Proposed Registration Decision PRD2013-10

Pyrimethanil

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Table of Contents

Overview 1
Proposed Registration Decision for Pyrimethanil 1
What Does Health Canada Consider When Making a Registration Decision? 1
What Is Pyrimethanil? 2
Environmental Considerations 4
Value Considerations 4
Measures to Minimize Risk 5
Next Steps 5
Other Information 5
Science Evaluation 7
Pyrimethanil 7
1.0 The Active Ingredient, Its Properties and Uses 7
1.1 Identity of the Active Ingredient 7
1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product 7
1.3 Directions for Use 8
1.4 Mode of Action 8
2.0 Methods of Analysis 8
2.1 Methods for Analysis of the Active Ingredient 8
2.2 Method for Formulation Analysis 8
2.3 Methods for Residue Analysis 8
3.0 Impact on Human and Animal Health 9
3.1 Toxicology Summary 9
3.1.1 PCPA Hazard Characterization 10
3.2 Acute Reference Dose (ARfD) 11
3.3 Acceptable Daily Intake (ADI) 11
3.4 Occupational Risk Assessment 12
3.4.1 Toxicological Endpoints 12
3.4.2 Occupational Exposure and Risk 13
3.5 Food Residues Exposure Assessment 15
3.5.1 Residues in Plant and Animal Foodstuffs 15
3.5.2 Dietary Risk Assessment 15
4.0 Impact on the Environment 16
5.0 Value 17
5.1 Effectiveness Against Pests 17
5.1.1 Acceptable Efficacy Claims 17
5.4 Economics 17
5.5 Sustainability 17
5.5.1 Survey of Alternatives 17
5.5.2 Compatibility with Current Management Practices Including Integrated Pest Management 18
5.5.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance 18
5.5.4 Contribution to Risk Reduction and Sustainability 18

6.0 Pest Control Product Policy Considerations 18
7.0 Summary 19
7.1 Human Health and Safety 19
7.2 Environmental Risk 19
7.3 Value 20
8.0 Proposed Regulatory Decision 20
List of Abbreviations 21
Appendix I Tables and Figures 23
Table 1 Toxicity Profile of End-use Product Containing Pyrimethanil (Ecofog-160) 23
Table 2 Toxicity Profile of Technical Pyrimethanil 24
Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Pyrimethanil 24
Table 4 Food Residue Chemistry Overview of Risk Assessment 25
Table 5 Summary of Fungicide Alternatives for the Uses Supported with Ecofog-160 26
Table 6 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported 26
Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications 27
References 29

Overview

Proposed Registration Decision for Pyrimethanil

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Pyrimethanil Technical Fungicide and Ecofog-160, containing the technical grade active ingredient pyrimethanil, for postharvest treatment of apples and pears by thermal fogging to control gray mould and suppress blue mould.

Pyrimethanil is currently registered for use on field potatoes, various vegetables and fruits including pome fruits and on greenhouse vegetables with the products Scala SC Fungicide (Reg. No. 28011) and Scala SC Greenhouse Fungicide (Reg. No. 29975). For the detailed review of the chemistry, health, environmental and value data please refer to REG2006-04, *Pyrimethanil*.

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

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Pyrimethanil Technical Fungicide and Ecofog-160.

What Does Health Canada Consider When Making a Registration Decision?

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

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

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

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

nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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

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

What Is Pyrimethanil?

Pyrimethanil is the active ingredient present in Ecofog-160. It is a member of the anilinopyrimidine family of fungicides and belongs for the Group 9 of the Fungicide Resistance Action Committee. Pyrimethanil acts by preventing secretion of the fungal enzymes necessary for the pathogen infection process.

Health Considerations

Can Approved Uses of Pyrimethanil Affect Human Health?

Products containing pyrimethanil are unlikely to affect your health when used according to label directions.

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

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

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

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

A detailed assessment of the toxicology database for technical grade pyrimethanil can be found in the REG2006-04, *Pyrimethanil*. Ecofog-160 is a new end-use product for a new use of pyrimethanil, and additional toxicology data and information were provided with the current application. Waiver requests for the short-term inhalation toxicity and short-term dermal toxicity data requirements, as well as an acute toxicity package for Ecofog-160, were submitted. A new mouse oncogenicity study and a rat immunotoxicity toxicity study were also submitted.

In laboratory animals, the acute toxicity of the end-use product Ecofog-160 (containing pyrimethanil) was low via the oral, dermal and inhalation routes. It was moderately irritating to the eyes and minimally irritating to the skin, and caused an allergic skin reaction. Consequently, the hazard signal words "WARNING EYE IRRITANT" and "POTENTIAL SKIN SENSITIZER" are required on the product label.

Health effects in animals given repeated doses of the active ingredient pyrimethanil included effects on the thyroid and liver. There was no evidence that pyrimethanil damaged genetic material but it did, however, cause thyroid tumours in rats. Pyrimethanil did not cause birth defects in animals and did not affect the ability to reproduce. When pyrimethanil was given to pregnant or nursing animals, effects on the developing fetus (decreased body weights, increased runts) and juvenile animal (decreased body weight gains) were observed at doses that were toxic to the mother, indicating that the young do not appear to be more sensitive to pyrimethanil than the adult animal. Pyrimethanil caused functional effects, possibly related to the nervous system, at high doses in rats after a single dose.

