Proposed Re-evaluation Decision PRVD2021-06

Difenoconazole and Its Associated End-use Products

Consultation Document

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Proposed re-evaluation decision for difenoconazole and associated end use products

Under the authority of the *Pest Control Products Act,* all registered pesticides must be re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports and other regulatory agencies. Health Canada applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Difenoconazole is a systemic fungicide registered for the control of a wide range of fungal diseases on diverse field crops, fruits and vegetables, and turf. Currently registered products containing difenoconazole can be found in the Pesticide Label Search and in Appendix I.

This document presents the proposed re-evaluation decision for difenoconazole, including the proposed amendments (risk mitigation measures) to protect human health and the environment, as well as the science evaluation on which the proposed decision is based. All products containing difenoconazole that are registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period[1], during which the public (including the pesticide manufacturers and stakeholders) may submit written comments and additional information to PMRA Publications. The final re-evaluation decision will be published after taking into consideration the comments and information received during the consultation period.

Proposed re-evaluation decision for difenoconazole

Under the authority of the *Pest Control Products Act* and based on an evaluation of available scientific information, Health Canada is proposing continued registration of difenoconazole and all associated end-use products registered for sale and use in Canada.

With respect to human health, occupational and postapplication risks were shown to be acceptable when difenoconazole is used according to proposed conditions of registration, which include new mitigation measures, such as updated engineering controls, personal protective equipment, statements reducing potential drift and hazard statements on seed tags. Dietary risks were shown to be acceptable when used according to current conditions of registration.

Based on available scientific information, potential risks to the environment were shown to be acceptable when difenoconazole is used according to the proposed conditions of registration, which includes new mitigation measures such as additional precautionary label statements and spray buffer zones.

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

Difenoconazole controls a wide range of fungal diseases on different field crops, fruits, vegetables and turf as a foliar spray, post-harvest spray and as a seed treatment. It is of particular importance for the control of Fusarium dry rot in potato as there are few registered alternative active ingredients to manage this storage pathogen.

Risk mitigation measures

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment and must be followed by law. The proposed label amendments including any revised/updated label statements and/or mitigation measures, as a result of the re-evaluation of difenoconazole, are summarized below. Refer to Appendix VIII for details.

Human health

As a result of the re-evaluation of difenoconazole, the PMRA is proposing additional risk-reduction measures to minimize the potential human health risks. Additional revisions to the difenoconazole labels are proposed to update label statements to current policies and language.

Risk mitigation:

To protect workers, the general population and animals, the following risk-reduction measures are proposed:

- Corn, canola, rapeseed, mustard seed treatment
    - Closed transfer systems for commercial treatment
- Cereal seed treatment
    - Chemical-resistant coveralls for cleaners for commercial treatment
    - Closed cab planters
    - Coveralls when loading seed for planting
- Add statements to labels and seed tags to keep products out of reach of children and animals.
- Add statements to promote best management practices to minimize human exposure from spray drift or spray residues resulting from drift.

Environment

Risk mitigation:

To protect the environment, the following risk-reduction measures are proposed:

- Precautionary label statements to inform users of the potential hazard to beneficial arthropods, non-target terrestrial plants and aquatic organisms.
- Add label statement to inform users of the potential hazard to birds and small wild mammals where spilled or exposed treated seed must be incorporated into the soil or removed.

- Update terrestrial and aquatic spray drift buffer zones to protect non-target terrestrial plants and aquatic organisms.
- Add label statement to indicate the potential for carryover.

International context

Difenoconazole is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including the United States and the European Union. No decision by an OECD member country to prohibit all uses of difenoconazole for health or environmental reasons has been identified as of 6 November 2020.

Next steps

Upon publication of this proposed re-evaluation decision, the public, including the registrants and stakeholders are encouraged to submit additional information that could be used to refine risk assessments during the 90-day public consultation period.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of re-evaluation decision document,[2] which could result in revised risk mitigation measures. The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with Health Canada's responses.

Refer to Appendix I for details on products impacted by this proposed decision.

Additional scientific information

No additional scientific data are required at this time.

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

Science evaluation

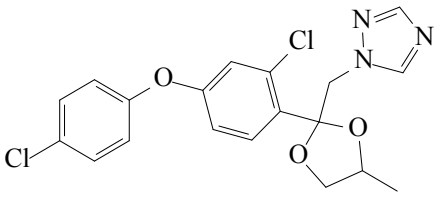
1.0 Introduction

Difenoconazole is a systemic fungicide registered for the control of a wide range of economically important fungal diseases on diverse field crops, fruits and vegetables, and turf. Appendix I lists all difenoconazole products that are registered under the authority of the *Pest Control Products Act*.

As described in the Re-evaluation Project Plan for Difenoconazole (REV2018-14), existing assessments of uses except seed treatments were considered to be adequate to the support the re-evaluation. Therefore, the re-evaluation was comprised of new assessments of toxicology for the human health assessment as well as dietary and occupational exposure, and environment assessments for seed treatment uses. Spray buffer zones and label standards were updated for foliar applications.

2.0 Technical grade active ingredient

2.1 Identity

Common name		Difenoconazole
Function		Fungicide
Chemical Family		Triazole
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	1-({2-[(2Ξ,4Ξ)-2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl}methyl)-1*H*-1,2,4-triazole OR 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-yl]methyl]-1*H*-1,2,4-triazole
CAS Registry Number		119446-68-3
Molecular Formula		$C_{19}H_{17}Cl_2N_3O_3$
Structural Formula		
Molecular Weight		406.3

Registration Number	Purity of the Technical Grade Active Ingredient
25631	95%
33568	96.91%

2.2 Physical and chemical properties

Property	Result
Vapour pressure at 25°C	3.3×10^{-5} mPa
Ultraviolet (UV) / visible spectrum	No absorption observed beyond 300 nm
Solubility in water at 25°C	15 mg/L
n-Octanol/water partition coefficient at 25°C	log K_{ow} = 4.4
Dissociation constant	pKa = 1.1 for the conjugate base

3.0 Human health assessment

3.1 Toxicology summary

Difenoconazole, also known as CGA-169374, belongs to the triazole group of chemicals. A detailed review of the toxicology 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 international testing protocols and Good Laboratory Practice. The toxicology assessment for difenoconazole also considered information found in the published scientific literature and newly available mode of action studies. The scientific quality of the data is acceptable and the database is considered adequate to characterize the potential health hazards associated with difenoconazole.

Absorption and excretion of single or repeat low oral gavage doses of triazole- or phenyl-radiolabelled difenoconazole was extensive and rapid in both sexes of rats. Peak plasma concentrations were reached within two hours of dosing. Most of the administered dose (AD) was eliminated in the excreta within 48 hours, with elimination essentially complete by 96 hours. The fecal route was the predominant route of excretion, primarily via bile, though urinary excretion was also significant. Following administration of single high oral gavage doses, lower elimination via bile and urine and higher elimination via feces, were observed. The half-life of elimination was 20 hours or 33–48 hours, for the low and high dose levels, respectively, with enterohepatic recirculation involved in re-absorption of biliary metabolites. Thus, the rate and the extent of absorption was lower following the administration of high compared to low oral gavage doses.

Total tissue residues seven days post-administration accounted for trace amounts of the AD, with the highest radiolabel found in the liver, plasma, adrenal glands and carcass. Single or repeat dosing did not alter elimination profiles; however, minor sex-related differences in metabolism were observed, with slightly faster absorption and elimination of the AD in females than in males.

Eleven metabolites were isolated from urine and feces, including two sulfonated metabolites identified in urine, indicating that difenoconazole was extensively metabolized. The proposed metabolic pathway of difenoconazole involves 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. Unchanged difenoconazole was not detected in the tissue or excreta, regardless of the dosing regimen.

Difenoconazole was of slight acute oral toxicity in rats. It was of low acute dermal and inhalation toxicity in rats. Difenoconazole was mildly irritating to the eyes and minimally irritating to the skin of rabbits and did not cause skin sensitization in guinea pigs using the Buehler test method. Two difenoconazole metabolites (CGA205374 and CGA205375) identified in the rat metabolism study were tested in acute oral toxicity studies in mice and found to exhibit low toxicity.

Short-term repeat dose dietary toxicity studies in mice, rats and dogs with difenoconazole revealed the liver to be the principal target organ of toxicity. Mice treated with difenoconazole displayed liver toxicity ranging from increased weights, hepatocellular enlargement and vacuolation, to focal/multi-focal single cell hepatocellular necrosis. Liver effects in treated rats were limited to increased 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 difenoconazole resulted in reduced body weight and food consumption, increased liver weights and, at higher dose levels, lenticular cataracts.

Short-term dermal administration of difenoconazole to rats, at the limit dose of testing, produced dermal irritation at the test site. There were only minor changes in the liver and some slight changes in related clinical chemistry parameters. However, short-term dermal administration of difenoconazole in rabbits resulted in severe signs of dermal irritation at lower dose levels than in the rat. Systemic toxicity, such as decreased body weight and hepatocyte vacuolation, was also noted in rabbits at the limit dose of testing.

Difenoconazole did not induce unscheduled DNA synthesis in vitro and produced negative results in a bacterial reverse mutation assay. Three chromosomal aberration studies were available, two in Chinese hamster ovary (CHO) cells and one in human lymphocytes. The studies with CHO cells yielded equivocal results, in that they were judged to be significant in one trial in each study, but the results could not be confirmed in a second independent trial. The study on chromosomal aberrations in human lymphocytes gave negative results and in an in vivo mouse micronucleus assay study, difenoconazole was also negative. The weight of evidence suggested that difenoconazole was not genotoxic. Three metabolites (CGA205375, CGA205374 and CGA189138), which were identified in the rat metabolism study, generated negative results in bacterial reverse mutation assays.

In a rat dietary chronic toxicity/carcinogenicity study, administration of difenoconazole resulted in decreased body weights, body weight gains and food consumption, as well as hepatocellular hypertrophy. There was no evidence of oncogenicity in rats. In a mouse dietary chronic toxicity/carcinogenicity study, significant liver toxicity was observed, including single cell necrosis, bile stasis, and fatty change. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas, concurrent with pronounced liver toxicity, were observed in male and female mice at the two highest dose levels. In females, significant premature mortality was also observed at these two dose levels. Thus, it was determined that the maximum tolerated dose (MTD) in females was exceeded at the tumourigenic dose levels.

The registrant proposed a constitutive androstane receptor (CAR)-mediated mode of action (MOA) for the formation of hepatocellular adenomas and carcinomas in mice. The data provided for the key events were largely consistent with the established MOA for CAR-mediated liver tumour formation. Activation of CAR nuclear receptor and altered gene expression secondary to CAR activation, as well as increased CYP450 enzyme activity levels, followed by increased hepatocyte hypertrophy and cell proliferation, were observed in the mechanistic studies. Hepatic vacuolation, fatty liver change, and biliary stasis, which are indicative of alteration in liver function and consistent with this MOA, were also noted in repeat-dose dietary toxicity studies in mice. All these observations occurred with dose and temporal concordance. This MOA was further supported when difenoconazole was tested in CAR knockout (KO) mice; these animals were refractory to the markers of the early key events of the MOA observed in the wildtype mice. Additionally, the available data supported the exclusion of alternative MOAs. For example, mechanistic studies examining specific enzyme activity levels demonstrated that difenoconazole did not activate aryl hydrocarbon receptor (AhR) or peroxisome proliferator-activated receptor alpha (PPARα). Evidence of cytotoxicity, such as changes in relevant clinical chemistry parameters and/or increased diffuse hepatic necrosis, was also not observed in the database. Some inconsistencies and uncertainties were noted in the data assessed to support the proposed CAR MOA. For example, the enzyme induction was not always consistent across the in vivo and in vitro data, and an increased incidence of hepatocellular altered foci was not observed in the database, a key event in the CAR MOA that typically precedes tumour formation. However, despite the remaining uncertainties, the available data were considered sufficient to support the proposed MOA in mice and a threshold approach to cancer risk assessment.

In a dietary 2-generation reproductive toxicity study in rats, decreased body weight and food consumption were noted in the parental and the offspring generations at the high dose level. However, F_1 offspring also demonstrated decreased body weight on post-natal day (PND) 21 at the mid-dose level, in the absence of parental toxicity. Reproductive toxicity was noted only at the highest dose level in this study, which consisted of decreased birth weight in F_1 pups. Due to the age of the 2-generation reproductive toxicity study, endpoints such as ovarian follicle counts, estrous cycle length and periodicity, or sperm parameters (motility and morphology), were not assessed.

In a gavage rat developmental toxicity study, difenoconazole exposure resulted in body weight loss, decreased body weight gain and food consumption, and increased clinical signs of toxicity, such as salivation, in the dams at the two highest dose levels. Body weight loss and increased salivation were noted within the first few days of treatment. At the highest dose level tested,

there were fewer fetuses per dam, an increased number of resorptions and an increase in post-implantation loss. At this same dose level, the fetuses showed slight increases in incidences of skeletal variations, such as increased incidence of bifid or unilateral ossification of thoracic vertebrae. In a gavage rabbit developmental toxicity study, significant maternal toxicity in dams in the form of drastically reduced body weight gain and food consumption was observed at the highest dose level tested. Body weight loss during the first few days of treatment and increased post-implantation loss, resorptions and abortions were also observed at the same dose level. Overall, these two studies showed the same pattern of maternal and developmental toxicity, with no evidence of treatment-related malformations or sensitivity of the young in either rats or rabbits.

The neurotoxic potential of difenoconazole was examined in rats following acute or short-term exposure. Several clinical signs were observed in the acute gavage dose range-finding and main 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 foot-splay reflexes, and stability and visual placing responses. Forelimb grip strength was decreased in males on the day of dosing. Decreased body weight and food consumption were noted during short-term dietary dosing, and males exhibited decreased hind limb grip strength. While these combined effects are suggestive of neurotoxicity, they are also commonly associated with general malaise following treatment. Additionally, there was no corroborating neuropathology in either study at any dose level. Overall, the reported results provide equivocal evidence of neurotoxicity. A developmental neurotoxicity (DNT) study waiver request was accepted based on lack of clear expression of neurotoxicity, lack of consistency of the observed effects such as either forelimb or hindlimb strength being affected, and an absence of neurotoxic effects in other endpoints assessed (motor activity, functional observational battery, and time to tail flick).

The immunotoxic potential of difenoconazole was examined in a short-term dietary immunotoxicity study in female mice in which animals were immunized with sheep red blood cells (RBC). Liver toxicity comprised of hepatocyte vacuolation and hypertrophy, as well as decreased serum sheep RBC specific IgM levels were noted at the mid- and high-dose levels. Additionally, necrosis in the liver was observed at the highest dose level. Histopathological examination of immune system-related tissues and organs was limited to the spleen in control and high dose level groups; thymus was not examined in any group. Overall, this study provided evidence of immunotoxicity based on decreased sheep RBC specific IgM levels.

The identity of select difenoconazole rat metabolites is presented in Table 1 of Appendix II. The toxicology reference values for use in the human health risk assessment are summarized in Appendix II, Table 2.

3.1.1 *Pest Control Products Act* hazard characterization

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

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

With respect to potential prenatal and postnatal toxicity, in the rat two-generation reproductive toxicity study, there were no reproductive or offspring effects apart from decreased pup body weight and body weight gains. The only indication of increased sensitivity of the offspring in this study included marginally decreased body weight in the F_1 pups noted on PND 21 in the absence of parental toxicity at the mid-dose level. However, since this effect was observed only in the F_1 pups and at a time period when young animals are close to weaning and potentially exposed to the test chemical via both the diet and the milk, the level of concern was low. Increases in the mean number of resorptions and post-implantation loss were observed in the rat and rabbit developmental toxicity studies at dose levels causing significant maternal toxicity. At the same dose levels, increased incidences of skeletal variations in the fetuses in the rat and increased abortions in the rabbit were noted.

