Proposed Registration Decision PRD2012-29

Tetraconazole Technical Fungicide

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Overview

Proposed Registration Decision for Tetraconazole Technical Fungicide

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 Tetraconazole Technical Fungicide and Mettle 125 ME Fungicide, containing the technical grade active ingredient tetraconazole, to control powdery mildew on grape, gooseberry, strawberry and sugar beet; black rot on grape; and cercospora leaf spot on sugar beet.

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

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of tetraconazole and Mettle 125 ME Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

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

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

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

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

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

Tetraconazole is a broad-spectrum triazole fungicide belonging to the DMI (DeMethylation Inhibitors) group. It inhibits the metabolic pathway that leads to fungal sterol production, which makes fungal cell membranes nonfunctional. Tetraconazole is a systemic fungicide and is absorbed quickly into the plant tissue. It has protectant and curative properties.

Health Considerations

Can Approved Uses of Tetraconazole Technical Fungicide Affect Human Health?

Mettle 125 ME Fungicide containing Tetraconazole Technical Fungicide is unlikely to affect your health when used according to label directions.

Potential exposure to Tetraconazole Technical Fungicide may occur through the diet (food and water), when handling and applying the end-use product Mettle 125 ME Fungicide or when entering treated sites. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

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

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

In laboratory animals, Tetraconazole Technical Fungicide was of slight acute toxicity via the oral route and low acute toxicity via the dermal and inhalation routes of exposure; consequently, the hazard signal words "CAUTION – POISON" are required on the label. It was minimally irritating to the eyes, non-irritating to the skin, and did not cause an allergic skin reaction. The acute toxicity of the end-use product Mettle 125 ME Fungicide was low via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the skin and eyes and did not cause an allergic skin reaction. Consequently, no hazard signal words are required on the label.

There was no indication that Tetraconazole Technical Fungicide caused damage to the nervous system or immune system. There was also no evidence to suggest that it damaged genetic material or caused birth defects in animals. In addition, the young do not appear to be more sensitive to Tetraconazole Technical Fungicide than the adult animal. Health effects in animals given repeated doses of Tetraconazole Technical Fungicide included effects on the skin at points of contact, bones, liver, kidneys, ovaries, adrenal glands and thyroid gland, as well as irritation of the upper respiratory mucosal membranes. Tetraconazole Technical Fungicide also caused liver tumours in the mouse. When Tetraconazole Technical Fungicide was given to pregnant or nursing animals, fertility was slightly reduced and effects on the skeleton, liver, kidneys and body weight of the developing fetus were observed. These effects, as well as slightly delayed maturation in the juvenile animal, were observed at doses that were toxic to the mother.

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

Residues in Water and Food

Dietary risks from food and water are not of concern

Aggregate dietary intake estimates (food plus water) revealed that the general population and infants less than one year old, the subpopulation which would ingest the most tetraconazole relative to body weight, are expected to be exposed to less than 48% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from tetraconazole is not of concern for all population sub-groups. There were no cancer risks of concern for tetraconazole.

An aggregate (food and water) dietary intake estimate for the highest exposed population (children 1 to 2 years old) used less than 2% of the acute reference dose, which is not a health concern.

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

Residue trials conducted throughout the United States using tetraconazole on sugar beets, strawberries and grapes were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation of this consultation document

Risks in Residential and Other Non-Occupational Environments

Occupational Risks From Handling Mettle 125 ME Fungicide

Occupational risks are not of concern when Mettle 125 ME Fungicide is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Mettle 125 ME Fungicide, as well as field workers re-entering freshly treated fields, can come in direct contact with tetraconazole residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying Mettle 125 ME Fungicide must wear a long-sleeved shirt, long pants, chemical resistant gloves, socks and footwear during mixing and loading, application, clean-up and repair. The label also requires that workers do not enter treated fields 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 risk to these individuals are not a concern.

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

Environmental Considerations

What Happens When Tetraconazole Is Introduced Into the Environment?

Tetraconazole enters the environment when used as a foliar treatment on field crops. Once in the terrestrial environment, tetraconazole binds to soil particles and has limited vertical movement in most soils profiles. Tetraconazole is very persistent in soil; therefore, it is expected to carryover from one growing season to the next and, over a long period of time, has potential for reaching groundwater. In aquatic systems, tetraconazole is expected to move from the water column into sediments where it will persist. Tetraconazole is rapidly metabolised and excreted in fish and is therefore not expected to bioconcentrate. Tetraconazole is not expected to evaporate from the soil or water surface; therefore, the atmospheric concentration of tetraconazole is expected to be negligible. Tetraconazole is not expected to form any major transformation products in the environment because the transformation products transform much more quickly than they are formed.

Mettle 125 ME Fungicide is to be applied by field boom and airblast sprayers. Non-target terrestrial and aquatic habitats can potentially be exposed to tetraconazole as a result of spray drift or runoff. When used according to the label directions, tetraconazole does not present a risk to earthworms, bees, and aquatic organisms. Tetraconazole application can present a risk to beneficial predatory arthropods, terrestrial plants, birds and small mammals; therefore, label statements are required on the product label to inform users of the potential risks. No-spray buffer zones are required between the treated area and downwind terrestrial habitats in order to minimize the potential risk to terrestrial plants from exposure to off-field drift.

Value Considerations

What Is the Value of Mettle 125 ME Fungicide?

Mettle 125 ME Fungicide, containing Tetraconazole Technical Fungicide, has demonstrated effectiveness in controlling powdery mildew on grape, gooseberry, strawberry and sugar beet; black rot on grape; and cercospora leaf spot on sugar beet. Mettle 125 ME Fungicide is formulated in micro emulsion (ME) and applied as a foliar treatment. Mettle 125 ME Fungicide adds an alternative to the triazoles fungicides which will contribute to the limited disease management options for these targeted diseases. In addition, registration of this product will give Canadian growers access to an effective fungicide that is already available in the United States.

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 Mettle 125 ME Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Environment

Tetraconazole can pose a risk to certain beneficial insects, terrestrial plants, birds and small mammals. Precautionary label statements informing users of the risks to these organisms are required on the product label. Spray drift of tetraconazole may pose a risk to non-target terrestrial vascular plants. To mitigate potential exposure via spray drift, a no-spray buffer zone of one metre is required to protect sensitive terrestrial habitats downwind. An advisory statement recommending products containing tetraconazole not be applied in areas treated the previous year is required due to tetraconazole’s persistence and concerns for carryover to the following growing season.

Next Steps

Before making a final registration decision on tetraconazole, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

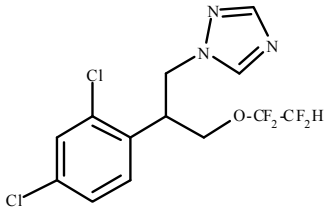
When the PMRA makes its registration decision, it will publish a Registration Decision on tetraconazole (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the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

Science Evaluation

Tetraconazole

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Tetraconazole
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(*RS*)-2-(2,4-dichlorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propyl 1,1,2,2-tetrafluoroethyl ether
2. Chemical Abstracts Service (CAS)	1-[2-(2,4-dichlorophenyl)-3-(1,1,2,2-tetrafluoroethoxy)propyl]-1*H*-1,2,4-triazole
CAS number	112281-77-3
Molecular formula	$C_{13}H_{11}Cl_2F_4N_3O$
Molecular weight	372.1
Structural formula	
Purity of the active ingredient	97.0%

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

Technical Product—Tetraconazole Technical Fungicide

Property	Result
Colour and physical state	Yellowish liquid
Odour	Slight aromatic
Melting range	N/A
Boiling point or range	Decomposes at 240˚C without boiling
Density	1.43 g/mL
Vapour pressure at 20°C	0.18 mPa (calculated)
Henry's law constant at 20°C	3.50×10^{-9} atm/m^3/mol^{-1}
Ultraviolet (UV)-visible spectrum	No significant absorption at $\lambda > 290$ nm
Solubility in water at 20°C	156 mg/L
Solubility in organic solvents at 20°C	Solvent — Solubility (%) Hexane — 2.4 ± 0.7 Ethyl alcohol — >46.7 Methyl alcohol — >52.2 Acetone — >40.3 Ethyl acetate — >42.2 Xylene — >29.9 1,2-Dichloroethane — >41.7
n-Octanol–water partition coefficient (K_{ow})	log K_{ow} = 3.56
Dissociation constant (pK_a)	pK_a = 0.5-0.8
Stability (temperature, metal)	Stable to sunlight, to metals (carbon steel, aluminum and copper) and to heat (to 190˚C)

End-use Product—Mettle 125 ME Fungicide

Property	Result
Colour	Light yellow
Odour	Characteristic
Physical state	Liquid
Formulation type	Emulsifiable concentrate
Guarantee	125 g/L
Container material and description	HDPE, 250 mL to 25 L
Density	1.09 g/mL
pH of 1% dispersion in water	6-8
Oxidizing or reducing action	Product does not contain strong oxidizing or reducing agents.
Storage stability	Stable for 24 months in HDPE container in the dark at ambient temperature.
Corrosion characteristics	Not corrosive to commercial packaging.
Explodability	Product does not contain explosive components.

1.3 Directions for Use

Mettle 125 ME Fungicide is formulated as a foliar treatment against powdery mildew on grape, gooseberry, strawberry and sugar beet; black rot on grape; and cercospora leaf spot on sugar beet. The use rates range from 219 to 365 mL/ha on grape, gooseberry and strawberry, and 950 mL/ha on sugar beet. Preventive applications are recommended. Optimal disease control is achieved when Mettle 125 ME Fungicide is applied in a regularly scheduled spray program.

1.4 Mode of Action

Tetraconazole inhibits the metabolic pathway that leads to fungal sterol production, which makes fungal cell membranes nonfunctional. Tetraconazole is a systemic, protectant and curative fungicide and is absorbed quickly into the plant tissue. It acts on the vegetative form of fungi blocking the growth of the pathogen mycelium, both outside and inside the treated plant.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

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

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

Gas chromatography methods with nitrogen phosphorus detection (GC-NPD) and mass spectrometry (GC-MS) 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.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Tetraconazole Technical Fungicide (hereinafter referred to as tetraconazole) is a tetrafluorinated systemic fungicide and is a member of the conazole (triazole) class of pesticides. It inhibits sterol-demethylation in the fungal sterol production pathway.

A detailed review of the toxicological database for tetraconazole was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The database also includes neurotoxicity, immunotoxicity, and various special investigative studies including tumour mode of action (MOA) studies. In addition to the required suite of genotoxicity studies, there were a number of additional such studies available to characterize the mammalian metabolites tetraconazole-acid, tetraconazole-alcohol and tetraconazole-difluoroacetic acid. The acute oral toxicity of tetraconazole-alcohol, tetraconazole-difluoroacetic acid and a mixture of the metabolites tetraconazole-dichlorophenyl-3OH and tetraconazole-dichlorophenyl-5OH were also investigated. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices (GLP). 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 tetraconazole.

The metabolism and toxicokinetic were investigated using radiolabelled tetraconazole in single and repeated dose oral studies in the rat. Absorption was rapid and dose dependent, with peak concentrations in the blood occurring between 1 and 27 hours post-dose; the peak levels were lower and occurred later in females compared to males. The extent of absorption was moderate to high, as evidenced by the recovery of 52-76% of the administered dose (AD) in the urine. Although not assessed directly, excretion via the bile into the feces was inferred, based on total radiolabel recoveries of 12 to 36% AD in the feces after 72 hours, which were greater than the recoveries of unchanged parent in the feces (< 6% AD). Excretion via exhalation was not assessed. The absorbed radioactivity was widely distributed. Tissue-specific residue concentrations were highest in the liver, kidney, ovaries and the adrenals. Radiolabel partitioned

rapidly into the fat, but did not become concentrated in this tissue. Metabolism was extensive. The primary transformation pathways were oxidation, reduction and conjugation reactions mediated by glutathione. The major metabolite was 1,2,4-triazole, which was present in the urine at 48 to 70% AD and in the feces at 6 to 10% AD. A sulfoxide conjugate of tetraconazole-acid (P1) and an N-acetylcysteine conjugate of tetraconazole-alcohol (P4) were prevalent in the urine and/or feces, with P1 and P4 predominating in females and males, respectively. Unconjugated tetraconazole-acid was also prevalent in the urine of females. Minor metabolites in the urine included a glucuronide conjugate of tetraconazole-alcohol (M3), M6, P2 and P3, as well as tetraconazole-acid in males. Minor metabolites in the feces included tetraconazole-alcohol and P5. Also, tetraconazole-dichlorophenyl-3OH (S5, < 4% AD) and tetraconazole-dichlorophenyl-5OH (S6, < 2% AD) both occurred in the feces (free) and urine (conjugated), while tetraconazole-difluoroacetic acid was detected only in the urine (<2% AD). Excretion was rapid; the half-lives were 11 to 16 hours. Less than 6% AD was retained in the carcass and tissues after 72 hours, indicating that retention and negligible. There was no also evidence of bioaccumulation with repeated doses. Increased urinary excretion with repeated exposures was considered indicative of metabolic adaptation. Overall, there were only minor differences in the metabolism and toxicokinetics of tetraconazole, regardless of the sex or dose level and whether dosing was single and repeated.

In the rat, the acute toxicity of tetraconazole was slight via the oral route and low via the dermal and inhalation routes of exposure. It was slightly irritating to the eyes and non-irritating to the skin of the rabbit, and was not a skin sensitizer in guinea pigs. The acute toxicity of Mettle 125 ME Fungicide was low in the rat via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the skin and eyes of the rabbit and was not a skin sensitizer in guinea pigs.

The mouse, rat and dog exhibited similar sensitivities in the short-term dosing studies. Based on the collective studies, conducted via the oral (mouse, rat and dog), dermal (rabbit) and inhalation (rat) routes of exposure, the liver, kidneys, bones (rodents), endocrine organs (ovaries, pituitary gland and adrenal glands) and the upper respiratory mucosa were identified as the primary target organs of toxicity. The skin also exhibited contact irritation with repeated exposure. Effects on the bones and the ovaries were more evident with chronic dosing in the rat. The thyroid gland was affected over short and chronic periods in the rat, but this was likely secondary to tetraconazole's effects on metabolism in the liver. The testes in rodents were also affected, but only at higher dose levels. Decreases in body weight and body weight gain also generally occurred at higher dose levels.

The earliest signs of hepatotoxicity occurred as increased weight, centrilobular hepatocellular hypertrophy and cytotoxicity (for example, hepatocyte necrosis). The latter effect was transient in rodents; likely due to metabolic adaptation in the liver. Altered lipid metabolism also occurred in the rat and dog following short-term dosing and in the mouse following chronic dosing. Generally, the short-term effects noted in the rodent liver did not progress appreciably with chronic dosing. At higher doses or with chronic exposure, additional effects in the rodent liver included accentuated lobular markings, eosinophilic hepatocyte areas (foci), pale or dark subcapsular foci, as well as bile duct and sinusoid changes. With chronic exposure to high doses the mouse also exhibited masses with raised pale or dark subcapsular areas.

Toxicity in the kidney was most evident in the dog, minimally evident in the rat and absent in the mouse after short-term exposure. In the dog and rat, effects included increased kidney weight and slightly increased blood ion levels. Additional effects in the dog included kidney enlargement, cortical tubule hypertrophy and apoptotic bodies, and transient alterations in urine chemistry. Durational effects in the rat were minimal (increased pyelitis, basophilic cortical tubules and slight changes in urine chemistry). At low to mid dose levels, increased kidney weight was the only chronic effect evident in the mouse. Additional kidney effects in the mouse were evident only at dose levels that also caused increased mortality.

In short-term studies, effects on the bones were not evident in the mouse or the dog and only minimally evident in the rat at moderately high doses. Chronic effects on the bones in the rat included increased pale/whitened incisors as well as osseus hypertrophy and thickening of the cranial bones. At higher dose levels, the incisors were overgrown and thickened and the brain exhibited secondary dorsal depression and dilated ventricles due to the excess growth of the cranial bones. Although comparable bone effects occurred in the mouse, they were evident only at notably higher dose levels than in the rat. Based on evidence from two special mechanistic toxicity studies, the effects on teeth and bones appear to be due to fluorosis caused by the metabolic release of fluoride ions from tetraconazole.

Endocrine-related effects were observed in both rodent species, but were most evident in the rat. Among such effects in the rat, decreased adrenal weight in males, altered thyroid function and perturbed hormone levels in the blood (steroid, thyroid and pituitary) were the most sensitive indicators of endocrine perturbation. Acute effects in the rat were limited to a non-adverse prolongation of diestrus and altered blood levels of several steroid hormones. Following short-term dosing, endocrine-related effects occurred in the rat, but not in the mouse. Adrenal weight was decreased in the male rat. At higher doses in the rat, pituitary, testes, uterus and ovary weights were also affected. There were only minimal durational effects on the adrenal and pituitary glands in the rat. In contrast, with longer dosing in the rat the corpora lutea were either less prominent or completely absent. In the rat, changes in the blood levels of ovarian and adrenal cortex hormones (aldosterone, corticosterone, progesterone and testosterone) were dose-concordant with alterations in the ovarian and adrenal weights. Additional long-term endocrine-related changes in the rat included increased fluid distension in the uterus and increased squamous metaplasia of the endometrial glands. All of these changes are consistent with treatment-related effects on endocrine system function. In the mouse long-term study, there were effects on the testes and the ovaries, but only at doses that were sufficiently high to also cause increased mortality.

There were no short-term systemic effects via the dermal route in the short-term dermal rabbit study up to the highest dose tested of the formulated end-use product. In contrast, dermal contact irritation occurred at the lowest dose tested. In the short-term inhalation study in the rat, effects at the lowest dose tested were largely restricted to the upper respiratory mucosa. These effects included increases in squamous cell metaplasia of the laryngeal mucosa, mononuclear cell infiltration of the larynx, and goblet cell hypertrophy of the nasal cavity and nasopharyngeal duct in both sexes. Systemic effects occurring at the lowest dose tested also included thyroid follicular cell hypertrophy in males. At the highest dose tested, lung weights were also increased.

There was no evidence of sensitivity in either the two-generation rat reproductive toxicity study or in the prenatal developmental toxicity studies in the rat and rabbit. Maternal toxicity in the rat developmental toxicity study occurred as decreased body weight, body weight gain and food consumption as well as increased water intake, liver weight and relative kidney weights. At the same dose level in the offspring, there were increased incidences of small fetuses and developmental variations (supernumerary ribs, hydroureter and hydronephrosis). Increased incidences of domed cranium and absent tail also occurred in offspring at this dose level in the rat range-finding developmental toxicity study, but these effects were not evident in the main study involving a larger number of animals. Developmental toxicity was not evident in the rabbit. Maternal effects in the rabbit were limited to decreased body weight and body weight gain at the highest dose tested. In the two-generation rat reproductive toxicity study, parental toxicity at the mid dose level involved increased mortality, decreased body weight and body weight gain in females, and decreased adrenal weight in males. Effects at the high dose level were consistent with other studies in the database, including increased ovary weight. Reproductive toxicity was not evident in males, but in females at the mid dose, there were increases in the duration of gestation, total litter loss and dystocia. In the offspring, relative liver weight was increased at the mid dose level. Effects in pups at the high dose included increased absolute liver weights, slight decreases in the number of litters and live pups, slight delays in developmental landmarks (for example, sexual maturation), and decreases in litter and pup body weights.

Tetraconazole was tested for potential genotoxic activity in a range of in vitro and in vivo assays. Based on the uniformly negative results of these studies, tetraconazole was not considered genotoxic. Consistent with this, there were no treatment-related oncogenic changes in the rat and the oncogenic changes in the mouse were considered threshold-dependent, rather than a consequence of direct genotoxicity. In the mouse, there were increased incidences of hepatocellular adenomas and carcinomas in males and females at 118 and 140 mg/kg bw/day and higher, respectively. The results from special mechanistic studies in rodents were sufficiently robust to support mitogenesis as the probable causative mode of action for the liver tumours in the mouse. The tumourigenic precursor events of tetraconazole's mitogenic mode of action in the mouse are similar to those of phenobarbital. However, the available information for *both* of these chemicals has not been sufficiently developed to establish that their modes of action should be considered the same (Nesnow et al. 2009). Given this, the occurrence of liver tumours in the mouse is considered relevant to humans.

Nervous system function was transiently altered in the rat following acute exposure to high doses of tetraconazole. There was decreased motor activity in both sexes on the day of exposure and transient clinical signs in females for one to several days. With repeated dosing in the rat, there was reduced overall activity in males at the highest dose tested. At the same dose level, female activity was increased, but this occurred primarily during the first week of exposure. Fluoride ions, released from tetraconazole during its metabolism, have the potential to influence nervous system function. However, there was no evidence of either central or peripheral nervous system damage in these neurotoxicity studies and no indication in the broader toxicity database that the nervous system was a specific target. Overall, tetraconazole was not considered selectively neurotoxic.

In an immunotoxicity study in the rat, there were slight decreases in the number of antibody-forming cells at the mid and high dose, but there was a high degree of variability in this assay and the complementary natural killer cell assay was negative. Given the uncertainty regarding the positive result, the lack of concordance between these two assays and the absence of any evident effect on the immune system in the broader toxicology database, tetraconazole was not considered selectively immunotoxic.

The toxicities of five minor metabolites were assessed. In the rat, tetraconazole-alcohol, tetraconazole-difluoroacetic acid and a mixture of tetraconazole-dichlorophenyl-3OH and tetraconazole-dichlorophenyl-5OH were of low acute oral toxicity. Similarly, tetraconazole-acid, tetraconazole-alcohol and tetraconazole-difluoroacetic acid were negative in a battery of in vitro and/or in vivo genotoxicity assays. In an in vitro mammalian clastogenicity assay, tetraconazole-acid caused chromosomal aberrations in some of the individual tests at doses that were largely cytotoxic. Although this was classified as a positive result, the effects occurred at concentrations that are unlikely to occur *in vivo*. Overall, the metabolites investigated were not considered to have in vivo genotoxic potential.

Results of the toxicology studies conducted on laboratory animals with tetraconazole and its associated end-use products 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 (Health)

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website. Tetraconazole and Mettle 125 ME Fungicide have been registered for pesticidal use in the United States since 2005. However, as of July 12, 2012, there have been no health-related incident reports involving the use of tetraconazole in the United States.

