Evaluation Report ERC2011-06

Difenoconazole

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Overview

Registration Decision for Difenoconazole

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Difenoconazole Technical Fungicide and Inspire™ Fungicide, containing the technical grade active ingredient difenoconazole, to control or suppress fungal diseases on a variety of fruit and vegetable crops.

Difenoconazole (Registration Number 25631) is currently registered in Canada as a seed treatment on wheat, and the detailed review for this use can be found in the Proposed Regulatory Decision Document PRDD99-01: *Difenoconazole* as well as in the Regulatory Decision Document RDD2001-04: *Difenoconazole Fungicide*.

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.

Although the risks and value have been found acceptable when all risk reduction measures are followed, the applicant must submit additional scientific information as a condition of registration.

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 difenoconazole and Inspire™ 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.

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

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

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

What Is Difenoconazole?

Difenoconazole is a Group 3 fungicide active ingredient that inhibits mycelial growth, which slows or stops the growth of the fungus and effectively prevents further infection or invasion of host tissues.

Health Considerations

Can Approved Uses of Difenoconazole Affect Human Health?

Difenoconazole is unlikely to affect your health when used according to label directions.

Potential exposure to difenoconazole may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g., 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 difenoconazole products are used according to label directions.

In laboratory animals, the technical grade active ingredient difenoconazole was of slight acute toxicity by the oral route; consequently, the hazard signal words "CAUTION – POISON" are required on the Difenoconazole Technical Fungicide label. It was of low acute toxicity dermally and through inhalation exposure. Difenoconazole was mildly irritating to the eyes, minimally irritating to the skin and did not cause an allergic skin reaction. The hazard signal words "CAUTION – EYE IRRITANT" are required on the Difenoconazole Technical Fungicide label.

The acute toxicity of the end-use product, Inspire™ Fungicide, which contains difenoconazole, was low via the oral, dermal and inhalation routes of exposure. It was slightly irritating to the skin and did not cause an allergic skin reaction. Inspire™ Fungicide was moderately irritating to the eyes; consequently, the hazard signal words "WARNING – EYE IRRITANT" are required on the Inspire™ Fungicide label.

There was limited evidence that difenoconazole caused damage to the nervous system or immune system. Difenoconazole did not cause birth defects in animals and there were no effects on the ability to reproduce. There was no evidence to suggest that difenoconazole damaged genetic material. Health effects in animals given repeated doses of difenoconazole included effects on the liver, body weight and food consumption. Difenoconazole caused liver tumours in mice, but not in rats. These tumours were observed at very high doses that were considered excessive.

When difenoconazole was given to pregnant animals, effects of a serious nature were observed on the developing fetus at doses that were toxic to the mother. There was an increased incidence of fetal mortality in utero, while the mothers had severely depressed body weight gains. The risk assessment takes these effects into account in determining the allowable level of human exposure to difenoconazole.

The risk assessment protects against the effects of difenoconazole 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 children (1-2 years old), the subpopulation which would ingest the most difenoconazole relative to body weight, are expected to be exposed to less than 35% and 89% of the acceptable daily intake, respectively. Based on these estimates, the chronic dietary risk from difenoconazole is not of concern for all population sub-groups. A lifetime cancer assessment was not performed since there was no cancer risk identified for difenoconazole.

An acute aggregate (food and water) dietary intake estimate for the highest exposed population (children 1-2 years old) was less than 52% of the acute reference dose, which is below the level of concern. An acute aggregate (food and water) dietary intake estimate for females (aged 13-49 years) was less than 31% of the acute reference dose for this population, which is not a health concern.

The *Food and Drugs Act (FDA)* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for FDA purposes through the evaluation of scientific data under the *Pest Control Products Act (PCPA).* 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 difenoconazole on various crops were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this Evaluation Report.

Risks in Residential and Other Non-Occupational Environments

Entry by the public into treated commercial areas is considered acceptable.

An aggregate risk assessment was performed for adults and children entering treated commercial areas for 'pick-your-own' harvest activities in pome fruit. No risks of concern were identified.

Occupational Risks From Handling Inspire™ Fungicide

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

Farmers and custom applicators who mix, load or apply Inspire™ Fungicide as well as field workers re-entering treated fields can come in direct contact with difenoconazole on the skin. Therefore, the label specifies that anyone mixing/loading and applying Inspire™ Fungicide must wear chemical-resistant gloves, protective eyewear, long-sleeved shirt and long pants and socks and shoes. The label also requires that workers do not enter treated fields or other treated sites for 1-10 days after application for specific activities in some crops. For all other uses, a restricted re-entry interval of 12 hours is specified. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to workers handling Inspire™ Fungicide is not of 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 Difenoconazole Is Introduced Into the Environment?

Difenoconazole will be persistent in terrestrial and aquatic environments and may affect beneficial arthropods and aquatic life. The effects of difenoconazole can be mitigated with the observance of precautionary measures including spray drift buffer zones for protection of aquatic life.

When difenoconazole is used to control diseases on a variety of crops, any difenoconazole deposited on the ground will remain in soil for a considerable period of time as it is broken down very slowly. With repeated yearly applications, difenoconazole will accumulate in soil and could eventually move to lower soil depths. Difenoconazole is not volatile and is not expected to bioaccumulate.

Amphibians would be at the highest risk through exposure from off-target spray drift entering aquatic systems resulting from the application of difenoconazole. There is also a risk to freshwater and marine/estuarine invertebrates and fish, and beneficial terrestrial arthropods.

Value Considerations

What Is the Value of Inspire™ Fungicide?

Difenoconazole, the active ingredient in Inspire™ Fungicide, controls or suppresses a range of economically important pathogens on fruit and vegetable crops.

Inspire™ Fungicide is a product formulated as a foliar treatment against various fungal diseases on fruit and vegetable crops. Inspire™ Fungicide is a broad spectrum fungicide with systemic and curative properties, offers a new fungicide chemistry to Canadian growers and may be applied as a foliar spray in alternating spray programs. Inspire™ Fungicide may also be applied in tank mixes with other crop protection products for pest resistance management, or to increase the disease spectrum on crops that are registered on both product labels.

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 Inspire™ Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

As there is a concern with users coming into direct contact with Inspire™ Fungicide on the skin, anyone mixing, loading and applying Inspire™ Fungicide must wear a long-sleeved shirt, long pants, chemical-resistant gloves and protective eyewear. The label also requires restricted re-entry intervals (REIs) of ten (10) days for cane-turning and vine girdling in grape, four (4) days for hand thinning in pome fruit, three (3) days for hand harvesting and irrigation in brassica vegetables, two (2) days for all other postapplication activities in grape, and one (1) day for scouting in brassica vegetables. A 12 hour REI is required for all other re-entry activities. In addition, standard label statements to protect against drift during application appear on the Inspire™ Fungicide label.

Environment

Label statements to mitigate the risk of spray drift to aquatic organisms

- Label statements to mitigate contamination of irrigation or drinking water supplies and aquatic habitats
- Buffer zones to mitigate the risk of spray drift to aquatic organisms
- Label statements to mitigate the risk of surface runoff from treated fields

- Label statements to mitigate accumulation in soil from repeated seasonal applications
- Label statements to mitigate the risk to beneficial arthropods

What Additional Scientific Information Is Being Requested?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the applicant must submit additional scientific information as a condition of registration. More details are presented in the Science Evaluation section of this Evaluation Report or in the Section 12 Notice associated with these conditional registrations. The applicant must submit the following information within the time frames indicated.

Human Health

As the nature of the residue in rotational crops has not been adequately demonstrated, an additional confined crop rotational study reflecting the maximum potential seasonal application rate in rotated crops (512 g a.i./ha) using phenyl-labelled difenoconazole is required.

Environment

Quantitative data on non-target terrestrial plants pertaining to seedling emergence and vegetative growth is required. Validated analytical methods for the determination of difenoconazole and its transformation products in water and biota (fish) are required.

Value

The following small-scale field or greenhouse trials are required for the disease claims with conditional registration:

- Three trials on alternaria blight of brassica (Cole) leafy vegetables;
- Three trials on powdery mildew of broccoli and cabbage;
- Three trials on purple blotch of garlic and/or leek;
- Three trials on powdery mildew of cucumber and/or melon;
- Three trials on gummy stem blight of cucumber and/or melon;
- Two trials on powdery mildew of grape;
- Three trials on anthracnose of tomato and/or pepper;
- Two trials on powdery mildew of apple;
- Two trials on scab of apple and/or pear.

All required data must be submitted by September 1, 2014.

Other Information

As these conditional registrations relate to a decision on which the public must be consulted,[3] the PMRA will publish a consultation document when there is a proposed decision on applications to convert the conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

The test data cited in this Evaluation Report (i.e. the test data relevant in supporting the registration decision) will be made available for public inspection when the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations (following public consultation). If more information is required, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

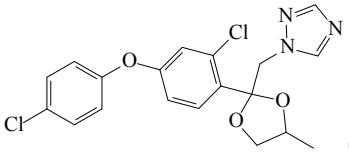
[3] As per subsection 28(1) of the *Pest Control Products Act.*

Science Evaluation

Difenoconazole

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Difenoconazole
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	3-chloro-4-[(2*RS*,4*RS*;2*RS*,4*SR*)-4-methyl-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl 4-chlorophenyl ether
2. Chemical Abstracts Service (CAS)	1-[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-ylmethyl]-1*H*-1,2,4-triazole
CAS number	119446-68-3
Molecular formula	$C_{19}H_{17}Cl_2N_3O_3$
Molecular weight	406.3
Structural formula	 (four stereoisomers)
Purity of the active ingredient	95.0 %

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

Technical Product— Difenoconazole Technical Fungicide

Please refer to the Proposed Regulatory Decision Document PRDD99-01: *Difenoconazole* for the chemistry review of Difenoconazole Technical Fungicide.

End-Use Product—Inspire™ Fungicide

Property	Result
Colour	Clear yellow to brown
Odour	Penetrating odour
Physical state	Liquid at 25°C
Formulation type	Emulsifiable concentrate
Guarantee	250 g/L
Container material and description	Fluorinated PE, HDPE, and stainless steel containers, 10 L to 1000 L
Density	1.070 g/cm^3 at 20°C
pH of 1% dispersion in water	5 – 7 at 25°C
Oxidizing or reducing action	Not an oxidizing substance
Storage stability	Stable for 1 year at 20°C in fluorinated HDPE
Corrosion characteristics	Not corrosive to fluorinated HDPE after one year storage at 20°C
Explodability	Not explosive

1.3 Directions for Use

Inspire™ Fungicide, a systemic fungicide, is proposed for use as a foliar spray to control or suppress specific diseases of fruit and vegetable crops (refer to Table 1.3.1). No more than two (2) sequential applications can be applied before alternating with another registered fungicide with a different mode of action. The higher rate and shorter interval should be applied under conditions of high disease pressures. Inspire™ Fungicide is to be tank mixed with various fungicides and insecticides for the control of labelled diseases and insect pests.

Table 1.3.1 Crop and Disease Claims Proposed for Inspire™ Fungicide

Crop & Crop Group	Disease Controlled
Brassica (Cole) Leafy Vegetables	Alternaria diseases (Alternaria spp.), anthracnose (Colletotrichum higginsianum), cercospora leaf spot (Cercospora brassicicola) and powdery mildew (Erysiphe polygoni)
Bulb Vegetables	Cercospora leaf spot (Cercospora duddiae), powdery mildew (Leveillula taurica), purple blotch (Alternaria porri) and rust (Puccinia allii)
Cucurbit Vegetables	Powdery mildew (Sphaerotheca fuliginea, Erysiphe cichoracearum), alternaria leaf blight (Alternaria cucumerina), alternaria leaf spot (Alternaria alternata), anthracnose (Colletotrichum orbiculare) and gummy stem blight (Didymella bryoniae)
Grapes	Powdery mildew (Uncinula necator), black rot (Guignardia bidwellii), anthracnose (Elsinoe ampelina), rotbrenner (Pseudopezicula tracheiphila) and angular leaf scorch (Pseudopezicula tetrespora)
Fruiting Vegetables	Early blight (Alternaria solani), black mold (Alternaria alternata), powdery mildew (Leveillula taurica) and anthracnose (Colletotrichum spp.)
Pome Fruit	Alternaria blotch (Alternaria mali), brooks fruit spot (Mycosphaerella pomi), cedar apple rust (Gymnosporangium juniperi-virginianae), flyspeck (Zygophiala jamacaicensis, formerly known as Schizothyrium pomi), powdery mildew (Podosphaera leucotricha), quince rust (Gymnosporangium clavipes), scab (Venturia inaequalis, Venturia pirina) and sooty blotch (Gloeodes pomigena)
Tuberous and corm vegetables subgroup	Black dot (Colletotrichum coccodes), brown spot (Alternaria alternata) and early blight (Alternaria solani)
Sugar beets	Cercospora leaf spot (Cercospora beticola) and powdery mildew (Erysiphe polygoni)

1.4 Mode of Action

Difenoconazole is a locally systemic fungicide. Difenoconazole is classified as a Group 3 fungicide, and belongs to the triazoles chemical group of fungicides. The mode of action of difenoconazole is demethylation of C-14 during ergosterol biosynthesis leading to accumulation of C-14 methyl sterols. The process slows or stops the growth of the fungus and effectively prevents further infection or invasion of host tissues. Therefore, difenoconazole is considered to be fungistatic or growth inhibiting rather than fungicidal or lethal.

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 Difenoconazole Technical Fungicide have been validated and assessed to be acceptable.

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

2.3.1 Methods for Residue Analysis in Environmental Media

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

2.3.2 Methods for Residue Analysis in Plants

Please refer to Proposed Regulatory Decision Document PRDD99-01: *Difenoconazole.*

2.3.3 Methods for Residue Analysis in Animals

A high performance liquid chromatography with triple quadruple mass spectrometric detection (HPLC-MS/MS) method REM 147.07 was developed and proposed for data generation and enforcement purposes. This method fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation (0.01 ppm per analyte for difenoconazole and CGA-205375 in tissues and eggs; and 0.005 ppm per analyte in milk). Acceptable recoveries (70-120%) were obtained in animal matrices. Adequate extraction efficiencies were demonstrated using radiolabelled difenoconazole in hen liver, muscle, fat and egg yolk analyzed with the enforcement method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

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

Absorption and excretion of single or repeat low oral doses of radiolabeled difenoconazole was extensive and rapid in both sexes of rats. High dose administration resulted in saturation of gastro-intestinal absorption. Most of the administered dose was eliminated in the excreta within 48 hours, with elimination essentially completed by 96 hours. The fecal route was the predominant route of excretion, primarily via bile; though urinary excretion was also significant. The half-life of elimination was 20 hours for low dose and 33–48 hours for the high dose with enterohepatic circulation involved in re-absorption of biliary metabolites. Total terminal residues seven days post-administration accounted for trace amounts of the administered dose with the highest radiolabel found in the liver, plasma and carcass. Single or repeat dosing did not alter elimination profiles.

Eleven metabolites were isolated from urine and feces, including two sulfonated metabolites identified in urine. The proposed metabolic scheme involved hydrolysis of the dioxane ring, followed by reduction of the ketone to the alcohol; hydroxylation of the outer phenyl ring; or bridge cleavage to yield free triazole and the carboxylic acid derivative of the diphenyl ether.

The technical grade active ingredient difenoconazole was of slight acute toxicity by the oral route in rats. It was of low acute toxicity dermally and through inhalation exposure in rats. Difenoconazole was mildly irritating to the eyes of rabbits, minimally irritating to the skin of rats and did not cause skin sensitization in guinea pigs. Two difenoconazole metabolites identified in the rat metabolism study were tested in acute oral toxicity studies in mice and were found to exhibit low toxicity.

The acute toxicity of the end-use product Inspire™ Fungicide, which contains difenoconazole, was low in rats via the oral, dermal and inhalation routes of exposure. Inspire™ Fungicide was moderately irritating to the eyes of rabbits. It was slightly irritating to the skin of rabbits and did not cause skin sensitization in guinea pigs.

Short-term repeat dose feeding studies in mice, rats and dogs with difenoconazole technical revealed the liver to be the principal target organ of toxicity. Mice treated with difenoconazole displayed liver toxicity ranging from increased liver weights, hepatocellular enlargement and vacuolation to focal/multi-focal single cell hepatocellular necrosis. Liver effects in treated rats were limited to increased liver weights and hepatocellular enlargement. In these studies, both mice and rats exhibited decreases in body weight and/or body weight gain, usually with corresponding decreases in food consumption. Treatment of dogs with technical difenoconazole revealed a reduction in body weight gain and food consumption, increased liver weights and, at higher dose levels, lenticular cataracts.

Short-term dermal administration of technical difenoconazole to rats produced dermal irritation at the test site. There were only minor changes in the liver and some slight changes in clinical chemistry parameters.

Technical difenoconazole was administered in the diet of mice and rats in long-term studies. In the mouse study, significant liver toxicity and premature mortality were noted along with significant reductions in body weight gain. A dose-related increase in the incidence of liver tumours concurrent with liver toxicity was observed in male and female mice at the two highest dose levels. It was determined that the maximum tolerated dose (MTD) was exceeded at those same dose levels based on the large decreases in body weight gain and increased mortality. In the rat study, administration of technical difenoconazole produced reduced body weights, body weight gains and food consumption as well as hepatocellular enlargement. There was no evidence of carcinogenicity in rats.