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 significant maternal toxicity. The *Pest Control Products Act* factor (PCPA factor) was reduced to threefold for scenarios in which this endpoint was used for risk assessment. For all other scenarios, the PCPA factor was reduced to onefold.

3.2 Dietary exposure and risk assessment

In a dietary exposure assessment, Health Canada determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to difenoconazole from potentially treated imports is also included in the assessment. These dietary assessments are age-specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

Health Canada considers limiting use of a pesticide when risk exceeds 100% of the reference dose. Health Canada's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed risk assessment procedures.

Residue estimates used in the dietary risk assessment (DRA) may be based conservatively (in other words, are high-end estimates) on the maximum residue limits (MRL) or the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency's (CFIA) National Chemical Residue Monitoring Program

and the United States Department of Agriculture Pesticide Data Program (USDA PDP). Specific and empirical processing factors as well as specific information regarding percent of crops treated may also be incorporated to the greatest extent possible.

Sufficient information was available to adequately assess the dietary risk from exposure to difenoconazole. Acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM–FCID™, Version 4.02, 05-10-c) program, which incorporates food consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the years 2005-2010 available through the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS).

Further details on the consumption data are available in Health Canada's Science Policy Note SPN2014-01, *General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments*.

Information on the residue chemistry of difenoconazole is available in the published documents, PRDD99-01 and ERC2011-06. Canadian MRLs for difenoconazole are specified for over 300 plant and animal commodities ranging from 0.01 ppm (cereals, corn, milk) to 35 ppm (leafy greens). The current enforcement residue definition for all plant crops is the parent difenoconazole. For all livestock commodities, the residue definition is the parent plus the metabolite CGA205375. The current MRLs and enforcement residue definition for difenoconazole can be found on the Pesticides section of the Canada.ca website. No changes are being proposed as a result of this re-evaluation.

The residue definition in drinking water (for risk assessment) is expressed as the sum of parent difenoconazole and its major transformation product, CGA205375.

Difenoconazole is a triazole-based fungicide. All triazole-based fungicides share common metabolites resulting from the release of the triazole ring (1,2,4-triazole) from the parent compound and its subsequent conjugation to produce triazolylacetic acid (TAA) and triazolylalanine (TA). Due to their intrinsic toxicological properties, residue chemistry and human health risks associated with these metabolites (resulting from the use of all registered triazole-based fungicides) will be assessed separately and not as part of the re-evaluation of difenoconazole (Refer to Section 3.6).

3.2.1 Determination of acute reference dose

Acute reference dose (females 13–49 years of age)

To estimate acute dietary risk in females 13–49 years of age, the rabbit gavage 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 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 were applied. As discussed in the *Pest Control Products Act*

Hazard Characterization section, the PCPA factor was reduced to threefold. **Thus, the composite assessment factor (CAF) is 300.**

The ARfD (females 13–49 years of age) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{25 \text{ mg/kg bw}}{300} = 0.08 \text{ mg/kg bw of difenoconazole}$$

Acute reference dose (general population – excluding females 13–49 years of age)

To estimate acute dietary risk for the general population, the rat gavage 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 were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to 1-fold. **Thus, the CAF is 100.**

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

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{25 \text{ mg/kg bw}}{100} = 0.3 \text{ mg/kg bw of difenoconazole}$$

3.2.2 Acute dietary exposure and risk assessment

The acute dietary risk was calculated considering the highest ingestion of difenoconazole that would be likely on any one day, and using food and drinking water consumption and residue values. The expected intake of residues is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARfD, the acute dietary exposure has been shown to be acceptable.

Acute food residue estimates for difenoconazole were based on Canadian and/or American highest average field trial (HAFT) residues, Canadian MRLs, American Tolerances, Codex MRLs, and anticipated residues in animal commodities. MRLs and Tolerances were used for crops which Health Canada did not have adequate field trial data. Residues in drinking water were taken from drinking water environmental estimated concentrations (EECs) from modelling based on the turf use as discussed in Section 3.3. Default or available experimental processing factors were applied for relevant processed commodities. The assessment considered all foods that may potentially be treated with difenoconazole including foods that may be treated in other countries and imported to Canada. All commodities were assumed to be 100% treated.

The acute dietary risk assessment was conducted for the general population and all population subgroups. The acute dietary exposure from food and drinking water for the general population, excluding females aged 13–49 years, ranged from 4% to 16% of the ARfD, with children 1–2 years old being the most exposed subpopulation.

The acute dietary exposure from food and drinking water for females aged 13–49 years was 18% of the ARfD (Appendix III, Table 1). Therefore, acute dietary risk is shown to be acceptable for difenoconazole.

3.2.3 Determination of acceptable daily intake (ADI)

To estimate dietary risk from repeated dietary exposure, the rat dietary 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, increased hepatocellular hypertrophy and decreased body weight gain and body weight 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 were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold. **Thus, 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 ADI provides a margin of 4600 to the NOAEL for the hepatocellular tumours in male mice.

3.2.4 Cancer assessment

In the mouse oncogenicity study, treatment-related liver adenomas and carcinomas were observed in male and female mice. Despite some uncertainties, the available data were considered sufficient to support the proposed MOA of CAR nuclear receptor-mediated hepatocarcinogenesis in mice, and a threshold approach to the cancer risk assessment. The liver tumours in female mice occurred at dose levels exceeding MTD and were, therefore, not considered relevant to the cancer risk assessment. The ADI provides a sufficient margin (4600) for the liver tumours in male mice.

3.2.5 Chronic dietary exposure and risk assessment

Generally, the chronic (cancer and non-cancer) dietary risk (from food and drinking water) is calculated using the average consumption of different foods and drinking water, and the average residue values on those foods and drinking water. For difenoconazole specifically, the average consumption values were used. However, for refinement purposes, median residue values from field trials were used and average residue values from monitoring data were used as noted below. The estimated exposure is then compared to the ADI, which is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects. When the estimated exposure is less than the ADI, then chronic dietary exposure (cancer and non-cancer) is shown to be acceptable.

Initially, the chronic dietary (food only) assessment was conducted using the following inputs: Canadian and/or American median residues from field trials, anticipated residues in animal commodities, and Canadian MRLs, American Tolerances, Codex MRLs; default or available experimental processing factors for relevant processed commodities; and 100% crop treated. MRLs and Tolerances were used for crops which Health Canada did not have adequate field trial data. The assessment considered all foods that may potentially be treated with difenoconazole including foods that may be treated in other countries and imported to Canada.

The chronic dietary risk assessment was conducted for the general population and all population subgroups. The initial chronic food-only dietary exposure for all populations ranged from 22% to 86% of the ADI. The highest exposed population subgroup was children 1–2 years old. As per standard procedure, since exposure from food only was greater than 80% for a population subgroup, Health Canada conducted a second, more refined, chronic assessment. A critical commodity analysis (CCA) was conducted to determine which foods contributed the most to the exposure of children 1–2 years old. These foods were: apples, potatoes, apple sauce, grapes, and pears.

The refined assessment was conducted using CFIA monitoring data (2013–2017) for apples, potatoes, grapes, and pears. In addition, for these monitored commodities available information on the proportion of domestic production and import supply was applied. The refined chronic food-only dietary exposure for all populations ranged from 10% to 28% of the ADI.

Chronic dietary exposure from both food and drinking water was determined by incorporating drinking water environmental estimated concentrations (EECs) from modelling based on the turf use as discussed in Section 3.3. Exposures for all populations ranged from 12% to 30% of the ADI and therefore chronic dietary risk (cancer and non-cancer) was shown to be acceptable.

3.3 Exposure from drinking water

Combined residues of difenoconazole and its major transformation product in potential drinking water sources were estimated from modelling.

3.3.1 Concentrations in drinking water

Estimated environmental concentrations (EECs) were based on combined residues of difenoconazole and the transformation product, CGA205375, in drinking water sources in Canada. EECs were calculated using the Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS) models on a standard Level 1 scenario, a small reservoir. EECs in groundwater were calculated using the PRZMGW model. All scenarios were run using 50-year weather data. Two use patterns for difenoconazole were modelled based on the possible use patterns for turf application: 2 × 245 g a.i./ha at a 14-day interval, and 1 × 250 g a.i./ha. These EECs cover any use of difenoconazole on turf with a maximum annual rate of 490 g a.i./ha and a maximum single application of 250 g a.i./ha, and the use of difenoconazole on crops to a maximum annual rate of 512 g a.i./ha.

Level 1 EECs are presented in Table 3.3.1. The daily surface water EEC for difenoconazole (16 µg/L) was used in the acute assessment, and the yearly groundwater EEC (8.4 µg/L) was used for the chronic assessment.

Table 3.3.1 Level 1 Estimated environmental concentrations (EECs) of difenoconazole in drinking water

Crop and annual application rate	Active Ingredient (Residue definition in water)	Groundwater[5] (µg a.i./L)		Surface Water (µg a.i./L)	
				Reservoir	
		Acute[1]	Chronic[2]	Acute[3]	Chronic[4]
Turf 2 × 245 g a.i./ha 14-day interval These EECs also cover one application per year at 250 g a.i./ha and a maximum yearly application of 512 g a.i./ha	Difenoconazole and CGA205375	8.5	**8.4**	**16**	6.3

[1] 90th percentile of daily average concentrations
[2] 90th percentile of yearly average concentrations
[3] 90th percentile of yearly peak concentrations
[4] 90th percentile of yearly average concentrations
[5] Groundwater EECs were generated for use expansion submissions (2009-1720, 2009-1722).

3.3.2 Drinking water exposure and risk assessment

Exposure from drinking water and food sources were combined to determine the total dietary exposure and risk. Refer to Sections 3.2.2 and 3.2.5 for additional details.

3.4 Occupational and non-occupational exposure and risk assessment

Occupational and non-occupational (residential) risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies being used to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the MOE is greater than the target MOE, then risk mitigation is not required. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

3.4.1 Toxicology reference values for occupational and non-occupational exposure

3.4.1.1 Short- and intermediate-term dermal and inhalation (occupational exposure scenario)

The available dermal toxicity studies did not assess the relevant endpoints of concern (post-implantation loss). A short-term inhalation toxicity study was not available.

For short- and intermediate- term exposure via the dermal and inhalation routes, the NOAEL of 25 mg/kg bw/day from the rabbit gavage developmental toxicity study was selected for risk assessment. Developmental toxicity was observed in this study in the form of increased post-implantation loss and number of resorptions per dose, as well as abortions.

The target MOE is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a factor of threefold for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section. The selection of this study and target MOE is considered to be protective of all worker populations including women who may be pregnant or nursing.

The NOAEL of 2 mg/kg bw/day for body weight effects on PND 21 in F_1 pups identified in the 2-generation reproductive toxicity study was lower than the NOAEL determined in the rabbit developmental toxicity study. However, the selection of this study and the endpoint was not deemed appropriate because the decreased body weight at the LOAEL in F_1 pups was noted only at the end of the weaning period when young animals are potentially exposed to the test chemical via both the diet and the milk.

3.4.1.2 Short- and intermediate-term dermal (non-occupational exposure scenarios)

A short-and intermediate-term residential risk assessment for children 6 to <11 years of age was undertaken. The 22-day dermal toxicity study in rabbits with a NOAEL of 100 mg/kg bw/day was selected. At the LOAEL of 1000 mg/kg bw/day, evidence of systemic toxicity characterized by decreased body weight gain and body weight loss was observed. The target MOE is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold.

A short-and intermediate-term residential risk assessment for general population, excluding the children 6 to <11 years of age, was also undertaken. The rabbit gavage developmental toxicity study with a NOAEL of 25 mg/kg bw/day was selected for risk assessment since the available dermal toxicity studies did not assess the relevant endpoints of concern (post-implantation loss). At the LOAEL of 75 mg/kg bw/day, developmental toxicity was observed in this study in the form of increased post-implantation loss and number of resorptions per dose, as well as abortions. At the same dose level, evidence of systemic toxicity characterized by decreased body weight gain and body weight loss was also observed.

The target margin of exposure (MOE) is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a PCPA factor of threefold as discussed in the *Pest Control Products Act* Hazard Characterization section. The selection of this study and target MOE is considered to be protective of all populations including pregnant women and their unborn children.

3.4.1.3 Cancer assessment

See Section 3.2.4.

3.4.1.4 Dermal absorption

For the assessment, the dermal absorption value was selected from the rat in vivo study based on current practices and policies. A dermal absorption value of 36% was determined for difenoconazole.

3.4.2 Non-occupational exposure and risk assessment

Since there are no domestic-class products containing difenoconazole are registered, a residential handler (mixer/loader/applicator) exposure is not anticipated. However, there is a potential for non-occupational exposure to difenconazole residues on treated golf courses (golfers), pome fruit trees in residential areas, and during commercial applications (bystanders).

3.4.2.1 Golf course turf

Difenoconazole is non-volatile (2.5×10^{-10} mmHg at 25°C), and postapplication inhalation exposure of golfers is considered negligible provided entry by golfers occurs when spray residues have settled and dried as required on current labels (PRD2015-10). Dermal exposure was estimated for adults (16+), youth (11 to <16), and children (6 to <11) on the day of the last application using default transferable turf residue values, appropriate transfer coefficients, and standard body weight assumptions. Calculated MOEs were greater than the target MOE. Based on the above the potential risk is considered to be acceptable under current conditions of use. No additional mitigation measures are proposed.

3.4.2.2 Pome fruit trees in residential areas

Based on the registered use pattern, individuals could potentially be exposed via the dermal route following commercial application of difenoconazole to pome fruit trees in residential areas. Adults (> 16 years old) and children (6 to 11 years old) were chosen as the index life stages to assess. Postapplication residential exposure to difenoconazole is expected to be short-term in duration (that is, less than 30 days of continuous exposure). It was assumed that individuals would enter previously treated areas on the same day the pesticide is applied. Adults and children have the potential for postapplication dermal exposure. Postapplication inhalation exposure while performing activities in previously treated fruit trees is expected to be low for difenoconazole due to low vapour pressure and the expected dilution in outdoor air. Also, inhalation of spray droplets will be limited since entry to treated residential areas must occur after spray residues have dried. To estimate postapplication dermal exposure, activity-specific transfer coefficients (TCs) from the United States Environmental Protection Agency (USEPA)

2012 Residential Standard Operating Procedures (SOPs) for activities conducted on residential fruit trees were used. The calculated MOEs exceeded the target MOEs for difenoconazole for all scenarios (MOEs were greater than 9000 for adults and greater than 20,000 for 6 to 11 years old). These MOEs are significantly above the target MOE, and thus, potential exposure risk to pome fruit trees treated in residential areas is considered to be acceptable.

3.4.2.3 Bystanders

To minimize spray drift from agricultural uses and golf course uses for potential bystander exposure, spray drift statements are currently on all products registered for agricultural uses and the potential risk to bystanders is considered acceptable under current conditions of use. Updates to spray drift statements are proposed to meet current labelling standard (Appendix VIII).

With respect to post-harvest treatment, bystander exposure should be negligible since the potential for drift is expected to be minimal. Standard drift statements are proposed to the products registered for post-harvest treatment and golf course uses to minimize potential spray drift (Appendix VIII).

3.4.3 Occupational exposure and risk assessment

3.4.3.1 Mixer, loader and applicator exposure and risk

Workers can be exposed to difenoconazole through mixing, loading and applying the pesticide. Based on the registered use pattern, mixer/loader/applicator exposure to difenoconazole is expected to occur via the dermal and inhalation routes and to be of short- to intermediate-term duration.

Exposure of workers was estimated using unit exposure values from the Pesticide Handlers Exposure Database and/or the Agricultural Handler Exposure Task Force data, and a dermal absorption factor for a route-to-route extrapolation. Assumptions included the default area treated per day values and workers wearing current label personal protective equipment.