3.1.1 Pest Control Products Act Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for tetraconazole. The database contains the full complement of required studies including developmental toxicity studies in the rat and the rabbit, and a reproductive toxicity study in the rat. A developmental neurotoxicity study was not warranted, based on an overall assessment of the mammalian toxicology database.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses or offspring compared to parental animals in the reproductive and prenatal developmental toxicity studies. Developmental toxicity (supernumerary ribs, hydroureter and hydronephrosis) was observed in the rat developmental toxicity study; however, these effects occurred in the presence of maternal toxicity characterized by decreased body weight, body weight gain and food consumption as well as increased water intake, liver weight and relative kidney weights. No developmental toxicity was observed in the rabbit developmental toxicity study. In the two-generation rat reproductive toxicity study, effects in the offspring included slight delays in developmental landmarks, decreased litter and pup body weights, increased liver weight and decreased litter and live pups numbers. These endpoints in the young occurred in the presence of serious maternal toxicity (increased mortality, decreased body weight and body weight gain, increases in the duration of gestation, total litter loss and dystocia).

Overall, endpoints in the young were well-characterized and there was no increase in susceptibility. On the basis of this information, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

General Population
To estimate acute dietary risk (1 day), the acute neurotoxicity study in the rat with a no observed adverse effect level (NOAEL) of 50 mg/kg bw was selected for risk assessment. At the lowest observed adverse effect level (LOAEL) of 200 mg/kg bw, decreased motor activity in both sexes and transient clinical signs in females were observed. These effects were the result of a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is 100.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{50 \text{ mg/kg bw}}{100} = 0.5 \text{ mg/kg bw of tetraconazole}$$

3.3 Acceptable Daily Intake (ADI)

To estimate repeated dietary exposure risk, the 2-year chronic dietary study in the rat with a NOAEL of 0.4 mg/kg bw/day was selected for risk assessment. At the LOAEL of 3.4 mg/kg bw/day, decreased body weight and altered liver function (altered fat distribution, accentuated lobular markings, hepatocyte necrosis) were observed along with pathological effects in the bones (pale/broken incisors, osseus hypertrophy and thickening of the cranial bones) in males and effects on reproductive organs in females (endometrial glands, uterus and ovary). This study provides the lowest NOAEL in the database and incorporates findings from the target organs and probable endocrine system effects. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.4 \text{ mg/kg bw/day}}{100} = 0.004 \text{ mg/kg bw/day of tetraconazole}$$

The ADI provides a margin of approximately 3,000 to the NOAEL for liver tumours in the mouse.

Cancer Assessment
There was adequate evidence to support a threshold-based mode of action for the liver tumours in the mouse. The dietary reference dose (i.e. the ADI) and the selected margin of exposures (MOEs) for occupational and bystander exposure provide a sufficient margin to this tumour type.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Short- and Intermediate-term Dermal
Due to dosing constraints, and because the formulated product was used, the short-term dermal toxicity study in the rabbit was inappropriate for risk assessment, thus necessitating the use of an oral study for risk assessment. For short- and intermediate-term occupational dermal risk assessment, a NOAEL of 0.7 mg/kg bw/day from the reproductive toxicity study in the rat was selected. At the LOAEL of 4.9 mg/kg bw/day, decreased adrenal weights were observed in adult males and increased mortality along with decreased body weights and body weight gains were observed in adult females. This study was selected as it encompassed the relevant duration of exposure and assessed the most sensitive target organ of toxicity.

The target MOE is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. This MOE is considered to be protective of all individuals including nursing infants and the unborn children of exposed female workers.

Short- and Intermediate-term Inhalation
For short- and intermediate-term occupational inhalation risk assessment, a LOAEL of 14.3 mg/kg bw/day (0.055 mg/L) from the 28-day inhalation toxicity study in the rat was selected. At this dose, there were increases in squamous cell metaplasia of the laryngeal mucosa, mononuclear cell infiltration of the larynx, and goblet cell hypertrophy in the nasal cavity and nasopharyngeal duct in both sexes, along with thyroid follicular cell hypertrophy in males. This study was selected as it encompasses the relevant route of exposure and is of an appropriate duration. The target MOE is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. An additional 3-fold uncertainty factor was applied for the lack of a NOAEL in the 28-day inhalation toxicity study. This MOE is considered to be protective of all individuals including nursing infants and the unborn children of exposed female workers.

Acute Aggregate
Acute aggregate exposure to tetraconazole may be comprised of food, drinking water and oral and dermal exposure from harvesting activity at pick-your-own farm operations. Toxicological endpoints and assessment factors chosen for the oral and dermal routes are the same as those for the acute reference dose (see section entitled Acute Reference Dose). Although the endpoints come from an oral toxicity study it was considered unlikely that the effects observed at the LOAEL would occur at lower dose levels when exposure occurs via the dermal route. The acute neurotoxicity study in the rat was selected instead of the 21-day dermal toxicity study in the rabbit because neurotoxicity effects were not assessed in the rabbit dermal toxicity study, and the study was not considered appropriate for risk assessment, as discussed above.

Occupational exposure to tetraconazole is characterized as short-to-intermediate in duration and is predominantly by the dermal and inhalation routes.

A short-to-intermediate term dermal endpoint of 0.7 mg/kg bw/day was selected from a rat reproductive toxicity study. The target MOE for dermal exposure to tetraconazole is 100.

A short-to-intermediate term inhalation endpoint of 14.3 mg/kg bw/day was selected from a 28-day rat inhalation toxicity study. The target MOE for inhalation exposure to tetraconazole is 300.

3.4.1.1 Dermal Absorption

In support of the tetraconazole application, the applicant submitted an in vivo dermal absorption study in rats and an in vitro dermal absorption study in rat and human skin. The submitted dermal penetration studies for tetraconazole were of good quality and the 'triple pack' approach was considered for setting a dermal absorption value. However, the submitted studies did not qualify for the draft NAFTA triple-pack approach, as they utilized different exposure durations (8 hours for the in vivo study and 24 or 48 hours for the in vitro study). Therefore, the dermal absorption value of 30%, based on the results from the low dose group (0.4 $\mu g/cm^2$) in the in vivo rat study after 96 hours of collection, is considered appropriate for use in risk assessment of tetraconazole.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator (M/L/A) Exposure and Risk Assessment

Individuals have potential for exposure to Mettle 125 ME Fungicide during mixing, loading and application. As chemical specific data for assessing human exposures were not submitted, dermal and inhalation exposure estimates for workers were estimated using the Pesticide Handlers Exposure Database (PHED), version 1.1. PHED is a compilation of generic mixer/loader and applicator passive dosimetry data which facilitates the generation of scenario-specific exposure estimates.

Exposure to workers mixing, loading and applying Mettle 125 ME Fungicide 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 mixer/loaders/applicators applying Mettle 125 ME Fungicide to strawberries, sugar beets and gooseberries using groundboom application equipment and to grapes and gooseberries using airblast application equipment. The exposure estimates were based on mixers/loaders/applicators wearing the proposed personal protective equipment (PPE) – a single layer and chemical-resistant gloves.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value of 30%. 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 70 kg adult body weight.

Dermal exposure estimates were compared to the NOAEL of 0.7 mg/kg bw/day to obtain the MOE; the target MOE is 100. Inhalation exposure estimates were compared to the NOAEL of 14.3 mg/kg bw/day to obtain the MOE; the target MOE is 300.

Table 3.4.1 PHED unit exposures for chemical handler risk assessment mixing, loading and applying Mettle 125 ME Fungicide.

Exposure Scenario		PHED unit exposure (µg/kg a.i. handled)		
		Dermal	Absorbed Dermal*	Inhalation
A	**PHED Scenario 3a. All Liquids, Open Mixing and Loading:** Single Layer plus CR gloves	51.14	15.34	1.60
B	**PHED Scenario 11: Groundboom Application, Open Cab:** Single Layer without CR gloves	32.98	9.89	0.96
C	**PHED Scenario 9: Airblast Application, Open Cab:** Single layer with CR gloves	561.72	168.52	5.80
A + B	Open Mixing/Loading; Open cab Groundboom Application	25.23		2.56
A + C	Open Mixing/Loading; Open Cab Airblast Application	183.86		7.40

* A dermal absorption factor of 30% was applied to the dermal exposure estimate.

Table 3.4.2 Mixer/loader/applicator risk assessment for workers handling Mettle 125 ME Fungicide

Crop	Job task/PPE	PHED unit exposure (µg/kg a.i. handled)[1]		Rate (kg a.i./ha)	ATPD (ha/day)[2]	Daily exposure (mg/kg bw/day[3]		MOE[4]	
		Dermal	Inhalation			Dermal	Inhal.	Dermal	Inhal.
PPE: Single layer (with chemical-resistant gloves when mixing and loading, and applying by airblast)									
Groundboom application									
Sugar Beets	Farmer MLA	25.23	2.56	0.119	107	4.59×10^{-3}	4.66×10^{-4}	153	30,687
	Custom MLA	25.23	2.56	0.119	360	1.54×10^{-2}	1.57×10^{-3}	45	9108
					186	7.98×10^{-3}	8.09×10^{-4}	88	17,676
					100	4.29×10^{-3}	4.35×10^{-4}	163	32,858
					32	1.37×10^{-3}	1.39×10^{-4}	510	102,683
Strawberries, Gooseberries	Farmer MLA	25.23	2.56	0.046	26	4.31×10^{-4}	4.37×10^{-5}	1624	327,231
	Custom MLA	25.23	2.56	0.046	26	4.31×10^{-4}	4.37×10^{-5}	1624	327,231

Crop	Job task/PPE	PHED unit exposure (µg/kg a.i. handled)[1]		Rate (kg a.i./ha)	ATPD (ha/day)[2]	Daily exposure (mg/kg bw/day[3]		MOE[4]	
		Dermal	Inhalation			Dermal	Inhal.	Dermal	Inhal.
Airblast application									
Grapes and Gooseberries	Farmer MLA	183.86	7.40	0.046	20	2.42×10^{-3}	9.73×10^{-5}	289	146,968
	Custom MLA	183.86	7.40	0.046	20	2.42×10^{-3}	9.73×10^{-5}	289	146,968

[1] PHED total unit exposures from Table 3.4.1
[2] Default Area Treated per day tables (2010)
[3] Daily exposure = (PHED unit exposure (µg/kg a.i. handled) × ATPD (ha) × Application rate (kg a.i./ha)) / (70 kg bw × 1000 µg/mg)
[4] Dermal: based on NOAEL= 0.7 mg/kg bw/day, target MOE = 100
Inhalation (farmers): based on NOAEL = 14.3 mg/kg bw/day, target MOE = 300
Shaded values represent margins of exposure that did not reach the target of 100.

The calculated MOE for dermal and inhalation exposure to chemical handlers mixing/loading and applying tetraconazole to strawberries, grapes and gooseberries exceeded the target MOE of 100 for dermal exposure and 300 for inhalation exposure. However, the calculated dermal MOE for custom applicators mixing/loading and applying tetraconazole to sugar beets did not reach the target MOE of 100. The calculated dermal MOE for sugar beets was based on a default area treated per day (ATPD) for custom applicators of 360 ha.

In order to mitigate the potential risk, additional sources of information were consulted to determine a more realistic area treated per day value for sugar beets. Statistics Canada Census of Agriculture data from 2006 indicates that the average size of a sugar beet farm at the 95th percentile is 186 ha. The Statistics on Pesticide Use Database (SPUD) stated that the area treated per day for a sugar beet farm is 100 ha. Furthermore, use description information provided by the registrant indicated that the expected area treated per day for a sugar beet farm is 32 ha.

Therefore taking into account all sources or information regarding the expected ATPD for sugar beets and the likelihood that an ATPD of 186 ha/day is an overestimate, while an ATPD of 32 ha is likely an underestimate, the actual ATPD is expected to be closer to the value of 100 ha from the SPUD database. Since acceptable MOEs were calculated for dermal and inhalation exposure when using an area treated per day of 100 ha, the potential exposure to custom applicators treating sugar beet fields is not expected to result in unacceptable risk.

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 Mettle 125 ME Fungicide performing activities such as hand harvesting, thinning, hand pruning, training, tying, irrigation, scouting, cane turning and girdling, leaf pulling and hand weeding. Exposure is expected to be of short- to intermediate-term in duration and to occur primarily by the dermal route.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients. Activity transfer coefficients are based on data generated by the Agricultural Re-entry Task Force (ARTF). Chemical-specific dislodgeable foliar residue data were not submitted. As such, a default dislodgeable foliar residue value of 20% of the application rate was used with a 10% daily dissipation rate in the exposure assessment.

Dermal exposure estimates were compared to the NOAEL of 0.7 mg/kg bw/day to obtain the MOE; the target MOE is 100.

Table 3.4.3 Postapplication exposure and risk from the proposed use of Mettle 125 ME Fungicide

Crops	# of apps.	Rate (g a.i./ha)	Postapplication activity	Days after last application	DFR ($\mu g/cm^2$)[1]	TC (cm^2/hr)[2]	Exposure (mg/kg bw/day)[3]	MOE[4]
Strawberries	4	46	Irrigation	0	0.1190	1100	0.0045	156
Gooseberries	2	46	Hand harvesting, thinning, hand pruning, training, tying	0	0.1130	1500	0.0058	120
Sugar beets	1	119	Irrigation	3	0.1735	1100	0.0065	107
			Scouting	0	0.2380	200	0.0016	429
Grapes	2	46	Cane turning and girdling in table grapes	23	0.0100	19300	0.0066	106
			Hand harvesting, training, thinning, hand pruning, tying, leaf pulling	15	0.0233	8500	0.0068	103
			Scouting, hand weeding and other minor contact activities	0	0.1130	700	0.0027	258

1 Calculated based on default DFR values (20% DFR, 10% dissipation per day).
2 Transfer coefficients from ARTF.
3 Exposure = (Peak DFR × TC × 8 hr/day × DAF of 30 %) / (70 kg bw × 1000 µg/mg)
4 Based on NOAEL = 0.8 mg/kg bw/day, target MOE = 100 (Table 3.4.2)

The calculated margins of exposure for the postapplication re-entry activities with the highest transfer coefficients reached the target MOE of 100 on day 0 after the last application for strawberries and gooseberries. However, for sugar beets and grapes, the target MOE was not reached on day 0 after the last application.

Therefore, in order to mitigate the potential risk to postapplication re-entry workers, restricted entry intervals are required for certain activities for sugar beets and grapes. Since the timing of application is during periods that are favourable for disease development, it is possible that applications may occur throughout the growing season. Therefore, it is assumed that postapplication re-entry activities of concern may occur at any time following application and restricted entry intervals are required. For sugar beets, a restricted entry interval of 3 days is required for irrigation. For grapes, a restricted entry interval of 23 days is required for cane turning and girdling in table grapes and a restricted entry interval of 15 days is required for hand harvesting, training, thinning, hand pruning, tying and leaf pulling.

Since the proposed preharvest interval (PHI) for grapes is 14 days and a restricted entry interval of 15 days is required for hand harvesting in order to reach an acceptable MOE, a label amendment will be required to change the PHI to 15 days.

3.4.3 Residential Exposure and Risk Assessment

There are no residential uses for Mettle 125 ME Fungicide. Therefore, a residential handler assessment was not required.

3.4.3.1 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal.

Pick-Your-Own Scenario
There is potential exposure to bystanders in pick-your-own scenarios for strawberries. Adults, children and youth harvesting at pick-your-own operations have the potential for acute exposure to tetraconazole residues as this activity is only expected to occur once per year. Acute dermal exposure from harvesting at pick-your-own facilities may also co-occur with acute dietary exposure.

For the pick-your-own risk assessment, a NOAEL of 50 mg/kg bw/day from an acute neurotoxicity study in rats was deemed the appropriate endpoint for the dermal and dietary exposure. Although the endpoint comes from an oral study, it was considered to cover both oral and dermal exposure. Therefore, since the toxicological effects are the same for both routes of exposure, the daily dose from both routes of exposure should be combined in an aggregate risk assessment.

Exposure estimates were generated following the guidance in the PMRA Draft Standard Operating Procedures (SOPs) for Pick-Your-Own Assessments. Dermal exposure to bystanders re-entering treated strawberry fields is calculated by combining crop-specific DFR with activity-specific TCs.

Table 3.4.4 Dermal exposure of Bystanders performing U-pick activities

Population	TC[a]	Duration	DFR value*	Body weight	Dermal Exposure[b,c]
	cm^2/hr	hr	$\mu g/cm^2$	kg	mg/kg bw
Adults (ages 19+ yrs))	1000	2	0.1190	70	0.00102
Youth (ages 10-18 yrs)	689	2	0.1190	39	0.00126
Child (ages 1-9 yrs)	356	2	0.1190	15	0.00169

* Application rate is 0.46 $\mu g/cm^2$, The DFR value estimate is from day 0 after last application as there is a PHI of 0 days for hand harvesting strawberries.

[a] The TCs for Children and Youth were adjusted based on skin surface area and the standard TC for adult workers hand-harvesting strawberries (1000 cm^2/hr). The average surface area (SA) for each age group is from NAFTA document (NAFTA, 1999).

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

$$\frac{\text{DFR Value } (\mu g\ cm^2) \times \text{TC } (cm^2/hr) \times \text{Hours worked per day (hr)} \times \text{Conversion Factor (1 mg/1000}\mu g) \times 0.3 \text{ Dermal absorption}}{\text{Body Weight}}$$

[c] Based on dermal Absorption Value of 30% from the in vivo rat study

Aggregate Exposure and Risk Assessment

To assess the potential dietary exposure to tetraconazole from strawberries in PYO operations, an acute deterministic dietary exposure assessment was conducted using DEEM-FCID^{TM} (Version 2.14). The proposed MRL of 0.25 ppm for Crop Subgroup 13-07G, which includes strawberries, was used as the input value. The assessment was conducted for children aged 1-9 years, youth aged 10-18 years, and adults over the age of 19. The appropriate values to aggregate with dermal exposure are the exposure estimates at the 95th percentile. For the aggregate exposure assessment, dermal and acute dietary exposure values are combined and compared to the endpoint of concern.

Table 3.4.5 Aggregate Risk assessment for adults, youth and children bystanders performing pick your own on a single day

Population	Dermal Exposure	Dietary Exposure	Total Exposure	Total MOE[a]
	(mg/kg bw/day)	(mg/kg bw/day)	(mg/kg bw/day)	target = 100
Adults (19+)	0.00102	0.000630	0.00165	30,303
Youth (10-18)	0.00126	0.000834	0.00189	26,455
Child (0-9)	0.00169	0.001903	0.00359	13,928

[a] Based on a NOAEL of 50 mg/kg bw/day from a rat acute neurotoxicity study and compared to a target MOE of 100.

Results indicate acceptable MOEs, for all identified sub-populations.

3.5 Food Residues Exposure Assessment

The residue definition for risk assessment and enforcement in plant products and animal commodities is tetraconazole. The data gathering/enforcement analytical method is valid for the quantification of tetraconazole residues in crop matrices and livestock matrices. The residues of tetraconazole are stable when stored in a freezer at -20°C for 69 days in grape juice, 91 days in raisins, 36 months in wheat grain and straw, 38 months in apples and grapes, and 40 months in sugar beet roots. Tetraconazole residues concentrated in the processed commodity sugar beet molasses (2.8×), but did not concentrate in the processed commodities sugar beet refined sugar, grape juice or raisins. An adequate feeding study was carried out to assess the anticipated residues in livestock matrices resulting from the current uses. Supervised residue trials conducted throughout the United States using end-use products containing tetraconazole at exaggerated rates in or on sugar beets, and at the proposed rates in or on strawberries and grapes are sufficient to support the proposed maximum residue limits.

3.5.1 Dietary Risk Assessment

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

Triazole Metabolites
Dietary exposure to 1,2,4-triazole (T), triazolyl-1-alanine (TA) and triazolyl-1-acetic acid (TAA) may occur from the use of tetraconazole on food commodities. Residues of TA in plant commodities are regulated in Canada not to exceed 2.0 ppm. These metabolites are common to all triazole fungicides, including tetraconazole. The cumulative risks from T, TA, and TAA will be addressed in a separate document.

3.5.1.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the refined chronic analysis: 100% crop treated, default and experimental processing factors, residues of tetraconazole in crops at supervised trial median residue (STMdRs) values, and residues of tetraconazole in animal commodities at anticipated residue values. The refined chronic dietary exposure from all supported tetraconazole food uses (alone) for the total population, including infants and children, and all representative population subgroups are 11% of the ADI. Aggregate exposure from food and water is considered acceptable. The PMRA estimates that chronic dietary exposure to tetraconazole from food and water is 18.0% (0.000722 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants (< 1 year) at 47.4% (0.001894 mg/kg bw/day) of the ADI.

3.5.1.2 Acute Dietary Exposure Results and Characterization

The following criteria were applied to the basic acute analysis: 100% crop treated, default processing factors, and residues of tetraconazole in/on crops and animal commodities at MRL levels. The basic acute dietary exposure from all supported tetraconazole food uses was estimated to be 0.6% of the ARfD for the general population (95th percentile, deterministic). Aggregate exposure from food and water is considered acceptable and below PMRA's level of concern. Specifically, an acute dietary exposure of 0.4-1.8% of the ARfD (95th percentile, deterministic) was obtained for all population subgroups, with children 1-2 years old as the highest exposed population subgroup.

3.5.2 Aggregate Exposure and Risk

The aggregate risk for tetraconazole consists of exposure from food and drinking water sources only; there are no residential uses. Given that strawberries can be treated with tetraconazole, there is potential for exposure to tetraconazole during pick-your-own harvesting activities (Refer to Section 3.4.3.1 - Bystander Exposure and Risk).

3.5.3 Maximum Residue Limits

Table 3.5.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Crop Subgroup 13-07F – Small fruit vine climbing subgroup, except fuzzy kiwifruit	0.2
Crop Subgroup 13-07G – Low growing berry subgroup	0.25
Sugar beet roots	0.05
Sugar beet molasses	0.15
Fat, kidney, meat, and meat byproducts (except liver) of cattle, goats, horses, hogs and sheep	0.02
Liver of cattle, goats, horses, hogs and sheep	0.05
Milk	0.01

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

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

The nature of the residues in animal and plant matrices, analytical methodology, field trial data, and the acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 5 and 6.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Based on its physical-chemical properties, tetraconazole is very soluble in water and is not likely to volatilize from moist soil or water surfaces. It has low volatility at environmentally relevant temperatures and is not expected to be present in the air at significant levels.

