Proposed Re-evaluation Decision PRVD2019-09

Uniconazole-P and Its Associated End-use Products

Consultation Document

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Proposed Re-evaluation Decision

Under the authority of the *Pest Control Products Act*, all registered pesticides must be regularly 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.

Uniconazole-P is a plant growth regulator registered for use on greenhouse ornamentals and greenhouse tomato seedlings for transplant only.

This document presents the proposed regulatory decision for the re-evaluation of uniconazole-P including the proposed risk mitigation measures to further protect human health, as well as the science evaluation on which the proposed decision was based. All products containing uniconazole-P registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period, during which the public including the pesticide manufacturers and stakeholders may submit written comments and additional information to the PMRA. The final re-evaluation decision will be published taking into consideration the comments and information received.

Outcome of Science Evaluation

Uniconazole-P is used in the greenhouse ornamental industry and tomato transplant seedling production in greenhouses. It is widely used on economically important ornamentals to enhance aesthetic appearance through producing more desirable, compact, and marketable crops.

With respect to human health, dietary risks and risks to workers from most uses are considered to be acceptable under the current conditions of use. However, risks are not considered to be acceptable for workers conducting postapplication activities for greenhouse ornamentals grown for cut flowers. Therefore, the use on greenhouse ornamentals grown for cut flowers is proposed for cancellation. In addition, label updates are proposed to meet the current labelling standard and to improve clarity.

When used according to the current label directions of products containing uniconazole-P, risks to the environment are considered to be acceptable.

Proposed Regulatory Decision for Uniconazole-P

Under the authority of the *Pest Control Products Act* and based on the evaluation of currently available scientific information, Health Canada is proposing that products containing uniconazole-P are acceptable for continued registration in Canada, provided that the additional proposed risk mitigation measures are in place.

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment that must be followed by law. As a result of the re-evaluation of uniconazole-P, further risk mitigation measures for product

labels are being proposed.

Proposed Risk Mitigation Measures

The updated label statements and mitigation measures required, as a result of the re-evaluation of uniconazole, are summarized below. Refer to Appendix VIII for details.

Human Health

To protect workers, the following risk mitigation measures are proposed:

- Cancellation of uniconazole-P use on greenhouse ornamentals grown for cut flowers
- Clarifications on the required personal protective equipment for workers mixing/loading and applying uniconazole-P
- Specifying that the use of handheld mist blowers/airblast or handheld fogging equipment is not allowed
- An update to the early re-entry interval statement on the Sumagic product label (Registration No. 25781)

International Context

Uniconazole-P is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including the United States, Australia and New Zealand. No decision by an OECD member country to prohibit all uses of uniconazole-P for health or environmental reasons has been identified.

Next Steps

The public, including the registrants and other stakeholders, can submit additional information that could be used to refine risk assessments during the 90-day public consultation period[1] upon publication of this proposed re-evaluation decision.

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.

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

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

Science Evaluation

1.0 Introduction

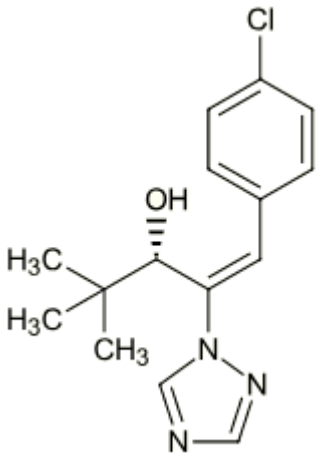
Uniconazole-P is a plant growth regulator used on greenhouse ornamentals and greenhouse tomato seedlings for transplant only. It can be used to retard the growth of greenhouse ornamentals including poinsettia, chrysanthemum, Easter lily, geranium and certain bedding plant species to produce more desirable, compact and marketable plants. It can also be used on greenhouse tomato seedlings for transplant to promote shorter, thicker and stronger stems to prevent stem breakage during the field transplanting process. Appendix I, Table 1 lists all uniconazole-P products that are currently registered under the authority of the *Pest Control Products Act* as of 21 February 2019. Unless otherwise indicated, these uses were supported by the registrants at the time of re-evaluation initiation and were therefore considered in the health and environmental risk assessments of uniconazole-P.

2.0 Technical Grade Active Ingredient

2.1 Identity

Common name		Uniconazole-P
Function		Plant Growth Regulator
Chemical Family		Triazole
Chemical name		
	1 International Union of Pure and Applied Chemistry (IUPAC)	(E)-(S)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl)pent-1-en-3-ol
	2 Chemical Abstracts Service (CAS)	(αS,βE)-β-[(4-chlorophenyl)methylene]-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol
CAS Registry Number		83657-17-4
Molecular Formula		$C_{15}H_{18}ClN_3O$

Structural Formula



Molecular Weight 291.78

Registration Number	Purity of the Technical Grade Active Ingredient
25780	78.6%
32171	79.4%

2.2 Physical and Chemical Properties

Property	Result
Vapour pressure at 25°C	5.3 mPa
Ultraviolet (UV)/visible spectrum	Does not absorb at □> 300 nm
Solubility in water at 20-25°C	8.41 mg/L
n-Octanol/water partition coefficient	logK_{ow} = 3.67 (for uniconazole)
Dissociation constant	Does not contain dissociable groups

3.0 Human Health

3.1 Toxicology Summary

Uniconazole-P is a plant growth regulator belonging to the triazole group of chemicals. A detailed review of the toxicological database for uniconazole-P 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 Practices.

The toxicology assessment for uniconazole-P also considered information found in the published

scientific literature. The scientific quality of the data is acceptable and the database is considered adequate to characterize the potential health hazards associated with uniconazole-P.

In a rat toxicokinetic study, ^{14}C-triazole labelled uniconazole-P was rapidly absorbed, extensively metabolized and rapidly eliminated following administration of single or repeated gavage doses. Slight sex-related differences in metabolism and excretion were noted. In females, urinary excretion was the predominant route of elimination regardless of dosing regimen. In males, urinary excretion was predominant after a single high oral dose, whereas fecal excretion was predominant following administration of single or repeated low oral doses. In both sexes, excretion was slightly prolonged following administration of a single high oral dose when compared to a single low oral dose. Excretion of radioactivity in expired air was negligible. Regardless of the dosing regimen, most of the radioactivity was excreted within 72 hours of the cessation of dosing.

Peak concentration in tissues was observed 1-8 hours post-dosing. Highest concentrations of radioactivity seven days post-dosing were detected in the adrenals, liver, fat, and kidneys. There was no evidence of tissue retention and residual radioactivity in the body was very low after seven days for all dosing regimens.

Uniconazole-P was extensively metabolized. The proposed major metabolic pathways in rats are two-stage oxidation of the methyl moiety of uniconazole-P and hydrolysis of the parent compound to release 1,2,4-triazole. Three major metabolites were identified in the urine and feces. A quantitative sex difference was observed for 1,2,4-triazole, one of the major metabolites, with higher levels detected in males (12-15% of the administered dose (AD) as compared to females (3-5% of AD). Unchanged uniconazole-P was detected solely in feces of both sexes, with higher amounts noted after high-dose administration.

In dogs, uniconazole-P was of low acute oral toxicity, while in rats it showed either slight or high acute oral toxicity, depending on the vehicle used. Uniconazole-P was of low dermal and inhalation toxicity in rats, it was minimally irritating to the rabbit eye, non-irritating to the rabbit skin and not a dermal sensitizer in guinea pigs when assessed by the Buehler method.

Repeat-dose studies conducted with diet or capsule in rats and dogs respectively, resulted in decreased body weight, effects on the liver and clinical chemistry changes. Hepatic effects included enlarged livers, cytoplasmic vacuolation and other histopathological findings. Several clinical chemistry parameters were altered including alkaline phosphatase and alkaline transaminase activity, both of which were increased. In rats and dogs, hepatic effects were similar following short- and long-term administration, but were observed at lower dose levels in long-term studies. Increased duration of dosing also resulted in a slight increase in severity of treatment-related toxicity in rats and dogs.

In a repeat-dose dermal toxicity study in rats, increased skin irritation was noted at the site of application. Despite a high background level of skin lesions, skin irritation noted in treated animals could not be conclusively dismissed and was, therefore, attributed to uniconazole-P exposure.

Evidence of systemic toxicity, including increased liver weights and histopathological findings in

the liver, was noted in this dermal study. No repeat-dose inhalation toxicity study was available.

In in vitro studies, uniconazole-P was negative for the induction of gene mutation in Salmonella, negative for sister chromatid exchange in hamster K1 cells, but was weakly clastogenic in a chromosomal aberration assay in hamster K1 cells in the presence of metabolic activation. In a supplemental in vitro study, uniconazole-P was negative for unscheduled DNA synthesis in rat hepatocytes. Two in vivo mouse micronuclei tests conducted via the intraperitoneal route were negative. Overall, the weight of evidence suggests that uniconazole-P is not genotoxic.

In a 2-year dietary chronic toxicity/oncogenicity study in rats, a slight increase in the incidence of astrocytoma was noted in male rats at the highest dose level. The incidence was only slightly above the historical range and therefore, the increase in astrocytoma in high-dose males was considered equivocal in terms of its relationship to treatment. In an 18-month dietary oncogenicity study in mice, increased liver weights and histopathology were noted in both sexes at the high dose level. A statistically significant increase in the incidence of hepatocellular adenomas and of the combined incidence of hepatocellular adenomas and carcinomas was observed in males at the high-dose level. An increase in the incidence of hepatocellular carcinoma was also noted in high dose males; however, the incidence was at the upper limit of the historical control range.

Mechanistic studies were provided to support a proposed mode of action (MOA) for liver tumour formation based on constitutive androstane receptor (CAR) induction. This MOA involves activation of CAR, followed by induction of specific metabolic enzymes which results in a transient increase in hepatocellular proliferation, formation of altered hepatic foci and ultimately liver tumours. The mechanistic studies offered qualitative evidence of liver cytochrome 2 (CYP2) induction following dietary exposure to uniconazole-P for two and four weeks at carcinogenic dose levels. Liver enzyme induction by uniconazole-P, was similar to the pattern observed following phenobarbital administration, a known CAR activator, and was associated with increased liver weight and hepatocellular hypertrophy. However, the available mechanistic studies failed to demonstrate an increase in hepatocellular replicative DNA synthesis following uniconazole-P exposure. Dose concordance of key and associative events was also not adequately demonstrated. Overall, when the results from the mechanistic and long-term studies were considered, there was insufficient evidence to support the proposed threshold-based MOA. Therefore, a linear low dose extrapolation (q_1*) approach was used for the cancer risk assessment based on the combined incidence of hepatocellular adenomas and carcinomas in male mice.

In a rat dietary two-generation reproductive toxicity study, there was no evidence of reproductive toxicity or sensitivity of the young. Systemic toxicity in parental animals, including decreased body weight and liver effects, was similar to that observed in general repeat-dose oral toxicity studies and was noted at dose levels which were similar to those administered to non-pregnant animals.

Effects in the offspring were limited to decreased pup body weights in both the F_1 and F_2 generations from post-natal day seven onwards, which occurred at a dose level causing maternal toxicity.