3.4.3.1.1 Foliar and turf application exposure and risk assessment

For mixers/loaders and applicators using groundboom, aerial, airblast, turf gun or chemigation equipment, the estimated combined MOEs (dermal plus inhalation) exceed the target MOE of 300 based on currently registered use pattern (ERC2011-06 and PRD2015-10). On this basis, risks to mixers/loaders and applicators involved in foliar applications to all agricultural crops and turf (golf course) are considered to be acceptable under current conditions of use. No additional mitigation measures are proposed.

3.4.3.1.2 Post-harvest application exposure and risk assessment

For workers involved in post-harvest treatment the estimated combined (dermal plus inhalation) MOEs exceed the target MOE of 300. On this basis, potential risks for workers mixing, loading, and applying difenoconazole as post-harvest treatment to potatoes and pome fruits are considered to be acceptable under current conditions of use. No additional mitigation measures are proposed.

3.4.3.2 Postapplication exposure and risk

Workers can be exposed to difenoconazole when entering a treated site to conduct activities, such as scouting and/or handling of treated crops.

3.4.3.2.1 Foliar and turf postapplication exposure and risk assessment

Based on the registered use pattern, postapplication exposure of workers entering treated fields and golf courses are expected to be short- to intermediate- term and via the dermal route. Inhalation exposure is expected to be minimal assuming at least 12 hours have passed before re-entry and based on difenoconazole's vapour pressure (2.4×10^{-10} mmHg at 25°C).

For workers entering a treated site, restricted-entry intervals (REIs) are calculated to determine the minimum length of time required before workers can enter after application. The REI is the duration of time that must elapse in order to allow residues to decline to a level where risks are considered to be acceptable for postapplication worker activities.

Exposure of workers entering treated sites was estimated using activity-specific transfer coefficients (TCs), a dermal absorption factor, and default dislodgeable residue (DFR) or turf transferrable residue (TTR) values. Additional assumptions included an 8-hour workday for all activities and an average worker body weight.

For workers entering treated sites (agricultural fields/orchards or golf courses), the estimated MOEs are above the target MOE of 300 assuming the currently required REIs (ERC2011-06). On this basis, the potential risks for postapplication workers entering treated sites (agricultural fields and golf courses) are considered to be acceptable under current conditions of use. No additional mitigation measures are proposed.

3.4.3.2.2 Post-harvest treatment exposure and risk assessment

Postapplication exposure of workers in post-harvest facilities is expected to be short- to intermediate- term and via the dermal route. Inhalation exposure is expected to be minimal based on difenoconazole's vapour pressure (2.4×10^{-10} mmHg at 25°C).

Dermal exposure was estimated using current label application rates, MRL, and surrogate transfer co-efficient from the Agricultural Re-entry Task Force database, a dermal absorption factor, standard assumptions included an eight hours working day and an average worker body weight.

For workers exposed to treated commodities (for example, sorting or stacking boxes), the calculated MOEs were above the target MOE of 300 on the day of application. On this basis, the potential risk for postapplication workers handling treated crops is considered to be acceptable under current conditions of use. No additional mitigation measures are proposed.

3.4.3.3 Seed treatment exposure and risk assessment

Commercial and on-farm seed treatment and planting of treated seeds was assessed for the following groups of seeds: cereal seeds (wheat, barley, oats, rye, triticale, sorghum, millet and buckwheat), corn seed (sweet, seed, pop and field), and canola (rapeseed and mustard) seeds. A potato seed piece treatment assessment was not conducted for this re-evaluation as a full assessment was conducted in 2016 with additional assessments completed on individual products after. As a result, potato seed piece product labels were not reviewed during this re-evaluation. The updated dermal absorption value is not expected to significantly impact the risk conclusions of that assessment.

There is potential exposure to mixers, loaders, and applicators when using difenoconazole to treat seeds, and to planters when handling difenoconazole-treated seeds. The following scenarios were assessed:

- Commercial liquid treatment of cereals, corn, and canola (mustard, rapeseed). Activities may include treating, bagging, sewing, stacking, tagging, and cleaning. Includes commercial facilities and mobile treaters
- On-farm liquid seed treatment of cereals and corn followed by planting treated seed
- Planting of commercially treated or imported seed (activities may include loading) for cereals, corn, canola, mustard and rapeseed.

Exposure to workers treating and/or planting seed is expected to be short- to intermediate-term (1 day to <6 months) in duration. On-farm treatment and planting of seeds generally occurs over a period of a few days to up to a few weeks, during spring planting.

Surrogate commercial and on-farm treatment exposure studies, as well as exposure studies for planting treated seeds, were used to estimate worker exposure. For the current difenoconazole assessment, seven worker exposure studies were used to evaluate the seed treatment uses, as noted in Appendix IV. The assessments for each scenario were conducted with the lowest level of personal protective equipment (PPE) used in the relevant surrogate study. These are the best data available for the assessment of worker exposure during the treatment and handling of seeds.

The results of the exposure and risk assessment for the seed treatment scenarios are summarized in Appendix IV.

For the commercial seed treatment scenario, target MOEs were met and risks were shown to be acceptable for all activities and all crops with the minimum study PPE. For corn and canola (mustard, rapeseed), closed mixing/loading is proposed, as data were not available to assess exposure for open mixing/loading. For cereals, open mixing and loading is acceptable, as risks were shown to be acceptable.

For the on-farm seed treatment scenario, target MOEs were met and risks were shown to be acceptable for all crops when considering the minimum study PPE. A closed cab planter was used in all of the on-farm exposure studies. However, as the MOEs were greater than 25 times the target MOE for the corn on-farm treating and planting assessment, an open cab planter would be acceptable for corn.

There is sufficient margin in the corn assessment to address the protection that would be provided by a closed cab. As the MOEs for on-farm treating and planting assessments for cereals were not greater than 25 times the target MOE, a closed cab tractor will be required for cereals.

For farmers loading and planting commercially treated or imported seeds, calculated MOEs exceeded the target MOE and risks were shown to be acceptable for all crops when considering the minimum study PPE. As noted above, a closed cab planter was used in all on-farm exposure studies. However, as the MOEs were greater than 25 times the target MOE for the corn, canola, mustard, and rapeseed planting assessments, a closed cab planter is not required for these crops. A closed cab is required for cereal loading and planting.

As noted above, the assessments for each seed treatment scenario were conducted with the lowest level of PPE used in the relevant surrogate exposure study. In certain cases, the label PPE is higher than the PPE used in the studies. However, as all difenoconazole seed treatment products are co-formulated with other active ingredients, the PPE will not be reduced on the labels, since the label PPE may be required for the co-formulated active ingredients. Additional PPE may also be on current labels due to the acute toxicity of each end-use product. Additional mitigation may be added to the label, where required, to match the mitigation in the exposure study as result of this difenoconazole evaluation. Furthermore, label statements may be updated to meet current standards. Refer to Appendix V for more information.

3.5 Aggregate Exposure and Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation).

3.5.1 Toxicology Endpoint Selection for Aggregate Risk Assessment

3.5.1.1 Short- and intermediate-term aggregate (females 13–49 years of age)

Short- and intermediate-term aggregate exposure to difenoconazole may be comprised of food, drinking water, residential postapplication dermal, and inhalation exposure. A short- and intermediate-term residential and dietary aggregate risk assessment for females 13–49 years of age was undertaken. The available dermal toxicity studies were not considered appropriate for endpoint selection, as they did not assess the relevant endpoint of concern (post-implantation loss). A short-term inhalation study was not available. Therefore, an oral study was used for all routes. The endpoint selected for short- and intermediate-term aggregate risk assessment 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 and abortions were identified.

The target MOE is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a PCPA factor of threefold as discussed in the *Pest Control Products Act* Hazard Characterization section.

3.5.1.2 Short- and intermediate-term aggregate (general population – excluding females 13–49 years of age)

A short-and intermediate-term residential and dietary aggregate risk assessment for the general population, excluding the females 13–49 years of age, was also undertaken. For the dermal component, the 22-day dermal toxicity study in rabbits with a NOAEL of 100 mg/kg bw/day was selected. At the LOAEL of 1000 mg/kg bw/day, evidence of systemic toxicity characterized by decreased body weight gain and body weight loss was observed. Since a short-term inhalation toxicity study was not available, an oral study was used for both oral and inhalation components. The rabbit gavage developmental toxicity study with a NOAEL of 25 mg/kg bw/day was selected. At the LOAEL of 75 mg/kg bw/day, evidence of systemic toxicity characterized by decreased body weight gain and body weight loss was observed. The target MOE is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold.

3.5.2 Residential, non-occupational and dietary aggregate exposure and risk assessment

In an aggregate risk assessment, the combined potential risk associated with food, drinking water and various residential (non-occupational) exposure pathways is assessed. A major consideration is the likelihood of co-occurrence of exposures and durations of exposures. Additionally, only exposures from routes that share common toxicological effects are aggregated. Only those uses and scenarios for which risks are shown to be acceptable are aggregated.

For difenoconazole, aggregate exposures would be expected for adults, youth (11 to < 16 years) or children (6 to <11 years) who would have residential exposure following application to established golf course turf or to residential fruit trees following application by a commercial applicator. This residential exposure would co-occur with dietary exposure from food and drinking water. Exposure would be predominately by the dermal and oral routes. Chronic dietary exposure was based on the refined chronic dietary assessment (see Section 3.2.5). Inhalation exposure is expected to be very low compared to other routes of exposure and therefore was not considered quantitatively. The duration of exposure would be short-term.

The following activities have the potential for co-occurrence:

Golf courses:

- Adults, youth (11 to <16 years) and children (6 to <11 years): postapplication dermal while golfing + chronic dietary

Residential fruit trees:

- Adults and children (6 to <11 years): residential postapplication dermal + chronic dietary

Calculated MOEs for aggregate exposure to difenoconazole exceeded target MOEs, and therefore, aggregate risks were shown to be acceptable. The aggregate risk assessment is outlined in Appendix V.

3.6 Cumulative assessment

Difenoconazole belongs to a group of pesticides known as the conazole fungicides. These pesticides are structurally similar and contain a triazole moiety. As a result of these structural similarities, conazole fungicides share common metabolites including 1, 2, 4-triazole and triazole conjugates. Variable toxicological responses are found for conazoles including hepatotoxicity and hepatocarcinogenicity in mice, thyroid tumours in rats, as well as developmental, reproductive, and neurological effects in rodents. No clear common mechanism for toxicity has been confirmed on which to base a cumulative assessment for any of these effects. However, a cumulative risk assessment for the common triazole metabolites will be addressed in a separate assessment.

3.7 Health incident reports

As of 14 January 2021, 11 human incidents and 17 domestic animal incidents involving difenoconazole had been submitted to the Health Canada. All of the incidents involved other active ingredients in addition to difenoconazole.

The majority of the human incidents considered to have some association to the pesticide exposure were minor or moderate in severity and involved respiratory exposure to difenoconazole products while using or handling the product, or while working with treated seed. Reported symptoms included vomiting, headache, irritated eyes or skin, lethargy, pain and nausea. No additional mitigation measures are proposed based on the low number of incidents, the low severity of the effects, and the varied exposure scenarios in the incident reports.

There was a repeated exposure scenario of animals accidentally ingesting seed treated with seed treatment products containing difenoconazole and other active ingredients. Of the incidents considered associated with the pesticide exposure, the majority of the reported effects were minor to moderate in severity, and included effects such as diarrhea, vomiting, tremors and lethargy. The more serious incidents occurred in the United States and reported effects include ataxia and death.

Based on the review of human and domestic animal incidents involving difenoconazole and other seed treatment pesticides, concerns pertaining to children and animals accidentally consuming treated seed were identified. Therefore, it is proposed that the statement “Keep treated seed out of reach of children and animals” be included on all seed bags/tags for difenoconazole seed treatment products to reduce the likelihood of exposure of children and animals to treated seed.

4.0 Environmental assessment

4.1 Fate and behaviour in the environment

Difenoconazole is soluble in water (15 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).

Hydrolysis and phototransformation were not routes of transformation for difenoconazole in soil and water. 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. 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 soil or water-sediment systems. 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 (SFO) were 103–1600 days. In anaerobic soils, the DT_{50} values were 679–947 days. In aerobic soil, the only major tranformation product was CGA205375, which reached a maximum of 9.7–10.2% of the applied. Under aerobic aquatic conditions, difenoconazole was persistent as the whole system DT_{50} values were 263–604 days based on SFO. Similarly, under anaerobic conditions, difenoconazole was persistent as the whole system DT_{50} was 411 days based on SFO. Once in the aquatic environment, difenoconazole partitions rapidly into the sediment. In aerobic water-sediment, CGA205375 was a major tranformation product reaching a maximum of 11.6% of the applied, and in anaerobic water-sediment, CGA 71019 was a major tranformation product reaching a maximum of 25.6% of the applied.

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, CGA205375 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 depth and was not detected below that depth.

The bioconcentration factor (BCF) of difenoconazole in fish reached a maximum of 570, however, residues were eliminated by 96–98% and 97% after 14 days of depuration.

4.2 Environmental risk characterization

Health Canada considered the most recent environmental risk assessment for foliar and turf uses of difenoconazole as part of the re-evaluation (ERC2011-06, PRD2015-10 and PRD2015-29). It was determined that these previous assessment remain current and potential risk to the environment from the foliar and turf uses are considered to be acceptable under the current conditions of use. Current updates to the environmental risk assessment are limited to the re-evaluation of seed treatment uses and updates to the labels such as existing spray buffer zones for the protection of terrestrial and aquatic habitats.

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 (in other words, protection at the community, population, or individual level).

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

4.2.1 Seed treatment environmental risk assessment

4.2.1.1 Birds and mammals

When pesticides are used as a seed treatment, the treated seed may be consumed as a food item. The risk assessment method for treated seed is similar to that of spray applications, except that the dietary items are treated seeds rather than dietary items sprayed with pesticide. Difenoconazole is registered as a seed treatment for the control of a broad spectrum of insect pests on a variety of cereals and potato. A risk assessment was conducted for birds and mammals to address the intake of treated seed.

The exposure of birds and mammals to a pesticide through consumption of treated seed is a function of the amount of pesticide on the seed, the body weight and food ingestion rate of the animal, and the number of seeds available for consumption. The screening level assessment assumes that the diet consists entirely of treated seeds and all of the treated seed that is planted is available for consumption over an extended period of time.

The acute and chronic toxicity endpoint values considered for the bird and mammal seed treatment risk assessment were the same as those previously reported in PRD2015-29; the most sensitive endpoints from acute and reproductive/developmental toxicity studies were chosen for the risk assessment (Appendix VI, Table 1).

Screening level Estimated Daily Exposures (EDEs) to birds and mammals were based on the highest difenoconazole seed treatment rate for barley (25.3 g a.i./100 kg seed). The EDEs and risk quotients are presented in Table 2 (Appendix VI). The RQs range from 2 to 7 for birds and 1 to 2 for mammals.

The screening level RQ values assume that all planted seed is available for consumption. The risk assessment for birds and mammals was expanded (Appendix VI, Tables 3–6), taking into consideration that not all seeds planted will be exposed and available to birds or mammals. The percentage of seeds remaining on the soil surface in field headlands is dependent on the seeding method and the time of year in which seeding occurs (in other words, 0.5% for precision drilling, 3.3% for standard drilling in spring, and 9.2% for standard drilling in autumn). This information was used along with typical seeding rate range for barley (2 row) to estimate the minimum and maximum area required for a bird and mammal to find enough seeds to reach the reproductive toxicity endpoint. Barley is assumed to be seeded using standard drilling in spring.

The number of seeds needed to be consumed per day to reach the toxicity endpoint was compared to the foraging area required for birds and mammals to reach the toxicity endpoint (Appendix VI, Tables 3 and 4). Potential risks were identified for small birds and small mammals given the low number of seeds needed to be consumed to reach the level of concern and the small foraging area required to find the number of seeds.