Tetraconazole is persistent in the terrestrial environment and is not expected to form any major transformations products. However, prolonged exposure of tetraconazole residues on thin soil layers to sunlight can result in the formation of several transformation products: M14360-alcohol, triazolyl acetic acid, M14360-acid, triazole and M14360-difluoroacetic acid. Both triazolyl acetic acid and M14360-alcohol are non-persistent in the terrestrial environment. M14360-acid is the most persistent transformation product but is less persistent than tetraconazole.

According to the results of laboratory soil column leaching studies and adsorption and desorption studies, tetraconazole has low mobility potential in most soils. Tetraconazole's high soil adsorption capacity implies limited vertical movement through the soil profile and a low potential for groundwater contamination. However, its high water solubility and persistence in the environment may allow it to reach groundwater under some environmental conditions after repetitive applications over long periods of time. Transformation products of tetraconazole are more mobile than tetraconazole. However, they are not expected to be found in significant quantities in ground water because tetraconazole is considerably more persistent than these transformation products, which are expected to transform at a faster rate than they are formed. Terrestrial field dissipation studies in the United States and Germany confirm that tetraconazole is persistent with limited mobility. The results of these field dissipation studies also indicate tetraconazole has the potential to accumulate in soil and carryover to the following growing season.

Tetraconazole can enter the aquatic environment through spray drift, overland runoff or through the movement of tetraconazole bound to soil particles. Upon entering the aquatic environment, tetraconazole is expected to partition from the water column into sediments due to its high soil adsorption ability. As it is stable to hydrolysis, phototransformation and biotransformation in aquatic systems, tetraconazole is persistent in the aquatic environment. No major transformation products were detected in laboratory aquatic studies.

Environmental fate data for tetraconazole and its transformation products are summarized in Appendix I, Table 7.

4.2 Environmental Risk Characterization

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

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

A risk assessment of tetraconazole, its end-use product Mettle 125 ME Fungicide and three transformation products: M14360-alcohol, M14360-triazolyl acetic acid and M14360-acid was undertaken for terrestrial organisms based on available toxicity data to earthworms (acute contact and reproduction), bees (acute contact and oral), three species of predatory arthropods (contact), one parasitic arthropod (contact), birds (acute oral, dietary and reproduction), mammals (acute oral and reproduction), and ten crop species of terrestrial plants (seedling emergence and vegetative vigours). For beneficial insects, toxicity studies for two tetraconazole formulations were reviewed: Tetraconazole 125 g/L ME (representative of Mettle 125 ME Fungicide) and Tetraconazole 40 g/L ME (a similar microemulsion formulation for the European market). A summary of the terrestrial toxicity data for tetraconazole is presented in Appendix I, Table 8. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as

surrogates for the wide range of species that can be potentially exposed following treatment with tetraconazole.

Earthworms and soil-dwelling arthropods
Acute and chronic exposure of earthworms to tetraconazole can cause mortality and decreased body weights. The end-use product, Tetraconazole 125 g/L ME and the transformation products, M14360-alcohol, M14360-triazolyl acetic acid and M14360-acid, are less toxic than tetraconazole.

The EEC is calculated based on a direct application of tetraconazole to bare soil at the maximum cumulative application rate. The EEC values for M14360-alcohol, M14360-triazolyl acetic acid and M14360-acid were determined according to a worst-case scenario assuming 100% conversion of tetraconazole and were corrected for the molecular weight ratio of the transformation products to tetraconazole. The risk to earthworms resulting from acute and chronic exposure to tetraconazole does not exceed the LOC; therefore, there is also no concern from acute exposure to the transformation products and the end-use product. (Appendix I, Table 9).

Bee (pollinators) and beneficial arthropods
Acute oral and contact exposure of adult honey bees to high residues of tetraconazole and Tetraconazole 125 g/L ME can result in mortality and behavioural abnormalities, such as discoordination, apathy, intensive cleaning and nervous behaviour. Tetraconazole is classified as relatively non-toxic to honey bees through acute contact and oral exposures in accordance with the classification of Atkins (1981). When applied according to the Mettle 125 ME Fungicide label directions, tetraconazole is not expected to pose a risk to honey bees as the RQs are significantly less than the LOC (Appendix I, Table 9).

Acute contact exposure of predatory mite (*Typhlodromus pyri*) and parasitoid (*Aphidius rhopalosiphi*) to tetraconazole, Tetraconazole 40 g/L ME and Tetraconazole 125 g/L ME can result in mortality and reduced reproduction. Acute exposure of green lacewing (*Chrysoperla carnea*) and ground beetle (*Poecilus cupreus*) up to 250 g a.i./ha of tetraconazole 40 g/L ME did not result in any significant increase in mortality or observable sublethal effects.

Typhlodromus pyri, *A. rhopalosiphi* and *C. carnea* can be exposed to tetraconazole residues on plant foliage while *P. cupreus* can be exposed to tetraconazole residues in soil. The EECs are based on the highest cumulative applications that results in the highest foliar and soil residues. Tetraconazole is not expected to pose a risk to green lacewing (*C. carnea*), ground beetle (*P. cupreus*) and parasitic wasp (*A. rhopalosiphi)* as the LOC is not exceeded. However, tetraconazole may pose a risk to the predatory mite (*T. pyri*) as the LOC is exceeded at the screening level risk assessment (Appendix I, Table 9). To further characterize the risk to *T. pyri*, different exposure scenarios were considered: on-field and off-field (one metre downwind from the last spray swath). The on-field tier one refinement included a 70% foliar interception factor in EEC calculations. The off-field refinement assumed a 6% spray drift 1 metre downward from a ground boom sprayer application and a further 10% interception factor for leaves in off-field vegetation. After refinement of the exposure scenarios, the LOC is exceeded for the on-field

scenario but not for the off-field scenario. Therefore, tetraconazole may pose a risk to *T. pyri* in treated fields (Appendix I, Table 10).

Non-target plants

The effects of tetraconazole on non-target plants was determined from the exposure of the representative formulated product Eminent 125 SL Fungicide (11.6% tetraconazole) to standard crop species. No treatment related effects were observed up to the highest treatment rate of 112 g a.i./ha. A definitive screening level RQ cannot be determined for terrestrial plants as the highest cumulative application rate is higher than the highest treatment rate used in the terrestrial plant toxicity studies. Therefore, the RQs for the terrestrial plants may potentially exceed the level of concern (Appendix I, Table 9). A refined Tier I assessment was conducted based on drift of tetraconazole to non-target plants located one metre downwind from the point of application. The refined RQs did not exceed the LOC for terrestrial plants (Appendix I, Table 11). Therefore, tetraconazole is not expected to pose a risk to non-target terrestrial vegetation beyond one metre off-field.

Birds and small wild mammals

Tetraconazole is moderately to highly toxic to birds and slightly toxic to rats. Acute exposure of birds and mammals to tetraconazole can cause mortality and various degrees of sublethal effects, such as reduced weight and food consumption, lethargy, loss of coordination etc. Chronic exposure to tetraconazole results in adverse reproductive effects in birds and mammals (for example, reduced second generation survival and reproductive success in both birds and mammals and longer gestational times in mammals) and other physiological effects on endocrine organs and hormones in mammals. There are no data available on endocrine effects in birds. Tetraconazole is not currently listed as a chemical for screening in the Endocrine Disruptor Screening Program by the USEPA, however, risks related to its potential for endocrine effects may be subjected to further characterization if more data become available.

For the bird and mammalian risk assessments, the ingestion of food items contaminated by tetraconazole spray residues is considered to be the main source of exposure. Hence, the risk assessment is based on estimated daily exposure which takes into account the concentration of tetraconazole on various food items immediately after application and the food ingestion rate of different sizes of birds and mammals. The screening risk assessment was performed based the most conservative exposure estimates. Based on reasonable worst-case exposure scenarios, tetraconazole is not expected to pose an acute risk to birds or mammals as the RQs for acute exposure do not exceed the LOC. Tetraconazole may pose a reproductive risk to both birds and mammals, except for the smallest size class of mammals, as the RQs for reproduction effects exceed the LOC (Appendix I, Table 12).

To further characterize the reproductive risk to birds and mammals, the assessment was expanded to include a range of tetraconazole residue concentrations on all relevant food items. (Appendix I, Table 13). Also, both on- and off-field exposure estimates were considered. The off-field exposure takes into account the projected drift deposition at one metre downwind from the site of application.

When considering maximum tetraconazole residues, the on-field reproductive RQs exceed the LOC for small and medium sized birds of all feeding guilds, large sized herbivorous birds, large sized insectivorous birds feeding on small insects, medium sized herbivorous mammals and large sized herbivorous mammals feeding on leafy foliage, if these animals feed primarily on tetraconazole treated fields. Therefore, these animals are potentially at risk if they feed exclusively on tetraconazole treated fields. The off-field reproductive RQs exceed the LOC for small sized insectivorous and frugivorous birds, medium sized insectivorous birds feeding on small insects, and large sized herbivorous birds, while the RQs do not exceed the LOC for either medium sized mammals or large sized mammals (Appendix I, Table 13). Therefore, mammals feeding exclusively off treated fields are not expected to be at risk.

When considering the mean tetraconazole residues, the on-field RQs exceed the LOC for small sized insectivorous and frugivorous birds, medium sized insectivorous birds feeding on small insects, medium sized frugivorous birds, large sized herbivorous birds feeding on short grass and forage crops. The off-field RQ for small sized insectivorous birds only slightly exceeds the LOC (RQ = 1.19). Therefore, average tetraconazole residues are not expected to pose a significant risk to birds feeding exclusively outside treated fields.

4.2.2 Risks to Aquatic Organisms

A summary of the freshwater and marine/estuarine toxicity data for tetraconazole, M14360-acid, M14360-alcohol, M14360-triazolyl acetic acid and Tetraconazole 125 g/L ME is presented in Appendix I, Table 14. A risk assessment for tetraconazole, these three transformation products and Mettle 125 ME Fungicide was based on the submitted toxicological data for *Daphnia magna* (acute and chronic), freshwater midge (chronic), freshwater fish (acute and chronic early life stage), freshwater algae, freshwater vascular plant, amphibians (using fish as surrogate data), marine invertebrates and marine fish. The potential exposure of tetraconazole to the aquatic environment was based on the screening level EECs from the direct application of tetraconazole to water bodies of two different depths (15 cm and 80 cm) at the maximum application rates for strawberries. The 80-cm deep water body was chosen to represent a permanent body of water and the 15-cm deep water body was chosen to represent a seasonal body of water typical of amphibian habitat. The result of the screening level risk assessment for aquatic organisms is presented in Appendix I, Table 15.

Freshwater invertebrates

Acute exposure of *Daphnia magna* to tetraconazole can result in mortality while chronic exposure can result in reduced growth and reproduction. Mettle 125 ME Fungicide and the transformation products of tetraconazole, M14360-acid, M14360-alcohol and M14360-triazolyl acetic acid, are less toxic to *D. magna* than tetraconazole. Chronic exposure of sediment dwelling midges (*Chironomus riparius*) to tetraconazole can affect their survival and emergence. The screening level risk quotients for exposure of D. magna and C. riparius, however, do not exceed the LOC.

Freshwater fish and amphibians
Acute exposure of freshwater fish to tetraconazole can result in mortality and some sublethal effects such as loss of equilibrium, moribundity, increased pigmentation and lethargy. Mettle 125 ME Fungicide and transformation products of tetraconazole, M14360-acid, M14360-alcohol and M14360-triazolyl acetic acid, are less toxic to rainbow trout (*Oncorhynchus mykiss*) than tetraconazole. None of these chemicals are expected to pose an acute risk to rainbow trout as the RQs of these chemical to rainbow trout do not exceed the LOC. Tetraconazole exerts a similar magnitude of toxicity to bluegill sunfish (*Lepomis macrochirus*) as to rainbow trout and is also not expected to pose any acute risk to bluegill sunfish, either. Chronic exposure of tetraconazole to fathead minnow during early life-stages can result in lower hatching success, mortality and reduced growth (weight and length); however, tetraconazole is not expected to pose a chronic risk to fish as the RQ for fathead minnow does not exceed the LOC.

Risk to amphibians was assessed using fish toxicity data as surrogate endpoints. Acute risk was based on the EC_{50} from the bluegill sunfish from the acute toxicity study while chronic risk was based on the NOEL from the fathead minnow from the early life stage study. The amphibian screening level RQs did not exceed the LOC; hence, tetraconazole is not expected to pose a risk to amphibians.

Freshwater Algae and Aquatic Vascular Plants
Exposure of algae and aquatic vascular plants to tetraconazole may result in growth inhibition. Mettle 125 ME Fungicide and transformation products of tetraconazole, M14360-acid, M14360-alcohol and M14360-triazolyl acetic acid, are less toxic to green algae (*Scenedesmus subspicatus*) than tetraconazole. Tetraconazole exerted a similar magnitude of toxicity to the freshwater vascular plants (*Lemna gibba*) as to freshwater algae. None of these chemicals are expected to pose a risk to freshwater algae or aquatic vascular plants as the RQs did not exceed the LOC.

Marine and Estuarine Species
Tetraconazole was acutely toxic to mysid shrimp (*Americamysis bahia*), eastern oyster (*Crassostrea virginica*) and sheepshead minnow (*Cyprinodon variegates*). Exposure to tetraconazole can result in mortality, abnormal swimming behaviour and lethargy in *A. bahia*, reduced shell grown in *C. virginica,* and mortality, lethargy and loss of equilibrium in *C.variegates.* The screening level RQs for these species, however, do not exceed the LOC. Therefore, tetraconazole is not expected to pose an acute risk to most marine estuarine species.

Effects and risk of tetraconazole to marine algae are not assessed as no studies have been submitted. Based on the effects and risks of tetraconazole to freshwater algae and other marine organisms, tetraconazole is not likely to pose significantly more risk to marine algae than to other aquatic species.

4.2.3 Incident Reports (Environment)

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of the Health Canada's website. 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. As of May 29th 2012, no environmental incident reports were found for tetraconazole in either databases.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

5.1.1.1 Control of powdery mildew on grape

Results from eleven trials conducted in the United States in 2006–2009 were reviewed. Powdery mildew infection on leaves was recorded in seven trials under moderate to high disease pressure (average disease severity at 42% in non-treated control). Mettle 125 ME Fungicide reduced disease severity by 80%, 90% and 83% at the rates of 219, 292 and 365 mL/ha, respectively. Powdery mildew infection on grape bunches was recorded in nine trials under moderate to high disease pressure (average severity at 47% in non-treated control). Mettle 125 ME Fungicide reduced disease severity by 86%, 93% and 90% at the rates of 219, 292 and 365 mL/ha, respectively. The efficacy of Mettle 125 ME Fungicide was comparable to the commercial standard in the same trials. The efficacy data supported a 14-day spray interval for control of powdery mildew on grapes. A 21-day spray interval under low to moderate disease pressure is also supported since an acceptable level of control was achieved even under high disease pressure in some trials. The claim for control of powdery mildew on grape is supported at the rates of 219-365 mL/ha.

5.1.1.2 Control of black rot on grape

Results from three trials conducted in the United States in 2006-2009 were reviewed. In one trial under moderate disease pressure, Mettle 125 ME Fungicide reduced black rot severity on fruit bunches and leaves by 38 and 69% at the rate of 365 mL/ha, respectively. Mettle 125 ME Fungicide only provided partial suppression and suppression of black rot on grape bunches and leaves. The low efficacy in this trial could be a result of the delayed second application since the disease was not effectively controlled in the early stages of crop development. In the other two trials under high disease pressure, Mettle 125 ME Fungicide reduced black rot severity on fruit bunches by 94-100%, and reduced disease incidence on leaves by 79-95% at the rate of 365 mL/ha. The efficacy of Mettle 125 ME Fungicide was comparable to the commercial standard applied in the same trials. The claim for control of black rot on grape is supported at the rates of 292-365 mL/ha.

5.1.1.3 Control of powdery mildew on gooseberry

There were no efficacy data submitted. However, the data from strawberry trials can be extrapolated to support this claim. Gooseberry powdery mildew is a common problem, affecting all varieties. Fungicide spray is needed at the pre-bloom stage prior to disease development to protect the plants from mildew infection. The causal pathogen, *Sphaerotheca macularis*, is the same as on strawberry. Since the claim for control of powdery mildew on strawberry is supported at the rates of 219-365 mL/ha and the same application rate has been shown to be effective for the control of powdery mildew on grape, the claim for control of powdery mildew on gooseberry is supported at the rates of 219-365 mL/ha.

5.1.1.4 Control of cercospora leaf spot on sugar beet

Results from nine trials conducted in the United States in 2001–2009 were reviewed. In six trials with cercospora leaf spot at moderate to high pressure, Mettle 125 ME Fungicide reduced disease severity by 60% which was comparable to the disease reduction achieved by the commercial standard. Mettle 125 ME Fungicide also reduced disease infection (either number of spot per leaf or percent infection) by 86% and 98% in two trials under low disease pressure, and reduced disease infection (number of spot per leaf) by 89% in one trial under moderate disease pressure. Yield benefits from Mettle 125 ME Fungicide treatments were also demonstrated in six out of nine trials. The claim for control of cercospora leaf spot on sugar beet is supported at the rates of 950 mL/ha.

5.1.1.5 Control of powdery mildew on sugar beet

Results from seven trials conducted in the United States, Austria and Germany in 2000–2005 were reviewed. In five trials with powdery mildew at moderate pressure, Mettle 125 ME Fungicide reduced disease severity by 90% in one trial at the rate of 800 mL/ha, and by 96% in another trial at the rate of 950 mL/ha. The rate of 800 mL/ha was tested in two Austrian trials under high disease pressure. Mettle 125 ME Fungicide reduced disease severity by 68% and 72% at the rate of 800 mL/ha in these trials. There was no commercial standard tested in these trials. Yield benefits from Mettle 125 ME Fungicide treatments were also demonstrated in some trials. The claim for control of powdery mildew on sugar beet is supported at the rates of 950 mL/ha.

5.1.1.6 Control of powdery mildew on strawberry

Results from two trials conducted in the United States in 2006 and 2008 were reviewed. In one trial under low disease pressure, Mettle 125 ME Fungicide reduced foliar disease severity by 89, 92 and 89% at the rates of 250, 334 and 417 mL/ha, respectively. The efficacy of Mettle 125 ME Fungicide was superior to the commercial standard. However, Mettle 125 ME Fungicide only partially suppressed foliar disease severity by 44-50% in another trial.

Results from five additional trials conducted in China, Poland, and Turkey from 1999 to 2009 were also reviewed. Powdery mildew was recorded as moderate to high disease pressure (severity at 45-86%) in these trials. Tetraconazole reduced disease severity by 72-94% (average 88% across all rates applied) at the rate range of 26.7-50 g a.i./ha (equivalent to Mettle 125 ME Fungicide at 219-417 mL/ha) in the Chinese and Turkish trials. Two applications were applied in these trials. A single tetraconazole rate of 61 g a.i./ha (equivalent to Mettle 125 ME Fungicide at 509 mL/ha) was tested in the Poland trial. The treatment reduced powdery mildew severity by 88% under a moderate disease pressure. The claim for control of powdery mildew on strawberry is supported at the rates of 219-365 mL/ha.

5.2 Phytotoxicity to Host Plants

No phytotoxicity or crop injury was reported.

5.3 Economics

No market analysis was done for this application.

5.4 Sustainability

5.4.1 Survey of Alternatives

Refer to Appendix I, Table 17 for a summary of the active ingredients currently registered for the same uses as Mettle 125 ME Fungicide.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

The use of Mettle 125 ME Fungicide is compatible with current integrated pest management practices and production practices.

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

According to the Fungicide Resistance Action Committee, tetraconazole is a Group 3 fungicide (DMI). The group is estimated to be at medium risk of disease resistance development and resistance management must be considered. For instance, powdery mildew (*Erysiphe necator*) on grape is currently listed as a pathogen with medium risk to develop fungicide resistance, and fungicide failure has also been reported on the control of cercospora leaf spot on sugar beet due to widespread resistance of *Cercospora beticola* to fungicides. Alternation or mixtures with an effective non cross-resistant fungicide are especially crucial. Resistance management recommendations are addressed on the product label.

5.4.4 Contribution to Risk Reduction and Sustainability

Mettle 125 ME Fungicide offers additional tools to Canadian growers for disease and resistance management on labelled crops. Mettle 125 ME Fungicide should be integrated into an overall disease management program.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

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

During the review process, tetraconazole and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

Tetraconazole does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 16 for comparison with Track 1 criteria.

Tetraconazole does not form any major transformation products that meet all Track 1 criteria. See Appendix I, Table 16 for comparison with Track 1 criteria.

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

6.2 Formulants and Contaminants of Health or Environmental Concern

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

Based on the formulating process used, impurities and formulants of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances and allergens known to cause anaphylactic-type reactions, are not expected to be present in the product Mettle 125 ME Fungicide or carried through from the technical grade active ingredient.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for tetraconazole is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. Tetraconazole is not selectively neurotoxic or immunotoxic. In short-term and chronic studies on laboratory animals, the primary targets were the liver, bones, kidney and several endocrine organs (adrenals, ovary, thyroid and pituitary). After longer-term dosing there was no evidence of oncogencity in the rat. There was evidence of liver oncogenicity in the mouse after longer-term dosing, but this effect was dependent on a threshold-based mode of action. 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.

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

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

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

The nature of the residue in plants and animals is adequately understood. The residue definition in plant products and animal matrices is tetraconazole. The proposed use of tetraconazole on grapes, gooseberries, strawberries, and sugar beets does not constitute an unacceptable chronic or acute dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend maximum residue limits to protect human health. The PMRA recommends that the following maximum residue limits be specified for residues of tetraconazole.

Commodity	Recommended MRL (ppm)
Crop Subgroup 13-07F – Small fruit vine climbing subgroup, except fuzzy kiwifruit	0.2
Crop Subgroup 13-07G – Low growing berry subgroup	0.25
Sugar beet roots	0.05
Sugar beet molasses	0.15
Fat, kidney, meat, and meat byproducts (except liver) of cattle, goats, horses, hogs and sheep	0.02
Liver of cattle, goats, horses, hogs and sheep	0.05
Milk	0.01

Mixers, loaders, applicators and workers entering treated fields are not expected to be exposed to levels of tetraconazole that will result in unacceptable risk when Mettle 125 ME Fungicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers. Risk to workers re-entering treated areas is not of concern provided that specified restricted entry intervals are observed.

Bystander exposure to individuals in pick-your-own scenarios is not expected to result in unacceptable risk when Mettle 125 ME Fungicide is used according to label directions.