In a rat gavage developmental toxicity study, an increased incidence of fetal skeletal variations (14th and cervical ribs) was observed in the presence of maternal toxicity (decreased bodyweights and body weight gains). In a rabbit gavage developmental toxicity study, no evidence of developmental toxicity was noted at the highest dose level tested. In this study, only marginal effects on body weight were noted in maternal animals at the high-dose level. However, based on the results from a dose range-finding study which showed that maternal animals could not have tolerated a significantly higher dose of uniconazole-P, the main study was considered acceptable.

There was no evidence of treatment-related malformations or sensitivity of the young in either rats or rabbits.

There were no guideline neurotoxicity studies available. In a published study that specifically assessed motor activity, no evidence of hyperactivity was observed on the day of dosing, following acute gavage administration of uniconazole-P (PMRA# 2873579). In registrant-submitted toxicology studies, potential evidence of neurotoxicity included decreased spontaneous activity and limb paralysis, following single high oral doses of uniconazole-P in rats and mice. However, no evidence of selective neurotoxicity was noted in repeat-dose dietary toxicity studies at similar dose levels. Therefore, concern for the neurotoxic potential of uniconazole-P is low.

The toxicology reference values used for human health risk assessment are summarized in Table 1 of Appendix II. The results of toxicology studies conducted in laboratory animals with uniconazole-P are summarized in Table 2 of Appendix II. The identity of the major uniconazole-P rat metabolites is presented in Table 3 of Appendix II.

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 standard complement of required studies for risk assessment were available for uniconazole-P, including oral gavage developmental toxicity studies in rats and rabbits and a dietary two-generation reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of fetuses or offspring compared to parental animals in the reproductive or developmental toxicity studies. In the two-generation rat reproductive toxicity study, at the highest dose level, decreased body weight in offspring was observed in the presence of maternal toxicity, which was characterized by decreased body weight and histopathological findings in the liver. Developmental effects comprised of an increased incidence of fetal skeletal variations in the rat developmental toxicity study also occurred in the presence of maternal toxicity. There was no evidence of developmental toxicity observed in the rabbit developmental toxicity study.

Overall, endpoints in the young were well-characterized and not considered serious in nature. On the basis of this information, the PCPA factor was reduced to 1-fold.

3.2 Dietary Exposure and Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Dietary exposure 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.

The PMRA considers limiting use of a pesticide when exposure exceeds 100% of the reference dose or when lifetime cancer risk estimate exceeds 1×10^{-6} (one-in-a-million). The PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute, chronic and cancer risk assessment procedures.

Canadian Maximum Residue Limits (MRLs) are established for uniconazole-P. MRLs for uniconazole-P are currently specified for commodities under crop subgroup 8-09A at 0.01ppm. Residues in all other agricultural commodities, including those approved for treatment in Canada but without specific MRLs, are regulated under Subsection B.15.002 (1) of the *Food and Drugs Regulations*, which requires that residues do not exceed 0.1ppm. A complete list of MRLs specified in Canada can be found on the PMRA's MRL Database, an online query application that allows users to search for specified MRLs, regulated under the *Pest Control Products Act*, both for pesticides or food commodities.

Acute, chronic and cancer dietary exposure and risk assessments for uniconazole-P were conducted using the Dietary Exposure Evaluation Model – Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02, 05-10-c) program, which incorporates consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the year 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 the PMRA's Science Policy Note (SPN 2014-01), *General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments.* For more information on the dietary risk estimates or the residue chemistry information used in the dietary assessment, see Appendix III and Appendix IV.

3.2.1 Determination of Acute Reference Dose (ARfD)

To estimate acute dietary risk, the maternal NOAEL of 5 mg/kg bw/day from the rat gavage developmental toxicity study was selected based on a decrease in maternal body weight gain within the first few days of dosing at the LOAEL of 25 mg/kg bw/day.

Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies

variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to onefold. Thus, the composite assessment factor (CAF) is 100.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{5 \text{ mg/kg bw/day}}{100} = 0.05 \text{ mg/kg bw}$$

3.2.2 Acute Dietary Exposure and Risk Assessment

The acute dietary risk was calculated considering the highest ingestion of residues of uniconazole-P that would be likely on any one day, and using food consumption 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 estimated exposure is less than the ARfD, the acute dietary exposure is acceptable.

The acute exposure assessment was conducted using the residue estimates from Canadian MRLs/American Tolerances, into the dietary exposure evaluation model (DEEM), and all crops were assumed to have been 100% treated.

The acute dietary exposure estimates at the 95th percentile were below 1% of the ARfD for the general population and all other subpopulations and thus, the acute risk is considered to be acceptable.

3.2.3 Determination of Acceptable Daily Intake (ADI)

To estimate risk from repeated dietary exposure, the one-year toxicity study in the dog and the two-year dietary chronic toxicity/oncogenicity study in the rat were considered co-critical studies. The effect levels established in these studies were similar, and these studies provide the lowest NOAELs in the database. In the one-year dog toxicity study, the NOAEL of 2 mg/kg bw/day was established based on increased liver weight, histopathological changes in the liver and elevated enzyme activity indicative of hepatotoxicity at the LOAEL of 20 mg/kg bw/day. In the rat two-year chronic toxicity/oncogenicity study, the NOAEL of 2 mg/kg bw/day was established, based on effects at the LOAEL of 9 mg/kg bw/day that included reduced bodyweights and liver effects including increased weight and increased incidence of histopathological findings. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. Thus, the CAF is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2 \text{ mg/kg bw/day}}{100} = 0.02 \text{ mg/kg bw/day}$$

The ADI provides a margin greater than 2400 to the dose level where an equivocal increase in the incidence of astrocytomas was observed in the rat two-year chronic toxicity/oncogenicity study.

3.2.4 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated using average consumption of different food residue values. The estimated exposure was 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 harmful effects. When the estimated exposure is less than the ADI, the chronic dietary exposure is acceptable.

The chronic dietary assessment was conducted using residue estimates from Canadian MRLs/American Tolerances into DEEM, and all crops were assumed to have been 100% treated.

The chronic dietary exposure from food sources were below 1% of the ADI for the general population and all other subpopulations and thus, the chronic risk is considered to be acceptable.

3.2.5 Cancer Assessment

There was evidence of oncogenicity in male mice following exposure to uniconazole-P. There was some evidence supporting a threshold-based mechanism for the observed liver tumours; however, the proposed MOA was not fully supported based on limitations in the information provided. Therefore, a linear low dose extrapolation (q_1*) approach was used for risk assessment. A q_1* of 1.76×10^{-2} $(mg/kg\ bw/day)^{-1}$ was derived based on the combined incidence of hepatocellular adenomas and carcinomas noted in male mice in the 18-month dietary oncogenicity study. A threshold approach to risk assessment was used for the increased incidence of astrocytomas in high dose males observed in the rat two-year chronic toxicity/oncogenicity study, given the equivocal nature of this effect relative to treatment. Refer to section 3.1 for additional details.

3.2.6 Cancer Dietary Exposure and Risk Assessment

The cancer dietary risk was calculated using average consumption of different food residue values. The estimated chronic exposure was then compared to the cancer potency factor (q_1*). A lifetime cancer risk that is equal or below 1×10^{-6} (one-in-a million) indicates acceptable risk for the general population when exposure occurs through pesticide residues in or on food, or to otherwise unintentionally exposed persons.

Based on the q_1* approach, the lifetime cancer risk estimate from food only exposure is 2×10^{-7} for the general population, and therefore the cancer risk is considered to be acceptable.

3.3 Exposure from Drinking Water

Based on the registered use pattern (indoor application only) of uniconazole-P to greenhouse tomato seedlings, and, ornamentals, residues are expected to be minimal in drinking water. An estimated environmental concentration (EEC) value is not required for the currently registered uses of uniconazole-P.

3.4 Occupational and Non-Occupational Exposure and Risk Assessment

Non-Cancer Risk Assessment

Non-cancer risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies 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 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.

Cancer Risk Assessment

The cancer risk is determined by calculating the lifetime average daily dose (LADD) from dermal, inhalation and/or oral exposure. The LADD is multiplied by the cancer potency factor (q_1*) to obtain a lifetime cancer risk estimate, which is a measurement of probability. A lifetime cancer risk in the range of 1×10^{-5} in worker populations and in the range of 1×10^{-6} in residential populations is generally acceptable.

3.4.1 Toxicology Endpoint Selection for Occupational and Non-Occupational Exposure

Short- and Intermediate-term Dermal Route

For short- and intermediate-term exposures via the dermal route, a NOAEL of 5 mg/kg bw/day from the 28-day dermal study in rats was selected for risk assessment. Increased liver weight and histopathological findings in the liver were noted in this study in females at the LOAEL of 25 mg/kg bw/day. For occupational scenarios, the target MOE selected for this endpoint is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

For the residential risk assessment, 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 PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. The selection of this study and target MOE is considered to be protective of all populations.

Short- and Intermediate-term Inhalation Route

For short- and intermediate-term risk assessment via the inhalation route, a repeat-dose inhalation toxicity study was not available. Therefore, the developmental NOAEL of 5 mg/kg bw/day from the developmental toxicity study in rats was selected based on an increased incidence of fetal skeletal variations at the LOAEL of 25 mg/kg bw/day. The target MOE is 100 and includes uncertainty factors of 10-fold for interspecies extrapolation, and 10-fold for intraspecies variability. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Long-term Dermal and Inhalation Route

For long-term dermal and inhalation risk assessment, the one-year toxicity study in the dog and the two-year dietary chronic toxicity/oncogenicity study in the rat were considered co-critical studies. The effect levels established in these studies were similar, and these studies provide the lowest NOAELs in the database. In the one-year dog toxicity study, a NOAEL of 2 mg/kg bw/day was established based on increased liver weight, histopathological changes in the liver and elevated enzyme activity indicative of hepatotoxicity at the LOAEL of 20 mg/kg bw/day. In the rat two-year chronic toxicity/oncogenicity study, a NOAEL of 2 mg/kg bw/day was established, based on effects at the LOAEL of 9 mg/kg bw/day that included reduced bodyweights and liver effects including increased weight and increased incidence of histopathological findings. The target MOE is 100 and includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of these studies and target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Cancer Assessment

There was evidence of oncogenicity in male mice following exposure to uniconazole-P. There was some evidence supporting a threshold-based mechanism for the observed liver tumours; however, the proposed MOA was not fully supported based on limitations in the provided information. Therefore, a linear low dose extrapolation (q_1*) approach was used for risk assessment. A q_1* of 1.76×10^{-2} $(mg/kg\ bw/day)^{-1}$ was derived based on the combined incidence of hepatocellular adenomas and carcinomas noted in male mice in the 18-month dietary carcinogenicity study. A threshold approach to risk assessment was used for the increased incidence of astrocytomas in high-dose males observed in the rat two-year chronic toxicity/oncogenicity study, given the equivocal nature of this effect relative to treatment.