The risk assessment protects against the effects of pyrimethanil by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate dietary intake estimates (food plus water) revealed that the general population and all infants less than 1 year old, the subpopulation which would ingest the most pyrimethanil relative to body weight, are expected to be exposed to less than 21% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from pyrimethanil is not of concern for all population subgroups.

Acute dietary (food and water) estimates for the general population and all population subgroups were less than 22% of the acute reference dose, and are not of health concern. The highest exposed subpopulation was all infants less than 1 year old.

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

The residue data submitted to support the registration of pyrimethanil as a postharvest application by thermal fogging on pome fruits are adequate. For the MRLs for this active ingredient on pome fruits, please refer to EMRL2010-26.

Occupational Risks From Handling Ecofog-160

Occupational risks are not of concern when Ecofog-160 is used according to the proposed label directions, which include protective measures.

Workers who mix, load or apply Ecofog-160 can come in dermal contact with pyrimethanil residues on the skin and can be exposed to pyrimethanil by inhalation. Therefore, the label specifies that mixer/loaders and fogging applicators must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes, socks and protective eyewear. Fogging applicators must also wear a full-face respirator or self-contained breathing apparatus (SCBA) to protect from blow-back of the superheated fog and exposure to pyrimethanil, in case of system failure of the application equipment. The label also requires that workers who enter treated storage rooms must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes, socks, and full-face SCBA gear. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for workers, the risks to these individuals are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible, provided that a specific venting and filtration system that yields 100% filter efficiency is put in place during and after application.

Environmental Considerations

What Happens When Pyrimethanil Is Introduced Into the Environment?

When pyrimethanil is applied as the fungicide Ecofog-160 to pome fruits by thermal fogging in closed storage facilities, minimum exposure of exterior soil and water is expected. Pyrimethanil has a low potential for volatilization and, therefore, is not expected to remain in the atmosphere for extended periods and is not expected to result in long range atmospheric transport.

Value Considerations

What Is the Value of Ecofog-160?

Ecofog-160 is a fungicide for post-harvest treatment of apples and pears through thermal fogging. Ecofog-160 is a preventative treatment effective in the control of gray mould and the suppression of blue mould, which are the two principal post-harvest diseases of pome fruit.

Measures to Minimize Risk

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

The key risk-reduction measures being proposed on the label of Ecofog-160 to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with pyrimethanil on the skin or through inhalation of spray mists, anyone mixing, loading and applying Ecofog-160 must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes, socks and protective eyewear. Fogging applicators must also wear a full-face respirator or self-contained breathing apparatus (SCBA) to protect from blow-back of the superheated fog and exposure to pyrimethanil, in case of system failure of the application equipment. In addition, since bystanders may be exposed to vented air from the storage rooms, a specific venting and filtration system that yields 100% filter efficiency must be in place during and after application.

Environment

For the proposed use on stored pome fruits in closed treatment facility, environmental exposure to pyrimethanil residues is expected to be minimal and, thus, no risk mitigation measures are required.

Next Steps

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

Other Information

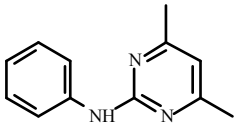
When the PMRA makes its registration decision, it will publish a Registration Decision on pyrimethanil (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the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

Science Evaluation

Pyrimethanil

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Pyrimethanil
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	*N*-(4,6-dimethylpyrimidin-2-yl)aniline
2. Chemical Abstracts Service (CAS)	4,6-dimethyl-*N*-phenyl-2-pyrimidinamine
CAS number	53112-28-0
Molecular formula	$C_{12}H_{13}N_3$
Molecular weight	199.3
Structural formula	
Purity of the active ingredient	99.5%

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

Technical Product—Pyrimethanil Technical

Property	Result
Physical state	Solid
Density at 20°C	1.15 g/cm^3

End-Use Product—Ecofog-160

Property	Result
Colour	Light yellow
Odour	Fruity
Physical state	Liquid

Property	Result
Formulation type	Solution
Guarantee	16.0% nominal
Container material and description	5 gallon high density polyethylene pails
Density at 20°C	1.011 g/mL
pH of 1% dispersion in water	6.0
Oxidizing or reducing action	Avoid contact with oxidizing and reducing agents, fire extinguishing agents and water
Storage stability	Stable at temperatures between 16 and 24°C for 2 years
Corrosion characteristics	Product was not corrosive to the package
Explodability	Non explosive

1.3 Directions for Use

Ecofog-160 is to be applied once through thermal fogging at a rate of 60 grams per metric ton of fruit. This preventative application must be made no more than 15 days after harvesting, prior to storage.

1.4 Mode of Action

Pyrimethanil is an anilinopyrimidine fungicide that belongs to the Group 9 of the Fungicide Resistance Action Committee (FRAC). Its mode of action consists of the inhibition of methionine biosynthesis, which prevents secretion of the fungal enzymes necessary for the pathogen infection process.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

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

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

Please refer to REG2006-04, *Pyrimethanil* for residue analytical methods for data generation and enforcement purposes.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Building on the data reviewed in the previous toxicology assessment (please refer to *REG2006-04-Pyrimethanil*.), the applicant submitted waiver requests for the short-term inhalation toxicity and short-term dermal toxicity data requirements. In addition, an acute toxicity package for the new end-use product Ecofog-160 was provided. A new mouse oncogenicity study conducted up to the limit dose and a rat immunotoxicity toxicity study were also conducted in response to a US EPA request and submitted to the PMRA. Based on an assessment of these data, there were no changes to the toxicology endpoints and reference doses for pyrimethanil. An overview of the data is summarized below.

