.

6.4.2 Terrestrial Organisms

The proposed use of pyriproxyfen was for greenhouse crops; therefore, its toxicity to birds, mammals and vascular plants was not assessed. Pyriproxyfen is expected to be harmful to some beneficial invertebrates at the proposed maximum field application rate. Exposure of invertebrates (adult and pupae) to pyriproxyfen resulted in decreased adult emergence, increased adult mortality and decreased number of attacked hosts.

6.4.3 Aquatic Organisms

There is no potential exposure to aquatic organisms; therefore, no risk assessment is carried out for aquatic organisms.

6.5 Risk Mitigation

Based on the data submitted (or published), the PMRA has conducted an assessment of the environmental safety associated with the use of pyriproxyfen. Application of the technical active ingredient pyriproxyfen and the formulated end-use product Distance Insect Growth Regulator (2×4.63 g a.i./100 L/500 m^2, 14-day interval) has identified concern, with non-target terrestrial invertebrates (i.e., predators and parasites). Therefore, the following label statement will be included on the label:

This product should not be applied during peak activity periods of beneficial insects.

7.0 Efficacy

7.1.1 Mode of Action

The active ingredient pyriproxyfen is classified as a juvenile hormone mimic and interferes with normal insect development and reproduction. Metamorphosis of immature life stages is affected, but adults are not directly controlled, although production of viable eggs is affected by transovarial activity. Pyriproxyfen is absorbed through the insect cuticle but may also act by ingestion. Therefore, thorough uniform coverage is important for consistent product performance. When applied as a foliar spray, pyriproxyfen demonstrates translaminar activity.

7.1.2 Crops

Distance Insect Growth Regulator (103 g/L pyriproxyfen) is for use on greenhouse ornamentals and greenhouse vegetables (tomatoes, peppers and cucumbers) for control of whiteflies (silverleaf whitefly, potato whitefly and greenhouse whitefly).

7.1.3 Effectiveness Against Pests

Whitefly on Greenhouse Ornamentals
Nine efficacy trials conducted in the United States were evaluated to assess control of whitefly on greenhouse ornamentals. Five efficacy trials demonstrated 66–100% reduction in numbers of nymphs 7 to 16 days after treatment after 1 application at 4.6 g a.i./100 L. Numbers of emerged pupae were reduced 75–100% as early as 13 days after treatment. The remaining 4 trials began assessments later than 16 days after treatment. When an application rate of 4.6 g a.i./100 L was evaluated with higher application rates in the same study, a rate response was not demonstrated. A minimum reapplication interval of approximately 14 days was demonstrated. For example, in the trial that reduced nymphal populations by 66% after one application, a second application

was required approximately 14 days after the first one. Translaminar activity of Distance Insect Growth Regulator was also demonstrated in several trials.

Whitefly on Greenhouse Vegetables (tomatos, cucumbers, peppers)
Efficacy trials were provided on Jerusalem cherry (*Solanum (pseudo) capsicum*) (1 trial, conducted in Spain), tomato (1 trial, conducted in Spain) and cucumber (1 trial, conducted in Greece) and sweet pepper (2 trials, conducted in Spain) in glasshouses. Sweet pepper assessments were on whitefly adults only; therefore, it could not be used as supporting data. Results on Jerusalem cherry, tomato and cucumber confirmed the results obtained for whitefly on greenhouse ornamentals, demonstrating that an application rate of 4.6 g a.i./100 L significantly reduced numbers of whitefly nymphs and numbers of emerged pupae compared to the untreated control, and that a second application may be required approximately 14 days after the first application. A significant rate effect was not demonstrated in these trials. Results for Jerusalem cherry and cucumber were consistent with those achieved on greenhouse ornamentals. The results for the single trial on tomato were also consistent with those on greenhouse ornamentals, but a similar level of reduction in whitefly nymphs was only demonstrated several days after the second application. Reasons for this were unclear. However, given the mode of action of pyriproxyfen, control of whiteflies on greenhouse tomato, cucumber and pepper at an application rate of 4.6 g a.i./100 L is expected as long as foliage is thoroughly covered.

7.1.4 Total Spray Volume

Pyriproxyfen is absorbed through the insect cuticle but may also act by ingestion. Therefore, thorough uniform coverage is important for consistent product performance. Distance Insect Growth Regulator should be applied to the point of runoff.

7.2 Phytotoxicity to Target Plants or Target Plant Products

No phytotoxicity to target plants was reported in any of the trials conducted when Distance Insect Growth Regulator was applied as a foliar application. However, the label contains a warning about possible phytotoxic effects to some varieties of ornamental plants and recommends small scale applications before making large scale applications. Also, the label states that phytotoxicity has been observed on the following plants: Salvia (*Salvia* spp.), Ghost Plant (*Gratopetalum paraguayense*), Boston Fern (*Nephrolepis exaltata*), Schefflers (*Schefflera* spp.), Gardenia (*Gardenia* spp.) and Coral Bells (*Heuchera sanguinea*). It is recommended that Distance should not be used on these plants. The label warns that Distance should not be applied to Poinsettia after bract formation.

There were no phytotoxic effects reported in any of the trials conducted on greenhouse tomato, cucumber or pepper.

7.3 Observations on Undesirable or Unintended Side Effects

Data or observations on toxicity to non-target organisms (e.g., beneficial insects such as parasitoids and predators) were not reported in any of the submitted efficacy trials.

7.3.1 Impact on Succeeding Crops

Undesirable or unintended side effects on succeeding crops were not reported and are not expected.

7.3.2 Impact on Adjacent Crops

Undesirable or unintended side effects on adjacent crops were not reported and are not expected.

7.3.3 Impact on Seed Viability

Not applicable

7.3.4 Tank Mixing Recommendations

Tank mixes were not proposed.

7.4 Economics

Information was not provided and not assessed.

7.5 Sustainability

7.5.1 Survey of Alternatives

Chemical Control Practices
The major insecticide active ingredients currently registered for control of whiteflies on the proposed crops include, but are not necessarily limited to, the following:

Greenhouse Crop	Available Alternative Active Ingredients
Ornamentals	Carbamates (bendiocarb), organophosphates (acephate, dichlorvos, chlorpyrifos, naled, malathion), pyrethrin, pyrethroids (permethrin), cyclodienes (endosulfan), neonicotinoids (imidacloprid, acetamiprid), insect growth regulators (kinoprene), pyribaden, pymetrozine and potassium salts of fatty acids
Tomatoes	Organophosphates (dichlorvos, naled), pyrethrin, pyrethroids (permethrin), cyclodienes (endosulfan), neonicotinoids (imidacloprid), pymetrozine and potassium salts of fatty acids.
Cucumbers	Organophosphates (dichlorvos, naled), pyrethrin, pyrethroids (permethrin), cyclodienes (endosulfan), neonicotinoids (imidacloprid) and potassium salts of fatty acids

Greenhouse Crop	Available Alternative Active Ingredients
Peppers	Pyrethrin, neonicotinoids (imidacloprid, acetamiprid), pymetrozine and potassium salts of fatty acids

Non-Chemical Control Practices
A number of cultural control practices have been developed for whiteflies in greenhouses. The entry of adult whiteflies into the greenhouse can be minimized by screening vents and keeping doorways and other openings to the greenhouse closed. Weeds should be removed in and around the greenhouse, and the greenhouse should be washed, cleaned as well as disinfected between crops, if possible. Yellow sticky traps can be used to trap adult whiteflies. If possible, severely infested greenhouses should be pruned to reduce whitefly populations.

The parasitic wasps, *Encarsia formosa* and *Eretmocerus eremicus* can be used against whitefly nymphs. Other insects that prey on whiteflies, such as lacewing larvae and predatory bugs (e.g., *Dicyphys hespersus* and *Orius* spp.) can also be released.

7.5.2 Compatibility With Current Management Practices Including Integrated Pest Management

Distance Insect Growth Regulator can be integrated with other chemical and cultural control practices and can be applied with conventional application equipment used in greenhouses. However, no data were evaluated to assess its compatibility with natural enemies for biological controls.

7.5.3 Contribution to Risk Reduction

Distance Insect Growth Regulator is a potential alternative to other classes of insecticides listed in Section 7.5.1. Pyriproxyfen is a classified as a Group 7 Insecticide, a juvenile hormone mimic. Another insect growth regulator in Group 7, kinoprene, is registered for control of whiteflies on greenhouse ornamentals. Kinoprene is not registered for use on greenhouse vegetables. Alternative chemistries are needed for use against whiteflies in the greenhouse because of problems with the development of resistance.

7.5.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Resistance to pyriproxyfen in whiteflies has been documented in Israel, Spain and the United States (Denholm and Horowitz 2000, Dennehy et al. 2005). The Q Biotype of *Bemisia tabaci,* which is less susceptible to pyriproxyfen than other strains of whitefly, has also been detected in several countries in throughout the Mediterranean and in Guatemala and Mexico (Brown et al. 2005).