3.4.2 Dermal Absorption Factor

A dermal absorption value of 46% was determined for uniconazole-P based on a percutaneous absorption study in male rats. This dermal absorption value is considered to be conservative in that it assumes that all residues in the solvent washes and skin are bioavailable. It is not expected to underestimate absorption.

3.4.3 Occupational Exposure and Risk Assessment

There is potential for exposure to uniconazole-P through mixing, loading, or applying the pesticide, and when entering a treated site to conduct postapplication activities such as scouting.

3.4.3.1 Mixer/loader/Applicator Exposure and Risk Assessment

Based on the current use pattern, potential exposure of mixers/loaders/applicators in greenhouses is expected to range from short/intermediate (tomato seedlings) to long-term duration (ornamentals) and to occur via both dermal and inhalation routes of exposure.

The following exposure scenarios were assessed based on the currently registered use pattern:

- mixing/loading of liquid formulation and applying using manually-pressurized handwand
- mixing/loading of liquid formulation and applying using mechanically-pressurized handgun
- mixing/loading of liquid formulation and applying using backpack sprayer
- mixing/loading of liquid formulation for overhead irrigation application

No appropriate chemical-specific handler exposure data were available for uniconazole-P; therefore, dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database (PHED) Version 1.1, and the Agricultural Handler Exposure Task Force (AHETF).

Exposure of mixers/loaders/applicators was estimated using unit exposure (UE) values from PHED: hand-held equipment and AHETF: open mixing/loading of liquid for workers wearing Personal Protective Equipment (PPE) consisting of a long-sleeved shirt, long pants, and chemical-resistant gloves.

Toxicological reference values used in the assessment are summarized in Appendix II. Dermal and inhalation risks were not combined as there is no common endpoint of concern for dermal and inhalation routes of exposure.

The risk assessment for a mixer/loader/applicator is presented in Appendix V (Tables 5.1 and 5.2). The estimated dermal and inhalation MOEs for workers wearing PPE specified above are greater than the target MOEs and lifetime cancer risks are less than 1×10^{-5}. On this basis, non-cancer and cancer risks are considered to be acceptable for workers mixing/loading and applying uniconazole-P to greenhouse tomato seedling and ornamentals. PPE listed on the current end-use product labels, including waterproof rain gear (for example, Tyvek coveralls) and a respirator, is expected to further reduce the potential for exposure.

To meet the current labelling standards, clarifications to PPE requirements are proposed for the end use product labels (Appendix VIII).

Mist blowers or fogging equipment is not expected to be used for uniconazole-P applications. Therefore, for clarity, a standard label statement advising that the use of such equipment is not allowed is proposed for the end use product labels (Appendix VIII).

3.4.3.2 Postapplication Exposure and Risk Assessment

For workers entering greenhouses to conduct postapplication activities for greenhouse tomato seedlings or ornamentals, dermal exposure is considered to be the primary route of exposure. Considering the low volatility of this active ingredient (4×10^{-5} mm Hg at 20 $^{\circ}$C) and assuming at least 12 hours have passed before entering the treated site, inhalation exposure to uniconazole-P is not expected for postapplication workers re-entering treated sites.

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 non-cancer and cancer risks are considered to be acceptable for postapplication worker activities.

A standard 12-hour REI is currently required on both end-use product labels. In addition, one of the end-use product labels (Sumagic, Registration No. 25781) allows early re-entry provided that workers wear PPE specified on the product label. An update to this statement is proposed on the Sumagic product label (Registration No. 25781), to clarify that only applicators are allowed to enter treated areas within 12-hours for short-term task not involving hand labour if at least 4 hours has passed since application and PPE specified on the label is worn (Appendix VIII).

Greenhouse tomato seedlings

Since uniconazole-P is applied to greenhouse tomato transplants at early stages of growth (2-4 leaf stage), the main route of worker exposure is not expected to be through foliar contact but through the handling of treated seedling plugs during transplanting tomato. Exposure resulting from transplanting is expected to be of a short-term duration.

The results of the postapplication risk assessment are presented in Appendix VI, Table 1. For postapplication workers transplanting tomato seedlings, the estimated MOE is above the target dermal MOE and the lifetime cancer risk is less than 1×10^{-5}. On this basis, non-cancer and cancer risks for workers transplanting tomato seedlings are considered to be acceptable. A standard 12-hour REI requirement is included on the current product label. No additional mitigation measures are proposed.

Ornamentals

Uniconazole-P is expected to be used on cut flowers (specifically, chrysanthemums). Therefore, the postapplication risk assessment considered potential risks to workers conducting postapplication activities for ornamentals (except cut flowers) and for cut flowers (specifically, Chrysanthemums).

Based on the currently registered use pattern for uniconazole-P, exposure of workers is expected to be of a long-term duration given potential multiple crop cycles in greenhouses.

Exposure of postapplication workers was estimated using activity-specific TC and default dislodgeable foliar residue (DFR) values. The DFR refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant. The transfer coefficient (TC) is a measure of the relationship between exposure and DFRs for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies. The TCs are specific to a given crop and activity combination and reflect standard agricultural work clothing worn by adult workers. The activity-specific TC from the Agricultural Re-Entry Task Force (ARTF) was used.

Due to the limitations of the available chemical-specific DFR study, the use of default DFRs was considered to be more appropriate. Default peak (on the day of application; day 0) and 30-day time-weighted average (TWA) DFR values were calculated assuming a 25% residue deposition following a single or multiple applications (minimum re-treatment interval (RTI) as per current product labels) and a residue dissipation rate of 2.3% per day.

Ornamentals (except cut flowers)

The results of the postapplication risk assessment are presented in Appendix VI, Table 2. The estimated MOE is above the target dermal MOE and the lifetime cancer risk is less than 1×10^{-5}. On this basis, non-cancer and cancer risks for postapplication workers coming in contact with treated greenhouse ornamentals (except cut flowers) are considered to be acceptable. The standard minimum 12-hour REI requirement is currently included on current products labels. No additional mitigation measures are proposed.

Ornamentals – cut flowers

The results of the postapplication risks assessment for ornamentals grown for cut flowers are presented in Appendix VI, Table 3. For workers coming in contact with treated chrysanthemums, the estimated MOEs range from 98 to 6849 (target dermal MOE of 100). The MOE of 98 (for disbudding and hand pruning) is considered to be acceptable given the conservatism in the risk assessment. On this basis, the non-cancer risks to postapplication workers are considered to be acceptable. The lifetime cancer risks are above 1×10^{-5} for workers involved in hand harvesting and/or disbudding and hand pruning (Appendix VI, Table 3). On this basis, the cancer postapplication risks are not considered to be acceptable under current conditions of use. REIs ranging from 4 to 18 days would be necessary to mitigate the potential risks. The estimated REIs may not be feasible.

Based on the results of the risk assessment, the PMRA proposes to cancel the use of uniconazole-P on greenhouse ornamentals grown for cut flowers (Appendix VI). The stakeholders are invited to provide input regarding the feasibility of the proposed mitigation measures.

3.4.4 Non-Occupational Exposure and Risk Assessment

Domestic-class products containing uniconazole-P are not registered in Canada; therefore, residential handler exposure is not anticipated. The potential for bystander exposure during commercial indoor (greenhouse) applications of uniconazole-P is considered to be negligible.

The only source of potential residential exposure is from contact with commercially treated ornamentals (retail plants).

Residential exposure is expected to occur via the dermal route on an intermittent basis and to be of short-term duration. Dermal exposure of adults, youth, and children was assessed according to the United States Environmental Protection Agency (USEPA) Standard Operating Procedures for Residential Pesticide Exposure Assessment (section 4) (USEPA, 2012). The lifetime cancer risk was estimated using conservative assumptions such as the maximum registered application rate for ornamentals and a lifetime exposure. The results of the residential postapplication risks

assessment are presented in Appendix VII, Table 1. The estimated MOEs are above the target dermal MOE and the lifetime cancer risk is $1 \times x10^{-6}$. On this basis, non-cancer and cancer risks for individuals handling retail plants are considered to be acceptable. No additional risk mitigation measures are proposed.

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 from all known or plausible exposure routes (oral, dermal and inhalation).

For uniconazole-P, dietary exposure was limited to food only, which was determined to be acceptable. The only source of potential residential exposure is from contact with commercially treated ornamental plants (retail plants), and it is considered to be acceptable. Under the current conditions of use, the residential exposure to uniconazole-P residues on retail plants is expected to occur on an intermittent basis and for short-term duration. On this basis, the aggregate risk is considered to be acceptable. No additional mitigation measures are proposed.

3.6 Cumulative Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Uniconazole-P 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, triazole 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 document.

3.7 Incident Reports

As of 23 January 2019, no human or domestic animal incident reports involving uniconazole-P have been submitted to the PMRA.

4.0 Environment

Uniconazole-P is registered in Canada for greenhouse use only and can enter the environment when it is present in greenhouse process water discharge.

4.1 Fate and Behaviour in the Environment

Uniconazole-P has a low solubility in water (8.41 mg a.i./L), and is not volatile (vapour pressure of 4.0×10^{-5} mm Hg (5.3×10^{-3} Pa) at 20 °C and 6.7×10^{-5} mm Hg (8.9×10^{-3} Pa) at 25 °C). The octanol/water partitioning coefficient (log K_{ow}) is 3.7.

Hydrolysis did not occur at pH 5, 7, and 9. Photolysis in water (DT_{90} of 4 to 10 days) is expected

to be a significant route of transformation of uniconazole-P (primary transformation products are Z isomers). Phototransformation on soil (DT_{50} of 78.5 days) is not expected to be a significant route of transformation of uniconazole-P.

Uniconazole-P is expected to be persistent in soil under aerobic conditions (DT_{50} > 1 year). No major transformation products were reported. Uniconazole-P had a low to moderate potential for mobility in soil (adsorption K_{oc} range from 185 to 873). A standard leaching hazard label statement is currently included on both commercial-class product labels.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. For greenhouse uses of uniconazole-P, potential exposure was considered for aquatic organisms (potential for exposure of adjacent aquatic habitats to discharge of process waters from the greenhouse), and a qualitative risk assessment was considered.

Uniconazole-P is classified as practically non-toxic to honeybees (LD_{50} > 227 µg/bee). It is expected to be slightly to moderately toxic to freshwater fish (LC_{50} 14.8 and 7.5 mg/L for rainbow trout and carp, respectively) and slightly toxic to freshwater invertebrates (EC_{50} > 10 mg/L for *Daphnia magna*) (USEPA, 2015).

Based on the current use pattern (indoor use), minimal exposure to non-target terrestrial organisms, and no direct exposure to aquatic organisms are expected. However, the potential for indirect exposure to the discharge of greenhouse process water was considered. To minimize the potential exposure of aquatic organisms from the discharge of greenhouse process water, the current labels for the end-use products include use directions prohibiting the discharge of greenhouse process water.

Overall, the risk to the environment is considered to be acceptable under the current conditions of use. No additional mitigation measures are proposed.

4.3 Environmental Incident Reports

As of 23 January 2019, there were no environmental incidents received for the active ingredient uniconazole-P.