7.2 Environmental Risk

Tetraconazole is persistent in soils and aquatic systems. It has low mobility in soils, but may eventually reach ground water with long-term repeated use. It has low volatility and atmospheric concentrations are expected to be negligible. Tetraconazole has low bioconcentration potential. Tetraconazole may pose a risk to non-target arthropods, birds, mammals and terrestrial plants. Therefore, statements on the product label are required to inform users of the potential risks. In order to minimize the potential exposure resulting from off-field drift, non-spray buffer zones will be required between the treated area and downwind terrestrial habitats.

7.3 Value

Since the diseases claimed are of serious concern to the production of the crops in question, there is a strong grower demand for this product in Canada, especially considering that the product is currently registered in the United States. Making the product available for Canadian growers offers a new fungicide option for use, and improves the level of efficacy of pest control on these crops. Some other triazoles fungicides (i.e. prothioconazole, metconazole and myclobutanil) are already registered in Canada, but this product will add an additional product in the same chemical group which will contribute to disease management options for these targeted diseases. An additional value consideration is that the supported uses address two priorities identified in the Canadian Grower Priority Database, those being powdery mildew on sugar beet and strawberry.

A summary of the proposed and accepted uses for Mettle 125 ME Fungicide is presented in Appendix I, Table 18.

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 Tetraconazole Technical Fungicide and Mettle 125 ME Fungicide, containing the technical grade active ingredient tetraconazole, to control powdery mildew on grape, gooseberry, strawberry and sugar beet; black rot on grape; and cercospora leaf spot on sugar beet.

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

♂	male
♀	female
µg	micrograms
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
ALT	alanine amino transferase
AP	alkaline phosphatase
APTT	activated partial thromboplastin time
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
AST	aspartate aminotransferase
ATPD	area treated per day
AUC	area under curve
BAF	bioaccumulation factor
BCF	bioconcentration factor
BUN	blood urea nitrogen
bw	body weight
BW	generic body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
cm	centimetres
C_{max}	maximum concentration
CR	chemical resistant
CT_{50}	clearance time 50% (the time required to observe a 50% decline in concentration in test animal)
CT_{90}	clearance time 90% (the time required to observe a 90% decline in concentration in test animal)
d	day(s)
DAF	dermal absorption factor
DFR	dislodgeable foliar
DMI	demethylation inhibitors
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the time required to observe a 90% decline in concentration)
dw	dry weight
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
ECD	electron capture detection
EDE	estimated daily exposure
EEC	estimated environmental exposure concentration

EP	end-use product
ER_{50}	effective rate on 50% of the population
ErC_{50}	EC_{50} in terms of reduction of growth rate
EROD	7-ethoxyresorufin O-deethylase
EyC_{50}	EC_{50} in terms of reduction of yield
fc	food consumption
fe	food efficiency
FIR	food ingestion rate
g	gram
GAP	good agricultural practices
GC	gas chromatography
GDH	glutamate dehydrogenase
GIT	gastrointestinal tract
GGT	gamma-glutamyl transferase
hr	hour(s)
ha	hectare(s)
HAFT	highest average field trial
HC	historical control
HDPE	high-density polyethylene
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
K_{desorb}	soil desorption coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	limit of detection
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
MAS	maximum average score
MBD	more balanced diet
MCHC	mean cell haemoglobin concentration
ME	micro emulsion
mg	milligram
mL	millilitre
M/L/A	mixer/loader/applicator
mM	millimolar
MOA	mode of action
MOE	margin of exposure
mPa	megapascals
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable

NAFTA	North American Free Trade Agreement
NC	not classified
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NPD	nitrogen phosphorus detection
NZW	New Zealand white
OCT	ornithine carbamoyl transferase
PBI	plantback interval
PCNA	proliferating cell nuclear antigen
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
pK_a	dissociation constant
PLT	platelets
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
PROD	7-pentoxyresorufin O-dependentylase
PYO	pick your own
Q_1*	cancer potency factor
rel	relative
RQ	risk quotient
rT_3	reverse triiodothyronine hormone
SA	surface area
SL	soluble liquid concentrate
SOP	standard operating procedures
SPUD	Statistics on Pesticide Use Database
STMdR	supervised trial median residue
STMR	supervised trial mean residue
$t_{1/2}$	half-life
T_{max}	time of maximum concentration
T	1,2,4-triazole
T_3	tri-iodothyronine
T_4	thyroxine
TA	triazolyl-1-alanine
TAA	triazolyl-1-acetic acid
TC	transfer coefficient
THP	triazolylhydroxypropionic acid
TP	transformation product(s)
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
UDPGT	uridine diphosphate glucuronosyl transferase
UDS	unscheduled DNA synthesis
UK	United Kingdom
USEPA	United States Environmental Protection Agency

UV	ultraviolet
WBC	white blood cells
wk	week(s)
wt	weight(s)

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		Reference
Soil	not provided	parent	GC-MS	0.05 mg/kg		1904091
Sediment	not provided	parent	GC-NPD	0.010 mg/kg		1904092 1904184
Water	not provided	parent	GC-NPD	0.1 µg/L (drinking water)		1904094
				1.0 µg/L (river and pond water)		1904095
Plant	Method 2258 Enforcement Method	Tetraconazole	GC/NPD	0.01 ppm 0.02 ppm	Cereal grain Cereal straw, grapes, apples, tomatoes	1905037
Animal	Method 2258 Enforcement Method	Tetraconazole	GC/ECD	0.01 ppm 0.02 ppm	Milk, eggs Fat and meat of cattle	1905037

Table 2 Toxicity Profile of Mettle 125 ME Fungicide[1]

Study Type/Animal/PMRA #	Study Results
Acute Oral Sprague-Dawley rats PMRA # 1904971	LD_{50} > 5050 mg/kg bw **Low toxicity**
Acute Dermal NZW rabbits PMRA # 1904973	LD_{50} > 5050 mg/kg bw **Low toxicity**
Acute Inhalation (nose-only) Sprague-Dawley rats PMRA # 1904975	LC_{50} > 2.10 mg/L **Low toxicity**
Primary Dermal Irritation NZW rabbits PMRA # 1904979	$MAS_{24,\ 48\ \&\ 72\ hrs}$ = 0.2/8 **Minimally irritating**
Primary Eye Irritation NZW rabbits PMRA # 1904977	$MAS_{24,\ 48\ \&\ 72\ hrs}$ = 9.3/110 **Minimally irritating**
Dermal Sensitization (Buehler) Hartley guinea pigs PMRA # 1904981	**Non-Sensitizing**

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

Table 3 Toxicity Profile of Technical Tetraconazole[1]

Study Type/Animal/PMRA #	Study Results
Metabolism/Toxicokinetic, oral (gavage, single dose and 14-day repeat dosing) Sprague-Dawley rats PMRA # 1904048, 1904056, 1904060, 1904063 to 1904065, 1904067, 1904070, 1904077, 1904080 to 1904087, 1904111, 1904112, 2194362, 2194363 ^{14}C-phenyl and ^{14}C-triazole radiolabels	**Rate and extent of absorption:** Absorption of tetraconazole was rapid and dose dependent. Maximum blood concentrations (C_{max}) occurred from ~1 to 27 hrs post-dose (T_{max}), depending on the dose level, sex and radiolabel; single-dose T_{max} values were ~1 to 8 hrs at the low dose and ~4 to 27 hrs at the high dose; the later times were for ♀ and for the ^{14}C-triazole radiolabel. Regardless of the dose, ♂ C_{max} values were slightly higher and area-under-the-curve (AUC) values were slightly lower compared to ♀. The AUC values were also higher for the ^{14}C-triazole compared to the ^{14}C-phenyl label. The extent of uptake was moderate to high, as evidenced by the total recoveries in the urine. Overall, absorption characteristics were similar with single and repeated doses. **Distribution / target organ(s):** Distribution was extensive, but with no evidence of bioaccumulation. Although the ^{14}C-phenyl label accumulated rapidly in the fat, there was no evidence that it was specifically retained in this or any other tissue after single or repeated doses. The highest tissue-specific residue concentrations occurred in the GIT, liver, kidney, adrenal glands and ovaries, regardless of the dose level, radiolabel used and whether dosing was single or repeated. Apart from the ovary, which had higher radioactivity than the testes, there were only minimal differences in the distribution between the sexes. Lower tissue levels after repeated dosing was considered evidence of metabolic adaptation. **Metabolism:** With the ^{14}C-triazole label, 1,2,4-triazole was the major metabolite in the urine (♂ 65-70% AD; ♀ 48-63% AD) after 48 hrs; concurrent levels in the feces were lower (♂ 6-10% AD; ♀ 8-10% AD). The major transformation pathways included oxidation, reduction and conjugation mediated by glutathione. With the ^{14}C-phenyl label, the major metabolites were P1 (sulfoxide conjugate; ♂ 9-19% AD; ♀ 35-45% AD) in the urine and P4 (N-acetylcysteine conjugate) in urine (♂ 19% AD; ♀ 2% AD) and feces (♂ 12% AD; ♀ 3% AD). Minor metabolites included tetraconazole-acid (6 to 18% AD in urine, with lower values in ♂), tetraconazole-alcohol (< 8% AD in feces) and M3, M6, P2 (< 9% AD in urine), P3 (< 7% AD in urine) and P5 (< 8% AD in feces). In addition, minor amounts of tetraconazole-dichlorophenyl-3OH (S5, < 4% AD) and tetraconazole-dichlorophenyl-5OH (S6, < 2% AD) occurred in the feces (free) and urine (conjugated), while tetraconazole-difluoroacetic acid was detected in the urine (<2% AD). Only a minor amount of the recovered radiolabel was unidentified. **Rate and extent of excretion:** Excretion was rapid; it was nearly complete after 48 hrs. There were no substantive differences in the excretion half-lives ($t_{1/2}$) between sexes or dose levels, but the values for the ^{14}C-triazole label were slightly less those of the ^{14}C-phenyl label. The major route of excretion was via the urine. Both sexes excreted greater amounts in the urine (52-76% AD) than in the feces (12-36% AD) within 72 hrs. Compared to the ^{14}C-phenyl label, the extent of excretion of the ^{14}C-triazole label was higher in the urine and lower in the feces. Biliary excretion was not assessed, but was inferred from the levels of unchanged parent in the feces (< 6% AD), which were much lower than the total radiolabel recoveries in the feces. Excretion was largely independent of the sex, dose level and radiolabel. Acclimation via increased urinary excretion was evident with repeated dosing.

Study Type/Animal/PMRA #	Study Results
Acute Oral (acute toxic class) Wistar rats PMRA # 1903873	LD_{50} (♀) = 1,000 mg/kg bw **Slight Toxicity**
Acute Oral Sprague-Dawley rats PMRA # 1903883	LD_{50} (♂/♀) = 1,248/1,031 mg/kg bw **Slight toxicity**
Acute Dermal Sprague-Dawley rats PMRA # 1903885	LD_{50} > 2,000 mg/kg bw **Low toxicity**
Acute Inhalation (whole body) Sprague-Dawley rats PMRA # 1903888	LC_{50} > 3.66 mg/L **Low toxicity**
Primary Dermal Irritation NZW rabbits PMRA # 1903893	$MAS_{24, 48 \& 72 hrs}$ = 0/8 **Non-irritating**
Primary Eye Irritation NZW rabbits PMRA # 1903890	$MAS_{24, 48 \& 72 hrs}$ = 0.67/110 (♂) **Minimally irritating**
Dermal Sensitization (maximization method) Hartley guinea pigs PMRA # 1903894	**Non-sensitizer**
Dermal Sensitization (maximization method) Hartley guinea pigs PMRA # 1903897	**Non-sensitizer**
90-Day Oral (diet) CD-1 mice Non-guideline PMRA # 1903905	NOAEL (♂/♀) = 4/4 mg/kg bw/day LOAEL (♂/♀) = 16/20 mg/kg bw/day Based on ↑ serum ALT, liver wt, hepatocyte hypertrophy (centrilobular) and single cell degeneration, pale areas in liver; ↑ serum AST, ↓ BUN, ↑ liver single cell necrosis and areas of necrosis (♀)

Study Type/Animal/PMRA #	Study Results
28-Day Oral (gavage), range-finding Sprague-Dawley rats Non-guideline PMRA # 1903913	A NOAEL was not established as this was a dose range-finding study ≥ 70 mg/kg bw/day: ↑ clinical signs (brown peri-oral staining, hair loss, dirty tails), ↓ bwg, ↓ plasma glucose, ↑ liver wt; ↓ fe, ↑ total protein, albumin and globulin, ↑ calcium, ↑ kidney wt, enlarged liver (♂); ↓ WBC, ↑ ovary wt (♀) ≥ 200 mg/kg bw/day: ↑ clinical signs, ↑ creatinine, ↓ AST, ↑ accentuated lobular markings in the liver, ↑ pale incisors; ↓ bw, ↓ WBC and lymphocytes, ↑ BUN, ↑ broken incisor (♂); ↑ mortality, ↑ sodium and phosphorous (♀) 500 mg/kg bw/day: ↑ mortality, ↑ clinical signs, pathology in decedents: ↑ congestion of adrenals, ↑ gastric distention, ↑ forestomach congestion
28-Day Oral (diet), range-finding Sprague-Dawley rats Non-guideline PMRA # 1903914	A NOAEL was not established as this was a dose range-finding study ≥ 1.57 mg/kg bw/day: ↑ GDH (*non-adverse*) (♂) 4.19 mg/kg bw/day: ↑ ALT (*non-adverse*), ↓ adrenal wt (♂)
28-Day Oral (diet), range-finding Sprague-Dawley rats Non-guideline PMRA # 1903912	A NOAEL (♂/♀) was not established as this was a dose range-finding study ≥ 4.4/3.8 mg/kg bw/day: ↑ relative kidney wt; ↑ liver wt, ↑ enlarged liver, ↓ adrenal wt (♂) ≥ 17.5/16.0 mg/kg bw/day: ↑ hepatocellular hypertrophy (centrilobular and/or midzonal); altered testes wt (♂); ↑ potassium and phosphorus (♀) ≥ 68.4/62.3 mg/kg bw/day: ↓ spleen wt; ↓ bwg (wk 1), ↓ glucose, ↑ globulin and AP, ↓ pituitary wt, ↑ relative testes wt (♂); ↓ bw, bwg and fc, ↑ BUN, liver wt, enlarged liver and pale incisors, ↓ adrenal, heart and ovary wts (♀) 229/217 mg/kg bw/day: ↑ clinical signs, pale livers, accentuated liver markings and hepatocyte fine vacuolation (centrilobular and midzonal), ↓ absolute brain wt; ↓ bw, bwg and fc, ↑ potassium, phosphorus and BUN, ↓ cholesterol and absolute heart wt, ↑ pale incisors (♂); ↓ glucose, ↑ AP, cholesterol and small uteri, ↓ uterine and pituitary wts (♀) ~ 1,000 mg/kg bw/day: ↑ mortality, clinical signs and inappetence, ↓ fecal output and bw loss, ↑ gross and microscopic pathology in the liver
90-Day Oral (diet) Sprague-Dawley rats PMRA # 1903903, 1903904	NOAEL (♂/♀) = 4.1/5.5 mg/kg bw/day LOAEL (♂/♀) = 23.9/28.7 mg/kg bw/day Based on ↓ ALT and AST, ↑ cholesterol, potassium and MCHC, ↑ liver and kidney wts, ↑ hepatocyte hypertrophy (centrilobular) and lipid accumulation; ↑ bw, bwg and fe, ↓ monocytes, ↑ calcium, globulin, urine volume, enlarged liver and swollen liver (♂); ↓ bw, bwg, fe, AP, GDH and uterus wt (♀)
28-Day Oral (diet), range-finding Beagle dogs Non-guideline PMRA # 1903906	A NOAEL (♂/♀) was not established as this was a dose range-finding study 10.6/12.2 mg/kg bw/day: ↑ AP, firm dark nodules on diaphragmatic lobe of the lungs; ↓ ALT (♂) ≥10.6/12.2 mg/kg bw/day: ↑ rel liver wt 11.7/12.9 mg/kg bw/day: generalized reddening of the lungs, red streak on pulmonary valve of the heart (♂); pale liver (♀) ≥11.7/12.9 mg/kg bw/day: ↓ bwg 19.5/13.6 mg/kg bw/day: ↓ bw and fc, ↑ AP, ↓ AST; ↑ ALT (♂)

Study Type/Animal/PMRA #	Study Results
12-Month Oral (diet) Beagle dogs PMRA # 1903910	NOAEL (♂/♀) = 2.95/3.33 mg/kg bw/day LOAEL (♂/♀) = 12.97/14.50 mg/kg bw/day Based on ↑ enzymes (AP, ALT, AST, OCT, GGT) and phosphorus in the blood, ↑ APTT and PLT, ↓ WBC, ↑ liver pathology (centrolobular hepatocyte rarefaction and fat accumulation, eosinophilic hepatocyte inclusions, apparent hepatocyte hypertrophy) and kidney pathology (apparent cortical tubular hypertrophy, apoptotic bodies in cortical tubules), ↑ liver and kidneys wts; ↓ AST, ↑ cholesterol, enlarged kidneys (♂); ↑ urine protein and specific gravity, ↑ pale liver lobes and lobular marking (♀)
21-Day Dermal NZW rabbits PMRA # 1903915	Dermal toxicity NOAEL = not established LOAEL = 30.1 mg a.i./kg bw/day Based on ↑ slight to well-defined erythema in most animals (↑ edema occurred at higher dose levels) Systemic toxicity NOAEL = 240.8 mg a.i./kg/day LOAEL was not established
28-Day Inhalation Wistar rats Non-guideline PMRA # 1903916	NOAEL = Not established. LOAEL = 14.3 mg/kg bw/day (0.055 mg/L) Base on ↑ squamous cell metaplasia of the laryngeal mucosa, mononuclear cell infiltration of larynx and goblet cell hypertrophy in the nasal cavity and nasopharyngeal duct; ↑ thyroid follicular cell hypertrophy and body temperature (♂)
18-Month Oncogenicity, oral (diet) Crl:CD-1 (ICR) mice PMRA # 1903969, 1903972, 1903975, 1903977, 1903978, 1903979, 1903981, 1903983, 1903985, 1903986, 2202273	NOAEL (♂/♀) = 1.4/1.6 mg/kg bw/day LOAEL (♂/♀) = 12.0/14.8 mg/kg bw/day Based on ↑ absolute liver wt, pale livers with accentuated lobular markings and hepatocyte fat accumulation; ↑ kidney wt, hepatocyte changes (centrilobular hypertrophy, eosinophilic ± vacuolation, generalized vacuolation) and pigmented macrophages in the liver (♂) Neoplastic Lesions: ≥118/140 mg/kg bw/day: ↑ hepatocellular tumours [adenomas: ♂, 18, 16, 12, 44, 68% (HC, 8 to 24%, mean = 14%); ♀, 0, 0, 0, 22, 52% (HC, 0 to 2%, mean < 1%), carcinomas: ♂, 2, 4, 4, 8, 40% (HC, 0 to 14%, mean = 5%); ♀, 0, 0, 0, 2, 34% (HC, mean = 0%), combined tumours: ♂, 20, 18, 14, 44, 84; ♀, 0, 0, 0, 22, 64% (HC, 10 studies ± 2 years)] **Evidence of oncogenicity.**
24-Month Oncogenicity, oral (diet) Sprague-Dawley rats PMRA # 1903941, 1903943, 1903945, 1903946, 1903949, 1903952, 1903955, 1903958, 1903962, 1903964, 1903966, 1903967, 1903968, 2205021	NOAEL (♂/♀) = 0.4/0.6 mg/kg bw/day LOAEL (♂/♀) = 3.4/4.4 mg/kg bw/day Based on ↓ pituitary wt, ↓ ALT, altered cholesterol (♂/♀, ↓ / ↑), ↑ hepatocyte hypertrophy (centrilobular), eosinophilic vacuolization and foci/areas, pale incisors; ↓ interim bw, ↑ centrilobular hepatocyte fine vacuolization and fat (interim), necrosis (interim), accentuated lobular markings (interim), osseus hypertrophy and thickening of cranial bones and pale lower incisors, ↓ dental health (♂); ↑ bile duct hyperplasia and pale subcapsular areas, ↓ periportal vacuolation in liver, ↑ uterus fluid distension, absent corpora lutea (interim gross pathology and histopathology), ↓ prominent corpora lutea (gross pathology at termination) and squamous metaplasia of endometrial glands (interim), ↓ hypertrophic adrenal cortical cells (♀) **No evidence of oncogenicity.**

Study Type/Animal/PMRA #	Study Results
Reproductive, oral (diet), range-finding Sprague-Dawley rats Non-guideline PMRA # 1903990	A NOAEL was not established as this was a dose range-finding study Parental toxicity: ≥6.9 mg/kg bw/day: ↑ mortality related to dystocia (♀) 34.2 mg/kg bw/day: ↓ bw, bwg, pre-mating fc (F_0), fe (F_0), ↑ liver wt (♀) Reproductive toxicity: 34.2 mg/kg bw/day: ↓ implantation sites, ↓ sex ratio, ↑ pup loss during early lactation period, ↑ duration of gestation (♀) Offspring toxicity: 34.2 mg/kg bw/day: ↓ pup wt during lactation period, ↓ litter size and weight, ↑ liver wt
Two-Generation Reproductive, oral (diet) Sprague-Dawley rats PMRA # 1903991, 1903992, 1903993, 1903995	Parental toxicity: NOAEL (♂/♀) = 0.7/0.8 mg/kg bw/day LOAEL (♂/♀) = 4.9/5.9 mg/kg bw/day Based on ↓ adrenal wt (♂); ↑ mortality, ↓ bw, ↓bwg (♀) Reproductive toxicity: NOAEL (♂/♀) = 35.5/0.8 mg/kg bw/day LOAEL (♂/♀) = not established/5.9 mg/kg bw/day Based on ↑ duration of gestation (associated with total litter losses) and dystocia (♀) Offspring toxicity: NOAEL = 0.8 mg/kg bw/day LOAEL = 5.9 mg/kg bw/day Based on ↑ rel. liver wt (*histopathology was not assessed*) **No evidence of offspring sensitivity**
Prenatal Developmental, oral (gavage), range-finding Sprague-Dawley rats Non-guideline PMRA # 1904001	A NOAEL (♂/♀) was not established as this was a dose range-finding study Maternal toxicity: ≥30 mg/kg bw/day: ↓ bwg and fc during gestation, ↑ kidney wt 100 mg/kg bw/day: ↑ post-dose salivation, brown staining, hair loss, water consumption and liver wt, Developmental toxicity: 100 mg/kg bw/day: ↑ domed craniums and absent tail
Prenatal Developmental, oral (gavage) Sprague-Dawley rats PMRA # 1904001	Maternal toxicity: NOAEL = 22.5 mg/kg bw/day LOAEL = 100 mg/kg bw/day Based on ↑ post-dose salivation and brown staining, ↓ bw, bwg and fc during gestation, ↑ water consumption, liver wt and relative kidney wt Developmental toxicity: NOAEL = 22.5 mg/kg bw/day LOAEL = 100 mg/kg bw/day Based on ↑ 'small' fetuses,↑ variations (supernumerary ribs, hydroureter, hydronephrosis) **No evidence of teratogenicity**

