Proposed Registration Decision PRD2015-15

# Etoxazole

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# Overview

## Proposed Registration Decision for Etoxazole

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 Etoxazole Technical and TetraSan 5 WDG Miticide, containing the technical grade active ingredient etoxazole, to control spider mites in greenhouse tomatoes and greenhouse ornamentals.

Etoxazole has been previously reviewed by the PMRA to establish import maximum residue limits for a variety of fruit, vegetables, mint, hops, tea and tree nuts. Refer to the Evaluation Reports in Health Canada's Public Registry for application numbers 2008-0581 and 2011-2152 for a summary of the previous reviews for etoxazole.

An evaluation of available scientific information found that, under the approved conditions of use, TetraSan 5 WDG Miticide 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 Etoxazole Technical and TetraSan 5 WDG Miticide.

## 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.

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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."

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

Before making a final registration decision on etoxazole, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on etoxazole, 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 Etoxazole?

Etoxazole is an active ingredient that regulates mite growth. It does not kill adults, but prevents treated juvenile mites from successfully moulting, and prevents treated eggs from hatching. Treated adult females lay significantly fewer viable eggs. Etoxazole is the active ingredient found in TetraSan 5 WDG Miticide, which is a commercial agricultural product for control of spider mites in greenhouse tomatoes and greenhouse ornamentals.

## Health Considerations

### Can Approved Uses of Etoxazole Affect Human Health?

**TetraSan 5 WDG Miticide, containing etoxazole, is unlikely to affect your health when used according to label directions.**

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

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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*.

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

In laboratory animals, the technical grade active ingredient etoxazole was of low acute toxicity by the oral and dermal routes and of slight acute toxicity by inhalation exposure. Etoxazole was non-irritating to the eyes and skin and did not cause an allergic skin reaction. Based on these findings, the signal word and hazard statement "CAUTION – POISON" are required on the label.

The end-use product TetraSan 5 WDG Miticide, containing etoxazole, was of low acute toxicity by the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eyes and skin and did not cause an allergic skin reaction. Based on these findings, no acute hazard labelling is required.

Health effects in animals given repeated doses of etoxazole included effects on the liver and dental abnormalities. Etoxazole did not cause cancer in animals and did not damage genetic material. It did not adversely affect the nervous or immune systems, nor did it affect the ability to reproduce.

When etoxazole was given to pregnant rabbits, minor effects on fetal bone development were observed. These findings occurred at very high doses that also produced toxicity in the mothers. When etoxazole was administered to rats during pregnancy and/or nursing, effects on the juvenile animal (pup deaths) were observed at doses that were not toxic to the mother, suggesting that the young may be more sensitive to etoxazole than the adult animal.

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

**Residues in Water and Food**

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

Chronic non-cancer dietary intake estimates (food alone) revealed that the general population and children 1-2 years old, the subpopulation which would ingest the most etoxazole relative to body weight, are expected to be exposed to less than or equal to 26% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from etoxazole is not of health concern for all population subgroups.

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

Animal studies revealed no acute health effects. Consequently, a single dose of etoxazole 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 adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

MRLs established in Canada for etoxazole may be found using the Maximum Residue Limit Database on the Maximum Residue Limits for Pesticides webpage.

### Occupational Risks From Handling TetraSan 5 WDG Miticide

**Occupational risks are not of concern when TetraSan 5 WDG Miticide is used according to the label directions, which include protective measures.**

Workers who mix, load or apply TetraSan 5 WDG Miticide can come in direct contact with etoxazole residues via the skin or through inhaling spray mists during application. Furthermore, workers re-entering freshly treated greenhouses can come in direct skin contact with etoxazole residues on treated foliage. Therefore, the label specifies that during mixing, loading, application, clean-up and repair, workers must wear a long-sleeved shirt, long pants, shoes, socks and chemical-resistant gloves. The label also requires that workers do not enter treated greenhouses for 12 hours after application. Taking into consideration these label statements, the number of applications, and the expectation of the exposure period for handlers and workers, the occupational health risk to these individuals is not expected to be of concern.

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

## Environmental Considerations

### What Happens When Etoxazole Is Introduced Into the Environment?

**When used according to label directions, etoxazole does not pose an unacceptable risk to the environment.**

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

In Canada, etoxazole is used in greenhouses only and, therefore, will not be released directly into the environment. Should etoxazole enter the environment, it is expected to be broken down easily by soil microorganisms. Etoxazole does not mix readily in water and is immobile in soil, and therefore is not expected to move downward through soil and enter groundwater if it were to enter the environment. Etoxazole is not likely to accumulate to a significant level in animal tissue.

Etoxazole is used as a foliar spray for control of pests on greenhouse grown tomato and ornamental plants, and therefore beneficial arthropods and pollinators, which may be used for greenhouse pest management and pollination, could be exposed to spray droplets or residues

through contact or oral exposure. Etoxazole is not expected to pose an acute risk to adult worker bees or adult beneficial arthropods through direct contact or ingestion. Etoxazole may affect immature life stages of certain beneficial arthropods and bees. However, as a common practice, adult bumble bees are used for pollination and greenhouse hives are not maintained. Therefore exposure of etoxazole to larvae is of negligible concern. Even so, label statements are required to inform users about the potential risk to immature arthropod and bee life stages, and how to reduce this risk. Etoxazole is toxic to aquatic invertebrates and fish, therefore, label statements prohibiting release of untreated greenhouse effluent directly into aquatic systems will be included.

## Value Considerations

### What Is the Value of TetraSan 5 WDG Miticide?

**Foliar application of TetraSan 5 WDG Miticide controls Lewis mite, twospotted spider mite, carmine mite and European red mite on greenhouse ornamentals and twospotted spider mite and carmine mite on greenhouse tomatoes.**

TetraSan 5 WDG Miticide has value for control of spider mites including Lewis mite, twospotted spider mite, carmine mite and European red mite on greenhouse ornamentals, and spider mites including twospotted spider mite and carmine mite on greenhouse tomatoes. Growers have identified etoxazole as a priority for control of mites on greenhouse tomatoes and greenhouse ornamentals. Etoxazole contributes to resistance management because it is a new mode of action for use against spider mites. It could also be a replacement for some registered alternatives which are being phased out, or which have other limitations such as phytotoxicity.

## 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 TetraSan 5 WDG Miticide 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 etoxazole residues on the skin or through inhalation of spray mists, anyone mixing, loading and applying TetraSan 5 WDG Miticide must wear a long-sleeved shirt, long pants, shoes, socks and chemical-resistant gloves. The label also requires that nobody can enter treated greenhouses for 12 hours after application.

**Environment**

Risk based label statements are required to inform users that etoxazole may affect some species of immature beneficial arthropods. Etoxazole is a mite growth regulator. Based on its mode of action, a precautionary statement regarding potential risk to bee larvae will also be required on the label.

Label statement stating ‘toxic to aquatic organisms’ is required on the label. In addition, statements to prevent aquatic exposure of etoxazole, by prohibiting release of untreated greenhouse effluent directly into aquatic systems, are required on the label.

## Next Steps

Before making a final registration decision on etoxazole, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please 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 etoxazole (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).

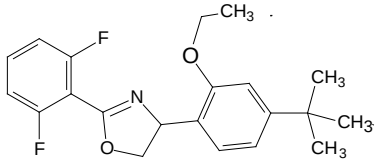
# Science Evaluation

## Etoxazole

Etoxazole has been previously reviewed by the PMRA to establish import maximum residue limits (MRLs). Refer to the Evaluation Reports in Health Canada's Public Registry for application numbers 2008-0581and 2011-2152 for a summary of the previous reviews for etoxazole.

## 1.0 The Active Ingredient, Its Properties and Uses

### 1.1 Identity of the Active Ingredient

| | |
|---|---|
| **Active substance** | Etoxazole |
| **Function** | Acaricide |
| **Chemical name** | |
| **1. International Union of Pure and Applied Chemistry (IUPAC)** | *rac*-(4*R*)-2-(2,6-difluorophenyl)-4-(4-*tert*-butyl-2-ethoxyphenyl)-4,5-dihydro-1,3-oxazole<br>or<br>(*RS*)-5-*tert*-butyl-2-[2-(2,6-difluorophenyl)-4,5-dihydro-1,3-oxazol-4-yl]phenetole |
| **2. Chemical Abstracts Service (CAS)** | 2-(2,6-difluorophenyl)-4-[4-(1,1-dimethylethyl)-2-ethoxyphenyl]-4,5-dihydrooxazole |
| **CAS number** | 153233-91-1 |
| **Molecular formula** | $C_{21}H_{23}F_2NO_2$ |
| **Molecular weight** | 359.4 |
| **Structural formula** |  |
| **Purity of the active ingredient** | 97.2% |

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

### Technical Product—Etoxazole Technical

| Property | Result |
|---|---|
| Colour and physical state | White powder |
| Odour | Musty odour |
| Melting range | 101.5-102.5°C |
| Boiling point or range | N/A |
| Density at 20°C | 1.2389 (relative density); 0.602 g/cm$^3$ (bulk density) |
| Vapour pressure at 25°C | $7.0 \times 10^{-6}$ Pa |
| Ultraviolet (UV)-visible spectrum | $\lambda_{max}$ (nm) / $\varepsilon$ ($M^{-1}cm^{-1}$)<br>Neutral 220 / 17379<br>272 / 3993<br>275 / 3617<br>Acidic 222.5 / 16670<br>272.5 / 4404<br>278 / 3993<br>Basic 272.5 / 3993<br>278 / 3597 |
| Solubility in water at 20°C | $7.04 \times 10^{-5}$ g/L |
| Solubility in organic solvents at 20°C | Solvent — Solubility (g/L)<br>Acetone — 309<br>1,2-Dichloroethane — 402<br>Ethyl acetate — 249<br>n-Heptane — 18.7<br>Methanol — 104<br>Xylene — 252 |
| *n*-Octanol-water partition coefficient ($K_{ow}$) | log $K_{ow}$ = 5.52 |
| Dissociation constant (p$K_a$) | No measurable p$K_a$ |
| Stability (temperature, metal) | The product is stable for 14 days at 54°C; contact with metals is unlikely during storage and use. |