Three incidents were reported to the United States Ecological Incident Information System (EIIS) (1995-1998). One incident reported direct treatment of uniconazole to two oak trees causing damage to the plants. Two incidents were reported in which uniconazole was directly applied to petunia plants (one indicated treatment occurred in a greenhouse). Plant damage including brownish spots of leaves and scarring on stem tissue was reported.

Treatment details of the incidents were not reported in EIIS, however, the USEPA determined the certainty of the oak tree incidents as probable and the petunia plants as possible. No additional risk mitigation measures were identified as a result of these incidents.

5.0 Value Assessment

Uniconazole-P is important for the greenhouse ornamental industry and tomato transplant seedling production in greenhouses. It is widely used on economically important ornamentals to enhance aesthetic appearance through producing more desirable, compact, and marketable crops. Compared to alternative active ingredients used as plant growth retardants, uniconazole-P is registered for use on wider range of ornamental crops, is effective at lower rates of application, and has longer lasting results. Uniconazole-P is the only plant growth regulator (PGR) registered for use on greenhouse tomato seedlings for transplant to promote shorter, thicker and stronger stems to prevent stem breakage during the field transplanting process.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

In accordance with the PMRA Regulatory Directive DIR99-03,[3] the assessment of uniconazole-P against Track 1 criteria of Toxic Substances Management Policy (TSMP) under *Canadian Environmental Protection Act* was conducted. It determined that:

- Uniconazole-P does not meet all Track 1 criteria, and is not considered a Track 1 substance.

- Uniconazole-P does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical grade active ingredient are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette.*[4] The list is used as described in the PMRA

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

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

Notice of Intent NOI2005-01[5] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[6] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Uniconazole-P technical grade active ingredient product does not contain contaminants of health or environmental concern.

7.0 Conclusion of Science Evaluation

With respect to human health, risks are not considered to be acceptable for workers conducting postapplication activities for greenhouse ornamentals grown for cut flowers. Therefore, the use on greenhouse ornamentals grown for cut flowers is proposed for cancellation. In addition, label updates are proposed to meet the current labelling standard and to improve clarity. Exposure from the remaining uses is unlikely to affect human health when used according to the additional proposed label directions.

Dietary exposure was limited to food only (no exposure via drinking water), which was considered to be acceptable. The only source of potential residential exposure is from contact with commercially treated ornamental plants (retail plants), and it is considered to be acceptable. Under the current conditions of use, the residential exposure to uniconazole-P residues on retail plants is expected to occur on an intermittent basis and for short-term duration. On this basis, the aggregate risk is considered to be acceptable. No additional mitigation measures are proposed.

Uniconazole-P is used in the greenhouse ornamental industry and tomato transplant seedling production in greenhouses. It is widely used on economically important ornamentals to enhance aesthetic appearance through producing more desirable, compact, and marketable crops. When used according to the current label directions, risks to the environment are considered to be acceptable.

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

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

List of Abbreviations

abs	absolute
AD	administered dose
ADI	acceptable daily intake
a.i.	active ingredient
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARfD	acute reference dose
ARTF	Agricultural Re-Entry Task Force
AST	aspartate aminotransferase
BrdU	bromodeoxyuridine
BSP	bromsulphthalein
BUN	blood urea nitrogen
bw	body weight
bwg	bodyweight gain
C	Celsius
CAF	composite assessment factor
CAR	constitutive androstane receptor
CHO	Chinese hamster ovary
CMC	carboxymethyl cellulose
DA	dermal absorption
DEEM	Dietary Exposure Evaluation Model
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
EC_{50}	effective concentration on 50% of the population
EEC	Estimated Environmental Concentration
F_1	first generation
F_2	second generation
fc	food consumption
FCID™	Food Commodity Intake Database™
fe	food efficiency
g	gram(s)
GAP	Good Agricultural Practice
GD	gestation day
GI	gastrointestinal
GSH	glutathione
ha	hectare
HC	historical control
Hct	hematocrit
Hgb	hemoglobin
hr(s)	hour(s)

K_{oc}	organic-carbon partition coefficient
kg	kilogram(s)
L	litre(s)
LADD	lifetime average daily dose
LC_{50}	median lethal concentration
LD	lactation day
LD_{50}	median lethal dose
log K_{OW}	octanol-water partition coefficient
LOAEL	lowest observed adverse effect level
µM	micromolar
m	meter(s)
mg	milligram(s)
MAS	maximum average score for 24, 48 and 72 hours
MIS	maximum irritation score
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MOA	mode of action
MOE	margin of exposure
MRL	Maximum Residue Limit
MTD	Maximum tolerated dose
NHANES	National Health and Nutrition Examination Survey
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
P	parental generation
PCE	polychromatic erythrocytes
PCPA	*Pest Control Products Act*
PEG	polyethylene glycol
pH	measure of the acidity or basicity of an aqueous solution
PHED	Pesticide Handlers Exposure Database
PHI	pre-harvest interval
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppm	parts per million
q_1*	cancer potency factor
RBC	red blood cells
REI	restricted entry interval
rel	relative
RTI	retreatment interval
ss	statistically significant
SCE	sister chromatid exchange
TC	transfer coefficient
TSMP	Toxic Substances Management Policy
TWA	time-weighted average
UDS	unscheduled DNA synthesis
USEPA	United States Environmental Protection Agency
wk	week
wt	weight

WBC	white blood cells
WWEIA	What We Eat in America
♂	males
♀	females
↑	increased
↓	decreased

Appendix I Registered Uniconazole-P Products as of 21 February 2019

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee %
25780	T	Valent Canada, Inc.	Valent Uniconazole-P Technical	solution	76%
32171	T	Fine Agrochemicals Limited	Technical Uniconazole-P	solid	79.4%
25781	C	Valent Canada, Inc.	Sumagic Plant Growth Regulator	emulsifiable concentrate	0.055%
32342	C	Fine Agrochemicals Limited	Concise	solution	0.055%

T – technical grade products, C – commercial-class product

Appendix II Toxicological Tables

Table 1 Toxicology Reference Values for Use in Health Risk Assessment for Uniconazole-P

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Oral developmental toxicity study in rats	NOAEL = 5 mg/kg bw/day ↓ bwg at GD 6-9 in maternal animals	100
ARfD = 0.05 mg/kg bw			
Repeated dietary	Two co-critical studies: Two-year dietary Chronic Toxicity/Oncogenicity study in rats One-year oral toxicity study in dogs	NOAEL = 2 mg/kg bw/day ↓ bw, ↓ bwg and histopathological changes in the liver NOAEL = 2 mg/kg bw/day ↑ liver wt and histopathological changes in the liver	100
ADI = 0.02 mg/kg bw/day			
Short- and intermediate-term dermal	28-day dermal toxicity in rats	NOAEL = 5 mg/kg bw/day ↑ liver wt, histopathological changes in the liver	100
Short- and intermediate- term inhalation[2]	Oral developmental toxicity study in rats	NOAEL = 5 mg/kg bw/day ↑ incidence of fetal skeletal variations (cervical and 14th ribs)	100
Long-term dermal and inhalation[2,3]	Two co-critical studies: Two-year dietary Chronic Toxicity/Oncogenicity study in rats One-year oral toxicity study in dogs	NOAEL = 2 mg/kg bw/day ↓ bw and bwg and histopathological changes in the liver NOAEL = 2 mg/kg bw/day ↑ liver wt and histopathological changes in the liver	100
Aggregate (oral and dermal)	Oral developmental toxicity study in rats	NOAEL = 5 mg/kg bw/day Increased incidence of fetal skeletal variations (cervical and 14th ribs)	100
Cancer	18-month oncogenicity study in mice	q_1* = 1.76×10^{-2} based on the combined incidence of hepatocellular adenomas and carcinomas in male mice	

[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, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

[3]Since an oral NOAEL was selected, a dermal absorption factor of 46% was used in a route-to-route extrapolation

Table 2 Toxicity Profile of Technical Uniconazole-P

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

Study Type/ Animal/PMRA#	Study Results
Toxicokinetic Studies	
Metabolism gavage Sprague-Dawley Rat PMRA# 2755777	Rats received either a single oral low dose (1 mg/kg bw), a repeat oral low dose (1 mg/kg bw/day for 14 days of unlabeled uniconazole-P followed by a single oral gavage dose of 1 mg/kg bw), or a single oral high dose (200 mg/kg bw) of ^{14}C-triazole labelled uniconazole-P. The labelled and unlabelled compounds were dissolved in corn oil. **Absorption:** Extensive absorption was noted in both sexes with all dosing regimens. Total eliminated radioactivity 72 hrs after the last dose was ≥ 96.3% of AD. **Distribution:** There were no sex- or dose-related differences in distribution. Peak concentration in tissues was observed 1-8 hrs after administration. These levels were noted in adrenals (2.5-4.1 ppm), liver (2.3-2.6 ppm), fat (0.3-1.1 ppm) and kidneys (0.5-0.6 ppm). There was no evidence of bioaccumulation. Residual radioactivity in organs/tissues for all dosing regimens was very low after 7 days (0.002-1.8 ppm). Highest levels were detected in skin with hair and carcass. Detectable levels were also noted in the gastrointestinal tract and liver. **Metabolism:** Uniconazole-P was extensively metabolized and five metabolites (three major and two minor) were identified in both urine and feces which collectively accounted for 83-91% of AD. The parent compound was only detected in feces and accounted for 1-13% of AD. Compared to the single high or low dosing regimens, a slightly lower level of the parent compound was noted after repeated administration in both sexes. The major routes of biotransformation was oxidation of the methyl moiety to form an alcohol (CH_2OH-7E), followed by oxidation to form a carboxylic acid (COOH-7E) and hydrolysis of the parent compound to release 1,2,4-triazole. Other alternate metabolic pathways resulted in formation of the minor metabolites 4-OH-7E and CC acids. Total levels of 4-OH-7E, CH_2OH-7E, COOH-7E and CC acids were comparable regardless of sex or dosing regimen. Sex-related differences were noted in the levels of 1,2,4-triazole (12-15% of AD in ♂ vs 3-5% of AD in ♀). In blood, kidney and liver, the same major metabolites as were detected in urine and feces, and the parent compound, were present. **Excretion:** There were slight sex-related differences in elimination. In ♀, urinary excretion was the predominant route of elimination regardless of dosing (53.2-65.6% of AD). In ♂, urinary excretion was predominant after a single high-oral dose (57.4% of AD), whereas fecal excretion was predominant following single or repeated low oral doses (53.6-57.6% of AD). The difference in excretion pattern between the sexes was due to increased excretion of COOH-7E, the primary metabolite, in urine in ♀. Excretion was slower in the high-dose groups and % of AD excreted via the urine was slightly higher but the majority of the radioactivity (≥80.7%) was still excreted within 48 hrs.