Study Type/Animal/PMRA #	Study Results
Prenatal Development, oral (gavage), range-finding Rabbit, NZW Non-guideline PMRA # 1904002	NOAELs were not established as this was a dose range-finding study Maternal toxicity: ≥40 mg/kg bw/day: ↑ inappetence, low fecal output, emaciation, ↓ fc and bw, ↑ liver wt, kidney wt, liver pallor and pale areas, mottled liver, abortions (1 associated with a mortality) and post-implantation loss 80 mg/kg bw/day: ↑ mortality and early resorptions Developmental toxicity: 40 mg/kg bw/day: ↓ litter & fetal wt, ↑ fetal loss
Prenatal Development, oral (gavage) Rabbit, NZW PMRA # 1904002	Maternal toxicity: NOAEL = 15 mg/kg bw/day LOAEL = 30 mg/kg bw/day Based on ↓ bw & bwg during dosing Developmental toxicity: NOAEL = 30 mg/kg bw/day LOAEL not established **No evidence of developmental toxicity or sensitivity of the young.**
Bacterial Reverse Mutation Assay (Ames test) PMRA # 1904015	Cytotoxicity for majority of strains at ≥1,000 µg/plate (-S9) or at 2,000 µg/plate (+S9). **Negative**
In vitro Mammalian Clastogenicity PMRA # 1904042	Cytotoxicity at ≥31.3 µg/mL (-S9, 6 hr treatment, 24 hrs harvest and treatment); ≥15 µg/mL (-S9, 48 hrs treatment); ≥15.6 µg/mL (+S9, 6 hr treatment, 24 hr harvest). **Negative**
In vitro Mammalian Cell Assay (forward gene mutation) PMRA # 1904044	Cytotoxicity at ≥100 µg/mL (±S9) **Negative**
In vivo Cytogenetics, oral (gavage, micronucleus assay) CD-1 mice PMRA # 1904043	Not cytotoxic to the target tissue. **Negative**
In vitro Unscheduled DNA synthesis (UDS) assay Human (cell line) PMRA # 1904046	Cytotoxicity at ≥64 µg/mL (±S9), positive controls acceptable **Negative**
Acute Neurotoxicity, oral (gavage), range-finding Sprague-Dawley rats Non-guideline PMRA # 2018550	A NOAEL was not established as this was a dose range-finding study 600 mg/kg bw: 1 ♀ at 5 hrs post-dose had slightly soiled fur, slightly impaired mobility, low arousal, body drags, and ↓ respiratory rate; this animal was euthanized at 7 hrs post-dose, due to further deterioration of its condition 750 mg/kg bw: 1 ♂ had slightly soiled fur, hunched gait, slight lacrimation, slightly drooping palpebral eyelid close, ataxia, ↓ respiratory rate, soft & flabby muscle tone, totally impaired mobility and very low arousal, with deterioration progressing between 3 to 7 hrs post-dose

Study Type/Animal/PMRA #	Study Results
Acute Neurotoxicity, oral (gavage) Sprague-Dawley rats PMRA # 2018551	NOAEL = 50 mg/kg bw LOAEL = 200 mg/kg bw Based on ↓ overall total cumulative locomotor activity counts on Day 0, ↓ ambulatory locomotor activity counts on Day 0; ↑ clinical signs (♀)
28-Day Neurotoxicity, oral (diet), range-finding Sprague-Dawley rats Non-guideline PMRA # 2054724	A NOAEL was not established as this was a dose range-finding study 40.7 mg/kg bw/day: ↓ bw, ↓ bwg (♀)
90-Day Neurotoxicity, oral (diet) Sprague-Dawley rats PMRA # 2054725	NOAEL (♂/♀) = 8.7/9.5 mg/kg bw/day NOAEL (♂/♀) = 46/51 mg/kg bw/day Based on ↓ overall activity (↑ rate of habituation) (♂); ↓ bw and bwg, ↑ overall activity (↓ habituation during wk 1 only) (♀)
28-day Immunotoxicity, oral (diet) Sprague-Dawley rats PMRA # 2054726	NOAEL = 2 mg/kg bw/day LOAEL = 10 mg/kg bw/day ≥ 10 mg/kg bw/day: ↓ spleen cell specific activity and total spleen activity in the antibody plaque-forming cell assay The natural killer cell assay was negative.
14-day Special investigative study, oral (diet) Crj:CD-1 (ICR) mice Non-guideline PMRA # 1904049	Investigation of xenobiotic enzyme induction in the liver. A NOAEL (♂/♀) was not established as this was a supplemental study. ≥ 12.9/15.5 mg/kg bw/day: ↑ microsomal protein, ↑ cytochrome P450 (except ♂, Day 7), ↑ PROD 93/110 mg/kg bw/day: ↑ cytochrome P450 (♂, Day 7), ↑ liver wt (~87%)
28-day Special investigative study, oral (diet) Crl:CD-1 (ICR) BR mice Non-guideline PMRA # 1903931	Investigation of xenobiotic enzyme induction in the liver. A NOAEL (♂/♀) was not established as this was a supplemental study. ≥ 3.9/4.6 mg/kg bw/day: ↑ microsomal protein, cytochrome P450 concentration, PROD and ethylmorphine N-demethylase activities; ↓ bwg (♂); ↑ liver wt , EROD, lauric acid-12-hydroxylase, p-nitrophenol-UDPGT activities (♀) ≥ 150/175 mg/kg bw/day: ↓ lauric acid 11-hydroxylase activity; ↓ bw, ↑ liver wt, ↑ lauric acid 12-hydroxylase and p-nitrophenol-UDPGT activities (♂) 225/293 mg/kg bw/day: ↓ fc (♂);↓ bwg (♀)
28-day Special investigative study, oral (diet) Sprague-Dawley rats Non-guideline PMRA # 1903933	Investigation of xenobiotic enzyme induction in the liver. A NOAEL (♂/♀) was not established as this was a supplemental study. ≥ 0.8/0.9 mg/kg bw/day: ↑ cytochrome P450 concentration, PROD, ethylmorphine N-demethylase and p-nitrophenol-UDPGT activities (♂) ≥ 150/175 mg/kg bw/day: ↑ microsomal protein (♂); ↑ PROD, ethylmorphine N-demethylase and p-nitrophenol-UDPGT activities (♀) 225/293 mg/kg bw/day: ↓ fc and bwg, ↑ liver wt; ↓ bw (♂);↑ microsomal protein and cytochrome P450 concentration (♀)

Study Type/Animal/PMRA #	Study Results
7-day Special investigative study, oral (diet) Sprague-Dawley rats Non-guideline PMRA # 1903898	Investigation of liver cell proliferation (PCNA) and mitotic index. A NOAEL (♂/♀) was not established as this was a supplemental study. ≥ 1.0/0.9 mg/kg bw/day: ↑ mitotic index on day 3, ↓ mitotic index on day 7 (♀) ≥ 7.9/8.1 mg/kg bw/day: ↑ PCNA staining on day 3, ↓ PCNA staining on day 7; ↓ fc on day 7, ↑ mitotic index on day 3 (♂) 60/58 mg/kg bw/day: ↓ fc on day 3, ↑ liver wt; ↓ bw on day 7 (♂)
28-day Special investigative study, oral (diet) Sprague-Dawley rats Non-guideline PMRA # 1903919	Investigation of liver and thyroid histopathology, liver xenobiotic enzyme induction, thyroxine (T_4) pharmacokinetics and circulating hormone levels (T_3, rT_3, T_4, TSH). A NOAEL was not established as this was a supplemental study. ≥ 1.0 mg/kg bw/day: ↑ liver microsomal cytochrome P450 enzyme concentration (per g liver), liver thyroxine-UDPGT activity (per g liver), TSH on day 29, thyroid wt and follicular cell hypertrophy ≥ 8.3 mg/kg bw/day:↑ liver wt, centrilobular hepatocyte hypertrophy, liver microsomal cytochrome P450 enzyme concentration (per mg protein), liver thyroxine-UDPGT activity (per mg protein), blood thyroxine clearance and T_3 on day 29, ↓ T_4 63.4 mg/kg bw/day: ↓ bw, bwg and fc, ↑ liver microsomal protein, TSH on day 15 and infolding of the thyroid follicular epithelium
28-day Special investigative study, oral (diet) Sprague-Dawley rats Non-guideline PMRA # 1903920	Investigation of uptake and accumulation of ^{125}Iodide in the thyroid (Perchlorate discharge test) and circulating hormone levels (T_3, rT_3, T_4, TSH). A NOAEL was not established as this was a supplemental study ≥ 0.9 mg/kg bw/day: ↓ T_4 on day 29, ↑ thyroid wt, slight total ^{125}Iodide sequestration and discharge in the thyroid (considered secondary to hormone change) 54.8 mg/kg bw/day: ↓ T_4 on day 15, ↑ TSH on days 15 and 29
Special investigative metabolism/toxicokinetics study (single dose, oral gavage) Sprague-Dawley rats Non-guideline PMRA # 1903900	Investigation of fluoride levels in plasma and urine. A NOAEL was not established as this was a supplemental study Fluoride could not be detected in the blood at any dose tested or in the urine at the lowest dose tested (4.1 mg/kg bw). This was due to the inherent limitations of the assay used and the relatively high levels of background fluoride present in the blood and urine There was a dose related increased in total urinary fluoride at 43.0 or 90.5 mg/kg bw. The fluoride levels at these dose levels returned to pre-dose levels after 5 days. The mean total amount of fluoride recovered (% AD) was 50% (33 – 64% AD) and 66% (49 – 88% AD) for the mid and high dose groups, resp. It was unclear whether greater retention of fluoride had occurred at the higher dose.
42-day Special investigative study, oral (diet) Sprague-Dawley rats Non-guideline PMRA # 1903925	Comparative investigation of two fluorinated compounds. A NOAEL was not established as this was a supplemental study 50.4 mg tetraconazole/kg bw/day : ↑ slight hyporeactivity, ↓ fe, ↑ pale/whitened incisors (some with small erosions, *non-adverse*) 23.7 mg sodium fluoride/kg bw/day: ↑ diarrhoea, ↑ reddened nose and eyes, ↓ fe, ↑ pale/whitened incisors (some with small erosions, *non-adverse*)

Study Type/Animal/PMRA #	Study Results
Special investigative reproduction-related study, single oral (gavage) Sprague-Dawley rats Non-guideline PMRA # 1903997, 1903998, 1903748	Investigation of estrous cycle. NOAEL (♀) = 50 mg/kg bw LOAEL (♀) not established Based on the absence of adverse effects. A non-adverse prolongation of the duration of diestrus, from 1 day to 2 days, was observed in animals that were dosed during either estrus (4/6 animals) or metestrus (6/6 animals). Similarly, the duration of estrus was prolonged, from 1 day to 2 days, in two animals that were dosed during diestrus (♀)
Special investigative reproduction-related study, single oral (gavage) Sprague-Dawley rats Non-guideline PMRA # 1903999, 1904000, 1903748	Investigation of estrous cycle and serum steroid hormone levels. NOAEL (♀) not established LOAEL (♀) = 50 mg/kg bw Based on effects observed during estrus, which included ↓ corticosterone and aldosterone and a 2-day diestrus period on the 3rd day post-dose in half of the animals and based on effects observed during metestrus, which included ↑ testosterone, ↑ corticosterone, ↓ progesterone and a 2-day diestrus period on the 2nd day post-dose in all animals (♀)
90-day Special investigative reproduction-related study, oral (diet) Sprague-Dawley rats Non-guideline PMRA # 1903936, 1903939	Investigation of serum steroid hormone levels and sperm quality NOAEL (♂/♀) = 0.70 mg/kg bw/day/not established LOAEL (♂/♀) = 4.9/0.75 mg/kg bw/day Based on ↓ bw, bwg, aldosterone, corticosterone, progesterone and adrenal wt (♂); ↓ aldosterone (♀)
Metabolite Studies, tetraconazole-Alcohol	
Acute Oral Sprague-Dawley rats PMRA # 1903874	LD_{50} > 2,000 mg/kg bw (♂/♀) 2,000 mg/kg bw: ↑ mortality and clinical signs **Low toxicity**
Bacterial Reverse Mutation Assay (Ames test) PMRA # 1904005	Non-cytotoxic up to limit dose **Negative**
In vivo Cytogenetics, oral (gavage, micronucleus assay) CD-1 mice PMRA # 1904032	**Negative**
Metabolite Studies, tetraconazole-Acid	
Bacterial Reverse Mutation Assay (Ames test) PMRA # 1904003	Tested up to the limit dose, not cytotoxic at 5,000 µg/plate **Negative**
In vitro Mammalian Cell Assay (forward gene mutation) PMRA # 1904021	Tested up to the limit dose, highly cytotoxic at ≥ 1.18 mM (± S9, 3 hrs) or ≥ 0.59 mM (-S9, 24 hrs) **Negative**

Study Type/Animal/PMRA #	Study Results
In vitro Mammalian Clastogenicity PMRA # 1904028	Dose-related increase in aberrations (chromatid breaks/exchanges, chromosome breaks) at ≥ 7 mM (-S9, in 1 of 2 assays) or ≥ 8 mM (+S9, in 1 of 2 assays) and the absence of cytotoxicity **Positive**
In vivo Cytogenetics, (intraperitoneal, micronucleus assay) CD-1 mice PMRA # 1904031	No cytotoxicity. Main assay: ≥375 mg/kg bw: ↑ clinical signs (piloerection, underactivity, hunched posture, abnormal gait, irregular respiration, partially closed eyelids) (♂) ≥750 mg/kg bw: ↑ flattened posture (♂) 1,500 mg/kg bw: ↑ respiration rate, ↓ body temperature (♂) Preliminary assay: ≥ 1,000 mg/kg bw: piloerection, underactivity, flattened and hunched posture, abnormal gait, irregular respiration, partially closed eyelids ≥ 1,500 mg/kg bw: ↓ body temperature (♂); ↑ respiration (♀) 2,000 mg/kg bw: ↑ mortality (♂) **Negative**
Metabolite Studies, Tetraconazole-difluoroacetic acid	
Acute Oral Sprague-Dawley rats PMRA # 1903881	LD_{50} > 5,000 mg/kg bw (♂/♀) diarrhea up to 6 hrs post-dose **Low toxicity**
Bacterial Reverse Mutation Assay (Ames test) PMRA # 1904012	Tested up to the limit dose, slightly cytotoxic at 5,000 µg/plate **Negative**
Metabolite Studies, Mixture of Tetraconazole-dichlorophenyl-3OH and Tetraconazole-dichlorophenyl -5OH	
Acute Oral Sprague-Dawley rats PMRA # 1903880	LD_{50} > 2,000 mg/kg bw **Low toxicity**

[1] 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.

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Tetraconazole[1]

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[2] or Target MOE
Acute dietary general population	Acute neurotoxicity study in the rat	NOAEL = 50 mg/kg bw Decreased locomotor and ambulatory motor activity; clinical signs in females	100
	ARfD = 0.5 mg/kg bw		
Repeated dietary	24-month chronic toxicity/oncogenicity study in the rat	NOAEL = 0.4 mg/kg bw/day Interim body weight, pathology in the liver and bones in males; pathology of reproductive organs in females	100
	ADI = 0.004 mg/kg bw/day		
Short- to Intermediate-term dermal[3]	Reproductive toxicity study in the rat	NOAEL = 0.7 mg/kg bw/day Adrenal weight in parental males; mortality in both generations, body weight and body weight gain in parental females	100
Short- to Intermediate-term inhalation	28-day inhalation toxicity study in the rat	LOAEL = 14.3 mg/kg bw/day (0.055 mg/L) Squamous cell metaplasia of laryngeal mucosa, mononuclear cell infiltration of the larynx, and goblet cell hypertrophy of the nasal cavity and the nasopharyngeal duct; follicular cell hypertrophy of the thyroid in males	300
Aggregate	Acute neurotoxicity study in the rat	NOAEL = 50 mg/kg bw Decreased locomotor and ambulatory motor activity; clinical signs in females	100
Cancer	Liver tumours in the mouse were considered a non-genotoxic threshold-dependent effect; consequently a Q_1* is not required for the risk assessment.		

1 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.

2 CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target margin of exposure for occupational and pick-your-own assessments.

3 Since an oral NOAEL was selected, a dermal absorption factor of 30% was used in a route-to-route extrapolation.

Table 5 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN GRAPES			PMRA # 1905003, 1905004	
Radiolabel Position	[Phenyl-14C]-tetraconazole		[Triazole-14C]-tetraconazole	
Test Site	Grown in pots, outdoors			
Treatment	Four foliar applications			
Rate	(23.1 g a.i./ha)(4 applications)= 92.4 g a.i./ha		(27.6 g a.i./ha)(4 applications)= 110.4 g a.i./ha	
End-use product	Radiolabelled compound diluted in water			
Preharvest interval	60 days			
Matrix	PHI (days)	[14C-Phenyl] TRR (ppm)	[14C-Triazole] TRR (ppm)	
Fruit	60	0.217	0.166	
Wine	60	0.034	0.038	
Wine Sediment	60	0.921	0.743	
Metabolites Identified	Major Metabolites (> 10% TRR)		Minor Metabolites (< 10% TRR)	
Radiolabel Position	[14C-Phenyl]	[14C-Triazole]	[14C-Phenyl]	[14C-Triazole]
Fruit	Tetraconazole	Tetraconazole	None	None
Wine	Tetraconazole	Tetraconazole	None	None
Wine Sediment	Tetraconazole	Tetraconazole	None	None

Metabolic Pathway
It appears that tetraconazole is slowly converted to polar metabolites, which are then incorporated into the plant matrix. Cleavage of the carbon chain that links the triazole ring to the phenyl ring does not appear to occur during metabolism. The major residue in grapes is the unchanged parent, tetraconazole.

NATURE OF THE RESIDUE IN SUGAR BEETS			PMRA # 1905009, 1905010, 1904997
Radiolabel Position	[Phenyl-14C]-tetraconazole		[Triazole-14C]-tetraconazole
Test Site	Grown in pots, outdoors		
Treatment	Three applications to the leaves and soil.		Three foliar applications
Rate	(100 or 500 g a.i./ha)(3 applications)= 300 or 1500 g a.i./ha		(100 g a.i./ha)(3 applications)= 300 g a.i./ha
End-use product	Radiolabelled compound diluted in water, with an adjuvant		Radiolabelled compound diluted in water
Preharvest interval	23 days		0 and 35 days
Matrix	PHI (days)	[14C-Phenyl] TRR (ppm)	[14C-Triazole] TRR (ppm)
Leaves [300 g a.i./ha]	23	5.034	--
Roots [300 g a.i./ha]	23	0.0073	--
Roots [1500 g a.i./ha]	23	0.0421	--
Leaves [300 g a.i./ha]	0	--	3.107
Leaves [300 g a.i./ha]	35	--	1.336

Metabolites Identified	Major Metabolites (> 10% TRR)		Minor Metabolites (< 10% TRR)	
Radiolabel Position	[14C-Phenyl]	[14C-Triazole]	[14C-Phenyl]	[14C-Triazole]
Leaves [300 g a.i./ha]	Tetraconazole M14360-alcohol-O-malonyldiglucoside	Tetraconazole	M14360-DFA M14360-acid M14360-alcohol M14360(C-1)-alcohol M14360-alcohol-O-glucoside M14360-alcohol-O-diglucoside M14360-hydroxydetriazolyl-O-malonyldiglucoside	M14360-DFA M14360-acid M14360-alcohol Triazole TAA THP
Roots [300 g a.i./ha]	Tetraconazole	--	None	
Roots [1500 g a.i./ha]	Tetraconazole	--	M14360-DFA M14360-acid M14360-alcohol-conjugate	--

Metabolic Pathway
Both studies indicate that tetraconazole is oxidized to M14360-DFA, followed by hydrolysis to M14360-alcohol which may form a conjugate, or be oxidized to M14360-acid. Further metabolism may result in ring separation, or the formation of other minor metabolites.