No evidence of mutagenic or clastogenic potential of technical difenoconazole was observed in the database. An Ames assay was negative, while an *in vitro* cytogenetics test with human lymphocytes yielded equivocal results. Technical difenoconazole did not induce unscheduled DNA synthesis *in vitro*. In the *in vivo* study, difenoconazole did not induce a positive result (i.e., the induction of micronuclei) in the mouse micronucleus assay. The weight of evidence suggested that difenoconazole was not genotoxic. Three metabolites that were identified in the rat metabolism study were tested in Ames assays and all three gave negative results.

In a multi-generation rat reproduction study, decreased body weight gain and food consumption were noted in the parental generations. The offspring exhibited similar body weight effects at the same dose. In the reproductive toxicity study, difenoconazole did not show sensitivity of the young in rats.

In the rat developmental toxicity study, difenoconazole produced decreased body weight gain and food consumption and increased salivation in the dams at the two highest dose levels. At the highest dose tested, there were fewer fetuses per dam, an increased number of resorptions and an increase in post implantation loss. At that same dose level, the fetuses showed slight increases in incidences of skeletal variations. The rabbit developmental toxicity study produced significant toxicity in dams in the form of drastically reduced body weight gain and food consumption at the highest dose tested. It was determined that the MTD was exceeded at the highest dose tested. At the mid-dose, increased post-implantation loss and resorptions per doe were observed in conjunction with decreased fetal body weights at this same dose level. In the developmental toxicity studies, difenoconazole did not show a sensitivity of the young in either rats or rabbits.

The acute and short-term neurotoxic potential of difenoconazole was examined in rats. Several clinical signs were observed in the acute studies including upward curvature of the spine, nasal staining, irregular breathing, tip toe gait, piloerection, sides pinched in, as well as decreases in activity, righting and splay reflexes, stability and visual placing responses. Forelimb grip strength was decreased in males on the first day of dosing. Several of the same clinical signs were noted during short-term dosing. Body weight and food consumption were also decreased. Males exhibited decreased hind limb grip strength. While these combined clinical signs are suggestive of neurotoxicity, they are also commonly associated with general malaise. The dose levels that resulted in these clinical signs in the short-term study were overtly toxic and there was no corroborating neuropathology in either study at any dose level. Overall, the reported results provide equivocal evidence of neurotoxicity.

Results of the toxicology studies conducted on laboratory animals with difenoconazole and its associated end-use product are summarized in Tables 2 and 3 of Appendix I. The toxicology endpoints for use in the human health risk assessment are summarized in Table 4 of Appendix I.

Incident Reports

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 PMRA website. Incidents from Canada and the United States were searched and reviewed for the active difenoconazole. As of December 22, 2010, there were nine incident reports submitted in Canada for products containing difenoconazole. In all nine cases, difenoconazole was accompanied by one to three other active ingredients in the product formulations. Four of the nine reports involved human exposures with symptoms including local irritation (two cases), headache, vomiting and dizziness (one case) and flu-like symptoms with malaise (one case).

The animal reports contained a wide range of effects from vomiting to death following ingestion of unknown quantities of treated seed. Overall, there were no toxicological trends identified. No reports were found on the United States Environmental Protection Agency (EPA) or California Environmental Protection Agency websites. The PMRA concluded that the information from the available incident reports did not impact the risk assessment. Detailed information for the incidents can be found on the PMRA Public Registry.

3.1.1 PCPA Hazard Characterization

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

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

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of offspring compared to parental animals in the reproductive toxicity study. Increases in the mean number of resorptions and post-implantation loss were observed in the rat and rabbit developmental toxicity studies; however, these effects occurred in the presence of maternal toxicity. There were also increased incidences of skeletal variations in the rat developmental toxicity study at the same doses as the resorptions. In the rat two-generation reproductive toxicity study, there were no significant reproductive or offspring effects apart from decreased body weight and body weight gains.

Overall, the database is adequate for determining the sensitivity of the young. There is a low concern for sensitivity of the young and effects on the young are well-characterized. The fetal resorptions and post-implantation losses were considered serious endpoints, although the concern was tempered by the presence of maternal toxicity. The PCPA factor was reduced to 3-fold for scenarios in which this endpoint was relevant. For all other scenarios, the PCPA factor was reduced to 1-fold.

3.2 Determination of Acute Reference Dose

Acute Reference Dose (females 13-49)
To estimate acute dietary risk (one day) in reproductive-age females, the rabbit developmental toxicity study with a NOAEL of 25 mg/kg bw/day was selected for risk assessment. At the LOAEL of 75 mg/kg bw/day, increased post-implantation loss and resorptions per doe were identified. These effects may have been 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 PCPA Hazard Characterization section, the PCPA factor has been reduced to 3-fold. The composite assessment factor (CAF) is 300.

The ARfD (females 13-49) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{25 \text{ mg/kg bw}}{300} = 0.083 \text{ mg/kg bw of difenoconazole}$$

Acute Reference Dose (general population)
To estimate acute dietary risk (one day) in the general population, the rat acute neurotoxicity study with a NOAEL of 25 mg/kg bw was selected for risk assessment. At the LOAEL of 200 mg/kg bw, forelimb grip strength was reduced in males. This effect was the result of a single exposure and is therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor has been reduced to 1-fold. The composite assessment factor (CAF) is 100.

The ARfD (general population) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{25 \text{ mg/kg bw}}{100} = 0.25 \text{ mg/kg bw of difenoconazole}$$

3.3 Determination of Acceptable Daily Intake

To estimate dietary risk of repeat exposure, the rat chronic toxicity/oncogenicity study with a NOAEL of 1.0 mg/kg bw/day was selected for risk assessment. At the LOAEL of 24 mg/kg bw/day, hepatocellular hypertrophy and decreased body weight gains were observed. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor has been reduced to 1-fold. The CAF is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{1.0 \text{ mg/kg bw/day}}{100} = 0.01 \text{ mg/kg bw/day of difenoconazole}$$

The ADI provides a margin of 2500 to the NOAEL for post-implantation loss in the rabbit developmental toxicity study.

The available data suggests that the observed mouse liver tumours in males and females only occurred at dose levels exceeding the MTD; therefore a cancer risk assessment was not performed. There is a margin of 4630 between the ADI and the NOAEL for liver tumours.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Short- and Intermediate-term Dermal and Inhalation
For short- and intermediate-term occupational exposures via the dermal and inhalation routes, the NOAEL of 25 mg/kg bw/day from the rabbit developmental toxicity study was selected for risk assessment. Developmental toxicity was observed in this study in the form of increased post-implantation loss and increased number of resorptions per doe. Worker populations could include pregnant or lactating women and therefore these endpoints were considered appropriate for the occupational risk assessment. The available 28-day dermal study did not assess the relevant endpoints of concern (i.e. post-implantation loss). A short-term inhalation study was not available.

The target margin of exposure (MOE) for these scenarios is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a factor of 3-fold for the reasons outlined in the PCPA Hazard Characterization section. The selection of the rabbit developmental toxicity study and MOE of 300 is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Pick-Your-Own (females 13-49)
Acute aggregate exposure to difenoconazole may be comprised of food, drinking water and oral and dermal exposure from harvesting activity at pick-your-own farm operations. The endpoint selected for risk assessment in reproductive-age females was the NOAEL of 25 mg/kg bw/day in the rabbit developmental toxicity study. At the LOAEL of 75 mg/kg bw/day, increased post-implantation loss and resorptions per doe were identified. These effects may have been the result of a single exposure and are therefore relevant to an acute risk assessment. The available 28-day dermal study did not assess the relevant endpoints of concern (i.e. post-implantation loss).

The target MOE for this scenario is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a factor of 3-fold for the reasons outlined in the PCPA Hazard Characterization section. The selection of the rabbit developmental toxicity study and MOE of 300 is considered to be protective of unborn children of exposed pregnant females.

Pick-Your-Own (general population)
Acute aggregate exposure to difenoconazole may be comprised of food, drinking water and oral and dermal exposure from harvesting activity at pick-your-own farm operations. The endpoint selected for risk assessment in the general population was the NOAEL of 25 mg/kg bw in the rat acute neurotoxicity study. At the LOAEL of 200 mg/kg bw, forelimb grip strength was reduced in males. This effect was the result of a single exposure and is therefore relevant to an acute risk assessment. The available 28-day dermal study did not assess the relevant endpoints of concern (reduced forelimb grip strength).

The target MOE for this scenario is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. The selection of the rat acute neurotoxicity study and MOE of 100 is considered to be protective of the general population (excluding reproductive-age females).

Cancer Assessment
The available data suggests that the observed mouse liver tumours in males and females only occurred at dose levels exceeding the MTD; therefore a cancer risk assessment was not performed. There is a margin of 4630 between the ADI and the NOAEL for liver tumours.

3.4.1.1 Dermal Absorption

Chemical specific dermal penetration data were submitted for difenoconazole. An *in vivo* dermal absorption study was submitted, in which sixteen male HanBrl: WIST (SPF) rats were dosed at 0.5 μg/cm^2, 13 μg/cm^2, 2372 μg/cm^2, or 2558 μg/cm^2 of difenoconazole, formulated as SCORE EC (A-7402 G; guarantee 250 g a.i./L), dissolved in 100 μL of blank formulation per 10 cm^2 skin. The groups were further divided into four subgroups consisting of four animals each. Exposure time to the formulated test substance was six hours for all animals. At the end of the exposure period the remaining test substance was removed from the skin by washing. Four animals from each dose group were sacrificed at 6, 24, 48, or 72 hours after start of exposure, to

measure depletion of the radioactivity associated with the application site. Recoveries ranged from 88-106%. Calculated dermal absorption was the sum of the residues found in the skin test site, tape strips, urine, cage wash, feces, carcass, GI tract, and blood. Dermal absorption values ranged from 29-51% for the low dose group, 14-21% for the mid dose group and 5-16% for the high dose groups.

An *in vitro* dermal absorption study in rat and human skin membrane was also submitted, in which radiolabeled SCORE 250 EC (A-7402) was applied to skin membranes prepared from male HanBrl: WIST (SPF) rat and human (cadaver) abdominal skin. Dermal absorption at the applied doses of 0.5 $\mu g/cm^2$, 12 $\mu g/cm^2$, and 2345 $\mu g/cm^2$ was assessed over 24 hours. Five to seven samples per dose were used and recoveries ranged from 96-100%. While the results of the *in vitro* study indicate that the percutaneous absorption of radiolabeled SCORE 250 EC was greater through rat skin membrane than through human skin membrane, a quantitative comparison of dermal absorption values was not possible as the exposure duration used for the *in vitro* study differed from that used in the *in vivo* study.

Given the uncertainty regarding actual deposition under field conditions, it is considered appropriate to derive an estimate of dermal absorption based on the average value of four samples in the low dose group with a 6-hour exposure time and a 24-hour sacrifice time post-dosing in the *in vivo* dermal penetration study in the rat, as percent dermal absorption was greatest in this group. Therefore, the dermal absorption estimate of 51% was considered most appropriate to adopt for risk assessment purposes.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/Loader/Applicator Exposure and Risk Assessment

Individuals have potential for exposure to Inspire™ 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. Data with the highest confidence were used when available. Exposure estimates are outlined in Table 3.4.1.

Table 3.4.1 PHED Unit Exposure Estimates for Mixer/Loader and Applicators With Proposed Personal Protective Equipment While Handling Inspire™ Fungicide (µg/kg bw/day)

Scenario	Exposure (in µg/kg a.i. handled)			
	Dermal Exposure		InhalationExposure	TotalExposure
	Total	Absorbed[1]		
A. Liquid, open mixing and loading, single layer + gloves	51.14	26.08	1.6	27.68
B. Groundboom application, open cab, single layer no gloves	32.98	16.82	0.96	17.78
C. Airblast application, open cab, single layer + gloves	561.72	286.48	5.8	292.28
A + B: M/L/A with groundboom, combined total exposure				45.46
A + C: M/L/A with airblast, combined total exposure				319.96

[1]Adjusted for 51% dermal absorption; default inhalation absorption is 100%

Exposure estimates were derived for mixer/loaders and applicators applying Inspire™ Fungicide to all proposed crops using groundboom or airblast application equipment. Handlers are assumed to have potential short- to intermediate-term dermal and inhalation exposure to Inspire™ Fungicide. Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption factor. Dermal exposure estimates are based on mixers, loaders and applicators of Inspire™ Fungicide wearing a long-sleeved shirt, long pants and chemical-resistant gloves. 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.

Exposure estimates were compared to the NOAEL of 25 mg/kg bw/day to obtain the margin of exposure (MOE); the target MOE is 300. The risk assessment results are summarized in Table 3.4.2. All uses exceed the target MOE and are considered acceptable based on the label directions and personal protective equipment.

Table 3.4.2 Mixer/Loader/Applicator Risk Assessment

Crop	Scenario	Dermal + Inhalation Exposure (µg/kg a.i. handled)	ATPD (ha)[1]	Maximum Application Rate (kg a.i./ha)	Daily Dose (mg/kg bw/day)[2]	Combined MOE[3]
Brassica Vegetables, Bulb Vegetables, Cucurbits	Farmer, groundboom	45.46	26	0.128	0.002	11567
	Custom applicator, groundboom	45.46	360	0.128	0.030	835
Pome Fruit, Grapes	Farmer and custom applicator, airblast	319.96	20	0.073	0.007	3746
Fruiting Vegetables	Farmer and custom applicator, airblast	319.96	20	0.128	0.012	2137
	Farmer, groundboom	45.46	26	0.128	0.002	11567
	Custom applicator, groundboom	45.46	360	0.128	0.030	835
Tuberous and Corm Vegetables	Farmer and custom applicator, airblast	319.96	20	0.128	0.012	2137
	Farmer, groundboom	45.46	107	0.128	0.009	2811
	Custom applicator, groundboom	45.46	360	0.128	0.030	835

[1]ATPD default values are 20 ha/day for airblast applications, 26 ha/day for small crop groundboom applications, 107 ha/day for large area groundboom applications, and 360 ha/day for custom groundboom applications

[2]Daily dose = [Dermal + inhalation exposure (µg/kg a.i. handled) x ATPD (ha) x Application rate (kg a.i./ha)]/ (70 kg bw x 1000 µg/mg)

[3]MOE = NOAEL (25 mg/kg bw/day)/Daily dose (mg/kg bw/day)

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers entering areas treated with Inspire™ Fungicide to perform cultural activities such as hand harvesting, irrigation, scouting, hand thinning, and hand weeding. Given the nature of activities performed, the duration of exposure is considered short- to intermediate-term and the primary route of exposure for workers that enter treated crops would be dermal, through contact with residues on leaves.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients (TC) and the dermal absorption factor (DA) for difenoconazole. Activity transfer coefficients are based on reviewed Agricultural Re-Entry Task Force studies, of which Syngenta is a member, and United States EPA Policy 3.1 data. Chemical-specific dislodgeable foliar residue data were not submitted. As such, a default dislodgeable foliar residue value of 20% of the application rate on the day of application and a default daily dissipation rate of 10% were used in the exposure assessment. Exposure was adjusted using a dermal absorption of 51% and normalized by using 70 kg adult body weight. Exposure estimates were compared to the NOAEL of 25 mg/kg bw/day to obtain the MOE; the target MOE is 300. As exposure estimates on the day of last application were below the target MOE of 300 for certain re-entry activities in some crops, restricted re-entry intervals (REIs) were required for certain activities (see Table 3.4.3).

Table 3.4.3. Postapplication Risk Assessment of Re-Entry Activities for All Crops

Crop Group	Crop	Activity	App. Rate (µg/ cm²)	TC (cm²/h)[1]	# of App.	REI DFR (µg/cm²)[2]	Exposure (mg/kg bw/day)[3]	MOE[4]	REI
Brassica Vegetables	Broccoli, Brussels Sprout, Cabbage, Cauliflower	Hand harvesting, irrigation	1.28	5000	4	0.2823	0.0823	304	3 days
	Broccoli, Brussels Sprout, Cabbage, Cauliflower	Scouting	1.28	4000	4	0.3485	0.0823	308	1 day
	Broccoli, Brussels Sprout, Cabbage, Cauliflower	Hand weeding	1.28	2000	4	0.3872	0.0451	554	12 hours

Crop Group	Crop	Activity	App. Rate (µg/ cm²)	TC (cm²/h)[1]	# of App.	REI DFR (µg/cm²)[2]	Exposure (mg/kg bw/day)[3]	MOE[4]	REI
Bulb Vegetables	Dry Onions	Irrigation, scouting, thinning, hand weeding	1.28	300	4	0.465	0.0081	3075	12 hours
	Green Onions	Hand harvesting, thinning	1.28	2500	3	0.437	0.0637	393	12 hours
Cucurbits	Cantaloupe, Cucumber, Summer Squash, Watermelon	Hand harvesting, pruning, thinning	1.28	2500	4	0.465	0.0678	369	12 hours
Pome Fruit	Apple, Pear	Hand thinning	0.73	8000	5	0.179	0.0835	300	4 days
	Apple, Pear	Hand pruning, propping, training	0.73	3000	5	0.2728	0.0477	524	12 hours
	Apple, Pear	Hand harvesting	0.73	3000	5	0.0624[1]	0.0109	2291	12 hours
Grape	Grapes	Cane turning, girdling	0.73	19300	7	0.0742	0.0834	300	10 days
	Grapes	Hand harvesting, training, thinning, hand pruning	0.73	8500	7	0.1723	0.0854	293	2 days
	Grapes	Scouting, hand weeding	0.73	700	7	0.1723	0.007	3556	2 days
Fruiting Vegetables	Eggplant, Bell Pepper, Chili Pepper, Tomato	Hand harvesting, stalking, tying	1.28	1000	4	0.465	0.0271	922	12 hours
Tuberous Vegetables	Potato, Sweet Potato	Irrigation, scouting	1.28	1500	4	0.465	0.0407	615	12 hours
	Sweet Potato	Hand harvesting	1.28	2500	4	0.465	0.0678	369	12 hours
Sugar Beets	Sugar Beets	Scouting, irrigation	1.28	1500	4	0.465	0.0407	615	12 hours

[1]From *Agricultural Transfer Coefficients*, EPA Policy 3.1, revised August 7, 2000 and *Transfer Coefficients for Grapes, Trellis Crops and Caneberries* (PMRA, 2005)

[2]DFR at the minimum REI, calculated assuming 20% of the applied rate on the day of application and 10% dissipation per day.