Ecofog-160 (containing pyrimethanil) was of low acute toxicity by the oral, dermal and inhalation routes of exposure in rats. It was moderately irritating to the eyes and minimally irritating to the skin of rabbits, and was a dermal sensitizer in guinea pigs according to the Maximization test method.

A waiver request for a short-term dermal toxicity study in rats was submitted. Technical grade pyrimethanil was of low acute toxicity via the dermal route, was non-irritating to the eyes and skin and was negative for dermal sensitization. Based on the lack of irritation in the acute irritation studies and the availability of pyrimethanil dermal absorption data, an oral endpoint was considered to be protective of potential dermal effects. Therefore, the waiver for the 28-day rat dermal toxicity study was accepted.

A waiver request for a 28-day inhalation toxicity study in rats was submitted. Pyrimethanil was of low acute toxicity via the inhalation route, non-irritating to the eyes and skin and was negative for dermal sensitization. Despite the relatively low toxicity of pyrimethanil in animals, potential inhalation exposure could occur during the thermal fogging application process and there is a lack of data for repeated inhalation exposures in rats; therefore, this risk scenario was not adequately characterized. However, based on the personal protective equipment (PPE) requirements (i.e. a full-face respirator (or self-contained breathing apparatus [SCBA]) with a single layer and chemical-resistant gloves during treatment and during re-entry) for Ecofog-160, as well as the use of a filtration system to prevent bystander exposure, there are no residual concerns for the lack of a short-term inhalation toxicity study in rats and a study is not required at this time.

As discussed in REG2006-04, *Pyrimethanil*, the target organ of pyrimethanil toxicity in mice was the thyroid in both sexes. Urogenital tract lesions consisting of balanopothitis of the penis, preputial gland adenitis/abscess, seminal vesicle and urinary bladder distension and prostatitis were observed at the highest dose tested in the first mouse study (211 mg/kg bw/day) but no similar effects were seen at higher doses in the second mouse oncogenicity study up to the limit dose. Treatment-related effects in the second mouse oncogenicity study included colloid alteration and cystic follicles in the thyroids of both sexes, with males being affected at lower dose levels than females.

Pyrimethanil was not genotoxic in a standard battery of *in vitro* and *in vivo* assays. There was no evidence of oncogenicity up to the limit dose in mice. As discussed in REG2006-04, *Pyrimethanil*, treatment-related increases in thyroid follicular cell adenomas and carcinomas were observed at the high dose level (221/291 mg/kg bw/day males/females) in rats. A mode of action was proposed and the data provided supported a threshold approach. Overall, the existing cancer risk assessment was not changed.

In a 28-day oral immunotoxicity study in female rats, there was no change to the number of immunoglobulin M (IgM) antibody-forming cells in the treated groups compared to controls; however, the high coefficients of variation decreased the confidence in these results. Treatment-related decreased thymus weights and increased atrophic or small thymuses were observed at the mid-dose level and higher. A review of other repeat-dose toxicity studies did not indicate any treatment-related immune effects. Based on the weight of evidence, there were no residual concerns regarding immunotoxicity after pyrimethanil treatment.

Results of the additional toxicology information submitted for pyrimethanil reviewed under the current submission, as well as the acute toxicity studies for its associated end-use product Ecofog-160, are summarized in Table 1 of Appendix I. The toxicology endpoints for use in the human health risk assessment are summarized in Table 3 of Appendix I.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website. Incidents from Canada and the United States were searched for pyrimethanil, and any additional information submitted by the applicant during the review process was considered. As of 8 February 2013, there were no health-related incident reports for this active in the PMRA Incident Reporting database.

3.1.1 PCPA Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for pyrimethanil. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of the young compared to parental animals in any of the available studies. The only treatment-related effects in offspring in the 2-generation reproductive toxicity study included decreased body weights and body weight gains in the presence of similar effects in the parents. In a rat developmental toxicity study, treatment-related decreases in fetal and litter weights were observed at the same dose level that maternal effects were observed. In a rabbit developmental toxicity study, treatment-related decreased fetal weights and increased numbers of runts were observed in the presence of maternal toxicity. There was no evidence of teratogenicity or sensitivity of the young in rats or rabbits after an *in utero* exposure. Overall, there is a low concern for sensitivity of the young and effects on the young are well-characterized and not considered serious in nature. On the basis of this information, the PCPA factor has been reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

General Population (including females 13–49 years of age)

To estimate acute dietary risk, the acute neurotoxicity study in rats with a NOAEL of 100 mg/kg bw was selected for risk assessment. At the LOAEL of 1000 mg/kg bw, ataxic gait, decreased motor activity, reduced hind-limb grip strength and decreased body temperature were observed in males and dilated pupils were noted in females. These effects occurred within the first day of dosing and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. **The composite assessment factor (CAF) is 100-fold.**

The ARfD is calculated according to the following formula:

$$\text{ARfD (gen. pop)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{100 mg/kg bw}}{\text{100}} = \text{1 mg/kg bw of pyrimethanil}$$

This toxicological endpoint and reference dose is the same as that outlined in REG2006-04, *Pyrimethanil*.