Study Type/ Animal/PMRA#	Study Results
Acute Toxicity Studies	
Acute Oral Toxicity gavage Sprague-Dawley Rat PMRA# 1231088	**LD_{50} = 460 mg/kg bw (♂)** **LD_{50} = 430 mg/kg bw (♀)** Vehicle: corn oil **Clinical signs:** In both sexes at ≥ 200 mg/kg bw ↓ spontaneous activity, ataxia, limb paralysis, loss of righting reflex, irregular respiration, dyspnea, lacrimation and piloerection were noted. Effects gradually developed 1 hr post-dosing and disappeared within 7 days. Mortality was observed both sexes ≥ 280 mg/kg bw. **Necropsy:** Hemorrhagic changes in stomach, presence of brownish urine in the bladder, accentuated lobular pattern of the liver and cloudiness of the aqueous humour of the eye, were observed in the dead animals. In both sexes, congestion and cytoplasmic vacuolation, was noted in the liver of decedents. In animals that survived until terminal sacrifice, yellow whitish lesions in the liver (♂ ≥ 280 mg/kg bw; ♀ ≥ 390 mg/kg bw) and white lesions in the testes were noted (≥ 550 mg/kg bw) **High acute oral toxicity (GHS Category 3)**
Acute Oral Toxicity gavage Sprague-Dawley Rat PMRA# 1231089	**LD_{50} = 2020 mg/kg bw (♂)** **LD_{50} = 1790 mg/kg bw (♀)** Vehicle: aqueous suspension of 10% PEG 400, 1% methocel **Clinical signs:** At ≥ 250 mg/kg bw in ♀ and ≥ 500 mg/kg bw in ♂: ↓ spontaneous activity (within 2-4 h), ataxia, limb paralysis, loss of righting reflex, irregular respiration, dyspnea, lacrimation, urinary incontinence, hypothermia, piloerection (on day of treatment). All clinical signs of toxicity resolved within 8 days. Mortality in both sexes ≥ 1700 mg/kg bw. **Necropsy:** In decedents, hemorrhagic changes in stomach and accentuated lobular pattern of liver were observed in the decedents. In the liver, cytoplasmic vacuolation, hepatocyte hypertrophy and single cell and focal necrosis were observed. **Slight acute oral toxicity**
Acute Oral Toxicity capsule Beagle Dog PMRA# 1231090 1143120	**LD_{50} ≥ 5000 mg/kg bw** No mortality; however, all the animals at the highest dose vomited a white substance which appeared to be the test compound in the first four hrs after administration. **Low acute oral toxicity**
Acute Dermal Toxicity (Limit test) Sprague-Dawley Rat PMRA# 1231091	**LD_{50} ≥ 5000 mg/kg bw** No mortality or clinical signs of toxicity. No skin irritation noted. **Low acute dermal toxicity**
Acute Inhalation Toxicity Whole body Sprague-Dawley Rat	**LC_{50} ≥ 2.75 mg/L (highest achievable concentration)** **Clinical signs:** At ≥ 0.740 mg/L, ↓ spontaneous activity, urinary incontinence. At ≥ 2.75 mg/L hyperpnea followed by dyspnea, abnormal respiration, nasal discharge, salivation, staining around snout, ataxia, dark red substance attaching around eyes and piloerection. Clinical signs appeared 2 hrs after initiation of exposure and disappeared within 6 days

Study Type/ Animal/PMRA#	Study Results
PMRA# 1231092	after termination of exposure. **Necropsy:** Yellow white liver lesions were noted in the liver at ≥ 0.268 mg/L. At higher doses, cytoplasmic vacuolation of hepatocytes, liver fibrosis in sub-capsular region and focal necrosis of hepatocytes were observed. **Low acute inhalation toxicity**
Acute Inhalation Toxicity Whole body Sprague-Dawley Rat PMRA# 1231093	**LC_{50} ≥ 2.8 mg/L** **Clinical signs:** At ≥ 2.8 mg/L ↓ spontaneous activity, hyperpnea, ataxia, dark red substance around eyes, urinary incontinence and closed eyes. Signs appeared 0.5 hr after initiation of exposure and gradually disappeared within 4 days of termination of exposure. **Necropsy:** Yellow white-lesion of the liver, slight to severe hepatocellular vacuolation. Focal fibroplasia and focal pigmentation of the liver. **Low acute inhalation toxicity**
Primary Eye Irritation New Zealand White Rabbit PMRA # 1231077	MIS = 5.5 at 1 hr MAS: 1.17 One hr after application, the test material induced slight redness of conjunctiva in all rabbits, slight chemosis of conjunctiva and congestion of iris in 3 rabbits. Slight corneal opacity was noted 24 hrs post-application, in 2 rabbits and slight congestion of iris and redness of conjunctiva in 1 rabbit. All irritation resolved by 48 hrs. **Minimally irritating to the eyes**
Primary Skin Irritation New Zealand White Rabbit PMRA# 1231077	**Non-irritating to the skin**
Dermal Sensitization – Buehler's method Hartley Guinea Pig PMRA# 1231078	**Not a dermal sensitizer**

Study Type/ Animal/PMRA#	Study Results
Short-Term Toxicity Studies	
90-day Toxicity dietary Sprague-Dawley Rat PMRA# 1231079 2778924	**NOAEL = 8 mg/kg bw/day (♂/♀)** **≥ 8/8 mg/kg bw/day:** ↑ incidence of thyroid cytoplasmic vacuolation and small follicles (♂/♀); ↑ rel liver and thyroid wt (♀) [not adverse at this dose level] **≥ 73/79 mg/kg bw/day:** ↓ bw and bwg, ↓ fc and water intake in week 1, ↑ total protein, ↑ liver wt, ↑ incidence of enlarged liver, ↑ incidence and/or severity of hepatocyte cloudy swelling and cytoplasmic vacuolation (♂/♀); ↓ triglyceride, ↑ thyroid wt (♂); ↑ phospholipids, cholesterol, ↑ incidence of accentuated lobular pattern in the liver (♀) **228/229 mg/kg bw/day:** Stains on nose, forelegs, and genitals , ocular discharge in the first week,↑ urinary protein (slight), ↓ RBC, Hgb, Hct, MCH, MCHC (slight), ↑ total protein and albumin, ↑ incidence of discoloured liver; ↓ platelet, ↓WBC, lymphocytes, ↑ neutrophils, ↓ glucose, ↓ phospholipids, ↑ AST, ALT, leucine amino peptidase, ↑ BUN (♂)
90-Day Toxicity capsule Beagle Dog PMRA# 1231080	**NOAEL = 20 mg/kg bw/day** **≥ 20 mg/kg bw/day:** ↑ ALP (♂/♀); ↑ liver wt, ↑ incidence of soft feces (♂) [not adverse at this dose level] **≥ 80 mg/kg bw/day:** ↑ incidence of exaggerated liver lobular architecture and hepatocellular enlargement; ↑ incidence of enlarged yellowish liver (♂); ↓ bw wk 7 onwards, ↓ bwg, ↓ fc, ↓ calcium levels (very slight), ↑ incidence of liver cytoplasmic vacuolation (♀) **320 mg/kg bw/day:** ↑ incidence of white substance in feces, ↑ incidence of ballooning degeneration in the liver, ↑ smooth endoplasmic reticulum of hepatocytes (♂/♀); mortality (1), ↓ spontaneous movement and prostration (decedent only), ↓ bw wk 7 onwards, ↓ bwg, ↓ fc, ↑ BSP retention on wk 6, presence of hemorrhagic maculate in the right ventricle of the heart of one ♂, ↑ incidence of liver cytoplasmic vacuolation (♂); ↑ incidence of enlarged liver, ↑ rel liver wt (♀)
One-year Toxicity capsule Beagle Dog PMRA# 1231107	**NOAEL = 2 mg/kg bw/day** **≥ 20 mg/kg bw/day:** ↑ ALP, ↓ thymus wt (♂/♀); ↑ liver wt, singular incidence of hepatocellular enlargement with ↑ cytoplasmic homogeneity (♂) **200 mg/kg bw/day:** ↑ compound-coloured feces, ↓ bw from wk 2 onwards, initial bw loss, ↓ bwg, ↓ fc in wk 1, ↑ ALT, cholesterol (slight), ↑ rel kidney wt, ↑ adrenal wt, ↑ incidence of hepatocellular enlargement with ↑ cytoplasmic homogeneity, ↑ incidence of bile pigment (♂/♀); ↑ liver wt (♀)
28-Day Dermal Toxicity Sprague-Dawley Rat PMRA # 1231081	**Systemic Toxicity NOAEL = 50/5 mg/kg bw/day (♂/♀);** **Dermal irritation NOAEL = 5 mg/kg bw/day (♀); LOAEL = 50 mg/kg bw/day (♂)** Vehicle: Aqueous 0.7% CMC + 0.5% Tween 80 **Main study: (0, 50, 200, 500 mg/kg bw/day ♂/♀)** **≥ 50 mg/kg bw/day:** ↑ skin irritation, ↑ liver wt; ↑ hepatocyte vacuolation and centrilobular hypertrophy (♀) **≥ 200 mg/kg bw/day:** ↓ bw on day 2; ↓ bwg in week 1, ↑ yellow mottled striped or striated area of foci in the liver, ↑ hepatocyte vacuolation and centrilobular hypertrophy (♂); ↑ cholesterol, ↑ total protein, globulin (slight) (♀)

Study Type/ Animal/PMRA#	Study Results
	500 mg/kg bw/day: ↓ bw day 2-9, ↑ total protein, globulin (slight), singular incidence of liver focal necrosis (♂); ↑ yellow mottled striped or striated area of foci in the liver (♀) **Follow-up study at lower dose levels (♀ only): (0, 5, 25 mg/kg bw/day)** **25 mg/kg bw/day:** ↑ skin irritation and skin lesion, ↑ liver wt, ↑ incidence of hepatocytic vacuolation and centrilobular hypertrophy
Chronic Toxicity/Oncogenicity Studies	
Two-Year Chronic Toxicity/Oncogenicity Study dietary Sprague-Dawley Rat PMRA# 1231082 1231083 1231085 1231094 1231095 1231096 1231097 1231098 1231099 2801287	**NOAEL = 2 mg/kg bw/day (♂/♀)** **≥ 9/12 mg/kg bw/day:** ↓ bw, bwg, ↑ incidence of centrilobular hepatocellular enlargement and vacuolization; ↑ rel liver wt bw/day (♀) **49/60 mg/kg bw/day:** ↓ bw (week 3 onwards), ↓fc, ↓ triglycerides, ↑ liver wt (interim and terminal) ↑ incidence of raised area in the liver, ↑ incidence of necrosis of individual hepatocytes; ↑ incidence of astrocytoma (equivocal) (♂); ↓ overall bwg, ↑ cholesterol (slight) (♀) **Astrocytoma incidences at 0, 0.5/0.6, 1.9/2.4, 9/12, 49/60 mg/kg bw/day ♂/♀ respectively:** **♂: 0/50, 0/50, 0/50, 3/50** **♀: 2/50, 0/50, 1/50, 0/50** **Equivocal increased incidence of astrocytomas**
18-month Oncogenicity Study dietary CD-1 Mouse PMRA # 1231100 1231101 1231102 1231103 1231104 1231105 1231106 2778925	**NOAEL = 28 mg/kg bw/day (♂); 40 mg/kg bw/day (♀)** **215/276 mg/kg bw/day:** ↓ in fc on wk 2 only, ↑ liver/gallbladder wt at interim and terminal sacrifice, ↑ diffuse hepatocellular enlargement and vacuolization, ↑ liver pigmented macrophage; ↑ focal liver necrosis and chronic inflammation, ↑ amyloid deposition on tissues (heart, thyroid, parathyroid, liver, kidney) incidence of hypospermia, ↑ incidence of liver masses, ↑ incidence of liver adenomas, carcinomas and combined liver adenomas and carcinomas (♂); endometrial stromal polyp (♀) Liver tumour incidences in ♂ at 0, 1.5, 5.7, 28, 215 mg/kg bw/day respectively: Adenomas: 4/50, 6/50, 3/50, 8/50, 14*/50 Carcinomas: 1/50, 1/50, 2/50,1/50, 6/50 Combined (adenomas and carcinomas): 5/50, 7/50, 5/50, 9/50, 20*/50 * statistically significant (Fisher's Exact test at $p < 0.01$) **Evidence of carcinogenicity**
Developmental/Reproductive Toxicity Studies	
2-Generation Reproductive Toxicity Study dietary Sprague-Dawley Rat	**Parental Toxicity:** **Parental NOAEL = 7.5 mg/kg bw/day** **≥ 0.75 mg/kg bw/day:** ↑ liver wt F_1 (♀)(not adverse)