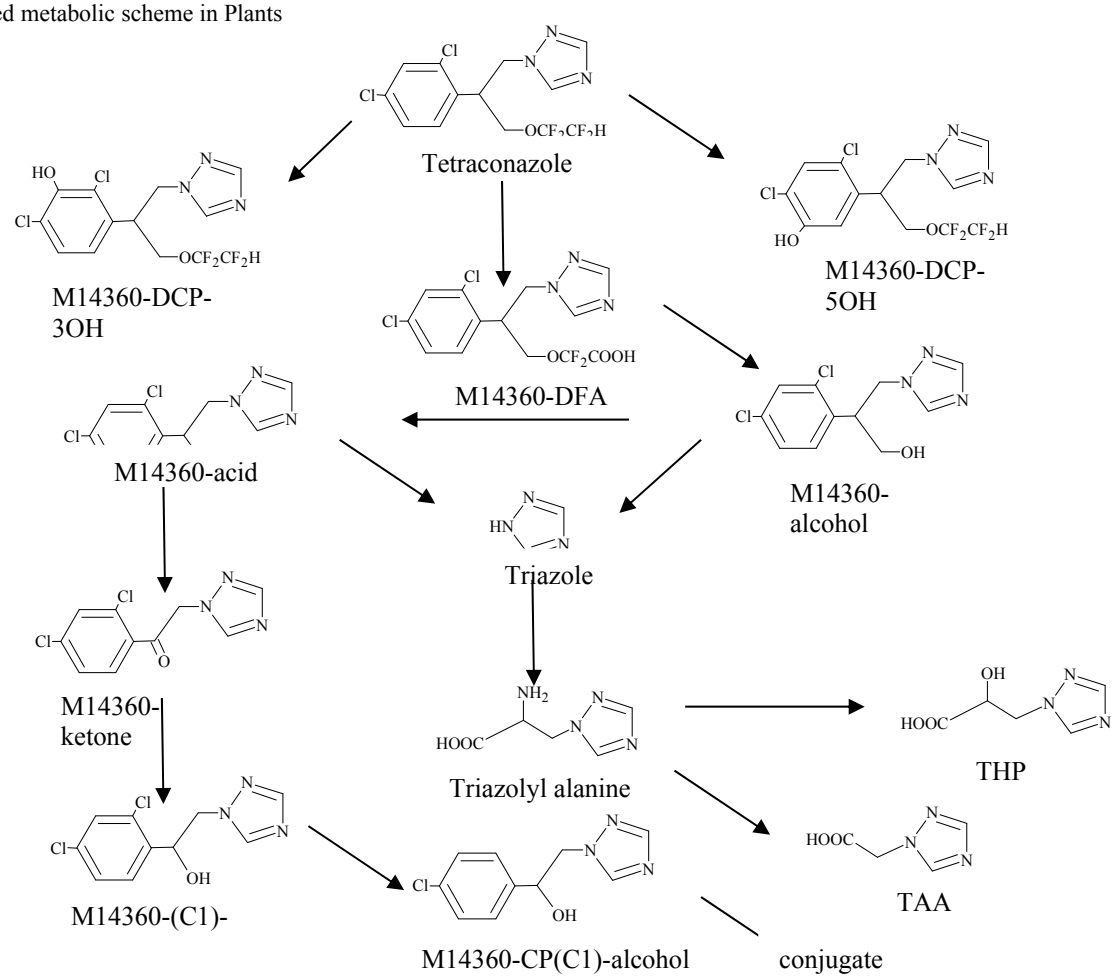
NATURE OF THE RESIDUE IN WHEAT			PMRA # 1905007, 1905006, 1905008, 1904994, 1905013, 1905011	
Radiolabel Position	[Phenyl-14C]-tetraconazole		[Triazole-14C]-tetraconazole	
Test Site	PMRA # 1905006, 1905007, 1905008 Outdoors, in the US PMRA # 1904994, 1905013 Outdoors, in pots, in the UK			
Treatment	PMRA # 1905006, 1905007, 1905008 2 foliar applications PMRA # 1904994, 1905013 3 foliar applications			
Rate	PMRA # 1905006, 1905007, 1905008 (2 applications)(124 g a.i./ha)=248 g a.i./ha PMRA # 1904994, 1905013 (3 applications)(100-120 g a.i./ha)=340-350 g a.i./ha			
End-use product	Radiolabelled compound diluted in water			
Preharvest interval	PMRA # 1905006, 1905007, 1905008 41 days PMRA # 1904994, 1905013 44 days			
Matrix	PHI (days)	[14C-Phenyl] TRR (ppm)	[14C-Triazole] TRR (ppm)	
Grain	41	0.091	0.662	
Straw	41	5.708	7.318	
Straw	44	11.475	12.453	
Metabolites Identified	Major Metabolites (> 10% TRR)		Minor Metabolites (< 10% TRR)	
Radiolabel Position	[14C-Phenyl]	[14C-Triazole]	[14C-Phenyl]	[14C-Triazole]
Grain	Tetraconazole	TA TAA	--	Tetraconazole
Straw [41-day PHI]	Tetraconazole	Tetraconazole	M14360-acid M14360-alcohol	M14360-acid M14360-alcohol
Straw [44-day PHI]	Tetraconazole	Tetraconazole	M14360-DFA M14360-acid M14360-alcohol M14360(C-1)-alcohol M14360-CP(C-1)-alcohol M14360-ketone M14360-dichlorophenyl-3-OH M14360-dichlorophenyl-5-OH	M14360-DFA M14360-acid M14360-alcohol M14360(C-1)-alcohol M14360-CP(C-1)-alcohol M14360-ketone M14360-dichlorophenyl-3-O M14360-dichlorophenyl-5-OH
Metabolic Pathway It appears that tetraconazole is oxidized to M14360-DFA, followed by hydrolysis to M14360-alcohol, which may form a conjugate, or be oxidized to M14360-acid. Further metabolism results in the formation of other minor metabolites.				

CONFINED ACCUMULATION IN ROTATIONAL CROPS – CARROTS, LETTUCE, SORGHUM, WHEAT				PMRA # 1905020, 1905022, 1905176	
Radiolabel Position		[Phenyl-14C]-tetraconazole and [Triazole-14C]-tetraconazole			
Test site		Pots maintained outdoors			
Formulation used for trial		Radiolabelled compound was dissolved in acetonitrile, and then diluted with distilled water.			
Application rate and timing		Soil surface treated directly with product at a rate of 500 g a.i./ha and aged for 30, 120, 223, and 365 days prior to planting of rotational crops.			
Metabolites Identified		Major Metabolites (> 10% TRR)		Minor Metabolites (< 10% TRR)	
Matrix	PBI (days)	[14C-Phenyl]	[14C-Triazole]	[14C-Phenyl]	[14C-Triazole]
Carrot roots	30	Tetraconazole	TA THP	None	Tetraconazole
	120	Tetraconazole	TA THP	None	Tetraconazole
	223	Tetraconazole	--	None	--
	365	Tetraconazole	TA THP	M14360-DFA M14360-acid	Tetraconazole
Carrot leaves	30	Tetraconazole	THP	M14360-DFA M14360-acid M14360(C-1)alcohol conjugate	Tetraconazole
	120	Tetraconazole M14360-acid	TA THP	M14360-DFA M14360(C-1)alcohol conjugate	Tetraconazole
	365	Tetraconazole M14360-acid	TA THP	M14360-DFA M14360(C-1)alcohol conjugate M14360-ketone-conjugate	Tetraconazole
Lettuce	30	Tetraconazole M14360(C-1)alcohol	TA THP	M14360-ketone-conjugate	Tetraconazole
	120	Tetraconazole M14360(C-1)alcohol	TA THP	M14360-ketone-conjugate	Tetraconazole
	223	Tetraconazole M14360(C-1)alcohol	--	M14360-ketone-conjugate	--
	365	Tetraconazole M14360(C-1)alcohol	THP	M14360-ketone-conjugate	Tetraconazole TA

Wheat Forage	30	Tetraconazole	TA TAA THP	M14360-DFA M14360-acid M14360-alcohol conjugate M14360(C-1)alcohol conjugate	Tetraconazole
	120	Tetraconazole	TA TAA THP	M14360-DFA M14360-acid M14360-alcohol conjugate M14360(C-1)alcohol conjugate M14360-ketone conjugate	Tetraconazole
	365	Tetraconazole	TA TAA THP	--	Tetraconazole
Wheat Straw	30	Tetraconazole M14360-DFA	Tetraconazole TA THP	M14360-acid M14360-alcohol conjugate M14360(C-1)alcohol conjugate M14360-ketone conjugate	TAA
	120	Tetraconazole M14360-DFA	Tetraconazole TA TAA THP	M14360-acid M14360-alcohol conjugate M14360(C-1)alcohol conjugate M14360-ketone conjugate	None
	365	Tetraconazole	TA TAA THP	M14360-DFA M14360-acid M14360-alcohol conjugate M14360(C-1)alcohol conjugate	Tetraconazole

Wheat Grain	30	Tetraconazole M14360-acid	TA TAA	None	Tetraconazole
	120	Tetraconazole M14360-acid	TA TAA	None	Tetraconazole
	365	Tetraconazole	TA TAA	None	Tetraconazole
Sorghum Grain	223	Tetraconazole	--	None	--

Proposed metabolic scheme in Plants

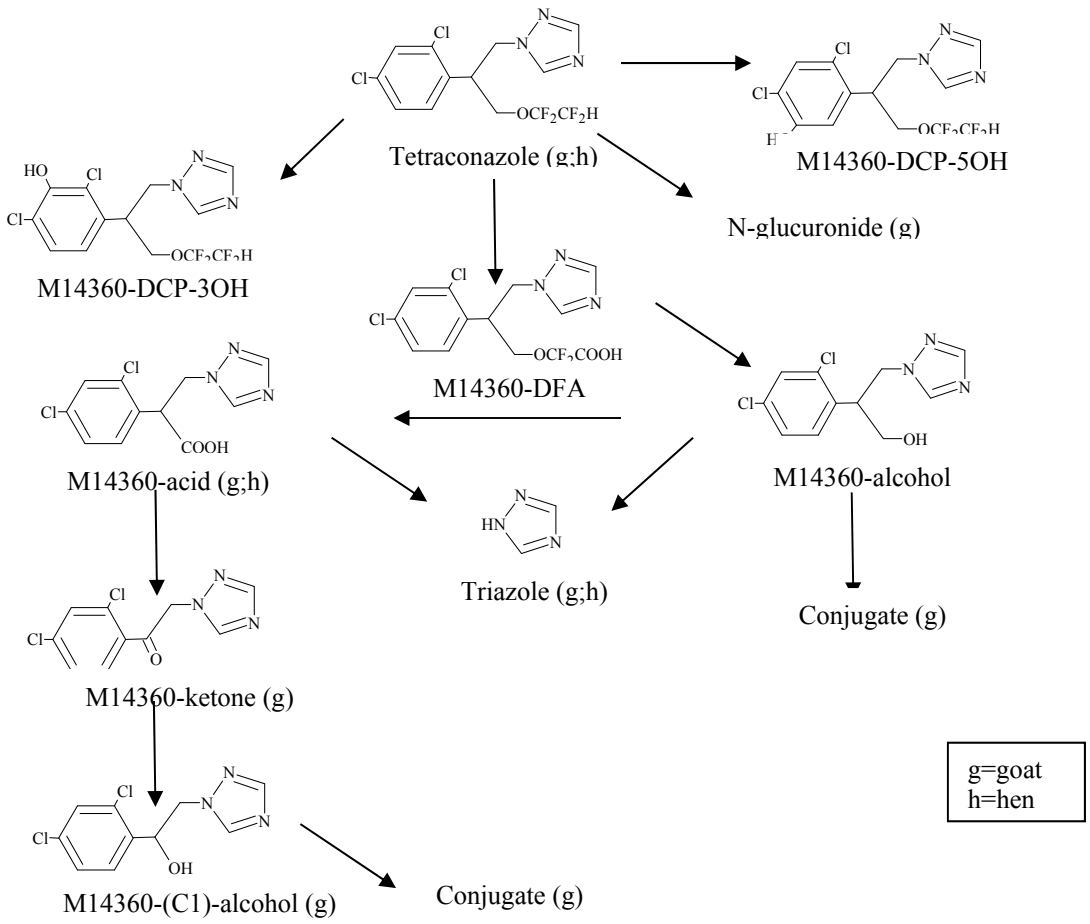


NATURE OF THE RESIDUE IN LAYING HEN			PMRA # 1904991	
Two groups of six laying hens were fed a daily oral dose of tetraconazole (M14360) for 3 consecutive days. The compound was radiolabelled in either the triazole ring or the phenyl ring. The target dose was 10 ppm in the diet per day (~1.3-1.4 mg tetraconazole/kg bw/day). The hens were sacrificed within 22 hrs of the last dose. At the time of sacrifice, 23.3 % of the AD (14.39 ppm), and 29.7% AD (20.89 ppm) had been excreted in hens dosed with [14C-triazole]- and [14C-phenyl]-tetraconazole, respectively. The proportion of TRRs detected in eggs was low (<0.7 % AD for yolks [both labels]; 1.4 % and 1.5% AD for whites in the phenyl study and triazole study, respectively), indicating minimal transfer of tetraconazole residues to eggs. TRRs in yolks and whites increased over time from Day 1 to Day 3. The highest tissue concentrations of residues were detected in fat (11.612 and 11.293 ppm for [14C-triazole]- and [14C-phenyl]-treated animals, respectively). There were also detectable residues in liver (3.518 and 3.560 ppm for [14C-triazole]- and [14C-phenyl]-treated animals, respectively). Residues in muscle were the lowest of the tissues that were tested (0.599 and 0.532 ppm for [14C-triazole]- and [14C-phenyl]-treated animals, respectively). Metabolic Pathway It appears that tetraconazole is initially oxidized to tetraconazole-DFA. Further metabolism may lead to the formation of tetraconazole-acid, and ring separation, resulting in free triazole.				
Matrices			% of Administered Dose	
			[14C-Phenyl]	[14C-Triazole]
Excreta			23.3	29.7
Muscle			3.7	3.2
Fat			9.0	8.4
Liver			2.5	2.4
Eggs			<2.2	<2.1
Metabolites identified	Major Metabolites (> 10% TRR)		Minor Metabolites (< 10% TRR)	
Radiolabel Position	[14C-Phenyl]	[14C-Triazole]	[14C-Phenyl]	[14C-Triazole]
Eggs	Tetraconazole	Tetraconazole	M14360-DFA	M14360-DFA Triazole
Muscle	Tetraconazole	Tetraconazole	M14360-DFA M14360-DCP-3OH	M14360-DFA M14360-DCP-3OH Triazole
Fat	Tetraconazole	Tetraconazole	None	None
Liver	Tetraconazole	Tetraconazole	M14360-DFA M14360-DCP-3OH	M14360-DFA M14360-DCP-3OH Triazole

NATURE OF THE RESIDUE IN LACTATING GOAT		PMRA # 1904989, 1904990, 1904993
In two separate studies, one lactating goat was fed a daily oral dose of tetraconazole for five consecutive days in each study. The compound was radiolabelled in either the triazole ring, or the phenyl ring. The target dose rate was 20 mg/day for the goat treated with triazole-labelled substance, and 19.2 mg/day for the goat treated with phenyl-labelled tetraconazole (equivalent to ~0.45 ppm/day in the diet). The goats were terminated by intravenous injection within 24 hrs of the final dose. The majority of the AD was excreted (64.38 % and 77.5% AD in triazole- and phenyl-label study, respectively). In milk, TRRs were low (0.4-3.86% AD). Peak residue concentrations (0.59-0.118 ppm) in milk were reached on the 5th day of dosing. The highest tissue concentrations of residues were detected in the liver (3.21-3.440 ppm; 3.31-3.5% AD). Metabolic Pathway Tetraconazole appears to be metabolized to triazole. This may occur through initial oxidation to tetraconazole-DFA, followed by hydrolysis to form tetraconazole-alcohol. Glutathione conjugation of tetraconazole-alcohol and/or –acid and subsequent triazole cleavage may also occur.		
Matrices	% of Administered Dose	
	[14C-Phenyl]	[14C-Triazole]
Urine and feces	76.2	63.6
Muscle	5.7	1.2
Fat	3.2	3.5
Kidney	0.1	0.1

Liver			3.3	3.5
Milk			3.9	0.4
Metabolites identified	Major Metabolites (> 10% TRR)		Minor Metabolites (< 10% TRR)	
Radiolabel Position	[14C-Phenyl]	[14C-Triazole]	[14C-Phenyl]	[14C-Triazole]
Liver	Tetraconazole	Tetraconazole	M14360-alcohol M14360-ketone Tetraconazole conjugates	Triazole
Kidney	Tetraconazole	Tetraconazole Triazole	M14360-ketone Tetraconazole conjugates	None
Fat	Tetraconazole	Tetraconazole Triazole	M14360-ketone	None
Muscle	Tetraconazole	Tetraconazole Triazole	M14360-ketone	Tetraconazole
Milk	Tetraconazole	Tetraconazole Triazole	M14360-DFA	None

Proposed Metabolic Scheme in Livestock



STORAGE STABILITY	PMRA # 1905048, 1905050, 1905042, 1905044, 1905051, 2191774

Wheat (grain, straw), sugar beet roots, grape (fruit), apples: The data indicated that tetraconazole residues are stable when stored frozen (-20 °C) for up to 1076 days (~3 years) in wheat grain, 1076 days (~3 years) in wheat straw, 1192 days (~40 months) in sugar beet roots, 1158 days (~38 months) in grapes, and 1142 days (~38 months) in apples.

Grape juice, raisins: The data indicate that tetraconazole residues are stable when stored frozen (-20 °C) for up to 69 days in grape juice, and 91 days in raisins.

CROP FIELD TRIALS - Grapes	PMRA # 1905163

Twelve residue field trials were conducted on grapes, the representative crop for Crop Subgroup 13-07F, in the US in Zones 1, 10, and 11. Tetraconazole, was applied to grapes in two spray applications at total application rates of 88.5-94.2 g a.i./ha (~1X GAP) at all trial sites. Mature grapes were harvested at 14-16-day, and 28-31 day PHIs at all trial sites. Adjuvants were not included in any of the spray mixtures.

Residue decline samples were harvested at 0, 7, 15, 22, 28-31, and 37 day PHIs (Plot A), and at 0, 5, 10, 15, and 22 day PHIs (Plot B) at one trial site. Residues decreased with increasing PHI in grapes.

Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Tetraconazole Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Grapes	89.6-94.2	14-16	26	<0.01	0.087	0.084	0.019	0.030	0.024
	88.5-93.0	28-31	24	<0.01	0.091	0.057	0.013	0.022	0.019

CROP FIELD TRIALS - Strawberries	PMRA # 1905113

Eight field residue trials were conducted on strawberries, the representative crop for Crop Subgroup 13-07G, in the US in Zones 1, 2, 3, 5A, 10, and 12. Tetraconazole was applied to strawberries in four foliar directed or broadcast applications at total application rates of 195.6-203.5 g a.i./ha (~1X GAP). Commercially mature strawberries were harvested at PHIs of 0 and 1 day at all trial sites. Adjuvants were not included in any of the spray mixtures.

Residue decline samples were harvested at PHIs of 0, 1, 4, 7, and 14 days at one trial site. Residues appeared to decrease with increasing PHI.

Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Tetraconazole Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Strawberries	195.6-203.5	0	16	<0.05	0.21	0.20	0.08	0.10	0.047
		1	16	<0.05	0.18	0.16	0.08	0.09	0.044

CROP FIELD TRIALS – Sugar Beets	PMRA # 1905173

Eleven residue field trials were conducted on sugar beets in the US in Zones 5, 5A, 7, 8, 9, 10, and 11. Sugar beets were treated with 6 broadcast applications of tetraconazole at a total actual application rate of 715.1-727.4 g a.i./ha (~6X GAP). Adjuvants were not included in any of the spray mixtures. Sugar beet top and root samples were harvested at a 14-day PHI at all trial sites.

Residue decline sugar beet root and sugar beet top samples were harvested at one trial site at PHIs of 0, 3, 7, 14, 30, and 60 days. Tetraconazole residues declined over time in top samples. Although tetraconazole residues fluctuated over time in sugar beet root residue decline samples, they were lower in samples harvested at a 60-day PHI than they were in samples harvested at a 0-day PHI.

Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Tetraconazole Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Roots	715.1-727.4	14	22	0.013	0.103	0.086	0.030	0.040	0.027
Tops			22	1.13	5.90	4.94	2.12	2.41	1.10

CROP FIELD TRIALS – Sugar Beets							PMRA # 1905104		
One residue field trial study was conducted on sugar beets in the US in Zone 10. There were two plots of sugar beets treated at the same site with either 3 or 6 foliar broadcast applications of tetraconazole. The total application rate was 724.0 and 358.7 g a.i./ha (~3X and ~6X GAP) for sugar beets treated 6 times and 3 times, respectively. Sugar beet roots and tops were harvested from both plots at a 14-day PHI. An adjuvant was not included in any of the spray mixtures. Residue decline behavior was not assessed.									
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Tetraconazole Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Roots	358.7	14	2	<0.01	0.012	<0.01	--	<0.01	N/A
	724.0	14	2	0.019	0.059	0.039	--	0.039	N/A
Tops	358.7	14	2	0.737	0.842	0.790	--	0.790	N/A
	724.0	14	2	1.15	2.27	1.71	--	1.71	N/A

PROCESSED FOOD AND FEED - Grape	PMRA # 1905163
Test Site	Two trials in the US.
Treatment	Spray application.
Rate	Two applications at 218.6-228.7 g a.i./ha/application for a total rate of 447.2-455.1 g a.i./ha/season (~5X GAP).
End-use product	Liquid formulation
Preharvest interval	14-15 days
Processed Commodity	Processing Factor
Grape juice	0.08X
Raisins	0.8X
PROCESSED FOOD AND FEED – Sugar Beets	PMRA # 1905194
Test Site	One trial in the US.
Treatment	Broadcast application.
Rate	Six applications at 592.9-604.1 g a.i./ha/application for a total rate of 3.59 kg a.i./ha/season (~30X GAP).
End-use product	Suspension concentrate
Preharvest interval	14 days
Processed Commodity	Processing Factor
Sugar beet dry pulp	2.1X
Sugar beet molasses	2.8X
Sugar beet refined sugar	0.1X

LIVESTOCK FEEDING – Dairy cattle	PMRA # 1905203, 1905201

Three groups of lactating cows were dosed orally twice daily with tetrazonazole for 28-30 consecutive days. Based on a daily feed intake of 20 kg/day, the dosing rate was 0.35 ppm, 1.05 ppm, and 3.5 ppm in the diet. Milk was collected from each animal twice daily, and tissues (liver, kidney, skeletal muscle, subcutaneous fat, peritoneal fat) were collected within 24 hrs of sacrifice. With the exception of 2 animals, all cows were terminated within 24 hrs of the final dose. One cow was sacrificed 7 days after the last dose, and a second cow was terminated 14 days after the final dose to study the depuration phase.

Tetraconazole was present in all whole milk samples at the highest dosing level (3.5 ppm), was present in 2 whole milk samples at the 1.05 ppm dosing level, and was not quantifiable at the lowest dosing level (0.35 ppm) in animals sacrificed within 24 hrs of the last dose. Residues of tetraconazole were all non-quantifiable in samples collected from animals sacrificed 7 days and 14 days following the final dose. At the 3.5 ppm dosing level, mean residues of tetraconazole in whole milk were <LOQ on the first day after dosing began, and reached a maximum of 0.025 ppm 18 days after the first dose was administered.

Residues of tetraconazole were not quantifiable in any of the skimmed milk samples. Mean residues of tetraconazole were quantifiable in all cream samples at all dosing levels (0.020-0.021, 0.053-0.092, and 0.266-0.300 ppm at the 0.35, 1.05, and 3.5 ppm dosing level, respectively).

In tissues, the highest mean residues of tetraconazole observed in the liver at all dosing levels (0.268, 0.376, and 1.345 ppm at the 0.35, 1.05, and 3.5 ppm dosing level, respectively). Mean residues of tetraconazole were lower in samples from animals that were sacrificed 7 days and 14 days following the final dose than they were in samples from animals sacrificed within 24 hrs of the final dose. Tetraconazole mean residues were higher in peritoneal fat (<0.017, 0.051, and 0.119 ppm at the 0.35, 1.05, and 3.5 ppm dosing level, respectively) than they were in kidney (<0.01, 0.024, and 0.055 ppm at the 0.35, 1.05, and 3.5 ppm dosing level, respectively), subcutaneous fat (<0.015, 0.029, and 0.077 ppm at the 0.35, 1.05, and 3.5 ppm dosing level, respectively), and muscle (<0.01, <0.01, and <0.09 ppm at the 0.35, 1.05, and 3.5 ppm dosing level, respectively). The lowest tetraconazole residues in tissues were observed in muscle.