3.3 Acceptable Daily Intake (ADI)

To estimate risk from repeat dietary exposure, the 104-week combined chronic/oncogenicity study in rats with a NOAEL of 17 mg/kg bw/day was selected for risk assessment. At the LOAEL of 221 mg/kg bw/day, decreased body weight gains, decreased food consumption, increased cholesterol and thyroid and liver histopathology and increased thyroid tumours were observed. This study provides the lowest NOAEL in the database and is supported by the following co-critical studies: 78-week mouse oncogenicity, 1-year dog and 2-generation reproductive toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. **The composite assessment factor (CAF) is 100-fold.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{17 \text{ mg/kg bw/day}}{100} = 0.17 \text{ mg/kg bw/day of pyrimethanil}$$

The ADI provides a margin of 1240 to the dose at which thyroid tumours were observed in rats.

This toxicological endpoint and reference dose is the same as that outlined in REG2006-04, *Pyrimethanil*.

Cancer Assessment

There was adequate evidence to support a threshold-based mechanism to the tumours (thyroid follicular cell adenomas and combined follicular cell adenomas and carcinomas) in rats. The dietary reference dose (i.e. the ADI) and the selected MOEs for occupational and bystander exposure provide a sufficient margin to this tumour type. The cancer risk assessment has not changed as a result of the new mouse oncogneicity study.

3.4 Occupational Risk Assessment

3.4.1 Toxicological Endpoints

Short- and Intermediate-term Dermal

For short- and intermediate-term occupational exposures via the dermal route, the NOAEL of 30 mg/kg bw/day from the one year dog oral gavage toxicity study was selected for risk assessment. Vomiting and clinical signs, as well as decreased body weight, body weight gains and food consumption were observed in both sexes at the high dose level of 250 mg/kg bw/day. A waiver request for a short-term dermal toxicity study in rats was accepted.

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

Short- and Intermediate-term Inhalation

For short- and intermediate-term occupational exposures via the inhalation route, the NOAEL of 30 mg/kg bw/day from the one year dog oral gavage toxicity study was selected for risk assessment. Vomiting and clinical signs, as well as decreased body weight, body weight gains and food consumption were observed in both sexes at the high dose level. A waiver request for a short-term inhalation toxicity study in rats was accepted.

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

3.4.1.1 Dermal Absorption

An *in vivo* rat study examined the dermal absorption of pyrimethanil in male Sprague-Dawley rats. The animals were administered a single dermal application with nominal doses of 60 µg a.i./cm^2, 6 µg a.i./cm^2, 0.6 µg a.i./cm^2 of [^{14}C] pyrimethanil in suspension concentrate formulation (the Scala SC fungicide formulation) and monitored up to 120 hours post-dosing. Groups of 4 rats were given the above three doses with exposures and sacrifices for 0.5, 1, 2, 4, 10, and 24 hours to quantify the absorption on and in the skin as well as in the excreta, blood and residual carcass. In addition, the excretion of radioactivity was quantified up to 120 hours following application of the lowest dose rate with a skin wash at 10 hours and 24 hours post-application.

The most appropriate dermal absorption value for risk assessment purposes is based on the low dose (0.6 µg/cm^2) and an application site wash at 10 hours with sacrifice at 120 hours. The low dose is the most conservative as it was more readily absorbed and is comparable to applicator exposures in the field. The 10 hour exposure period is considered most applicable to typical worker exposure times. The direct dermal absorption (excreta and tissue) for this group was 57.20% and the indirect dermal absorption (direct plus skin compartment) was 57.46%. The active ingredient in the skin compartment appeared to be potentially absorbable as the mean levels in the various treated skin fractions had a tendency to decrease in time with a concurrent increase in the excretion values. The mean overall recovery for this group was 99.20%. Therefore, a dermal absorption value of 57% is considered appropriate for risk assessment purposes.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for dermal and inhalation exposure to Ecofog-160 during mixing, loading and application. For mixing and loading of Ecofog-160, the amount handled per day is less than that of the registered foliar use of pyrimethanil on pome fruits, which was assessed in REG2006-04, *Pyrimethanil* for workers wearing a single layer and chemical-resistant gloves. As such, exposure to mixer/loaders is not expected to result in risks of concern.

To apply Ecofog-160 by thermal fogging, the thermal fogger is placed on a flat, secure surface outside the treatment room at a height of about one meter. The metal pipe extending from the resistance heater section of the machine is placed through a hole in the door that seals the storage room from the remainder of the facility or the outside. A sleeve is placed over the discharge pipe and the opening to seal the storage room off the application area. Therefore, the applicators and all other personnel are separated by this barrier from the fog discharge at the end of the pipe. To maintain ambient air pressure the door to the storage rooms also has a hole to which a venting pipe is attached. The vented air is always outside of the facility and at a height and distance away from where any individuals would be directly exposed.

The thermal fogger heats the formulation and a blower in the machine will blow the vapor out of the pipe opening in the sealed store room at a target discharge temperature of 180°C. These hot temperatures would produce serious thermal burn injury if the applicator or any other person came into contact with the vapor discharge. The fog is applied at a rate of 55 m^3/hr and is intended to disperse through the storage room and settle on the apples as it cools.