[3]Exposure = [Day 0 DFR after Last App (µg/cm^2) x TC (cm^2/h) x DA (%) x Workday (8 h)]/(70 kg bw x 1000 µg/mg)

[4]MOE = NOAEL (mg/kg bw/day)/Exposure (mg/kg bw/day)

With the exception of brassica vegetables, grapes and pome fruit, an REI of 12 hours after treatment is acceptable for all postapplication activities. For brassica vegetables, a three (3) day REI is required for hand harvesting and irrigation and a one (1) day REI is required for scouting, while a 12 hour REI is acceptable for all other postapplication activities. For grapes, a 10 day REI is required for cane turning and vine girdling, while an REI of two (2) days is acceptable for all other postapplication activities. For pome fruit, a four (4) day REI is required for hand thinning, while a 12 hour REI is acceptable for all other postapplication activities.

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Post-application Exposure and Risk (Pick-Your-Own)

The general population, including children, could be exposed to Inspire™ Fungicide through pick-your-own (PYO) activities in pome fruit orchards. Exposure is expected to be acute in duration (1-2 times per season) and could include both dietary and dermal exposure.

An aggregate exposure assessment was conducted to estimate exposure for individuals who pick and eat treated fruit on the same day. Table 3.4.4 presents exposure estimates for pickers entering treated apple orchards, which are considered representative of all other pome fruits. The transfer coefficient for hand harvesting was used to estimate exposure to foliar residues for pickers. Default dissipation values were used to estimate the peak DFR on the earliest possible day of harvest (eg. 14 days after the last application). Dermal exposure was adjusted using a dermal absorption of 51% and an exposure duration of two hours was assumed. The acute dietary exposures to apples were estimated based on the maximum residue limit (MRL) for pome fruits, reported at the 95th percentile (deterministic).

Table 3.4.4 MOEs for Aggregate Pick-Your-Own Scenarios in Pome Fruit Orchards

Population Sub-group	TC (cm^2/h)	DFR on day 14 (ug/cm^2)	Body Weight (kg)	Dermal Exposure (mg/kg bw/day)[2]	Dietary Exposure (mg/kg bw/day)	Total Exposure (mg/kg bw/day)[3]	Acute Aggregate Endpoint (mg/kg bw/day)	Target MOE (mg/kg bw/day)	Aggregate MOE (mg/kg bw/day)
Children (0-9 years)	1068	0.0624	15	0.0089	0.0127	0.0215	25	100	1161
Youth (10-18 years)	2066	0.0624	39.1	0.0066	0.0057	0.0123	25	100	2027
Adult (19+ years)	3000	0.0624	70	0.0053	0.0039	0.0093	25	100	2699
Females (13-49 years)	3000	0.0624	70	0.0053	0.0045	0.0098	25	300	2551

[1]Transfer coefficient for hand harvesting scaled for children and youth based on body surface area; children: 6565 cm^2; youth: 12700 cm^2; adults: 18440 cm^2

[2]Exposure = [Day 14 DFR after Last App (µg/cm^2) x TC (cm^2/h) x DA (%) x Duration (2 h)]/(kg bw x 1000 µg/mg)

[3]Total exposure = dermal exposure + dietary exposure

[4]MOE = NOAEL (mg/kg bw/day)/Exposure (mg/kg bw/day)

The post-application aggregate exposure and risk estimates associated with PYO orchard scenarios indicate acceptable MOEs for all sub-populations. Therefore, no further mitigation measures are required for PYO operations treated with Inspire™ Fungicide.

3.4.3.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversion, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition (RD) for risk assessment and enforcement in plant products is difenoconazole. The nature of the residue in rotational crops is not considered to be adequately characterized to support foliar use. As such, additional confined crop rotational data are being requested. The RD for risk assessment and enforcement in animal commodities is difenoconazole and the metabolite CGA-205375. The data gathering and enforcement analytical methods are valid for the quantification of difenoconazole residues in various crops and difenoconazole and CGA-205375 in livestock matrices. The residues of difenoconazole in crops are stable when stored in a freezer at ≤-20°C for up to 24 months. Raw agricultural commodities (RAC) were processed and difenoconazole was found to concentrate in tomato paste, raisins and apple wet pomace (1.6x, 3.5x, and 9.6x, respectively). Livestock feeding studies in dairy cattle and hens were adequate to estimate residue levels in animal matrices. Supervised residue trials conducted throughout the United States using end-use products containing difenoconazole at rates reflecting the use pattern on brassica, bulb vegetables, cucurbits, grapes, fruiting vegetables, pome fruits, potatoes and sugar beets are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

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

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The refined chronic dietary exposure analysis was based on default and experimental processing factors, median difenoconazole residues from supervised crop field trials and MRL level residues for difenoconazole and the metabolite CGA-205375 in animal commodities, and assumed that 100% of crops were treated. The refined chronic dietary exposure from all

supported difenoconazole food uses (alone) for the total population, including infants and children, and all representative population subgroups is 27.1% of the ADI. Aggregate exposure from food and water is considered acceptable. The PMRA estimates that chronic dietary exposure to difenoconazole from food and water is 34.4% (0.003436 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children (1-2 years) at 88.2% (0.008815 mg/kg bw/day) of the ADI.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The basic acute dietary exposure analysis was based on default processing factors, MRL level residues of difenoconazole in all commodities and assumed 100% of crops were treated. The basic acute dietary exposure (food alone) for all supported difenoconazole commodities is estimated to be 14.3% (0.035828 mg/kg/day) of the ARfD for the total population and 50.9% (0.127180 mg/kg/day) of the ARfD for the most exposed sub population (children 1-2 years). The basic acute dietary exposure (food alone) for females 13–49 years old is 29.0% (0.024042 mg/kg/day) of the ARfD (95th percentile, deterministic). Aggregate exposure from food and water is considered acceptable: 14.7% (0.036835 mg/kg/day) of the ARfD for the total population, 51.4% (0.128411 mg/kg/day) for the most exposed sub population (children 1-2 years) and 30.1% (0.025012 mg/kg/day) of the ARfD for females 13–49 years old (95th percentile, deterministic).

3.5.3 Aggregate Exposure and Risk

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

3.5.4 Maximum Residue Limits

Table 3.5.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Liver of cattle, goat, horse, hog, and sheep	0.1
Bulb Onion Subgroup (Crop Subgroup 3-07A)	0.2
Curcurbit Vegetables Group (CropGroup 9)	0.7
Head & Stem Brassica Subgroup (Crop Subgroup 5A)	1.9
Grapes	4.0
Green Onion Subgroup (Crop Subgroup 3-07B)	6.0
Raisins	6.0
Leafy Brassica greens Subgroup (Crop Subgroup 5B)	35

For additional information on Maximum Residue Limits (MRL) 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 Tables 1, 5 and 6 of Appendix I.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

The fate and behaviour of difenoconazole in the terrestrial environment is summarized in Table 7 of Appendix I.

Difenoconazole is soluble in water (15.0 mg/L) and is non-volatile from moist soil and surface water (Henry's Law Constant = 8.22×10^{-12} atm.m^3/mol). It has the potential to bioaccumulate based on its octanol-water partition coefficient (log K_{ow} = 4.4). On the basis of its UV-visible absorption, it is not expected to phototransform on soil under natural light.

Hydrolysis and phototransformation would not be routes of transformation for difenoconazole in soil. Difenoconazole was stable to hydrolysis in aqueous solutions at pH 5, 7 and 9 and the phototransformation half-life in soil was 349-823 days. Overall, biotransformation was not an important route in the transformation of difenoconazole in soil. Difenoconazole was moderately persistent to persistent in aerobic soil and persistent in anaerobic soil. In aerobic soils, the DT_{50} values based on single first-order kinetics were 103-1600 days. In anaerobic soils, the DT_{50} values were 679-947 days. In the majority of soil biotransformation studies, major transformation products were not identified. In two of the aerobic soil studies, the only major tranformation product was CGA-205375, which reached a maximum of 9.7-10.2% of the applied (day 120).

Under terrestrial field conditions, difenoconazole was considered as slightly persistent to persistent as DT_{50} values were 28-892 days. Carryover of difenoconazole into the next growing season was determined to be 68% based on the DT_{50} of 892 days.

On the basis of the K_{oc} values of 2237-11034, difenoconazole is considered to be slightly mobile to immobile in soil. Similarly, its major transformation product, CGA-205375 is considered to be slightly mobile to immobile in soil as K_{oc} values were 3214 to 6432. Under terrestrial field conditions, difenoconazole was detected to a soil depth of 45-60 cm indicating a potential to leach through soil. The transformation product, CGA-205375 was detected in the 0-15 cm depth at a maximum of 5.3% of the total applied and was detected once in the 15-30 cm depth. CGA-71019 was detected periodically in the 0-15 and 15-30 cm depths. Neither transformation product was detected below the 15-30 cm soil depth.

The fate and behaviour of difenoconazole in the aquatic environment is summarized in Table 8 of Appendix I.

Difenoconazole is soluble in water (15.0 mg/L) and is non-volatile from surface water (Henry's Law Constant = 8.22 x 10^{-12} atm.m^3/mol). It has the potential to bioaccumulate based on its octanol-water partition coefficient (log K_{ow} = 4.4) and to partition into aquatic sediment based on its adsorption to soil (K_{oc} = 2237-11034). On the basis of its UV-visible absorption, it is not expected to phototransform in water under natural light.

Hydrolysis would not be a route of transformation as difenoconazole was stable in aqueous solutions at pH 5, 7 and 9. In water, the half-life of difenoconazole under irradiated conditions was 6-228 days based on a 12 hour light:12 hour dark cycle, which indicated that phototransformation was not an important route of transformation. Overall, biotransformation was not an important route in the transformation of difenoconazole in water-sediment systems. Under aerobic aquatic conditions, difenoconazole was persistent as the whole system DT_{50} values were 307-494 days based on single first-order kinetics. Similarly, under anaerobic conditions, difenoconazole was persistent as the whole system DT_{50} was 411 days based on single first-order kinetics.

Difenoconazole partitions out of the water column and accumulates in sediment to a maximum of 81% of applied after 112 days. In aerobic water-sediment, CGA-205375 was a major tranformation product in a river water-sandy loam system reaching a maximum of 11.6% of the applied (after 90 days) and was largely unchanged thereafter (10.5-11.4% up to day 183). In anaerobic water-sediment, CGA 71019 was a major tranformation product in a river water-sand system reaching a maximum of 25.6% of the applied in the aqueous phase and 10.3% of applied in the sediment (day 350).

The bioconcentration factors (BCF) for ^{14}C-difenoconazole in bluegill edible and nonedible tissue were 170X and 570X, respectively. The whole body BCF was 330X. By Day 14 of the depuration phase, however, the bluegill had eliminated 96%, 98% and 97% of the ^{14}C-residues in edible, nonedible and whole body tissue, respectively, that were present on the last day of exposure (Day 28 of exposure).

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).

The risk assessment first utilizes a deterministic evaluation that integrates the environmental exposure represented by the EECs and, the environmental toxicity as represented by the most sensitive test species, to determine the likelihood of adverse ecological effects. One method of achieving this integration is through the estimation of a Risk Quotient (RQ). The RQ is usually calculated by comparing a threshold toxicity endpoint, usually a LC_{50}, LD_{50}, EC_{50}, EC_{25}, NOEC or NOEL for the most-sensitive test species, to an expected environmental concentration (EEC) based on the maximum cumulative application rate. The mathematical relationship among RQ, toxicity endpoint and the EEC is:

RQ = EEC ÷ toxicity endpoint

In addition, uncertainty factors are applied to the acute toxicity endpoints to account for interspecies variability. For fish and amphibians, the LC_{50} is divided by an uncertainty factor of 10. For terrestrial and aquatic invertebrates, algae and aquatic vascular plants, the LC_{50} or EC_{50} is divided by an uncertainty factor of 2.

For describing the risk associated with the RQ, the Level of Concern (LOC) is considered. The LOC is equal to a RQ of 1.0 and functions as the cut-off criteria for estimating risk. Thus, if the LOC is exceeded (RQ>1) then, a concern is identified. For RQ < 1.0, there is a negligible risk as the LOC is not exceeded. In cases where the LOC is exceeded, then a refined assessment is conducted in which the risk is based on exposure to difenoconazole through spray drift and surface runoff.

4.2.1 Risks to Terrestrial Organisms

Table 9 of Appendix I summarizes the risks to terrestrial organisms resulting from the application of difenoconazole.

In earthworms, the RQ was 2.0 which indicated that the LOC was exceeded. There was a negligible risk to honey bees as the RQ was 0.003. In beneficial arthropods, a risk was identified in the predatory mite, where the RQs were 1.2 and 1.7 for mortality and reproduction, respectively.

The risk to birds and mammals from the use of difenoconazole is not expected to be of concern. The acute risk was negligible in birds and mammals as the RQs were <1. On a reproductive basis, the screening level RQs ranged from <1-1.5 and <1-2.8 in birds and mammals, respectively. This potential for reproductive risk was further characterized and determined not to be of concern for the following reasons. The reproduction RQ for birds and mammals only slightly exceeds the LOC for some food guilds using the maximum residues, but is well below the LOC (RQ <1) using the mean residues. This suggests a low probability of adverse reproductive effects under actual field conditions. Moreover, the proportion of the diet of each food item required to reach the LOC is relatively high, which suggest that birds and mammals would need a large amount of highly contaminated food items to elicit reproduction adverse effects.

Under actual conditions, a variety of contaminated and uncontaminated food items is likely to be consumed. Overall, it was concluded that there is not a concern for risk to birds and mammals from the use of difenoconazole.

In terrestrial plants, the risk assessment was incomplete as there were no data generated on standard measurement parameters such as dry weight and plant height. There were data available on visual signs of phytotoxicity which suggested that difenoconazole may not have any effects on non-target plants. Quantitative data on seedling emergence and vegetative growth has been identified as an outstanding data requirement.

4.2.2 Risks to Aquatic Organisms

Table 10 of Appendix I summarizes the risks to aquatic organisms resulting from the application of difenoconazole.

In freshwater invertebrates, the acute RQ of 0.2 indicated that the acute risk was negligible. There was a chronic risk, however, as the RQs ranged from 0.7-8.2. Similarly, in freshwater fish, the acute RQ of 0.8 indicated that the acute risk was negligible, however, difenoconazole posed a chronic risk as the RQs were 0.5-5.3. Amphibians were the most sensitive aquatic species to difenoconazole. The RQs were 0.2-3.0 and 0.5-28 for acute and chronic exposure. In freshwater and marine plants, RQ values of 0.1-0.9 indicates there was a negligible risk. In marine invertebrates and fish, there was a negligible acute risk as the RQs were 0.9 and 0.8, respectively. There was a chronic risk, however, to marine invertebrates and fish as the RQs were 0.9-10 and 0.5-5.2, respectively. In marine algae, the risk was negligible as the RQ was 0.3.

4.2.3 Incident Reports

According to the USA EPA database, there were no incident reports for difenoconazole. For Canada, there were six reports in which domestic and companion animals were exposed to treated seed. Four cases were with seed treatments containing the active ingredients, thiamethoxam, difenoconazole, metalaxyl-M, and fludioxonil. The remaining two cases were with seed treatments containing difenoconazole and metalaxyl-M. The most severe case was the death of a horse where the cause was unknown. The report indicated that toxicity from the product was not expected with the estimated amount of seed consumed (2-4 kg). The other reports ranged from minor to major in their severity and included dogs and cows recovering from signs of toxicity after consuming treated seed. In these, the report indicated that toxicity from the product was not expected with the small amount of active ingredients contained in the seed treatment. None of these reports were deemed suitable for consideration in the environmental risk assessment of mammals.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

5.1.1.1 Control of alternaria blight (*Alternaria brassicae*) on brassica (Cole) leafy vegetables crop group

Results from four field trials conducted on cabbage, and Chinese cabbage in the USA (NY, CA and FL) and the UK were reviewed. Alternaria disease pressure was low to moderate (incidence at 4–31%) across all trials. The efficacy of Inspire™ Fungicide (applied at 125-128 g a.i./ha) on alternaria disease ranged between 84% and 94% of untreated control in three trials with the exception of 72% of control in one trial where most fungicide treatments achieved relatively lower efficacy compared to other trials. The causal pathogen was identified as *Alternaria brassicae* in three trials and the *Alternaria* species was not specified in one trial. The claim is conditionally supported pending an additional three trials on broccoli to confirm the efficacy.

5.1.1.2 Control of powdery mildew (*Erysiphe polygoni*) on brassica (Cole) leafy vegetables crop group

Results from two field trials conducted on cabbage in the UK were reviewed since powdery mildews are common and widespread under diversified environmental conditions, no matter where the disease appears. The UK trials are deemed as valid for the efficacy review. Powdery mildew pressure was low (incidence at 11% on lower leaves) in one trial and moderate (incidence at 21% on upper leaves) in the second trial. Data demonstrated good control of powdery mildew with Inspire™ Fungicide (92-100% of control). There was no data presented for the proposed low rate. The efficacy of the proposed low rate was shown in one trial on sugar beet, a non-cole crop, and applied rates at 73 and 100 g a.i./ha demonstrated 91% of powdery mildew control. As such, the claim is conditionally supported pending an additional three trials on broccoli and cabbage to confirm the efficacy.