### End-Use Product— TetraSan 5 WDG Miticide

| Property | Result |
|---|---|
| Colour | Brown |
| Odour | N/A |
| Physical state | Granules |
| Formulation type | Wettable granules (WG) |
| Guarantee | 5% |
| Container material and description | Water-soluble packaging and polyethylene bottles (0-500 g) |
| Bulk density at 20°C | 0.630-0.676 g/cm$^3$ |
| pH of 1% dispersion in water | 6.43-6.69 |
| Oxidizing or reducing action | No oxidizing/reducing action |

| Property | Result |
|---|---|
| Storage stability | The product is stable for one year when stored under warehouse conditions in water-soluble bags contained within moisture occlusive foil/film bags and in polyethylene bottles with polypropylene closures. |
| Corrosion characteristics | The product is non-corrosive to the packaging material. |
| Explodability | The product does not contain any components which are explosive. |

### 1.3 Directions for Use

TetraSan 5 WDG Miticide is to be applied at 600-1200 g/1000 L (30-60 g a.i./1000 L) on greenhouse tomatoes and greenhouse ornamentals except those grown for cut flowers. TetraSan 5 WDG Miticide is to be applied at 600 g/1000 L (30 g a.i./1000 L) on greenhouse ornamentals grown for cut flowers. Two applications per crop cycle may be made on greenhouse ornamentals except those grown for cut flowers, for which only one application is permitted. Two applications per crop cycle may be made on greenhouse tomatoes only if the amount of product applied per hectare in each application is 95 g a.i./ha or less. Because the application rate is expressed on the label as a concentration (i.e., g a.i./1000L), the spray volume must be calculated so that the maximum amount of product per hectare for greenhouse tomatoes (i.e. 95 g a.i./ha) is not exceeded.

The first application should be made at the first sign of infestation and before large numbers of adult mites are present. If permitted, a second may be made if necessary, no sooner than 14 days after the first application for greenhouse ornamentals (except cut flowers) and 21 days after the first application for greenhouse tomatoes. When a rate range is permitted, higher rates should be used for moderate to heavy infestations, especially with dense plant canopies. If rapid control (<7 days) of adult mites is required, the product should be applied in combination with a registered contact adulticide.

### 1.4 Mode of Action

Etoxazole is a mite growth regulator belonging to Mode of Action (MOA) class 10B, Mite Growth Inhibitors. Like other mite growth regulators, it does not cause adult mortality, but it does affect juveniles and eggs. Etoxazole disrupts chitin biosynthesis, therefore preventing treated juvenile mites from successfully moulting, and preventing treated eggs from hatching. Treated adult females lay significantly fewer viable eggs.

## 2.0 Methods of Analysis

### 2.1 Methods for Analysis of the Active Ingredient

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

### 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

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

Residues in plant and animal foodstuffs were previously reviewed. The methods provided for the analysis of the active ingredient and the impurities in Etoxazole Technical have been validated and assessed to be acceptable.

## 3.0 Impact on Human and Animal Health

### 3.1 Toxicology Summary

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

Technical etoxazole was of low acute toxicity to rats and mice via the oral route of exposure. In rats it was of low acute toxicity via the dermal route and of slight acute toxicity by inhalation exposure. It was non-irritating to the eyes and skin of rabbits and was not a skin sensitizer when tested in guinea pigs using the Maximization method.

TetraSan 5 WDG Miticide was of low acute toxicity to rats via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eyes and skin of rabbits and was not a skin sensitizer when tested in guinea pigs using the Buehler method.

Subsequent to the establishment of MRLs, additional toxicology studies were submitted to support the Canadian registration and use of etoxazole in Canada. A summary of the findings of these additional studies is provided below.

In a rat short-term dermal toxicity study, no signs of systemic toxicity or irritation were noted up to the limit dose of 1000 mg/kg bw/day. A repeated-exposure inhalation toxicity study was not conducted with etoxazole. A waiver for this data requirement for the petitioned uses was accepted on the basis of the low volatility of etoxazole (vapour pressure of $7.0 \times 10^{-6}$ Pa at 25 ºC) and the margins of exposure calculated when using a toxicological endpoint from an oral toxicity study. A repeated exposure inhalation study may be required for future use expansion of etoxazole.

In the rat acute neurotoxicity study conducted via oral gavage, there were no clinical signs of toxicity or neuropathological findings. Following repeated dietary administration in rats, there were no clinical or pathological findings indicative of neurotoxicity.

A rat 28-day dietary immunotoxicity study was conducted in which serum IgM responses following immunization with antigen SRBC were measured. There was no evidence of a disregulation of the immunologic response in this study.

Overall, on the basis of the findings in the toxicology database, etoxazole was not genotoxic or carcinogenic. Etoxazole did not adversely affect immune function or produce neurotoxicity. There was no effect on reproductive performance. There was no evidence of increased susceptibility of the young in the developmental toxicity studies, but serious effects in offspring occurred in the absence of significant toxicity in parental animals in the reproductive toxicity study. In short-term and chronic studies on laboratory animals, the primary target was the liver, with dental abnormalities also observed in rodents.

The Evaluation Report for Etoxazole Technical submission number 2008-0581 contains an error with regards to the offspring NOAEL (no observed adverse effect level) reported in the 2-generation dietary reproductive toxicity study in the rat. The correct offspring NOAEL is 33.4 mg/kg bw/day and the correct offspring LOAEL (lowest observed adverse effect level) is 159 mg/kg bw/day. The updated toxicology entry for this study has been included in the current document in Appendix 1, Table 3. Results of the amended and newly submitted toxicology studies conducted on laboratory animals with etoxazole and the associated end-use product are summarized in Appendix I, Tables 2 and 3. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 4.

**Incident Reports**

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Incidents were searched for the active ingredient etoxazole. Etoxazole is a new active ingredient pending registration for use in Canada. No human or domestic animal incidents involving the active ingredient etoxazole have been reported to the PMRA and the applicant did not submit any additional data.

### 3.1.1 *Pest Control Products Act* Hazard Characterization

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

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

With respect to potential prenatal toxicity, there was no indication of increased susceptibility of fetuses compared to maternal animals in the developmental toxicity studies in rats and rabbits. In the rat developmental toxicity study, there were no signs of toxicity noted in fetuses at a dose level producing decreased food consumption and body weight gain in maternal animals. In the rabbit developmental toxicity study, skeletal variations (increased fetal and litter incidences of $27^{th}$ pre-sacral vertebra and $27^{th}$ presacral vertebra with a $13^{th}$ rib) were observed in fetuses in the presence of effects on the maternal animal, as characterized by body weight loss, reductions in body weight gain and liver enlargement. In the rat reproductive toxicity study, reduced pup viability was observed on post natal days (PND) 0-4 at a dose that did not result in evidence of maternal toxicity. Overall, the database is adequate for determining sensitivity of the young, and effects on the young are well characterized. The serious endpoint of reduced pup viability in the rat reproductive toxicity study was observed in the absence of maternal toxicity. On the basis of this information the full 10-fold *Pest Control Products Act* factor was retained when using this endpoint to establish the point of departure for assessing risk for exposure scenarios.

### 3.2 Acute Reference Dose (ARfD)

Not required as there were no effects attributable to a single dose.

### 3.3 Acceptable Daily Intake (ADI)

To estimate risk from repeated dietary exposure, the offspring NOAEL of 33.4 mg/kg bw/day from the 2-generation rat reproductive toxicity study was selected for risk assessment. At the LOAEL of 159 mg/kg bw/day, an increased incidence of pup deaths between PND 0 and 4 and a reduced viability index were observed in the absence of maternal toxicity.

Although the one-year dog study yielded the lowest NOAEL of the database (4.6 mg/kg bw/day), it was not considered to be appropriate for the determination of the ADI since it would not be protective of the critical endpoint of concern, i.e., reduced offspring viability, following the application of the required *Pest Control Products Act* factor.

Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the 10-fold *Pest Control Products Act* factor was retained. **The composite assessment factor (CAF) is thus 1000.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{33.4 \text{ mg/kg bw/day}}{1000} = 0.03 \text{ mg/kg bw/day of etoxazole}$$

The ADI provides a margin of 164 to the lowest NOAEL in the database (4.6 mg/kg bw/day in the one-year dog study), a margin of greater than 4000 to the NOAEL (64 mg/kg bw/day) for dental abnormalities in the rat, and a margin of greater than 13,000 to the NOAEL (200 mg/kg bw/day) for skeletal variations in the rabbit developmental toxicity study.

**Cancer Assessment**

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

## 3.4 Occupational and Residential Risk Assessment

### 3.4.1 Toxicological Endpoints

Occupational exposure to etoxazole is characterized as short-, intermediate- or long-term and is predominantly by the dermal and inhalation routes.

**Dermal (all durations)**

For short-, intermediate- and long-term occupational exposures via the dermal route, the offspring NOAEL of 33.4 mg/kg bw/day from the 2-generation dietary rat reproductive toxicity study was selected for risk assessment. At 159 mg/kg bw/day, an increased incidence of pup deaths between PND 0 and 4 and a reduced viability index were observed in the absence of maternal toxicity. Worker populations could include pregnant or lactating women and, therefore, these endpoints were considered appropriate for the occupational risk assessment. The short-term dermal toxicity study did not address the relevant endpoint of concern, i.e. reduced viability, thus, necessitating the use of an oral study for risk assessment.

The target margin of exposure (MOE) is 1000. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. In light of concerns regarding offspring toxicity (as outlined in the *Pest Control Products Act* Hazard Characterization section), an additional 10-fold factor was applied for this endpoint. 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.