7.6 Conclusions

The following conclusions are based on a complete review of the submitted efficacy data for Distance Insect Growth Regulator:

- Adequate efficacy data have been submitted to support the control of silver leaf whitefly, sweet potato whitefly and greenhouse whitefly on greenhouse ornamentals, greenhouse tomato, greenhouse cucumber and greenhouse pepper when Distance Insect Growth Regulator is applied as a foliar spray at a concentration of 45 ml product per 100 L. The application timing is summarized in Table 7.6.1.1.

- No phytotoxic effects to foliage were reported in any of the provided efficacy trials when Distance Insect Growth Regulator was used. However, phytoxicity warnings for ornamental plants are required on the label.

7.6.1 Summary

Distance Insect Growth Regulator is for control of silver leaf whitefly, sweet potato whitefly and greenhouse whitefly on greenhouse ornamentals, greenhouse tomato, greenhouse cucumber and greenhouse pepper. The technical active ingredient pyriproxyfen is a juvenile hormone mimic and interferes with normal insect development and reproduction.

Adequate efficacy data have been submitted to support the use of Distance Insect Growth Regulator for control of silver leaf whitefly, sweet potato whitefly, and greenhouse whitefly on greenhouse ornamentals, greenhouse tomato, greenhouse cucumber, and greenhouse pepper. The acceptable application rate and a summary of application timing are provided in Table 7.6.1.1. The minimum interval between applications is 14–28 days, if required. Although no phytotoxic effects were reported in efficacy trials, phytotoxic warnings for greenhouse ornamentals are required on the label.

Table 7.6.1.1 Acceptable Use of Distance Insect Growth Regulator

Pest/Crop	Application Rate	Summary of Application Timing
Control of silverleaf whitefly, sweet potato whitefly, greenhouse whitefly on greenhouse ornamentals and greenhouse vegetables (tomato, cucumber and pepper)	45 ml product per 100 L	Apply as a foliar spray. Apply the spray mixture uniformly to all plant surfaces and to the point of runoff. Make first application when adult insects begin to appear. If necessary, make a second application from 14 to 28 days after the first application. Use longer interval when plants are not rapidly flushing new growth. Use shorter interval when plants are flushing new growth. Apply a maximum of two applications per cropping cycle. If the cropping cycle is less than 6 months, do not apply more than twice per 6 months. If rapid control of adult insects is required, apply a registered adulticide.

8.0 Toxic Substances Management Policy Considerations

During the review of pyriproxyfen, the PMRA has taken into account the federal Toxic Substances Management Policy[6] and has followed its Regulatory Directive DIR99-03[7]. It has been determined that this product does not meet TSMP Track 1 criteria because of the following:

- Pyriproxyfen does not meet the criteria for persistence. Its values for half-life in soil (6–9 days) are below the TSMP Track 1 cut-off criteria for soil (≥182 days).
- Pyriproxyfen is not bioaccumulative. Although the *n*-octanol–water partition coefficient (log K_{ow}) is 5.37, the bioconcentration factor is between 465 and 2 390, which is below the TSMP Track 1 cut-off criterion of ≥ 5000. Bioaccumulation studies indicate rapid depuration of the parent compound from fish.
- Pyriproxyfen meets the criteria for toxicity (see Section 6.2).
- Pyriproxyfen does not form any major transformation products that meet the TSMP Track 1 criteria.

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

[7] Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, is available through the Pest Management Information Service. Phone: 1-800-267-6315 within Canada or 613-736-3799 outside Canada (long distance charges apply); fax: 613-736-3758; e-mail: pmra_infoserv@hc-sc.gc.ca; or through our website at www.pmra-arla.gc.ca.

- Pyriproxyfen (technical grade) does not contain any byproducts or microcontaminants that meet the TSMP Track 1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

The formulated end-use product is not known to contain any USEPA inert List 1 formulants or any known TSMP Track 1 substances.

9.0 Proposed Regulatory Decision

9.1 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing full registration for the sale and use of pyriproxyfen technical grade active ingredient and the end-use product Distance Insect Growth Regulator Insecticide to control whiteflies (silver leaf whitefly, sweet potato whitefly and greenhouse whitefly) on greenhouse ornamentals and greenhouse vegetables (tomato, cucumber and pepper). An evaluation of current scientific data from the applicant, scientific reports and information from other regulatory agencies resulted in the determination that, under the proposed conditions of use, the end-use product has value and does not present an unacceptable risk to human health or the environment.

9.2 Additional Data Requirements

There are no additional data requirements for the proposed crops.

List of Abbreviations

λ	wavelength
µg	microgram
4′-OH-Pyr	4-(4-hydroxyphenoxy)phenyl (*RS*)-2-(2-pyridyloxy)propyl ether
5″-OH-Pyr	(*RS*)-5-hydroxy-2-{1-methyl-2-(4-phenoxyphenoxy)ethoxyl} pyridine
AD	applied dose
ADI	acceptable daily intake
a.i.	active ingredient
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
AST	aspartate aminotransferase
atm	atmospheres
BUN	blood urea nitrogen
bw	body weight
BWG	body-weight gain
CHO	Chinese ovary cell
cm	centimetre(s)
DACO	data code
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DNCB	dinotrochlorobenzene
DPH-Pyr	4-hydroxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether
DT_{50}	disappearance time for 50% of highest amount
EC	emulsifiable concentrate
EEC	expected environmental concentration
FC	food consumption
g	gram(s)
GC	gas chromatography
GC-MSD	gas chromatography with a mass selective detector
GC-NPD	gas chromatography with a nitrogen-phosphorous detector
GC-TID	gas-liquid chromatography with a thermoionic detector
h	hour(s)
ha	hectare
HAFT	highest average field trial
HB	hemoglobin
HCT	hematocrit
Hg	mercury
HPLC	high performance liquid chromatography
HPLC-fluorescence	high performance liquid chromatography with a fluorescence detector
ILV	independent laboratory validation
IPM	integrated pest management
K_d	Freudlich adsorption coefficient

kg	kilogram(s)
K_{oc}	organic carbon adsorption coefficient
K_{ow}	*n*-octanol–water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LDH	lactate dehydrogenase
LOAEL	lowest observed adverse effect level
LOEC	lowest observed effect concentration
LOEL	lowest observed effect level
LOD	level of detection
LOQ	level of quantification
m	metre(s)
m^3	metre(s) cubed
MAS	maximum average score
MCV	mean corpuscular volume
mg	milligram(s)
MIS	maximum irritation score
ml	millilitre
mm	millimetre
MOE	margin of exposure
MRL	maximum residue limit
nm	nanometer(s)
NaCl	sodium chloride
N/A	not applicable
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NPD	nitrogen-phosphorous detector
NZW	New Zealand white
Pa	Pascal
pH	-log10 hydrogen ion concentration
PHI	preharvest interval
pKa	-log10 acid dissociation constant
PMRA	Pest Management Regulatory Agency
POP	4-phenoxyphenol
POPA	(*RS*)-2-hydroxypropyl 4-phenoxyphenyl ether
ppb	parts per billion [µg/kg] or [µg/L]
ppm	parts per million [mg/kg] or [mg/L]
PYPA	(*RS*)-2-(2-pyridyloxy)propyl alcohol
PYPAC	(*RS*)-2-(2-pyridyloxy)propionic acid
Q*	cancer risk factor
RBC	red blood cell
ROC	residue of concern
SC	soluble concentrate
STDEV	standard deviation

TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume/volume
WBC	white blood cell

Appendix I Toxicology

Table 1 Pyriproxyfen and Distance Insect Growth Regulator

METABOLISM

Rate and extent of absorption and excretion: Crl:CD (Sprague-Dawley) rats were given a single oral dose of 2 mg/kg bw or 1000 mg/kg bw ^{14}C Pyriproxyfen or a single oral dose of 2 mg/kg bw ^{14}C Pyriproxyfen following 2 mg/kg bw/day unlabelled Pyriproxyfen over 2 weeks. In male and female rats, the maximum total tissue ^{14}C residue concentrations were 7.3% and 5.2% of dosed ^{14}C respectively, 8 hours following a single oral low dose. Blood residue concentrations in females were considerably lower than in males. Urinary and fecal excretion was rapid in all dose groups with 63–83%, 88-96% or 92–98% of the administered dose eliminated within 24 hours, 2 days and 7 days, respectively. The major route of excretion was fecal (80–90% of administered dose) in all dose groups and ≤ 12% of the administered dose was excreted through the urinary route. There were no significant differences in total ^{14}C residue excretion between sexes and dose groups. Females eliminated up to twice as much 4' OH- Pyriproxyfen in their feces than males. ^{14}C residues were eliminated more slowly from adipose tissue than other tissues. Excretion via expired air was negligible.