5.1.1.3 Control of purple blotch (Alternaria porri) on bulb vegetables group

Results from three onion field trials conducted in the USA (MI and TX) were reviewed. Purple blotch disease pressure was low (severity at 6%) in one trial and moderate (severity at 15-35%) in the other two trials. Data demonstrated good control of purple blotch with Inspire™ Fungicide at the rate of 128 g a.i./ha, and the efficacy was comparable to Switch (Registration number 28189) or Pristine (Registration number 27985) which are currently registered for purple blotch on onion in Canada. Inspire™ Fungicide also demonstrated acceptable levels of control on alternaria diseases in brassica vegetables and early blight in tomato and potato. As such, the claim is conditionally supported pending an additional three trials on garlic and/or leek to confirm the efficacy.

5.1.1.4 Control of powdery mildew (*Sphaerotheca fuliginea*) on cucurbit vegetables group

Results from three field trials conducted on zucchini in the USA (NY and TX) were reviewed. Powdery mildew pressure was moderate to high (incidence at 20-71% in the last assessment). Data demonstrated good control of powdery mildew with Inspire™ Fungicide applied at the rate of 128 g a.i./ha, receiving 85-90% of disease control in lower leaves and 78-89% of control in upper leaves. There were no registered standards tested in these trials. The powdery mildew pathogen in all three trials was identified as *Sphaerotheca fuliginea*. The pathogen *Erysiphe cichoracearum* was not present in any of these trials and therefore not supported. Efficacy data were generated using only the proposed high rate of 128 g a.i./ha. As such, the claim is conditionally supported pending an additional three trials on cucumber and/or melon using rates of 91 and 128 g a.i./ha, as well as a lower rate to confirm the efficacy and establish the lowest effective rate (LER).

Suppression of gummy stem blight (Didymella bryoniae) on cucurbit vegetables group
Results from four watermelon field trials conducted in the USA (MD, FL, GA and TX) were reviewed. Gummy stem blight disease pressure was low in one trial (severity at 3.5%) and moderate to high (severity at 11-68%) in the other three trials. Data demonstrated suppression of gummy stem blight when Inspire™ Fungicide was used with Bravo® 500 Fungicide (Registration number 15723) in a spray program, and the level of disease control was 55-72% (average 65%). Three other fungicides [Bravo® 500 Fungicide, Endura (EPA Registration number 7969-197) and Pristine] were used in the trials, however, only Pristine is currently registered for suppression of gummy stem blight on greenhouse cucumber in Canada. The efficacy was comparable to Pristine in these trials. The claim is conditionally supported pending an additional three trials on cucumber and/or melon to confirm the efficacy.

5.1.1.6 Control of powdery mildew (Uncinula necator) on grape

Results from four field trials conducted in the USA (FL and CA) were reviewed. Powdery mildew pressure was low in two trials (severity at 10-11%) and high in other two trials (severity at 55-98%). The application rates tested ranged from 50 g a.i./ha up to 200 g a.i./ha (73-128 g a.i./ha on the proposed label), efficacy was consistently high (98-100% control) regardless of disease pressure. Flint 50WG (Registration number 27529) was used in one trial as a commercial standard with 99% of control. The lowest rate applied (50 g a.i./ha) had the same level of disease control compared to other rates (73, 91 and 128 g a.i./ha) in two trials at high disease pressure. The claim is conditionally supported pending an additional two trials to confirm the efficacy and establish the LER.

5.1.1.7 Control of early blight (Alternaria solani) on fruiting vegetables group

Results from four tomato field trials conducted in the USA (MS, FL and NY) were reviewed. Alternaria early blight disease pressure was moderate to high (severity at 38-99%) in the trials. Data demonstrated good disease control of tomato early blight when Inspire™ Fungicide was used with Bravo® 500 Fungicide in a spray program or used alone, and better control was achieved when alternating Inspire™ Fungicide with Bravo® 500 Fungicide in a spray program. The efficacy of Inspire™ Fungicide in alternation with Bravo® 500 Fungicide ranged from 87% to 92% compared to 75–92% for Inspire™ Fungicide alone. Inspire™ Fungicide was applied only at the high proposed rates (125-127 g a.i./ha) in these trials, however, the results from potato early blight trials can be used to support the use of the rate range on tomato because the same pathogen (*Alternaria solani*) attacks both crops. The results from the tomato trials also support the use of Inspire™ Fungicide on the fruiting vegetables crop group since the pathogen infects all major fruiting vegetables in the Solanaceae family. The LER was also established from the potato trials.

5.1.1.8 Control of anthracnose (Colletotrichum acutatum) on fruiting vegetables group

Results from two field trials (one on tomato and one on pepper) conducted in the USA (FL) were reviewed. Anthracnose disease pressure was moderate (severity at 18-36%) in both trials. *Colletotrichum acutatum* was the causal pathogen in these trials. Efficacy of Inspire™ Fungicide was compared to Quadris (Registration number 26153), which is currently registered for controlling tomato anthracnose. Data demonstrated an acceptable level of disease control (79-81%), and the efficacy of Inspire™ Fungicide was comparable to Quadris in one trial, but less effective than Quadris in another trial. Only the high proposed rate was applied in these trials. The claim is conditionally supported pending an additional three trials on tomato and/or pepper to confirm the efficacy and establish the LER.

5.1.1.9 Control of brooks fruit spot (Mycosphaerella pomi) on pome fruit group

Results from one trial in apple conducted in the USA (NC) were reviewed. Brooks fruit spot disease pressure was high, and the infection on fruits was 100%. Data demonstrated an acceptable level of disease control (81%) when Inspire™ Fungicide was applied at the rate of 73 g a.i./ha, however, disease control at the rate of 55 g a.i./ha was less effective at 71%. It was noted that, Inspire™ Fungicide also demonstrated effective control of black rot in grapes at the rate of 98 g a.i./ha (with 97% of control); and the causal pathogen of black rot, *Guignardia bidwellii,* is closely related to *Mycosphaerella*. The claim is supported at the rate of 73 g a.i./ha.

5.1.1.10 Control of cedar apple rust (*Gymnosporangium juniperi-virginianae*) on pome fruit group

Six trials were submitted to support the claim, and results from three trials in apple conducted in the USA (NY and VA) were reviewed. The efficacy of Inspire™ Fungicide could not be evaluated in three trials as the spray programs included other pesticide products, making it difficult to determine which effects were as a result of the difenaconazole treatment. Cedar apple rust disease pressure was low in one trial (incidence at 7%) and moderate in two other trials (incidence at 51-60%). Data demonstrated good disease control (86-100%) when Inspire™ Fungicide was applied at the rate of 73 g a.i./ha at moderate disease pressure. The claim is supported at the rate of 73 g a.i./ha.

5.1.1.11 Control of flyspeck (Zygophiala jamacaicensis) on pome fruit group

Six trials were submitted to support the claim, and results from four trials in apple conducted in the USA (NC, NY and VA) were reviewed. The efficacy of Inspire™ Fungicide could not be evaluated in two trials as the spray programs included other pesticide products, making it difficult to determine which effects were as a result of the difenaconazole treatment. Flyspeck disease pressure was low (incidence at 7%) to moderate (incidence at 50%). Data demonstrated good disease control (84-100%) when Inspire™ Fungicide was applied at the rate of 73 g a.i./ha. Inspire™ Fungicide applied in two trials at 50-55 g a.i./ha also achieved good disease control, but numerically less than the higher rate in the same trial. The claim is supported at the rate of 73 g a.i./ha.

5.1.1.12 Suppression of powdery mildew (Podosphaera leucotricha) on pome fruit group

Five trials were submitted to support the claim, and results from four trials in apple conducted in the USA (PA, NY and VA) were reviewed. The efficacy of Inspire™ Fungicide could not be evaluated in one trial as the spray program included other pesticide products, making it difficult to determine which effects were as a result of the difenaconazole treatment. Powdery mildew disease pressure was low (incidence at 6-8%) in three trials and moderate (incidence at 57%) in one trial. Data demonstrated an acceptable level of disease control (75-93%) at low disease pressure when Inspire™ Fungicide was applied at the rate of 73 g a.i./ha. However, the level of disease control was less effective (68%) at moderate disease pressure. The claim is conditionally supported pending an additional two trials to confirm the efficacy.

5.1.1.13 Control of quince rust (Gymnosporangium clavipes) on pome fruit group

Results from two trials in apple conducted in the USA (NY and VA) were reviewed. Quince rust disease pressure was low (incidence at 3-4%) in both trials. Data demonstrated good disease control (100%) when Inspire™ Fungicide was applied at the rate of 73 g a.i./ha. Although the disease pressure was not adequate to assess the efficacy of Inspire™ Fungicide, the results from cedar apple rust can be extrapolated to support the claim (see Section 5.1.1.10). The claim is supported at the rate of 73 g a.i./ha.

5.1.1.14 Control of scab (Venturia inaequalis, Venturia pirina) on pome fruit group

Nine trials were submitted to support the claim, and results from six trials in apple conducted in the USA (MI, NY and VA) were reviewed. The efficacy of Inspire™ Fungicide could not be evaluated in three trials as the spray programs included other pesticide products, making it difficult to determine which effects were as a result of the difenaconazole treatment. Scab disease pressure was moderate to high (23-99% infection) in these trials. Data demonstrated good disease control (89-100%) when Inspire™ Fungicide was applied at the rate of 73 g a.i./ha. A rate of 50 g a.i./ha was applied in one trial, which demonstrated the same level of disease control as compared to 73 g a.i./ha. The claim is conditionally supported pending an additional two trials to confirm the efficacy and establish the LER.

5.1.1.15 Control of sooty blotch (Gloeodes pomigena) on pome fruit group

Five trials were submitted to support the claim, and results from three trials in apple conducted in USA (NC, NY and VA) were reviewed. The efficacy of Inspire™ Fungicide could not be evaluated in two trials as the spray programs included other pesticide products, making it difficult to determine which effects were as a result of the difenaconazole treatment. Sooty blotch disease pressure was moderate to high (incidence at 13-100%). Good disease control was achieved (91-99%) at lower disease pressure (incidence at 13-20%) when Inspire™ Fungicide was applied at the rate of 73 g a.i./ha. The efficacy was greatly reduced (49%) when disease pressure was high at 100%. Inspire™ Fungicide applied in two trials at 50-55 g a.i./ha achieved disease control comparable to, though less than the higher rate in the same trial. The claim is supported at the rate of 73 g a.i./ha.

5.1.1.16 Control of early blight (Alternaria solani) on potato, Chinese artichoke, Jerusalem artichoke, edible canna, chufa and sweet potato

Results from four trials in potato conducted in Canada (AB, MB and ON) were reviewed. Early blight disease pressure was moderate to high (incidence at 17-80%). Good disease control was achieved (77-98%) when Inspire™ Fungicide was applied at the rate of 78-123 g a.i./ha in three trials. The lowest rate (39 g a.i./ha) also significantly reduced the infection (46-72% control) compared to non-treated controls in two trials, however, the level of control was lower than the rate of 78 g a.i./ha. Therefore, the rate of 78 g a.i./ha can be considered as the LER for this disease. The claim is supported on potato. As this pathogen also affects Chinese artichoke, Jerusalem artichoke, edible canna, chufa and sweet potato, the claim is also supported for these crops.

5.1.1.17 Control of cercospora leaf spot (Cercospora beticola) on sugar beet

Results from four trials in sugar beet conducted in the USA (CA, MI, ND and FL) were reviewed. Cercospora leaf spot disease pressure was low to moderate (incidence at 5-39%). Good disease control was achieved (83-99%) in three trials, but the level of control in one trial was only 60% after four applications. The lower rate of 73 g a.i./ha was applied in two trials with equal or less disease control compared to the higher rates in the same trials. The claim is supported at the rates of 73-128 g a.i./ha.

5.1.1.18 Control of powdery mildew (Erysiphe polygoni) on sugar beet

Results from three trials in sugar beet conducted in the USA (MI, FL and CA) were reviewed. Powdery mildew disease pressure was low (incidence at 8%) in one trial and moderate (incidence at 53-67%) in the other two trials. Data demonstrated good disease control (86-100%) at all rates applied (73, 100, 125, 127 and 128 g a.i./ha). The claim is supported at the rates of 73-128 g a.i./ha.

5.1.1.19 Inspire™ Fungicide tank mix with Revus™ Fungicide, Bravo® 500 Fungicide or Bravo® 720 Fungicide, Vangard® 75WG Fungicide, Dithane DG 75 Fungicide, Manzate Pro-Stick Fungicide, Penncozeb 75DF Fungicide, Supra Captan 80WDG Fungicide, Allegro 500F Fungicide, Matador 120EC Insecticide, Agri-Mek 1.9% EC Insecticide/Miticide, Actara 240SC Insecticide and Fulfill 50WG Insecticide

Various tank mixes were proposed for brassica leafy vegetables, bulb vegetables, cucurbit vegetables, grapes, fruiting vegetables, pome fruits, and potato. The efficacy and compatibility of tank mixes of Inspire™ Fungicide with Revus™ Fungicide (Registration number 29074), Bravo 500® Fungicide (Registration number 15723) and Bravo® 720 Fungicide (Registration number 29225) were demonstrated in potato trials. The efficacy and compatibility of tank mixes of Inspire™ Fungicide with Vangard® 75WG Fungicide (Registration number 25577), Dithane DG 75 Fungicide (Registration number 29221) and Manzate Pro-Stick Fungicide (Registration number 28217) were demonstrated in apple trials. The results of tank mix trials can be extrapolated to other tank mix partners, including Penncozeb 75DF Fungicide (Registration number 25397), Supra Captan 80WDG Fungicide (Registration number 24613) and Allegro 500F Fungicide (Registration number 27517) since: 1) the uses on the proposed crops are currently registered; 2) the use patterns for the tank mixes are compatible with the registered use patterns and; 3) these tank mixes have value by increasing the disease spectrum.

The efficacy and compatibility of tank mixes of Inspire™ Fungicide with Agri-Mek 1.9% EC Insecticide/Miticide (Registration number 24551) were demonstrated in apple trials. The results can be extrapolated to other tank mix partners, including Matador 120EC Insecticide (Registration number 24984), Actara 240SC Insecticide (Registration number 28407) and Fulfill 50WG Insecticide (Registration number 27274) since: 1)
the uses on the proposed crops are currently registered; 2) the use patterns for the tank mixes are compatible with the registered use patterns and; 3) these tank mixes have value by controlling disease and insect pest at same time**.**

All tank mix recommendations are as per their currently registered label rates, and are fully supported.

5.2 Phytotoxicity to Host Plants

There was no phytotoxicity reported to the crops tested in any of the trials submitted.

5.3 Economics

No market analysis was done for this active ingredient.

5.4 Sustainability

5.4.1 Survey of Alternatives

Refer to Table 12 of Appendix I for a summary of the active ingredients currently registered for the same uses as Inspire™ Fungicide.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

The use of Inspire™ 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

Inspire™ Fungicide contains difenoconazole, a Group 3 fungicide (DMI). The group is estimated to be at medium risk of disease resistance development. Resistance to difenoconazole has not yet been reported. Resistance management precautions are recommended. Repeated application of Inspire™ Fungicide alone should not occur on the same crop in one season against risky pathogens in areas of high disease pressure for that particular pathogen. For crop/pathogen situations where repeated spray applications are made during the season, alternation or mixtures with an effective non cross-resistant fungicide from a different fungicide group are recommended.

5.4.4 Contribution to Risk Reduction and Sustainability

Inspire™ Fungicide offers new fungicide chemistry to Canadian growers for use on brassica (Cole) leafy vegetables, bulb vegetables, cucurbit vegetables, fruiting vegetables, grapes, pome fruits, potato, Chinese artichoke, Jerusalem artichoke, edible canna, sweet potato and sugar beets. Inspire™ Fungicide can be tank-mixed with several other fungicides for pest resistance management, or to increase the disease spectrum on crops that are registered on both product labels.

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, difenoconazole and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[4] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions (Table 11 of Appendix I):

- Difenoconazole does not meet all the Track 1 criteria

- Difenoconazole does meet the Track 1 criterion for persistence because the half-life values in soil (103-1600 days) and water (307-494 days), do exceed the Track 1 criterion for soil and water.

- Difenoconazole does not meet the Track 1 criterion for bioaccumulation, as its octanol-water partition coefficient (log K_{ow} = 4.4) is just below the Track 1 criterion and the highest BCF in fish was 570.

6.2 Formulants and Contaminants of Health or Environmental Concern

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

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

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

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

7 DIR2006-02, PMRA Formulants Policy.

(substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade difenoconazole is expected to contain traces of TSMP Track 1 polychlorinated dibenzodioxins and furans generated during the manufacturing process;

- The EP, Inspire Fungicide, contains a List 2 aromatic petroleum distillate which has been indicated on the product label.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for difenoconazole is adequate to define the majority of toxic effects that may result from exposure to this active ingredient. There was limited evidence of neurotoxic potential in rats following acute and short-term dosing. In short-term and chronic studies on laboratory animals, the primary target was the liver (increased weight, hypertrophy, fatty change and necrosis). Body weight gain and food consumption were also adversely affected in most repeat-dose studies. Liver tumours were only found in mice at dose levels that were considered excessive; therefore, they were not considered relevant for the risk assessment. There was no evidence of cancer in rats. Serious effects were noted in both the rat and rabbit developmental toxicity studies (primarily increases in post-implantation loss). These effects occurred in the presence of significant maternal toxicity. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixers, loaders, applicators and workers entering treated orchards and fields are not expected to be exposed to levels of difenoconazole that will result in unacceptable risk when Inspire™ Fungicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

Risk to workers entering treated areas is not of concern as long as the specified restricted re-entry intervals are observed. Risk to the general population, including children, at pick-your-own orchards is not of concern.