**Inhalation (all durations)**

For short-, intermediate- and long-term occupational exposures via the inhalation route, the offspring NOAEL of 33.4 mg/kg bw/day from the 2-generation dietary rat reproductive toxicity study was selected for risk assessment. At 159 mg/kg bw/day, an increased incidence of pup deaths between PND 0 and 4 and a reduced viability index was observed in the absence of maternal toxicity. Worker populations could include pregnant or lactating women and, therefore, these endpoints were considered appropriate for the occupational risk assessment. A repeat-dose inhalation toxicity study was not available and, thus, use of a NOAEL from an oral study was appropriate.

The MOE is 1000. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. In light of concerns regarding offspring toxicity (as outlined in the *Pest Control Products Act* Hazard Characterization section), an additional 10-fold factor was applied for this endpoint. 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

Chemical-specific data for dermal absorption of etoxazole were not submitted. Based on a weight-of-evidence approach including considerations of the physical/chemical properties of etoxazole (low solubility in water at physiological pH and high log $K_{ow}$), as well as supporting data from dermal toxicity studies for etoxazole, and information from a structurally-related chemical, a refined dermal absorption value of 50% is supported.

### 3.4.2 Occupational Exposure and Risk

Workers who mix, load and apply TetraSan 5 WDG Miticide in greenhouses are expected to have short- to intermediate-term exposure since the product is applied once or twice per crop cycle. Workers entering treated greenhouses to perform routine re-entry activities are expected to have long-term exposure since dissipation in an indoor environment is expected to be slow, and there is the potential for exposure throughout the duration of the crop cycle.

#### 3.4.2.1 Mixer/Loader/Applicator Exposure and Risk Assessment

Individuals have potential for exposure to etoxazole during mixing, loading and application. Exposure to workers mixing, loading and applying TetraSan 5 WDG Miticide is expected to be short- to intermediate-term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixers/loaders/applicators applying TetraSan 5 WDG Miticide to tomatoes and ornamentals in greenhouses using a backpack sprayer, spray cart with low pressure handwand, or high volume spraying. The exposure estimates are based on mixers/loaders/applicators wearing a long-sleeved shirt, long pants, shoes, socks and chemical-resistant gloves. Exposure estimates were also derived for mixers/loaders handling water-soluble packets, wearing the same personal protective equipment, and using an automated stationary mist blower for application.

Dermal and inhalation exposures for workers involved with mixing, loading and applying in greenhouses were estimated using the Pesticide Handlers Exposure Database (PHED), version 1.1. Since there are no data available for the mixer/loader/applicator exposure of wettable granules in water-soluble packaging, the calculated exposure values are based on liquid formulations applied by low pressure handwand, high pressure handwand and backpack sprayers. This assessment is not expected to result in an underestimation, since the mixer/loader exposure is expected to be lower for water-soluble packets than for liquid.

Dermal exposure was estimated by using the unit exposure values with the amount of product handled per day and the dermal absorption value of 50%. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (NOAEL) to obtain the MOE; the target MOE is 1000 for both dermal and inhalation risk. Table 3.4.2.1.1 presents the estimates of exposure and risk for workers mixing/loading and applying TetraSan 5 WDG Miticide. The combined MOEs were all above 1000. No health risks of concern are expected when workers follow the recommended precautions on the product label.

**Table 3.4.2.1.1 Mixer/Loader/Applicator Risk Assessment for TetraSan 5 WDG Miticide for Workers Wearing a Single Layer and Chemical-Resistant Gloves.**

| Exposure scenario/ Application method | PHED unit exposure[1] (µg/kg a.i. handled) | Maximum concentration (g a.i./L) | VTPD[2] (L/day) | Daily Exposure[3] (mg/kg bw/day) | Combined MOE[4] |
|---|---|---|---|---|---|
| **Water-soluble packet formulation at the maximum concentration of 60 g a.i./1000L applied at the maximum spray volume of 1870 L/ha (applicator exposure is negligible when applied by automated stationary mistblower).** | | | | | |
| Closed mix/load; Application by automated stationary mistblower | 10.99 | 0.06 | 5610 | $4.62 \times 10^{-5}$ | 722312 |
| **Liquid formulation at the maximum concentration of 60 g a.i./1000L applied at the maximum spray volume of 1870 L/ha. (Tetrasan 5 WDG Miticide is a water-dispersible granule formulation packaged as water-soluble packets; therefore, the mixer/loader exposure is expected to be lower than that for liquid.)** | | | | | |
| Manually-pressurized handwand | 516.89 | 0.06 | 150 | $5.81 \times 10^{-5}$ | 574381 |
| Mechanically-pressurized handwand | 2943.75 | 0.06 | 3800 | $8.39 \times 10^{-3}$ | 3981 |
| Backpack | 2785.03 | 0.06 | 150 | $3.13 \times 10^{-4}$ | 106602 |

[1] PHED unit exposures: Combined = (50% Dermal) + Inhalation;
Light inhalation rate for manually- or mechanically-pressurized handwand; moderate inhalation rate for backpack
[2] Volume treated per day (VTPD) values from Default Area Treated per day tables (2010)
For the automated stationary mistblower, VTPD calculated considering a maximum spray volume of 1870 L/ha and an average greenhouse area of three hectares
[3] Daily exposure = (PHED unit exposure × VTPD × Concentration × $10^{-3}$ kg/g) / (80 kg bw × 1000 µg/mg)
[4] MOE = NOAEL / Exposure. Based on dermal and inhalation NOAEL = 33.4 mg/kg bw/day (target MOE = 1000).

### 3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with TetraSan 5 WDG Miticide to perform various activities including hand pruning, hand harvesting and debudding. Given the nature of activities performed, dermal contact with treated surfaces could occur throughout the crop cycle. The duration of exposure is considered to be long-term since the dissipation of residues is expected to be slow in an indoor environment, and the primary route of exposure for workers re-entering treated areas would be through dermal exposure. Inhalation exposure is not expected to occur since workers and bystanders are not allowed to enter until 12 hours after application, and etoxazole is non-volatile according to NAFTA criteria. The vapour pressure of etoxazole is estimated to be $7.0 \times 10^{-6}$ Pa at 20°C, which is less than the NAFTA waiver for an inhalation study of $<1 \times 10^{-5}$ kPa at 20-30°C for indoor use. As such, inhalation exposure is not considered to be a significant route of exposure for people entering treated areas compared to the dermal route.

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

Exposure estimates were compared to the toxicological endpoint to obtain the MOE; the target MOE is 1000. No health risks of concern were identified when workers re-enter treated greenhouses 12 hours after application.

**Table 3.4.2.2.1 Postapplication Exposure and Risk Estimates for Etoxazole on Day 0 After the Last Application**

| Crop/Activity | Rate/Appl (g a.i./ha) | # of appl per crop cycle | Retreatment Interval (days) | Peak DFR[1] (µg/cm$^2$) | TC[2] (cm$^2$/hr) | Dermal exposure[3] (mg/kg bw/day) | MOE[4] |
|---|---|---|---|---|---|---|---|
| GH Ornamentals except cut flowers | 112.2 | 2 | 14 | 0.5610 | 230 | 0.0065 | 5177 |
| GH Cut Flowers | 56.1 | 1 | N/A | 0.1403 | 4000 | 0.0281 | 1191 |
| GH Tomatoes | 95.0 | 2 | 21 | 0.4750 | 1400 | 0.0332 | 1005 |
| | 112.2 | 1 | N/A | 0.2805 | 1400 | 0.0196 | 1701 |

[1] Calculated using the default 25% dislodgeable on the day of application and 0% dissipation per day for greenhouses
[2] Transfer coefficients obtained from ARTF
[3] Exposure = (Peak DFR [µg/cm$^2$] × TC [cm$^2$/hr] × 8 hours × 50% dermal absorption) / (80 kg bw × 1000 µg/mg)
[4] Based on a NOAEL of 33.4 mg/kg bw/day, target MOE = 1000
GH = Greenhouse, N/A = Not applicable, TC = Transfer coefficient, DFR = Dislodgeable foliar residue
Minimum restricted entry interval is 12 hours to allow residues to dry.

### 3.4.3 Residential Exposure and Risk Assessment

There are no residential uses for TetraSan 5 WDG Miticide and, as such, a residential risk assessment was not required.

#### 3.4.3.1 Bystander Exposure and Risk

Bystanders are not expected to be inside greenhouses while treatments occur; therefore, exposures are not expected for bystanders. Application is limited by label statements which state that only protected handlers may be in the area during application, and that the product must not be applied in a way that will contact workers or other persons, either directly or through drift.

## 3.5 Food Residues Exposure Assessment

### 3.5.1 Residues in Plant and Animal Foodstuffs

The previously reviewed residue trials with etoxazole on greenhouse tomatoes are sufficient to support the Canadian registration and use of TetraSan 5 WDG Miticide on greenhouse tomatoes. Residues of etoxazole in/on tomatoes treated according to the approved label for TetraSan 5 WDG Miticide will be covered under the MRL of 0.2 ppm for etoxazole in/on tomatoes. No tomato processing study is needed as the proposed use is only for greenhouse-grown tomatoes, which are predominantly utilized for the fresh market.

### 3.5.2 Dietary Risk Assessment

A chronic non-cancer dietary risk assessment was conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 3.16, 03-08-d) program which incorporates food consumption data from the National Health and Nutritional Examination Survey, What We Eat in America (NHANES/ WWEIA) dietary survey for the years 2003-2008 available through CDC's National Center for Health Statistics (NCHS).

The assessment was conducted for food alone, as there is no expectation of extoxazole residues in drinking water based on the approved uses of TetraSan 5 WDG Miticide on greenhouse tomatoes and greenhouse ornamentals.