Distribution and target organs: Maximum tissue concentrations were highest in liver, blood (males only), kidneys and adipose tissues. The ^{14}C levels in adipose tissue were the highest tissue levels after seven days. All other non-adipose tissues contained ^{14}C residue concentrations of ≤ 0.001, ≤ 0.6 or ≤ 0.003 ppm for the low, high or repeated dose groups, respectively.

Metabolism and toxicologically significant compounds: More than 17 and 11 metabolites were present in feces and urine, respectively. Ten of these metabolites were identified. Following a single dose, excretion of pyriproxifen via fecal route was 25–37% unchanged. After repeated dosing, 6–11% was unchanged via fecal route. No parent compound was detected in urine. The major metabolic reaction was oxidation at the 4 position of the terminal phenyl group. There were no significant qualitative differences in the metabolic profile between sexes following acute dosing for oxidation at the 4 ‘ and 2 ‘ positions. In females of the repeated dose group, the amount of metabolite produced by oxidation at the 4 ‘ position was significantly greater as compared to males. The amount of unmetabolized pyriproxyfen in feces was significantly lower for the repeat dose group than for the single low and high dose groups. This finding suggested the possibility that the technical pyriproxyfen may influence its own absorption from the gastrointestinal tract. This possibility was investigated by a vehicle effect study and the results show that repeated dosing of the corn oil vehicle could increase absorption of pyriproxyfen from the gastrointestinal tract.

STUDY	SPECIES, STRAIN and DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
ACUTE STUDIES—TECHNICAL			
Oral	Rat, Sprague-Dawley (5/sex/dose) 0, 1000, 2500 or 5000 mg/kg bw in corn oil	LD_{50} > 5000 mg/kg bw	**Low toxicity.** No deaths. Clinical signs (↓ spontaneous activity, soft feces, diarrhea, ↓ BWG at ≥ 2500 mg/kg bw) resolved within 2 days.
Dermal	Rat, Sprague-Dawley (5/sex/dose) 0, 2000 mg/kg bw in corn oil	LD_{50} > 2000 mg/kg bw	**Low toxicity.** No deaths, no clinical signs of toxicity.

STUDY	SPECIES, STRAIN and DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Inhalation	Rat, Sprague-Dawley (5/sex/dose) 4 hours, whole body exposure 0 (neg. control), 0 (corn oil vehicle), 0.6 or 1.3 mg/L	LC_{50} > 1.3 mg/L	**Slight toxicity.** Transient clinical signs of toxicity, salivation (2/5 ♂ s and 1/5 ♀), urinary incontinence (♀), ↓ BWG (♂) at 1.3 mg/L. These signs disappeared within 1 hour of exposure termination. No signs were observed in other groups. Test substance was dissolved in corn oil and this may result in a higher absorption rate and present different lung effects than had the test atmosphere consisted of ground test material (i.e., dust).
Skin irritation	Rabbit, NZW (3/sex)	MAS was 4.5 (at 24, 48 and 72 hours)	**Non-irritating**
Eye irritation	Rabbit, NZW (3/sex)	MIS was 4.7 (at 1 hour)	**Minimally irritating**
Skin sensitization (maximization)	Guinea pig, Hartley (♂) 20 animals/group for test and control 10 animals/group for positive control (DNCB) Induction (intradermal): 0.5% technical in corn oil Induction (dermal): 25% test substance in petrolatum Challenge: 25% test substance in petrolatum	Negative	**Not a dermal sensitizer**
ACUTE STUDIES—Distance Insect Growth Regulator (11.58% a.i.)			
Oral	Rat, Sprague-Dawley 5/sex/dose, 3000, 4000 or 5000 mg/kg bw undiluted	LD_{50} ♂ = 4733 mg/kg ♀ = 3773 mg/kg Combined = 4302 mg/kg bw	**Low toxicity**. 1 death/dose group occurring between 22 hours and 4 days; clinical signs in decedents (bw loss, lacrimation, hypothermia, breathing problems and prostration); survivors exhibited salivation, moist rales, lethargy, laboured breathing, moderate alopecia; signs largely cleared in survivors by day 5.
Dermal	Rabbit, NZW albino 5/sex 2000 mg/kg bw undiluted	LD_{50} ♂ > 2000 mg/kg ♀ > 2000 mg/kg Combined > 2000 mg/kg	**Low toxicity**. No mortalities; slight to moderate erythema and edema disappearing by day 10.

STUDY	SPECIES, STRAIN and DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Inhalation	Rat, Sprague-Dawley 5/sex, 3.1 mg/L (nose only; analytically determined)	LC_{50} ♂ > 3.1 mg/L ♀ > 3.1 mg/L Combined > 3.1 mg/L	**Low toxicity**. Wet fur/matted coat following exposure; red nasal discharge clearing by 2 days; chromodacryorrhea (1 animal); slight, dried red material in facial area, yellow anogenital stains; all symptoms cleared by day 6.
Primary Skin Irritation	Rabbit, NZW albino 3/sex, undiluted, 0.5 ml for 4 hours	MAS = 2.72 (24, 48 and 72 hours) MIS = 3 (72 hours)	**Mildly irritating.** Slight to severe erythema to day 7 some to day 10; very slight edema in some to 4 days; desquamation; resolution of irritation by end of study (except 2 animals with desquamation)
Primary Eye Irritation	Rabbit, NZW albino 3/sex 0.1 ml; 7 (5/6) or 10 days (1/6)	MAS = 5.56 (24, 48 and 72 hours) MIS = 12.7 at 1 hour	**Mildly irritating**. Chemosis, redness, slight discharge; one incident of corneal ulceration at 24 and 48 hours; all symptoms resolved by day 7 (5/6 animals) or day 10 (6/6 animals).
Skin Sensitization Buehler	Guine pig, Dunkin Hartley 10/sex 5/sex for control. Induction: undiluted for 6 hours Challenge: once with 25% v/v prep. for 6 hours. Positive control: DNCB	Negative	**Not a dermal sensitizer**
SHORT-TERM TOXICITY			
21-day dermal	Rat, Sprague-Dawley (5/sex/dose) 0, 100, 300 or 1000 mg/kg bw/day in corn oil	NOAEL = 1000 mg/kg bw/day LOAEL could not be determined as no effects were noted up to the highest dose tested.	No compound-related changes were noted.
28-day inhalation	Rat, Sprague-Dawley (10/sex/dose) 0.269, 0.482 or 1.00 mg/L in corn oil Equivalent conc. in mg/kg bw/day: 47, 84, 174 4 hours/day for 28 consecutive days, whole body exposure	NOAEL = 0.482 mg/L (83.8 mg/kg) LOAEL = 1.00 mg/L (174 mg/kg)	**1.00 mg/L:** salivation during initial exposures, ↑ LDH (♂), ↓ abs. lung weight (♂), ↑ WBC (♀). No lung histopathological examination was conducted.

STUDY	SPECIES, STRAIN and DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
90-day dietary	Rat, Crl:CDBR (10/sex/dose) 0, 400, 2000, 5000 or 10 000 ppm (24/28, 118/141, 309/356 or 642/784 mg/kg bw/day in ♂/♀)	NOAEL = 400 ppm (24/28 mg/kg bw/day in ♂/♀) LOAEL = 2000 ppm (118/141 mg/kg bw/day in ♂/♀)	**≥ 2000 ppm** (118/141 mg/kg bw/day in ♂/♀)**:** ↓ RBC parameters, ↑ cholesterol and phospholipid. **≥ 5000 ppm (**309/356 mg/kg bw/day in ♂/♀)**:** ↓ body weight (↓ 9% ♂/♀ at 5000 ppm; ↓ 12% ♂/♀ at 10 000 ppm); ↑ liver weight, ↑ eosinophilic cytoplasmic content in the liver.
90-day dietary	Mouse, Crl:CD-1 (ICR) BR, 10/sex/dose 0, 200, 1000, 5000 or 10 000 ppm (28/38, 149/197, 838/964 or 2035/2345 mg/kg bw/day in ♂/♀)	NOAEL = 1000 ppm (149/197 mg/kg bw/day in ♂/♀) LOAEL = 5000 ppm (838/964 mg/kg bw/day in ♂/♀)	**≥ 5000 ppm** (838/964 mg/kg bw/day in ♂/♀)**:** ↓ survival (8/10 ♂), ↓ BWG (♂), ↓ RBC, ↓ HB, ↓ HCT, ↓ MCV, ↑ platelets, ↑ WBC, ↑ liver weight (♂), ↑ adrenal gland weight (♂), ↑ phospholipids (♀), ↑ BUN, ↑ AST (♂), ↑ ALT (♂), thymic lymphoid depletion (♂), thymic atrophy, bone marrow myeloid hyperplasia (♂), spleen pigmentation (♂), renal effects (tubular nephrosis, dilation of renal tubules and pelvis, focal mineralization). **10 000 ppm** (2035/2345 mg/kg bw/day in ♂/♀)**:** ↓ survival at week 13 (3/9 ♂ and 1/10 ♀) , transient ↓ BWG, thymic lymphoid depletion, spleen pigmentation, myeloid hyperplasia, extra medullary hematopoiesis.
90-day capsule	Dog, Beagle (4/sex/dose) 0, 100, 300 or 1000 mg/kg bw/day	NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day	**≥ 300 mg/kg bw/day:** ↑ liver weight, hepatocellular enlargement (♀), ↑ cholesterol (♀), ↑ phospholipid (♀). **1000 mg/kg bw/day:** hepatocellular enlargement, cytoplasmic changes (believed to be a form of smooth endoplasmic reticulum proliferation) in the liver (adaptive).