Study Type/ Animal/PMRA#	Study Results
PMRA# 1231111	**≥ 7.5 mg/kg bw/day:** ↑ rel liver wt P (♀)(not adverse) **75 mg/kg bw/day:** Two P ♀s died in early lactation period likely the result of prolong and difficult labor, ↓ P bw during premating, ↓ P fc during premating, ↑ incidence of enlarged liver in P/F_1, ↑ P/F_1 liver wt, ↑ incidence of hepatocellular enlargement and vacuolization and liver focal necrosis in P/F_1; ↑ incidence of centrilobular to mid-zonal necrosis and focal coagulative necrosis in F_1, ↓ bwg in F_1 post weaning (♂); ↓ bw from wk 5 onwards, ↓ bwg during premating in P (♀) **Reproductive Toxicity:** **Reproductive NOAEL = 75 mg/kg bw/day** **No evidence of reproductive toxicity at the highest dose tested.** **Offspring Toxicity:** **Offspring NOAEL = 7.5 mg/kg bw/day** **75 mg/kg bw/day:** ↓ F_1 and F_2 bw from PND 7 onwards **No evidence of sensitivity of the young**
Developmental Toxicity gavage Sprague-Dawley Rat PMRA# 2755773	**Supplemental – dose range finding study** **Maternal Toxicity** **≥ 25 mg/kg bw/day:** ↓ bwg (GD 6-12) **≥ 50 mg/kg bw/day:** ↑ incidence of ocular discharge, bw loss (GD 6-9), ↓ fc GD 6-9 **≥ 100 mg/kg bw/day:** ↑ incidence of piloerection **250 mg/kg bw/day:** ↑ clinical signs of toxicity (bradypnea ↓ spontaneous activity, ptosis, ocular discharge, lacrimation, piloerection, ataxic gait, hypothermia) at the beginning of treatment. Clinical signs diminished with time, ↓ terminal bw, ↓ fc during treatment, ↑ pale colour and yellow-whitish lesion of the liver **Developmental Toxicity:** **250 mg/kg bw/day:** ↓ # of implantations, live fetuses, ↑ fetal death **No evidence of treatment-related malformations** **No sensitivity of the young**
Developmental Toxicity gavage Sprague-Dawley Rat PMRA# 1232447 2755774	Vehicle: 0.5% aqueous CMC **Maternal Toxicity** **Maternal NOAEL = 5 mg/kg bw/day** **≥ 25 mg/kg bw/day:** ↓ bwg GD 6-9 and GD 6-12 **50 mg/kg bw/day:** ↓ fc on GD 9 **Developmental Toxicity** **Developmental NOAEL = 5 mg/kg bw/day** **≥ 25 mg/kg bw/day:** ↑ incidence of cervical ribs and 14th ribs **No evidence of treatment-related malformations** **No evidence of sensitivity of the young**

Study Type/ Animal/PMRA#	Study Results
Developmental Toxicity gavage New Zealand White Rabbit 5♀/group PMRA# 2755775	**Supplemental – dose range finding study** Vehicle: 0.5% aqueous CMC **Maternal Toxicity** **≥ 10 mg/kg bw/day:** ↓ fc (GD 10-19) **≥ 30 mg/kg bw/day:** ↑ mortality, clinical signs of toxicity (languid behavior, red fluid around urogenital area/anus, urine stains, anorexia), bw loss during treatment period, ↑ incidence of post-implantation loss **≥ 50 mg/kg bw/day:** ↑ clinical signs of toxicity (ataxia), ↓ gravid uterine weight, ↑ incidence of pale and enlarged liver, ↓ number of corpora lutea and implantation sites,↑ incidence of early resorptions **≥ 100 mg/kg bw/day:** All rabbits sacrificed in extremis between GD 12-15, ↑ clinical signs of toxicity (nasal discharge) **Developmental Toxicity** Not assessed
Developmental Toxicity gavage New Zealand White Rabbit 16♀/group PMRA# 1232458	Vehicle: 0.5% aqueous CMC **Maternal Toxicity** **Maternal NOAEL = 10 mg/kg bw/day** **20 mg/kg bw/day:** ↑ incidence of anorexia during treatment (very slight), bw loss between GD 7-19, ↑ fc GD10-16, ↑ pale kidney (slight) **Developmental Toxicity** **Developmental NOAEL = 20 mg/kg bw/day** No evidence of developmental toxicity at the highest dose tested. **No evidence of treatment-related malformations** **No evidence of sensitivity of the young**
Genotoxicity Studies	
Bacterial Reverse Mutation Test Salmonella typhimurium strains: TA98, TA100, TA1535, TA1537, TA1538 E. coli WP2 uvrA PMRA# 1232470	**Negative, with or without metabolic activation**
Micronucleus Test-IP injection ICR-Mouse Bone Marrow Cells	At 400 mg/kg bw, 1 animal from the 48 hr time point and 3 from the 72 hr time point died before the scheduled sacrificed and were replaced**.** **≥ 100 mg/kg bw:** bw loss **400 mg/kg bw:** ↑ mortality**,** limb paralysis, ↓ water consumption on day 0-2, ↓ fc,

Study Type/ Animal/PMRA#	Study Results
PMRA# 1232495	↑ of micronucleated polychromatic erythrocytes (PCEs) ↓ in the proportion of PCEs to total erythrocytes (polychromatic + normochromatic) was noted after 72 hrs at a dose above MTD **Negative**
Micronucleus Test-IP injection ICR-Mouse Bone Marrow Cells PMRA# 2755776	**≥ 200 mg/kg bw:** piloerection and suppression of spontaneous activity **400 mg/kg bw:** limb paralysis ↑ of PCEs was noted after 72 hrs at a dose above MTD **Negative**
Chromosomal Aberration CHO-K1 cells PMRA# 1232481	-S9: ↑ in polyploid cells at 100 and 200 µM after 24 hrs but within HC and therefore not considered clastogenic. +S9: No cells in metaphase at 300 µM. Slight ↑ in cells with aberrations at 100 and 200 µM. **Weakly clastogenic in the presence of S9 activation**
Sister Chromatid Exchange Test CHO-K1 cells PMRA# 1232492	-S9: High cytotoxicity observed ≥ 200 µM and therefore not enough metaphase cells could be scored. No increase in sister chromatid exchange (SCE) +S9: ↑ in SCE was observed at 200 µM. In a confirmatory assay, at 200 µM and 250 µM. However, excessive cytotoxicity was observed at concentrations ≥ 200 µM **Negative**
Unscheduled DNA Synthesis Sprague-Dawley Rat Hepatocytes PMRA# 1232496	**Supplemental: non-guideline** **Negative**
Mechanistic Studies (Supplemental)	
14 and 28-day liver mechanistic study – liver enzyme Dietary CD-1 Mouse PMRA# 2833769 2837534	2-weeks: **160 mg/kg bw/day:** ↑ liver wt, ↑ centrilobular hypertrophy, ↑ focal and single cell necrosis and diffuse vacuolation in the liver, ↑ hepatic microsomal protein and CYP450 content 4-weeks: **160 mg/kg bw/day:** ↑ liver wt, ↑ centrilobular hypertrophy, ↑ focal and single cell necrosis and diffuse vacuolation in the liver, ↑ hepatic microsomal protein and CYP450 content, ↑ liver CYP 2B1/2 protein (slight, qualitative analysis). The severity of liver histopathological findings increased with the duration of exposure but not liver wt.. Weak evidence of ↑ CYP2B1/2 expression following 4-week exposure period.

Study Type/ Animal/PMRA#	Study Results
14 and 28-day liver mechanistic study – gene expression, histopathology, cell proliferation Dietary CD-1 Mouse PMRA# 2833770 2839186	2-weeks: **≥ 29 mg/kg bw/day:** ↑ Eosinophilic change in the liver **223 mg/kg bw/day:** ↑ liver wt, ↑ enlarged liver with grayish-white focus and prominent reticular pattern, ↑ centrilobular hypertrophy, ↑ focal necrosis and diffuse vacuolation in the liver. 4-weeks: **223 mg/kg bw/day:** ↑ liver wt, ↑ enlarged liver with grayish-white focus and prominent reticular pattern, ↑ centrilobular hypertrophy, ↑ focal and single cell necrosis and diffuse vacuolation in the liver, ↑ proliferation of the smooth endoplasmic reticulum. Recovery group (4-week recovery period following a 4 week exposure period: No effects on liver wt or liver histopathological findings were noted in the uniconazole-P treated recovery group. Hepatocellular proliferation: No ↑ proliferation after 2 or 4 weeks as determined by BrdU labeling. Under the same conditions, ↑ hepatocellular proliferation was observed in phenobarbital treated animals at both time-points. Oxidative Stress and Apoptosis: No changes in markers of oxidative stress (lipid peroxide and reduced GSH) or apoptosis in uniconazole-P treated-groups. Gene expression analysis: **223 mg/kg bw/day:** ↑ expression of CYP2B and CYP2C genes by DNA Chip after 2 or 4 weeks exposure. Hierarchical clustering analysis was performed using up- or down-regulated genes. Uniconazole-P and phenobarbital treatment groups clustered together.
Special Studies (non-guideline)	
Motor activity assessment following acute dosing gavage Long-Evans Rat PMRA# 2873579	Animals were administered a single oral dose of uniconazole. Motor activity assessment was performed in all animals on the day of dosing. The exact timing was not specified but was stated as being between 30 minutes and 2 hrs. Results from the test groups were compared to both a non-treated and vehicle control group. Results stated that uniconazole did not produce hyperactivity; however, it is unclear whether exposure resulted in either no effects or a decrease in motor activity.