The risk assessment was expanded to consider all seed treatments (Appendix VI, Tables 5 and 6). Birds and mammals are not expected to consider seed potato as a food, therefore, the potential exposure to wild birds and mammals is expected to be minimal and they are excluded from the expanded risk assessment. Data from bird field bait station studies looking at the number of seeds consumed per visit and dehusking behaviour was compared to the number of seeds to reach endpoint and area required to forage for certain seed types. Field data for wheat is considered to be a good surrogate for rye, triticale and buckwheat. The seed consumption data from the field studies represents a worst case scenario (high seed availability at the baiting stations). The number of seeds left on the soil surface after seeding would be expected to attract fewer birds and have lower feeding rates due to required foraging. For birds and mammals, the area required to forage and the number of seeds required to reach the reproductive endpoints are small for wheat, barley, oat, triticale, rye and buckwheat, especially at the maximum registered rate.

The exposure of granivorous birds and mammals to difenoconazole on treated seed may be reduced by dehusking feeding behaviour; this reduction can be as high as 85%. Based on field observations of birds feeding from untreated seed bait stations, birds less than 50 g in body weight did not consistently dehusk seeds (for example, wheat, barley); observed dehusking behaviour ranged from not at all for some bird species to 100% for other species. For granivorous mammals, several studies have demonstrated that dehusking occurs under laboratory as well as under semi-field conditions but do not provide quantitative information on the effect of dehusking.[3] The efficiency of dehusking by laboratory mice and wild *Apodemus* mice is

[3] Information (Barber et al. 2003, Ludwigs et al. 2007) originates from: Pesticide Risk Assessment For Birds And Mammals - Selection of relevant species and scenarios for higher tier risk assessment in accordance with the EFSA draft Guidance document under Directive 91/414. August 2010.

strongly dependent on seed structure (for example, dehusking of sunflower seeds where the seed coat and the fruit coat are not grown together was highly effective (90%) whereas dehusking of corn seeds was less effective, 62–65%).[3] Dehusking behaviour is inconsistent and is therefore not assumed in the risk assessment.

The environmental risk assessment shows that difenoconazole seed treatments on wheat, barley, oats, triticale, rye and buckwheat may pose a potential reproductive risk to small birds and mammals. A label statement is required to inform users of the potential hazard to bird and mammals. Risk mitigation measures include requirements to incorporate or remove any spilled or exposed treated seed from the soil surface to help reduce exposure. Used according to label directions, the potential risk is considered low and is expected to be limited to seeds treated at the highest seed treatment rates only.

4.2.1.2 Pollinators

Pollinators may be exposed to difenoconazole seed treatment residues in plant pollen and nectar. The Tier I screening level risk assessment for pollinators uses highly conservative estimations of pollen and nectar exposure and conservative effect endpoints from laboratory studies. For seed treatments, the Tier I exposure method uses 1 mg a.i./kg concentration as an upper-bound for pesticides in nectar and pollen. In order to compare the application rate to the toxicity endpoints derived in laboratory studies (µg a.i./bee), a conversion from kg a.i./ha to µg a.i./bee is required. The oral exposure estimate for adult bees is calculated by multiplying 1 µg a.i./g by the consumption value for adults (0.292 g/day) or larvae (0.124 g/day) (Appendix VI, Table 7).

Potential risk to adult bees following acute oral exposure: The LOC (0.4) is not exceeded when considering the endpoints for the technical grade active ingredient (LC_{50} > 71 µg a.i./bee) for adult honey bees (RQ of <0.004).

Potential risk to adult bees following chronic oral exposure: The oral exposure estimate for adult bees is 0.29 µg a.i./bee, calculated as described above. This estimate is compared to the chronic oral endpoint (NOED = 10.6 µg a.i./bee/day), and the LOC (1.0) is not exceeded (RQ <0.03).

Potential risk to bee larvae following acute and chronic exposure: The oral exposure estimate for seed treatments for larvae is 0.124 µg a.i./larva, calculated as described above. When the oral exposure estimate for seed treatments is compared with the acute endpoint (LD_{50} > 100 µg a.i./larva), the LOC (0.4) is not exceeded (RQ of <0.001). When the oral exposure estimate is compared with the chronic endpoint (NOED = 40 µg a.i./larva/day), the LOC for chronic exposures of 1.0 is not exceeded (RQ of 0.003).

The use of difenoconazole seed treatments are expected to pose a negligible risk to bees (Appendix VI, Table 7).

4.2.1.3 Aquatic organisms

When used according to the current label directions, potential environmental risk to aquatic organisms is considered to be acceptable when difenoconazole is used as a seed treatment. No additional risk mitigation measures are proposed.

4.2.2 Environmental incident reports

Only new incidents reported since the previous review of difenoconazole (PRD2015-29) are reviewed here. Two minor environmental incidents are reported involving difenoconazole and the death of honeybees. Both of these incidents also reported a number of other active ingredients. In these cases, the causality was assessed as part of a broader re-evaluation of the neonicotinoids and their impact on bee health. Difenoconazole was reported because it was a component of a seed treatment to which the bees may have been exposed. Difenoconazole is relatively non-toxic to bees and it was not considered to have contributed to these bee deaths.

4.3 Environmental assessment conclusions

The use of difenoconazole seed treatments is expected to pose a negligible risk to pollinators and aquatic organisms. The ingestion of certain seed treated with difenoconazole may pose a reproductive risk to small birds and mammals; these seeds include wheat, barley, oats, triticale, rye and buckwheat. The proposed risk mitigation measures include requirements to incorporate or remove any spilled or exposed treated seed from the soil surface to help reduce exposure. When used according to the instructions on the label, the potential risk is considered to be low and is expected to be limited to seeds treated at the highest seed treatment rates only.

From the foliar use of difenoconazole (agriculture and turf), the potential risk to the environment is considered to be acceptable under the current conditions of use. However, to meet the current standards, updated buffer zones and environmental statements are proposed (Appendix VIII).

Under the current conditions of use, environmental risk is considered to be acceptable for post-harvest treatment of difenoconazole.

4.4 Toxic substances management policy considerations

In accordance with the PMRA Regulatory Directive DIR99-03,[4] the assessment of triticonazole against Track 1 criteria of Toxic Substances Management Policy (TSMP) under *Canadian Environmental Protection Act* was conducted. Health Canada has reached the conclusion that: difenoconazole does not meet all Track 1 criteria, and is not considered a Track 1 substance (refer to Appendix VII, Table 1)

Difenoconazole does not form any transformation products that meet all Track 1 criteria.

4.4.1 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the technical grade active ingredient and formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*[5] The list is

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

[5] SI/2005-114, last amended on 24 June 2020. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

used as described in the Health Canada's Science Policy Note SPN2020-01[6] and is based on existing policies and regulations including the Toxic Substances Management Policy and Formulants Policy, and taking into consideration the Ozone-depleting Substances and Halocarbon Alternatives Regulations under the Canadian Environmental Protection Act, 1999 (substances designated under the Montreal Protocol). Health Canada has reached the following conclusions:

Technical grade difenoconazole may contain traces of TSMP Track 1 polychlorinated dibenzodioxins and furans generated during the manufacturing process. Analysis of the technical grade active ingredient material has shown no polychlorinated dibenzodioxins and furans were detected at the level of detection of 1–44 parts per trillion. Inspire Fungicide contains a List 2 aromatic petroleum distillate (which has been indicated on the product label).

5.0 Value assessment

Difenoconazole is a systemic fungicide registered for the control of a wide range of economically important fungal diseases on diverse field crops, fruits and vegetables, and turf. Due to its broad spectrum action with preventive and curative properties, and compatibility with other fungicides, difenoconazole is valued by various agricultural sectors for use as a seed treatment and as a foliar spray.

Difenoconazole is also valued by end users for control of post-harvest diseases that lead to spoilage of pome fruits, sweet potatoes and potatoes in storage. It is of particular value as a potato seed piece treatment for the management of Fusarium dry rot, as there are limited alternative active ingredients available to manage this pathogen.

[6] PMRA's Science Policy Note SPN2020-01, *Policy on the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under paragraph 43(5)(b) of the *Pest Control Products Act*

List of abbreviations

µg	micrograms
AD	administered dose
ADI	acceptable daily intake
AhR	aryl hydrocarbon receptor
ARfD	acute reference dose
ASAE	American Society of Agricultural and Biological Engineers
BR	barrier reared
bw	body weight
CAF	composite assessment factor
CAR	Constitutive Androstane Receptor
CD	caesarean derived
CEPA	*Canadian Environmental Protection Act*
CFIA	Canadian food inspection agency
CHO	Chinese hamster ovary
cm	centimetres
DA	dermal absorption
DACO	data code
DER	data evaluation record
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
EEC	Environmental Exposure Concentrations
EFSA	European Food Safety Authority
ERC	evaluation report conditional
F_1	first generation
FQPA	*Food Quality Protection Act*
g	gram(s)
hCAR	human CAR nuclear receptor
hPXR	human PXR nuclear receptor
HED	Health Effects Division
IgM	immunoglobulin M
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
kg	kilogram
km/h	kilometers per hour
K_{oc}	organic-carbon partition coefficient
K_{ow}	n–octanol-water partition coefficient
KO	knockout
L	litre(s)
LC_{50}	lethal concentration 50%
LD_{50}	dose lethal to 50% of the test population
LOAEL	lowest observed adverse effect level
m	metre
max	maximum
min	minimum
mg	milligram

mmHg	millimetre of mercury
MOA	mode of action
MOE	margin of exposure
mol	mole
mPa	millipascal
MRL	maximum residue limit
mRNA	messenger ribonucleic acid
MSHA	Mine Safety and Health Administration
MTD	Maximum Tolerable Dose
NHANES	National health and nutrition examination survey
nm	Nanometre
NOAEL	no observable adverse effect level
NOED	no observed effect dose
NIOSH	National Institute for Occupational Safety and Health
OECD	Organisation for Economic Co-operation and Development
PDP	Pesticide Data Program
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	post-natal day
PPARα	peroxisome proliferator-activated receptor alpha
PPE	personal protective equipment
ppm	parts per million
PRD	proposed registration decision
PRDD	proposed regulatory decision document
PXR	Pregnane X receptor
RBC	red blood cells
REI	restricted entry interval
RQ	risk quotient
SOP	standard operating procedure
TC	Transfer coefficient
TK	thymidine kinase
TSMP	Toxic Substances Management Policy
TTR	transferable turf residue
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
VUI	Verified Use Information
w/w	weight by weight
WWEIA	What we eat in America

Appendix I Registered products containing difenoconazole in Canada

Table 1 Registered difenoconazole products in Canada as of 2021-01-14

Registration Number	Marketing class	Registrant	Product name	Formulation type	Guarantee
33568	Technical	Globachem N.V.	GLB Difenoconazole Technical	Solid	DFZ-96.91%
25631	Technical	Syngenta Canada Inc.	Difenoconazole Technical Fungicide	Solid	DFZ-95%
25776	Manufacturing Concentrate	Syngenta Canada Inc.	Dividend MG for use in Manufacturing	Suspension	DFZ-32.8%
25777	Commercial	Syngenta Canada Inc.	Dividend XL RTA Fungicide	Suspension	MFN-0.27% DFZ-3.37%
26637	Commercial	Syngenta Canada Inc.	Helix Liquid Seed Treatment	Suspension	THE-10.3% MFN-0.39% FLD-0.13; DFZ-1.24%
29490	Commercial	Syngenta Canada Inc.	Dividend Extreme Fungicide	Suspension	MFN-1.93% DFZ-7.73%
30004	Commercial	Syngenta Canada Inc.	Inspire fungicide	Emulsifiable Concentration	DFZ-250 g/L
30436	Commercial	Syngenta Canada Inc.	Cruiser Maxx® Vibrance (TM) Cereals Seed Treatment	Suspension	THE-30.7 g/L, SDX-8.0 g/L, MFN-9.5 g/L, DFZ-36.9 g/L
30437	Commercial	Syngenta Canada Inc.	Vibrance XL Seed Treatment	Suspension	SDX-13.8 g/L, MFN-16.5 g/L, DFZ-66.2 g/L
30518	Commercial	Syngenta Canada Inc.	Quadris Top	Suspension	DFZ-125 g/L, AZY-200 g/L
30599	Commercial	Syngenta Canada Inc.	Maxim D	Suspension	FLD-19.4 g/L, DFZ-19.4 g/L
30827	Commercial	Syngenta Canada Inc.	Inspire Super Fungicide	Emulsifiable Concentration	DFZ-86 g/L, CYP-249 g/L
31024	Commercial	Syngenta Canada Inc.	Cruiser Maxx Potato Extreme	Suspension	THE-250 g/L, FLD-62.5 g/L, DFZ-123 g/L,
31050	Commercial	Syngenta Canada Inc.	Stadium Fungicide	Suspension	FLD-143 g/L, DFZ-112 g/L, AZY-143 g/L
31408	Commercial	Syngenta Canada Inc.	Vibrance Quattro	Suspension	SDX-15.4 g/L, MFN-9.2 g/L, FLD-7.6 g/L, DFZ-36.8 g/L
31453	Commercial	Syngenta Canada Inc.	Cruiser Vibrance Quattro	Suspension	THE-61.5 g/L, SDX-15.4 g/L, MFN-9.2 g/L, FLD-7.7 g/L, DFZ-36.9 g/L
31454	Commercial	Syngenta Canada Inc.	Helix Vibrance	Suspension	THE-269 g/L, SDX-3.4 g/L, MFN-5 g/L, FLD-1.7 g/L, DFZ-16 g/L
31526	Commercial	Syngenta Canada Inc.	Aprovia Top	Emulsifiable Concentration	DFZ-117 g/L, BZV-78 g/L
31527	Commercial	Syngenta Canada Inc.	Ascernity Fungicide	Emulsifiable Concentration	DFZ-79 g/L, BZV-24 g/L
31537	Commercial	Syngenta Canada Inc.	Bravo Top Fungicide	Suspension	TET-500 g/L, DFZ-50 g/L
31564	Commercial	Syngenta Canada Inc.	Academy Fungicide	Suspension	FLD-147 g/L, DFZ-247 g/L

Registration Number	Marketing class	Registrant	Product name	Formulation type	Guarantee
32015	Commercial	Syngenta Canada Inc.	Exempla Fungicide	Suspension	DFZ-225 g/L, AZY-225 g/L
32624	Commercial	Syngenta Canada Inc.	Vibrance Flexi Canola	Suspension	SDX-8.4 g/L, MFN-12.5 g/L, FLD-4.2 g/L, DFZ-40 g/L
32625	Commercial	Syngenta Canada Inc.	Vibrance Flexi Cereals	Suspension	SDX-8.4 g/L, MFN-12.5 g/L, FLD-4.2 g/L, DFZ-40 g/L
33020	Commercial	Syngenta Canada Inc.	A20259 Fungicide	Suspension	FMF-75 g/L, DFZ-125 g/L
33171	Commercial	Syngenta Canada Inc.	Vibrance Ultra Potato	Suspension	SDX-77.2 g/L, IMB-154.3 g/L, DFZ-77.2 g/L
33206	Commercial	Syngenta Canada Inc.	Miravis Duo Fungicide	Suspension	FMF-75 g/L, DFZ-125 g/L
33489	Commercial	Syngenta Canada Inc.	Bravo Top 550 Fungicide	Suspension	TET-500 g/L, DFZ-50 g/L

DFZ: difenoconazole; AZY: azoxystrobin; CYP: cyprodinil; FLD: fludioxonil; BZV: benzovindiflupyr; TET: chlorothalonil; FMF: pydiflumetofen; IMB: mandipropamid; MFN: metalaxyl m and s isomer; SDX: sedexane; THE: thiamethoxam