STUDY	SPECIES, STRAIN and DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
52-week capsule	Dog, Beagle (4/sex/dose) 0 (capsule only), 30, 100, 300 or 1000 mg/kg bw/day	NOAEL = 30 mg/kg bw/day LOAEL = 100 mg/kg bw/day	**≥ 100 mg/kg bw/day:** ↓ BWG (♂), ↑ triglycerides (♂), ↑ ALP (♂.), ↑ cholesterol (♀). **≥ 300 mg/kg bw/day:** ↓ BWG, ↑ platelets (♂), ↑ ALP, ↑ triglycerides (♀), ↑ kidney weight (♀), submucosal fibrosis of the gall bladder (♂). **1000 mg/kg bw/day:** 2 ♂ sacrificed due to toxicity, salivation, diarrhea,↓ BWG (♀), body-weight loss (♂), ↑ platelets (♀), ↑ prothrombin time (♂), ↑ ALT (♂), ↑ AST (♂), ↑ bilirubin (♂), ↑ urinary volume and↓ pH (♂), centriacinar fibrosis, bile duct hyperplasia, active chronic inflammatory infiltrate, nodular hyperplasia (♂), submucosal fibrosis of the gall bladder (♀), submucosal edema of the gall bladder.
CHRONIC TOXICITY AND ONCOGENICITY			
78-week dietary	Mouse, CD-1 (10 animals /sex/dose) 0, 120, 600 or 3000 ppm (0, 16/21, 79/107 or 413/530 mg/kg bw/day in ♂/♀)	NOAEL = 120 ppm (16/21 mg/kg bw/day in ♂/♀) LOAEL = 600 ppm (79/107 mg/kg bw/day in ♂/♀)	**≥ 600 ppm** (79/107 mg/kg bw/day in ♂/♀): ↓ survival after week 64 in males compared to controls. **3000 ppm** 413/530 mg/kg bw/day in ♂/♀)**:** ↓ survival after week 60 in males;↓ BWG up to week 24 (♂); ↓ HB and other RBC parameters and ↑ polychromatic RBC at week 52 (♀); granular/pitted/rough kidneys; renal and glandular stomach amyloidosis; ↑ abs. and rel. liver weight at week 52 (♀). There is a genetic predisposition for development of systemic amyloidosis in the CD-1 strain. Amyloidosis was the primary cause of death in the majority of unscheduled deaths and mean time to death was decreased in a dose-related manner. The low number of survivors at scheduled termination is of concern with respect to the detection of increased incidences of neoplasia at study termination. However, differences in survival were not evident until after 60 weeks of study. Therefore, it is unlikely that the decreased survival would have affected the detection of neoplasia in this study. **No evidence of carcinogenicity**

STUDY	SPECIES, STRAIN and DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
2-year dietary	Rat, Sprague-Dawley Crl:CDBR (50 animals/ sex/dose in main study and 30 animals/sex/dose in satellite study used for clinical chemistry measurements; 10/sex/dose sacrificed at week 52) 0, 120, 600 or 3000 ppm (0, 5/7, 27/36 or 138/183 mg/kg bw/day in ♂/♀)	NOAEL = 600 ppm (27/36 mg/kg bw/day in ♂/♀) LOAEL = 3000 ppm (138/183 mg/kg bw/day in ♂/♀)	**3000 ppm** (138/183 mg/kg bw/day in ♂/♀)**:** ↓ BWG (10%); ↑ cholesterol weeks 26 (♂/♀) and 52, 78 (♂); ↑ phospholipid week 26; ↑ rel. liver weight interim sac (♀). The effects noted in the high dose animals at study termination were mild and indicated the possibility that the maximum tolerated dose was not reached in this study. Based on the toxicity observed in the short-term rat study, however, the dose levels for this study were appropriately chosen. **No evidence of carcinogenicity at the doses tested**
REPRODUCTION AND DEVELOPMENTAL TOXICITY			
2-generation	Rat, Sprague-Dawley, Crl:CD[SD]BR (26 animals /sex/dose) 0, 200, 1000 or 5000 ppm Parental animals (♂/♀): approximately equal to 13/21, 64/103 and 328/531 mg/kg bw/day F_1 animals (♂/♀): approximately equal to 17/20, 80/106 and 424/562 mg/kg bw/day	**Parental** NOAEL = 1000 ppm LOAEL = 5000 ppm **Reproductive** NOAEL = 5000 ppm (highest dose tested) **Offspring** NOAEL = 1000 ppm LOAEL = 5000 ppm	**Parental generation** **5000 ppm:** ↓ BWG premating, ↑ BWG during lactation, sporadic ↓ FC during premating and gestation **Parental F_1 generation** **5000 ppm:** ↓ BWG premating, ↑ BWG during lactation (♀), sporadic ↓ FC during premating and gestation, ↑ liver weight (absolute and relative ♂/♀), chronic interstitial nephritis (♂), focal clear cells of the liver (♂), ↑ relative kidney weight (♂). **Offspring** **5000 ppm:** ↓ pup body weight LD 14 and 21. Pup weights (F_1 and F_2) were significantly decreased from controls in both sexes. No effects on reproductive parameters. No evidence of increased sensitivity of the young.

STUDY	SPECIES, STRAIN and DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Developmental toxicity	Rat, Slc:SD (36 ♀/dose group) 0, 100, 300 or 1000 mg/kg bw/day in corn oil Gestation days 7–17 10–13 dams/ group were allowed to deliver and sacrificed after weaning Parameters examined for dams and pups were: clinical signs and mortality. no. of live born and stillborn offspring, sex and external anomalies. Pup body weight and gonadal development after weaning. Sensory function test was done on day 20 postpartum in all pups. Behavioural and motor coordination tests were performed on 1pup/sex/litter at 4 and 5 weeks of age. Learning ability test was done on pups at 6 weeks of age. Reproductive performance test was performed on pups (1/sex/litter) at 11 weeks of age.	**Maternal** NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day **Developmental** NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day	**<u>Maternal Effects</u>** **≥ 300 mg/kg bw/day:** ↓ BWG, ↓ FC, ↑ WBC, ↑ relative liver and kidney weights **1000 mg/kg bw/day:** ↑ mortality 12/42, (all deaths occurring during the first half of gestation after 4 doses, soft stool, erythema, swelling of the periproctal region, body-weight loss first few days of dosing. Dams that died showed hypoactivity, wasting, bloody dirtiness around the nose, blanching of the auricle and extremities, hypothermia, kidney and liver congestion, splenic atrophy, adrenal enlargement, thymic involution, stomach haemorrhage or ulceration, ↓ relative thymus weight, ↑ relative adrenal weight, 100% resorptions in 2 dams. No findings in dams sacrificed at the end of lactation except ↓ absolute spleen weight in the 1000 mg/kg bw/day group. **<u>Fetal Effects</u>** **≥ 300 mg/kg bw/day:** ↑ incidence of opening of the 7th cervical vertebra foramen transversium. **<u>Offspring Effects</u>** (dams allowed to deliver) **≥ 300 mg/kg bw/day:** ↑ total incidence of skeletal variations (no single variation was significantly increased) **1000 mg/kg bw/day:** ↑ incidence of renal pelvis dilatation in 8-week old pups, ↑ pup kidney weight. No effects on sensory function, behavioural and motor coordination, learning ability and reproductive performance in pups. No evidence of increased sensitivity of the young. Not teratogenic.