The nature of the residue in plants and animals is adequately understood. The residue definition for enforcement and risk assessment is difenoconazole in plant commodities, and difenoconazole and CGA-205357 in animal matrices. The proposed use of difenoconazole on brassica (cole) vegetables, bulb vegetables, cucurbit vegetables, fruiting vegetables, pome fruit, grapes, tuberous and corm vegetables (including potato), 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. The PMRA recommends that the following maximum residue limits be specified for difenoconazole:

Table 7.4.1 Maximum Residue Limits for Difenoconazole

Crops	Recommended MRL (ppm)
Bulb Onion Subgroup (Crop Subgroup 3-07A):	0.2
Curcurbit Vegetables Group (CropGroup 9)	0.7
Head & Stem Brassica Subgroup (Crop Subgroup 5A):	1.9
Grapes	4.0
Green Onion Subgroup (Crop Subgroup 3-07B):	6
Raisins	6.0
Leafy Brassica greens Subgroup (Crop Subgroup 5B):	35

The PMRA recommends that the following maximum residues limits be specified for difenoconazole and CGA-205375:

Table 7.4.2 Maximum Residue Limits for Difenoconazole and CGA-205375

Animal matrices	Recommended MRL (ppm)
Liver of cattle, goat, horse, hog, and sheep	0.1

7.2 Environmental Risk

Difenoconazole is persistent in soil and water as DT_{50} values were 103-1600 days in aerobic soil, 679-947 days in anaerobic soil, 307-494 days in aerobic water systems and 411 days in anaerobic water systems. Hydrolysis and phototransformation on soil are not routes of transformation for difenoconazole. In water, the phototransformation of difenoconazole is likely not an important route of transformation as the half-life values varied from 6 to 228 days. Difenoconazole is slightly mobile to immobile in soil (K_{oc} = 2237-11034) and has the tendency to partition to sediments of aquatic systems where it persists. Although the log K_{ow} (octanol-water partition coefficient) of 4.4 indicated a potential for bioaccumulation, residues in fish (BCF = 570X) were eliminated by 96-98% after 14 days of depuration. On the basis of the TSMP assessment, difenoconazole does not meet the criteria for a Track I substance. Under field conditions, difenoconazole is expected to be non-volatile (Henry's Law Constant = 8.22×10^{-12} $atm.m^3/mol$) and is slightly persistent to persistent in soil (DT_{50} = 28-892 days). Difenoconazole could leach to a soil depth of 45-60 cm and may carryover into the next growing season by as much as 68%.

In terrestrial organisms, a risk was identified in earthworms and beneficial arthropods. A full assessment of the impact of difenoconazole on non-target plants could not be determined as quantitative data on plant growth were not provided.

In aquatic organisms, the highest risk was exhibited in amphibians. There was also a chronic risk to freshwater and marine invertebrates and fish.

To complete the risk assessment on non-target terrestrial plants, the registrant is required to address the lack of quantitative data on seedling emergence and vegetative growth and to provide validated analytical methods for the determination of difenoconazole and its transformation products in water and biota (fish).

7.3 Value

Sufficient evidence of efficacy was provided to support the use of Inspire™ Fungicide to control or suppress various diseases on brassica (Cole) leafy vegetables, bulb vegetables, cucurbit vegetables, fruiting vegetables, grapes, pome fruits, potato, Chinese artichoke, Jerusalem artichoke, edible canna, sweet potato and sugar beets. Inspire™ Fungicide offers new fungicide chemistry to Canadian growers for use on various vegetable and other crops listed above. Inspire™ Fungicide can be tank mixed with various fungicides and insecticides to control labelled diseases and insect pests, to manage development of pest resistance, and to improve the efficiency of pest control practices.

A summary of the proposed and accepted/conditionally accepted uses for Inspire™ Fungicide is presented in Table 13 and 14 of Appendix I.

7.4 Unsupported Uses

Certain uses proposed for Inspire™ Fungicide are not supported by the PMRA either because value has not been adequately demonstrated or the proposed use is not relevant in Canada. Unsupported uses are listed below:

Table 7.4.3 Use Claims Proposed that were Unsupported

Proposed Claim	Reason for Not Supporting the Claim
1) Control of alternaria leaf blight (Alternaria cucumerina) & alternaria leaf spot (Alternaria alternata) on cucurbit vegetables at the rates of 91 - 128 g a.i./ha.	a) No trial data provided; b) Rationale was not adequate to support the claim.
2) Control of rotbrenner (Pseudopezicula tracheiphila) and angular leaf scorch (Pseudopezicula tetrespora) on grape at the rates of 73 - 128 g a.i./ha.	a) Rotbrenner is not found in Canada; b) Lack of supporting data for angular leaf scorch.
3) Aerial application for potato grown in Manitoba, Saskatchewan and Alberta.	Lack of supporting data or rationale.
4) Control of anthracnose (Colletotrichum higginsianum) on brassica (Cole) leafy vegetables at the rates of 91 - 128 g a.i./ha.	No supporting data provided. Use withdrawn at the request of the registrant.

Proposed Claim	Reason for Not Supporting the Claim
5) Control of cercospora leaf spot (Cercospora brassicicola) on brassica (Cole) leafy vegetables at the rates of 91 - 128 g a.i./ha.	
6) Control of cercospora leaf spot (Cercospora duddiae) on bulb vegetables at the rates of 91 - 128 g a.i./ha.	
7) Control of powdery mildew (Leveillula taurica) on bulb vegetables at the rates of 91 - 128 g a.i./ha.	
8) Control of alternaria blotch (Alternaria mali) on pome fruit at the rate of 73 g a.i./ha.	
9) Control of black dot (Colletotrichum coccodes) on tuberous and corm vegetables at the rates of 73 - 128 g a.i./ha.	
10) Control of brown spot (Alternaria alternata) on tuberous and corm vegetables at the rates of 73 - 128 g a.i./ha.	
11) Control of rust (Puccinia allii) on bulb vegetables at the rates of 91 - 128 g a.i./ha.	Insufficient data were provided (one trial from Spain). Use withdrawn at the request of the registrant.
12) Control of anthracnose (Colletotrichum orbiculare) on cucurbit vegetables at the rates of 91 - 128 g a.i./ha.	Insufficient data were provided (one trial from USA). Use withdrawn at the request of the registrant.
13) Control of black rot (Guignardia bidwellii) on grapes at the rates of 73 - 128 g a.i./ha.	
14) Control of anthracnose (Elsinoe ampelina) on grapes at the rates of 73 - 128 g a.i./ha.	
15) Control of powdery mildew (Leveillula taurica) on fruiting vegetables at the rates of 73 - 128 g a.i./ha.	Insufficient data were provided (one trial from Italy). Use withdrawn at the request of the registrant.
16) Control of black mold (Alternaria alternata) on fruiting vegetables at the rates of 73 - 128 g a.i./ha.	Insufficient data were provided (two trials from USA). Use withdrawn at the request of the registrant.

8.0 Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Difenoconazole Technical Fungicide and Inspire™ Fungicide, containing the technical grade active ingredient difenoconazole, to control or suppress fungal diseases on a variety of fruit and vegetable crops.

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

Although the risks and value have been found acceptable when all risk-reduction measures are followed, as a condition of these registrations, additional scientific information is being requested from the applicant. For more details, refer to the Section 12 Notice associated with these conditional registrations. The applicant will be required to submit this information within the time frames indicated below.

NOTE: The PMRA will publish a consultation document at the time when there is a proposed decision on applications to convert these conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

Human Health

As the nature of the residue is rotational crops has not been adequately demonstrated, an additional confined crop rotational study reflecting the maximum potential seasonal application rate in rotated crops (512 g a.i./ha) using phenyl-labelled difenoconazole is required.

Environment

Quantitative data on non-target terrestrial plants pertaining to seedling emergence and vegetative growth is required. Validated analytical methods for the determination of difenoconazole and its transformation products in water and biota (fish) are required.

Value

The following small-scale field or greenhouse trials are required for the disease claims with the conditional registration:

- Three trials on alternaria blight of brassica (Cole) leafy vegetables;
- Three trials on powdery mildew of broccoli and cabbage;
- Three trials on purple blotch of garlic and/or leek;
- Three trials on powdery mildew of cucumber and/or melon;
- Three trials on gummy stem blight of cucumber and/or melon;
- Two trials on powdery mildew of grape;
- Three trials on anthracnose of tomato and/or pepper;
- Two trials on powdery mildew of apple;
- Two trials on scab of apple and/or pear.

All required data must be submitted by September 1, 2014.

List of Abbreviations:

µg	microgram(s)
µL	microlitre(s)
a.i.	active ingredient
AB	Alberta
ADI	acceptable daily intake
APP	application(s)
ARfD	acute reference dose
atm	atmosphere
ATPD	area treated per day
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
bwg	body weight gain
CA	California (USA state)
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CHO	Chinese hamster ovary
cm	centimetre(s)
cm^2	centimetre(s) squared
cm^3	centimetre(s) cubed
d	day(s)
DA	dermal absorption
DALA	day(s) after last application
DFR	dislodgeable foliar residue
DMI	DeMethylation inhibitor
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EEC	estimated environmental concentration
EPA	Environmental Protection Agency
F1	first generation
F2	second generation
fc	food consumption
FDA	*Food and Drugs Act*
FL	Florida (USA state)
g	gram(s)
GA	Georgia (USA state)
GC-NPD	gas chromatography with nitrogen phosporus detector
GI	gastrointestinal
h	hour(s)
ha	hectare(s)
HAFT	highest average field trial
HDPE	high density polyethylene (plastic)

HLC	Henry's Law Constant
HPLC	High-performance liquid chromatography
ID	identification
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram (s)
K_d	adsorption quotient
K_{oc}	adsorption quotient normalized to organic carbon
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LC	Liquid chromatography
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LER	lowest effective rate
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	level of detection
LOEL	low observed effect level
LOQ	limit of quantitation
m^3	metre(s) cubed
M/L/A	mixer, loader and applicator
MAS	maximum average score
Max	maximum
MB	Manitoba
MD	Maryland (USA state)
mg	milligram(s)
MI	Michigan (USA state)
Min	minimum
MIS	maximum irritation score
mL	millilitre(s)
MOE	margin of exposure
mol	mole(s)
MRBD	maximum reasonably balanced diet
MRL	maximum residue limit
MS	mass spectrometry
MS	Mississippi (USA state)
MTD	maximum tolerated dose
MTDB	maximum theoretical dietary burden
n	number
na	not applicable
NC	North Carolina (USA state)
ND	North Dakota (USA state)
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NY	New York (USA state)
NZW	New Zealand white

ON	Ontario
P	parental generation
pa	Pascal
PA	Pennsylvania (USA state)
PBI	plantback interval
PCPA	*Pest Control Product Act*
PE	polyethylene (plastic)
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
PMRA	Pest Management Regulatory Agency
ppm	parts per million
ppt	parts per trillion
PYO	pick-your-own
RAC	raw agricultural commodity
RD	residue definition
REI	restricted-entry interval
rel	relative
RQ	risk quotient
Std. Dev.	standard deviation
STMdR	supervised trial median residue
STMR	supervised trial mean residue
TA	triazole alanine
TC	transfer coefficient
TGAI	technical grade active ingredient
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
TX	Texas (USA state)
UK	United Kingdom
USA	United States of America
UV	ultraviolet
VA	Virginia (USA state)
v/v	volume per volume dilution
wt	weight

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	MethodType	LOQ	Reference
Plant	AG-575A	Difenoconazole	GC-NPD	0.01 ppm for grain and 0.05 ppm for straw and forage	PRDD99-01
	REM 147.08		LC-MS/MS	0.01 ppm (oilseed rape seed, olives, olive oil, sugar beet leaves and roots, cherries, tomatoes, tomato puree, grapes, broccoli, leek, apples and wheat grain)	1605742, 1605743
Animal	REM 147.07	Difenoconazole, CGA 205375	LC-MS/MS	0.01 ppm (liver, kidney, muscle, fat and eggs)	1758002, 1758003, 1605736, 1605737, 1605738, 1605740
	AG-544A	Difenoconazole	LC-MS/MS	0.01 ppm (tissue) 0.005 ppm (milk)	PRDD99-01
Soil	None	Difenoconazole	HPLC-MS-MS	1.0 ng/g	1757693, 1757695
		CGA 205375		1.0 ng/g	
		CGA 71019		1.0 ng/g	

Table 2 Toxicity Profile of Inspire™ Fungicide Containing Difenoconazole*

Study Type/Animal/Reference	Study Results
Acute Oral Toxicity (gavage) Up-Down Procedure Sprague-Dawley rats PMRA 1757969	LD_{50} = 3129 mg/kg bw Deaths between 1 and 2 days **Low toxicity**
Acute Dermal Toxicity Wistar rats PMRA 1757970	LD_{50} > 5000 mg/kg bw No mortality **Low toxicity**
Acute Inhalation Toxicity Wistar rats PMRA 1757971	LC_{50} > 5.17 mg/L One male died on day 3 **Low toxicity**

Study Type/Animal/Reference	Study Results
Eye Irritation NZW rabbits PMRA 1757972	 MAS 22.9/110, MIS 25.3/110 at 24 & 48 hours Clear by 21 days **Moderately irritating**
Skin Irritation NZW rabbits PMRA 1757973	 MAS 1.2/8 **Slightly irritating**
Skin Sensitization Guinea Pigs PMRA 1757974	 There were no reactions following an undiluted challenge **Not a skin sensitizer**

*Effects are known or assumed to occur in both sexes unless otherwise noted.

Table 3 Toxicity Profile of Technical Difenoconazole and Some Metabolites*

Study Type/Animal/Reference	Study Results
Acute Oral Toxicity (gavage) Sprague-Dawley rats PMRA 1175763	LD_{50} = 1453 mg/kg bw Deaths between 3 and 5 days **Slight toxicity**
Acute Oral Toxicity (gavage) Tif:MAGF mice PMRA 1175763	Supplemental LD_{50} > 2000 mg/kg bw Deaths between 2 and 5 days **Low toxicity**
Acute Dermal Toxicity NZW rabbits PMRA 1175764	LD_{50} > 2010 mg/kg bw No mortality **Low toxicity**
Acute Inhalation Toxicity Sprague-Dawley rats PMRA 1175765	LC_{50} > 3.30 mg/L No mortality **Low toxicity**

Study Type/Animal/Reference	Study Results
Eye Irritation NZW rabbits PMRA 1175766	MAS 19.5/110 **Mildly irritating**
Skin Irritation NZW rabbits PMRA 1175767	MAS 0.1/8 **Minimally irritating**
Skin Sensitization Guinea Pigs PMRA 1175769	There were no reactions following an undiluted challenge **Not a skin sensitizer**
90-Day Oral Toxicity (diet) CD-1 mice PMRA 1175782	NOAEL = 30.8 mg/kg bw/day **≥ 383.6 mg/kg bw/day:** ↑ liver wt, hepatocellular hypertrophy, vacuolization; ↓ bwg, ovary wt (♀)
28-Day Oral Toxicity (diet) Range-finding Wistar rats PMRA 1757641	Supplemental **≥ 74.8 mg/kg bw/day:** ↑ liver wt
90-Day Oral Toxicity (diet) Wistar rats PMRA 1175771	NOAEL = 3.3 mg/kg bw/day **≥ 19.9 mg/kg bw/day:** ↑ rel liver wt; ↓ bwg, ↓ fc (♂)
90-Day Oral Toxicity (diet) Sprague Dawley rats PMRA 1175803	NOAEL = 1.3 mg/kg bw/day **≥ 12.3 mg/kg bw/day:** ↓ bw, bwg, fc, ↑ rel liver wt (♀)
6-Month Oral Toxicity (diet) Beagle dogs PMRA 1175772	NOAEL = 31.3 mg/kg bw/day **≥ 96.6 mg/kg bw/day:** ↓ bwg; bilateral lenticular cataract, iridic changes, ↑ liver wt (♀)

Study Type/Animal/Reference	Study Results
28-Day Dermal Toxicity Wistar rats PMRA 1757594	NOAEL (systemic) = 1000 mg/kg bw/day NOAEL (irritation) = 100 mg/kg bw/day **1000 mg/kg bw/day:** ↑ liver wt, minimal centrilobular hypertrophy and slight clin chem alterations Slight ↑ in number of cell rows at treatment site and thickness of the retained lamellar keratin layer
12-Month Oral Toxicity (diet) Beagle dogs PMRA 1175774	NOAEL = 3.4 mg/kg bw/day **≥ 16.4 mg/kg bw/day:** ↓ bwg, fc (♀)
18-Month Oral Toxicity (diet) CD-1 mice PMRA 1175790, 1175791	NOAEL = 4.7 mg/kg bw/day **≥ 46.3 mg/kg bw/day:** ↓ bwg; ↑ hepatocellular necrosis, hepatocellular hypertrophy (♂);↑ liver wt (♀) **Evidence of carcinogenicity at doses exceeding MTD**
24-Month Oral Toxicity (diet) Sprague-Dawley rats PMRA 1175795, 1175796, 1175797, 1175798	NOAEL = 1.0 mg/kg bw/day **≥ 24.1 mg/kg bw/day:** ↓ bwg , ↑ hepatocellular hypertrophy **No evidence of carcinogenicity**
2-Generation Reproductive Toxicity (diet) Sprague-Dawley rats PMRA 1175804, 1175805	Parental Toxicity NOAEL = 17.7 mg/kg bw/day **172.4 mg/kg bw/day**: ↓ bwg, fc (P, F_1) Offspring Toxicity NOAEL = 17.7 mg/kg bw/day **172.4 mg/kg bw/day:** ↓ bw, bwg (F_1, F_2) Reproductive Toxicity NOAEL = 172.4 mg/kg bw/day **No evidence of sensitivity of the young**
Developmental Toxicity (gavage) Sprague-Dawley rats PMRA 1175801	Parental Toxicity NOAEL = 20 mg/kg bw/day **≥ 100 mg/kg bw/day:** ↓ bwg, fc, ↑ salivation Developmental Toxicity NOAEL = 100 mg/kg bw/day **200 mg/kg bw/day:** ↑ bifid or unilateral ossification of thoracic vertebrae, ↑ # ossified hyoid with ↓ sternal ossification, ↑ # ribs with thoracic vertebrae, ↓ # lumbar vertebrae, ↑ mean # resorptions, ↑ post-implantation loss **No evidence of sensitivity of the young**