Table 3 Major Uniconazole-P Metabolites in Rats

Coded Name	Chemical name
4-OH-7E	ES-2-chloro-4-(3-hydroxy-4,4-dimethyl-2-(1H-,2,4-triazol-1-yl)pent-1-en-1-yl)phenol
CH_2OH-7E	5-(4-chlorophenyl)-2,2-dimethyl-3-(1H-1,2,4-triazol-1-ylmethyl)pentane-1,3-diol
COOH-7E	ES-5-(4-chlorophenyl)-3-hydroxy-2,2-dimethyl-4-(1H-1,4,4-triazol-1-yl)pent-4-enoic acid
CC acids	E and Z-3-(4-chlorophenyl)-2-1H, (1,2,4-triazol-1-yl)acrylic acid

Appendix III Dietary Exposure and Risk Assessments

Table 1 Summary of Dietary Exposure and Risk Assessment [Food Only]

Population Subgroup	Acute Dietary (Food Only)[1]		Chronic Dietary (Food Only)[2]		Cancer Dietary[3]	
	Exposure (mg/kg bw)	%ARfD	Exposure (mg/kg bw/day)	%ADI	Exposure (mg/kg bw/day)	Lifetime cancer risk
General Population	0.000034	< 1	0.000009	< 1	0.000009	2×10^{-7}
All Infants (< 1 year old)	0.000024	< 1	0.000004	< 1	n/a	
Children 1-2 years old	0.000065	< 1	0.000016	< 1		
Children 3-5 years old	0.000067	< 1	0.000016	< 1		
Children 6-12 years old	0.000043	< 1	0.000010	< 1		
Youth 13-19 years old	0.000030	< 1	0.000008	< 1		
Adults 20-49 years old	0.000031	< 1	0.000008	< 1		
Adults 50+ years old	0.000029	< 1	0.000007	< 1		
Females 13-49 years old	0.000029	< 1	0.000007	< 1		

[1]Acute Reference Dose (ARfD) of 0.05 mg/kg bw for the general population. Acute exposure reported at the 95th percentile.
[2]Acceptable Daily Intake (ADI) of 0.02 mg/kg bw/day applies to the general population.
[3] $q_1^* = 0.0176$ (mg/kg/day)$^{-1}$

Appendix IV Food Residue Chemistry Summary

Uniconazole-P is currently registered for use on greenhouse ornamentals and transplant tomato seedlings, in Canada. Since uniconazole-P is not registered for direct animal use and feed crops in Canada, residue chemistry data on livestock animals are not required and no residue definition in animal commodities has been established.

The nature of the residues in fruiting vegetables in crop subgroup 8-09A, is adequately understood based on an acceptable metabolism study conducted on greenhouse tomatoes. For crop subgroup 8-09A, the current residue definition (RD) for enforcement purposes is uniconazole-P, including the Z-isomer. For risk assessment, the residue definition is uniconazole-P, its R-enantiomer, and the Z-isomer of uniconazole. No changes are proposed to both definitions for this re-evaluation. Similarly, there are no proposed changes to the established MRLs (0.01ppm for crop subgroup 8-09A).

Analytical method RM-25-1b was previously reviewed and deemed acceptable for enforcement purposes. Methods RM-25-1, RM-25-1a, and RM-25-1b are acceptable for data gathering using methyl alcohol, dichloromethane (DCM), acetonitrile (ACN) as extraction solvents, Florisil column chromatography, gas chromatography (GC), and nitrogen-phosphorus specific detector (NPD). RM-25-1a and RM-25-1b include confirmatory analysis with GC method using mass selective detection (MSD). The listed methods are all sequential revisions to the original residue method RM-25, where minor differences exist between each version. These methods are unable to distinguish between the R and S enantiomers of the E-isomer of uniconazole and uniconazole-P and have not been tested for the triazole metabolites or the Z-isomer.

Freezer storage stability tests were conducted concurrent to the supervised residue trials. The data demonstrated that tomato samples fortified with 0.05 ppm of uniconazole-P were stable during frozen storage (-15 to - 25˚C) for up to 315 days.

Twelve trials were conducted and met the current Residue Chemistry Guidelines. Residues in tomatoes are <LOQ of 0.01ppm when treated according to the Good Agricultural Practice (GAP).

Two rationales were submitted to waive the requirements for residue decline and processed food data. Based on the rationales and information on file, the requirements were waived since the application timing is at the early 2 leaf stage, no detectable residues were found in tomato samples from the submitted residue field trials, and no residues are anticipated in tomatoes harvested at the 100 day pre-harvest interval (PHI).

Confined and field rotational trial data are not required as greenhouse transplant tomato seedlings are not considered a rotational crop.

Appendix V Mixer/loader and Applicator Exposure and Risk Assessment

Table 1 Short-term risks to workers mixing/loading and applying uniconazole-P to greenhouse tomato seedlings

Application equipment	Maximum AR[a] (kg a.i./ha)	ATPD[b] (ha)	Daily exposure (mg/kg bw/day)		MOE		LADD[g] (mg/kg bw/day)	Cancer risk[h]
			Dermal[c]	Inhalation[e]	Dermal[d]	Inhalation[f]		
Open mix/load and application (MLA) using handheld equipment (PHED); Open mix/load (liquid - AHETF) PPE: long sleeved-shirt, long pants and chemical-resistant gloves								
Manually-pressurized handwand	0.019	0.021	4.79×10^{-6}	2.30×10^{-7}	> 1 000 000	> 1 000 000	5.13×10^{-8}	9×10^{-10}
Mechanically-pressurized handgun	0.019	0.054	7.16×10^{-4}	1.94×10^{-5}	6980	> 200 000	7.35×10^{-6}	1×10^{-7}
Backpack sprayer	0.019	0.021	2.77×10^{-5}	3.16×10^{-7}	> 18 000	> 1 000 000	2.75×10^{-7}	5×10^{-9}
Overhead irrigation	0.019	1.000	1.39×10^{-5}	1.50×10^{-7}	> 300 000	> 1 000 000	1.38×10^{-7}	2×10^{-9}

AR = application rate; ATPD = area treated per day; MOE = margin of exposure; LADD = lifetime adjusted daily dose

[a] Maximum AR (kg a.i./ha) as per current product labels

[b] ATPD (ha) - hand held equipment - estimated assuming default L/day (150 L for backpack and manually-pressurized handwand, 3800 L/day for mechanically-pressurized handgun) and a minimum spray volume specified on the current label; overhead irrigation – greenhouse hectarage expected to be treated in a day

[c] Dermal exposure (mg/kg bw/day) = dermal unit exposure (mg/kg a.i.) × ATPD (ha) × Maximum AR (kg a.i./ha)/average worker body weight (80 kg)

[d] Dermal MOE based on a NOAEL of 5 mg/kg/bw/day from a 28-day dermal study in rats; target MOE = 100

[e] Inhalation exposure (mg/kg bw/day) = inhalation unit exposure (mg/kg a.i.) × ATPD (ha) × Maximum AR (kg a.i./ha)/average worker body weight (80 kg)

[f] Inhalation MOE based on a NOAEL of 5 mg/kg/bw/day; target MOE = 100 (Appendix II, Table 1)

[g] LADD (mg/kg bw/day) = [(Dermal exposure (mg/kg bw/day) adjusted for a 46% dermal absorption + inhalation exposure (mg/kg bw/day)) × ATPD (ha) × Maximum AR (kg a.i./ha)/average worker body weight (80 kg)] × frequency of exposure (50 days/year) × lifetime exposure (40 yrs./78 yrs.)

[h] Cancer risk = LADD × q_1* of 1.76×10^{-2}; occupational cancer risk threshold 1×10^{-5}

Table 2 Long-term risks to workers mixing/loading and applying uniconazole-P to greenhouse ornamentals

Application equipment	Maximum AR[a] (kg a.i./ha)	ATPD[b] (ha)	Daily exposure (mg/kg bw/day)		MOE[e]			LADD[g] (mg/kg bw/day)	Cancer risk[h]
			Dermal[c]	Inhalation[d]	Dermal	Inhalation	Combined[f]		
Open mix/load and application (MLA) using handheld equipment (PHED); Open mix/load (liquid - AHETF) PPE: long sleeved-shirt, long pants and chemical-resistant gloves									
Manually pressurized handwand	0.0663	0.075	2.70×10^{-5}	2.81×10^{-6}	> 74 000	> 71 000	> 67 000	2.09×10^{-6}	4×10^{-8}
Mechanically pressurized handgun	0.0663	1.900	4.05×10^{-3}	2.38×10^{-4}	494	8412	467	3.01×10^{-4}	5×10^{-6}
Backpack sprayer	0.0663	0.075	1.56×10^{-4}	3.86×10^{-6}	> 12 000	> 51 000	> 12 000	1.12×10^{-5}	2×10^{-7}
Overhead irrigation	0.0663	1.200	2.68×10^{-5}	6.27×10^{-7}	> 74 000	> 3 000 000	> 73 000	1.92×10^{-6}	3×10^{-8}

AR = application rate; ATPD = area treated per day; MOE = margin of exposure; LADD = lifetime adjusted daily dose

[a] Maximum AR (kg a.i./ha) – as per current product labels

[b] ATPD (ha) – for hand held equipment estimated assuming default L/day (150 L for backpack and manually pressurized handwand, 3800 L/day for mechanically pressurized handgun) and a minimum spray volume specified on the current labels, overhead irrigation - 95th percentile of flower greenhouse

[c] Dermal exposure (mg/kg bw/day) = Dermal unit exposure (mg/kg a.i.) × ATPD (ha) × Maximum AR (kg a.i./ha) × 46% dermal absorption/average worker body weight (80 kg)

[d] Inhalation exposure (mg/kg bw/day) = Inhalation unit exposure (mg/kg a.i.) × ATPD (ha) × Maximum AR (kg a.i./ha)/average worker body weight (80 kg)

[e] Based on a dermal and inhalation NOAEL of 2 mg/kg/bw; target MOE = 100 (Appendix II, Table 1)

[f] Combined MOE = NOAEL/(Exp_{dermal} + $Exp_{inhalation}$); long-term target MOE = 100

[g] LADD (mg/kg bw/day) = Combined (dermal plus inhalation) exposure (mg/kg bw/day) × frequency of exposure (50 days/year) × lifetime exposure (40 yrs./78 yrs.)

[h] Cancer risk = LADD × q_1* of 1.76×10^{-2}; occupational cancer risk threshold 1×10^{-5}

Appendix VI Postapplication Exposure and Risk Assessment for Greenhouse Workers

Table 1 Short-term postapplication risks to workers transplanting tomato seedlings

Crop	Maximum AR[a] (g a.i./ha)	Dermal exposure (mg/kg bw/day)	Dermal MOE[c]	LADD[d] (mg/kg bw/day)	Cancer risk[e]
Tomato seedlings	19	5.36×10^{-5}	93 217	1.04×10^{-6}	2×10^{-8}

AR = application rate; MOE = margin of exposure; LADD = lifetime adjusted daily dose

[a] Maximum AR (g a.i./ha) as per current product label

[b] Dermal exposure (mg/kg bw/day) – daily dermal exposure dose (Canada, 2011) adjusted for an average worker body weight (80 kg)

[c] Dermal MOE based on a NOAEL of 5 mg/kg bw/day; target MOE = 100 (Appendix II, Table 1)

[d] LADD (mg/kg bw/day) = Dermal exposure (mg/kg bw/day) × frequency of exposure (30 days/year) × lifetime exposure (40 yrs./78 yrs.)