STUDY	SPECIES, STRAIN and DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Developmental toxicity	Rabbit, JW-NIBS (15–18/group) 0, 100, 300 or 1000 mg/kg bw/day Gestation days 6–18 Material was a solid that was melted and cooled just prior to use and administered directly.	**Maternal** NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day **Developmental** NOAEL = 300 mg/kg bw/day LOAEL = 1000 mg/kg bw/day	**Maternal** **≥ 300 mg/kg bw/day:** ↓ BWG and FC at 300 mg/kg bw/day, significant at 1000 mg/kg bw/day), abortions / premature deliveries (3/14) at 300 mg/kg bw/day, significant at 1000 mg/kg bw/day (6/13). In dams that delivered prematurely, abnormally coloured intestinal contents, gall bladder distention, watery/abnormally coloured bile, trace gastrointestinal hemorrhage and gas retention as well as kidney discolouration were observed. **1000 mg/kg bw/day:** maternal deaths, splenic congestion. **Developmental** **1000 mg/kg bw/day**: Slightly ↑ incidence of abnormal location of posterior vena cava. No evidence of increased sensitivity of the young. Not teratogenic.
GENOTOXICITY			
STUDY	**SPECIES and STRAIN or CELL TYPE and CONCENTRATIONS or DOSES**		**RESULTS**
Gene mutations in bacteria	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538; *E. Coli* WP2uvrA 10, 50, 100, 1000 or 5000 µg/plate; with and without activation		**Negative**
Gene mutations in mammalian cells (in vitro)	Chinese hamster V79 lung cells 10, 30, 100 or 300 µg/ml without activation 3, 10, 30 or 100 µg/ml with activation		**Negative**
Unscheduled DNA repair (in vitro)	HeLa S3 cells with and without activation (test material: 0.1, 0.2, 0.4, 0.4, 1.6, 3.2, 6.4, 12.8, 25.6, 51.2, 102.4, 204.8 µg/ml)		**Negative**
Chromosome aberrations (in vitro)	Chinese hamster ovary cells (CHO-K1) 10, 30 or 100 µg/ml without activation 30, 100 or 300 µg/ml with activation		**Negative**
Micronucleus assay (in vivo)	CD-1 mice, ♂ and ♀ 0 or 5000 mg/kg bw (single oral dose in corn oil; bone marrow harvested 24, 48 and 72 hours postdosing)		**Negative**

Compound-Induced Mortality
Increased mortality was observed in the teratogenicity studies in rats and rabbits at the 1000 mg/kg bw/day dose level. In the long-term toxicity/carcinogenicity study in the mouse, decreased survival was noted in males at doses ≥ 79 mg/kg bw/day. Increased mortality was observed in males at ≥ 838 mg/kg bw/day and in females at 2345 mg/kg bw/day in the 90-day oral study in mice.

ARfD: Pyriproxyfen showed very low acute toxicity. Because no acute effects were apparent, pyriproxyfen is unlikely to present an acute hazard. It is not necessary to set an ARfD.

ADI: The ADI is 0.16 mg/kg bw based on the NOAEL of 16.0 mg/kg bw/day established in the chronic mouse study, with a 100-fold uncertainty factor to account for intraspecies variability and interspecies extrapolation. The NOAEL in this study was based on decreased survival associated with systemic amyloidosis.

Toxicological Endpoints for Occupational Risk Assessment

Short-term dermal exposure: The NOAEL of 1000 mg/kg bw/day from the rat 21-day dermal study is recommended for short-term dermal exposure. No compound related changes were noted at this dose, which was the highest dose tested.

Short-term inhalation exposure: The NOAEL of 0.482 mg/L (equivalent to 84 mg/kg bw) from the 28-day rat inhalation study is recommended for short-term inhalation exposure. The NOAEL was based on salivation, increased LDH and decreased absolute lung weight in males and increased water consumption in females noted at the LOAEL.

Intermediate to chronic dermal and inhalation scenarios: The chronic 78-week dietary study in mouse provided the lowest NOAEL of the database and was considered the most appropriate study to assess the intermediate and chronic dermal and inhalation scenarios. The NOAEL was 16 mg/kg bw/day in males, based on decreased survival in both sexes after week 60.

The target MOE for the above exposure scenarios is 100.

Appendix II Residues

Table 1 Integrated Food Residue Chemistry Summary

Directions for Use of Distance Insect Growth Regulator (103 g pyriproxyfen/L) on Greenhouse Cucumbers, Peppers and Tomatoes						
Greenhouse Crop	**Formulation/Type**	**Interval (day)**	**Rate (g a.i./ha)**	**No./ Crop Cycle**	**Maximum Rate (g a.i./ha)**	**PHI (days)**
Cucumbers	Emulsifiable concentrate (EC)	14–28	92.7	2	185.4	3
Peppers						
Tomatoes						
Use directions and label restrictions: i) do not apply more than twice per crop cycle; ii) the minimum application interval is 14 days; iii) make the first application when monitoring indicates adult insects begin to appear; iv) if necessary, make a second application from 14 to 28 days after the first application; v) use the shorter interval for established infestations and when plants are rapidly flushing new growth; and vi) use the longer interval for newly established infestations and when plants are not rapidly flushing new growth.						

PHYSICOCHEMICAL PROPERTIES	
Water solubility at 25°C (mg/L)	0.367 $\pm$ 0.004
Solvent solubility (g/100 ml)	7.67 (hexane) 6.01 (methanol)
Octanol/water partition coefficient (log K_{ow}) at 25°C	5.37
Dissociation constant (pKa)	Not determined due to solubility problems
Vapor pressure at 23°C (Pa)	1.33×10^{-7}
Relative density (g/ml)	1.242
Melting point (°C)	47.4
UV/Visible absorption spectrum	270 nm (in water)

ANALYTICAL METHODOLOGY				
Parameters	**Plant Matrices**			
Method ID	DFG Method S 19 (extended revision) (cucumber)	NNA-90-0016 (tomato)	RM-33P-1 (oily and high moisture crops)	RM-33P-1-3 (fruit: apple, pear and citrus)
Type	Data gathering	Data gathering	Data gathering	Data gathering
Analytes	Pyriproxyfen	Pyriproxyfen	Pyriproxyfen	Pyriproxyfen
Instrumentation	GC-MSD	GC-TID	GC-NPD	GC-NPD
LOQ	0.01 ppm	0.01 ppm	0.02 ppm	0.02 ppm

Standard	External standardization method	External standardization method	External standardization method	External standardization method
ILV	None	None	None	None
Extraction/ clean-up	Extraction with acetone by homogenization. Clean-up by i) partition with ethyl acetate:cyclohexane (1:1; v:v); and NaCl and ii) gel permeation chromatography on Bio Beads S-X3 polystyrene gel.	Extraction with acetone by stirring. Clean-up by i) partition with aqueous sodium chloride (5%) and methylene chloride and ii) Florisil column chromatography.	Extraction with acetone by homogenization. Clean-up by i) partition with hexane and acetonitrile (oily crops) or with aqueous NaCl (5%) and dichloromethane (high moisture crops) and ii) silica gel column chromatography.	Extraction with acetone by homogenization. Clean-up by: i) partition with acetonitrile (hexane saturated) and hexane (acetonitrile saturated) (citrus crops only); and with aqueous NaCl (5%) and dichloromethane and ii) silica gel column chromatography
Method ID	RM-33P-1-3a	RM-33P-8	RM-33P-9	RM-33P-2-2
Type	Data gathering (fruit: apple, pear and citrus)	Data gathering and enforcement (tomato)	Data gathering (tomato and pepper)	Data gathering (cottonseed)
Analytes	Pyriproxyfen	Pyriproxyfen		Pyriproxyfen
Instrumentation	GC-NPD	GC-NPD		GC-NPD
LOQ	0.02 ppm	0.02 ppm		0.02 ppm
Standard	External standardization method	External standardization method		External standardization method
ILV	None	None	None	An ILV method was conducted using cottonseed. The recovery values obtained indicated that RM-33P-2-2 was reliable.

Extraction/ clean-up	Extraction with acetone by homogenization. Clean-up by i) partition with acetonitrile (hexane saturated) and hexane (acetonitrile saturated) (citrus crops only); and with aqueous NaCl (5%) and dichloromethane and ii) silica gel column chromatography.	Extraction with acetonitrile or acetonitrile:water (4:1; v:v) by homogenization and the aqueous residue was acid refluxed. Clean-up by partitioning of hydrolyzed aqueous residue with NaCl (5%) and dichloromethane and by silica gel column chromatography.		Extraction with acetonitrile:water (4:1; v:v) by homogenization. Pyriproxyfen residues were further cleaned up by sequential partition with i) NaCl (5%) and dichloromethane and ii) hexane and acetonitrile; and by silica gel column chromatography.
Radiovalidation	None	Conducted with pomace and juice samples from the tomato metabolism study. Indicated that the GC-NPD method can adequately extract residues of pyriproxyfen tomato matrices.	None	None
Multiresidue method	Using Level II DG modules, recoveries of pyriproxyfen from apples spiked at 0.10 and 0.50 ppm were acceptable for Protocol D (99.3–108%). For protocol E, recoveries from apples spiked at 0.05 ppm (61.2–88.2%) using C1-50% and C2-3 eluants were also acceptable. Recoveries of pyriproxyfen for Protocol F from cottonseed spiked at 0.05 ppm and 0.50 ppm were acceptable at 86.0–98.6% using C2-3 eluants. Based on the acceptable recovery data using protocols D, E and F, the multiresidue method was deemed adequate as an enforcement method for residues of pyriproxyfen in plant matrices.			