Under normal conditions, minor contact of pyrimethanil is expected from some potential leakage from the applicator nozzle. As such, risks of concern are not expected for workers wearing a long-sleeved shirt, long pants, chemical-resistant gloves, shoes, socks, and protective eyewear. However, during situations of system failure due to equipment malfunction or insufficient room seal, the superheated fog may be blown back to the applicator. Therefore, the applicator always must wear a full-face respirator or self-contained breathing apparatus (SCBA) during application in case of system failure to protect from the blow-back of the superheated fog, as well as exposure to pyrimethanil.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

Workers that may enter storage rooms treated with Ecofog-160 are expected to be exposed to pyrimethanil mainly via the inhalation route. To protect workers from postapplication exposure, the label states that entry into the treated area by any person other than properly trained and equipped handlers is prohibited from the start of application until the treated area is ventilated for 8 hours with no ventilation followed by 1 hour of mechanical ventilation, or for 24 hours with no ventilation. In case workers must enter the treated storage rooms during treatment or before the room is fully ventilated, handlers must wear chemical-resistant headgear, full-face SCBA gear, long-sleeved shirt, long pants, chemical-resistant gloves, shoes, and socks.

Storage rooms for harvested pome fruits have atmospheric conditions maintained at low levels of oxygen (1 to 3%) and low temperatures (slightly above freezing point) to prevent spoilage of fruit. As such, anyone who enters the storage rooms must wear full SCBA gear, since the more acute danger from entering the room is the lack of oxygen. The use of SCBA will mitigate these concerns and provide adequate protection from inhalation exposure to pyrimethanil.

3.4.2.3 Bystander Exposure and Risk

Bystanders may be exposed to pyrimethanil via inhalation from the air vented from the treated storage room. To address bystander exposure, the applicant submitted a study which tested different types of filters for their efficiency in reducing the amount of pyrimethanil in the vented air, to investigate the type of filter that should be used in the filtering system during commercial applications. The filtering system was assembled prior to the application. An exhaust manifold made of PVC or corrugated piping was installed along the perimeter floor of the storage room. Vent holes (¾-inch in diameter) at 18-inch centers were drilled in the tubing along the back wall to help aid in the natural dispersion of fog throughout the room. The exhaust manifold was then plumbed outside of the room through the sealed door of the storage room, connecting to the venting pipe outside of the door. The venting pipe was then connected to the filter box and in-line duct fan, and was extended away from the boundary of the storage room for the air to be vented at a height several feet above the breathing zone level. In the study, during the thermal fogging application, the air concentrations of pyrimethanil in the storage room (prior to filtering) and leaving the room through the venting pipe (after filtering) were monitored. Twenty-six tests were conducted with various combinations of filters during application. One set of filters (filter type "(6) 20"x25" 3M 2200 air filters + 2" carbon") was tested twice and had 100% efficiency. The maximum concentration of the two tests was 2150 mg/m^3 of pyrimethanil before filtering, which was reduced to 0 mg/m^3 after filtering. As such, the applicant has stated that this filter combination will be used in all commercial applications of Ecofog-160.

Therefore, for risks to bystanders to not be of concern, the specific venting and filtration system that yielded 100% filter efficiency must be in place when venting during and after application; this results in the concentration of pyrimethanil in the vented air to be negligible. In addition, with other filter combinations, it was observed that reused filters had lower efficiencies than new filters. As such, the filter set must be replaced after one venting period to maintain proper filter efficiency.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

Please refer to REG2006-04, *Pyrimethanil* and the Evaluation Report for 2007-8746 for a summary of the previously reviewed data and the rationale for the regulatory decision. The information captured herein only relates to the acceptability of the residue data provided to the Pest Management Regulatory Agency in support of the registration of pyrimethanil as a postharvest application to pome fruits in Canada.

Apple and pear residue trials conducted in Europe and the US were previously assessed for the establishment of MRLs due to the addition of the postharvest use pattern in exporting countries, including the thermal fogging application on pome fruits. As this is a postharvest treatment carried out under controlled conditions, the residue data are considered acceptable to support the registration of Ecofog-160 for postharvest thermal fogging on pome fruits in Canada.

3.5.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

A refined chronic dietary exposure assessment was conducted using Canadian MRLs, US tolerances for imported commodities, supervised trial median residues (STMdRs), and experimental and empirical processing factors. Aggregate exposure from food and water is considered acceptable and below PMRA's level of concern. The PMRA estimates that the refined chronic dietary exposure to pyrimethanil from all supported pyrimethanil food uses and water is 6.4% of the acceptable daily intake (ADI) for the total population (0.010815 mg/kg bw/day). The highest exposure and risk estimate is for all infants less than one year old at 21.0% of the ADI (0.035731 mg/kg bw/day). Please refer to the Evaluation Report for application 2009-3851 for details.

3.5.2.2 Acute Dietary Exposure Results and Characterization

A refined acute dietary exposure assessment was conducted using Canadian MRLs, US tolerances for imported commodities, highest residues, and experimental and empirical processing factors. Aggregate exposure from food and water is considered acceptable and below PMRA's level of concern. Specifically, an acute dietary exposure of 3.7% to 21.3% of the acute reference dose (ARfD) was obtained for all representative population subgroups. The highest exposed population subgroup was all infants less than one year old. Please refer to the Evaluation Report for application 2009-3851 for details.

3.5.3 Aggregate Exposure and Risk

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

3.5.4 Maximum Residue Limits

Please refer to the Maximum Residue Limit Database in the Pesticides and Pest Management Regulatory Agency section of Health Canada's website for the established MRLs for pyrimethanil.

The nature of the residues in animal and plant matrices, analytical methodology and residue trial data were assessed under REG2006-04, *Pyrimethanil*, applications 2010-4146, 2010-5853, 2007-8746 and 2009-3851. The acute and chronic dietary risk estimates are summarized in Table 4 in Appendix I.