Study Type/Animal/Reference	Study Results
Developmental Toxicity (gavage) NZW rabbits PMRA 1175780	Parental Toxicity NOAEL = 25 mg/kg bw/day **75 mg/kg bw/day:** ↓ bwg, fc, ↑ post-implantation loss, ↑ resorptions/doe, 2 does aborted and one died Developmental Toxicity NOAEL = 25 mg/kg bw/day **75 mg/kg bw/day:** ↓ fetal bw, ↑ post-implantation loss, ↑ resorptions/doe **No evidence of sensitivity of the young**
Acute Neurotoxicity Range-finding Wistar rats PMRA 1757637	Supplemental **≥ 300 mg/kg bw:** ↓ activity; ↓ visual placing response, tip toe gait, ↓ righting and splay reflexes (♀) All animals were free of clinical signs by day 4
Acute Neurotoxicity Wistar rats PMRA 1757638	NOAEL = 25 mg/kg bw **200 mg/kg bw:** decreased forelimb grip strength, day 1 (♂) **Equivocal evidence of neurotoxicity**
Short-term Neurotoxicity Wistar rats PMRA 1757642	NOAEL = 17.3 mg/kg bw/day **107.0 mg/kg bw/day:** ↓ bw, bwg , ↑ liver wt; ↓ food efficiency, ↓ hind limb grip strength (♂); ↓ food consumption (♀) **Equivocal evidence of neurotoxicity**
Bacterial Reverse Mutation Assay *E. coli and S. typhimurium* PMRA 1175792	**Negative** Cytotoxicity at 681 µg/plate Precipitation at 681 µg/plate
In Vivo Mouse Micronucleus Tif:MAGF mice PMRA 1175794	**Negative**
Unscheduled DNA Synthesis Wistar rats PMRA 1180858	**Negative** Reduced cell growth at 62.5 µg/mL Precipitation at 15.63 µg/mL
In Vitro Mammalian Clastogenicity CHO cells PMRA 1757627	**Equivocal at 83.9 µg/mL with S9** **Negative without S9** Cytotoxic at the highest dose levels
In Vitro Mammalian Clastogenicity CHO cells PMRA 1757630	**Equivocal at 17.6 µg/mL with S9** **Negative without S9** Cytotoxic at the highest dose levels

Study Type/Animal/Reference	Study Results
In Vitro Mammalian Clastogenicity Human lymphocytes PMRA 1757632	**Negative** Cytotoxic at 5 µg/mL
Acute Oral Toxicity (gavage) CGA 205374 mammalian metabolite ICR mice PMRA 1757645	LD_{50} > 5000 mg/kg bw No mortality **Low toxicity**
Acute Oral Toxicity (gavage) CGA 205375 mammalian metabolite ICR mice PMRA 1757646	LD_{50} = 2309 mg/kg bw Deaths between 31 and 3 days **Low toxicity**
Bacterial Reverse Mutation Assay CGA 189138 mammalian metabolite *E. coli and S. typhimurium* PMRA 1757620	**Negative** Reduced cell growth at 500 µg/plate
Bacterial Reverse Mutation Assay CGA 205374 mammalian metabolite *E. coli and S. typhimurium* PMRA 1757622	**Negative** Cytotoxicity at 5000 µg/plate Precipitation at 313 µg/plate
Bacterial Reverse Mutation Assay CGA 205375 mammalian metabolite *E. coli and S. typhimurium* PMRA 1757624	**Negative** Cytotoxicity at 40 µg/plate

*Effects are known or assumed to occur in both sexes unless otherwise noted; 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 Difenoconazole

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] orTarget MOE
Acute dietary general population	Acute neurotoxicity	NOAEL = 25 mg/kg bw Reduced grip strength	100
	ARfD = 0.25 mg/kg bw		
Acute dietary females aged 13-49	Rabbit developmental toxicity	NOAEL = 25 mg/kg bw Increased post-implantation loss	300
	ARfD = 0.083 mg/kg bw		

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] orTarget MOE
Repeated dietary	Rat chronic/oncogenicity	NOAEL = 1 mg/kg bw/day Decreased body weight gain and increased hepatocellular hypertrophy	100
	ADI = 0.01 mg/kg bw/day		
Short- and intermediate-term dermal[2]	Rabbit developmental toxicity	NOAEL = 25 mg/kg bw/day Increased post-implantation loss	300
Short- and intermediate- term inhalation[3]	Rabbit developmental toxicity	NOAEL = 25 mg/kg bw/day Increased post-implantation loss	300
Acute aggregate (pick-your-own scenarios) [2] general population	Acute neurotoxicity	NOAEL = 25 mg/kg bw Reduced grip strength	100
Acute aggregate (pick-your-own scenarios) [2] females aged 13-49	Rabbit developmental toxicity	NOAEL = 25 mg/kg bw Increased post-implantation loss	300

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational and pick-your-own assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor (51%) was used in a route-to-route extrapolation

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

Table 5 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN PLANTS
The nature of the residue was previously assessed in wheat, tomato, potato and grape (for details, please refer to PRDD99-01). Application rates (500-988 g a.i./ha) are representative of the anticipated foliar application rates of difenoconazole, and are sufficiently high to provide adequate characterization and identification of the terminal residues in all crops. The nature of the residue in plant commodities is considered to be adequately understood in plant commodities, and the residue definition for enforcement and risk assessment purposes is confirmed as the parent, difenoconazole.

CONFINED ACCUMULATION IN ROTATIONAL CROPS
The nature of the residue in rotated crops (lettuce, wheat, sugar beet, mustard, turnips and corn) was previously assessed (for details, please refer to PRDD99-01). The major metabolites identified in triazole-labelled crops were triazole alanine (TA) and further metabolic products of TA. Only limited characterization of phenyl-labelled crops was possible due to the low total radioactive residues (TRRs) in these matrices. The confined accumulation studies were considered aceeptable to support the original registration of difenoconazole, as the application rates (14.3-125 g a.i./ha) were exaggerated with respect to the seed treatment use. However, the nature of the residue in rotational crops is not considered to be adequately characterized to support the current use, as the foliar application of difenoconazole is anticipated to lead to higher residues in rotated crops than previously assessed. As such, an additional confined rotational crop reflecting phenyl-ring labelling at a rate representative of the maximum potential seasonal application rate (512 g a.i./ha) is required as a condition of registration.

NATURE OF THE RESIDUE IN LAYING HEN		**PMRA 1722722**
Laying hens were dosed orally once daily for four consecutive days with [triazole-^{14}C]-CGA-169374 (difenoconazole) at 100 ppm in the diet. Eggs were collected twice daily, excreta was collected once daily. Tissues were collected at sacrifice, six hours after the final dose.		
Matrices		**% of Administered Dose**
Excreta		65.53
Muscle		3.53
Fat		1.12
Liver		1.32
Eggs		1.18
Metabolites identified	**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Radiolabel Position	**[triazole-^{14}C]-Difenoconazole**	**[triazole-^{14}C]-Difenoconazole**
Liver	CGA-205375, CGA-71019	Difenoconazole, CGA-205374
Muscle	CGA-205375, CGA-71019	difenoconazole
Fat	CGA-205375, difenoconazole	CGA-71019
Egg white	CGA-71019	CGA-205375
Egg yolk	CGA-205375, CGA-71019	difenoconazole

NATURE OF THE RESIDUE IN LACTATING GOAT	**PMRA 1722724**
Two lactating goats were dosed orally with [phenyl-^{14}C]-CGA-169374 (difenoconazole) at 100 ppm in diet for four consecutive days. Milk was collected twice daily, urine and feces were collected once daily. Tissues were collected at sacrifice, six hours after the final dose.	
Matrices	**% of Administered Dose**
Urine	29.10
Feces	37.21
Muscle	1.43

NATURE OF THE RESIDUE IN LACTATING GOAT		PMRA 1722724
Fat		0.35
Kidney		0.06
Liver		1.47
Milk		0.28
Metabolites identified	**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Radiolabel Position	**[phenyl-^{14}C]-Difenoconazole**	**[phenyl-^{14}C]-Difenoconazole**
Muscle	CGA-205375	difenocoanzole, CGA-189138, glycine-189138, glucuronide-205375, dulfate-205375, OH-205375
Fat	CGA-205375	difenoconazole, CGA-205374, OH-205375
Kidney	CGA-205375, glucuronide-205375, sulphate-205375, glycine-189138	difenoconazole, sulfate-OH-205375, OH-205375, CGA-189138, glucuronide-OH-169374, glucuronide-OH-205375, glucuronide-OH-169375
Liver	CGA-205375	difenoconazole, CGA-189138, glycine-189138, glucuronide-205375, sulphate-205375, sulphate-OH-205375, OH-205375, glucuronide-OH-169374
Milk	CGA-205375, sulphate-205375, glycine-189138	Difenoconazole, glucuronide-205375, sulphate-OH-205375, OH-205375, CGA-189138, sulphate-OH-169374

Proposed Metabolic Scheme in Livestock

The predominant metabolic pathway for difenoconazole in laying hens involves cleavage of the dioxolan ring to form the ketone CGA-205374, followed by reduction to form CGA-205375. Cleavage of the alkyl bridge between the triazole and biphenyl portion of the molecule results in the formation of free triazole (CGA-71019).

The predominant metabolic pathway for difenoconazole (CGA-169374) in lactating goats involves cleavage of the dioxolan ring to form CGA-205375 directly or through the reduction of the intermediate ketone CGA-205374 (observed in fat tissue only). CGA-205375 can then form Phase II metabolites at the site of hydroxylation: glucuronide conjugate and sulfate conjugate of CGA-205375. CGA-205375 and the two conjugates can be further hydroxylated at the outer phenyl ring for three minor hydroxyl metabolites. Cleavage of the triazole ring results in an intermediate metabolite, OH-acetic acid-CGA-169374, which is then rapidly reduced to CGA-189138. CGA-189138 can conjugate with an amino acid or a sugar to form the glycine conjugate of CGA-189138 and the glucuronide conjugate of CGA-189138, respectively.

NATURE OF THE RESIDUE IN LACTATING GOAT	PMRA 1722724

STORAGE STABILITY	PMRA 1722722, 1722724,

Residues of difenoconazole are stable in potatoes and tomatoes for at least two years, and in lettuce, soybeans and wheat forage for a period of one year (for details, please refer to PRDD99-01). Residues are stable for at least 24 months in tomato, sugar beet, cotton and wheat processed commodities. The storage stability of residues of difenoconazole and CGA-205375 was demonstrated concurrently with the animal feeding studies.

CROP FIELD TRIALS ON BULB VEGETABLES - GREEN ONIONS & DRY BULB ONIONS	PMRA 1758033

Three green onion field trials were conducted in California (Zone 10), Georgia (Zone 2), and Texas (Zone 6), and eight dry bulb onions trials were conducted in California (Zone 10, two trials), Colorado (Zone 8), Idaho (Zone 11), Illinois (Zone 5), New York (Zone 1), Texas (Zone 6), and Washington (Zone 12) during the 2006 growing season. Green onions were treated three times and dry bulb onions four times with difenoconazole 250EC at a rate of 0.129 kg a.i./ha per application. Applications were made using ground equipment using a non-ionic surfactant (0.1% v/v) as an adjuvant. The interval between applications was seven days and all applications were made in 47-935 L/ha of water. Seven DALA samples were collected for residue analysis.

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Green Onions	0.39	7	6	2.0	4.8	3.8	2.7	2.9	1.0
Bulb Onions	0.52	7	16	<0.01	0.09	0.07	0.02	<0.01	0.02

CROP FIELD TRIALS ON BRASSICA VEGETABLES - BROCCOLI, CABBAGE & MUSTARD GREENS	PMRA 1758030, 1758035

Six broccoli trials were conducted in Zones 6 (TX; one trial), 10 (CA; four trials), and 12 (WA; one trial); six cabbage trials were conducted in Zones 1 (NY; one trial), 2 (NC; one trial), 3 (FL; one trial), 5 (WI; one trial), 6 (TX; one trial) and 10 (CA; one trial); and five mustard greens trials were conducted in Zones 2 (GA; one trial), 4 (LA; one trial) 5 (IL; one trial), 6 (TX; one trial) and 10 (CA; one trial) during the 2007 growing season. Broccoli, cabbage and mustard greens were treated four times with difenoconazole 250EC at a rate of 0.129 kg a.i./ha per application. The interval between applications was seven days and all applications were made in 19-935 L/ha of water using ground equipment and a non-ionic surfactant (0.1255%). One day after the last application, one DALA and seven DALA samples were collected for residue analysis.

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Broccoli	0.52	1	12	0.12	0.61	0.53	0.34	0.34	0.13
Cabbage (with wrapper leaves)	0.52	1	12	0.06	1.6	1.3	0.30	0.55	0.49

NATURE OF THE RESIDUE IN LACTATING GOAT							PMRA 1722724		
Cabbage (without wrapper leaves)	0.52	1	12	<0.01	0.12	0.09	0.02	0.04	0.04
Mustard Greens	0.52	1	10	2.9	14.3	14.2	5.5	6.8	4.2
Broccoli	0.52	7	12	0.02	0.28	0.21	0.09	0.11	0.08
Cabbage (with wrapper leaves)	0.52	7	12	<0.01	0.38	0.34	0.19	0.19	0.13
Cabbage (without wrapper leaves)	0.52	7	12	<0.01	0.15	0.10	<0.01	0.02	0.04
Mustard Greens	0.52	7	10	0.78	6.1	5.7	1.6	2.2	1.9

CROP FIELD TRIALS ON CURCURBITS - CANTALOUPE, CUCUMBER & SUMMER SQUASH	PMRA 1758031

Six cucumber trials were conducted in Zones 2 (GA and NC; one trial each), 3 (FL; one trial) 5 (MI and WI; one trial each), and 6 (TX; one trial); six cantaloupe trials were conducted in Zones 2 (GA; one trial), 5 (IL; one trial), 6 (TX; one trial), and 10 (CA; three trials); and five summer squash trials were conducted in Zones 1 (NY**;** one trial), 2 (SC; one trial) 3 (FL; one trial), 5 (IL; one trial) and 10 (CA; one trial) during the 2006 growing season. Cantaloupes, cucumbers and squash were treated four times each with difenoconazole 250EC at a rate of 0.129 kg a.i./ha per application. Applications were made using ground equipment using a non-ionic surfactant (0.125% v/v). The interval between applications was seven days and all applications were made in 18.7 - 935 L/ha. At zero DALA and seven DALA samples were collected for residue analysis.

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Cantaloupe	0.515	0	12	0.03	0.44	0.35	0.11	0.12	0.12
Cucumber	0.515	0	12	<0.01	0.20	0.15	0.03	0.04	0.06
Summer Squash	0.515	0	12	<0.01	0.06	0.06	0.04	0.04	0.03
Cantaloupe	0.515	7	12	0.02	0.20	0.15	0.09	0.09	0.06
Cucumber	0.515	7	12	<0.01	0.01	<0.01	<0.01	<0.01	0.001
Summer Squash	0.515	7	12	<0.01	<0.01	<0.01	<0.01	<0.01	na

NATURE OF THE RESIDUE IN LACTATING GOAT	PMRA 1722724

CROP FIELD TRIALS ON GRAPES — **PMRA 1758091**

Twelve field trials were conducted on grapes in the USA encompassing California (Zone 10, eight trials), New York (Zone 1), Oregon (Zone 12), Pennsylvania (Zone 1), and Washington (Zone 11) during the 2007 growing season. At each trial site, plots were treated four times at seven day intervals with difenoconazole as an emulsifiable concentrate formulation (250EC) at a rate of 129 g a.i./ha per application. A non-ionic surfactant was added to the spray mixture for all applications at 0.125% (v/v). Seven DALA samples were collected for residue analysis.

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Grape	0.52	7	24	0.08	1.8	1.5	0.44	0.61	0.50

CROP FIELD TRIALS ON POME FRUITS - APPLES & PEARS — **PMRA 1605758**

Nineteen field trials (13 in apple and six in pear) were conducted in the US encompassing Zones 1 (four trials), 2 (one trial), 5 (two trials), 9 (one trial), 10 (four trials) and 11 (seven trials) during the 2004 growing season. At each trial site, apple and pear trees were treated five times at 7±2 day intervals with difenoconazole as an emulsifiable concentrate formulation (250EC) at a rate of 76 g a.i./ha per application. A non-ionic surfactant was added to the spray mixture for all applications at 0.125% (v/v). Fourteen DALA samples were collected for residue analysis.