Appendix II Toxicology information for health risk assessment

Table 1 Identity of select difenoconazole metabolites in rats

Common name (Other names)	Chemical name (IUPAC)
CGA205374	1-(2-chloro-4-(4-chloro-phenoxy)-phenyl)-2-(1,2,4-triazol)-1-yl-ethanone
CGA205375 (metabolite C)	1-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-2-(1,2,4-triazol)-1-yl-ethanol
CGA 71019	1,2,4-triazole
CGA 189138	2-chloro-4-(4-chlorophenoxy)-benzoic acid

Table 2 Toxicology reference values for difenoconazole health risk assessment

Exposure scenario	Study	Point of departure and endpoint	CAF/ MOE[1]
Acute Dietary (general population excluding females 13–49 years of age)	Acute neurotoxicity in rats (gavage)	NOAEL = 25 mg/kg bw Reduced forelimb grip strength in males	100
	ARfD = 0.3 mg/kg bw		
Acute Dietary (females 13–49 years of age)	Developmental toxicity in rabbits (gavage)	NOAEL = 25 mg/kg bw/day Increased post-implantation loss, resorptions	300
	ARfD = 0.08 mg/kg bw		
Chronic Dietary (all populations)	2-year dietary chronic toxicity/ carcinogenicity in rats	NOAEL = 1.0 mg/kg bw/day Decreased body weight, and body weight gain, and increased incidence of hepatocellular hypertrophy	100
	ADI = 0.01 mg/kg bw/day		
Short- and intermediate-term dermal[2] and inhalation[3]	Developmental toxicity in rabbits (gavage)	NOAEL = 25 mg/kg bw/day Increased post-implantation loss, resorptions and abortions	300
Short- and intermediate-term dermal (children 6–<11 years of age)	22-day dermal toxicity study in rabbits	NOAEL = 100 mg/kg bw/day Body weight loss and decreased body weight gain	100
Short- and intermediate-term aggregate (females 13–49 years of age)	Developmental toxicity in rabbits (gavage)	NOAEL = 25 mg/kg bw/day Common endpoint: Increased post-implantation loss, resorptions and abortions – relevant to oral, dermal and inhalation exposure scenarios	300
Short- and intermediate-term aggregate (general population excluding females 13–49 years of age)	Oral and inhalation: Developmental toxicity in rabbits (gavage) Dermal: 22-day dermal toxicity study in rabbits	Dermal NOAEL: 100 mg/kg bw/day Oral and inhalation NOAEL: 25 mg/kg bw/day Common endpoint: body weight loss and decreased body weight gain	Dermal: 100 Oral and inhalation: 100

Exposure scenario	Study	Point of departure and endpoint	CAF/ MOE[1]
Cancer	MOA-supported threshold approach for cancer risk assessment for hepatocellular adenomas and carcinomas in male mice. The endpoints selected for non-cancer risk assessment are protective of these findings.		

[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 residential assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor of 36% 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.

Appendix III Dietary risk assessments

Table 1 Acute dietary risk assessment for difenoconazole

Population subgroup	ARfD[1] (mg/kg bw)	95th Percentile food only	95th Percentile Food and drinking water
		% ARfD	% ARfD
All Infants	0.3	15	15
Children 1–2 years old		16	16
Children 3–5 years old		12	13
Children 6–12 years old		8	8
Males 13–19 years old		5	5
Males 20–49 years old		4	4
Adults 50+ years old		5	5
Females 13–49 years old	0.08	**17**	**18**

[1] Acute Reference Dose (ARfD) of 0.3 mg/kg body weight applies to population subgroups except females 13–49 years. ARfD of 0.08 applies to females 13–49 years. Bolded values indicate population group with the highest exposures.

Table 2 Chronic dietary risk assessment for difenoconazole

Population subgroup	Food only		Food and drinking water	
	% ADI [1]	% ADI [1] (Refined)	% ADI [1]	% ADI [1] (Refined)
General Population	30.5	15.0	32.2	16.7
All Infants	54.3	13.9	60.6	20.2
Children 1–2 years old	**86.2**	**28.1**	**88.5**	**30.4**
Children 3–5 years old	63.6	22.9	65.5	24.8
Children 6–12 years old	37.5	15.4	38.9	16.8
Youth 13–19 years old	22.4	10.5	23.6	11.7
Adults 20–49 years old	24.2	13.4	25.9	15.1
Adults 50+ years old	28.8	16.4	30.5	18.0
Females 13–49 years old	24.5	13.6	26.1	15.2

[1] Acceptable Daily Intake (ADI) of 0.01 mg/kg body weight/day applies to the general population and all population subgroups. Bolded values indicate population group with the highest exposures.

Appendix IV Occupational risk assessments

Table 1 Commercial seed treatment exposure and risk assessment for difenoconazole

Crop	Formulation	Activity	Application rate (g a.i./kg seed)	Throughput[a] (kg seed/day)	MOE (Target =300)		
					Dermal[b]	Inhalation[c]	Combined[d]
Krolski, 2010 (Corn) - Closed mix/load wearing single layer, CR gloves							
Corn	Liquid	Mixer/loader	0.239	125 000	726	18,000	698
		Bagger, sewer, stacker			1630	3580	1120
		Cleaner			1830	3470	1200
Krolski, 2010 (Canola) - Closed mix/load wearing coveralls over single layer, CR gloves							
Canola (mustard, rapeseed)	Liquid	Mixer/loader	0.242	67 000	6400	110 000	6050
		Bagger, sewer, stacker			46 700	82 200	29 800
		Cleaner			4,080	6510	2510
Brennecke and Muller, 2003 (Wheat) – Closed M/L, single layer plus jacket, CR gloves							
Cereals[e]	Liquid	Treater	0.253	92 000	2870	14 200	2,90
Wilson, 2009 (Wheat) – Closed M/L, single layer for baggers, CR coveralls over single layer for cleaners							
Cereals[e]	Liquid	Bagger, sewer, stacker	0.253	92 000	13 500	96 500	11 800
		Cleaner			11 900	124 000	10 900
Krolski, 2006 (Wheat) - Open mix/load wearing single layer, CR gloves							
Cereals[e]	Liquid	MLA	0.253	92 000	898	34 800	876

Single layer = long-sleeved shirt, long pants; CR = chemical resistant; MLA = mixer, loader, applicator; MOE = margin of exposure; DA = dermal absorption

[a] Throughput is dependent on seed type.

[b] Based on a short- and intermediate-term NOAEL of 25 mg/kg bw/day from an oral rabbit developmental toxicity study and a target MOE of 300. MOE = NOAEL/exposure. Exposure (excluding cleaners) = (application rate × kg/1000 g × throughput) × unit exposure × DA (36%) /80 kg body weight. Cleaner Exposure = [application rate × unit exposure × DA (36%)/80 kg body weight].

[c] Based on a short- and intermediate-term NOAEL of 25 mg/kg bw/day from an oral rabbit developmental toxicity study and a target MOE of 300. MOE = NOAEL/exposure. Exposure = (application rate × kg/1000 g × throughput) × unit exposure /80 kg body weight. Cleaner Exposure = [application rate × unit exposure /80 kg body weight].

[d] Based on a short- and intermediate-term NOAEL of 25 mg/kg bw/day from an oral rabbit developmental toxicity study and a target MOE of 300. Combined MOE =NOAEL/(dermal exposure + inhalation exposure).

[e] Wheat was used to represent exposure for all other registered cereal crops.

Table 2 On-farm seed treatment exposure and risk assessment for difenoconazole

Crop	Formulation	Activity	Application rate (g a.i./kg seed)	Throughput[a] (kg seed/day)	MOE (Target = 300)		
					Dermal[b]	Inhalation[c]	Combined[d]
Krolski, 2006 (Wheat) - Open mix/load, closed cab planter, wearing single layer, CR gloves							
Wheat (buckwheat, millet)[e]	Liquid	All tasks (loading, treating, planting)	0.253	28 350	5300	32 400	4550
Barley				19 600	7660	46 800	6580
Oats				9120	16 600	114 000	14 500
Rye				5380	28 100	193 000	24 500
Triticale				16 800	9000	61 800	7860
Sorghum				1 200	126 000	866 000	110 000
Corn, sweet			0.239	486	329 000	2 260 000	288 000
Corn, field				1260	127 000	873 000	111 000
Corn, pop				584	274 000	1 880 000	239 000

Single layer = long-sleeved shirt, long pants; CR = chemical resistant; MOE = margin of exposure; DA = dermal absorption

[a] Throughput is dependent on seed type, seeding rate and area planted.

[b] Based on a short- and intermediate-term NOAEL of 25 mg/kg bw/day from an oral rabbit developmental toxicity study and a target MOE of 300. MOE = NOAEL/exposure. Exposure = (application rate × kg/1000 g × throughput) × unit exposure × DA (36%)/80 kg body weight.

[c] Based on a short- and intermediate-term NOAEL of 25 mg/kg bw/day from an oral rabbit developmental toxicity study and a target MOE of 300. MOE = NOAEL/exposure. Exposure = (application rate × kg/1000 g × throughput) × unit exposure /80 kg body weight.

[d] Based on a short- and intermediate-term NOAEL of 25 mg/kg bw/day from an oral rabbit developmental toxicity study and a target MOE of 300. Combined MOE = NOAEL/(dermal exposure + inhalation exposure).

[e] Wheat was used as a surrogate crop for buckwheat and millet.

Table 3 Planting treated seed exposure and risk assessment for difenoconazole

Crop	Formulation	Activity	Application rate (g a.i./kg seed)	Throughput[a] (kg seed/day)	MOE (Target =300)		
					Dermal[b]	Inhalation[c]	Combined[d]
Zietz, 2009 (corn) - closed cab planter, wearing single layer, CR gloves							
Corn, sweet	Liquid	All tasks (loading, planting)	0.239	486	31 500	208 000	27 400
Corn, field				1260	12 200	80 200	10 600
Corn, pop				584	26 300	173 000	22 800
Dean, 1990 (canola) - closed cab planter, wearing single layer, CR gloves							
Canola (mustard, rapeseed)	Liquid	All tasks (loading, planting)	0.242	640	84 600	11 600 000	84 000
Mustard				896	60 400	8 310 000	60 000
Krainz, 2013 (wheat) - closed cab planter, wearing single layer plus jacket [e], CR gloves							
Wheat (buckwheat, millet)[f]	Liquid	All tasks (loading, planting)	0.253	28 350	664	773	357

Crop	Formulation	Activity	Application rate (g a.i./kg seed)	Throughput[a] (kg seed/day)	MOE (Target =300)		
					Dermal[b]	Inhalation[c]	Combined[d]
Barley				19 600	961	1120	517
Oats				9120	2060	2400	1110
Rye				5380	3500	4070	1880
Triticale				16 800	1120	1300	602
Sorghum				1200	15 700	18 300	8440

Single layer = long-sleeved shirt, long pants; CR = chemical resistant; MOE = margin of exposure; DA = dermal absorption

[a] Throughput is dependent on seed type, seeding rate and area planted.

[b] Based on a short- and intermediate-term NOAEL of 25 mg/kg bw/day from an oral rabbit developmental toxicity study and a target MOE of 300. MOE = NOAEL/exposure. Exposure = (application rate × kg/1000 g × throughput) × unit exposure × DA (36%)/80 kg body weight.

[c] Based on a short- and intermediate-term NOAEL of 25 mg/kg bw/day from an oral rabbit developmental toxicity study and a target MOE of 300. MOE = NOAEL/exposure. Exposure = (application rate × kg/1000 g × planting rate) × unit exposure/80 kg body weight.

[d] Based on a short- and intermediate-term NOAEL of 25 mg/kg bw/day from an oral rabbit developmental toxicity study and a target MOE of 300. Combined MOE = NOAEL/(dermal exposure + inhalation exposure).

[e] For mitigation, coveralls will be used to represent the use of the jacket in the study.

[f] Wheat is used as a surrogate for buckwheat and millet.

Appendix V Aggregate risk assessment

Table 1 Aggregate risk assessment for difenoconazole

Age group	Dermal exposure (mg/kg bw/day)	Chronic dietary + drinking water Exposure (mg/kg bw/day)	Aggregate MOE [a, b]
Golfers			
Adults (16 to <80)	0.00430	0.00159	4,250
Youth (11 to <16)	0.00500	0.00119	4,040
Children (6 to <11)	0.0115	0.00184	5,300
Residential Fruit Trees			
Adults (16 to <80)	0.00261	0.00159	5,960
Children (6 to <11)	0.00496	0.00184	8,110

[a] For adults and youth: based on a short- and intermediate-term aggregate NOAEL of 25 mg/kg bw/day from an oral rabbit developmental toxicity study and a target MOE of 300. Aggregate MOE = Aggregate NOAEL / (Dermal exposure + Background chronic dietary exposure (food and drinking water exposure)).

[b] For children: Combined aggregate MOE = 1/[(1/Dermal MOE)+(1/Background chronic dietary exposure MOE)]. MOEs = NOAEL/exposure. Dermal MOE was based on a short- and intermediate-term aggregate NOAEL of 100 mg/kg bw/day from a rabbit dermal toxicity study. Oral MOE was based on an aggregate NOAEL of 25 mg/kg bw/day from an oral rabbit developmental toxicity study. A target MOE of 100 applies to both routes, as well as for the combined aggregate MOE.

Appendix VI Toxicity and risks to the environment from seed treatment

Table 1 Avian and mammalian endpoints used in seed treatment risk assessment

Organism	Species	Endpoint	Endpoint after UF [1]
Avian acute	Mallard duck (*Anas platyrhynchos*)	LD_{50} = 2150 mg a.i./kg bw	215 mg a.i./kg bw/day
Avian reproduction		NOEC = 9.7 mg a.i./kg bw/day	9.7 mg a.i./kg bw/day
Mammalian acute	Rat	LD_{50} = 1453 mg a.i./kg bw	145.3 mg a.i./kg bw
Mammalian reproduction		NOEL = 17.7 mg a.i./kg/day	17.7 mg a.i./kg/day

[1] UF = uncertainty factor; the acute LD_{50} toxicity endpoint is divided by a factor of 10 to account for potential differences in species sensitivity as well as varying protection levels (for example, community, population, individual).

Table 2 Screening level seed treatment risk assessment for birds and mammals

Size and exposure	Study endpoint (mg a.i./kg bw/day / UF)	EDE (mg a.i./kg bw/day)	RQ
Small bird (0.02 kg)			
Acute	215.0	64.2	0
Reproduction	9.7	64.2	7
Medium bird (0.10 kg)			
Acute	215.0	50.5	0
Reproduction	9.7	50.5	5
Large bird (1.00 kg)			
Acute	215.0	14.7	0
Reproduction	9.7	14.7	2
Small mammals (0.015 kg)			
Acute	145.3	36.7	0
Reproduction	17.7	36.7	2
Medium mammals (0.035 kg)			
Acute	145.3	31.6	0
Reproduction	17.7	31.6	2
Large mammals (1.00 kg)			
Acute	145.3	17.4	0
Reproduction	17.7	17.4	1

RQ > 1 indicated by shaded cells.

Table 3 The number of barley seeds (2-row) treated with difenoconazole required to reach the bird reproductive endpoint and foraging area required to reach the endpoint

Study endpoint (mg a.i./kg bw/day / UF)		EDE (mg a.i./kg bw/day)	RQ	Number of seeds needed to reach endpoint		Area required (m^2)	
						Standard drilling - spring	
				min	max	min	max
Small bird (0.02 kg)							
Reproduction	9.7	64.2	7	18.6	15.2	1.9	3.5
Medium bird (0.10 kg)							
Reproduction	9.7	50.5	5	93.2	75.9	9.6	17.3
Large bird (1.00 kg)							
Reproduction	9.7	14.7	2	931.7	759.1	95.9	172.6

RQ > 1 indicated by shaded cells.