4.0 Impact on the Environment

Please refer to REG2006-04, *Pyrimethanil* for a full environmental assessment of pyrimethanil.

When pyrimethanil is applied as the fungicide Ecofog 160 to pome fruits by thermal fogging in closed storage facilities, there is a minimum risk for it to find its way into soil and water. Pyrimethanil has a low potential for volatilization and, therefore, is not expected to remain in the atmosphere for extended periods and is not expected to result in long range transport in the atmosphere.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

5.1.1.1 Control of gray mould (*Botrytis cinerea*) on apples and pears

In three small-scale trials, bins of commercially harvested pears ('d'Anjou') and apples ('Red Delicious', 'Fuji') were treated with Ecofog-160. Pears and apples were artificially inoculated with *Botrytis cinerea* prior to treatment. In two of the three submitted trials, Ecofog-160 at 60 g per metric ton of fruits significantly reduced gray mould incidence by 81% and 91% under moderate to high disease pressure. These efficacy results support the use of Ecofog-160 for control of gray mould on apples and pears.

5.1.1.2 Suppression of blue mould (*Penicillium expansum*) on apples and pears

One small-scale trial was submitted in support of the blue mould claim. A total of 100 pear ('d'Anjou') and apple ('Red Delicious') fruits per bin were inoculated with *Penicillium expansum*. Bins were then treated with Ecofog-160 at 100 g per metric ton of fruits, which corresponds to 1.6X the proposed rate. In unwounded fruits, Ecofog-160 fully controlled blue mould incidence under low disease pressure. In wound-inoculated fruits, the product significantly reduced blue mould incidence by 60% (pears) and 71% (apples) under severe disease pressure.

Scala SC Fungicide (Reg. No. 28011), containing 400 g/L pyrimethanil, is currently registered as a pre-harvest foliar treatment for suppression of *Penicillium* storage diseases on apples. This registered use provides supplementary evidence of pyrimethanil's antifungal activity against blue mould. Based on these considerations, the use of Ecofog-160 is acceptable for the claim of suppression, instead of control, of blue mould on apples and pears.

5.2 Economics

No market analysis was performed for this submission.

5.3 Sustainability

5.3.1 Survey of Alternatives

Refer to Appendix I, Table 5 for a summary of the active ingredients currently registered for the uses supported with Ecofog-160.

5.3.2 Compatibility with Current Management Practices Including Integrated Pest Management

Adequate cultural practices and sanitation measures are important means to prevent disease development in crops. Ecofog-160 would not interfere with these preventative measures when used as recommended.

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

According to FRAC, anilinopyrimidine fungicides such as pyrimethanil present a medium risk of resistance development. A pyrimethanil-resistant isolate of *Penicillium expansum* was collected in 2011 from a Washington State commercial packing house. Apples had been treated with a post-harvest drench of pyrimethanil for four consecutive years, which underlines the importance of applying adequate post-harvest resistance management practices to ensure the long-term effectiveness of the product. In that regard, Ecofog-160 may not be applied to fruits that have been previously treated with pyrimethanil via drench or dip/wash application. Label directions also recommend rotating Ecofog-160 with fungicides having different modes of action.

5.3.4 Contribution to Risk Reduction and Sustainability

Ecofog-160 represents a new and effective disease management tool against gray and blue mould on stored apples and pears. Furthermore, pyrimethanil has a different mode of action than the currently registered post-harvest treatments on pome fruit, i.e. thiabendazole and fludioxonil, and does not exhibit cross resistance to these active ingredients. Considering that 1) *Botrytis cinerea* and *Penicillium expansum* show a high risk of resistance development to fungicides, and 2) thiabendazole-resistant field populations of *Penicillium expansum* have been reported on pome fruit, the integration of Ecofog-160 into post-harvest rotational programs will contribute to resistance management. In addition, since Ecofog-160 is applied through thermal fogging, the possibility of pathogens or other contaminants being transferred to fruits via drench water is eliminated.

6.0 Pest Control Product Policy Considerations

During the review process, pyrimethanil and its associated end-use product Ecofog-160 Fungicide were assessed in accordance with the federal Toxic Substances Management Policy (TSMP) and the PMRA Regulatory Directive DIR99-03. The PMRA has reached the following conclusions:

- Pyrimethanil (technical grade) and its transformation products do not meet all the criteria for Track 1 substances.

- Pyrimethanil (technical grade) does not contain any byproduct or microcontaminant that meet the TSMP Track 1 criteria.

- Based on the formulating process used, impurities of human health or environmental concern as identified in the Canada Gazette, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances and allergens known to cause anaphylactic-type reactions, are not expected to be present in the product.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for pyrimethanil is adequate to define the majority of toxic effects that may result from exposure to pyrimethanil. There was no evidence of immunotoxicity in rats after short-term dosing or carcinogenicity in mice after chronic dosing. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. In short-term and chronic studies on laboratory animals, the primary target was the liver and thyroid in rodents. Pyrimethanil caused functional effects, possibly related to the nervous system, at high doses in rats after a single dose. There was no evidence that pyrimethanil was genotoxic; however, there was evidence of oncogenicity in rats after chronic dosing. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixer/loaders and applicators handling Ecofog-160, workers re-entering storage rooms and bystanders are not expected to be exposed to levels of pyrimethanil that will result in risks of concern when the Ecofog-160 is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

Aggregate dietary intake estimates (food plus water) revealed that the general population and all infants less than 1 year old, the subpopulation which would ingest the most pyrimethanil relative to body weight, are expected to be exposed to less than 21% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from pyrimethanil is not of concern for all population subgroups.