[e] Cancer risk = LADD × q_1* of 1.76×10^{-2}, occupational cancer threshold 1×10^{-5}

Table 2 Long-term postapplication risks to workers handling ornamentals (except cut flowers)

Crop	Re-entry Activity	DFR[a] (µg a.i./cm^2)	TC[b] (cm^2/hr)	Dermal exposure[c] (mg/kg bw/day)	Dermal MOE[d]	30-day TWA DFR[e] (µg a.i./cm^2)	LADD[f] (mg/kg bw/day)	Cancer risk[g]
Ornamentals (except cut flowers)	All activities except irrigation (hand-set)	0.1658	230	1.75×10^{-3}	1140	0.1207	4.49×10^{-4}	8×10^{-6}

DFR = Dislodgeable Foliar Residue; TWA time weighed average; TC = Transfer Coefficient; MOE = margin of exposure; LADD = lifetime adjusted daily dose

[a] DFR (day 0) estimated assuming 25% residue deposition following a single application at a rate of 66.33 g a.i./ha (most conservative scenario for the risk assessment)

[b] TC - from the Agricultural Re-Entry Task Force (ARTF)

[c] Dermal exposure (mg/kg bw/day) = DFR (µg a.i./cm^2) × 0.001 (µg/mg) × 46% dermal absorption × TC (cm^2/hr) × 8 hrs/day/average worker body weight (80 kg)

[d] Dermal MOE based on a NOAEL of 2 mg/kg bw/day; target MOE = 100 (Appendix II, Table 1)

[e] 30-day TWA DFR estimated assuming 25% residue deposition following a single application at a rate of 66.33 g a.i./ha with 2.3% dissipation per day over 30 days

[f] LADD (mg/kg bw/day) = [30-day TWA DFR (µg a.i./cm^2) × 0.001 (µg/mg) × 46% dermal absorption × TC (cm^2/hr) × 8 (hrs/day)]/average worker body weight (80 kg) × frequency of exposure (250 days/year) × lifetime exposure (40 yrs./78 yrs.)

[g] Cancer risk = LADD × q_1* of 1.76×10^{-2} (mg/kg/bw/day)$^{-1}$, occupational cancer threshold 1×10^{-5}

Table 3 Long-term postapplication risks to workers handling ornamentals - cut flowers (Chrysanthemums)

Crop	Re-entry Activity	DFR[a] (µg a.i./cm^2)	TC[b] (cm^2/hr)	Dermal exposure[c] (mg/kg bw/day)	Dermal MOE[d]	Non-cancer REI	30-day TWA DFR[e] (µg a.i./cm^2)	LADD[f] (mg/kg bw/day)	Cancer risk[g]	Cancer REI
Chrysanthemums (cut flowers) Single application 44.22 g a.i./ha	hand harvesting	0.1106	4000	1.27×10^{-2}	157	0	0.0805	1.30×10^{-3}	**2×10^{-5}**	**5**
	disbudding, hand pruning		4000	2.04×10^{-2}	98	0		5.20×10^{-3}	**9×10^{-5}**	**18**
	pinching, hand weeding, plant support/ staking, scouting, transplanting		230	1.17×10^{-3}	1709	0		2.99×10^{-4}	5×10^{-6}	0
Chrysanthemums (cut flowers) 2 applications 22.11 g a.i./ha RTI 7 days	hand harvesting	0.1022	4000	1.18×10^{-2}	170	0	0.0735	1.19×10^{-3}	**2×10^{-5}**	**4**
	disbudding, hand pruning		4000	1.88×10^{-2}	106	0		4.75×10^{-3}	**8×10^{-5}**	**17**
	pinching, hand weeding, plant support/ staking, scouting, transplanting		230	1.08×10^{-3}	1850	0		2.73×10^{-4}	5×10^{-6}	0
Chrysanthemums (cut flowers) 1 application 11.05 g a.i./ha RTI 7 days	hand harvesting	0.0276	4000	3.17×10^{-3}	630	0	0.0201	3.25×10^{-4}	6×10^{-6}	0
	disbudding, hand pruning		4000	5.08×10^{-3}	394	0		1.30×10^{-3}	**2×10^{-5}**	**5**
	pinching, hand weeding, plant support/ staking, scouting, transplanting		230	2.92×10^{-4}	6849	0		7.47×10^{-5}	1×10^{-6}	0

DFR –Dislodgeable Foliar Residues; TWA time weighed average; TC = Transfer Coefficient; MOE = margin of exposure; LADD = lifetime adjusted daily dose

[a] DFR (day 0) estimated assuming 25% residue deposition following application at the specified rate

[b] TC - from the Agricultural Re-Entry Task Force (ARTF)

[c] Dermal exposure (mg/kg bw/day) = (DFR (µg a.i./cm^2) × 0.001 (µg/mg) × 46% dermal absorption × TC (cm^2/hr) × daily exposure duration (5 hrs/day for harvesting flowers and 8 hrs/day for all other activities)/average worker body weight (80 kg)

[d] Dermal MOE based on a NOAEL of 2 mg/kg bw/day; target MOE = 100 (Appendix II, Table 1)

[e] 30-day TWA DFR – estimated assuming 25% residue deposition with 2.3% dissipation rate per day over 30 days

[f] LADD (mg/kg bw/day) = [30-day TWA DFR (μg a.i./cm^2) × 0.001 (μg/mg) × TC (cm^2/hr) × 46% dermal absorption × daily exposure duration (5 hrs/day for harvesting flowers and 8 hrs/day for all other activities)]/average worker body weight (80 kg) × frequency of exposure (100 days/year for harvesting cut flowers and 250 days/year for all other activities) × lifetime exposure (40 yrs./78 yrs.)

[g] Cancer risk = LADD × q_1* of 1.76×10^{-2} $(mg/kg/bw/day)^{-1}$, occupational cancer threshold 1×10^{-5}; shaded cells indicate cancer risks exceeding 1×10^{-5}

Appendix VII Residential Exposure and Risk

Table 1 Short-term postapplication risks for individuals handling retail plants

Lifestage	DFR[a] (μg/cm^2)	TC[b] (cm^2/hr)	Dermal exposure[c] (mg/kg bw/day)	Dermal MOE[d]	30-day TWA DFR[e] (μg/cm^2)	LADD[g] (mg/kg bw/day)	Lifetime Cancer Risk[g]
Adult	0.1658	1 700	0.0035	1419	0.1207	7.83×10^{-5}	1×10^{-6}
Youth	0.1658	1 400	0.0020	2456	0.1207	1.80×10^{-6}	
Children 6 < 11 yrs.	0.1658	930	0.0024	2075	0.1207	2.13×10^{-6}	

DFR –Dislodgeable Foliar Residues; TWA time weighed average; TC = Transfer Coefficient; MOE = margin of exposure; LADD = lifetime adjusted daily dose

[a] DFR (day 0) estimated assuming 25% residue deposition following a single application at a rate of 66.33 g a.i./ha

[b] TC from the 2012 US EPA Residential SOPs

[c] Dermal exposure (mg/kg bw/day) = DFR (μg a.i./cm^2) × 0.001 (μg/mg) × 46% dermal absorption × TC (cm^2/hr) × exposure duration (1 hr/day for adults and 0.5 hr/day for youth and children)/body weight (80 kg adults, 57 kg youth, and 32 kg children)

[d] Dermal MOE based on a NOAEL of 5 mg/kg bw/day; target MOE = 100 (Appendix II, Table 1)

[e] 30-day TWA DFR – estimated assuming 25% residue deposition following a single application at a rate of 66.33 g a.i./ha with a 2.3% dissipation rate per day over 30 days

[f] LADD (mg/kg bw/day) = 30-day TWA DFR (μg a.i./cm^2) × 0.001 (μg/mg) × 46% dermal absorption × TC (cm^2/hr) × exposure duration (1 hr/day for adults and 0.5 hr/day for youth and children)/body weight (80 kg adults, 57 kg youth, and 32 kg children) × frequency of exposure (30 days for adults and 15 days for youth and children) × years of exposure (63 years for adults and 5 years for youth and children)

[g] Lifetime Cancer Risk = sum of LADDs × q_1* of 1.76×10^{-2} (mg/kg/bw/day)$^{-1}$, residential cancer threshold 1×10^{-6}

Appendix VIII Proposed Label Amendments for Products Containing Uniconazole-P

The label amendments proposed below do not include all label requirements for individual products, such as disposal statements, and precautionary statements. Information on labels of currently registered products should not be removed unless it contradicts the following label statements.

PRINCIPAL DISPLAY PANEL

Update wording to specify the percent of active ingredient as 79% for Valent Uniconazole-P Technical (Registration No. 25780).

PRECAUTIONS

1. Personal Protective Equipment

Replace the following statement on commercial-class product labels (Registration Nos. 25781 and 32342):

> *When mixing, loading, and applying the product, wear waterproof rain gear (e.g., Tyvek coveralls) with a hood, respirator with an organic cartridge, chemical-resistant gloves, goggles, and rubber boots.*

With:

> *For mixing, loading, application, clean-up and repair wear waterproof rain gear (e.g., Tyvek coveralls) with a hood, chemical-resistant gloves, goggles, socks, rubber boots and a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides.*

2. Restricted-Entry Interval (REI)

Replace the following statement on the commercial-class product label Registration No. 25781:

> *Do not reenter treated area within 12 hours of application. If early reentry is required, then wear waterproof rain gear (e.g. Tyvek coveralls), respirator with an organic chemical cartridge, chemical resistant gloves and rubber boots.*

With:

> *DO NOT enter or allow worker entry into treated areas during the restricted-entry interval (REI) of 12 hours. If required, applicators may enter treated areas within 12 hours for short-term tasks not involving hand labour if at least 4 hours has passed since application and waterproof rain gear (e.g., Tyvek coveralls) with a hood, chemical-resistant gloves, goggles, socks, rubber boots and a NIOSH-approved organic-vapour-*

removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides is worn.

3. Ornamental Restriction

Add the following statement (Registration Nos. 25781 and 32342**):**

DO NOT apply to ornamentals grown for cut flowers.

DIRECTIONS FOR USE

Equipment Limitations

Add the following statement to the commercial-class product label Registration No. 25781:

Do not apply using handheld mist blowers/airblast or handheld fogging equipment.

Replace the following statement on the commercial-class product label Registration No. 32342:

Do not apply this product using fogging equipment (handheld or automated), or using handheld mist blowers/airblast equipment.

With:

Do not apply using handheld mist blowers/airblast or handheld fogging equipment.

References

Studies Considered in the Chemistry Assessment

A. Studies/Information Submitted by the Registrants

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2499135	2015, Preliminary Analysis, DACO: 2.11,2.11.1,2.11.2,2.11.3,2.11.4,2.12,2.12.1,2.13,2.13.1,2.13.2,2.13.3,2.13.4
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