Table 4 The number of barley seeds (2-row) treated with difenoconazole required to reach the mammalian reproductive endpoint and foraging area required to reach the endpoint

Study endpoint (mg a.i./kg bw/day / UF)		EDE (mg a.i./kg bw/day)	RQ	Number of seeds needed to reach endpoint		Area required (m^2)	
						Standard drilling - spring	
				min	max	min	max
Small mammals (0.015 kg)							
Reproduction	17.7	36.7	2	25.5	20.8	2.6	4.7
Medium mammals (0.035 kg)							
Reproduction	17.7	31.6	2	59.5	48.5	6.1	11.0

RQ > 1 indicated by shaded cells.

Table 5 Comparison of the estimated number of difenoconazole treated seeds to reach reproductive endpoint for small birds to the number of seeds observed consumed in the field

Seed crop[1] (mg a.i./seed)	Reproduction		Field data[4]		
	Number of seeds to reach endpoint (min to max.)[2]	Area required[3] (m^2)	Mean number of seeds consumed per visit	Max. number of seeds consumed per visit	Number of species (% dehusking)
Wheat (High rate: 0.0115)[5]	17–25	1–3	2–19	1–74	11 (0–100)
Wheat (Low rate: 0.0055)	36–52	3–7			
Canola mustard (high rate: 0.0005)	421	22–54	36–104	85–240	3 (43–100)
Sweet corn (high rate: 0.0613)	3–6	105–302	3–4	4–11	3
Sweet corn (low rate: 0.0300)	6–13	214–616			

Seed crop[1] (mg a.i./seed)	Reproduction		Field data[4]		
	Number of seeds to reach endpoint (min to max.)[2]	Area required[3] (m^2)	Mean number of seeds consumed per visit	Max. number of seeds consumed per visit	Number of species (% dehusking)
Barley - spring (high rate: 0.0128)	15–19	2–4	1–18	1–53	12 (0–100)
Barley - spring (low rate: 0.0049)	32–40	4–7			
Oat (High rate: 0.0111)	17–26	2–4	6–11	10–46	3
Oat (Low rate: 0.0054)	36–54	4–9			
Rye (High rate: 0.0088)	22–25	2	No field data available		
Rye (Low rate: 0.0042)	46–53	4			
Triticale (High rate: 0.0121)	16–17	1–3			
Triticale (Low rate: 0.0058)	34–36	2–6			
Buckwheat (high rate: 0.0076)	26	3–5			
Buckwheat (Low rate: 0.0036)	54	6–10			
Sorghum (High rate: 0.0077)	25–28	27–61			
Sorghum (Low rate: 0.0039)	50–57	54–122			
Millet (pearl) High rate: 0.0029)	67–118	9–101			
Millet (pearl) Low rate: (0.0014)	134–235	17–201			
Millet (proso) (High rate: 0.0014)	135	13			
Millet (proso) Low rate: 0.0007)	269	26			

[1] All crops are assumed to be seeded using standard drilling in spring with the exception of corn which is solely seeded using precision drilling (in other words, planter: vacuum or positive pressure).

[2] minimum to maximum number of seeds to reach endpoint based on seed size range (maximum to minimum).

[3] minimum and maximum area required based on minimum and maximum seeding rate (seeding rates based on VUI table - PMRA# 2793869).

[4] The seed preference data (in other words, mean and max number of seeds consumed per visit) is representative of bird species ranging in weight from 18 to 30g.

[5] The VUI presents a seed treatment rate for Spring and winter wheat. The seed treatment rate per seed was estimated using the BAM (Birds and Mammals) spreadsheet for Durum, Hard red, Extra strong and Canadian Prairie Spring wheat.

Table 6 Comparison of the estimated number of difenoconazole treated seeds to reach reproductive endpoint for small mammals to the required foraging area.

Seed crop[1] (mg a.i./seed)	Reproduction	
	# seeds to reach endpoint (min to max.)[2]	Area required[3] (m^2)
Wheat (High rate: 0.0115)[4]	23–34	2–5
Wheat (Low rate: 0.0054)	49–71	4–10
Canola mustard (high rate: 0.0005)	576	29–73
Sweet corn (high rate: 0.0613)	4–9	143–413
Sweet corn (low rate: 0.0300)	9–18	293–843
Barley - spring (high rate: 0.0128)	21–26	3–5
Barley - Spring (low rate: 0.0064)	44–54	6–10
Oat (High rate: 0.0128)	24–36	3–6
Oat (Low rate: 0.0054)	49–74	6–13
Rye (High rate: 0.0088)	30–35	3
Rye (Low rate: 0.0042)	64–73	5
Triticale (High rate: 0.0121)	22–23	2–4
Triticale (Low rate: 0.0058)	46–49	3–8
Buckwheat (high rate: 0.0076	35	4–6
Buckwheat (Low rate: 0.0036)	74	8–13
Sorghum (High rate: 0.0077)	34–39	37–84
Sorghum (Low rate: 0.0039)	69–77	74–168
Millet (pearl) High rate: 0.0029)	92–162	12–138
Millet (pearl) Low rate: (0.0014)	184–322	23–275
Millet (proso) (High rate: 0.0014)	185	18
Millet (proso) Low rate: 0.0007)	368	35

[1] All crops are assumed to be seeded using standard drilling in spring with the exception of corn which is solely seeded using precision drilling (in other words, planter: vacuum or positive pressure).
[2] minimum to maximum number of seeds to reach endpoint based on seed size range (maximum to minimum).
[3] minimum and maximum area required based on minimum and maximum seeding rate (seeding rates based on VUI table - PMRA# 2793869).
[4] The VUI presents a seed treatment rate for Spring and Winter wheat. The seed treatment rate per seed was estimated using the BAM (Birds and Mammals) spreadsheet for Durum, Hard red, Extra strong and CPS wheat.

Table 7 Screening level risk assessment of difenoconazole for pollinators (Honey bee *Apis mellifera*) for seed treatment application.

Exposure	Endpoint value	EEC[1]	RQ	Level of Concern[2]
Acute oral, adults				
Difenoconazole technical grade active ingredient	48-h LC_{50}: > 71 µg a.i./bee	1 µg a.i./g × 0.292 g/day = 0.29 µg a.i./bee	<0.004	Not exceeded
Chronic oral, adults				
A7402T (24.8% w/w)	10-d NOED: 10.6 µg a.i./bee/day	1 µg a.i./g × 0.292 g/day = 0.29 µg a.i./bee	0.03	Not exceeded
Acute oral, larvae				
Difenoconazole technical grade active ingredient	8-d LD_{50}: >100 µg a.i./larva	1 µg a.i./g × 0.124 g/day = 0.124 µg a.i./larva	<0.001	Not exceeded
Difenoconazole (93.9% w/w)	22-d NOED: 40 µg a.i./larva/day	1 µg a.i./g × 0.124 g/day = 0.124 µg a.i./larva	0.003	Not exceeded

[1] Seed treatment EEC = 1 µg a.i./g food (pollen and nectar; default value for seed treatments) × consumption rate (0.292 g food/day for adults or 0.124 g food/day for larvae)

[2] Level of concern = 0.4 for acute risk to pollinators and 1.0 for chronic risk to pollinators.

Appendix VII Toxic substances management policy considerations

Table 1 Toxic substances management policy considerations for difenoconazole comparison to TSMP track 1 criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient 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 days
	Water	Half-life ≥ 182 days	Half-life = 263–604 days
	Sediment	Half-life ≥ 365 days	Half-life = 411 days
	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} ≥ 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 (in other words, all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).

Appendix VIII Proposed label amendments for products containing difenoconazole

Information on approved labels of currently registered products should not be removed unless it contradicts the label statements provided below.

1.0 Label amendments relating to the health risk assessment

Label Amendments for Commercial Class Products Containing Difenoconazole

1. General Label Improvements

Add to PRECAUTIONS:

Replace:

...NIOSH/MSHA-approved dust mask...
…suitable dust mask…
…dust mask…
…half-mask respirator with suitable dust filter...

With:

...NIOSH-approved N95 filtering facepiece respirator (dust mask) that is properly fit tested…

Replace:

...quarter- or half-mask respirator...

With:

...respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides...

2. Label amendments for end-use product with post-harvest uses

Add to PRECAUTIONS:

Apply only when the potential for drift beyond the area to be treated is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings.

Add to STORAGE:

Store this product away from food or feed.

3. Label amendments for end-use products for seed treatment

Personal protective equipment (PPE) and engineering controls are specified below for seed treatment uses. Some labels may have one or more of these seed types registered (NB: corn only appears on labels with cereals as well). The label statements for all registered uses must be added to the label, unless the current mitigation is more restrictive.

Add to PRECAUTIONS:

Apply only in a way that this product will not contact workers or other persons, either directly or through drift. Only workers wearing personal protective equipment may be in the area when seed is being treated or bagged.

Add to STORAGE:

Store this product away from food or feed.

Add to Seed Tags:

All bags containing treated seed for sale or use in Canada must be labelled or tagged as follows, unless the current label mitigation is more restrictive:

Keep treated seeds out of reach of children and animals.

Store this product away from food or feed.

3a. Corn (sweet, seed, pop, field)

For commercial-class liquid seed treatment products registered for use on corn, label statements must be amended (or added) to include the following:

Add to PRIMARY PANEL:

When treating corn, for use in commercial seed treatment (facilities and mobile treaters) with closed transfer including closed mixing, loading, calibrating, and closed treatment equipment only. No open transfer of corn in commercial facilities is permitted. Open transfer is permitted for on-farm treatment of corn.

Add to PRECAUTIONS:

Use closed transfer for commercial seed treatment (facilities and mobile treaters). Closed transfer includes closed mixing, loading, calibrating and closed treatment equipment. No open transfer is permitted for commercial seed treatment of corn.

When treating, handling, or planting treated seed, wear a long-sleeved shirt, long pants, shoes plus socks, and chemical-resistant gloves.

Add to seed tags:
All bags containing treated seed for sale or use in Canada must be labelled or tagged as follows, unless the current label mitigation is more restrictive:

> When handling and planting treated seeds, wear a long-sleeved shirt, long pants, shoes plus socks, and chemical-resistant gloves

3b. Canola, rapeseed, mustard
For commercial-class liquid seed treatment products registered for use on canola, rapeseed, and mustard, label statements must be amended (or added) to include the following:

Add to PRIMARY PANEL:

> For use in commercial seed treatment (facilities and mobile treaters) with closed transfer including closed mixing, loading, calibrating, and closed treatment equipment only. No open transfer is permitted.

Add to PRECAUTIONS:

> Use closed transfer for commercial seed treatment (facilities and mobile treaters). Closed transfer includes closed mixing, loading, calibrating and closed treatment equipment. No open transfer is permitted.
>
> For all activities when treating, handling treated seed, cleaning or contacting contaminated equipment during commercial treatment, wear coveralls over a long-sleeved shirt, long pants, shoes plus socks, and chemical-resistant gloves.

Add to Seed Tags:
All bags containing treated seed for sale or use in Canada must be labelled or tagged as follows, unless the current label mitigation is more restrictive:

> When handling and planting treated seeds, wear a long-sleeved shirt, long pants, shoes plus socks, and chemical-resistant gloves

3c. Cereals (wheat, barley, oats, rye, triticale, sorghum, buckwheat, millet)
For commercial-class liquid seed treatment products registered for use on cereals, label statements must be amended (or added) to include the following:

Add to PRECAUTIONS:

> When cleaning seed treatment equipment, wear chemical-resistant coveralls over long-sleeved shirt, long pants, chemical-resistant footwear, socks, and chemical-resistant gloves.

When treating, bagging, sewing, stacking and when handling treated seed during commercial and on-farm treatment, wear a long-sleeved shirt, long pants, shoes plus socks, and chemical-resistant gloves.

When loading treated seeds into a planter, wear coveralls over a long-sleeved shirt, long pants, shoes plus socks, and chemical-resistant gloves. For all other planting activities and when handling treated seed, wear a long-sleeved shirt, long pants, shoes plus socks, and chemical-resistant gloves. Use only closed cab planting equipment. Chemical-resistant gloves do not need to be worn when inside the closed cab.

Add to seed tags:
All bags containing treated seed for sale or use in Canada must be labelled or tagged as follows, unless the current label mitigation is more restrictive:

When loading treated seeds into a planter, wear coveralls over a long-sleeved shirt, long pants, shoes plus socks, and chemical-resistant gloves. For all other planting activities and when handling treated seed, wear a long-sleeved shirt, long pants, shoes plus socks, and chemical-resistant gloves. Use only closed cab planting equipment. Chemical-resistant gloves do not need to be worn when inside the closed cab.

4. Label amendments for end-use products with foliar application

Add to STORAGE:

Store this product away from food or feed.

4a. For labels related to agricultural Uses:

Add to PRECAUTIONS:

Apply only to agricultural crops when the potential for drift to areas of human habitation and human activity, such as houses, cottages, schools and recreational areas, is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings.

4b. For labels related to use on turf:

Add to PRECAUTIONS:

Apply only when the potential for drift to areas of human habitation or other areas of human activity (other than golf courses), such as parks, school grounds, and playing fields, is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

5. Label amendments for end-use products with airblast application to pome fruit

Under DIRECTIONS FOR USE for POME FRUIT:

Add to SPECIFIC USE RESTRICTIONS or APPLICATION TIMING/INSTRUCTIONS:

DO NOT enter or allow entry into treated areas until sprays have dried.

2.0. Label amendments relating to the environmental risk assessment

1. Label amendments for technical grade active ingredient and manufacturing concentrates

Add to ENVIRONMENTAL PRECAUTIONS:

TOXIC to aquatic organisms.

DO NOT discharge effluent containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters.

Add to DISPOSAL:

Canadian manufacturers should dispose of unwanted active ingredients and containers in accordance with municipal or provincial regulations. For additional details and clean up of spills, contact the manufacturer or the provincial regulatory agency

2. Label amendments for end-use products for seed treatment

Add to ENVIRONMENTAL PRECAUTIONS:

TOXIC to aquatic organisms.

Toxic to birds and small wild mammals. Any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned-up from the soil surface.

3. Label amendments for end-use products with foliar uses

Add to ENVIRONMENTAL PRECAUTIONS:

TOXIC to aquatic organisms and non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.

Toxic to certain beneficial arthropods (which may include predatory and parasitic insects, spiders and mites). Minimize spray drift to reduce harmful effects on beneficial arthropods in habitats next to the application site such as hedgerows and woodland.

Difenoconazole is persistent and may carryover. It is recommended that this product not be used in areas treated with any products containing difenoconazole during the previous season.

To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil, or clay.

Avoid application when heavy rain is forecast.

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative filter strip between the treated area and the edge of the water body.

Add to DIRECTIONS FOR USE:

As this pesticide is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests.

DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

4. Label amendments for specific end-use products related to spray buffer zone requirements

Buffer zone requirements for difenoconazole-based end use products were based on the risk profile identified during the environmental risk assessment for the active ingredient difenoconazole and the associated co-formulation active ingredients benzovindiflupyr, chlorothalonil, cyprodinil, azoxystrobin and pydiflumetofen. Product-specific buffer zones were determined due to the complexity of matching existing buffer zones for other TGAIs with the multiple difenoconazole EPs. While some EPs require ASAE medium spray quality for field sprayers, while others require ASAE fine; all aerial applications require ASAE medium.

4a. Label amendments proposed for products containing difenoconazole only, PCP Reg. No. 30004

Add to DIRECTIONS FOR USE:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) fine classification. Boom height must be 60 cm or less above the crop or ground.

Airblast application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Reduce drift caused by turbulent wingtip vortices. Nozzle distribution along the spray boom length MUST NOT exceed 65% of the wing- or rotorspan.

Add to BUFFER ZONES:

A spray buffer zone is NOT required for:

- Uses with hand-held application equipment permitted on this label,
- Low-clearance hooded or shielded sprayers that prevent spray contact with crop, fruit or foliage.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands) and sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands).