Acute dietary (food and water) estimates for the general population and all population subgroups were less than 22% of the acute reference dose, and are not of health concern. The highest exposed subpopulation was all infants less than 1 year old.

The residue data submitted to support the registration of pyrimethanil as a postharvest application by thermal fogging on pome fruits are adequate. For the MRLs for this active ingredient on pome fruits, please refer to EMRL2010-26.

7.2 Environmental Risk

When pyrimethanil is applied as the fungicide Ecofog-160 to pome fruits by thermal fogging in closed storage facilities, there is a minimum risk for it to find its way into soil and water. Pyrimethanil has a low potential for volatilization and, therefore, is not expected to remain in the atmosphere for extended periods and is not expected to result in long range transport in the atmosphere.

7.3 Value

The data submitted to register Ecofog-160 are adequate to support the following claims:

- post-harvest control of gray mould on apples and pears
- post-harvest suppression of blue mould on apples and pears.

8.0 Proposed Regulatory Decision

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Pyrimethanil Technical Fungicide and Ecofog-160, containing the technical grade active ingredient pyrimethanil, for post-harvest treatment of apples and pears by thermal fogging to control gray mould and suppress blue mould.

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

List of Abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
Cal-DPR	California Department of Pesticide Regulation
EEC	expected environmental concentration
FRAC:	Fungicide Resistance Action Committee
g	gram(s)
HEC	human equivalent concentration
IgM	immunoglobulin M
kg	kilogram(s)
L	litre(s)
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
mg	milligram(s)
MAS	maximum average score for 24, 48 and 72 hours
MOE	margin of exposure
MRL	maximum residue limit
NC	not classified
NOAEL	no observed adverse effect level
PCPA	*Pest Control Product Act*
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
TGAI	technical grade active ingredient
US	United States
USEPA	United States Environmental Protection Agency
w	weight
♂	male
♀	female

Appendix I Tables and Figures

Table 1 Toxicity Profile of End-use Product Containing Pyrimethanil (Ecofog-160)

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

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague-Dawley rats PMRA #1894818	LD_{50} > 2000 mg/kg bw Low Toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA #1894819	LD_{50} > 2000 mg/kg bw Low Toxicity
Acute inhalation toxicity (nose-only) Sprague-Dawley rats PMRA #1897820	LC_{50} > 2.15 mg/L Low Toxicity
Dermal irritation New Zealand albino rabbits PMRA #1894822	MAS = 0.1 Minimally irritating
Eye irritation New Zealand albino rabbits PMRA #1894821	MAS = 28 Moderately irritating
Dermal sensitization (Maximization test) Hartley albino guinea pigs PMRA #1894823	Dermal sensitizer

Table 2 Toxicity Profile of Technical Pyrimethanil

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
21/28-day dermal waiver request PMRA #2172671	Both pyrimethanil and Ecofog-160 were of low acute dermal toxicity. Based on the lack of irritation in the acute irritation studies and the availability of pyrimethanil dermal absorption data, an oral endpoint was considered to be protective of potential dermal effects. Therefore, the waiver request was accepted.
28-day inhalation waiver request PMRA #217267	Low acute inhalation toxicity for both the TGAI and Ecofog-160. No treatment-related effects observed in the respiratory system after dietary exposure. There is no indication from the existing toxicology studies that respiratory exposure to pyrimethanil would result in more serious effects than via the oral route. There were residual concerns regarding the proposed occupational scenario (thermo-fogging) and the lack of toxicity data for repeated inhalation exposures to pyrimethanil. However, based on the personal protective equipment (PPE) requirements (i.e. a full-face respirator (or self-contained breathing apparatus [SCBA]) with a single layer and chemical-resistant gloves during treatment and during re-entry) for Ecofog-160, as well as the use of a filtration system to prevent bystander exposure, there were no residual concerns for the lack of a short-term inhalation toxicity study in rats and a study is not required at this time.
78-week oncogenicity CD-1 mice PMRA #1951603	NOAEL = not established/594 mg/kg bw/day LOAEL = 477/1217 mg/kg bw/day, based on ↑ thyroid discolouration and colloid alteration (♂) / ↑ enlarged and/or discoloured thyroid, and/or cystic follicles, colloid alteration of thyroid (♀) No evidence of oncogenicity.
28-day immunotoxicity dietary (SRBC-specific IgM quantification using ELISA) Sprague-Dawley rats (females) PMRA #1938624	Supplemental; high coefficients of variation (70–97% of the means) were noted for IgM data, which decreased confidence in the results. Effects including ↓ thymus weights and ↑ atrophic/small thymuses were observed at ≥69.5 mg/kg bw/day.

Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Pyrimethanil

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Acute rat neurotoxicity study	NOAEL = 100 mg/kg bw Ataxia, decreased body temperature, decreased motor activity; decreased hindlimb grip strength (males), dilated pupils (females)	100
	ARfD = 1.0 mg/kg bw		
Repeated dietary	104-week rat combined chronic/oncogenicity	NOAEL = 17 mg/kg bw/day Liver and thyroid effects Co-critical studies: mouse oncogenicity, 1-year dog, 2-generation reproductive toxicity	100
	ADI = 0.17 mg/kg bw/day		

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Short-term to intermediate-term dermal[2]	1-year dog toxicity	NOAEL = 30 mg/kg bw/day Vomiting, salivation, diarrhea, discolouration of feces, decreased body weight, body weight gain, food efficiency, water consumption; decreased food consumption (females)	100
Short-term to intermediate-term inhalation[3]	1-year dog toxicity	NOAEL = 30 mg/kg bw/day Vomiting, salivation, diarrhea, discolouration of feces, decreased body weight, body weight gain, food efficiency, water consumption; decreased food consumption (females)	100
Cancer	104-week rat combined chronic/oncogenicity	The increased thyroid follicular cell adenomas and combined adenomas and carcinomas observed at the high dose level were considered to be treatment-related. A threshold approach was used for the cancer risk assessment.	

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments
[2]Since an oral NOAEL was selected, a dermal absorption factor (57%) was used in a route-to-route extrapolation
[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 4 Food Residue Chemistry Overview of Risk Assessment

DIETARY RISK FROM FOOD AND WATER		
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**
		Food and Water
Refined chronic non-cancer dietary risk **ADI = 0.17 mg/kg bw/day** **Estimated chronic drinking water concentration = 189.5 μg a.i./L**	**All infants < 1 year**	21.0
	Children 1-2 years	19.3
	Children 3–5 years	14.5
	Children 6–12 years	7.8
	Youth 13–19 years	4.2
	Adults 20–49 years	4.8
	Adults 50+ years	5.5
	Females 13–49 years	5.0
	Total population	6.4
	POPULATION	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**
		Food and Water
Refined acute dietary exposure analysis, 95th percentile **Estimated acute drinking water concentration = 195.3 μg a.i./L** **ARfD = 1 mg/kg bw**	**All infants < 1 year**	21.3
	Children 1-2 years	20.6
	Children 3–5 years	15.4
	Children 6–12 years	8.1
	Youth 13–19 years	4.2
	Adults 20–49 years	3.7
	Adults 50+ years	4.1
	Females 13–49 years	3.9
	Total population	6.3

Table 5 Summary of Fungicide Alternatives for the Uses Supported with Ecofog-160

Active ingredient, FRAC group	Crop	Disease	Method of application
fludioxonil (12)	pome fruit	gray mould, blue mould	post-harvest dip
pyrimethanil (9)	apples	storage diseases (*Botrytis*, *Penicillium**)	pre-harvest foliar spray
thiabendazole (1)	apples pears	*Penicillium* spp., *Botrytis cinerea*	post harvest dip, flood or spray
Pseudomonas syringae strain ESC-10 (NC)	apples pears	gray mould*, blue mould*	post-harvest spray

* registered for suppression

Table 6 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Proposed claim	Comments
Pome fruit: control of gray mould (*Botrytis cinerea*) with one Ecofog-160 application through thermal fogging at 60 g per metric ton of fruits.	Supported on apples and pears.
Pome fruit: control of blue mould (*Penicillium expansum*) with one Ecofog-160 application through thermal fogging at 60 g per metric ton of fruits.	Supported for suppression of blue mould on apples and pears.

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

Table 1 Differences Between MRLs in Canada and in Other Jurisdictions

Please refer to the Maximum Residue Limit Database in the Pesticides and Pest Management Regulatory Agency section of Health Canada's website for the established MRLs for pyrimethanil.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
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1251751	1990, Chemical Substances, [CBI REMOVED], DACO: 2.13.1 CBI
1251752	2006, Validation of [CBI REMOVED] AM000705DB1 - Determination of the by-products in Pyrimethanil techn. grade active ingredient, DACO: 2.13.1 CBI
1251753	2006, Validation of [CBI REMOVED] AM001005DB1 - Determination of the by-products in Pyrimethanil techn. grade active ingredient, DACO: 2.13.1 CBI
1251754	2006, Pyrimethanil Technical Grade – [CBI REMOVED]. Analytical Method AM000106DB1, DACO: 2.13.1 CBI
1251755	2006, Pyrimethanil technical grade: By-products - [CBI REMOVED]. Analytical Method AM000705DB1, DACO: 2.13.1 CBI
1251756	2006, Pyrimethanil technical grade: By-products, [CBI REMOVED]. Analytical Method AM001005DB1, DACO: 2.13.1 CBI
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1251758	2006, Validation of [CBI REMOVED] AM000106DB1 - Determination of the by-products in Pyrimethanil techn. grade active ingredient, DACO: 2.13.1 CBI
1251759	2006, Validation of [CBI REMOVED] AM001205DB2 - Determination of the assay in Pyrimethanil techn. grade active ingredient, DACO: 2.13.1 CBI
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1252150	1998, Pyrimethanil (Technical Grade Active Ingredient) AE B100309. Analytical Profiles of Five Production Batches Including Description and Validation Data for the Methods Applied., DACO: 2.13.3 CBI
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1894810	2006, Xedathane A: Product Identity, Manufacturing Process, Discussion of the Formulation of Impurities, and Certified Limits, DACO: 3.2.1,3.2.2,3.2.3,3.3.1,3.4.1
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1894820	2005, Acute Inhalation Toxicity Study in Rats - Limit Test, DACO: 4.6.3
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1894825 SUMMARY OF RESIDUE STUDIES FOR PYRIMETHANIL

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3.0 Value

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