#### 3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic non-cancer analysis (food alone) for etoxazole: 100% crop treated, Canadian MRLs, American tolerances and default processing factors. Codex MRLs were also used as input values for imported citrus crops that had no corresponding Canadian MRL or American tolerance. The basic chronic dietary exposure from all supported etoxazole food uses for the total population, including infants and children, and all representative population subgroups is less than or equal to 26% of the ADI. Exposure from food is considered acceptable. The PMRA estimates that chronic dietary exposure to etoxazole from food is 6% (0.002 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 years old at 26% (0.008 mg/kg bw/day) of the ADI.

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

#### 3.5.2.2 Acute Dietary Exposure Results and Characterization

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

### 3.5.3 Aggregate Exposure and Risk

There is no aggregate risk for etoxazole as exposure is from food only and there are no residential uses.

### 3.5.4 Maximum Residue Limits

MRLs established in Canada for etoxazole may be found using the Maximum Residue Limit Database on the Maximum Residue Limits for Pesticides webpage. Residues of etoxazole in/on greenhouse tomatoes treated according to the approved label for TetraSan 5 WDG Miticide will be covered under the currently established MRL of 0.2 ppm for etoxazole in/on tomatoes.

## 4.0 Impact on the Environment

### 4.1 Fate and Behaviour in the Environment

Based on physico-chemical properties, etoxazole is insoluble in water, is not likely to volatilize from moist soil or water surfaces under environmental conditions, and it has low potential for long-range transport in the atmosphere.

Etoxazole is non-persistent to slightly persistent in aerobic soils, with half-lives ranging between 12 and 23 days. The primary dissipation route of etoxazole is aerobic biotransformation, forming $CO_2$ and three other major transformation products: 2-amino-2-(4-*tert*-butyl-2-ethoxyphenyl) 2',6'-difluorobenzoate (R7), 2-amino-2-(4-*tert*-butyl-2-ethoxyphenyl)ethanol (R-8) and 5-*tert*-butyl-2-[2-(2,6-difluorophenyl)-1,3-oxazol-4-yl]phenetole (R-13). All of them exhibited declining trends over time during laboratory studies. Etoxazole may undergo hydrolysis at an appreciable rate under acidic conditions but at a much slower rate under neutral to alkali conditions.

Etoxazole sorbs strongly to soil constituents. It is considered immobile in soils and is a non-leacher based on criteria that considers persistence (aerobic soil biotransformation half-lives) and organic-carbon partition coefficients ($K_{oc}$).

Its low water solubility (0.07 mg/L) and high log $K_{ow}$ (5.52) indicate a potential for etoxazole to bioaccumulate. However, information shows that in a bluegill bioaccumulation study, etoxazole depurated rather quickly with half-lives of 3-6 days and the bioaccumulation factor (BCF) was 1300-1500. Therefore, the potential for bioaccumulation is much lower than that predicted by its chemical properties.

A summary of environmental fate data is presented in Appendix I, Table 6.

### 4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. The estimated environmental exposure concentration (EEC) is calculated based on the maximum application rates of 2 × 112 g a.i./ha with a 14-day interval and a half-life of 22.8 days (the longer of the two available values). Relevant ecotoxicology information includes toxicity data for pollinators and beneficial arthropods as they are commonly used in greenhouse production as a component of the integrated pest management (IPM) program. As such, the primary focus of the risk assessment is on potential effects to these organisms.

Environmental risk is characterized using the risk quotient (RQ) method which is the ratio of the EEC ÷ toxicity endpoint. For characterizing acute risk, acute toxicity values (for example, $LC_{50}$, $LD_{50}$, and $EC_{50}$) are divided by an uncertainty factor to account for differences in inter- and intra-species sensitivity as well as varying protection goals (for example, community, population, individual). Thus, the magnitude of the uncertainty factor depends on the group of organisms that are being evaluated (for example, ten for fish, two for aquatic invertebrates). The difference in value of the uncertainty factors reflects, in part, the ability of certain organisms at a certain trophic level (i.e. feeding position in a food chain) to withstand, or recover from, a stressor at the level of the population. The risk quotient is then compared to the level of concern (LOC). When a RQ exceeds LOC, mitigation measures are required.

### 4.2.1 Risks to Terrestrial Organisms

Risk of etoxazole and the end-use product TetraSan 5 WDG Miticide, containing 5% etoxazole, to terrestrial organisms was assessed based on evaluation of toxicity data for bees and arthropods as they are the primary concern for greenhouse production.

**Terrestrial invertebrates**

**Honeybees**

Effects of etoxazole on honeybees were studies with the technical for both acute contact and oral exposure. Following 48 hours of exposure, the mortality observed at an exposure rate of 200 µg a.i./bee was not different when compared to the controls.

When used in greenhouses for pollination, bees could be exposed to residues of etoxazole as a result of direct application, contact with residues, or ingestion of residues on food sources. Using the maximum single application rate of 112 g a.i./ha and a $LD_{50}$ of > 200 µg a.i./bee on an acute oral and contact basis, no risk is expected for adult bees exposed through either oral or contact exposure to etoxazole (Appendix I, Table 8).

As etoxazole is a mite growth regulator, there is a potential risk to brood. However, as a common practice, adult bumble bees are used for pollination and greenhouse hives are not maintained. Therefore, exposure of etoxazole to larvae is of negligible concern. Even so, a precautionary statement will be required on the label to indicate the potential risk to larvae, as a grower may choose to maintain bee hives for greenhouse pollination.

**Predators and parasites (beneficial arthropods)**

Laboratory studies were conducted with several species of beneficial arthropods at various life stages including eggs, larvae, nymph and adult (Appendix I, Table 7). Exposure to etoxazole at 55 g a.i./ha did not result in significant mortality (0-10%) for adults of all species tested; however, it had adverse effects on mortality and fecundity to all immature stages of test organisms, with the exception of parasitic wasp. Two additional studies conducted in vineyards where predatory mites (*Typhlodromus pyri*) were present showed that etoxazole resulted in decline in population density by 16.5-62.6%.

Although these studies were scientifically sound, they were not conducted in accordance with either OECD or OCSPPs guidelines and no endpoints can be derived. Consequently, quantitative risk assessment cannot be performed. However, based on the observed adverse effects to immature beneficial arthropods and considering that the adverse effects were observed at an application rate much lower than the maximum application rate for use in greenhouse in Canada, a potential risk was identified for beneficial arthropods. Therefore, statements will be required on the label to indicate the potential risk to beneficial arthropods that may be used in greenhouse production.

**Birds and mammals**

Based on the submitted information, etoxazole is practically non-toxic to birds and small wild mammals. The reported acute oral $LD_{50}$ for mallard duck was > 2000 mg a.i./kg and the acute dietary $LC_{50}$ for northern bobwhite and mallard duck was > 5200 mg a.i./kg diet, the highest doses tested. The reported acute oral $LD_{50}$ for rats was 4274 mg/kg body weight. Furthermore, there is a negligible potential exposure to birds and mammals since the product is only for use in greenhouses. Therefore, the use of etoxazole in greenhouse will not result in unacceptable risk to birds and mammals.

### 4.2.2 Risks to Aquatic Organisms

Based on the submitted information, etoxazole is very highly toxic to aquatic invertebrates (*daphnia magna* 48-hour acute $EC_{50}$ = 7.1 µg a.i./L) and moderately toxic to fresh water fish (rainbow trout $LC_{50}$ = 2.8 mg a.i./L, bluegill $LC_{50}$ = 1.4 mg a.i./L). However, considering its low solubility in water, immobility in soils and rapid degradation, there is no potential exposure to aquatic organisms through greenhouse uses. Nevertheless, a hazard statement will be required on the label to prevent the release of etoxazole to the aquatic environment through greenhouse effluent discharge.

### 4.2.3 Incident reports / additional considerations

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

Since etoxazole is a new active ingredient pending registration for use in Canada, there are no incident reports. Once products containing etoxazole are registered, the PMRA will monitor for incident reports.

Etoxazole has been registered for use in the United States for over 10 years. The USEPA EIIS database was consulted and it was determined that no environmental incident reports for etoxazole have been reported to the USEPA over this time period.

# 5.0 Value

## 5.1 Consideration of Benefits

Registration of etoxazole addresses grower priorities listed on the Canadian Grower Priority Database for control of mites on greenhouse tomatoes and greenhouse ornamentals. Etoxazole also represents a new MOA for use against mites in the greenhouse and, thus, can be useful for resistance management. Because of mites' short life cycle, they acquire resistance quickly and, therefore, it is important to have a variety of rotational partners from different MOA groups. Thus, although there are many registered alternative active ingredients, registration of etoxazole has value to greenhouse growers as part of an IPM program for mites.

Alternative active ingredients registered for control of mites on greenhouse ornamentals comprise members of MOA groups 1B (dichlorvos, naled, malathion), 6 (abamectin), 12 (fenbutatin oxide), 20B (acequinocyl), 21A (pyridaben), 23 (spiromesifen) and 25 (bifenazate), as well as potassium salts of fatty acids (not classified into any MOA group). Alternative active ingredients registered for control of mites on greenhouse tomatoes comprise members of MOA groups 1B (naled), 6 (abamectin), 12 (fenbutatin oxide), 20B (acequinocyl), 21A (pyridaben), 23 (spiromesifen) and 25 (bifenazate), as well as potassium salts of fatty acids (not classified into any MOA group).

Certain limitations have been noted with some of the registered alternatives. Use of malathion on some greenhouse ornamentals and some application types on greenhouse ornamentals will be phased out (RVD2012-10, *Malathion*); use of endosulfan is no longer permitted on greenhouse tomato and will not be permitted on greenhouse ornamentals from 31 December 2016 (REV2011-01, *Discontinuation of Endosulfan*); potassium salts of fatty acids have a short period of residual efficacy and phytotoxicity concerns on certain plants; and fenbutatin oxide is not used on greenhouse tomatoes due to lack of a U.S. tolerance on tomatoes. Etoxazole would be a replacement for these uses.