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Apple	0.38	14±2	34	0.02	0.59	0.47	0.16	0.20	0.14
Pear	0.38	14±1	16	0.01	0.30	0.27	0.10	0.13	0.08

CROP FIELD TRIALS ON POTATOES — **PMRA #1605756**

Sixteen field trials were conducted on potato in the USA encompassing Zones 1 (two trials), 2 (one trial), 3 (one trial), 5 (four trials), 9 (one trial), 10 (one trial) and 11 (six trials) during the 2004 growing season. Potato plants were treated four times at 7±1 day intervals with difenoconazole as an emulsifiable concentrate formulation (250EC) at a rate of 128 g a.i./ha per application. A non-ionic surfactant was added to the spray mixture for all applications at 0.125% (v/v). Fourteen, plus or minus two, DALA samples were collected for residue analysis.

NATURE OF THE RESIDUE IN LACTATING GOAT									PMRA 1722724
Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Potato	0.513	13-16	32	<0.01	0.01	0.01	0.01	0.01	0

CROP FIELD TRIALS ON SUGAR BEETS	PMRA 1605760

Twelve field trials were conducted on sugar beets in the USA encompassing Zones 5 (five trials), 7 (one trial), 8 (one trial), 9 (one trial), 10 (two trials) and 11 (two trials) during the 2004 growing season. Sugar beet plants were treated four times at 7±1 day intervals with difenoconazole as an emulsifiable concentrate formulation (250EC) at a nominal rate of 129 g a.i./ha per application. A non-ionic surfactant was added to the spray mixture for all applications at 0.125% (v/v). Seven DALA samples were collected for residue analysis.

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Sugar beet roots	0.513	7	24	<0.01	0.28	0.23	0.03	0.06	0.07
Sugar beet tops	0.513	7	24	0.15	5.80	5.2	1.1	1.6	1.5

CROP FIELD TRIALS ON FRUITING VEGETABLES - TOMATOES AND PEPPERS	PMRA 1605754

Twenty field trials (11 in tomato, six in bell pepper and three in non-bell pepper) were conducted in the USA encompassing Zones 1 (one tomato trial), 2 (one trial each for tomato and bell pepper), 3 (one trial each for tomato and bell pepper), 5 (one trial each for tomato and bell pepper), 6 (one trial each for bell pepper and non-bell pepper), 8 (one non-bell pepper trial) and 10 (seven trials for tomato, two trials for bell pepper and one trial for non-bell pepper) during the 2004 growing season. At each trial site, plots were treated four times at 7±1 day intervals with difenoconazole as an emulsifiable concentrate formulation (250EC) at a rate of 129 g a.i./ha per application. A non-ionic surfactant was added to the spray mixture for all applications at 0.125% (v/v). Zero DALA samples were collected for residue analysis.

Commodity	Total Application Rate (kg a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Tomato	0.515	0	22	0.01	0.41	0.39	0.16	0.18	0.11
Bell pepper	0.520	0	12	0.05	0.20	0.18	0.11	0.11	0.05
Non-bell pepper	0.518	0	6	0.09	0.29	0.26	0.16	0.17	0.08

NATURE OF THE RESIDUE IN LACTATING GOAT	PMRA 1722724
RESIDUE DECLINE	**PMRA 1758033, 1758030, 1758031, 1758091, 1605758, 1605756, 160570, 1605754**
Residue decline was assessed in bulb vegetables (green onions and bulb onions), brassica vegetables (cabbage, broccoli & mustard greens), Curcubit vegetables (cantaloupe, cucumber & summer squash), grapes, pome fruits (apples & pears), potatoes, sugar beets and fruiting vegetables (tomatoes & bell peppers) harvested at multiple PHIs ranging from 1–19 DALA. For the majority of crops, residues of difenoconazole were demonstrated to decrease with increasing PHIs except for bulb vegetables (green onion & bulb onions), apples, tomatoes and bell peppers where residues did not generally increase or decrease with increasing PHI.	

PROCESSED FOOD AND FEED - GRAPES	PMRA 1758091
Test Site	Zone 10 (California)
Treatment	four treatments seven days apart
Rate	0.45 - 2.3 kg a.i./ha
End-use product	difenoconazole 250EC
Preharvest interval	seven days
Processed Commodity	**Processing Factor**
Raisins	3.5x
Grape Juice	0.24x

PROCESSED FOOD AND FEED - TOMATOES	PMRA 1605754
Test Site	Zone 10 (California)
Treatment	four treatments 7±1 days apart
Rate	0.501 & 2.57 kg a.i./ha
End-use product	difenoconazole 250EC
Preharvest interval	seven days
Processed Commodity	**Processing Factor**
Paste	1.6x
Puree	0.6x

PROCESSED FOOD AND FEED – SUGAR BEETS	PMRA 1605760
Test Site	Zone 10 (California), Zone 5 (Minnesota)
Treatment	four treatments 7±1 days apart
Rate	0.52 & 2.57 kg a.i./ha
End-use product	difenoconazole 250EC
Preharvest interval	seven days
Processed Commodity	**Processing Factor**
Refined Sugar	0.3x

NATURE OF THE RESIDUE IN LACTATING GOAT	PMRA 1722724
Molasses	0.5x
PROCESSED FOOD AND FEED - POTATOES	**PMRA 1605756**
Test Site	Zone 11 (Idaho), Zone 11 (Washington)
Treatment	four treatments 7±1 days apart
Rate	0.526 - 2.6 kg a.i./ha
End-use product	difenoconazole 250EC
Preharvest interval	14 ±2days
Processed Commodity	**Processing Factor**
Dried flakes	0.5x
PROCESSED FOOD AND FEED – APPLES & PEARS	**PMRA #1605758**
Test Site	Zone 11 (New York), Zone 11 (Washginton)
Treatment	five treatments 7±2 days apart
Rate	0.381 & 1.904 kg a.i./ha
End-use product	difenoconazole 250EC
Preharvest interval	14 days
Processed Commodity	**Processing Factor**
Juice	0.04x
Wet pomace	9.6x
FIELD ACCUMULATION IN ROTATIONAL CROPS - SPINACH, RADISH & WHEAT	**PMRA 1605801**
During the 2004 growing season, two field crop rotation trials were conducted in the USA. At each trial site, difenoconazole as a 250EC formulation was applied four times to the primary crop (tomato) at 128 g a.i./ha/application for a total of 512 g a.i./ha. Following the harvest of the primary crop, representative rotational crops (spinach, radish and wheat) were planted at 30 and 60 days after the last application.	

NATURE OF THE RESIDUE IN LACTATING GOAT									PMRA 1722724
Commodity	Total App Rate (kg a.i./ha)	PBI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Spinach	528-533	30	4	<0.01	0.02	0.02	0.015	0.015	0.006
Radish top			4	<0.01	<0.01	<0.01	0.01	0.01	na
Radish roots			4	<0.01	<0.01	<0.01	0.01	0.01	na
Wheat forage			4	<0.01	<0.01	<0.01	0.01	0.01	na
Wheat hay			4	<0.01	<0.01	<0.01	0.01	0.01	na
Wheat straw			4	<0.01	<0.01	<0.01	0.01	0.01	na
Wheat grain			4	<0.01	<0.01	<0.01	0.01	0.01	na
Spinach	528-533	60	4	<0.01	<0.01	<0.01	0.01	0.01	na
Radish top			4	<0.01	<0.01	<0.01	0.01	0.01	na
Radish roots			4	<0.01	<0.01	<0.01	0.01	0.01	na
Wheat forage			4	<0.01	<0.01	<0.01	0.01	0.01	na
Wheat hay			4	<0.01	<0.01	<0.01	0.01	0.01	na
Wheat straw			4	<0.01	<0.01	<0.01	0.01	0.01	na
Wheat grain			4	<0.01	<0.01	<0.01	0.01	0.01	na

LIVESTOCK FEEDING – DAIRY CATTLE	PMRA 1605805

Three treatment groups of three dairy cows each were dosed with gelatin capsules containing difenoconazole at 1ppm, 5 ppm, and 15 ppm in the diet for 29-30 consecutive days. Milk samples were collected twice a day. The cows were sacrificed 20-23 hours after the last dosing, and samples of liver kidney, fat (renal, mesenterial, subcutaneous) and muscle (round, tenderloin, diaphragm) were collected. Milk and tissue samples were analyzed for residues of difenoconazole and CGA-205375.

Matrix	Feeding Level (ppm/day)	Residue Levels (ppm)						
		n	LOQ	Min	Max	Median	Mean	Standard Deviation
Difenoconazole								
Milk	1	27	0.005	<0.005	<0.005	<0.005	<0.005	--
Liver		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Fat		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Muscle		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Kidney		3	0.01	<0.01	<0.01	<0.01	<0.01	--

NATURE OF THE RESIDUE IN LACTATING GOAT						PMRA 1722724		
Milk	5	27	0.005	<0.005	<0.005	<0.005	<0.005	--
Liver		3	0.01	0.01	0.02	0.01	0.01	0.01
Fat		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Muscle		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Kidney		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Milk	15	27	0.005	<0.005	<0.005	<0.005	<0.005	--
Liver		3	0.01	0.03	0.03	0.03	0.03	--
Fat		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Muscle		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Kidney		3	0.01	<0.01	<0.01	<0.01	<0.01	--
CGA-205375								
Milk	1	27	0.005	<0.005	<0.005	<0.005	<0.005	--
Liver		3	0.01	0.05	0.07	0.06	0.06	0.01
Fat		3	0.01	<0.01	0.02	0.01	0.01	0.01
Muscle		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Kidney		3	0.01	<0.01	0.01	0.01	0.01	--
Milk	5	27	0.005	<0.005	0.007	0.005	0.005	0.0004
Liver		3	0.01	0.14	0.23	0.22	0.20	0.05
Fat		3	0.01	0.03	0.05	0.05	0.04	0.01
Muscle		3	0.01	0.01	0.01	0.01	0.01	--
Kidney		3	0.01	0.03	0.04	0.04	0.04	0.01
Milk	15	27	0.005	0.008	0.02	0.02	0.012	0.012
Liver		3	0.01	0.52	0.66	0.53	0.57	0.08
Fat		3	0.01	0.12	0.14	0.12	0.13	0.01
Muscle		3	0.01	0.04	0.05	0.05	0.05	0.01
Kidney		3	0.01	0.09	0.12	0.12	0.11	0.02

Calculation of Livestock Maximum Reasonably Balanced Diet (MRBD) in Beef Cattle, Dairy Cattle, and Swine.

The potential for transfer of difenoconazole residues into meat and milk exists because there are livestock feedstuffs associated with the registered uses on cereals and the proposed uses on apple, potato and sugar beet. The calculated MRBD, based on the residue data for apple, sugar beet, potato (culls) and cereals, and the experimental processing factors for apple wet pomace, sugar beet (molasses, dried pulp) and potato culls is 0.35 ppm for beef cattle, 1.49 ppm for dairy cattle and 0.02 ppm for swine.

NATURE OF THE RESIDUE IN LACTATING GOAT	PMRA 1722724

Calculation of the Anticipated Residues in Cattle and Swine Commodities

Commodity	Feeding level (ppm)	Maximum Residues (ppm)*	MTDB (ppm)		Anticipated Residue (ppm)	
			Beef/Dairy	Hog	Beef/Dairy	Hog
Milk	5	0.012	1.49	--	0.007	--
Fat	5	0.06	1.49	0.02	0.02	0.0102
Kidney	5	0.05	1.49	0.02	0.02	0.0102
Liver	5	0.26	1.49	0.02	0.07	0.0009
Muscle	15	0.06	1.49	0.02	0.002	0.0100

*difenoconazole + CGA-205375.

Anticipated residues at the MRBD in liver, kidney and fat were calculated using linear regression analysis, while anticipated residues in milk and muscle were determined based on the ratio of residue to feed. For maximum residue calculations, LOQ (0.005 ppm for milk, 0.01 ppm for tissues) was used for values reported as <LOQ.

LIVESTOCK FEEDING – LAYING HENS	PMRA 1605803

Four treatment groups of 15 laying hens each were dosed with difenoconazole at 0.3 ppm, 1 ppm, 3 ppm and 10 ppm in feed for 28 consecutive days. Eggs were collected at ~3-day intervals. The hens were sacrificed 20-24 hours after the last dosing, and composite samples of tissues (skin plus attached fat, peritoneal fat, liver, breast plus thigh muscle) were collected. Egg and tissue samples were analysed for residues of difenoconazole and the metabolite CGA-205375.

Matrix	Feeding Level (ppm/day)	Residue Levels (ppm)						
		n	LOQ	Min	Max	Median	Mean	Standard Deviation
Difenoconazole								
Eggs	0.3, 1, 3 and 10	108	0.01	<0.01	<0.01	<0.01	<0.01	--
Skin with fat		12	0.01	<0.01	<0.01	<0.01	<0.01	--
Peritoneal fat		12	0.01	<0.01	<0.01	<0.01	<0.01	--
Liver		12	0.01	<0.01	<0.01	<0.01	<0.01	--
muscle		12	0.01	<0.01	<0.01	<0.01	<0.01	--

NATURE OF THE RESIDUE IN LACTATING GOAT						PMRA 1722724		
CGA-205375								
Eggs	0.3	27	0.01	<0.01	<0.01	<0.01	<0.01	--
Skin with fat		3	0.01	Not analyzed				
Peritoneal fat		3	0.01					
Liver		3	0.01					
muscle		3	0.01					
Eggs	1	27	0.01	<0.01	0.01	0.01	0.01	--
Skin with fat		3	0.01	Not analyzed				
Peritoneal fat		3	0.01					
Liver		3	0.01					
muscle		3	0.01					
Eggs	3	27	0.01	<0.01	0.04	0.03	0.03	0.01
Skin with fat		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Peritoneal fat		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Liver		3	0.01	<0.01	<0.01	<0.01	<0.01	--
muscle		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Eggs	10	27	0.01	<0.01	0.17	0.13	0.10	0.05
Skin with fat		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Peritoneal fat		3	0.01	<0.01	<0.01	<0.01	<0.01	--
Liver		3	0.01	<0.01	<0.01	<0.01	<0.01	--
muscle		3	0.01	<0.01	<0.01	<0.01	<0.01	--

Calculation of Livestock Maximum Reasonably Balanced Diet (MRBD) in Poultry

The potential for transfer of difenoconazole residues into poultry meat and eggs exists because there are livestock feedstuffs associated with the registered uses on cereals. The calculated MRBD, based on the Canadian MRLs for cereals is 0.01 ppm for poultry.

NATURE OF THE RESIDUE IN LACTATING GOAT			PMRA 1722724	
Calculation of the Anticipated Residues in Poultry Commodities				
Commodity	**Feeding level (ppm)**	**Maximum Residues (ppm)***	**MTDB (ppm)**	**Anticipated Residue (ppm)**
Muscle	10	0.02	0.01	<0.02
Fat	10	0.02	0.01	<0.02
Liver	10	0.02	0.01	<0.02
Eggs	0.3	0.02	0.01	<0.02
*difenoconazole + CGA-205375. Anticipated residues at the MRBD were calculated based on the ratio of residue to feed. For maximum residue calculations, LOQ (0.01 ppm) was used for value <LOQ.				