Matrix	Feeding Level (ppm/d)	n	LOD	Min	Max	Median	Mean	Standard Deviation
Milk [Day 1]	3.5	5	0.003	<0.01	<0.01	<0.01	<0.01	0
Milk [Day 3]	3.5	5	0.003	0.013	0.018	0.016	0.015	0.002
Milk [Day 5]	3.5	5	0.003	0.013	0.022	0.015	0.017	0.004
Milk [Day 7]	0.35	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	1.05	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	3.5	5	0.003	0.013	0.027	0.017	0.019	0.006
Milk [Day 10]	3.5	5	0.003	0.012	0.025	0.014	0.017	0.006
Milk [Day 14]	0.35	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	1.05	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	3.5	5	0.003	0.013	0.029	0.017	0.018	0.007
Milk [Day 18]	3.5	5	0.003	0.013	0.048	0.023	0.025	0.014
Milk [Day 21]	0.35	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	1.05	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	3.5	5	0.003	0.014	0.023	0.017	0.018	0.004
Milk [Day 24]	3.5	5	0.003	0.015	0.025	0.016	0.019	0.004
Milk [Day 28]	0.35	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	1.05	3	0.003	<0.01	0.016	<0.01	<0.012	0.003
	3.5	5	0.003	0.016	0.029	0.021	0.022	0.005
Skimmed Milk [Day 14]	0.35	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	1.05	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	3.5	5	0.003	<0.01	<0.01	<0.01	<0.01	0
Skimmed Milk [Day 28]	0.35	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	1.05	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	3.5	5	0.003	<0.01	<0.01	<0.01	<0.01	0
Cream [Day 14]	0.35	3	0.003	0.020	0.022	0.021	0.021	0.001
	1.05	3	0.003	0.046	0.068	0.047	0.054	0.012
	3.5	5	0.003	0.194	0.340	0.248	0.266	0.057
Cream [Day 28]	0.35	3	0.003	0.017	0.023	0.020	0.020	0.003
	1.05	3	0.003	0.068	0.125	0.084	0.092	0.029
	3.5	5	0.003	0.224	0.391	0.275	0.300	0.075

LIVESTOCK FEEDING – Dairy cattle						PMRA # 1905203, 1905201		
Liver	0.35	3	0.003	0.144	0.371	0.290	0.268	0.115
	1.05	3	0.003	0.073	0.662	0.392	0.376	0.295
	3.5	3	0.003	1.012	1.636	1.386	1.345	0.314
Kidney	0.35	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	1.05	3	0.003	0.014	0.039	0.020	0.024	0.013
	3.5	3	0.003	0.040	0.067	0.057	0.055	0.014
Muscle	0.35	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	1.05	3	0.003	<0.01	<0.01	<0.01	<0.01	0
	3.5	3	0.003	0.010	0.015	0.011	0.012	0.003
Subcutaneous Fat	0.35	3	0.003	<0.01	0.026	<0.01	<0.015	0.009
	1.05	3	0.003	0.025	0.033	0.030	0.029	0.004
	3.5	3	0.003	0.011	0.159	0.061	0.077	0.075
Peritoneal Fat	0.35	3	0.003	<0.01	0.029	0.011	0.017	0.011
	1.05	3	0.003	0.031	0.069	0.052	0.051	0.019
	3.5	3	0.003	0.041	0.199	0.116	0.119	0.079

There are treated animal feedstuffs resulting from the use of tetraconazole on sugar beets (molasses and dried pulp).

The More Balanced Diet (MBD) was used to calculate the dietary burden and anticipated residues in animal matrices. The dietary burden was determined to be 0.06 ppm in both dairy cattle and beef cattle. The dietary burden in poultry and swine is 0 ppm.

Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops** **Rotational crops**	 Tetraconazole Tetraconazole
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops** **Rotational crops**	 Tetraconazole Tetraconazole
METABOLIC PROFILE IN DIVERSE CROPS	Similar
ANIMAL STUDIES	
ANIMALS	**Ruminant**
RESIDUE DEFINITION FOR ENFORCEMENT	Tetraconazole
RESIDUE DEFINITION FOR RISK ASSESSMENT	Tetraconazole
METABOLIC PROFILE IN ANIMALS **(goat, hen, rat)**	Similar
FAT SOLUBLE RESIDUE	Yes

DIETARY RISK FROM FOOD AND WATER			
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Only	**Food and Water**
Refined chronic non-cancer dietary risk **ADI = 0.004 mg/kg bw** **Estimated chronic drinking water concentration = 14 μg a.i./L**	**All infants < 1 year**	23.2	47.4
	Children 1–2 years	23.3	34.2
	Children 3 to 5 years	23.7	34.0
	Children 6–12 years	16.9	24.0
	Youth 13–19 years	10.9	16.3
	Adults 20–49 years	8.6	15.5
	Adults 50+ years	6.9	14.2
	Total population	10.7	18.0
Basic acute dietary exposure analysis, 95th percentile **ARfD = 0.5 mg/kg bw** **Estimated acute drinking water concentration = 14 μg a.i./L**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Only	**Food and Water**
	All infants < 1 yr	1.04	1.35
	Children 1-2 yrs	1.76	1.84
	Children 3-5 yrs	1.25	1.35
	Children 6-12 yrs	0.73	0.82
	Youth 13-19 yrs	0.45	0.50
	Adults 20-49 yrs	0.35	0.43
	Adults 50+ yrs	0.30	0.37
	Females 13-49 yrs	0.35	0.43
	Total Population	0.64	0.72

Table 7 Fate and Behaviour in the Environment

Property	Test Substance	Value	Comments	PMRA#
Abiotic transformation				
Hydrolysis	Tetraconazole	Half life: stable	Not an important route of transformation	1904098
Phototransformation on soil	Tetraconazole	Indoor continuous xenon light: stable (>16 days)	Not an important route of transformation (> 3 days)	1904099
		Outdoor sunlight DT_{50}: 43.7-191 days DT_{90}: 314-636 days	Transformation products: M14360-alcohol (max. 15.5% AR) Triazolyl acetic acid (TAA) (max. 14.11% AR) M14360-acid (max. 8.88% AR) Triazole (max. 6.63% AR) M14360-difluoroacetic acid (max. 6.07% AR)	1904113 1904115
Phototransformation in water (pH 7)	Tetraconazole	DT_{50} = 10.9 days continuous irradiation	Not an important route of transformation Transformation products: Hydroxy-triazolyl-isobutanoic acid (max. 15.6% AR) M14360-dihydro-isoquinoline triazole (max. 9.305% AR) Tetrafluoroethoxy-triazolyl-isobutanoic acid (max. 10.27% AR) Triazole (max. 7.035% AR) M14360-alcohol (max. 7.27% AR)	1904101

Property	Test Substance	Value	Comments	PMRA#
Biotransformation				
Biotransformation in aerobic soil	Tetraconazole	DT_{50}: 895-2160 days DT_{90}: 2970-7170 days	Persistent	1904104 1904108
	M14360-acid	DT_{50}: 74-221 days DT_{90}: 382-7350 days	Moderately persistent to persistent Transformation products: Hydroxyphenyl-M14360-acid (max. 30.49% AR) M14360-(C1)-alcohol (max. 14.31% AR)	1904105
	M14360-alcohol	DT_{50}: 4.74-10.9 hrs DT_{90}: 15.7-36.2 hrs	Non-persistent Transformation products: M14360-acid (max. 93.93% AR)	1904106
	Triazolyl acetic acid	DT_{50}: 6.14-11.1 days DT_{90}: 20.4-36.9 days	Non-persistent Transformation products were detected but not identified.	1904107
Biotransformation in anaerobic soil (flooded)	Tetraconazole	Total system: DT_{50}: 12400-48500 days DT_{90}: 41300-161000 days	Persistent	1904118
Aerobic water sediment	Tetraconazole	Water: DT_{50}: 1.6-1.9 days DT_{90}: 18.1-43.4 days Total system DT_{50}: 310-372 days DT_{90}: 1030-1240 days	Persistent	1904117
Anaerobic soil (flooded)	Tetraconazole	Water: DT_{50}: 3.22-3.29 days DT_{90}: 12.1-12.4 days Total system: DT_{50}: 12400-48500 days DT_{90}: 41300-161000 days	Persistent	1904118
Mobility				
Adsorption / desorption in soil	Tetraconazole	K_d = 23.79-25.19 mL/g K_{oc} = 586-18012 mL/g K_{desorb} = 1.11-3.10 mL/g	Low mobility to immobility	2018560
	M14360-acid	<u>SP-2.1 sand</u> K_d = 0.57-2.296 mL/g K_{oc} = 25.09-174 mL/g K_{desorb} = 1.815 mL/g	Medium mobility to very high mobility	1904124

Property	Test Substance	Value	Comments	PMRA#
	Triazolyl acetic acid	AR-1 loamy sand K_d = 0.202-0.367 mL/g K_{oc} = 1.878-22.67 mg/L K_{desorb} = 0.104-0.22 mL/g	Very highly mobile	1904127
Soil leaching	Tetraconazole	**Non-aged** 0-5 cm depth: 66.30-101.06%AR 5-10 cm depth: <0.04-23.36% AR Leachates: <0.003-0.1267% AR		1904133 1904134
		Aged *Incubation in dark* 0-10 cm depth: 98.37% AR 10-20 cm depth: 0.08% AR leachates: 0.15% AR *Incubation under sun* 0-10 cm depth: 36.09% AR for tetraconazole 17.80% AR for TP 10-20 cm depth: 0.26% AR for tetraconazole 5.46% AR for TP 20-30 cm depth: 3.45% AR for TP leachates: 0% AR for tetraconazole 33.15% AR for TP		1904139 1904140
Partitioning				
Bioconcentration in fish	Tetraconazole	Steady state BCF = 24.5 (edible) 52.3 (non-edible) 35.7 (whole fish) Kinetic BCF = 23.0 (edible) 48.1 (non-edible) 33.1 (whole fish) Clearance time CT_{50} = 0.19 day CT_{90} = 0.82 day	Not likely to bioconcentrate in the environment	1904201

Table 8 Effects on Non-Target Terrestrial Organisms

Organism	Exposure	Test substance [b]	Endpoint value	Degree of toxicity[a]	PMRA#
Invertebrates					
Earthworm	14 d-Acute	Tetraconazole	LC_{50} = 69 mg a.i./kg soil dw	N/A	1904148
		M14360-acid	LC_{50} > 500 mg/kg soil dw	N/A	1904149
		M14360-alcohol	LC_{50} > 1000 mg/kg soil dw	N/A	1904150
		M14360-triazolyl acetic acid	LC_{50} > 1000 mg/kg soil dw	N/A	1904151
		Tetraconazole 125 g/L ME	LC_{50} > 1000 mg EP/kg soil dw LC_{50} > 114 mg a.i./kg soil dw	N/A	1904152
	56 d-Chronic (28-day adult exposure, 28-day reproduction)	Tetraconazole	NOEC = 4.1 mg a.i./kg dw soil (adult body weight and reproduction)	N/A	1904166
		M14360-acid	NOEC = 125 mg/kg dw soil (highest test concentration)	N/A	1904170
Bee	48 hr-Oral	Tetraconazole	LD_{50} > 130 µg a.i./bee	Relatively non-toxic	1904155
	96 hr-Contact		LD_{50} = 63.0 µg a.i./bee	Relatively non-toxic	
	72 hr-Oral	Tetraconazole 125 g/L ME	LD_{50} = 23.1 µg a.i./bee	Relatively non-toxic	1904153
	72 hr-Contact		LD_{50} = 24.3 µg a.i./bee	Relatively non-toxic	
Predatory arthropod					
Typhlodromus pyri	14 d-Contact glass plate	Tetraconazole 40 g/L ME	LR_{50} = 32.2 g a.i./ha	N/A	1904156
		Tetraconazole 125 g/L ME	LR_{50} = 13.9 g a.i./ha	N/A	1904159
Chrysoperla carnea	14 – 23 d-Contact	Tetraconazole 40 g/L ME	LR_{50} > 250 g a.i./ha	N/A	1904157
Poecilus cupreus	14 d-Contact	Tetraconazole 40 g/L ME	LR_{50} > 250 g a.i./ha	N/A	1904158

Organism	Exposure	Test substance [b]	Endpoint value	Degree of toxicity[a]	PMRA#
Parasitic arthropod					
Aphidius rhopalosiphi	48 hr-Contact glass plate	Tetraconazole 40 g/L ME	LR_{50} = 106.1 g a.i./ha	N/A	1904160
		Tetraconazole 125 g/L ME	LR_{50} = 114 g a.i./ha	N/A	1904164
	48 hr-Contact barley plant	Tetraconazole 40 g/L ME	LR_{50} = > 250 g a.i./ha ER_{50} = 125 g a.i./ha (reproduction)	N/A	1904162
	48 h-Contact with aged residues (0, 7, 14 days) barley plant	Tetraconazole 40 g/L ME	LR_{50} > 250 g a.i./ha (0, 7, 14-d residues); $NOEC_{mortality}$ = 125 g a.i./ha (0-day residues; 7 and 14-d = 250 g a.i./ha); $NOEC_{reproduction}$ = 250 g a.i./ha (0, 7, 14-d residues)	N/A	1904163
Birds					
Bobwhite quail	Acute oral	Tetraconazole	LD_{50} = 131 mg a.i./kg bw	Moderately toxic	1904203
		Tetraconazole 125 g/L ME	LD_{50} = 960 mg EP/kg bw, or LD_{50} = 109.2 mg a.i./kg bw	Slightly toxic	1904202
	5 d-Dietary	Tetraconazole	LD_{50} = 92.0 mg a.i./kg bw	Highly toxic	1904207
	22 wk-Reproduction	Tetraconazole	NOEL = 1.1 mg a.i./kg bw LOEL = 2 mg a.i./kg bw	N/A	1904212 1904213 2018564 2018565
Mallard duck	Acute oral	Tetraconazole	Not available – study unacceptable	-	1904205
	5 d-Dietary	Tetraconazole	LD_{50} = 55.6 mg a.i./kg bw	Highly toxic	1904211
	22 wk-Reproduction	Tetraconazole	NOEL = 2.0 mg a.i./kg bw LOEL = 7 mg a.i./kg bw	N/A	1904214 1904215 1904216

Organism	Exposure	Test substance [b]	Endpoint value	Degree of toxicity[a]	PMRA#
Mammals					
Rat	Acute	Tetraconaozle	LD_{50} (♂/♀)= 1248/1031 mg a.i./kg bw	Slightly toxic	1903883
		Eminent 125 SL (125 g/L tetraconazole)	LD_{50} > 5050 mg EP/kg bw	Practically non-toxic	1904971
	2-generation Reproduction	Tetraconazole	NOAEL = 5.9 mg a.i./kg bw/day (70 ppm) LOAEL = 40.6 mg a.i./kg bw/day (490 ppm)	N/A	1903991 1903992 1903993 1903995
Vascular plants					
Ten crop species	14 d-Seedling emergence	Eminent 125 SL (125 g/L tetraconazole)	EC_{25} > 112 g a.i./ha	N/A	1904226
	14 d-Vegetative vigour	Eminent 125 SL (125 g/L tetraconazole)	EC_{25} > 112 g a.i./ha	N/A	1904227

[a] USEPA classification, where applicable
[b] Tetraconazole 125 g/L ME and Eminent 125 SL have similar formulation as Mettle 125 ME Fungicide and are considered to be equivalent to Mettle 125 ME Fungicide.

Table 9 Screening Level Risk Assessment on Terrestrial Non-Target Organisms

Organism	Exposure	Test substance	Endpoint value (With uncertainty factor applied)	EEC[a]	RQ	LOC Exceeded?
Invertebrates						
Earthworm	14 d-Acute	Tetraconazole	$1/2LC_{50}$ = 34.5 mg a.i./kg soil dw	0.0805 mg a.i./kg soil dw	< 0.01	No
		M14360-acid	$1/2LC_{50}$ > 250 mg/kg soil dw	0.0619 mg/kg soil dw	< 0.01	No
		M14360-alcohol	$1/2LC_{50}$ > 500 mg/kg soil dw	0.0588 mg/kg soil dw	< 0.01	No
		M14360-triazolyl acetic acid	$1/2LC_{50}$ > 500 mg/kg soil dw	0.0275 mg/kg soil dw	< 0.01	No
		Tetraconazole 125 ME (EP)	$1/2LC_{50}$ > 57 mg a.i./kg soil dw	0.0805 mg a.i./kg soil dw	< 0.01	No

Organism	Exposure	Test substance	Endpoint value (With uncertainty factor applied)	EEC[a]	RQ	LOC Exceeded?
	56 d-Chronic (28-day adult exposure, 28-day reproduction)	Tetraconazole	$NOEC_{reproduction}$ = 4.1 mg a.i./kg soil dw	0.0805 mg a.i./kg soil dw	0.02	No
		M14360-acid	NOEC = 125 mg/kg soil dw	0.0619 mg/kg soil dw	< 0.01	No
Bee	72 hr-Oral	Tetraconazole 125 g/L ME	LD_{50} = 25.9 kg a.i./ha[b]	0.119 kg a.i./ha	< 0.01	No
	72 hr-Contact	Tetraconazole 125 g/L ME	LD_{50} = 27.2 kg a.i./ha[b]	0.119 kg a.i./ha	< 0.01	No
Predatory arthropod						
Typhlodromus pyri	14 d-Contact glass plate	Tetraconazole 40 g/L ME	LR_{50} = 32.2 g a.i./ha	118.8 g a.i./ha	**3.7**	**Yes**
		Tetraconazole 125 g/L ME	LR_{50} = 13.9 g a.i./ha	118.8 g a.i./ha	**8.6**	**Yes**
Chrysoperla carnea	14–23 d-Contact	Tetraconazole 40 g/L ME	LR_{50} > 250 g a.i./ha	118.8 g a.i./ha	< 0.48	No
Poecilus cupreus	14 d-Contact	Tetraconazole 40 g/L ME	LR_{50} > 250 g a.i./ha	118.8 g a.i./ha	< 0.72	No
Parasitic arthropod						
Aphidius rhopalosiphi	48 hr-Contact glass plate	Tetraconazole 40 g/L ME	LR_{50} = 106.1 g a.i./ha	118.8 g a.i./ha	1.1	No
		Tetraconazole 125 g/L ME	LR_{50} = 114 g a.i./ha	118.8 g a.i./ha	1.0	No
	48 hr-Contact barley plant	Tetraconazole 40 g/L ME	LR_{50} > 250 g a.i./ha	118.8 g a.i./ha	< 0.48	No
			$ER_{50reproduction}$ = 125 g a.i./ha	118.8 g a.i./ha	0.95	No
	48 hr-Contact with aged residues (0, 7, 14 days) barley plant	Tetraconazole 40 g/L ME	LR_{50} > 250 g a.i./ha (0, 7, 14-d residues)	118.8 g a.i./ha	< 0.48	No
			$NOEC_{mortality}$ = 125 g a.i./ha (0-day residues)	118.8 g a.i./ha	0.95	No
			$NOEC_{mortality}$ = 250 g a.i./ha (7 and 14-d residues)	118.8 g a.i./ha	0.48	No
			$NOEC_{reproduction}$ = 250 g a.i./ha (0, 7, 14-d residues)	118.8 g a.i./ha	0.48	No

Organism	Exposure	Test substance	Endpoint value (With uncertainty factor applied)	EEC[a]	RQ	LOC Exceeded?
Vascular plants	14 d-Seedling emergence	Eminent 125 SL (125 g/L tetraconazole)	EC_{25} > 112 g a.i./ha	181.1 g a.i./ha	**< 1.6**	**Yes**
	14 d-Vegetative vigour	Eminent 125 SL (125 g/L tetraconazole)	EC_{25} > 112 g a.i./ha	118.8 g a.i./ha	**< 1.1**	**Yes**

[a] At the screening level, EECs are based on a direct application at maximum cumulative application rate and thus considers the maximum label application rate, the number of applications, the application interval and the dissipation between applications.
For tetraconazole in soil: 4 × 45.6 g a.i./ha at 14 day interval. Dissipation in soil: estimated single first-order DT_{50} of 1868 days (estimated by multiplying the longest soil DT_{50}.
For tetraconazole on foliage:1x119 g a.i./ha with default dissipation on foliagehalf-life of 10 days.
For M14360-alcohol, M14360-triazolyl acetic acid and M14360-acid was determined by assuming 100% conversion of tetraconazole and were corrected for the molecular weight ratio of the transformation products to tetraconazole.

[b] Toxicity in µg/bee converted to the equivalent kg a.i./ha using a conversion factor of 1.12 (Atkins *et al.*, 1981)
RQ = risk quotient = exposure/toxicity. Shaded cells indicate that the level of concern is exceeded (LOC = 2 for *T pyri* and *A. rhopalosiphi* in glass plate tests; LOC = 1 for other species).