Etoxazole belongs to MOA subgroup 10B, a new MOA subgroup in Canada. Cross-resistance to subgroup 10A miticides has been reported in the US. However, the only subgroup 10A active ingredient registered in Canada, clofentezine (Apollo SC Ovicidal Miticide, Registration Number 21035), is registered for outdoor uses only, and so would not be used on mites in the greenhouse. The Arthropod Pesticide Resistance Database notes that resistance to etoxazole has been observed in twospotted spider mites in South Korea. Resistance management statements are present on the proposed label of TetraSan 5 WDG Miticide. Careful stewardship is required to mitigate the likelihood of target mites developing resistance to etoxazole.

### 5.2 Effectiveness Against Pests

Five greenhouse trials, two field trials, three use history documents, a scientific journal article and pest information were provided and reviewed. The efficacy data demonstrated that the supported rates were effective for control of twospotted spider mite and Lewis mite, and these data were extrapolated to the other two proposed mite species. The data and use histories confirmed that the product is slow-acting, and supported the proposed minimum reapplication intervals. The scientific journal article and field trials supported the claim that the product controls eggs, and the scientific journal article supported the claim that treated adult females produce fewer viable eggs.

### 5.3 Non-Safety Adverse Effects

No phytotoxicity was observed in any of the reviewed efficacy trials.

### 5.4 Supported Uses

TetraSan 5 WDG Miticide is supported for use on greenhouse ornamentals for control of spider mites including Lewis mite, twospotted spider mite, carmine mite and European red mite, and on greenhouse tomatoes for control of spider mites including twospotted spider mite and carmine mite. Details of the supported use pattern are provided in Section 1.3, “Directions For Use”.

## 6.0 Pest Control Product Policy Considerations

### 6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, *i.e.* persistent (in air, soil, water and/or sediment), bioaccumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

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

- Etoxazole does not meet all Track 1 criteria, and is not considered a Track 1 substance. Refer to Appendix I, Table 9 for comparison with Track 1 criteria.

### 6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[5] The list is used as described in the PMRA Notice of Intent NOI2005-01[6] and is based on existing policies and regulations including: DIR99-03,[7] and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Based on the manufacturing 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 technical product etoxazole;

- Based on the formulating processes 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 formulation product TetraSan 5 WDG Miticide.

## 7.0 Summary

### 7.1 Human Health and Safety

The toxicology database submitted for etoxazole is adequate to define the majority of toxic effects that may result from exposure. Etoxazole was not considered to be genotoxic, neurotoxic or immunotoxic and there was no evidence of carcinogenicity in rats or mice after longer-term dosing. There was no effect on reproductive performance. There was no evidence of increased susceptibility of the young in the developmental toxicity studies, but serious effects in offspring occurred in the absence of significant toxicity in parental animals in the reproductive toxicity study.

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

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

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

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

In short-term and chronic studies on laboratory animals, the primary target was the liver, with dental abnormalities also observed in rodents. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixers, loaders and applicators handling TetraSan 5 WDG Miticide and workers re-entering treated greenhouses are not expected to be exposed to levels of etoxazole that will result in health risks of concern when TetraSan 5 WDG Miticide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers while applying TetraSan 5 WDG Miticide to greenhouse ornamentals and greenhouse tomatoes.

The nature of the residues in plants and animals is adequately understood. The approved uses of etoxazole do not constitute a risk of concern for chronic dietary exposure (food alone) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to establish maximum residue limits to protect human health.

### 7.2 Environmental Risk

In Canada, etoxazole is for use in greenhouses only, and therefore, will not be released directly into the environment. When used according to label directions, etoxazole does not pose an unacceptable risk to the environment. Mitigation label statements are required to protect beneficial arthropods and aquatic organisms.

### 7.3 Value

TetraSan 5 WDG Miticide has value for control of spider mites including Lewis mite, twospotted spider mite, carmine mite and European red mite on greenhouse ornamentals, and spider mites including twospotted spider mite and carmine mite on greenhouse tomatoes. The supported uses address grower needs listed on the Canadian Grower Priority Database. Etoxazole contributes to resistance management because it is a new mode of action for use against the supported pests. It could also be a replacement for some registered alternatives which are being phased out, or which have other limitations (for example, phytotoxicity, or lack of a US import tolerance).

## 8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Etoxazole Technical and Tetrasan 5 WDG Miticide, containing the technical grade active ingredient etoxazole, to control spider mites in greenhouse tomatoes and greenhouse ornamentals.

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

| | |
|---|---|
| ↑ | increased |
| ↓ | decreased |
| ♀ | female |
| ♂ | male |
| < | less than |
| > | greater than |
| ≥ | greater than or equal to |
| λ | wavelength |
| ε | emittance |
| ℃ | degrees Celsius |
| µg | microgram(s) |
| a.i. | active ingredient |
| ADI | acceptable daily intake |
| appl | application |
| ARfD | acute reference dose |
| ARTF | Agricultural Re-entry Task Force |
| atm | atmosphere |
| BAF | bioaccumulation factor |
| BCF | bioconcentration factor |
| bw | body weight |
| CAF | composite assessment factor |
| CAS | Chemical Abstracts Service |
| CDC | Centers for Disease Control and Prevention |
| CEPA | *Canadian Environmental Protection Act* |
| cm | centimetre(s) |
| $cm^2$ | centimetre(s) squared |
| $cm^3$ | centimetre(s) cubed |
| DAT | days after treatment |
| DEEM-FCID | Dietary Exposure Evaluation Model – Food Commodity Intake Database |
| DFR | dislodgeable foliar residue |
| $EC_{50}$ | effective concentration on 50% of the population |
| EEC | estimated environmental concentration |
| EIIS | USEPA Ecological Incident Information System |
| ELISA | enzyme-linked immunosorbent assay |
| fc | food consumption |
| FDA | *Food and Drugs Act* |
| g | gram(s) |
| GC-MS | Gas chromatography with mass spectrometry |
| GH | greenhouse |
| GUS | groundwater ubiquity score |
| ha | hectare(s) |
| HPLC-MS/MS | high performance liquid chromatography with tandem mass spectrometry |
| hr | hour(s) |
| ID | Identification |
| IgM | immunoglobulin M |

| | |
|---|---|
| IPM | Integrated Pest Management |
| IUPAC | International Union of Pure and Applied Chemistry |
| kg | kilogram(s) |
| $K_d$ | soil-water partition coefficient |
| $K_{oc}$ | organic-carbon partition coefficient |
| $K_{ow}$ | *n*–octanol-water partition coefficient |
| kPa | kilopascal(s) |
| L | litre(s) |
| $LC_{50}$ | lethal concentration 50% |
| $LD_{50}$ | lethal dose 50% |
| LOAEL | lowest observed adverse effect level |
| LOC | level of concern |
| LOQ | limit of quantitation |
| $m^3$ | metre(s) cubed |
| M | molar concentration (mol/L) |
| MAS | maximum average score |
| mg | milligram(s) |
| MIS | maximum irritation score |
| MOA | mode of action |
| MOE | margin of exposure |
| mol | mole(s) |
| MRL | maximum residue limit |
| MS | mass spectrometry |
| m/z | mass-to-charge ratio of an ion |
| N/A | not applicable |
| NAFTA | *North American Free Trade Agreement* |
| NCHS | National Center for Health Statistics |
| NHANES/WWEIA | National Health and Nutritional Examination Survey, What We Eat in America |
| nm | nanometre(s) |
| NOAEL | no observed adverse effect level |
| NZW | New Zealand white |
| OECD | *Organization of Economic Corporation and Development* |
| OCSPP | USEPA Office of Chemical Safety and Pollution Prevention |
| Pa | Pascal |
| PHED | Pesticide Handlers Exposure Database |
| p*K*a | dissociation constant |
| PMRA | Pest Management Regulatory Agency |
| PND | post natal day |
| ppm | parts per million |
| rel | relative |
| RQ | risk quotient |
| SRBC | sheep red blood cells |
| TC | transfer coefficient |
| TSMP | Toxic Substances Management Policy |
| USEPA | United States Environmental Protection Agency |
| UV | ultraviolet |

| | |
|---|---|
| WDG | wettable dispersible granule |
| WG | wettable granules |
| VTPD | volume treated per day |

# Appendix I Tables and Figures

## Table 1 Residue Analysis

| Matrix | Method ID | Analyte | Method Type | LOQ | Reference |
|---|---|---|---|---|---|
| Soil | RM-37S-2 | Etoxazole | GC-MS 359.3 m/z | 0.02 ppm | 2401614 |
| | | R3 | 361.0 m/z | | 2401616 |
| | | R13 | 342.0 m/z | | |
| | RM-37SM | R4 | HPLC-MS/MS $EI^+$ 377.8 → 220.9 | 0.02 ppm | 2401615 |
| | | R7 | 377.8 → 360.9 | | 2401617 |
| | | R8 | 237.9 → 220.9 | | |
| | | R11 | HPLC-MS/MS $EI^+$ 156.9 → 113.1 | | |

R3: *N*-(2,6-difluorobenzoyl)-4-*tert*-butyl-2-ethoxybenzamide
R4: *N*-[1-(4-*tert*-butyl-2-ethoxyphenyl)-2-hydroxyethyl]-2,6-difluorobenzamide
R7: 2-amino-2-(4-*tert*-butyl-2-ethoxyphenyl)ethyl 2',6'-difluorobenzoate
R8: 2-amino-2-(4-tert-butyl-2-ethoxyphenyl)ethanol
R11: 2,6-difluorobenzoic acid
R13: 5-*tert*-butyl-2-[2-(2,6-difluorophenyl)-1,3-oxazol-4-yl]phenetole