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:		
			Freshwater Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	
Field sprayer	Canola and Crop Subgroup 20A		2	1	0
	Brassica (cole) leafy vegetables, bulb vegetables, curcubit vegetables, fruiting vegetables, artichoke (Chinese, Jerusalem), edible canna, chufa, potato, sweet potato, sugar beets		5	1	1
Airblast	Pome Fruit: apple, crab apple, Oriental pear, quince	Early growth stage	20	3	2
		Late growth stage	10	2	1
	Grapes (except Concord and	Early growth stage	25	4	3

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:		
			Freshwater Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	
	some non-vinifera hybrids)	Late growth stage	15	2	2
Aerial	Canola	Fixed wing	10	1	0
		Rotary wing	5	1	0
	Potato	Fixed wing	30	1	15
		Rotary wing	25	1	15

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

4b. Label amendments proposed for co-formulated products containing difenoconazole and pydiflumetofen, PCP Reg. No. 33020 and 33206

Add to DIRECTIONS FOR USE:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) fine classification. Boom height must be 60 cm or less above the crop or ground.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Reduce drift caused by turbulent wingtip vortices. Nozzle distribution along the spray boom length MUST NOT exceed 65% of the wing- or rotorspan.

Add to BUFFER ZONES:

A spray buffer zone is NOT required for:

- Uses with hand-held application equipment permitted on this label,
- Low-clearance hooded or shielded sprayers that prevent spray contact with crop, fruit or foliage.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands) and sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands).

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:		
			Freshwater Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	
Field sprayer	Fruiting vegetables, cucurbit vegetables		4	1	1
	Potato, tuberous and corm vegetables		5	1	1
Aerial	Potato	Fixed wing	20	1	15
		Rotary wing	15	1	15

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

4c. Label amendments proposed for co-formulated product containing difenoconazole and azoxystrobin, PCP Reg. No. 30518

Add to DIRECTIONS FOR USE:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

Chemigation: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Applications **MUST** be conducted **WITHOUT** the use of end guns.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Reduce drift caused by turbulent wingtip vortices. Nozzle distribution along the spray boom length MUST NOT exceed 65% of the wing- or rotorspan.

Add to BUFFER ZONES:

A spray buffer zone is NOT required for:

- Uses with hand-held application equipment permitted on this label,
- Low-clearance hooded or shielded sprayers that prevent spray contact with crop, fruit or foliage.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands) and sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands).

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:		
			Freshwater Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	
Field sprayer	Lowbush cranberries*, potato, sweet potato, carrot, bulb vegetables-green onion, fruiting vegetables, dried shelled pea and beans		1	1	1
	Brassica leafy vegetables, bulb vegetables-dry bulb onion, cucurbit vegetables		2	1	1
Aerial	Potato	Fixed wing	20	1	15
		Rotary wing	15	1	15

*Includes application by chemigation sprayer.

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

4d. Label amendments proposed for co-formulated product containing difenoconazole and azoxystrobin, PCP Reg. No. 32015

Add to DIRECTIONS FOR USE:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Reduce drift caused by turbulent wingtip vortices. Nozzle distribution along the spray boom length MUST NOT exceed 65% of the wing- or rotorspan.

Add to BUFFER ZONES:

A spray buffer zone is NOT required for:

- Uses with hand-held application equipment permitted on this label,
- Low-clearance hooded or shielded sprayers that prevent spray contact with crop, fruit or foliage.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands) and sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands).

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:		
			Freshwater Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	
Field sprayer	Soybean (hay), canola and Crop Subgroup 20A		1	1	0
	Potato, soybean, Crop Subgroup 6C (pulses)		1	1	1
Aerial	Soybean (hay),	Fixed wing	10	1	0

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:		
			Freshwater Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	
	canola and Crop Subgroup 20A	Rotary wing	10	1	0
	Soybean, Crop Subgroup 6C (pulses)	Fixed wing	15	1	15
		Rotary wing	15	1	15
	Potato	Fixed wing	20	1	15
		Rotary wing	15	1	15

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

4e. Label amendments proposed for co-formulated product containing difenoconazole and benzovindiflupyr, PCP Reg. No. 31526

Add to DIRECTIONS FOR USE:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

Airblast application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Reduce drift caused by turbulent wingtip vortices. Nozzle distribution along the spray boom length MUST NOT exceed 65% of the wing- or rotorspan.

Add to BUFFER ZONES:

A spray buffer zone is NOT required for:

- Uses with hand-held application equipment permitted on this label,
- Low-clearance hooded or shielded sprayers that prevent spray contact with crop, fruit or foliage.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:				
			Freshwater Habitat of Depths:		Estuarine/Marine Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m	
Field sprayer	Canola (Crop Subgroup 20A)		5	1	1	1	0
	Fruiting vegetables (Crop Group 8), tuberous and corm vegetables (Crop Subgroup 1C), cucurbit vegetables (Crop Group 9), small fruit vine climbing subgroup (Crop Subgroup 13-07F)		15	2	1	1	1
Airblast	Pome fruits (Crop Group 11)	Early season	45	20	2	0	2
		Late season	35	10	1	0	1
	Small fruit vine climbing subgroup (Crop Subgroup 13-07F)	Early season	50	25	2	0	3
		Late season	40	15	1	0	2
Aerial	Canola	Fixed wing	175	10	1	1	0
		Rotary wing	150	10	1	1	0
	Potato	Fixed wing	800	35	1	1	15
		Rotary wing	725	30	1	1	15

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

4f. Label amendments proposed for co-formulated product containing difenoconazole and benzovindiflupyr, PCP Reg. 31527

Add to DIRECTIONS FOR USE:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

DO NOT apply using aerial application equipment.

Add to BUFFER ZONES:

A spray buffer zone is NOT required for:

- Uses with hand-held application equipment permitted on this label,
- Low-clearance hooded or shielded sprayers that prevent spray contact with crop, fruit or foliage.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop	Buffer Zones (metres) Required for the Protection of:				
		Freshwater Habitat of Depths:		Estuarine/Marine Habitat of Depths:		Terrestrial Habitat:
		Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m	
Field sprayer	Turf	25	3	1	1	1

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and

apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

4g. Label amendments proposed for co-formulated product containing difenoconazole and cyprodinil, PCP Reg. No. 30827

Add to DIRECTIONS FOR USE:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) fine classification. Boom height must be 60 cm or less above the crop or ground.

Airblast application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

DO NOT apply using aerial application equipment.

Add to BUFFER ZONES:

A spray buffer zone is NOT required for:

- Uses with hand-held application equipment permitted on this label,
- Low-clearance hooded or shielded sprayers that prevent spray contact with crop, fruit or foliage.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:				
			Freshwater Habitat of Depths:		Estuarine/Marine Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m	
Field sprayer	Blueberry (lowbush, highbush), Currant, Elderberry, Gooseberry, Huckleberry, Highbush Cranberry		10	4	3	1	1
Airblast	Grape, Amur river grape	Early season	20	10	10	4	1
		Late season	10	5	5	2	1
	Pome fruit (Apple; Crab apple; Pear; Pear, Oriental; Quince)	Early season	25	15	5	2	2
		Late season	15	5	3	1	1
	Blueberry (lowbush, highbush), Currant, Elderberry, Gooseberry, Huckleberry, Highbush Cranberry	Early season	30	20	10	4	3
		Late season	20	10	5	2	2

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

4h. Label amendments proposed for co-formulated product containing difenoconazole and chlorothalonil, PCP Reg. No. 31537

Add to DIRECTIONS FOR USE:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

Airblast application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer

rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Reduce drift caused by turbulent wingtip vortices. Nozzle distribution along the spray boom length MUST NOT exceed 65% of the wing- or rotorspan.

Add to BUFFER ZONES:

A spray buffer zone is NOT required for:

- Uses with hand-held application equipment permitted on this label,
- Low-clearance hooded or shielded sprayers that prevent spray contact with crop, fruit or foliage.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:				
			Freshwater Habitat of Depths:		Estuarine/Marine Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m	
Field sprayer	Carrot, potato, tomato, cabbage, bulb onion, green onion, broccoli, Brussels sprouts, cabbage, cauliflower		2	1	2	1	1
Aerial	Potato	Fixed wing	70	4	70	20	15
		Rotary wing	55	1	55	15	15

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

3.0. Label amendments relating to the value assessment

1. Label amendments for commercial class products

General label statement revisions:

- Tank mix partners must be registered and clearly indicated by product name on difenoconazole product labels. Tank mix partners that are not currently registered for specified uses must be removed from product labels.

- The Minor Use Liability statement must be updated to the currently approved wording.

References

A. Information considered in the chemistry risk assessment

List of studies/information submitted by registrant

PMRA Document Number	Title
1252286	CGA 169374: Difenoconazole - Product Chemistry Summary (including Stereochemistry). DACO: 2.14.1, 2.14.10, 2.14.11, 2.14.12, 2.14.13, 2.14.2, 2.14.3, 2.14.4, 2.14.6, 2.14.7, 2.14.8, 2.14.9, 2.16, 2.5, 2.6, 2.7, 2.8, 2.9
1252295	CGA 169374: Physical and Chemical Properties, Stability to metals and metal ions and sunlight. DACO: 2.14.14
1252297	CGA 169374: Physical and Chemical Properties, Stability to metal ions. DACO: 2.14.14
1252280	CGA 169374 Starting Materials (Specifications and MSDS), Ciba-Geigy Corporation, 64 pages, DACO 2.11.2
1252279	CGA 169374 Difenoconazole Manufacturing Process, Ciba-Geigy Ltd., 1 page, DACO 2.11.3 CBI
1252257	Manufacturing Process Technical CGA-169374 Difenoconazole, Ciba-Geigy Corporation, 4 pages, DACO 2.11.3
1250793	Difenoconazole Technical Fungicide: TGAI Certification of Limits. DACO: 2.12.1 CBI
1252365	Difenoconazole Technical Fungicide TGAI Discussion of Formation of Impurities. DACO: 2.11.4 CBI
2576532	Difenoconazole - Analysis of Five Representative Batches Produced at [CBI Removed] and Final Report. DACO: 2.13.3 CBI
1252259	Discussion of Formation of Impurities Difenoconazole CGA 169372. DACO: 2.11.4 CBI
1252272	CGA 169374 Report on Toxic By-Products. DACO 2.13.1 CBI
2636335	Sub-Report 16.067A Reporting of Determination of PCDD/F Produced at [CBI Removed] Final Report. DACO: 2.13.4 CBI

B. Information considered in the toxicological risk assessment

List of studies/information submitted by registrant

PMRA Document Number	Title
1175763	1987, Acute oral toxicity study in rats, DACO: 4.2.1
1175764	1987, Acute dermal toxicity study in rabbits, DACO: 4.2.2
1175765	1991, Acute inhalation toxicity study in rats, DACO: 4.2.3
1175766	1991, Primary eye irritation study of CGA-169374 technical in rabbits, DACO: 4.2.4

PMRA Document Number	Title
1175767	1991, Primary dermal irritation study of CGA-169374 technical in rabbits, DACO: 4.2.5
1175769	1987, Dermal sensitization in guinea pigs, DACO: 4.2.6
1175771	1986, 13-week oral toxicity (feeding) study in the rat, DACO: 4.3.1
1175772	1987, 26-week oral toxicity study in dogs, DACO: 4.3.2
1175774	1988, Chronic toxicity study in dogs, DACO: 4.3.2
1175775	1992, Supplemental information for short term chronic toxicity study in dogs, DACO: 4.3.2
1175776	1989, Statistical analysis of survival and tumor data for oncogenicity study in mice, DACO: 4.4.3
1175777	1992, Supplemental information for oncogenicity study in mice, DACO: 4.4.3
1175778	1992, The effects of CGA-169374 tech. on selected biochemical and morphological liver parameters to male mouse, DACO: 4.4.3
1175779	1993, Assessment of the liver tumors observed in CD-1 mice fed excessive levels of difenoconazole (CGA-169374): a mitogenic response
1175780	1987, Teratology study in rabbits, DACO: 4.5.3
1175781	1992, Supplemental information for teratology study in rabbits, DACO: 4.5.3
1175782	1987, Subchronic toxicity/metabolism study in mice, DACO: 4.3.1, 4.5.9
1175790	1989, Oncogenicity study in mice, final report, DACO: 4.4.3
1175791	1989, Oncogenicity study in mice, final report, DACO: 4.4.3
1175792	1990, Gene mutation test – salmonella and Escherichia/liver-microsome test, DACO: 4.5.4
1175793	1985, Chromosome studies on human lymphocytes in vitro structural chromosomal aberration test, DACO: 4.5.6
1175794	1992, Structural chromosomal aberration test, micronucleus test, DACO: 4.5.7
1175795, 1175796, 1175797, 1175798	1989, Combined chronic toxicity and oncogenicity study of CGA-169374 technical in rats, DACO: 4.4.1, 4.4.2, 4.4.4
1175799	1989, Statistical analysis of survival and tumor data for combined chronic toxicity and oncogenicity study in rats, DACO: 4.4.1, 4.4.2, 4.4.4
1175800	1992, Supplemental information for combined chronic toxicity and oncogenicity study of CGA-169374 technical in rats, DACO: 4.4.1, 4.4.2, 4.4.4
1175801	1987, Developmental toxicity study of CGA-169374 technical (FL-851406) administered orally via gavage to CRL:COBS CD (SD) BR presumed pregnant rats, DACO: 4.5.2
1175802	1992, Supplemental information for developmental toxicity study of CGA-169374 technical (FL-851406) administered orally via gavage to CRL:COBS CD (SD) BR presumed pregnant rats, DACO: 4.5.2
1175803	1987, Subchronic toxicity/metabolism study in rats, DACO: 4.5.9
1175804, 1175805	1988, A two-generation reproductive study in albino rats, DACO: 4.5.1
1175809	1992, Supplemental information for a two-generation reproduction study in albino rats, DACO: 4.5.1

PMRA Document Number	Title
1175812	1990, Amendment to characterization and identification of major triazole-14C and phenyl 14C CGA-169374 metabolites in rats, DACO: 4.5.9
1175813	1992, Absorption, distribution and excretion of CGA-169374 in rats, DACO: 4.5.9
1175814	1990, Characterization and identification of major triazole-14C and phenyl-14C CGA-169374 metabolites in rats, DACO: 4.5.9
1175815	1987, Metabolism of triazole-14C-CGA-169374 in the rat, DACO: 4.5.9
1175816	1987, Metabolism of phenyl-14C-CGA-169374 in the rat, DACO: 4.5.9
1175817	1988, Metabolism of triazole-14C and phenyl-14C-CGA-169374 in the rat, DACO: 4.5.9
1175843	1986, Appendix E, historical control data for CRL:COBS CD (SD) BR rats – fetal alterations, DACO: 4.5.2
1175844	1992, Characterization and stability reports of CGA-169374 technicals used in toxicological studies
1175845	1988, Oral toxicity (feeding) study in dogs assessment of cataractogenic potential, final report, DACO: 4.3.8
1175847	1997, CGA 169374 technical: oncogenicity study on mice, subchronic toxicity/metabolism study in mice, neoplastic and nonneoplastic histopathology incidence summary tables, preliminary notes, DACO: 4.4.3
1175852	1990, Absorption, distribution and excretion of CGA-169374 in rats, DACO: 4.5.9
1176415	1987, 21-day dermal toxicity study in rabbits, DACO: 4.3.5
1180858	1992, CGA-169374: tests for other genotoxic effects autoradiographic DNA repair test on rat hepatocytes
1757579	1990, Acute oral toxicity study in mice, DACO: 4.2.1
1757593	2009, Difenoconazole dermal toxicity – Note to reviewer, DACO: 4.3.5
1757594, 1757595	2000, 28-day repeated dose dermal toxicity study in rats- final report, DACO: 4.3.5
1757620	1991, CGA189138 (metabolite of difenoconazole): reverse mutation assay of CGA189138 - final report, DACO: 4.5.4
1757621	2006, CGA189138 (metabolite of difenoconazole): reverse mutation assay of CGA189138 – study profile, DACO: 4.5.4
1757622	1991, CGA205374 (metabolite of difenoconazole): reverse mutation assay of CGA05374 - final report, DACO: 4.5.4
1757623	2006, CGA205374 (metabolite of difenoconazole): reverse mutation assay of CGA05374 – study profile, DACO: 4.5.4
1757624	1991, CGA205375 (metabolite of difenoconazole): reverse mutation assay of CGA205375 - final report, DACO: 4.5.4
1757625	2006, CGA205375 (metabolite of difenoconazole): reverse mutation assay of CGA205375 – study profile, DACO: 4.5.4
1757627	2001, Induction of chromosome aberrations in cultured Chinese hamster ovary (CHO) cells - final report, DACO: 4.5.5,4.5.6
1757628	2006, Induction of chromosome aberrations in cultured Chinese hamster ovary (CHO) cells – study profile, DACO: 4.5.5,4.5.6