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

PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (Wheat, tomato, potato, grape)** **Rotational crops**		Difenoconazole To be confirmed	
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops** **Rotational crops**		Difenoconazole To be confirmed	
METABOLIC PROFILE IN DIVERSE CROPS		The metabolism of difenoconazole was demonstrated to be similar in four diverse crops.	
ANIMAL STUDIES			
ANIMALS		**Ruminant, Laying Hen**	
RESIDUE DEFINITION FOR ENFORCEMENT		Difenoconazole, CGA-205375	
RESIDUE DEFINITION FOR RISK ASSESSMENT		Difenoconazole, CGA-205375	
METABOLIC PROFILE IN ANIMALS **(goat, hen, rat)**		Similar metabolic profile in goat, hen and rat.	
FAT SOLUBLE RESIDUE		No	
DIETARY RISK FROM FOOD AND WATER			
Refined chronic non-cancer dietary risk **ADI = 0.01 mg a.i./kg bw** **Estimated chronic drinking water concentration = 8.4 μg a.i./L**	**POPULATION**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Only	**Food and Water**
	All infants < 1 year	25.9	31.7
	Children 1–2 years	85.5	88.2
	Children 3 to 5 years	69.9	72.4

PLANT STUDIES			
	Children 6–12 years	44.2	45.8
	Youth 13–19 years	30.1	31.4
	Adults 20–49 years	25.9	27.6
	Adults 50+ years	27.5	29.3
	Total population	27.1	34.4
Basic acute dietary exposure analysis, 95th percentile **Estimated acute drinking water concentration = 42 μg a.i./L**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Only	**Food and Water**
ARfD = 0.25 mg a.i./kg bw	**All infants < 1 year**	26.1	27.4
	Children 1–2 years	50.9	51.4
	Children 3 to 5 years	34.6	35.2
	Children 6–12 years	16.2	16.7
	Youth 13–19 years	9.8	10.2
	Adults 20–49 years	9.0	9.4
	Adults 50+ years	9.9	10.2
	Total Population	14.3	14.7
ARfD = 0.083 mg a.i./kg bw	**Females 13–49 years**	29.0	30.1

Table 7 Fate and behaviour of difenoconazole in the terrestrial environment

Property	Value	Transformation products	Comments	PMRA#
Physical and Chemical Properties				
Vapour pressure at 25°C (Pa)	3.3×10^{-8}		Non-volatile	1988930
Henry's law constant at 25°C	$1/H = 2.77 \times 10^{9}$ $K = 8.22 \times 10^{-12}$ atm.m^3/mol		Non-volatile from water and wet soil	1988930
Ultraviolet (UV) / visible spectrum	λ_{max} at 275 nm and 235 nm		Not expected to undergo phototransformation under natural light.	1988930
Solubility in water at pH 7 and 25°C (mg/L)	15.0		Soluble in water	1988930
n-Octanol/water partition coefficient (log K_{ow})	4.4 (25°C)		Potential for bioaccumulation	1988930
Dissociation constant	None in physiological range		Not expected to dissociate at environmental pH	1988930

Property	Value	Transformation products	Comments	PMRA#
Abiotic transformation				
Hydrolysis	Stable at pH 5, 7 and 9		Not a route of transformation	1988930
Phototransformation on soil	Half-life = 349-823 days		Not a route of transformation	1757939
Biotransformation				
Biotransformation in aerobic soil	DT_{50} = 103-1600 days	CGA 205375, CGA 205374 CGA 189138 CGA 190978 CGA 71019	Moderately persistent to persistent	1757940 1757941 1757942 1757945 1757946 1988930
Biotransformation in anaerobic soil	DT_{50} = 679-947 days		Persistent	1988930
Mobility				
Adsorption / desorption in soil	K_{oc} = 2237-11034		Slightly mobile to immobile	1175824 1757949 1757936
Field studies				
Field dissipation	DT_{50} = 28-892 days	CGA 205375 CGA-71019	Slightly persistent to persistent	1176289 1757933
Field leaching	Leached to 45-60 cm soil depth		Potential to leach through soil	1757933

Table 8 Fate and behaviour of difenoconazole in the aquatic environment

Study type	Value	Transformation products	Comments	PMRA#
Physical and Chemical Properties				
Vapour pressure at 25°C (Pa)	3.3×10^{-8}		Non-volatile	1988930
Henry's law constant at 25°C	$1/H = 2.77 \times 10^{9}$ $K = 8.22 \times 10^{-12}$ $atm.m^3/mol$		Non-volatile from water and wet soil	1988930
Ultraviolet (UV) / visible spectrum	λ_{max} at 275 nm and 235 nm		Not expected to undergo phototransformation under natural light.	1988930
Solubility in water at pH 7 and 25°C (mg/L)	15.0		Soluble in water	1988930
n-Octanol/water partition coefficient (log K_{ow})	4.4 (25°C)		Potential for bioaccumulation	1988930
Dissociation constant	None in physiological range		Not expected to dissociate at environmental pH	1988930
Abiotic transformation				
Hydrolysis	Stable at pH 5, 7 and 9		Not a route of transformation	1988930

Study type	Value	Transformation products	Comments	PMRA#
Phototransformation in water	6-228 days	CGA 142856, CGA 107069, CGA 71019	Not an important route of transformation	1757936 1757937 1757938
Biotransformation				
Biotransformation in aerobic water systems	DT_{50} = 307-494 days	CGA 205375	Persistent	1757947 1757948
Biotransformation in anaerobic water systems	DT_{50} = 411 days	CGA 205375 CGA 205374 CGA 71019	Persistent	1757726
Partitioning				
Adsorption / desorption in sediment	Increased in sediment from 49% (day 2) to 81.5% (day 112)		Partitions into sediment	1757948
Bioconcentration	BCF = 170-570		Bioconcentration expected to be negligible as 96-98% of ^{14}C-residues eliminated during depuration	1757786

Table 9 Summary of Risk to Terrestrial Organisms

Organism	Exposure	Endpoint value	RQ	Conclusion
Earthworm	Acute	250 g a.i./ha	2.0	LOC exceeded
Bee	Contact	LD_{50} = 100 µg a.i./bee (112 kg a.i./ha)	0.003	Negligible risk
Predatory mite (*Typhlodromus. pyri*)	Contact	LR_{50} = 207 g a.i./ha (mortality)	1.2	LOC exceeded
		NOEC = 151.8 g a.i./ha (reproduction)	1.7	LOC exceeded
Birds	Acute oral	215 mg a.i./kg bw/day	<1	Negligible risk
	Acute dietary	50.5 mg a.i./kg bw/day	<1	Negligible risk
	Reproductio n	9.7 mg a.i./kg bw/day (NOEL)	<1 – 1.5	Not a concern
		11.5 mg a.i./kg bw/day (LOEL)	1.25	Not a concern
Mammals	Acute oral	145.3 mg a.i./kg bw/day	<1	Negligible risk
	Reproductio n	17.7 mg a.i./kg bw/day	<1- 2.8	Not a concern
Vascular plant	Seedling emergence	Data not available		
	Vegetative vigour	Data not available		

Table 10 Summary of Risk to Aquatic Organisms

Organism	Exposure	Endpoint value (µg a.i./L)	RQ	Conclusion
Freshwater species				
Daphnia magna	Acute	385	0.2	Negligible risk
	Chronic	5.6	0.7-8.2	LOC exceeded
Rainbow trout	Acute	81.0	0.8	Negligible risk
Fathead minnow	Chronic	8.7	0.5-5.3	LOC exceeded
Amphibians	Acute	81.0	0.2-3.0	LOC exceeded

Organism	Exposure	Endpoint value (µg a.i./L)	RQ	Conclusion
Amphibians	Chronic	8.7	0.5-28	LOC exceeded
Freshwater alga (diatom)	Acute	50	0.1-0.9	Negligible risk
Vascular plant (duckweed)	Acute	900	0.1	Negligible risk
Marine species				
Marine invertebrate (mysid)	Acute	75	0.9	Negligible risk
	Chronic	4.6	0.9-10	LOC exceeded
Sheepshead minnow	Acute	81.9	0.8	Negligible risk
	Chronic	8.8	0.5-5.2	LOC exceeded
Marine alga (diatom)	Acute	215	0.3	Negligible risk

Table 11 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
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	
Predominantly anthropogenic[2]	Yes		Yes	
Persistence[3]:	Soil	Half-life ≥ 182 days	Half-life = 103-1600	
	Water	Half-life ≥ 182 days	Half-life = 307-494	
	Sediment	Half-life ≥ 365 days	Half-life = 411	
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure () and Henry's Law Constant ().	
Bioaccumulation[4]	Log $K_{OW} \geq 5$		4.4	
	BCF ≥ 5000		170-570	
	BAF ≥ 5000		Not available	
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	

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

Table 12 Summary of Alternatives for the Same Uses as Inspire™ Fungicide

Crop	Disease	Active ingredient and FRAC Fungicide Group
Brassica (Cole) leafy vegetables group	Alternaria diseases (*Alternaria* spp.)	*Bacillus subtilis* (44) Chlorothalonil (M5) Zineb (M3)
	Powdery mildew (*Erysiphe polygoni*)	Copper sulphate (M2) (for broccoli, cabbage and cauliflower)
Bulb vegetables group	Purple blotch (*Alternaria porri*)	Boscalid (7) Fosetyl AL (33) Mancozeb (M3) Maneb (M3) Pyraclostrobin (11)
Cucurbit vegetables group	Powdery mildew (*Sphaerotheca fuliginea, Erysiphe cichoracearum*)	*Bacillus subtilis* (44) Chlorothalonil (M5) (for cucumber only) Folpet (M4) Mancozeb (M3) Myclobutanil (3) (for greenhouse cucumber only) Potassium bicarbonate (NC) Pyraclostrobin (11) Sulphur (M6) (for greenhouse cucumber only)
	Gummy stem blight (*Didymella bryoniae*)	Boscalid (7) Mancozeb (M3) Myclobutanil (3) (for greenhouse cucumber only) Pyraclostrobin (11) Zineb (M3)
Grape	Powdery mildew (*Uncinula necator*)	Azoxystrobin (11) Copper (M1) *Bacillus subtilis* (44) Boscalid (7) Folpet (M4) Kresoxim-Methyl (11) Myclobutanil (3) Potassium bicarbonate (NC) Pyraclostrobin (11) Quinoxyfen (13) Sulphur (M6) Trifloxystrobin (11)
Fruiting vegetables group	Early blight (*Alternaria solani*)	Copper (M1) (For tomato only) *Bacillus subtilis* (44) Boscalid (7) Captan (M4) (For tomato only) Chlorothalonil (M5) (For tomato only) Mancozeb (M3) Maneb (M3) Metiram (M3) (For tomato only) Pyraclostrobin (11) Ziram (M3) (For tomato only)
	Anthracnose (*Colletotrichum acutatum*)	Captan (M4) (For tomato only) Chlorothalonil (M5) Folpet (M4) (For tomato only) Maneb (M3) Metiram (M3) (For tomato only) Pyraclostrobin (11) Ziram (M3) (For tomato only)

Crop	Disease	Active ingredient and FRAC Fungicide Group
Pome fruit group	Brooks fruit spot (*Mycosphaerella pomi*)	Boscalid (7) Ferbam (M3) (For apple only) Folpet (M4) (For apple only) Pyraclostrobin (11) Thiram (M3) (For apple only)
	Cedar apple rust (*Gymnosporangium juniperi-virginianae*)	Ferbam (M3) (For apple only) Mancozeb (M3) (For apple only) Metiram (M3) (For apple only) Myclobutanil (3) (For apple only) Thiram (M3) (For apple only) Trifloxystrobin (11)
	Flyspeck (*Zygophiala jamacaicensis*)	Boscalid (7) Ferbam (M3) (For apple only) Folpet (M4) (For apple only) Pyraclostrobin (11) Thiram (M3) (For apple only) Trifloxystrobin (11)
	Powdery mildew *(Podosphaera leucotricha*)	*Bacillus subtilis* (44) (For apple only) Boscalid (7) Cyprodinil (9) (For apple only) Flusilazole (3) (For apple only) Kresoxim-Methyl (11) (For apple only) Metiram (M3) (For apple only) Myclobutanil (3) (For apple only) Pyraclostrobin (11) Sulphur (M6) Thiophanate-methyl (1) Trifloxystrobin (11)
	Quince rust (*Gymnosporangium clavipes*)	Ferbam (M3) (For apple only) Mancozeb (M3) (For apple only) Metiram (M3) (For apple only) Myclobutanil (3) (For apple only)
	Scab (*Venturia inaequalis, Venturia pirina*)	*Bacillus subtilis* (44) Boscalid (7) Cyprodinil (9) (For apple only) Ferbam (M3) (For apple only) Flusilazole (3) (For apple only) Folpet (M4) (For apple only) Kresoxim-Methyl (11) (For apple only) Mancozeb (M3) (For apple only) Metiram (M3) (For apple only) Myclobutanil (3) (For apple only) Pyraclostrobin (11) Pyrimethanil (9) Sulphur (M6) Thiophanate-methyl (1) Thiram (M3) (For apple only) Trifloxystrobin (11)
	Sooty blotch *(Gloeodes pomigena*)	Boscalid (7) Ferbam (M3) (For apple only) Folpet (M4) (For apple only) Pyraclostrobin (11) Thiram (M3) (For apple only) Trifloxystrobin (11)
Potato	Early blight (*Alternaria solani*)	*Bacillus subtilis* (44) Chlorothalonil (M5) Fenamidone (11) Metiram (M3) Pyraclostrobin (11) Pyrimethanil (9)

Crop	Disease	Active ingredient and FRAC Fungicide Group
Sugar beet	Cercospora leaf spot (*Cercospora beticola*)	Copper (M1) Metconazole (3) Metiram (M3) Prothioconazole (3) Pyraclostrobin (11) Thiophanate-methyl (1)
	Powdery mildew (*Erysiphe polygoni*)	Pyraclostrobin (11)

Table 13 Use (label) Claims Proposed by Applicant and Accepted

Proposed claim	Accepted claim
1) Control of alternaria early blight (*Alternaria solani*) on fruiting vegetables at the rates of 73 - 128 g a.i./ha.	Supported as proposed.
2) Control of cedar apple rust (*Gymnosporangium juniperi-virginianae*) on pome fruit at the rate of 73 g a.i./ha.	Supported as proposed on pome fruit crop group (apple, crab apple, pear, oriental pear and quince).
3) Control of brooks fruit spot (*Mycosphaerella pomi*) on pome fruit at the rate of 73 g a.i./ha.	
4) Control of flyspeck (*Zygophiala jamacaicensis*) on pome fruit at the rate of 73 g a.i./ha.	
5) Control of quince rust (*Gymnosporangium clavipes*) on pome fruit at the rate of 73 g a.i./ha.	
6) Control of sooty blotch *(Gloeodes pomigena)* on pome fruit at the rate of 73 g a.i./ha.	
7) Control of alternaria early blight (*Alternaria solani*) on tuberous and corm vegetables at the rates of 73 - 128 g a.i./ha.	Supported with no aerial application. Accepted as proposed on potato, Chinese artichoke, Jerusalem artichoke, edible canna, chufa and sweet potato.
8) Control of cercospora leaf spot (*Cercospora beticola*) on sugar beet at the rates of 73 - 128 g a.i./ha.	Supported as proposed.
9) Control of powdery mildew (*Erysiphe polygoni*) on sugar beet at the rates of 73 - 128 g a.i./ha.	

Table 14 Use (label) Claims Proposed by Applicant and Conditionally Accepted

Proposed claim	Conditionally Accepted VSAD claim
1) Control of alternaria diseases (*Alternaria* spp.) on brassica (Cole) leafy vegetables at the rates of 91 - 128 g a.i./ha.	Supported for alternaria blight (*Alternaria brassicae*) only.
2) Control of powdery mildew (*Erysiphe polygoni*) on brassica (Cole) leafy vegetables at the rates of 91 - 128 g a.i./ha.	Supported as proposed.
3) Control of purple blotch (*Alternaria porri*) on bulb vegetables at the rates of 91 - 128 g a.i./ha.	
4) Control of powdery mildew (*Sphaerotheca fuliginea, Erysiphe cichoracearum*) cucurbit vegetables at the rates of 91 - 128 g a.i./ha.	Supported for *Sphaerotheca fuliginea* only on cucurbit vegetables crop group (citron melon, field cucumber, gherkin, edible gourd, Chinese waxgourd, *Momordica* spp., muskmelons, pumpkin, summer squash, winter squash and watermelon).

Proposed claim	Conditionally Accepted VSAD claim
5) Control of gummy stem blight (*Didymella bryoniae*) on cucurbit vegetables at the rates of 91 - 128 g a.i./ha.	Supported as suppression, rather than control on cucurbit vegetables crop group (citron melon, field cucumber, gherkin, edible gourd, Chinese waxgourd, *Momordica* spp., muskmelons, pumpkin, summer squash, winter squash and watermelon).
6) Control of powdery mildew (*Uncinula necator*) on grape at the rates of 73 - 128 g a.i./ha.	Supported only at 73 g a.i./ha.
7) Control of anthracnose (*Colletotrichum* spp.) on fruiting vegetables at the rates of 73 - 128 g a.i./ha.	Supported for *Colletotrichum acutatum* only at 128 g a.i./ha.
8) Control of powdery mildew *(Podosphaera leucotricha)* on pome fruits at the rate of 73 g a.i./ha.	Supported as suppression, rather than control on pome fruit crop group (apple, crab apple, pear, oriental pear and quince).
9) Control of scab (*Venturia inaequalis, Venturia pirina*) on pome fruits at the rate of 73 g a.i./ha.	Supported as proposed.

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

With the exception of the additional commodities from the newly expanded Crop Groups 8-09 (Fruiting Vegetables) and 11-09 (Pome Fruits), the specified MRLs for crop commodities are the same as those in the USA. The Canadian MRL for liver of cattle, goat, horse, hog and sheep differs from the tolerance established in the USA for this commodity (40 CFR Part 180). Canadian MRLs do differ from the MRLs established by Codex (Codex MRLs) for certain commodities (see Table 1).

Table 1 Differences Between MRLs in Canada and in Other Jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)	Codex* (ppm)
Broccoli	1.9 (*Head and stem Brassica subgroup 5A)*	1.9 (*Brassica head and stem, subgroup 5A)*	0.1
Brussels sprouts			0.2
Cabbages, head			0.2
Cauliflower			0.2
Liver of cattle, goat, horse, hog and sheep	0.1	0.2	0.2 *(edible offal (mammalian))*
Grapes	4.0	4.0	0.1

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

MRLs 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, Canada, the USA 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.

Appendix III Crop Groups: Numbers and Definitions

Crop Group Number	Name of the Crop Group	Commodity
CG3-07A	Bulb Onion Subgroup	Garlic, great headed garlic, dry bulb onions, shallot bulbs, potato onions, daylilies, fritillaria bulbs, serpent garlic, lilies, Chinese onions, pearl onions
CG3-07B	Green Onion Subgroup	Leeks, green onions, Welch onion tops, shallot leaves, fresh chive leaves, fresh Chinese chive leaves, elegans hosta, fritillaria leaves, kurrats, Lady's leeks, Beltsville bunching onions, fresh onions, macrostem onions, Tree onion tops, wild leeks
CG5A	Head & Stem Brassica Subgroup	Broccoli, chinese broccoli, brussel sprouts, cabbages, Napa Chinese cabbages, Chinese mustard cabbages, cauliflower, kohlrab
CG5B	Leafy Brassica greens Subgroup	Broccoli raab, bok choy Chinese cabbages, collards, kale, mustard greens, mustard spinach, rape greens
CG9	Curcurbit Vegetables	chayote fruit, Chinese waxgourds, citron melons, cucumbers, West Indian gherkins, edible gourds (other that those listed in this item), balsam apples, balsam pears, Chinese cucumbers, cantaloupes, muskmelons (other that those listed in this item), pumpkins, summer squash, winter squash, watermelons

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A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

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