ANALYTICAL METHODOLOGY		
Parameters	**Animal Matrices**	
Method ID	RM-33G-2	RM-33T-1
Type	Data gathering (milk)	Data gathering (bovine tissue)
Analytes	Pyriproxyfen	Pyriproxyfen
Instrumentation	GC-NPD	GC-NPD
LOQ	0.02 ppm	0.02 ppm
Standard	External standardization method	External standardization method
ILV	None	None

Extraction/ clean-up	Extraction with ethyl acetate:methanol (2:1; v:v) using an Omnimixer. Clean-up by partition with i) saturated NaCl and ethyl acetate and ii) acetonitrile:hexane (1:1; v:v). The acetonitrile phase was cleaned up using alumina chromatography.	Extraction with ethyl acetate:methanol (3:1; v:v) using a Omnimixer. Clean-up by partition with i) acetonitrile:hexane (1:1; v:v) and ii) NaCl and ethyl acetate; and by alumina chromatography.
Radiovalidation	Conducted with milk collected from the goat metabolism study (pyridyl label). The method adequately extracted bioincurred residues of pyriproxyfen.	Conducted with liver collected from the goat metabolism study (pyridyl label). The method adequately extracted bioincurred residues of pyriproxyfen.
Multiresidue method	A study report for the screening of pyriproxyfen through the United States Food and Drug Administration multiresidue methods was not submitted. As the proposed uses are on greenhouse vegetables, which are not livestock feed commodities (Appendix A, Table 1 in Section 8 of Regulatory Directive DIR98-02), analysis of pyriproxyfen through the multiresidue methods at this time.	

NATURE OF THE RESIDUE IN PLANTS—APPLE		
Radiolabel position	[phenoxyphenyl-^{14}C]-pyriproxyfen	[2,6-pyridyl-^{14}C]-pyriproxyfen
Test site	Outdoor test plots	
Treatment	Foliar spray	
Rate (g a.i./ha)	1st at 170.0; 2nd at 177.8; and 3rd at 181.3	1st at 172.3; 2nd at 175.0; and 3rd at 177.3
Seasonal rate (g a.i./ha)	529.1	524.6
PHI	45 days after the 3rd application	

Total radioactive residues (TRRs) in whole apples (calculated as the sum of the TRRs from the surface wash, juice and pomace fractions) were 0.199 ppm and 0.171 ppm for the phenoxyphenyl and pyridyl labels, respectively. Within the apple, the TRRs were concentrated in the pomace fraction, 0.180 ppm for the phenoxyphenyl label and 0.143 ppm for the pyridyl label. ^{14}C-Residues were quantified at lower levels in the juice, 0.014 ppm for the phenoxyphenyl label and 0.024 ppm for the pyridyl label. Only a small fraction of the applied radioactivity was removed in the surface wash (0.004–0.005 ppm). Approximately 85–88% of the TRRs (0.160–0.162 ppm) were extracted from whole apples. Non-extractable residues accounted for 12.4–14.9% of the TRRs (0.023–0.028 ppm).

Metabolites identified	Major metabolites (> 10% TRRs)		Minor metabolites (< 10% TRRs) [free and/or conjugate]	
Radiolabel position	[phenoxyphenyl-^{14}C]-pyriproxyfen	[2,6-pyridyl-^{14}C]-pyriproxyfen	[phenoxyphenyl-^{14}C]-pyriproxyfen	[2,6-pyridyl-^{14}C]-pyriproxyfen
Whole apple	Pyriproxyfen, 4′-OH-Pyr	Pyriproxyfen	DPH-Pyr, POP, POPA, 4′-OH-POPA, 4′-OH-POP, 5″-OH-Pyr	4′-OH-Pyr, PYPA, PYPAC, DPH-Pyr, 5″-OH-Pyr
Pomace	Pyriproxyfen, 4′-OH-Pyr	Pyriproxyfen	DPH-Pyr, POP, POPA, 4′-OH-POPA, 5″-OH-Pyr	4′-OH-Pyr, PYPA , PYPAC, DPH-Pyr, 5″-OH-Pyr

Juice	-	-	Pyriproxyfen, 4′-OH-Pyr, DPH-Pyr, POP, POPA, 4′-OH-POPA, 4′-OH-POP, 5″-OH-Pyr	Pyriproxyfen, 4′-OH-Pyr, PYPA, PYPAC, DPH-Pyr

NATURE OF THE RESIDUE IN PLANTS—CUCUMBER				
Radiolabel position	[phenoxyphenyl-^{14}C]-pyriproxyfen		[2,6-pyridyl-^{14}C]-pyriproxyfen	
Test site	Greenhouse (Japan)			
Treatment	Foliar—applied to surface of leaves with a microsyringe (treated area was ~400 cm^2)	Foliar—applied to the surface of 2 fruits (treated area was ~30 cm^2)	Foliar—applied to surface of leaves with a microsyringe (treated area was ~400 cm^2)	Foliar—applied to the surface of 2 fruits (treated area was ~30 cm^2)
Rate (g a.i./ha)	51.2	103	49.2	99
Seasonal rate (g a.i./ha)	51.2	103	49.2	99
PHI	0, 1, 3, 7, 14 and 21 days after treatment	0, 3 and 7 days after treatment	0, 1, 3, 7, 14 and 21 days after treatment	0, 3 and 7 days after treatment

^{14}C-Residues in the surface wash from treated leaves decreased from 100 to 101% of the applied radioactivity (AR) immediately after treatment to ~21–38% of the AR at 21 days after treatment. At 21 days after treatment, ~53% of the AR (phenoxyphenyl label) and ~66% of the AR (pyridyl label) were extracted from treated leaves with methanol:water (4:1; v:v). Bound residues accounted for 11.0% of the AR (phenoxyphenyl label) and for 8.8% of the AR (pyridyl label). Total extractable residues, including residues in the surface wash, accounted for < 80.4–102.4% of the AR for the pyridyl label and for 88–101.8% of the AR for the phenoxyphenyl label over the 21-day sampling period. In non-treated shoots, 0.2% (phenoxyphenyl label) and 0.6% (pyridyl label) of the radioactivity applied to the leaves was recovered 21 days after application. In non-treated fruit, 0.2% (phenoxyphenyl label) and 2.1% (pyridyl label) of the radioactivity applied to the leaves was recovered 21 days after application. These results indicate that there was minimal translocation of pyriproxyfen in the cucumber plant following a topical foliar application.

^{14}C-Residues in the surface wash of treated fruit decreased from ~92 to 93% of the AR immediately after treatment to 1.4% of the AR (pyridyl label) and to 2.1% of the AR (phenoxyphenyl label) 7 days after treatment. At 7 days after application, ~81–84% of the AR were extracted with methanol:water (4:1; v:v); and bound residues accounted for 8.9% of the AR (pyridyl label) and 12.7% of the AR (phenoxyphenyl label). Total extractable residues, including residues in the surface wash, accounted for < 69.2–103.8% of the AR for the pyridyl label and for 83.2–104.2% of the AR for the phenoxyphenyl label over the 7-day sampling period.