## Table 2 Toxicity Profile of TetraSan 5 WDG (5% Etoxazole)

**(**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<br><br>Sprague-Dawley rat<br><br>PMRA #2402390 | $LD_{50}$ ♂ ≥ 4507 mg/kg bw<br>♀ ≥ 2567 mg/kg bw<br>♂♀ ≥ 4274 mg/kg bw<br><br>Low toxicity.<br><br>Clinical signs (observed in a dose-related frequency with increasing dose): death, irregular gait, laboured breathing; anogenital staining, red-staining of the snout and extremities, hunched appearance, rales, ↓ fc and fecal volume, unformed stool (♂); excessive salivation or lacrimation, watery stool (♀) |
| Acute dermal toxicity<br><br>Sprague-Dawley rat<br><br>PMRA #2402391 | $LD_{50}$ ≥ 5000 mg/kg bw<br><br>Low toxicity.<br><br>Clinical signs: red stains on snout and extremities (♀) |
| Acute inhalation toxicity (nose-only)<br><br>Sprague-Dawley rat<br><br>PMRA #2402393 | $LC_{50}$ ≥ 2.05 mg/L<br><br>Low toxicity.<br><br>Clinical signs: excessive salivation, clear nasal discharge, red nasal discharge, dried red material on the facial area, laboured breathing, rales; death (♂). |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Dermal irritation<br><br>NZW rabbit<br><br>PMRA #2402396 | MAS = 0.2, MIS = 1.3 (at one hour)<br>All scores 0 at 48 hours.<br><br>Minimally irritating. |
| Eye irritation<br><br>NZW rabbit<br><br>PMRA #2402395 | MAS = 2.2, MIS = 4.7 (at one hour)<br>All scores 0 at 72 hours.<br><br>Minimally irritating. |
| Dermal sensitization<br>(Modified Buehler test)<br><br>Hartley guinea pig<br><br>PMRA #2402398 | Non-sensitizer. |

## Table 3 Toxicity Profile of Technical Etoxazole – Amended and Newly Submitted Studies

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

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Acute dermal toxicity<br><br>Sprague-Dawley rat<br><br>PMRA #1550986 | $LD_{50}$ > 2000 mg/kg bw<br><br>Low toxicity.<br><br>No clinical signs of toxicity observed. |
| Acute inhalation toxicity<br>(nose-only)<br><br>Fischer rat<br><br>PMRA #1550987 | $LC_{50} \geq 1.04$ mg/L<br><br>Slight toxicity.<br><br>Clinical signs: reddish adhesive material on nasal region. |
| Dermal irritation<br><br>NZW rabbit<br><br>PMRA #1550989 | MAS = 0, MIS = 0<br><br>Non-irritating. |
| Eye irritation<br><br>NZW rabbit<br><br>PMRA #1550988 | MAS = 0, MIS = 6.3 (at one hour)<br>All scores 0 at 24 hours.<br><br>Non-irritating. |

| | |
|---|---|
| Dermal sensitization (Maximization Method)<br><br>Hartley guinea pig<br><br>PMRA #1550990 | Non-sensitizer. |
| 28-day dermal toxicity<br><br>Sprague-Dawley rat<br><br>PMRA#1551004 | NOAEL = 1000 mg/kg bw/day<br><br>LOAEL = Not established. No adverse effects observed at the highest dose tested (limit dose of 1000 mg/kg bw/day). |
| 90-day inhalation toxicity<br><br>Waiver rationale<br><br>PMRA# 2401598 | Waiver request granted for current submission only based on low volatility and margins of exposure. |
| Reproductive toxicity (diet)<br><br>Sprague-Dawley rat<br><br>PMRA#1551030 | Parental toxicity<br>NOAEL (♂) = 35.6 mg/kg bw/day (400 ppm)<br>LOAEL (♂) = 157 mg/kg bw/day (2000 ppm)<br>Effects at LOAEL: ↑ liver weight, increased incidence of centrilobular hepatocellular fatty change.<br><br>NOAEL (♀) = 159 mg/kg bw/day (2000 ppm)<br>LOAEL (♀) = Not established. No adverse effects observed at the highest dose tested (2000 ppm).<br><br>Offspring toxicity<br>NOAEL = 33.4 mg/kg bw/day (400 ppm)<br>LOAEL = 159 mg/kg bw/day (2000 ppm)<br>Effects at LOAEL: ↓ viability index PND 4, ↑ pup deaths PND 0-4.<br><br>Reproductive toxicity<br>NOAEL = 139/159 mg/kg bw/day (2000 ppm)<br>LOAEL = Not established. No adverse effects observed at the highest dose tested (2000 ppm).<br><br>Serious endpoint (pup death) in absence of adverse effects on maternal animal. |
| Preliminary acute oral neurotoxicity (gavage)<br><br>Sprague-Dawley rat<br><br>PMRA#2401600 | A NOAEL and LOAEL were not established as this study was considered to be supplemental.<br><br>Effects at 300 mg/kg bw/day included: ↓ exploration. |
| Acute oral neurotoxicity (gavage)<br><br>Sprague-Dawley rat<br><br>PMRA#2401601, 2401602 | NOAEL = 2000 mg/kg bw/day<br><br>LOAEL = Not established. No effects observed at the highest dose tested (2000 mg/kg bw/day).<br><br>No neuropathological findings observed. |

| | |
|---|---|
| Preliminary 28-day oral neurotoxicity/ immunotoxicity (diet)<br><br>Fischer rat<br><br>PMRA#2401610, 2401612 | A NOAEL and LOAEL were not established as this study was considered to be supplemental.<br><br>Section A – Neurotoxicity<br>Effects at 75.8/80.7 mg/kg bw/day (1000 ppm) included: ↑ rel liver weight (♂). No evidence of neurotoxicity.<br><br>Section B – Immunotoxicity (♀ only)<br>Effects at 81.3 mg/kg bw/day (1000 ppm) included: ↑ rel liver weight. No evidence of disregulation of the immunologic response. |
| 90-day oral neurotoxicity (diet)<br><br>Sprague-Dawley rat<br><br>PMRA#2401605, 2401607 | NOAEL = 282/334 mg/kg bw/day (5000 ppm)<br>LOAEL = 858/1034 mg/kg bw/day (15000 ppm)<br>Effects at LOAEL: ↑ elongation of incisors, liver enlargement; ↑ partial loss and whitening of incisors (♂); ↓ bw (weeks 8-13) (♀).<br><br>No neuropathological findings observed. |
| 28-day oral immunotoxicity (diet)<br>ELISA Assay<br><br>Sprague-Dawley rat (♀)<br><br>PMRA#2401608 | NOAEL = 82.2 mg/kg bw/day<br><br>LOAEL = 418 mg/kg bw/day<br>Effects at LOAEL: ↑ whitening of the incisors, liver enlargement.<br><br>No evidence of disregulation of the immunologic response. |

## Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Etoxazole

| Exposure Scenario | Study | Point of Departure and Endpoint | CAF[1] or Target MOE |
|---|---|---|---|
| Acute dietary general population | Not required. | | |
| Repeated dietary general population | 2-generation reproductive toxicity (rat) | NOAEL (Offspring) = 33.4 mg/kg bw/day; increased incidence of pup deaths between PND 0-4 and a reduced viability index | 1000 |
| | ADI = 0.03 mg/kg bw/day | | |
| Dermal (all durations)[2] | 2-generation reproductive toxicity (rat) | NOAEL (Offspring) = 33.4 mg/kg bw/day; increased incidence of pup deaths between PND 0-4 and a reduced viability index | 1000 |
| Inhalation (all durations)[3] | 2-generation reproductive toxicity (rat) | NOAEL (Offspring) = 33.4 mg/kg bw/day; increased incidence of pup deaths between PND 0-4 and a reduced viability index | 1000 |
| Cancer | Not required as there was no evidence of oncogenicity. | | |

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

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

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

## Table 5 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

| PLANT STUDIES | | |
|---|---|---|
| **RESIDUE DEFINITION FOR ENFORCEMENT**<br>**Primary crops (Apple, orange, eggplant, cottonseed)** | Etoxazole | |
| **RESIDUE DEFINITION FOR RISK ASSESSMENT**<br>**Primary crops (Apple, orange, eggplant, cottonseed)** | Etoxazole | |
| **METABOLIC PROFILE IN DIVERSE CROPS** | Similar in apple, orange, eggplant and cottonseed. | |
| **ANIMAL STUDIES** | | |
| **ANIMALS** | **Ruminant** | **Poultry** |
| **RESIDUE DEFINITION FOR ENFORCEMENT** | Etoxazole | Etoxazole |
| **RESIDUE DEFINITION FOR RISK ASSESSMENT** | Etoxazole<br>(muscle, fat, milk) | Etoxazole<br>(muscle, fat, eggs) |
| | Etoxazole +<br>Metabolite 1<br>(liver, kidney) | Etoxazole +<br>Metabolite R-16<br>(liver egg whites) |
| **METABOLIC PROFILE IN ANIMALS**<br>**(goat, hen, rat)** | Similar in goat, hen and rat. | |
| **FAT SOLUBLE RESIDUE** | Yes, based on a log $K_{ow}$ of 5.52 | |

| DIETARY RISK FROM FOOD ALONE | | |
|---|---|---|
| | **POPULATION** | **ESTIMATED RISK**<br>**% of ACCEPTABLE DAILY INTAKE (ADI)** |
| | | **Food Alone** |
| **Basic chronic non-cancer dietary exposure analysis**<br><br>**ADI = 0.03 mg/kg bw/day** | **All infants < 1 year** | 12.6 |
| | **Children 1–2 years** | 26.0 |
| | **Children 3 to 5 years** | 17.3 |
| | **Children 6–12 years** | 8.0 |
| | **Youth 13–19 years** | 4.0 |
| | **Adults 20–49 years** | 4.4 |
| | **Adults 50+ years** | 4.4 |
| | **Females 13-49 years** | 4.0 |
| | **Total population** | 6.0 |