PMRA Document Number	Title
1757630	2001, Cytogenetic test on Chinese hamster cells in vitro - final report, DACO: 4.5.5,4.5.6
1757631	2006, Cytogenetic test on Chinese hamster cells in vitro – study profile, DACO: 4.5.5,4.5.6
1757632	2001, In vitro cytogenetic assay in human lymphocytes - final report, DACO: 4.5.5,4.5.6
1757633	2006, In vitro cytogenetic assay in human lymphocytes – study profile, DACO: 4.5.5,4.5.6
1757637	2006, Preliminary acute neurotoxicity study in rats - final report, DACO: 4.5.12
1757638	2006, Acute neurotoxicity study in rats - final report, DACO: 4.5.12
1757640	2006, Acute neurotoxicity study in rats – study profile, DACO: 4.5.12
1757641	2006, 28-day dietary range finding study in rats - final report, DACO: 4.5.13
1757642	2006, Subchronic neurotoxicity study in rats - final report, DACO: 4.5.13
1757643	2006, Subchronic neurotoxicity study in rats - study profile, DACO: 4.5.13
1757644	2006, Difenoconazole – criteria that justify a waiver for a developmental neurotoxicity study – assessment, DACO: 4.5.14
1757645	1991, Acute oral toxicity study of CGA205374 in mice - final report, DACO: 4.8
1757646	1991, Acute oral toxicity study of CGA205375 in mice - final report, DACO: 4.8
2773253	1986, 28-day cumulative oral toxicity (feeding) study with CGA 169374 in the rat, DACO: 4.3.3
2773254	1986, CGA-169374 technical gene mutations test L5178Y/TK+/- mouse lymphoma mutagenicity test, DACO: 4.5.5
2773255	1986, Nucleus anomaly test in somatic interphase nuclei of Chinese hamster, DACO: 4.5.6
2773256	1985, CGA-169374 technical test for other genotoxic effects autoradiographic DNA repair test on rat hepatocytes, DACO: 4.5.8
2773257	2005, Difenoconazole (CGA 169374): request for restatement of 1994 EPA cancer classification and risk assessment approach using current terminology, DACO: 4.8
2830318	2017, Difenoconazole – 7-day study to investigate hepatocellular proliferation and liver enzymatic induction following administration of difenoconazole to male CAR/PXR double knock-out, C57BL/6NTAc wildtype and CD-1 wild-type mice, DACO: 4.8
2830319	2017, Difenoconazole – 1- and 7-day bridging study to investigate acute toxicity and toxicokinetics following administration of difenoconazole to male CAR/PXR double KO mice and hCAR/hPXR mice, DACO: 4.8
2830320	2017, Difenoconazole – 1- and 7-day bridging study to investigate acute toxicity and toxicokinetics following administration of difenoconazole to male CD-1 and C57BL/6J mice, DACO: 4.8
2830321	2016, Difenoconazole – pregnane X receptor (PXR) trans-activation assays with human, rat, and mouse PXR, DACO: 4.8
2830322	2016, Difenoconazole – CAR3 transactivation assay with mouse, rat, and human CAR, DACO: 4.8

PMRA Document Number	Title
2830323	2016, Difenoconazole – enzyme activities, mRNA levels, and DNA synthesis induction in cultured male CD-1 mouse hepatocytes, DACO: 4.8
2830325	2016, Difenoconazole – assessment of mouse cytochrome P450 2b and 3a inhibition by difenoconazole, final report, amendment 1, DACO: 4.8
2830326	2016, Difenoconazole – enzyme and DNA synthesis induction in cultured male human hepatocytes
2830327	2011, Difenoconazole – 28 day oral (dietary) immunotoxicity study in mice using sheep red blood cells as the antigen, DACO: 4.8
2838969	2018, Difenoconazole – mode of action and human relevance assessment of liver tumor induction in mice, DACO: 4.8
2875397	2018, Difenoconazole – historical control data on adrenal cortex histopathology in a 2-year rat chronic/carcinogenicity study assessment, DACO: 4.4.1, 4.4.2, 4.4.4
2838968	2018, Difenoconazole – applicability of stereoisomer content in mammalian toxicology studies to current production batches in Canada, DACO: 4.8

Additional information considered

Published information

PMRA Document Number	Title
2404256, 2867309	2011, EFSA – conclusion on the peer-review of the pesticide risk assessment of the active substance difenoconazole. DACO: 12.5
2937490	1999, USEPA – PP#5E04526. Difenoconazole (CGA-169374 Sico® 259 EC fungicide) in/on imported bananas and PP#2F4107. Difenoconazole (Dividend®) in/on wheat and animal RACs. HED risk assessment. DACO: 12.5
2937491	2007, JMPR – Difenoconazole, tox monograph, 201-272. DACO: 12.5.4
2937492	2006, European Commission, Draft Renewal Assessment (DAR) – Difenoconazole – List of endpoints. DACO: 12.5
2937493	2017, European Commission, Draft Renewal Assessment (DAR) – Difenoconazole Volume 3 Annex B.6. Toxicology. DACO: 12.5.4
2115162	2011, Health Canada – Difenoconazole Evaluation Report. ERC2011-06
2937494	2015, USEPA – Difenoconazole: Human Health Risk Scoping Document in Support of Registration Review. DACO: 12.5
2937495	2015, USEPA – Difenoconazole: Human Health Risk Assessment for Proposed New Foliar Uses on Globe Artichoke, Gingseng and Greenhouse Grown Cucumbers and Conversion of the Established Foliar Uses/Tolerances for Stone Fruit Group 12 and Tree Nut Crop Group 14 to Stone Fruit Group 12-12 and Tree Nut Group 14-12. DACO: 12.5
2937496	2007, USEPA – PP#: 6F7115. Difenoconazole in/on Fruiting Vegetables, Pome Fruit, Sugar Beets, Tuberous and Corm Vegetables, and Imported Papaya. Health Effects Division (HED) Revised Risk Assessment. DACO: 12.5

PMRA Document Number	Title
2937497	2017, USEPA – Difenoconazole: Human Health Risk Assessment for Proposed New Foliar Uses on Cotton, Rice and Wild Rice. DACO: 12.5

Unpublished information

PMRA Document Number	Title
1255052	1996, USEPA – Difenoconazole – USEPA DERs – CGA-169374: toxicology data, DACO: 12.5.2
1255063	1992, USEPA – Difenoconazole – USEPA DERs – CGA-169374: metabolism data, DACO: 12.5.2
1255073	1998, USEPA – Difenoconazole: 21-day dermal toxicity study in rabbits
1986684	2009, USEPA – Difenoconazole FQPA human health risk assessment for the section 3 registration, DACO: 12.5
2422477	2010, USEPA – Difenoconazole FQPA human health risk assessment to support establishment of import tolerances on mango and wax apple (also known as wax jambu)
2773268	2007, HED request for: Difenoconazole (CGA 169374): request for restatement of 1994 EPA cancer classification and risk assessment approach using current terminology, DACO: 4.8
2830328	2012, USEPA DER for: Difenoconazole – 28 day oral (dietary) immunotoxicity study in mice using sheep red blood cells as the antigen, DACO: 12.5

C. Information considered in the dietary risk assessment

Published information

PMRA Document Number	Title
ERC2011-06	Health Canada 2011. Evaluation Report of Difenoconazole. Pest Management Regulatory Agency, Health Canada, Ottawa, Ontario, Canada. ISSN: 1911-8082. 88 p.
PRDD99-01	Health Canada 1999. Proposed Regulatory Decision Document of Difenoconazole. Submission Management and Information Division, Pest Management Regulatory Agency, Health Canada, Ottawa, Ontario, Canada. 57 p.
2867309	European Food Safety Authority, 2011, Conclusion on the peer review of the pesticide risk assessment of the active substance difenoconazole - EFSA Journal 2011, Volume 9, Issue 1, DACO: 12.5.8
2937490	US EPA Memo, March 22, 1999. HED Risk Assessment. PP#5E04526 Difenoconazole in/on Imported Bananas and PP#2F4107 Difenoconazole in/on Wheat and Animal RACs

D. Information considered in the occupational and non-occupational risk assessment

List of studies/information submitted by registrant

PMRA Document Number	Title
1757977	2003, Difenoconazole 250 EC (A7402G): The Percutaneous Penetration Of [Triazole-U-14C] CGA169374 Formulated as SCORE 250 EC (A-7402G) Through Rat and Human Split-Thickness Skin Membranes (In Vitro)- Final Report, DACO: 5.8
1757978	2003, Difenoconazole 250 EC (A7402G): Dermal Absorption Of [Triazole-U-14C] CGA169374 Formulated as SCORE 250 EC (A-7402G) In The Rat (In Vivo)- Final Report, DACO: 5.8
2396870	2013, Agricultural Handler Exposure Task Force (AHETF) - Survey Results of Commercial and Downstream Seed Treating Facilities, DACO: 5.3,5.4
2313613	2009, Fluquinconazole and Prochloraz: Determination of operator exposure during cereal seed treatment with Jockey fungicide in Germany, United Kingdom and France, DACO: 5.4
2313618	2013, Observational Study to Determine Dermal and Inhalation Exposure To Workers in Commercial Seed Treatment Facilities: Mixing/Treating with a Liquid Pesticide Product and Equipment Clean-out, DACO: 5.3,5.4
2313619	2013, Determination of Operator Exposure to Tebuconazole during Treatment of Barley Seed with Raxil S (040 FS) in the UK, DACO: 5.3,5.4
2433727	2012, Fluquinconazole and Prochloraz: Determination of Operator Exposure during Cereal Seed Treatment with `Jockey¿ Fungicide in Germany, United Kingdom and France, DACO: 5.3,5.4,5.5
2313625	2013, GAUCHO 480 SC - Worker Exposure During On-farm and Commercial Seed Treatment of Cereals, DACO: 5.3,5.4
2313628	2013, Determination of Operator Exposure to Imidacloprid During Loading/Sowing of Gaucho Treated Maize Seeds under Realistic Field Conditions in Germany and Italy, DACO: 5.3,5.4
2313627	2013, Determination of Dermal and Inhalation Exposure to Operators During Loading and Sowing Seed Treated with Austral Plus Net Using Conventional or Pneumatic Sowing Machines, DACO: 5.3,5.4

Published information

PMRA Document Number	Title
2115162	Canada, 2011. Evaluation Report, ERC2011-06, Difenoconazole
2077133	Canada, 2012. Evaluation Report for Category B, Subcategory 2.1, 2.6, 3.11, 3.12 Application 2011-1385. Quadris Top

PMRA Document Number	Title
2214346	Canada, 2013a. Evaluation Report for Category B, Subcategory B.2.1, B.2.3, B.2.4, B.2.6, B.3.6, B.3.11, B.3.12 Application 2012-0168. Inspire Super Fungicide
2199164	Canada, 2013b. Evaluation Report for Category B, Subcategory 3.4 and 3.5 Application 2011-2432. Inspire Fungicide
2258349	Canada, 2013c. Evaluation Report for Category B, Subcategory 2.6 Application 2012-2314. Stadium Fungicide
2375023	Canada, 2014a. Evaluation Report for Category B Subcategory 2.6 Application 2013-2256. Bravo Top Fungicide
2461983	Canada, 2014b. Evaluation Report for Category B, Subcategory 2.6 and 3.12 Application 2013-5117. A20682 Fungicide
2528336	Canada, 2015a. Proposed Registration Decision, PRD2015-10, Difenoconazole
2448015	Canada, 2015b. Evaluation Report for Category B, Subcategory 3.1, 3.10, 3.11, 3.12, 3.13, 3.6 Application 2014-0882. Inspire Super Fungicide
2672084	Canada, 2016, Evaluation Report for Category B, Subcategory 4.1 Application
2843176	Canada, 2018a. Evaluation Report for Category B, Subcategory 3.1, 3.11, 3.12 Application 2016-4117. Exempla
2877896	Canada, 2018b. Re-evaluation decision RVD2018-11, Chlorothalonil and Its Associated End-use Products for Agricultural and Turf Uses
2873799	Canada, 2018c. Evaluation Report for Category C, Subcategory 6.3 (URMULE) Application 2018-1496. QUADRIS TOP
2993594	Canada, 2019. Evaluation Report for Category C, Subcategory 6.3 (URMULE) Application 2019-0783. Quadris Top Fungicide

Additional information considered

Unpublished information

PMRA Document Number	Title
1039216	1990, Exposures of Workers to Isofenphos during Planting of Oftanol Treated Canola Seed, DACO: 5.4

E. Information considered in the environmental risk assessment

List of studies/information submitted by registrant

PMRA Document Number	Title
2841009	Kling A., 2017. Difenoconazole - Acute Oral and Contact Toxicity to the Honey Bee, *Apis mellifera* L. under Laboratory Conditions. Eurofins Agroscience Services EcoChem GmbH, Niefern-Öschelbronn, Germany. Unpublished study report number S17-01522. (Syngenta report no. S17-01522). DACO 9.2.4.1
2841010	Kling A., 2017. Difenoconazole - Honey bee (*Apis mellifera* L.) 22 Day Larval Toxicity Test (Repeated Exposure). Eurofins Agroscience Services EcoChem GmbH, Niefern-Öschelbronn, Germany. Unpublished study report number S17-01517. (Syngenta report no. S17-01517). DACO 9.2.4.3
2773259	Ruhland S., 2015. Difenoconazole EC (A7402T) – Chronic Toxicity to the Honeybee *Apis mellifera* L. in a 10 Day Continuous Laboratory Feeding Study. BioChem agrar, Analytik GmbH, Gerichshain, Germany. Unpublished study report number 151048024B. DACO 9.2.4.4
2968083	Difenoconazole - Honey Bee (*Apis mellifera* L.) Chronic Oral Toxicity Test 10 Day Feeding Test in the Laboratory. DACO 9.2.4.4
2940338	Yeomans, P., Mould, R.. 2018. CGA169374 - Aerobic aquatic-sediment metabolism of 14CGA169374 final report. Smithers Viscient (ESG) Ltd., 108 Woodfield Drive, Harrogate, North Yorkshire. Laboratory Report Number 3201506. Sponsored by Syngenta Ltd. DACO 8.2.3.5.4.

Additional information considered

Published information

PMRA Document Number	Title
2115162	Canada, 2011. Evaluation Report, ERC2011-06, Difenoconazole
2258349	Canada, 2013c. Evaluation Report for Category B, Subcategory 2.6 Application 2012-2314. Stadium Fungicide
2528336	Canada, 2015a. Proposed Registration Decision, PRD2015-10, Difenoconazole
2855568	Canada, 2015c. Proposed Registration Decision, PRD2015-29, Difenoconazole