Metabolites identified	Major metabolites (> 10% TRRs)		Minor metabolites (< 10% TRRs) [free and/or conjugate]	
Radiolabel position	[phenoxyphenyl-^{14}C]-pyriproxyfen	[2,6-pyridyl-^{14}C]-pyriproxyfen	[phenoxyphenyl-^{14}C]-pyriproxyfen	[2,6-pyridyl-^{14}C]-pyriproxyfen
Treated leaves (21 days after treatment)	Pyriproxyfen, 4′-OH-Pyr	Pyriproxyfen, 4′-OH-Pyr	DPH-Pyr, POPA, 4′-OH-POPA, DPH-POPA	DPH-Pyr, 2-OH-Py, PYPA
Treated fruit (7 days after treatment)	4′-OH-Pyr	4′-OH-Pyr	Pyriproxyfen, DPH-Pyr, POPA, 4′-OH-POPA, 4′-OH-POP	Pyriproxyfen, DPH-Pyr

NATURE OF THE RESIDUE IN PLANTS—TOMATO		
Radiolabel position	[phenoxyphenyl-^{14}C]-pyriproxyfen	[2,6-pyridyl-^{14}C]-pyriproxyfen
Test site	Outdoor test plots	
Treatment	Foliar spray	
Rate (g a.i./ha)	1st at 164.0; 2nd at 141.5; 3rd at 148.5	1st at 147.0; 2nd at 152.3; 3rd at 155.5
Seasonal rate (g a.i./ha)	454	454.8
PHI	7 days after the 3rd application	

TRRs) in whole tomatoes (0.335 ppm and 0.259 ppm for the phenoxyphenyl and pyridyl labels, respectively) were calculated as the sum of the radioactivity in the surface wash (0.011 ppm and 0.005 ppm for the phenoxyphenyl and pyridyl labels, respectively), juice (0.048 ppm and 0.085 ppm for the phenoxyphenyl and pyridyl labels, respectively) and pomace (0.276 ppm and 0.169 ppm for the phenoxyphenyl and pyridyl labels, respectively) fractions. ^{14}C-Residues were concentrated in the pomace and were comparatively lower in the juice. Differences between the two labels were attributed to variations in the amount of spray reaching the fruit; fruit size at application and harvest; and foliage density. Approximately 95% of the TRRs (0.251–0.335 ppm) were extracted from whole tomatoes with ~ 2–3% of the TRRs (0.005-0.011 ppm) in the surface wash, ~14–32% of the TRRs (0.048–0.085) in the juice and ~61–79% of the TRRs (0.161–0.276 ppm) in the pomace.
Non-extractable residues in tomatoes accounted for only 4.6–5.3% of the TRRs (0.014–0.016 ppm) and these were entirely in the pomace.

Metabolites identified	Major metabolites (> 10% TRRs)		Minor metabolites (< 10% TRRs) [free and/or conjugate]	
Radiolabel position	[phenoxyphenyl-^{14}C]-pyriproxyfen	[2,6-pyridyl-^{14}C]-pyriproxyfen	[phenoxyphenyl-^{14}C]-pyriproxyfen	[2,6-pyridyl-^{14}C]-pyriproxyfen
Whole tomato	Pyriproxyfen	Pyriproxyfen, PYPA	4′-OH-Pyr, 4′-OH-POPA, 4′-OH-POP, DPH-Pyr	4′-OH-Pyr, PYPAC, 2-OH-PY, DPH-Pyr
Pomace	Pyriproxyfen	Pyriproxyfen	4′-OH-Pyr, 4′-OH-POPA, 4′-OH-POP, DPH-Pyr	4′-OH-Pyr, PYPAC, PYPA , DPH-Pyr

Juice	—	—	4′-OH-POPA, 4′-OH-POP, DPH-Pyr	PYPAC, PYPA, 2-OH-PY, DPH-Pyr

CONFINED ROTATIONAL CROP STUDY—WHEAT, RADISH, LETTUCE				
Radiolabel position	[phenoxyphenyl-^{14}C]-pyriproxyfen		[2,6-pyridyl-^{14}C]-pyriproxyfen	
Test Site	Greenhouse			
Formulation used for trial	Not reported			
Application rate and timing	196.4 g a.i./ha at 30 days prior to seeding of radish, lettuce and wheat		202 g a.i./ha at 30 days prior to seeding of radish, lettuce and wheat	
Metabolites identified	Major metabolites (> 10% TRRs)		Minor metabolites (< 10% TRRs)	
Radiolabel Position	[phenoxyphenyl-^{14}C]-pyriproxyfen	[2,6-pyridyl-^{14}C]-pyriproxyfen	[phenoxyphenyl-^{14}C]-pyriproxyfen	[2,6-pyridyl-^{14}C]-pyriproxyfen
Lettuce leaf, radish root, radish leaf, wheat forage (30-day plantback interval)	As the TRRs in lettuce leaf, radish (leaf and root) and wheat forage for the phenoxyphenyl label, and as the TRRs in lettuce leaf and radish root for the pyridyl label were < 0.01 ppm, further characterization of the ^{14}C-residues was not conducted.			
Wheat (chaff, forage, straw) and radish leaf (30-day plantback interval)	^{14}C-Residues were mostly bound, accounting for 89% of the TRRs (0.052–0.072 ppm) in wheat grain, 58–71% of the TRRs (0.0225–0.034 ppm) in wheat straw, 40% of the TRRs (0.0043 ppm) in wheat forage, 48–70% of the TRRs (0.0279–0.040 ppm) in wheat chaff for both labels and for 37% of the TRRs (0.0040 ppm) in radish leaf for the pyridyl label only. Extracts with ^{14}C-residues greater than 0.01 ppm were further analyzed. The HPLC analyses of the water soluble residues in wheat straw and wheat chaff for both labels indicated several unidentified components, each at ≤ 0.01 ppm.			

NATURE OF THE RESIDUE IN RUMINANT					
Species	Radiolabel		Dose Level	Length of Dosing	Sacrifice
Goat (*Capra hircus*)	[phenoxyphenyl-^{14}C]-pyriproxyfen	[2,6-pyridyl-^{14}C]-pyriproxyfen	10 ppm	5 consecutive days	6 hours from last dose to sacrifice

Pyriproxyfen was readily excreted primarily in the feces (57.9–58.1% of the AD [applied dose] and 49.4–62.0% of the AD) and to a lesser extent in the urine (17.0–17.9% of the AD and 7.6–12.6% of the AD) for the phenoxyphenyl and pyridyl labels, respectively. The gastrointestinal tract plus contents accounted for 24.0–24.4% of the AD (28.0–35.7 ppm) and for 30.6–31.0% of the AD (22.6–40.1 ppm) for the phenoxyphenyl and pyridyl labels, respectively. Only 0.41–0.62% (0.573–0.845 ppm) and 0.57–0.95% (0.815–1.26 ppm) of the AD was recovered from edible tissues; and only 0.30–0.79% (0.286–0.432 ppm) and 0.45–0.85% of the AD (0.320–0.537 ppm) was recovered in milk for the phenoxyphenyl and pyridyl labels, respectively. The TRRs in the blood collected prior to sacrifice accounted for < 0.01% of the AD (0.036–0.041 ppm) and residues in the heart accounted for 0.01% of the AD (0.03–0.04 ppm).

Metabolites identified	Major metabolites (> 10% of the TRRs)		Minor metabolites (< 10% of the TRRs)	
Radiolabel Position	[phenoxyphenyl-^{14}C]-pyriproxyfen	[2,6-pyridyl-^{14}C]-pyriproxyfen	[phenoxyphenyl-^{14}C]-pyriproxyfen	[2,6-pyridyl-^{14}C]-pyriproxyfen
Loin muscle	Pyriproxyfen, 4′-OH-Pyr	pyriproxyfen, 4′-OH-Pyr-sulfate, 2-OH-Py	4′-OH-Pyr-sulfate, POP, 4′-OH-POP	4′-OH-Pyr, PYPAC, PYPA- conjugate, 2,5-OH-PY
Rear leg muscle	Pyriproxyfen, 4′-OH-Pyr-sulfate	Pyriproxyfen, 2-OH-Py	4′-OH-Pyr, POP, 4′-OH-POP	4′-OH-Pyr-sulfate, 4′-OH-Pyr, PYPAC, PYPA-conjugate
Omental fat	Pyriproxyfen, 4′-OH-Pyr	Pyriproxyfen, 4′-OH-Pyr	4′-OH-Pyr-sulfate, POP, 4′-OH-POP	4′-OH-Pyr-sulfate
Perirenal fat	Pyriproxyfen, 4′-OH-Pyr	Pyriproxyfen, 4′-OH-Pyr	4′-OH-Pyr-sulfate, POP, 4′-OH-POP	4′-OH-Pyr-sulfate
Kidney	4′-OH-Pyr-sulfate, 5″-OH-Pyr-sulfate, POP-sulfate	4′-OH-Pyr-sulfate, PYPA-conjugate	Pyriproxyfen, 4′-OH-Pyr, POP, 4′-OH-POP, 4′-OH-POP-sulfate, POPA, 4′-OH-POPA, DPH-Pyr	Pyriproxyfen, 4′-OH-Pyr, 5″-OH-Pyr, PYPAC
Liver	4′-OH-Pyr-sulfate, POPA	4′-OH-Pyr-sulfate	Pyriproxyfen, 4′-OH-Pyr, 5″-OH-Pyr, 5″-OH-Pyr-sulfate, POP, 4′-OH-POPA, DPH-Pyr	Pyriproxyfen, 4′-OH-Pyr, 5″-OH-Pyr, PYPA-conjugate, 2,5-OH-Py-conjugate
Milk (day 2)	Pyriproxyfen, 4′-OH-Pyr-sulfate	4′-OH-Pyr-sulfate, 2,5-OH-Py-conjugate	4′-OH-Pyr, POP-sulfate, 4′-OH-POP-sulfate, 4′-OH-POPA-sulfate, DPH-Pyr	Pyriproxyfen, 4′-OH-Pyr, DPH-Pyr
Milk (day 4)	4′-OH-Pyr-sulfate	4′-OH-Pyr-sulfate, 2,5-OH-Py-conjugate	Pyriproxyfen, 4′-OH-Pyr, POP-sulfate, 4′-OH-POP-sulfate, 4′-OH-POPA-sulfate, DPH-Pyr	Pyriproxyfen, 4′-OH-Pyr, DPH-Pyr

NATURE OF THE RESIDUE IN LAYING HEN

Because none of the commodities associated with the proposed crops are fed to poultry (Appendix A, Table 1 of the Residue Chemistry Guidelines in DIR98-02), information concerning the nature of the residue in poultry is not required at this time.