## Table 6 Fate and behaviour of etoxazole in the terrestrial environment

| Property | Test substance | Value | Comments | Reference |
|---|---|---|---|---|
| Hydrolysis | [$^{14}$C-*t*-butylphenyl]-etoxazole | 9.6 days (pH 5)<br>159 days (pH 7)<br>169 days (pH 9) | Not an important route of dissipation under environmentally relevant pH conditons | 2401618 |
| Phototransformation on soil | [$^{14}$C-*t*-butylphenyl] etoxazole and [$^{14}$C-difluorophenyl] etoxazole | 22.0-24.3 days | Not an important route | 2401629 |
| Phototransformation in air | N/A | N/A | N/A | |
| Biotransformation in aerobic soil | [$^{14}$C-*t*-butylphenyl] etoxazole and [$^{14}$C-difluorophenyl] etoxazole | 12.0-22.8 days | Non-persistent to slightly persistent, important route of dissipation | 2401619<br>2401620 |
| Biotransformation in anaerobic soil | N/A | N/A | N/A | |
| Adsorption in soil $K_d$/$K_{OC}$ | [$^{14}$C-*t*-butylphenyl]-etoxazole | 150.2±96.92 mL/g (62.7-278.9 mL/g)/ 9263±2149 mL/g / (8055-11619 mL/g) | Immobile | 2401622 |
| Volatilization | N/A | N/A | N/A | |
| Field dissipation | Etoxazole | 4-9 days | Non-persistent | 2401629 |

## Table 7 Toxicity of etoxazole on bees and beneficial arthropods at 55 g a.i./ha

| Study type | Test species | Life stage | Endpoint | Effects |
|---|---|---|---|---|
| Acute contact | Honeybees (*Apis mellifera*) | Adult | $LD_{50}$ | >200 µg a.i./bee |
| Acute oral | | | $LD_{50}$ | >200 µg a.i./bee |
| Laboratory (glass top) | Predatory mites (*Typhlodromus pyri*) | Adult | Mortality<br>Reproduction<br>Overall effect | 0%<br>100%<br>100% |
| | | Eggs | Reduction in hatchability | 50.9-75.4% |
| Field study (vineyard) | | Natural population | Reduction in population density (21 DAT) | 16.5% |
| Field study (vineyard) | | Natural population | Reduction in population density (20 DAT) | 62.6% |
| Laboratory limit test (glass top) | Predatory insect (*Orius laevigatus*) | Nymph (second instar) | Mortality<br>Fecundity<br>Overall effect | 80%<br>100%<br>100% |
| Laboratory limit test (glass top) | Predatory insect (*Chrysoperla carnea*) | Larvae (2-3 days old) | Mortality<br>Fecundity | 85%<br>100% |
| Laboratory limit test (sand box) | Parasitic insect (*Aleochara bilineata*) | Adult | Mortality<br>Reproduction | 10%<br>14% |
| Laboratory limit test | Parasitic wasp (*Aphidius rhopalosiphi*) | Adult | Mortality<br>Parasitism | 2.3%<br>50% |
| | | Juvenile (mummy) | Mortality<br>Parasitism | 18.4%<br>0% |

## Table 8 Risk to bees as a result of direct on-field exposure

| Exposure | Endpoint value ($LD_{50}$) | EEC | RQ | LOC[1] exceeded? |
|---|---|---|---|---|
| Acute contact | > 200 µg a.i./bee | 0.27 µg a.i./bee | < 0.002 | No |
| Acute oral | > 200 µg a.i./bee | 3.25 µg a.i./bee | < 0.02 | No |

[1] For honeybees, LOC is set at 0.4.

## Table 9 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

| Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria | | | |
|---|---|---|---|
| **TSMP Track 1 Criteria** | **TSMP Track 1 Criterion value** | | **Etoxazole** |
| CEPA toxic or CEPA toxic equivalent[1] | Yes | | Yes |
| Predominantly anthropogenic[2] | Yes | | Yes |
| Persistence[3]: | Soil | Half-life ≥ 182 days | No<br>12.0 – 22.8 days |
| | Whole system | Half-life ≥ 182 days | N/A |
| | Water | Half-life ≥ 182 days | N/A |
| | Sediment | Half-life ≥ 365 days | N/A |
| | Air | Half-life ≥ 2 days or evidence of long range transport | Based on the vapour pressure ($7.0 \times 10^{-6}$ Pa at 25 °C) and Henry's law constant ($3.1 \times 10^{-7}$ atm·m$^3$/mol) long-range atmospheric transport is unlikely to occur. |
| Bioaccumulation[4] | Log $K_{ow} \geq 5$ | | **Yes**<br>5.52 |
| | BCF ≥ 5000 | | No (1300 – 1500) |
| | BAF ≥ 5000 | | N/A |
| Is the chemical a TSMP Track 1 substance (all four criteria must be met)? | | | No, does not meet TSMP Track 1 criteria. |

[1]All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (e.g., BAFs) are preferred over laboratory data (e.g., BCFs) which, in turn, are preferred over chemical properties (e.g., log $K_{ow}$).

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

MRLs established in Canada for etoxazole may be found using the Maximum Residue Limit Database on the Maximum Residue Limits for Pesticides webpage.

# References

## A. List of Studies/Information Submitted by Registrant

### 1.0 Chemistry

| PMRA Document Number | Reference |
|---|---|
| 1550954 | 2008, Chemistry Requirements for the Registration of Etoxazole Technical Category A Import Tolerance for Etoxazole Technical for Grape, Pome Fruit, Strawberry, Non Bearing Fruit Trees, Christmas Trees and Tree Nuts, DACO: 2.1, 2.2, 2.3, 2.3.1, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 CBI |
| 1550955 | 2008, 2.11.1-Manufacturing Summary, DACO: 2.11.1 CBI |
| 1550956 | 2000, Product Identity and Composition; Description of Materials Used to Produce the Product; Description of Production Process for the Technical YI-5301; Discussion of Formation of Impurities, DACO: 2.11.2, 2.11.3, 2.11.4 CBI |
| 1550957 | 2003, Analysis of Etoxazole and its Production Process Impurities in Etoxazole Technical; Certification of Ingredient Limits of Etoxazole Technical; Determination of [CBI Removed] in S-1283 Technical, DACO: 2.12.1, 2.13.1, 2.13.3, 2.13.4 CBI |
| 1550958 | 1998, Analysis of S-1283, and its Production Process Impurities in S-1283 Technical (830.1700); Certification of Ingredient Limits of S-1283 Technical (830.1750); Determination of S-1283 in S-1283 Technical (830.1800); Determination of [CBI Removed], DACO: 2.13.1,2.13.2,2.13.3,2.13.4 CBI |
| 1550959 | 1997, S-1283 (Pure) Physicochemical Properties, DACO: 2.14.1, 2.14.10, 2.14.11, 2.14.13, 2.14.14, 2.14.2, 2.14.3, 2.14.4, 2.14.6, 2.14.7, 2.14.9 CBI |
| 1550960 | 1996, S-1283 (Technical) Physicochemical Properties, DACO: 2.14.1, 2.14.14, 2.14.2, 2.14.3, 2.14.5, 2.14.8 CBI |
| 1550961 | 2000, Elevated Temperature Shelf-Life Storage Stabiltiy Characteristics of Etoxazole Technical, DACO: 2.14.13, 2.14.14 CBI |
| 1550962 | 1997, Shelf Life Storage Stability Characteristics of S-1283 Technical Grade, DACO: 2.14.14 CBI |
| 1550963 | 1997, Physical and Chemical Properties of S-1283, DACO: 2.14.12, 2.14.6 CBI |
| 1550964 | Environmental Protection Agency, 2003, Federal Regiser/Vol.68, No. 187/Friday, September 26, 2003/ Rules and Regulations., Etoxazole; Pesticide Tolerance (Final Rule), DACO: 2.15, 3.6, 4.8, 6.4, 7.8 CBI |
| 1550965 | Environmental Protection Agency, 2005, Federal Register / Vol. 70, No. 138 / Wednesday, July 20, 2005 / Rules and Regulations, pg. 41619-41625, Etoxazole; Pesticide Tolerance (Final Rule), DACO: 2.15, 3.6, 4.8, 6.4, 7.8 CBI |

| | |
|---|---|
| 2401596 | 2013, Summary of Product Identity for Etoxazole Technical, DACO: 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 |
| 2401597 | 2013, Submittal of Samples for Etoxazole Technical, DACO: 2.15 |
| 2470664 | 2014, Confirmation of Identity for Etoxazole Technical - Characterization Data for Impurity Standards, DACO: 2.13.2 |
| 2401614 | 2001, Determination of Etoxazole, R3, and R13 Metabolites in Soil Method RM-37s -2, DACO: 8.2.2.1 |
| 2401615 | 2001, Determination of Etoxazole Metabolites R4, R7, R8, and R11 in Soil Method RM-37SM, DACO: 8.2.2.1 |
| 2401616 | 2002, Independent Laboratory Validation of Valent Method RM-37s-2, "Determination of Etoxazole, R3 and R13 Metabolites in Soil", DACO: 8.2.2.1 |
| 2401617 | 2002, Independent Laboratory Validation of Valent Method RM-37SM, "Determination of Etoxazole Metabolites R4, R7, R8 and R11 in Soil", DACO: 8.2.2.1 |
| 2402384 | 2013, Summary of Product Identity for TetraSan 5 WDG Miticide, DACO: 3.1.1, 3.1.2, 3.1.3, 3.1.4 CBI |
| 2402385 | 2000, U.S. EPA Product Properties Test Guidelines - Group A and Group B of TetraSan 5 WDG, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.4.1, 7.2.2 |
| 2402386 | 2000, U.S. EPA Product Properties Test Guidelines - Group A and Group B of TetraSan 5 WDG, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.4.1, 7.2.2 CBI |
| 2402387 | 2000, Physical and Chemical Properties of TetraSan 5 WDG, DACO: 3.5.10, 3.5.11, 3.5.12, 3.5.13, 3.5.15, 3.5.2, 3.5.6, 3.5.7, 3.5.8, 3.5.9 |
| 2402388 | 2001, Shelf Life Storage Stability and Corrosion Characteristics of TetraSan 5 WDG, DACO: 3.5.10, 3.5.14, 3.5.4, 3.5.5, 5.13 |
| 2479534 | 2014, TetraSan 5 WDG: Product Identity, Composition and Analysis, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.4.1 |
| 2479535 | 2014, TetraSan 5 WDG: Product Identity, Composition and Analysis, DACO: 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.4.1 CBI |