Table 10 Refined Risk Assessment on Predatory Arthropod – *Typhlodromus pyri*

Organism	Exposure	Test substance	Endpoint value	EEC (g a.i./ha)	RQ	LOC Exceeded?
On-field						
Typhlodromus pyri	14 d-Contact glass plate	Tetraconazole 40 g/L ME	LR_{50} = 32.2 g a.i./ha	83.2	**2.6**	**Yes**
		Tetraconazole 125 g/L ME	LR_{50} = 13.9 g a.i./ha	83.2	**6.0**	**Yes**
Off-field						
Typhlodromus pyri	14 d-Contact glass plate	Tetraconazole 40 g/L ME	LR_{50} = 32.2 g a.i./ha	0.50	0.02	No
		Tetraconazole 125 g/L ME	LR_{50} = 13.9 g a.i./ha	0.50	0.04	No

Shaded cells indicate that the level of concern is exceeded

Table 11 Refined Risk Assessment on Non-target Terrestrial Plant

Organism	Exposure	Test Substance	Endpoint (g a.i./ha)	EEC (g a.i./ha)	RQ	LOC Exceeded?
Terrestrial Vascular plants	14 d-Seedling emergence	Eminent 125 SL (125 g/L tetraconazole)	EC_{25} > 112	10.9	< 0.1	No
	14 d-Vegetative vigour		EC_{25} > 112	7.1	< 0.06	No

Table 12 Screening Level Risk Assessment on Bird and Mammals

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)[a]	RQ	LOC Exceeded?
Small Bird (0.02 kg)					
Acute	13.10	Insectivore (small insects)	5.99	0.46	No
Reproduction	1.10	Insectivore (small insects)	5.99	**5.44**	**Yes**
Medium Sized Bird (0.1 kg)					
Acute	13.10	Insectivore (small insects)	4.67	0.36	No
Reproduction	1.10	Insectivore (small insects)	4.67	**4.25**	**Yes**
Large Sized Bird (1 kg)					
Acute	13.10	Herbivore (short grass)	4.87	0.37	No
Reproduction	1.10	Herbivore (short grass)	4.87	**4.43**	**Yes**
Small Mammal (0.015 kg)					
Acute	103.10	Insectivore (small insects)	3.44	0.03	No
Reproduction	5.9	Insectivore (small insects)	3.44	0.58	No
Medium Sized Mammal (0.035 kg)					
Acute	103.10	Herbivore (short grass)	10.79	0.10	No
	103.10	Herbivore (leafy foliage)	20.33	0.20	No
Reproduction	5.9	Herbivore (short grass)	10.79	**1.83**	**Yes**
	5.9	Herbivore (leafy foliage)	20.33	**3.45**	**Yes**
Large Sized Mammal (1 kg)					
Acute	103.10	Herbivore (short grass)	5.76	0.06	No
	103.10	Herbivore (leafy foliage)	10.86	0.11	No
Reproduction	5.9	Herbivore (short grass)	5.76	**5.76**	**Yes**
	5.9	Herbivore (leafy foliage)	10.86	**10.86**	**Yes**

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

Table 13 Further Characterization of the Reproductive Risk to Birds and Mammals

Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
		On-field[b]		Off Field[c]		On-field[b]		Off Field[c]	
		EDE (mg a.i./kg bw)[a]	RQ	EDE (mg a.i./kg bw)[a]	RQ	EDE (mg a.i./kg bw)[a]	RQ	EDE (mg a.i./kg bw)[a]	RQ
Small Bird (0.02 kg)									
1.10	Insectivore (small insects)	5.99	**5.44**	2.34	**2.13**	3.34	**3.03**	1.31	**1.19**
1.10	Granivore (grain and seeds)	1.50	**1.36**	0.59	0.53	0.71	0.65	0.28	0.25
1.10	Frugivore (fruit)	2.99	**2.72**	1.17	**1.07**	1.43	**1.30**	0.56	0.51
Medium Sized Bird (0.1 kg)									
1.10	Insectivore (small insects)	4.67	**4.25**	1.83	**1.66**	2.61	**2.37**	1.02	0.93
1.10	Insectivore (large insects)	1.17	**1.06**	0.46	0.42	0.56	0.51	0.22	0.20
1.10	Granivore (grain and seeds)	1.17	**1.06**	0.46	0.42	0.56	0.51	0.22	0.20
1.10	Frugivore (fruit)	2.34	**2.12**	0.91	0.83	1.11	**1.01**	0.44	0.40
Large Sized Bird (1 kg)									
1.10	Insectivore (small insects)	1.36	**1.24**	0.53	0.49	0.76	0.69	0.30	0.27
1.10	Insectivore (large insects)	0.34	0.31	0.13	0.12	0.16	0.15	0.06	0.06
1.10	Granivore (grain and seeds)	0.34	0.31	0.13	0.12	0.16	0.15	0.06	0.06
1.10	Frugivore (fruit)	0.68	0.62	0.27	0.24	0.33	0.30	0.13	0.12
1.10	Herbivore (short grass)	4.87	**4.43**	1.91	**1.74**	1.73	**1.57**	0.68	0.62
1.10	Herbivore (long grass)	2.98	**2.71**	1.17	**1.06**	0.97	0.88	0.38	0.35
1.10	Herbivore (forage crops)	4.51	**4.10**	1.77	**1.61**	1.49	**1.36**	0.58	0.53
Medium Sized Mammal (0.035 kg)									
5.9	Insectivore (small insects)	3.02	0.511	1.18	0.200	1.68	0.285	0.66	0.112
5.9	Insectivore (large insects)	0.75	0.128	0.30	0.050	0.36	0.061	0.14	0.024
5.9	Granivore (grain and seeds)	0.75	0.128	0.30	0.050	0.36	0.061	0.14	0.024
5.9	Frugivore (fruit)	1.51	0.256	0.59	0.100	0.72	0.122	0.28	0.048
5.9	Herbivore (short grass)	10.79	**1.828**	4.23	0.716	3.83	0.649	1.50	0.254
5.9	Herbivore (long grass)	6.59	**1.116**	2.58	0.437	2.15	0.365	0.84	0.143
5.9	Herbivore (forage crops)	9.98	**1.691**	3.91	0.663	3.30	0.559	1.29	0.219
5.9	Herbivore (leafy foliage)	20.33	**3.445**	7.96	1.350	6.72	**1.139**	3.56	0.446
Large Sized Mammal (1 kg)									
5.9	Insectivore (small insects)	1.61	0.273	0.63	0.107	0.90	0.152	0.35	0.060
5.9	Insectivore (large insects)	0.40	0.068	0.16	0.027	0.19	0.033	0.08	0.013
5.9	Granivore (grain and seeds)	0.40	0.068	0.16	0.027	0.19	0.033	0.08	0.013
5.9	Frugivore (fruit)	0.81	0.137	0.32	0.054	0.38	0.065	0.15	0.026
5.9	Herbivore (short grass)	5.76	0.977	2.26	0.383	2.05	0.347	0.80	0.136
5.9	Herbivore (long grass)	3.52	0.597	1.38	0.234	1.15	0.195	0.45	0.076

Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
		On-field[b]		Off Field[c]		On-field[b]		Off Field[c]	
		EDE (mg a.i./kg bw)[a]	RQ	EDE (mg a.i./kg bw)[a]	RQ	EDE (mg a.i./kg bw)[a]	RQ	EDE (mg a.i./kg bw)[a]	RQ
5.9	Herbivore (forage crops)	5.33	0.904	2.09	0.354	1.76	0.299	0.69	0.117
5.9	Herbivore (leafy foliage)	10.86	**1.841**	4.25	0.721	3.59	0.609	1.90	0.238

[a] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987).

[b] On-field residues are based on a direct application at maximum cumulative application and thus considers the maximum label application rate the number of applications, the application interval and the dissipation between applications.

[c] The off-field assessment was based on the highest projected drift deposition relevant to the tetraconazole use pattern (74% drift for early season airblast applications).
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(BW in g) $^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher *et al*. (1994).
RQ = risk quotient = exposure/toxicity. Shaded cells indicate that the level of concern (LOC = 1) is exceeded.

Table 14 Effects on Aquatic Organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Freshwater species					
Water flea (*D. magna*)	48 hr-Acute	Tetraconazole	EC_{50} = 2.63 mg a.i./L	Moderately toxic	1904179
			EC_{50} = 3.07 mg a.i./L	Moderately toxic	1904180
		M14360-acid	EC_{50} > 100 mg/L	Practically non-toxic	1904175
		M14360-alcohol	EC_{50} = 68.0 mg/L	Slightly toxic	1904176
		M14360-triazolyl acetic acid	EC_{50} > 100 mg/L	Practically non-toxic	1904177
		Tetraconazole 125 g/L ME (EP)	EC_{50} = 50.2 mg EP/L, or = 5.71 mg a.i./L	Slightly toxic	1904178
	21 d-Chronic	Tetraconazole	NOEC = 0.51 mg a.i./L (adult mortality and reproduction)	N/A	1904181
			NOEC = 0.19 mg a.i./L (time to first brood and reproduction)	N/A	1904183
Midge (*C. riparius*)	28 d-Chronic	Tetraconazole	NOEC = 2.83 mg a.i./L (emergence rate)	N/A	1904229
			EC_{50} = 4.98 mg a.i./L	N/A	

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Rainbow trout (*O. mykiss*)	96 hr-Acute	Tetraconazole	LC_{50} = 3.91 mg a.i./L	Moderately toxic	1904192
			$LC_{50} \geq$ 5.2 mg a.i./L	Moderately toxic	1904194
		M14360-acid	LC_{50} = 61.4 mg/L	Slightly toxic	1904188
		M14360-alcohol	LC_{50} = 24 mg/L	Slightly toxic	1904189
		M14360-triazolyl acetic acid	LC_{50} > 100 mg/L	Practically non-toxic	1904191
		Tetraconazole 125 ME (EP)	EC_{50} = 25.9 mg EP/L, or = 3.0 mg a.i./L	Slightly toxic	1904224
Bluegill sunfish (*L. macrochirus*)	96 hr-Acute	Tetraconazole	LC_{50} = 3.85 mg a.i./L	Moderately toxic	1904195
			LC_{50} = 5.8 mg a.i./L	Moderately toxic	1904197
Fathead minnow (*P. promelas*)	34 d-Chronic Early Life Stage	Tetraconazole	NOEC = 0.30 mg a.i./L (dry weight and length)	N/A	1904200
			NOEC = 1.09 mg a.i./L (dry weight and length)	N/A	1904199
Freshwater algae					
Green algae (*S. subspicatus*)	72 hr-Acute	Tetraconazole	ErC_{50} = 0.41 mg a.i./L EyC_{50} = 0.27 mg a.i./L	N/A	1904218
		M14360-acid	ErC_{50} and EyC_{50} > 100 mg/L	N/A	1904220
		M14360-alcohol	ErC_{50} = 12.2 mg/L EyC_{50} = 4.0 mg/L	N/A	1904221
		M14360-triazolyl acetic acid	ErC_{50} = 135.1 mg/L EyC_{50} = 12.2 mg/L	N/A	1904223
		Tetraconazole 125 ME (EP)	ErC_{50} = 6.6 mg EP/L EyC_{50} = 1.7 mg EP/L, or ErC_{50} = 0.75 mg a.i./L EyC_{50} = 0.19 mg a.i./L	N/A	1904225
Vascular plant duckweed	7 d-Dissolved		EC_{50} = 0.31 mg a.i./L (frond	N/A	1904228

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
(*L. gibba*)			number)		
Marine species					
Mysid shrimp (*A. bahia*)	96 hr-Acute	Tetraconazole	LC_{50} = 0.44 mg a.i./L	Highly toxic	1904186
Eastern oyster (*C. virginica*)	96 hr-Acute	Tetraconazole	EC_{50} = 1.0 mg a.i./L	Highly toxic	1904187
Sheepshead minnow (*C. variegatus*)	96 hr-Acute	Tetraconazole	LC_{50} = 4.6 mg a.i./L	Moderately toxic	1904198

[a] USEPA classification, where applicable

Table 15 Screening Level Risk Assessment on Aquatic Organisms

Organism	Exposure	Test substance	Endpoint value	EEC[a] (mg/L)	RQ	LOC Exceeded?
Freshwater species						
Water flea (*D. magna*)	48 hr-Acute	Tetraconazole	$1/2EC_{50}$ = 1.32 mg a.i./L	0.0219	0.02	No
		M14360-acid	$1/2EC_{50}$ > 50 mg/L	0.0168	< 0.01	No
		M14360-alcohol	$1/2EC_{50}$ = 34 mg a.i./L	0.0160	< 0.01	No
		M14360-triazolyl acetic acid	$1/2EC_{50}$ > 50 mg a.i./L	0.0075	< 0.01	No
		Tetraconazole 125 ME (EP)	$1/2EC_{50}$ = 2.86 mg a.i./L	0.0219	0.01	No
	21 d-Chronic	Tetraconazole	NOEC = 0.19 mg a.i./L	0.0219	0.12	No
Midges (*C. riparius*)	28 d-Chronic	Tetraconazole	NOEC = 2.83 mg a.i./L	0.0219	0.01	No
Rainbow trout (*O. mykiss*)	96 hr-Acute	Tetraconazole	$1/10LC_{50}$ = 0.391 mg a.i./L	0.0219	0.06	No
		M14360-acid	$1/10LC_{50}$ = 6.14 mg a.i./L	0.0168	< 0.01	No
		M14360-alcohol	$1/10LC_{50}$ = 2.4 mg a.i./L	0.0160	0.01	No
		M14360-triazolyl acetic acid	$1/10LC_{50}$ > 10 mg/L	0.0075	< 0.01	No
		Tetraconazole 125 ME (EP)	$1/10LC_{50}$ = 0.30 mg a.i./L	0.0219	0.07	No
Bluegill sunfish (*L. macrochirus*)	96 hr-Acute	Tetraconazole	$1/10LC_{50}$ = 0.385 mg a.i./L	0.0219	0.06	No

Organism	Exposure	Test substance	Endpoint value	EEC[a] (mg/L)	RQ	LOC Exceeded?
Fathead minnow (*P. promelas*)	34 d-Chronic Early Life Stage	Tetraconazole	NOEC = 0.30mg a.i./L	0.0219	0.07	No
Amphibians						
	96 hr-Acute	Tetraconazole	$1/10LC_{50}$ = 0.385 mg a.i./L	0.117	0.30	No
	34 d-Chronic	Tetraconazole	NOEC = 0.30 mg a.i./L	0.117	0.39	No
Freshwater algae						
Green algae (*S. subspicatus*)	72 hr-Acute	Tetraconazole	$1/2EC_{50}$ = 0.135 mg a.i./L	0.0219	0.16	No
		M14360-acid	$1/2EC_{50}$ > 50 mg/L	0.0168	< 0.01	No
		M14360-alcohol	$1/2EC_{50}$ = 2.0 mg/L	0.0160	0.01	No
		M14360-triazolyl acetic acid	$1/2EC_{50}$ = 6.1 mg/L	0.0075	< 0.01	No
		Tetraconazole 125 ME (EP)	$1/2EC_{50}$ = 0.095 mg a.i./L	0.0219	0.23	No
Vascular plant (*L. gibba*)	7 d	Tetraconazole	$1/2EC_{50}$ = 0.16 mg a.i./L	0.0219	0.14	No
Marine species						
Mysid shrimp (*A. bahia*)	96 hr-Acute	Tetraconazole	$1/2LC_{50}$ = 0.22 mg a.i./L	0.0219	0.10	No
Eastern oyster (*C. virginica*)	96 hr-Acute	Tetraconazole	$1/2EC_{50}$ = 0.50 mg a.i./L	0.0219	0.04	No
Sheepshead minnow (*C. variegatus*)	96 hr-Acute	Tetraconazole	$1/10LC_{50}$ = 0.46 mg a.i./L	0.0219	0.05	No

[a] At the screening level, EECs are based on a direct application at maximum cumulative application rate and thus considers the maximum label application rate, the number of applications, the application interval and the dissipation between applications.
For tetraconazole: 4 × 45.6 g a.i./ha at 14-day interval. Dissipation in water: half-life of 372 days (longest laboratory whole system half-lives).
For M14360-alcohol, M14360-triazolyl acetic acid and M14360-acid was determined by assuming 100% conversion of tetraconazole and were corrected for the molecular weight ratio of the transformation products to tetraconazole.
RQ = risk quotient = exposure/toxicity.

Table 16 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints	Transformation Products Endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		Yes. Risk quotients above the PMRA Level of Concern for terrestrial vertebrates and invertebrates.	No. Available RQs for all TPs < LOC
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Yes 80th percentile of aerobic soil $t_{1/2}$s = 1986 days	M14360-acid longest DT_{50} = 221 days (representative half-life [DT_{90} / 3.32 = 2214 days). M14360-alcohol longest DT_{50} < 1 day. M14360-triazolyl acetic acid longest DT_{50} = 11 days.
	Water	Half-life ≥ 182 days	No Longest DT_{50} = 1.9 days	Not available
	Sediment	Half-life ≥ 365 days	Yes Longest whole-system $t_{1/2}$ = 372 days (no clear pattern of decline in sediment)	Not available
	Air	Half-life ≥ 2 days or evidence of long range transport	No Estimated photochemical oxidative $t_{1/2}$ = 1.16 days (Applicant value; PMRA # 1903828). Volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (1.8×10^{-4} Pa) and Henry's Law Constant (3.50×10^{-9} $atm/m^3/mol^{-1}$).	Not available. Not expected to be volatile, based on parent compound.
Bioaccumulation[4]	Log $K_{ow} \geq 5$		No Value = 3.56	No Values < 3 (PMRA #1903828)
	BCF ≥ 5000		No	Not available

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Active Ingredient Endpoints	Transformation Products Endpoints
		Steady-state BCF = 35.7 L/kg (whole-fish)	
	BAF ≥ 5000	Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

[1] All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (i.e. all other TSMP criteria are met).

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

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

[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).

Table 17 Alternative active ingredients registered for control of claimed diseases on the Mettle 125 ME Fungicide accepted label.

Crop	Disease	Active ingredient and FRAC Fungicide Group	
		Conventional	Non-conventional
Grape	Powdery mildew	Boscalid (7) Boscalid + pyraclostrobin (7 + 11) Copper (M1) Dinocap + mancozeb (29 + M3) Fluopyram + pyrimethanil (7 + 9) Kresoxim-methyl (11) Metrafenone (U8) Myclobutanil (3) Pyraclostrobin (11) Quinoxyfen (13)	Potassium bicarbonate (NC) *Bacillus subtillis* (44) (suppression only) Sulphur (M2)
	Black rot	Boscalid + pyraclostrobin (7 + 11) Captan (M4) Copper (M1) Ferbam (M3) Kresoxim-methyl (11) Metiram (M3) Myclobutanil (3) Pyraclostrobin (11) Trifloxystrobin (11)	Sulphur (M2)
Gooseberry	Powdery mildew	Boscalid + pyraclostrobin (7 + 11) (suppression only) Copper (M1)	Sulphur (M2)
Sugar Beet	Cercospora leaf spot	Copper (M1) Mancozeb (M3) Metconazole (3) Prothioconazole (3) Pyraclostrobin (11) Thiophanate methyl (1)	
	Powdery mildew	Pyraclostrobin (11) Trifloxystrobin (11)	
Strawberry	Powdery mildew	Boscalid (7) Boscalid + pyraclostrobin (7 + 11) Fluopyram (7) Myclobutanil (3) Pyraclostrobin (11) Quinoxyfen (13)	*Reynoutria sachalinensis* (NC) (suppression only) *Streptomyces lydicus* (NC) (suppression only) Sulphur (M2)

Crop	Disease	Active ingredient and FRAC Fungicide Group	
		Conventional	Non-conventional
		Trifloxystrobin (11)	

Table 18 Use (label) Claims Proposed by Applicant and Accepted

Proposed claim	Accepted claim
1) Control of powdery mildew (*Erysiphe necator*) at the rates (219 - 365 mL/ha) on grape with maximum two (2) applications and 730 mL/ha product per season, a 14-day spray interval under high disease pressure or favourable conditions for disease development, and a 21-day interval under low to moderate disease pressure.	As proposed.
2) Control of black rot (*Guignardia bidwellii*) at the rates (219 - 365 mL/ha) on grape with maximum two (2) applications and 730 mL/ha product per season and a 14-day spray interval.	Accepted with rate range from 292 to 365 mL/ha for preventive application.
3) Control of powdery mildew (*Sphaerotheca macularis*) at the rates of 219 - 365 mL/ha on gooseberry with maximum two (2) applications and 730 mL/ha product per season, a 14-day spray interval under high disease pressure or favourable conditions for disease development, and a 21-day interval under low to moderate disease pressure.	As proposed.
4) Control of cercospora leaf spot (*Cercospora beticola*) at the rate of 950 mL/ha on sugar beet with one (1) application per season.	As proposed.
5) Control of powdery mildew (*Erysiphe polygoni*) at the rate of 950 mL/ha on sugar beet with one (1) application per season.	As proposed.
6) Control of powdery mildew (*Sphaerotheca macularis* f. sp. *fragariae*) at the rates of 219 - 365 mL/ha on strawberry with maximum four (4) applications and 1460 mL/ha product per season, a 14-day spray interval under high disease pressure or favourable conditions for disease development, and a 21-day interval under low to moderate disease pressure.	As proposed.

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

The specified Canadian MRLs for plant matrices are the same as those in the United States. The MRLs for animal matrices differ from the tolerances established in the United States (40 CFR Part 180).

Table 1 Differences Between Canadian MRLs and in Other Jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)	Codex* (ppm)
Crop Subgroup 13-07F (Small fruit vine climbing subgroup, except fuzzy kiwifruit)	0.2	0.2	Not reviewed by Codex
Crop Subgroup 13-07G (Low growing berry subgroup)	0.25	0.25	
Sugar beet roots	0.05	0.05	
Sugar beet molasses	0.15	0.15	
Fat, kidney, meat, and meat byproducts (except liver) of cattle, goats, horses, hogs and sheep	0.02	0.01 (meat of cattle, goat, hog, horse, poultry, and sheep; fat and meat byproducts [except liver] of hog) 0.05 (poultry fat, and poultry meat byproducts) 0.15 (fat and meat byproducts[except liver] of cattle, goat, horse, and sheep	
Liver of cattle, goats, horses, hogs and sheep	0.05	1.5 (liver of cattle, goat, horse, and sheep) 0.05 (hog liver)	
Milk	0.01	0.03 (Milk) 0.75 (Milk fat)	

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

Maximum residue limits may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian

MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
1903830	2003, Active substance: Tetraconazole Document J (doc.MII), DACO: 2.11, 2.11.1, 2.11.2, 2.11.3, 2.11.4, 2.12.1, 2.13.1, 2.13.2, 2.13.3, 2.13.4, 2.2 CBI
1903831	2003, Manufacturing method for the production of Tetraconazole, DACO: 2.11.1, 2.11.2, 2.11.3 CBI
1903833	1995, Discussion of the Formation of Tetraconazole Impurities, DACO: 2.11.4
1903834	1992, Analysis of product M 14360 Analytical Grade: Sample Batch N. 19084/1, DACO: 2.12.1 CBI
1903835	1999, Impurezza [CBI removed], Presente in Vari Lotti Di Tetraconazole Tecnico, Avente Nello [CBI removed]., DACO: 2.13.2 CBI
1903836	2010, Identification by GC/MS of an unknown impurity in Tetraconazole., DACO: 2.13.2 CBI
1903837	2007, Tetraconazole Technical: Analysis of active ingredient and impurities in batches [CBI removed], DACO: 2.13.3 CBI
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2.0 Human and Animal Health

Toxicology

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