CROP FIELD TRIALS—GREENHOUSE CUCUMBER

The submitted cucumber trials were conducted under European greenhouse conditions typical of the producing region of the country (Southern France, Italy, Spain and Greece) where the studies were initiated.

Commodity	Total rate g a.i./ha	PHI (days)	Analyte	Residue levels (ppm)					
				n	Min.	Max.	HAFT	Mean/ Median	STDEV
Greenhouse cucumber	224.5–232.6	0	Pyriproxyfen	4	0.01	0.07	0.07	0.035/ 0.03	0.025
	217.1–232.6	3		8	< 0.01	0.02	0.02	0.011/ 0.01	0
	224.5–232.6	38874		4	< 0.01	< 0.01	< 0.01	< 0.01/ < 0.01	0

CROP FIELD TRIALS—GREENHOUSE PEPPER (BELL)

The submitted pepper trials were conducted under European greenhouse conditions typical of the producing region of the country (Southern France, Italy, Spain and Greece) where the studies were initiated. Residues were corrected for the in-storage dissipation of pyriproxyfen residues in pepper.

Commodity	Total rate g a.i./ha	PHI (days)	Analyte	Residue levels (ppm)					
				n	Min.	Max.	HAFT	Mean/ Median	STDEV
Greenhouse pepper	226.6–229.0	0	Pyriproxyfen	4	0.16	0.27	0.27	0.228/ 0.24	0.05
	220.0–229.0	38779		8	0.08	0.49	0.49	0.239/ 0.21	0.127
	226.6–229.0	7		4	0.1	0.31	0.31	0.163/ 0.12	0.1

CROP FIELD TRIALS—GREENHOUSE TOMATO

The submitted tomato trials were conducted under European greenhouse conditions typical of the producing region of the country (Italy, Spain and Greece) where the studies were initiated.

Commodity	Total rate g a.i./ha	PHI (days)	Analyte	Residue levels (ppm)					
				n	Min.	Max.	HAFT	Mean/ Median	STDEV
Atominal EC (100 g pyriproxyfen/L)									
Greenhouse tomato	447.1–454.4	0	Pyriproxyfen	5	0.03	0.35	0.35	0.132/ 0.08	0.128
		38718		5	0.06	0.43	0.43	0.196/ 0.11/	0.159
		38779		5	0.04	0.43	0.43	0.154/ 0.12	0.159
		7-8		5	0.03	0.22	0.22	0.126/ 0.11	0.078
Admiral 10 EC (100 g pyriproxyfen/L)									

Greenhouse tomato	216.8–218.8	0	Pyriproxyfen	2	0.06	0.06	0.06	0.06/ 0.06	-
	216.8–226.4	3		6	0.05	0.17	0.17	0.095/ 0.09	0.043
	216.8–218.8	7		2	0.04	0.11	0.11	0.075/ 0.075	-

RESIDUE DECLINE

No apparent trend was observed in the residue decline data submitted for the greenhouse tomato trials. For the pepper trials, residues of pyriproxyfen generally decreased by the end of the sampling period. The cucumber residue decline data indicated that residues of pyriproxyfen decreased to varying degrees at 3 days after application and remained unchanged at 6–7 days after application (< LOQ).

MAXIMUM RESIDUE LIMITS

Cucumber	0.02 ppm
Bell pepper	0.80 ppm
Tomato	0.25 ppm

FIELD ACCUMULATION IN ROTATIONAL CROPS

A field accumulation rotational study was not required for the purpose of this submission as the proposed crops are greenhouse vegetables.

PROCESSED FOOD AND FEED

Fraction	Mean residue levels (ppm)	Concentration factor
Greenhouse Tomato (pyriproxyfen)		
Tomato	0.055	—
Peeled tomato	< 0.01	0.2
Peels	0.44	8
Juice	< 0.01	0.2
Purée	0.065	1.2
Ketchup	0.04	0.7
Canned tomato	< 0.01	0.2
Greenhouse Pepper (pyriproxyfen)		
Pepper	0.27 (corrected)	—
Canned pepper	0.015	0.06
Field Tomato (pyriproxyfen)		
Tomato	0.04	—
Purée	< 0.01	0.25
Paste	0.02	0.5

LIVESTOCK FEEDING

Although a dairy cattle feeding study was submitted, greenhouse cucumbers, peppers and tomatoes are not considered livestock feed items as per Table I, Appendix A in Section 8 of the Residue Chemistry Guidelines (DIR98-02). Therefore, the proposed crops would have no impact on the dietary burden of livestock. Although a poultry feeding study was not submitted, such a study type is not required for the purpose of this submission.

Tissues/Matrices	Feeding level (ppm)	Pyriproxyfen residues (ppm)	Anticipated residues (ppm)
Whole milk	30	< 0.01	—
Skim milk	30	< 0.01	—
Cream	30	0.012–0.015	—
Liver	30	< 0.01	—
Kidney	30	< 0.01	—
Fat	1	< 0.01	—
	9	0.011–0.025	—
	30	0.046–0.072	—
Muscle	30	< 0.01	—

STORAGE STABILITY

Plants

Samples of macerated untreated apple, tomato and pepper; and samples of untreated apple processed fractions (juice, pomace) spiked with pyriproxyfen at a level of 0.10 ppm were stored at -20ºC for a duration of 33–550 days. Residues of pyriproxyfen were stable in apple pomace (50 days) and in tomato (280 days) but deceased in apple fruit (~0.065% per day; p = 0.010), apple juice (~0.998% per day; p = 0.002) and in pepper (~0.237% per day; p = 0.010). Based on the storage duration of samples from the magnitude of the residue studies, corrections due to in-storage dissipation were required only for samples from the pepper greenhouse trials.

Animals

Samples of untreated control bovine fat, liver and muscle, spiked with pyriproxyfen at the 0.1 ppm level, were stored at -20ºC for a duration of 31–33 days. Residues of pyriproxyfen decreased in fat (~0.612% per day; p = 0.015), liver (~1.33% per day; p = 0.005) and muscle (~0.484% per day; p = 0.022). The storage intervals of the liver, fat and muscle samples during the livestock feeding study corresponded to decreases in pyriproxyfen residues of 14.6%, 14.1% and 11.6%, respectively. As the calculated decrease in pyriproxyfen residues were only ~12–15%, corrections due to in-storage dissipation were not made.

Table 2 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES		
ROC FOR ENFORCEMENT **Primary Crops** **Rotational Crops**	 Pyriproxyfen Pyriproxyfen	
ROC FOR RISK ASSESSMENT **Primary Crops** **Rotational Crops**	 Pyriproxyfen Pyriproxyfen	
METABOLIC PROFILE IN DIVERSE CROPS	Similar in apple, cucumber and tomato	
ANIMAL STUDIES		
ANIMALS	**Poultry**	**Ruminant**
ROC FOR ENFORCEMENT	Not applicable	Pyriproxyfen
ROC FOR RISK ASSESSMENT	Not applicable	Pyriproxyfen
METABOLIC PROFILE IN ANIMALS	Similar in rat and ruminant	
FAT SOLUBLE RESIDUE	Potential for fat sequestration based on a log K_{ow} of 5.37. This was confirmed in the goat metabolism study where pyriproxyfen concentrated in fat tissue.	

DIETARY RISK (from food alone)			
Chronic Non-Cancer Dietary Risk **ADI = 0.16 mg/kg bw/day** **Note: An EEC value was not estimated for pyriproxyfen as there is little potential for its migration to drinking water sources through the proposed greenhouse uses.**	**POPULATION**	**ESTIMATED RISK (% of ADI)**	
		Basic (MRL)	**Refined**
	All infants < 1 year old	6.1	6
	Children 1–2 years	14.7	14.1
	Children 3–5 years	10.1	9.6
	Children 6–12 years	5.3	4.9
	Youth 13–19 years	2.8	2.5
	Adults 20–49 years	2.4	2.2
	Adults 50+ years	2.6	2.4
	Total population	3.6	3.4
Acute Dietary Exposure Analysis, 95th percentile		An ARfD was not established for pyriproxyfen.	
Q*		A Q* was not established for pyriproxyfen.	

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