## 2.0 Human and Animal Health

| PMRA Document Number | Reference |
|---|---|
| 1550986 | 1999, Acute Dermal Toxicity to Rats of YI-5301, DACO: 4.2.2 |
| 1550987 | 2003, YI-5301: Acute Inhalation Toxicity Study in Rats, DACO: 4.2.3 |
| 1550988 | 1999, Eye Irritation to the Rabbit of YI-5301, DACO: 4.2.4 |

| | |
|---|---|
| 1550989 | 1999, Skin Irritation to the Rabbit of YI-5301, DACO: 4.2.5 |
| 1550990 | 1995, YI-5301: Skin Sensitization in the Guinea-Pig (incorporating a positive control using formalin), DACO: 4.2.6 |
| 1551004 | 1999, 28-Day Repeated Dose Dermal Toxicity Study of S-1283 TG in Rats, DACO: 4.3.5 |
| 2401598 | 2009, Waiver Request: Etoxazole 90-Day Rat Inhalation Study, DACO: 4.3.6 |
| 2401600 | 2011, Etoxazole Technical Dose Range-Finding Study for Acute Neurotoxicity Study in Rats, DACO: 4.5.12 |
| 2401601 | 2011, Etoxazole Technical Acute Oral Neurotoxicity Study in Rats, DACO: 4.5.12 |
| 2401602 | 2011, Etoxazole Technical Acute Oral Neurotoxicity Study in Rats, DACO: 4.5.12 |
| 2401603 | 2009, Etoxazole Technical Positive Control Data of Neurotoxicity Study for Reports no. SKT -0090 and SKT -0092, DACO: 4.5.12 |
| 2401605 | 2012, Etoxazole Technical Repeated Dose 90-Day Oral Neurotoxicity Study in Rats, DACO: 4.5.13 |
| 2401607 | 2012, Etoxazole Technical Repeated Dose 90-Day Oral Neurotoxicity Study in Rats, DACO: 4.5.13 |
| 2401608 | 2011, Etoxazole Technical 4-Week Oral Feeding Immunotoxicity Study in Rats, DACO: 4.8(B) |
| 2401610 | 2011, Etoxazole Technical 4-Week Feeding Immunotoxicity and Neurotoxicity Preliminary Study in Rats, DACO: 4.5.12,4.8(B) |
| 2401612 | 2011, Etoxazole Technical 4-Week Feeding Immunotoxicity and Neurotoxicity Preliminary Study in Rats, DACO: 4.5.12,4.8(B) |
| 2443225 | 2011, Basal diet (pulverized MF Mash): Background data for repeated oral dose neurotoxicity study in rats, DACO: 4.5.13 |
| 2482104 | 2011, Etoxazole Technical: Validation of an Analytical Method in the Diet for Rodents, DACO: 4.8 |
| 2482105 | 2011, Etoxazole Technical: Stability Study in Diet for Rodents, DACO: 4.8 |
| 2402390 | 1999, S-1283 5 WDG: Acute Oral Toxicity Study in Rats, DACO: 4.6.1 |
| 2402391 | 1999, S-1283 5 WDG: Acute Dermal Toxicity Study in Rats, DACO: 4.6.2 |
| 2402393 | 1999, S-1283 5 WDG: Acute (4-Hour) Inhalation Toxicity Study in the Rat via Nose-Only Exposure, DACO: 4.6.3 |
| 2402395 | 1999, S-1283 5 WDG: Acute Eye Irritation Study in Rabbits, DACO: 4.6.4 |

| | |
|---|---|
| 2402396 | 1999, S-1283 5 WDG: Acute Dermal Irritation Study in Rabbits, DACO: 4.6.5 |
| 2402398 | 1999, S-1283 5 WDG: Skin Sensitization Study in Guinea Pigs (Buehler Method), DACO: 4.6.6 |

## 3.0 Environment

| PMRA Document Number | Reference |
|---|---|
| 2401613 | 2013. Environmental Chemistry and Fate for Etoxazole. DACO: 8.1, 8.2.3.1, 8.2.4.1, 8.4.1 |
| 2401618 | 1996. The Hydrolysis of YI-5301. DACO: 8.2.3.2 |
| 2401619 | 1997. $^{14}$C-S-1283 Aerobic Soil Metabolism and Route of Degradation. DACO: 8.2.3.4.2 |
| 2401620 | 1999. Metabolism of [*tert*-butylphenyl-14C] and [difluorophenyl-$^{14}$C] S-1283 in Aerobic Soil. DACO: 8.2.3.4.2 |
| 2401622 | 1996. $^{14}$C-S-1283 Adsorption/Desorption on Soil. DACO: 8.2.4.2 |
| 2401629 | 2000. Summary of Data Supporting the Registration of Etoxazole Technical and the Use of TetraSan 5 WDG on Greenhouse Ornamentals. DACO: 12.5, 12.7 |
| 2467539 | 1993. Study of Unintentional Effects of the Product PHF 9502 on Two Populations of *T. Pyri*. DACO: 9.2.5 |
| 2467541 | 1997. A Laboratory Study to Evaluate the Effects of PHF 9502 Containing 110 g/L Etoxazole (S-I 283) on the Heteropteran Bug *Orius Laevigatus*. DACO: 9.2.5 |
| 2467544 | 1997. Non-intentional effects on *T. pyri*. DACO: 9.2.5 |
| 2467546 | 1997. A Laboratory Evaluation of the Effects of the Acaricide PHF 9502, Containing 110 G/L Etoxazole, On the Lacewing *Chrysoperia carnea.* DACO: 9.2.5 |
| 2467548 | 1997. A Laboratory Evaluation of the Effects of the Acaricide PHF 9502, Containing 110 G/L Etoxazole, On the Staphylinid Beetle *Aleochara bilineata*. DACO: 9.2.5 |
| 2467549 | 1997. Non Target Effects on *T. Pyri.* DACO: 9.2.5 |
| 2467561 | 1997. A Laboratory Study to Evaluate the Effects of PHF 9502 Containing 110 g $l^{-1}$ Etoxazole (S-1283) on the Adult and Juvenile Life Stages of the Parasitic Wasp *Aphidius rhopalosiphi*. DACO: 9.2.6 |
| 2494525 | 1996. Yl-5301: Acute Toxicity to Honey Bees (*Apis mellifera*). DACO: 9.2.4.1, 9.2.4.2 |

## 4.0 Value

| PMRA Document Number | Reference |
|---|---|
| 2402357 | 2014, Value Summary for TetraSan 5 WDG Miticide, for Use on Greenhouse Ornamentals and Greenhouse Tomatoes, DACO: 10.1,10.2.1,10.2.2,10.2.3.1,10.2.3.3,10.3.1,10.4,10.5.1,10.5.2,10.5.3,10.5.4,10.7.1,10.7.2. |

| | |
|---|---|
| 2402359 | 2014, Appendix: Value Summary for TetraSan 5 WDG Miticide, for Use on Greenhouse Ornamentals and Greenhouse Tomatoes, DACO: 10.1,10.2.1,10.2.2,10.2.3.1,10.2.3.3,10.3.1,10.4,10.5.1,10.5.2,10.5.3,10.5.4,10.7.1,10.7.2. |
| 2402362 | 2014, Summary Tables: Value Summary for TetraSan 5 WDG Miticide, for Use on Greenhouse Ornamentals and Greenhouse Tomatoes, DACO: 10.1,10.2.1,10.2.2,10.2.3.1,10.2.3.3,10.3.1,10.4,10.5.1,10.5.2,10.5.3,10.5.4,10.7.1,10.7.2. |
| 2402364 | 2013, Use History for TetraSan 5 WDG Mititicide for Use on Greenhouse Tomatoes, DACO: 10.2.4. |
| 2402366 | 2013, Use History for TetraSan 5 WDG Mititicide for Use on Greenhouse Tomatoes, DACO: 10.2.4. |
| 2402368 | 2013, Use History for TetraSan 5 WDG Mititicide for Use on Greenhouse Ornamentals, DACO: 10.2.4 |
| 2441507 | Tawfiq M. Al-Antary and Isra W. Salim, 2012, The Effects of Three Acaricides on Egg Hatchability of Three Populations of the Two-Spotted Spider Mite *Tetranychus urticae* Koch (Acari: Tetranychidae), DACO: 10.2.1 |
| 2441508 | 2010, Spider Mites on Ornamentals, DACO: 10.2.2 |
| 2441509 | 2005, Spider and Russet Mite Control on Fresh Market Tomatoes, Spring 2005, DACO: 10.2.3.3 |
| 2441510 | 2004, Control of Spider and Russet Mites on Tomato, Spring 2004, DACO: 10.2.3.3. |
| 2441511 | 2014, Excel File - Graphs of submitted data, DACO: 10.2.3.3. |

## B. Additional Information Considered

### i) Published Information

#### 1.0 Environment

USEPA, 2010. Petition for Etoxazole - Tab E -Reduced Risk Petition/ OP Replacement Petition MRID 45630502 - Environmental Fate and Effects.

#### 2.0 Value

Arthropod Pesticide Resistance Database, www.pesticideresistance.org, (Accessed 22 August 2014)